CHAPTER 10
HIV AND AIDS

Comprehensive guidelines are available for ART and the care of adults and children with HIV infection in the 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.[i]

10.1 ANTIRETROVIRAL THERAPY

B24

Antiretroviral therapy (ART) consists of combinations of antiretroviral medicines that are capable of suppressing HIV replication (defined as an undetectable viral load). Continued use of ART with a detectable viral load results in the development of resistance to some or all of the medicines in the regimen. High levels of adherence are essential for long-term success with ART.

The current recommended first-line ART regimen contains two nucleoside reverse transcriptase inhibitors (NRTIs) together with an integrase strand transfer inhibitor (InSTI) dolutegravir. Previously a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, together with two NRTIs, were recommended for first-line ART. Dolutegravir is better tolerated than the NNRTIs and has a much higher barrier to the development of resistance.

Dolutegravir, together with two NRTIs, is now also recommended in a patient who has failed an NNRTI-based (formerly first-line) regimen. Previously a protease inhibitor (PI), together with two NRTIs, was recommended for second-line ART, but dolutegravir is better tolerated than PIs. Switching people established on ART to the newer dolutegravir-based ART regimens needs to be carefully done to reduce the risk of the emergence of resistance (refer to National Department of Health HIV Guidelines and "Switching existing clients to DTG-containing regimens" section in Table 10.1: ART regimens).

ELIGIBILITY FOR ART

Eligibility to start ART:

All adults with confirmed HIV infection, irrespective of CD4 count or WHO clinical stage.

LoE: Ia[ii]

Immediate initiation:

ART should be initiated immediately in pregnancy and during breastfeeding.

LoE:IIa[iii]

Timing of ART initiation:

» Where a patient is willing and ready, ART should be initiated on the same day as HIV diagnosis, except in patients with TB or cryptococcal meningitis (see Timing of ART initiation below).

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):
- CD4 <50 cells/mm^3: initiate ART within 2 weeks of starting TB treatment.
- CD4 ≥50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, as this does not increase the risk of mortality and reduces the risk of deterioration due to immune reconstitution inflammatory syndrome (IRIS).

LoE:Ia[iv]

» In patients with TB meningitis (irrespective of CD4 count), defer ART until 8 weeks after initiating TB treatment.

LoE:IIIa[v]

» In patients with cryptococcal meningitis, defer ART until 4–6 weeks after starting antifungal treatment (earlier initiation has been shown to increase the risk of death).

LoE:IIIa[vi]

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, there is no need to delay. ART can be started immediately.

LoE:IVb[vii]

PSYCHOSOCIAL INDICATORS OF READINESS FOR ART

It is essential that patients have good insight into the need for long-term therapy and high levels of adherence. Pay careful attention to adherence planning. Encourage patients to disclose their HIV status to somebody to act as a treatment supporter. If this is not possible then the patient should join a support group.

Manage depression.

Active substance abuse/alcoholism is an impediment to adherence and, if possible, should be addressed prior to initiating ART.

LoE:IIIb[viii]

ART REGIMENS

INITIATING ART	
Treatment-naïve patients	Individuals ≥30kg: TDF + 3TC + DTG ("TLD") *LoE:IIa*[ix] **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. *LoE:IIa*[x] Patients on rifampicin-based TB treatment: TDF + FTC + EFV

	OR TDF + 3TC + DTG *plus* additional dose of DTG 50 mg 12 hours later. The extra DTG dose can be stopped two weeks after completion of TB therapy. *LoE:IIIb*[xi] (Also see AH STG Section 6.6: HIV in pregnancy)
Contraindications/ intolerance to DTG	TDF + 3TC/FTC + EFV
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + ATV/r *LoE:IIb*[xii] **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r 800/200 mg 12-hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 mg and then 800/200 mg). The LPV/r can be switched back to ATV two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	If chronic hepatitis B coinfection and eGFR 30-50 ml/min: TAF + FTC + DTG. Other scenarios: ABC + 3TC + DTG *LoE:IIIb*[xiii]
Contraindication to TDF/TAF and ABC intolerance/hypersensitivity	AZT + 3TC with DTG
Note: In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, the following alternative dual-therapy regimens may be used **after** consulting a specialist: • DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) • EFV + LPV/r • DTG + LPV/r *LoE:IIb*[xiv]	

VIROLOGICAL FAILURE	
Management of viraemia on TLD	If plasma VL >50 copies/mL: » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. If plasma VL remains > 50: » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time). » If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).
SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS	
Patient on: » **TDF/FTC/EFV** » **ABC/3TC/EFV (or NVP)** » **AZT/3TC/EFV (or NVP)** » **AZT/3TC/DTG** » **Any LPV/r- or ATV/r-containing regimen for <2 years** » **Any LPV/r- or ATV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xv]
Patient on: » **ATV/r or LPV/r regimen for >2 years and ≥2 consecutive viral loads ≥1000 copies/mL**	If adherence >80%, discuss with an HIV expert* to authorise and interpret a resistance test before switching. If adherence < 80%, switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above. *LoE:IIb*[xvi]

CLIENTS WITH DTG RESISTANCE	
Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available from TLART@health.gov.za or from https://www.righttocare.org/)
RIFAMPICIN-BASED TB TREATMENT	
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg 12 hours after TLD dose. *LoE:IIIb*[xvii] If on ATV/r: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy.

ABC=Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC=Lamivudine, DTG= Dolutegravir, EFV=Efavirenz FTC=Emtricitabine, LPV/r=Lopinavir/ritonavir, TDF=Tenofovir disoproxil fumarate TAF= Tenofovir alafenamide

Table 10.1: ART regimens

*For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

HIV Hotlines:

» National HIV & TB Health Care Worker Hotline: **0800 212 506**

» Right to Care Paediatric, Adolescent and Adult HIV Helpline: **082 352 6642**

» KZN Paediatric Hotline: **0800 006 603**

Note:

» Always check hepatitis B surface antigen (HBsAg) before stopping TDF

» If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare.

» Continue TDF if HBsAg positive.

Currently available ARV FDC preparations on contract:

- ABC 600 mg + 3TC 300 mg
- TDF 300 mg + FTC 200 mg
- AZT 300 mg + 3TC 150 mg
- LPV 100 mg + ritonavir 25 mg
- LPV 200 mg + ritonavir 50 mg
- TDF 300 mg + FTC 200 mg + EFV 600 mg
- TDF 300 mg + DTG 50 mg + 3TC 300 mg
- ATV 300 mg + ritonavir 100mg
- ABC 600 mg + 3TC 300 mg + DTG 50 mg

Source: Contract circular HP13-2022ARV http://www.health.gov.za/

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Do VL, recommence ART regimen unless there is a clinical indication to defer ART, repeat VL at 3 months. Recommence previous regimen (unless patient would qualify for a switch to TLD anyway as per above, in which case start dolutegravir-based regimen, e.g. TLD).

» If VL does not to decrease to <1000 copies/mL at 3 months, manage as per virological failure above.

LoE:IIIb[xviii]

ART: DOSING AND IMPORTANT ADVERSE EFFECTS				
Generic name	**Class**	**Usual dose**	**Renal adjusted dose**	**Important adverse drug reactions (ADRs) and timing**
Tenofovir disoproxil fumarate (TDF)	NRTI	300 mg daily	Avoid in renal impairment (eGFR <50 mL/min)	» Acute kidney injury (rare - weeks to months). » Decline in eGFR (months to years) » Fanconi syndrome (rare – months to years) » Reduced bone mineral density (months to years).
Abacavir (ABC)	NRTI	600 mg daily	Dose adjustment not required	» Hypersensitivity reaction (1 to 6 weeks) fever, rash, constitutional symptoms, gastrointestinal symptoms and respiratory symptoms.
Zidovudine (AZT)	NRTI	300 mg 12 hourly	eGFR <10 mL/min: 300 mg daily	» Anaemia, neutropenia (weeks to months). » Gastro-intestinal upset. » Headache. » Myopathy (rare). » Hyperlactataemia / steatohepatitis (medium risk - months). » Lipoatrophy (months to years).
Lamivudine (3TC)	NRTI	300 mg daily (or 150 mg 12 hourly)	eGFR 10-30 mL/min: 150 mg daily	» Anaemia due to pure red cell aplasia (rare).

			eGFR <10 mL/min: 50 mg daily	
Emtricitabine (FTC)	NRTI	200 mg daily	eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days Note: FTC is not available as a single-ingredient formulation.	» Palmar hyperpigmentation. » Anaemia due to pure red cell aplasia (rare). LoE:IVb[xix]
Efavirenz (EFV)	NNRTI	600 mg at night	Dose adjustment not required	» Central nervous system symptoms: vivid dreams, problems with concentration, confusion, mood disturbance, psychosis (days to weeks). » Encephalopathy, often with cerebellar features (uncommon – months to years). LoE:IVb[xx] » Rash (1 to 6 weeks). » Hepatitis (weeks to months) » Gynaecomastia.
Tenofovir alafenamide (TAF)	NRTI	25 mg daily If coformulated with FTC, avoid if eGFR <30 ml/min. If used as a single agent, avoid if eGFR <15 ml/min and not on haemodialysis.		» Acute kidney injury » Fanconi syndrome » Reduced bone mineral density
Lopinavir/ ritonavir (LPV/r)	Boosted PI	400/100 mg 12 hourly **OR** 800/200 mg daily (only if PI-naïve)	Dose adjustment not required	» Gastrointestinal upset. » Dyslipidaemia (weeks). » Rash and/or Hepatitis (1 to 6 weeks).
Atazanavir/ ritonavir (ATV/r)	Boosted PI	ATV 300 mg with ritonavir 100 mg daily	Dose adjustment not required	» Unconjugated hyperbilirubinaemia (common, but benign). » Dyslipidaemia (low risk). » Hepatitis (rare - 1 to 6 weeks). » Renal stones (uncommon).
Dolutegravir (DTG)	InSTIs	50 mg once daily	Dose adjustment not required	» Hypersensitivity (rare, weeks) » Insomnia (common) » Headache (common) » Other neuropsychiatric symptoms » Nausea, diarrhoea (common) » Hepatitis (uncommon) » Increase in serum creatinine (<30 mmol/L within the first few weeks

				of DTG initiation) due to inhibition of creatinine secretion by DTG; this is clinically insignificant as glomerular filtration rate is not reduced but will modestly affect eGFR which is determined using serum creatinine.

Table 10.2: Dosing and important adverse effects associated with ART
The time-onset information with respect to adverse drug reactions (ADRs) serves as an estimate. Patients may present with ADRs with the onset deviating from that indicated in the table.

LoE:IIIb[xxi]

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

» https://www.hiv-druginteractionslite.org/checker
» http://www.mic.uct.ac.za/ download the ARV/EML interaction checker.
» Package inserts.

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION			
Class	**ARV**	**Interaction with rifampicin**	**Dose of ARV with rifampicin**
NRTI	3TC/FTC/ TDF/ AZT/ABC	No clinically significant pharmacokinetic interactions	No dose adjustment required.
NNRTI	EFV	Non-significant change (EFV concentrations may increase in patients who are genetic slow metabolisers of EFV and are on isoniazid which also inhibits EFV metabolism).	No dose adjustment required (600 mg at night).
PI	LPV/r	LPV plasma concentrations significantly decreased	Double the dose of LPV/r to 800/200 mg 12 hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. Dose should be gradually titrated upward over 1-2 weeks. Adjusted dose should be continued for 2 weeks after rifampicin is stopped.
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly – replace rifampicin with rifabutin 150 mg daily (see monitoring instructions below).
InSTI	DTG	Significant reduction in concentration of DTG	Dose increased to 50 mg 12 hourly*

Table 10.3: ART interactions with rifampicin and dose-adjustment recommendations.

LoE:IIIb[xxii]

In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with:

- Rifabutin, oral, 150 mg daily.
  - Monitor FBC monthly for anaemia and neutropenia.

- Monitor clinically for symptoms of uveitis (e.g. pain, photophobia, variable loss of vision, circumcilliary injection, a miotic pupil) – immediately stop rifabutin pending ophthalmology opinion.

LoE:IIIb[xxiii]

DRUG INTERACTIONS WITH DOLUTEGRAVIR		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Preparations containing polyvalent cations (Mg^{2+}, Ca^{2+}, Fe^{2+}, Al^{3+}, Zn^{2+}) Antacids Sucralfate Mineral supplements	Significant reduction in concentration of DTG	Magnesium- and aluminum-containing preparations should be taken 6 hours before or 2 hours after DTG. Calcium- and iron- containing preparations can be taken concomitantly with DTG when administered with food. **Note:** Iron and calcium should be taken at least 4 hours apart from one another.
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of DTG	Avoid co-administration if possible. Consider valproate or lamotrigine. *For carbamazepine:* Double DTG dose to 50 mg 12 hourly.
Metformin	May increase metformin concentration	*Metformin initiation:* Initiate metformin at a low dose (500-1000mg total daily dose), titrating up as needed. Do not exceed 2 g daily. *DTG initiation:* If patient stabilised on metformin dose ≤ 2g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2g daily, reduce dose of metformin to ≤ 2g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30mL/min. See Appendix II for further guidance on patients with renal impairment.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

Table 10.4: Drug interactions with DTG *LoE:IIIb*[xxiv]

DRUG INTERACTIONS WITH BOOSTED PIs		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Substrates of cytochrome P450 3A4 (e.g. most statins, calcium channel blockers, most SSRIs, most	Significant increase in levels of *CYP3A4* substrates	Avoid co-administration or use lower doses of *CYP3A4* substrates (always consult interaction resources).

benzodiazepines)		
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of PI	Avoid co-administration. Consider valproate or lamotrigine.
Proton pump inhibitors	Significant reduction in ATV levels	Avoid co-administration. *LoE:IIIb*[xxv]
Rifampicin	Significant reduction in levels of PI	Double LPV/r dose. Avoid co-administration of other PIs (replace rifampicin with rifabutin).

Table 10.5: Drug interactions with boosted PIs

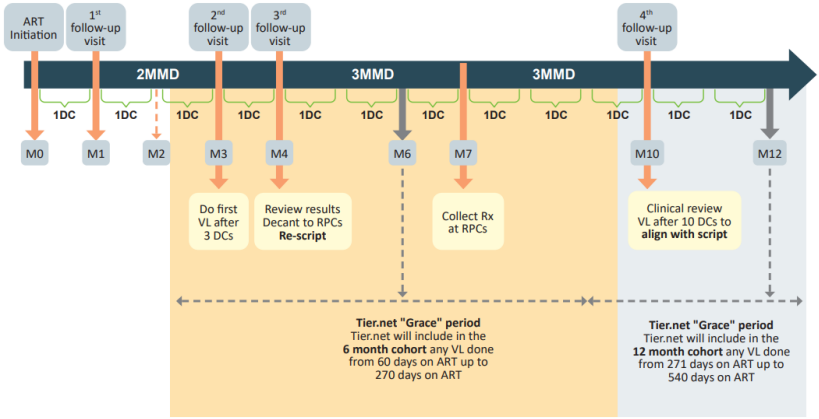
MONITORING ON ART	
Baseline evaluation	» Confirm HIV positive result with second test. » WHO staging. » Check CD4 count. » <u>If CD4 <200 cells/mm^3:</u> *LoE:IVb*[xxvi] – Check cryptococcal antigen (if positive, perform LP regardless of whether symptoms are present or not). – Initiate cotrimoxazole prophylaxis (See Section 10.2.2: Cotrimoxazole prophylaxis). – Reflex CrAg testing is done on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately. » Screen for pregnancy or ask if planning to conceive. » Screen for mental health, STIs and NCDs. » Screen for TB using the WHO screening questionnaire (any one of cough, fever, night sweats, or weight loss). » Sputum TB-NAAT* in all who can produce sputum, regardless of symptoms. » Urine LAM for inpatients or outpatients who are symptomatic if CD4 <200, or advanced HIV disease or current serious illness. » If planning to use TDF: check creatinine (avoid TDF if eGFR <50 mL/minute). » Haemoglobin *LoE:IIIb*[xxvii] » Check HBsAg (if positive, TDF should form part of the regimen). » Cervical cancer screening *TB-NAAT: TB Nucleic Acid Amplification Tests (e.g. GeneXpert Ultra MTB/RIF) *LoE:IIb*[xxviii]
On ART	» Monitoring schedule has been adapted to minimise the number of visits required per annum.

	» VL at 3 and 10 months after initiating ART and every 12 months thereafter, if virologically suppressed. Align timing with client's scripting cycle. » CD4 at 10 months after initiating ART (align with VL). Stop CD4 count monitoring when >200 cells/mm^3 and virologically suppressed. If virological or clinical failure occurs, or if client returns >90 days after missing an appointment, then a CD4 count should be done as cotrimoxazole may need to be commenced/recommenced. Repeat CD4 count every 6 months if VL remains ≥ 1000 copies/mL » If on TDF: creatinine at month 3, month 10, and every 12 months thereafter. Align with VL monitoring schedule. » If on AZT: FBC and differential count at 1 and 3 months after initiating AZT, then only if clinically indicated. » ALT if symptoms of hepatitis develop. » If on a protease inhibitor (PI): cholesterol and triglycerides at 3 months after initiating PI. If above acceptable range, do fasting cholesterol and TGs and if still above acceptable range, obtain expert advice.

Table 10.6: Monitoring on ART

HIV VIRAL LOAD MONITORING SCHEDULE

Routine VL monitoring	Intervention	Comments
First VL after ART initiation	Do 1st VL after **3 dispensing cycles**	• Allows for earlier detection of factors influencing viral suppression • Allows for earlier decanting for suppressed clients to minimise visits and promote continued engagement in care • This VL will form part of the **6 month VL completion cohort** in Tier.net
Second routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done from **10 dispensing cycles** but should be aligned with the clients scripting cycle	• This VL will form part of the **12 month VL completion cohort** in Tier.net
Third routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done **from 22 dispensing cycles**, but should be aligned with the clients scripting cycle	• This VL will form part of the 24 month **VL completion cohort** in Tier.net
Fourth and all subsequent VLs	VLs will be taken at intervals of 12 dispensing cycles for all clients who remain virally suppressed	
The timing of dispensing cycles, follow-up visits, and VL monitoring is illustrated in the diagram below		



- For the 1st VL taken after 3 dispensing cycles, clients should be requested to return to the facility one DC later to review results and so that the client can be assessed for RPCs eligibility.
- For all subsequent VL monitoring (and other routine monitoring investigation) in clinically well clients: Clients should be rescripted at the same visit that their VL is taken. Clients should not be required to come back to the facility the following month for VL result review prior to rescript. Rather, recall to the facility only those clients with an elevated VL or other abnormal result.
- Facilities should ensure that results management processes are in place to ensure that results are reviewed by a clinician, that abnormal results are identified, and the client is appropriately actioned. The NHLS Results for Action (RfA) reports are a useful tool to facilitate the review of results.

! Breastfeeding women should have their VL monitored every 6 months starting from the time of delivery

DC: Dispensing cycle; MMD: Multi-month dispensing; RPCs: Repeat prescription collection strategies

Figure 10.1: Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

Dyslipidaemia E78.0-5 + (Y41.5 + B24)
The protease inhibitors can cause significant dyslipidaemia. Fasting lipids should be done 3 months after starting protease inhibitors. LPV/r is associated with a higher risk of dyslipidaemia (especially hypertriglyceridaemia) than ATV/r.

Patients on LPV/r with the following should switch to ATV/r and repeat the fasting lipids in three months:
» triglycerides >10 mmol/L
» total cholesterol >6 mmol/L with a high risk (i.e. >20% risk of developing a CVD event in 10 years).

Patients with persistent dyslipidaemia despite switching to ATV/r may need lipid lowering therapy. Criteria for initiating lipid lowering therapy are the same as for HIV seronegative patients. (See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention).

Many statins (including simvastatin) cannot be used with protease inhibitors, as protease inhibitors inhibit the metabolism of the statin resulting in extremely high blood levels.

Patients, who fail to respond to lifestyle modification and have hypertriglyceridemia >10 mmol/L, treat with a fibric acid derivative, e.g.:
- Bezafibrate, oral, 400 mg at night.

OR
If LDL cholesterol is raised (See Section 3.1: Ischaemic heart disease and atherosclerosis, prevention):
- Atorvastatin, oral, 10 mg daily (do not exceed this dose due to a drug interaction with PIs).

Anaemia and neutropenia D64.9/D70 + (Y41.5 + B24)
AZT causes macrocytosis and can cause anaemia and neutropenia (note that it does not cause thrombocytopenia). AZT does not need to be stopped with mild anaemia and/or neutropenia, but must be stopped and replaced with an alternative medication if:
» anaemia is symptomatic,
» anaemia is severe (Hb <8.0 g/dL), or
» the neutrophil count is below 0.75×10^9/L.
Lamivudine and emtricitabine can cause pure red cell aplasia, but this is rare.

Hypersensitivity L27.0-1 + (Y41.5 + B24)
Note that pre-existing dermatological conditions (especially papulopruritic eruptions and acne) may worsen after commencing ART due to immune reconstitution inflammatory syndrome; see Section 10.1.2: Immune

reconstitution inflammatory syndrome (IRIS)) – this is not a hypersensitivity reaction and ART should be continued.

Other medicines, notably cotrimoxazole, can also cause hypersensitivity.

Hypersensitivity rashes occur commonly in the 8-week period after starting EFV. NNRTI-associated rashes can be severe and life-threatening.

If any of the following features occur when a patient is on EFV, then EFV must be permanently discontinued:
» Blistering
» Lesions affecting mucous membranes (mouth, eyes, or genitals)
» Fever.

Patients with lesions affecting the mucous membranes, or with significant blistering, likely have Stevens Johnson syndrome or toxic epidermal necrolysis, and will require admission.

With mild rashes EFV can be continued with careful observation and the rash will often subside.
If rash worsens or does not improve within a week discontinue EFV.
DTG can cause systemic hypersensitivity syndrome with rash, but this is very uncommon. DTG should be permanently discontinued if this occurs.

ABC can cause a rash as part of a systemic hypersensitivity reaction, which is confined to people who are *HLA-B*5701* positive. ABC should be permanently discontinued if this occurs. *LoE:IVb*[xxix]

Hyperlactataemia E87.2 + (Y41.5 + B24)
Symptomatic hyperlactataemia occurs due to mitochondrial toxicity of NRTIs. The estimated risk of symptomatic hyperlactataemia differs among the NRTIs, with zidovudine having moderate risk and the other NRTIs very low risk.

Risk factors for hyperlactataemia include:
» females,
» obesity,
» prolonged use of NRTIs (> 3 months), or
» development of NRTI-induced fatty liver.

Clinical symptoms of hyperlactataemia are non-specific and may include:
» nausea
» abdominal pain
» malaise
» liver dysfunction (due to steatosis)
» vomiting
» weight loss
» tachycardia

A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated to confirm metabolic acidosis.

Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):
Alter therapy, selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
Stop the ART temporarily.
Consult with an HIV specialist regarding the future ART plan.
Admission to a high care unit is recommended in patients with acidosis.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

Hepatotoxicity K71.9 + (Y41.5 + B24)
All currently available antiretrovirals are potentially hepatotoxic. EFV has the highest risk. NRTIs uncommonly cause acute hepatitis, but may result in steatohepatitis after prolonged use, which manifests with mildly elevated liver enzymes, affecting GGT and alkaline phosphatase more than the transaminases, and ALT more than AST. Patients on atazanavir may develop jaundice due an unconjugated hyperbilirubinaemia, which is not accompanied by liver injury. This is a cosmetic issue and the atazanavir can be substituted if the patient is unable to tolerate the jaundice. However, all protease inhibitors can rarely cause hepatitis, so it is important to exclude this in patients developing jaundice on ATV/r. DTG can cause a hepatitis, but this is rare.

Other potentially hepatotoxic medicines prescribed in PLHIV include anti-tuberculous therapy, fluconazole and cotrimoxazole. Cotrimoxazole, amoxicillin/clavulanate, and macrolides may cause cholestatic hepatitis that may take months to resolve.

The exclusion of viral hepatitis is important in the work-up of drug-induced liver injury (DILI). Testing for hepatitis A, B and C should be undertaken. Hepatitis B is common, and flares of viral hepatitis may occur after ART initiation (i.e. IRIS). Furthermore, life threatening flares may occur when antiretrovirals that are also active against hepatitis B (i.e. TDF, 3TC and FTC) are withdrawn.

Other potential causes include disseminated TB, IRIS, alcohol, alternative remedies, fatty liver, sepsis and HIV cholangiopathy.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients with any of the following criteria:
    - ALT >5 x upper limit of normal (ULN)
    - Jaundice
    - Other symptoms of hepatitis (e.g. right upper quadrant pain, nausea or vomiting).

» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude:
  - Extrahepatic biliary obstruction.
  - Fatty liver due to NRTIs.
  - Disseminated TB.

Management:

Upper Limit of Normal (ULN)	<2.5 x ULN	2.5 – 5 x ULN	> 5 x ULN
ALT	Repeat in 2 weeks	Repeat in 1 week	Stop ART

*Stop the relevant medicines at lower levels if symptoms of hepatitis (right upper quadrant pain, nausea / vomiting) or jaundice are present.
Table 10.7: Management of hepatotoxicity associated with ART

If ART is considered to be the cause, substitute ART as follows:
» If the hepatitis occurred on efavirenz, substitute with DTG or a boosted PI.
» If hepatitis occurred on PI, substitute with DTG.
» NRTI fatty liver – discontinue AZT (if relevant) and replace with safer NRTI (TDF or ABC) – if not on AZT and hepatitis is severe switch to NRTI-sparing regimen (see footnote in Table 10.1: ART regimens, located in Section 10.1: Antiretroviral therapy. Importantly, consult a specialist).

Hepatitis in patients on ART and anti-tuberculosis therapy
Drug-induced liver injury (DILI) is a known adverse effect of anti-tuberculosis therapy and ART and is a common problem in HIV/TB co-infected patients. First-line TB medicines associated with DILI include isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA). Anti-tuberculosis therapy commonly causes transient, mild, asymptomatic elevations in serum aminotransferase levels that may not necessarily require discontinuation of therapy.

If hepatitis develops, as defined above, stop all antiretrovirals, cotrimoxazole and all potentially hepatotoxic TB medicines (i.e. INH, RIF and PZA).

TB immune reconstitution inflammatory syndrome (TB-IRIS) should be considered in the differential diagnosis (see Section 10.1.2: Immune reconstitution inflammatory syndrome (IRIS)). This condition presents shortly after ART initiation in patients with TB. The GGT and ALP are elevated to a greater degree than the transaminases. Mild jaundice with a conjugated hyperbilirubinaemia and tender hepatosplenomegaly may be present.

Investigations:
» Request an ALT.
» Request viral hepatitis screen, full liver function tests and INR in patients if ALT >5 x ULN and/or jaundice and/or symptoms of hepatitis are present.
» Perform a liver ultrasound if GGT or ALP are significantly elevated or if conjugated bilirubin is elevated, to exclude extrahepatic biliary obstruction.
» Reassess the grounds for TB diagnosis.
» Check if patient is on intensive or continuation phase of TB treatment.

Management:

» Stop TB therapy, initiate background TB therapy and continue throughout rechallenge:
  - Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative if Hb <8g/dL, but only for short term use).
  - Levofloxacin, oral, 750–1000 mg daily or Moxifloxacin, oral, 400 mg daily.
  - Ethambutol, oral, 800–1200 mg daily.
» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

Day 1:	• Rifampicin, oral 600 mg daily. ○ If <60 kg: rifampicin, oral 450 mg daily.
Day 3:	» Check ALT.
Day 4–6:	**ADD** • Isoniazid, oral 300 mg daily.
Day 7:	» Check ALT.
Day 8:	» Stop moxifloxacin/levofloxacin and linezolid (continue ethambutol). Consider pyrazinamide rechallenge only in cases of TB meningitis or intolerance/resistance to other medicines. • Pyrazinamide, oral 25 mg/kg daily.
Day 10:	» Check ALT. » Thereafter, monitor ALT twice weekly for the first 3 weeks, then every two weeks for a month, then monthly until 3 months. • Restart ART 2 weeks after completing rechallenge of TB therapy. ○ Monitor ALT every 2 weeks for 2 months after ART rechallenge.

Table 10.8: Management of drug-induced liver injury (DILI) *LoE:IVb*[xxx]

» If drug rechallenge is unsuccessful, then manage as per algorithm in Figure 10.2.

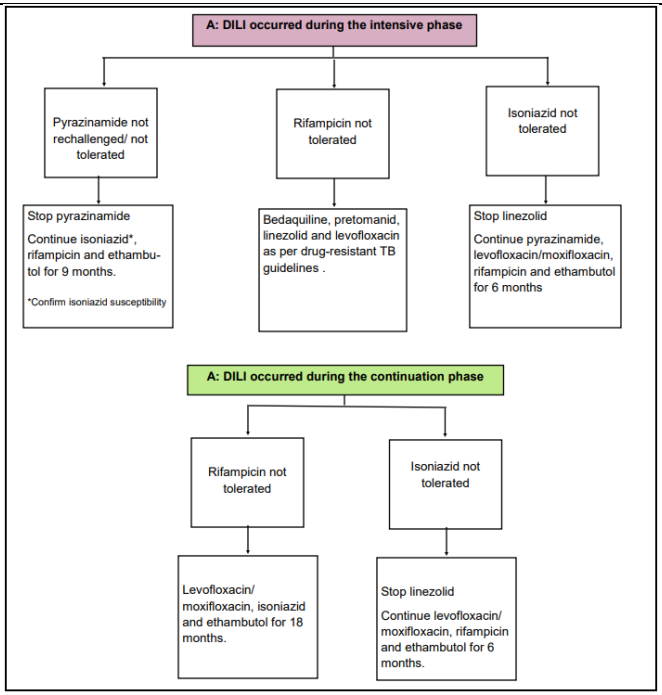


Figure 10.2: Management of TB if drug re-challenge unsuccessful

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

D89.3 + (Y41.5 + B24)

DESCRIPTION

IRIS occurs when improving immune function unmasks a previously occult opportunistic disease ("unmasking IRIS"), or causes paradoxical deterioration of an existing opportunistic disease ("paradoxical IRIS"). IRIS is more common in patients with advanced HIV disease, particularly those with a CD4 count <100 cells/mm^3. IRIS nearly always presents during the first 3 months of ART, with the median time of onset being about two weeks. The diagnosis of paradoxical IRIS is often difficult as new opportunistic diseases, or drug resistance of the organism causing the opportunistic infection, need to be excluded.

TB is the commonest opportunistic disease involved in IRIS reactions in South Africa. Paradoxical TB IRIS presents as recurrence or worsening of TB symptoms/signs, or new manifestations. The commonest presentation is with

enlarging lymph nodes, often with extensive caseous necrosis. Lung infiltrates or effusions may worsen or develop. It is important to exclude multi-drug resistance in all patients with suspected paradoxical TB IRIS.

Other common IRIS manifestations include:
» Inflammatory reactions to skin diseases, especially acne and Kaposi's sarcoma.
» Worsening cryptococcal meningitis.
» Flares of hepatitis B or C.

GENERAL MEASURES

Counselling is important to ensure that the patient understands that IRIS does not mean failure of ART.
Management of IRIS is mainly symptomatic, e.g. aspiration of TB lymph nodes or effusions.
Continue ART and therapy for the opportunistic infection.

MEDICINE TREATMENT

For pain and fever:

- Paracetamol, oral, 500 mg-1 g 4–6 hourly as required. (to a maximum of 4g in 24 hours)
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

Treatment for severe IRIS manifestations (e.g. compression of major structures by enlarging lymph nodes, expanding CNS tuberculomata, worsening meningitis):

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 1.5 mg/kg daily for 2 weeks.
  - Then 0.75 mg/kg daily for 2 weeks.

Prophylaxis for paradoxical TB IRIS in high-risk patients (CD4 ≤100 cells/mm^3) who have had antituberculosis treatment for <30 days before initiating ART:

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 2 weeks.
  - Then 20 mg daily for 2 weeks.

LoE:IIa[xxxi]

Note: Do not use steroids in patients with Kaposi sarcoma.

10.2 OPPORTUNISTIC DISEASES

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Z29.2 + (B24)

DESCRIPTION

Patients with HIV infection at any CD4 count are more susceptible to TB infection than HIV-uninfected patients. TPT is an effective intervention for reducing the incidence of TB in HIV-infected patients

Eligibility

All HIV-infected patients, irrespective of CD4 count, tuberculin skin test status, and ART status.

Exclusions

- » Suspected or confirmed TB
- » Liver Disease
- » Previous MDR- or XDR-TB
- » Painful peripheral neuropathy
- » Alcohol use disorder

Note:

- » Exclude TB prior to initiating TPT by screening for the following:
  - Cough (any duration)
  - Fever
  - Weight loss
  - Night sweats
- » Do not initiate TPT in patients if any of the above is present. These patients require further investigation for active TB.

Ideally start TPT together with ARVs: *LoE:IIb*[xxxii]

- TPT, e.g.:
- Isoniazid, oral, 300 mg daily for 12 months.
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

LoE:IIb[xxxiii]

ADD

- Pyridoxine, oral, 25 mg once daily for the full duration of the TPT regimen.
  - Instruct patient to present early if any of these symptoms arise.
  - Patients should be followed up monthly for the first 3 months.

NOTE: **For pregnant women:**
- Defer TPT until after delivery.
- Ensure that routine screening against TB is conducted at each antenatal visit.

LoE:IIb[xxxiv]

10.2.2 OPPORTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Z29.2 + (B24)

DESCRIPTION

Primary prophylaxis reduces the probability of developing many infections, e.g.:
» Pneumocystis pneumonia
» toxoplasmosis
» bacterial pneumonia
» bacteraemia
» cystoisosporiasis

LoE:IIa[xxxv]

Indications for primary prophylaxis:
» WHO Clinical stage III or IV.
» CD4 count <200 cells/mm^3.

MEDICINE TREATMENT

Prophylaxis

- Cotrimoxazole, oral, 160/800 mg daily. *LoE:IIa*[xxxvi]

Note:
Discontinue prophylaxis once the CD4 >200 cells/mm^3 (as measured at the routine CD4 count done at 1 year on ART). If the CD4 count was >200 cells/mm^3 when cotrimoxazole was commenced (e.g. patients with TB), continue for 6 months**.**

LoE:IIIb[xxxvii]

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

B20.4

DESCRIPTION

Mucosal candidiasis involving the oesophagus/trachea/bronchi is AIDS-defining (WHO clinical stage 4). Oesophagitis is by far the commonest manifestation.
Clinical features: symptoms of pain or difficulty on swallowing. Oral thrush is present in most patients.

GENERAL MEASURES

Maintain adequate hydration.

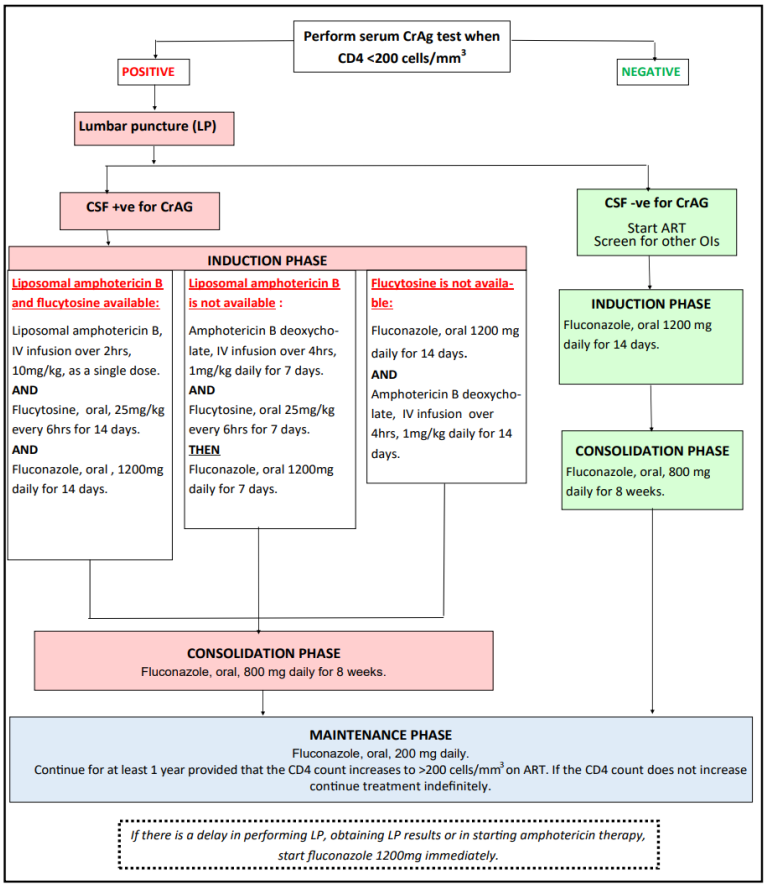
MEDICINE TREATMENT

- Fluconazole, IV/oral, 200 mg daily for 14 days.

- The usual route is oral but give IV if patient unable to swallow or is vomiting.
- An early relapse should be treated with a 4-week course of fluconazole, using a similar dose as above.
- If no response to fluconazole, collect sample to confirm diagnosis of candidiasis (perform fungal MC&S).

Note: Primary or secondary fluconazole prophylaxis for mucosal candidiasis is not recommended.

10.2.4 CRYPTOCOCCOSIS



Adapted from: Govender NP, Meintjes G, Mangena et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Figure 10.3: Algorithm for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons

10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

(B45.0-3/B45.7-9) + B20.5

DESCRIPTION

All ART-naïve patients with CD4 <200 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a diagnosis of cryptococcal infection). This is performed as a reflex test on the patient's CD4 sample if it is <100 cells/mm^3. If the CD4 count is between 100 and 199, a separate sample should be sent for CrAg testing. If the CrAg test is positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. Confirm cryptococcal meningitis by testing for CSF CrAg.

LoE:IIa[xxxviii]

MEDICINE TREATMENT

<u>If cryptococcal meningitis is excluded by negative CSF CrAg:</u>
Commence ART immediately - See Section 10.1: Antiretroviral therapy.

LoE:IIIa[xxxix]

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily. *LoE:IIIb*[xl]
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase, continue treatment indefinitely.

CAUTION

» Fluconazole is potentially teratogenic when used during the 1st trimester, but pregnant women should be counselled that the benefits of fluconazole likely outweigh the risks in the management of cryptococcosis.

» All pregnant women <20 weeks gestation exposed to fluconazole should have an ultrasound scan to detect congenital abnormalities. *LoE:IIIb*[xli]

» Although fluconazole is excreted into breast milk at concentrations similar to maternal plasma concentrations, the dose that the infant is exposed to with doses <400 mg is similar to the dose used in systemic treatment in infants. The benefits will likely outweigh the risks, even with higher doses, though this can be discussed with a specialist.

LoE:IVb[xlii]

10.2.4.2. CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Continue daily therapeutic lumbar puncture until there is clinical improvement.

MEDICINE TREATMENT

Induction phase

If liposomal amphotericin B and flucytosine are available: *LoE:IVb*[xliii]

- Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

AND

- Flucytosine, oral 25 mg/kg 6 hourly for 14 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

AND *LoE:IIa*[xliv]

- Fluconazole, oral 1200 mg daily for 14 days
  - Fluconazole requires dose adjustment in renal failure.

If liposomal amphotericin B is not available:

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity (see Appendix II for preventing, monitoring and management of toxicity).

AND

- Flucytosine, oral 25 mg/kg 6 hourly for 7 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (see Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200 mg daily for 7 days.

LoE:IVb[xlv]

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND *LoE:IIa*[xlvi]

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5% over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (see Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with: *LoE:IIIa*[xlvii]

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase *LoE:Ia*[xlviii]

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase, continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See Section 10.1: Antiretroviral therapy.

LoE:IIIa[xlix]

Note: Adjunctive corticosteroids have been shown to be detrimental.

LoE:Ia[l]

Flucytosine weight-based dosing:

Weight	Dose and frequency
30-39 kg	750 mg 6 hourly
40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

Table 10.9: Flucytosine weight-based dosing

REFERRAL

» Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.

» Persistent raised intracranial pressure despite daily therapeutic lumbar puncture.

10.2.5 CRYPTOSPORIDIOSIS DIARRHOEA

A07.2 + (B20.8)

DESCRIPTION

Chronic diarrhoea due to *Cryptosporidium parvum*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

There is no specific antimicrobial therapy for cryptosporidiosis. As with other opportunistic diseases, it responds well to ART.

Antimotility agents are partially effective, e.g.:

- Loperamide, oral, 4 mg initially, followed by 2 mg as required up to four times daily.

10.2.6 CYTOMEGALOVIRUS (CMV)

B20.2

DESCRIPTION

CMV disease outside the reticulo-endothelial system is an AIDS-defining illness (WHO clinical stage 4).
CMV disease is seen in patients with CD4 counts <100 cells/mm^3.
The commonest manifestations are:

» retinitis,
» GIT ulceration,
» pneumonitis, and
» polyradiculitis.

GIT and other organ involvement must be diagnosed on biopsy.
CNS disease must be diagnosed by PCR of CSF.
The diagnosis of CMV retinitis should be confirmed by an ophthalmologist.
Note: CMV serology (IgM and IgG), antigenaemia (pp65), or PCR on blood are not helpful in the diagnosis of CMV disease in HIV-infected adults.

MEDICINE TREATMENT

Valganciclovir is the treatment of choice, but this agent is toxic and expensive, and should only be used by a specialist familiar with its use.
To prevent recurrent disease, commence patients on ART as soon as possible after initiating valganciclovir (see Section 10.1: Antiretroviral therapy).
Maintenance therapy is only applicable to CNS disease and retinitis.
Monitor FBC regularly during therapy. Avoid other medicines associated with bone marrow suppression, particularly zidovudine.

Biopsy-proven GIT disease or pneumonitis

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks (Specialist initiated).

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days (Specialist initiated).

CNS disease

Initial treatment:

- Valganciclovir, oral, 900 mg 12 hourly for the first 3 weeks (Specialist initiated).

OR

If unable to tolerate oral medication:

- Ganciclovir, IV, 5 mg/kg 12 hourly for 14 days. Specialist initiated.

Maintenance treatment:

Only patients with a good clinical response should be considered for maintenance.

Valganciclovir, oral, 900 mg daily until CD4 count rises to >100 cells/mm^3 on ART, if available.Specialist initiated.

Note: Maintenance treatment is not indicated unless there has been a relapse.

REFERRAL/CONSULTATION

Specialist or tertiary

All patients.

10.2.7 CYSTOISOSPORIASIS

A07.3 + (B20.8)

DESCRIPTION

Diarrhoea due to *Cystoisospora belli*. Disease lasting >4 weeks is AIDS-defining (WHO clinical stage 4).

GENERAL MEASURES

Rehydration with oral rehydration solution (ORS).

MEDICINE TREATMENT

- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 10 days.

OR

If allergic to cotrimoxazole:

- Ciprofloxacin, oral, 500 mg 12 hourly for 10 days.

Secondary prophylaxis:

Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily.

10.2.8 MYCOBACTERIOSIS – DISSEMINATED NON-TUBERCULOUS

B20.0

DESCRIPTION

Disseminated infection due to non-tuberculous mycobacteria, usually *Mycobacterium avium* complex.

Diagnosis must be by culture from sterile sources, e.g. blood, tissue or bone marrow. Note that culture from a single sputum specimen is not adequate to make the diagnosis as this often reflects colonisation rather than disease.

Non-tuberculous mycobacteria can cause limited pulmonary disease, which is diagnosed if the sputum culture is positive repeatedly and there is a worsening pulmonary infiltrate.

Disseminated disease is AIDS-defining (WHO clinical stage 4).

MEDICINE TREATMENT

- Azithromycin, oral, 500 mg daily.

AND *LoE:IIIa*[ii]

- Ethambutol, oral, 15–20 mg/kg daily.

Treatment can be stopped when treatment has been continued for at least 12 months **AND** the CD4 count has increased to >100 cells/mm^3 on ART.

10.2.9 PNEUMOCYSTIS PNEUMONIA

B20.6

DESCRIPTION

Interstitial pneumonitis due to *Pneumocystis jirovecii* (formerly *carinii*). AIDS-defining illness (WHO clinical stage 4).

MEDICINE TREATMENT

All patients:

- Cotrimoxazole 80/400 mg, oral, 6 hourly for 21 days.
  - <60 kg three tablets
  - ≥60 kg four tablets

Monitor FBC and potassium when on high dose therapy.

OR

If vomiting:

- Cotrimoxazole, IV, 6 hourly for 21 days.
  - <60 kg 240/1200 mg
  - ≥60 kg 320/1600 mg

For hypoxic patients (PaO_2 <70 mmHg [<9.33 kPa], A-a gradient >35, or sats <92%):

- Oxygen by face mask or CPAP as necessary.

AND

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 80 mg daily for 5 days, then taper over 14 days (Refer to Appendix II for an example of a dose reduction regimen).

Cotrimoxazole intolerance and desensitisation

Attempt desensitisation in patients with a history of cotrimoxazole intolerance, unless hypersensitivity reaction was life-threatening, e.g. Stevens-Johnson syndrome (See Section 4.6: Erythema Multiforme, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis). Unless rash is severe or associated with systemic symptoms, continue treatment with careful observation for deterioration.

Desensitisation should be attempted using cotrimoxazole suspension 240 mg/5 ml. Dilute the suspension appropriately and consult with your pharmacist if necessary. DO NOT administer antihistamines or steroids.

Time (hours)	Cotrimoxazole dose (mL of 240mg/5mL suspension
0	0.0005
1	0.005
2	0.05
3	0.5
4	5
5	Two single strength tablets (each tablet = 80/400 mg) followed by full dose

Table 10.10: Desensitisation of cotrimoxazole

Alternatively, in case of intolerance and unsuccessful desensitisation:

- Clindamycin, oral, 600 mg 8 hourly for 21 days.

AND

- Primaquine, oral, 15 mg daily for 21 days.
  - Exclude G6PD deficiency before initiating therapy.
  - Primaquine is only available via the Section 21 application process.

If primaquine is not available, consider:

- Clindamycin, oral, 600 mg 8 hourly for 21 days.

AND

- Dapsone, oral, 100 mg daily for 21 days.

Secondary prophylaxis

Continue for at least 6 months and until CD4 count increases to >200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral daily.

Alternatively, in case of intolerance to cotrimoxazole:

- Dapsone, oral, 100 mg daily.

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to all alternative regimens.

10.2.10 CEREBRAL TOXOPLASMOSIS

B58 + (B20.8)

DESCRIPTION

Intracranial space-occupying lesions, with ring contrast enhancement on imaging, due to *Toxoplasma gondii*. AIDS-defining illness (WHO clinical stage 4).

The diagnosis of toxoplasmosis is very unlikely if either the serum toxoplasma IgG is negative or the CD4 count is > 200 cells/mm^3.

Diagnosis is confirmed by a clinical response to therapy, which occurs in 7–14 days. CT scan improvement usually occurs within 14–21 days. Interpreting the response to therapy may be difficult if steroids have been given concomitantly. Steroid therapy should only be given for life-threatening peri-lesional oedema.

MEDICINE TREATMENT

- Cotrimoxazole 160/800 mg, oral, 2 tablets 12 hourly for 28 days, followed by 1 tablet 12 hourly for 3 months.

Secondary prophylaxis

Continue for at least 6 months and until CD4 count increases to > 200 cells/mm^3 on ART.

- Cotrimoxazole 160/800 mg, oral, 2 tablets daily.

See guidance on cotrimoxazole desensitisation in Section 10.2.9: Pneumocystis pneumonia.

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to cotrimoxazole.

Note: Attempt desensitisation first (see Section 10.2.9: Pneumocystis pneumonia).

10.3 HIV AND KIDNEY DISEASE

N28.9 + (B23.8)

DESCRIPTION

A number of kidney disorders are associated with HIV infection.

Acute kidney injury due to sepsis, dehydration or nephrotoxicity from medicines occurs commonly.

The commonest chronic kidney disorder is HIV-associated nephropathy (HIVAN).

Typical features of HIVAN are:
» Heavy proteinuria.
» Rapidly progressive chronic kidney disease with preserved kidney size on imaging.

Early detection of kidney disease is important in order to implement interventions that may slow kidney disease progression, and for adjusting the dose of relevant medicines.
Risk factors for HIV renal disease:
» CD4 count <200 cells/mm^3.
» Use of nephrotoxic medications.
» Comorbidity such as diabetes mellitus, hypertension, or hepatitis C virus co-infection.
» ART may slow progression of HIVAN.

Screening for renal disease in HIV
» Tests should include:
  – Urine dipstick for haematuria and proteinuria (request urine protein:creatinine ratio if proteinuria is detected; discuss with a specialist if >0.15 g/mmol).
  – Serum creatinine and eGFR.

Dose adjustment of ART in renal impairment: Refer to Table 10.2: Dosing and important adverse effects associated with ART in Section 10.1: Antiretroviral therapy.

10.4 KAPOSI SARCOMA (KS)
B21.0

DESCRIPTION
Kaposi Sarcoma (KS) is a malignancy of lymphatic endothelial origin associated with Human Herpes Virus-8, also known as KS Herpes Virus, infection.
KS may involve the skin, oral cavity, lymph nodes or viscera (especially lung and GIT).
Most patients have multiple lesions.
Lymphoedema is a common complication.
10–20% of cases of visceral KS will have no oral or skin involvement.
KS is an AIDS-defining illness (WHO clinical stage 4).
Although most cases are diagnosed on the typical macroscopic appearance of skin and oral lesions, biopsy confirmation is necessary for atypical lesions and consideration for chemotherapy. One important differential diagnosis is bacillary angiomatosis, which develops more rapidly.

MEDICINE TREATMENT
All patients with KS should be commenced on ART (see Section 10.1: Antiretroviral therapy) and cotrimoxazole prophylaxis (see Section 10.2.2: Opportunistic infection prophylaxis, with cotrimoxazole) regardless of CD4 count.

Many patients with limited mucocutaneous KS will have complete resolution or substantial regression on ART alone.

REFERRAL

Prior to referral, all patients must be started on ART.

» Radiotherapy/intralesional chemotherapy for symptomatic local lesions.
» Systemic chemotherapy is indicated in patients with poor prognostic factors:
  - more than 25 skin lesions,
  - rapidly progressive disease,
  - visceral involvement,
  - extensive oedema, or
  - "B" symptoms, i.e. fever, night sweats, significant constitutional symptoms.
» Failure of KS to respond to ART.

10.5 POST-EXPOSURE PROPHYLAXIS

National HIV Health Care Worker Hotline: 0800 212 506 or 021 406 6782.

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

S61.0 + (W46.22 + Z20.6 + Z29.8)

DESCRIPTION

Antiretroviral therapy may prevent the risk of acquiring HIV following a significant occupational exposure.
It is essential to document occupational exposures adequately for possible subsequent compensation.
Other blood borne infections (hepatitis B and C) should also be tested for in the source patient and appropriate prophylaxis instituted in the case of hepatitis B.

Assessing the risk of occupational exposures

The risk of acquiring HIV following occupational exposure is determined by the nature of the exposure and the infectiousness of the source patient. High-risk exposures involve exposure to a larger quantity of viruses from the source patient, either due to exposure to larger quantity of blood or because the amount of virus in the blood is high.

Any one of the following is associated with an increased risk of HIV transmission:

» deep percutaneous sharps injuries
» percutaneous exposure involving a hollow needle that was used in a vein or artery
» visible blood on the sharp instrument involved in a percutaneous injury
» the source patient has terminal AIDS or is known to have a high viral load, i.e. >100 000 copies/mL

In instances when the risk of infection is extremely low or non-existent, post-

exposure prophylaxis (PEP) is not indicated, as the risks of PEP will far outweigh the benefits. PEP is **NOT** indicated when:

» The material the healthcare worker was exposed to is not infectious for HIV in the occupational setting, e.g. vomitus, urine, faeces or saliva, unless these are visibly blood stained.
» The exposure was on intact skin.
» The source patient is HIV negative, unless there are clinical features to suggest seroconversion illness, in which case PEP should be commenced until further tests are done – consult with a virologist or infectious diseases specialist.
» The healthcare worker is HIV infected, as this person should be assessed for ART initiation.

PEP REGIMENS

PEP should be commenced as soon as possible after the injury. Do not delay initiating PEP while awaiting confirmatory test results on the source patient and health care worker. PEP should be considered up to 72 hours after exposure and, in exceptional circumstances involving high-risk exposures, PEP may be considered up to 7 days after exposure.

When PEP is indicated (administered preferably as a fixed-dose combination):

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute. Do not delay initiation of PEP while awaiting baseline eGFR. Re-assess TDF eligibility once results become available).

AND

- Lamivudine, oral, 300 mg daily for 4 weeks

AND

Dolutegravir, oral 50 mg daily for 4 weeks. *LoE:IIIa*[iii]

If DTG is not tolerated:

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

AND

- Emtricitabine, oral, 200 mg daily for 4 weeks.

AND *LoE:IIIb*[iii]

- Atazanavir/ritonavir 300/100 mg, 1 tablet, oral daily for 4 weeks.

OR

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If TDF is contraindicated or if source patient is known to be failing a TDF-based regimen, replace TDF and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

AND

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

AND

- Continue third applicable drug (DTG or boosted PI – see above)

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

Zidovudine often causes nausea and headache and so should only be given if TDF is contraindicated.

Lopinavir/ritonavir often causes diarrhoea. If lopinavir/ritonavir is not tolerated switch to atazanavir/ritonavir. Atazanavir/ritonavir often causes unconjugated jaundice, which is benign but may not be tolerated, in which case switch to lopinavir/ritonavir. If both these protease-inhibitors are not well tolerated, consult a specialist.

Recommendations for post exposure prophylaxis (PEP) after occupational exposure to infectious material (includes blood, CSF, semen, vaginal secretions and synovial/pleural/ pericardial/ peritoneal/amniotic fluid) from HIV seropositive patients are given in the table, below.

Exposure	**HIV Status of source patient**	
	Negative	**Unknown or Positive**
Intact skin	no PEP	no PEP
Mucosal splash **or** **non-intact skin** **or** **percutaneous injury**	no PEP	PEP: • TDF+3TC+DTG **OR** • Other 3-drug regimen

Table 10.11: PEP for healthcare worker following occupational HIV exposure

When the source patient is known to be failing ART, modify the PEP regimen:
» If the patient is on zidovudine, use TDF
» If the patient is on TDF, use zidovudine.

	Source patient			
	Vaccination status	**HBsAg positive**	**HbsAg negative**	**HBsAg unknown**
Vaccination status and antibody response status of HCW	Unvaccinated or vaccination incomplete	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)	• Initiate Hep B vaccination (month 0, 1 and 6)	• HBIG, IM, 500 units* • Hep B vaccine (3 doses at monthly intervals)
	Vaccinated **AND** known to have HBsAb ≥10 units/mL[#]	No treatment	No treatment	No treatment

	Vaccinated **AND** HBsAb <10 units/mL or level unknown	• HBIG, IM, 500 units * • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)	No treatment	• HBIG, IM, 500 units* • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)

Table 10.12: PEP for healthcare workers following hepatitis B exposure

LoE:IVb[iv]

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.

[#] If the delay in obtaining HBsAb results is more than 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.

After vaccination ensure the health care worker has a HBsAb > 10 units/mL 1 – 2 months after the last vaccine dose.

LoE:IVb[iv]

Test	Source patient	Exposed health care worker			
	Baseline	**Baseline**	**2 weeks**	**6 weeks**	**4 months**
HIV	Rapid test **PLUS** ELISA	Rapid test **PLUS** ELISA		ELISA	ELISA
Hepatitis B	Surface antigen	Surface antibody**			Surface antigen and surface antibody**
Hepatitis C	HCV antibody	HCV antibody*		HCV PCR*	
Syphilis	RPR/ TP antibody	RPR/TP antibody*			RPR/TP antibody*
Creatinine		If TDF part of PEP	If TDF part of PEP		
FBC		If AZT part of PEP	If AZT part of PEP		

Table 10.13: Investigations and monitoring in occupational exposures

*Only if source patient was positive (in the case of syphilis, source patient must be RPR positive)

**Only if source patient was positive AND health care worker unvaccinated or HBsAb <10 units/mL

10.5.2 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

Z29.8

PEP should be offered to rape survivors who present within 72 hours (management is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational).

A patient presenting ≥72 hours since the alleged incident should not be given PEP but should be counselled about the possible risk of transmission, with HIV testing provided at the time of presentation and 4 months later. Rape

survivors who test HIV seropositive should be initiated on ART– see Section 10.1: Antiretroviral therapy.
Other important aspects of care for the rape survivor should not be forgotten, i.e. contraception, treatment for sexually transmitted infections, counselling and forensic specimens.

Emergency contraception after pregnancy is excluded
Do a pregnancy test in all women and female adolescents. Children must be tested and given emergency contraception from Breast Tanner Stage III. If unsure of staging, give emergency contraception when you detect any breast development (DO NOT REGARD MENARCHE AS AN INDICATION).

- Copper IUCD, e.g.:
- Cu T380A, inserted as soon as possible after unprotected intercourse and not later than 5 days.

LoE:IIIb[lvi]

OR

- Levonorgestrel 1.5 mg, oral, as a single dose as soon as possible after unprotected intercourse, and not later than 5 days.
  - If the woman vomits within 2 hours, repeat the dose.
  - Advise women that their period should be on time; very rarely it is delayed but it should not be more than 7 days late. If this occurs, they should come back for a pregnancy test.

LoE:Ia[lvii]

CAUTION
Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations.
Women on these medicines should preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.
Women > 80 kg or BMI ≥ 30 should also preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.

LoE:IIIb[lviii]

An anti-emetic:

LoE:IVb[lix]

- Metoclopramide oral, 10 mg 8 hourly as needed.

STI prophylaxis

- Ceftriaxone, IM, 250 mg as a single dose.
  - For ceftriaxone IM injection: Dissolve ceftriaxone 250 mg in 0.9 mL lidocaine 1% without epinephrine (adrenaline).

AND

- Azithromycin, oral, 1 g as a single dose.

LoE:IIIb[lx]

AND

- Metronidazole, oral, 2 g immediately as a single dose.

HIV PrEP
If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.

Perform HIV test 4 weeks after initiating PrEP. See PHC STGs and EML, Section 11.11: Pre-exposure prophylaxis (PrEP).

10.5.3 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Z29.8

Inadvertent (non-occupational) exposure to infectious material from HIV sero-positive persons often requires clinical judgement and includes:

» human bites (requires hepatitis B, but not HIV prophylaxis)
» sharing of needles during recreational drug use
» consensual sexual exposure, burst condoms
» contact sports with blood exposure

LoE:IVb[lxi]

For those who require PEP, management of inadvertent (non-occupational) HIV exposure is the same as for occupational HIV exposure. See Section 10.5.1: Post-exposure prophylaxis, occupational.

References:

[i] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[ii] Eligibility for ART: INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fätkenheuer G, Llibre JM, Molina JM, Munderi P, Schechter M, Wood R, Klingman KL, Collins S, Lane HC, Phillips AN, Neaton JD. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373(9):795-807. http://www.ncbi.nlm.nih.gov/pubmed/26192873

Eligibility for ART: TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug 27;373(9):808-22. http://www.ncbi.nlm.nih.gov/pubmed/26193126

Eligibility for ART- Immediate initiation of ART: Rosen S, Maskew M, Fox MP, Nyoni C, Mongwenyana C, Malete G, Sanne I, Bokaba D, Sauls C, Rohr J, Long L. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. PLoS Med. 2016 May 10;13(5):e1002015. https://www.ncbi.nlm.nih.gov/pubmed/27163694

Eligibility for ART- Immediate initiation of ART: National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

[iii] Immediate initiation of ART, pregnant and breastfeeding women: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Immediate initiation of ART, pregnant and breastfeeding women: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[iv] Timing of ART initiation (pulmonary TB): Uthman OA, Okwundu C, Gbenga K, Volmink J, Dowdy D, Zumla A,Nachega JB. Optimal Timing of Antiretroviral Therapy Initiation for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015 Jul 7;163(1):32-9.http://www.ncbi.nlm.nih.gov/pubmed/26148280

[v] Timing of ART initiation (tuberculous meningitis): Török ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, Dung NT, Chau NV, Bang ND, Tien NA, Minh NH, Hien NQ, Thai PV, Dong DT, Anh do TT, Thoa NT, Hai NN, Lan NN, Lan NT, Quy HT, Dung NH, Hien TT, Chinh NT, Simmons CP, de Jong M, Wolbers M, Farrar JJ. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis. 2011 Jun;52(11):1374-83. http://www.ncbi.nlm.nih.gov/pubmed/21596680

[vi] Timing of ART initiation (cryptococcal meningitis): Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 24;7(7):CD009012. https://pubmed.ncbi.nlm.nih.gov/30039850/

Timing of ART initiation (cryptococcal meningitis): National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

Timing of ART initiation (cryptococcal meningitis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[vii] Timing of ART initiation (asymptomatic cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Timing of ART initiation (asymptomatic cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, Rabie H, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/

[viii] Psychosocial indicators of readiness for ART: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[ix] Dolutegravir, oral (first-line ART): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART): Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS One. 2016 Oct_13;11(10):e0162775. https://www.ncbi.nlm.nih.gov/pubmed/27736859

Dolutegravir, oral (first-line ART): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[x] Dolutegravir, oral (first-line ART in pregnancy/ WOCP): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (risk of NTDs): National Department of Health. Notice: Updated guidance of dolutegravir in pregnancy, 29 June 2021 (Reference: 2021/06/29/EDP/01). https://www.knowledgehub.org.za/e-library

[xi] Dolutegravir, oral (first-line ART with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013; 62(1):21-27. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis 2020; 70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xii] National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Atazanavir/ritonavir vs lopinavir/ritonavir in HIV, 27July2021.
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xiii] Abacavir: Cruciani M, Mengoli C, Malena M, Serpelloni G, Parisi SG, Moyle G, Bosco O. Virological efficacy of abacavir: systematic review and meta-analysis. J Antimicrob Chemother. 2014 Dec;69(12):3169-80.http://www.ncbi.nlm.nih.gov/pubmed/25074854

[xiv] Dual therapy – dolutegravir/lamivudine: Cahn P, Madero JS, Arribas JR, Antinori A, Ortiz R, Clarke AE, et al; GEMINI Study Team. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet. 2019 Jan 12;393(10167):143-155. https://www.ncbi.nlm.nih.gov/pubmed/30420123

Dual therapy – dolutegravir/lamivudine: Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, et al. DOLAMA study: Effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine (Baltimore). 2019 Aug;98(32):e16813. https://www.ncbi.nlm.nih.gov/pubmed/31393412

[xv] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvi] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xvii]Dolutegravir, oral (double-dose with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).
https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7. https://pubmed.ncbi.nlm.nih.gov/23075918/

Dolutegravir, oral (double-dose with concomitant rifampicin): Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al; International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020 Feb 3;70(4):549-556. https://pubmed.ncbi.nlm.nih.gov/30918967/

[xviii] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xix]Emtricitabine, oral (red cell aplasia adverse drug reaction): Cohen K, Viljoen C, Njuguna C, Maartens G. Emtricitabine-associated red cell aplasia. AIDS. 2019 May 1;33(6):1095-1096. https://www.ncbi.nlm.nih.gov/pubmed/30946164

[xx]Efavirenz, oral (encephalopathy adverse drug reaction): Variava E, Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, Maartens G, Martinson NA. Brief Report: Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series. J Acquir Immune Defic Syndr. 2017 Aug 15;75(5):577-579. https://www.ncbi.nlm.nih.gov/pubmed/28520619

[xxi] Dosing of ART and ADRs: Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART and ADRs: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

Dosing of ART and ADRs: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Dosing of ART and ADRs: Datapharm Ltd. Electronic medicines compendium (emc). [Internet][Accessed 28 November 2019] https://www.medicines.org.uk/emc/

Dosing of ART (renal impairment): Dosing of ART and ADRs: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dosing of ART (renal impairment): Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al.; HIV Medicine Association of the Infectious Diseases Society of America. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 Nov 1;59(9):e96-138. http://www.ncbi.nlm.nih.gov/pubmed/25234519

Dosing of ART (renal impairment): Meintjes G, Moorhouse MA, Carmona S, Davies N, Dlamini S, van Vuuren C, Manzini T, et al. Adult antiretroviral therapy guidelines 2017. South Afr J HIV Med. 2017 Jul 15;18(1):776. doi: 10.4102/sajhivmed.v18i1.776. https://pubmed.ncbi.nlm.nih.gov/29568644/

[xxii] ART-rifampicin drug interaction: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART-rifampicin drug interaction: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxiii]Rifabutin: Zhang J, Zhu L, Stonier M, Coumbis J, Xu X, Wu Y, Arikan D, Farajallah A, Bertz R. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. J Antimicrob Chemother. 2011 Sep;66(9):2075-82. http://www.ncbi.nlm.nih.gov/pubmed/21712242

Rifabutin (dosing): Lan NT, Thu NT, Barrail-Tran A, Duc NH, Lan NN, Laureillard D, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. PLoS One. 2014 Jan 22;9(1):e84866. http://www.ncbi.nlm.nih.gov/pubmed/24465443

Rifabutin (dosing): Ramachandran G, Bhavani PK, Hemanth Kumar AK, Srinivasan R, Raja K, Sudha V, Venkatesh S, Chandrasekaran C, Swaminathan S. Pharmacokinetics of rifabutin during atazanavir/ritonavir co-administration in HIV-infected TB patients in India. Int J Tuberc Lung Dis. 2013 Dec;17(12):1564-8. https://www.ncbi.nlm.nih.gov/pubmed/24200269

[xxiv] Drug interactions with dolutegravir: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Drug interactions with dolutegravir: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxv] Atazanavir-PPI/H2-anatagonist interaction: University of Liverpool HIV Drug Interaction online tool. https://www.hiv-druginteractions.org/checker

Atazanavir-PPI interaction: Khanlou H, Farthing C. Co-administration of atazanavir with proton-pump inhibitors and H2 blockers. J Acquir Immune Defic Syndr. 2005 Aug 1;39(4):503. https://www.ncbi.nlm.nih.gov/pubmed/16010179

Atazanavir-PPI interaction: European Medicines Agency. Public Statement: Important new pharmacokinetic data demonstrating that REYATAZ(atazanavir sulfate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered, 21 December 2004. https://www.ema.europa.eu/en/documents/public-statement/important-new-pharmacokinetic-data-demonstrating-reyataz-atazanavir-sulfate-combined-norvir_en.pdf

[xxvi] Screen for Cryptococcus antigen: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxvii]Urine dipstick: Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006 Jun;69(12):2243-50. http://www.ncbi.nlm.nih.gov/pubmed/16672914

[xxviii] LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

LAM urine testing (DS-TB): National Department of Health. Guidance on the use of the lipoarabinomannan lateral flow assay (LF-LAM) for the diagnosis of tuberculosis in people living with HIV, July 2017. https://www.knowledgehub.org.za/

[xxix]Abacavir: South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022

[xxx]Management of drug-induced liver injury: Jong E, Conradie F, Berhanu R, Black A, John MA, Meintjes G, Menezes C. Consensus Statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. S Afri HIV Med 2013;14(3): 113-119.http://www.sajhivmed.org.za/index.php/hivmed/article/view/63

Management of drug-induced liver injury: Sharma SK, Singla R, Sarda P, Mohan A, Makharia G, Jayaswal A, Sreenivas V, Singh S. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity. Clin Infect Dis. 2010 Mar 15;50(6):833-9. https://www.ncbi.nlm.nih.gov/pubmed/20156055

[xxxi]Prednisone, oral (TB-IRIS on ART): Meintjes G, Stek C, Blumenthal L, Thienemann F, Schutz C, Buyze J, et al; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med. 2018 Nov 15;379(20):1915-1925. https://www.ncbi.nlm.nih.gov/pubmed/30428290

[xxxii]TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Isoniazid TB prophylaxis in PLHIV, November 2018. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind placebo-controlled trial. Lancet 2014;384(9944):682-90. http://www.ncbi.nlm.nih.gov/pubmed/24835842

TB preventive therapy (therapeutic class): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

TB preventive therapy (therapeutic class): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiii] Rifapentine-containing regimen (3HP): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rifapentine-containing regimen (3HP): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxiv] IPT in pregnancy: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Evidence review: IPT in pregnancy_v1.2_15 April 2024_final approved. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[xxxv]Cotrimoxazole, oral (pregnancy): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence summary: Is co-trimoxazole safe to use in pregnancy, March2024. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Cotrimoxazole, oral (pregnancy): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxvi]Cotrimoxazole, oral: Grimwade K, Swingler, G. Cotrimoxazole prophylaxis for opportunistic infections in adults with HIV. Cochrane Database Syst Rev. 2003;(3):CD003108. http://www.ncbi.nlm.nih.gov/pubmed/12917946

Cotrimoxazole, oral: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxvii]Cotrimoxazole, oral (criteria for discontinuation): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Cotrimoxazole, oral (criteria for discontinuation): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

[xxxviii]CrAg screening (CD4 < 100 cells/mm^3): Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, et al. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55. http://www.ncbi.nlm.nih.gov/pubmed/20597693

CrAg screening (CD4 < 100 cells/mm^3): Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159. https://pubmed.ncbi.nlm.nih.gov/29514236/

CrAg screening (CD4 < 100 cells/mm^3): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[xxxix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

ART (delayed): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xl]Fluconazole, oral (cryptococcosis): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (cryptococcosis): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal

disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

Fluconazole, oral (cryptococcosis): NICD data on file.

[xli] Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. N Engl J Med. 2013 Aug 29;369(9):830-9. http://www.ncbi.nlm.nih.gov/pubmed/23984730

Fluconazole, oral (pregnancy): Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016 Jan 5;315(1):58-67. http://www.ncbi.nlm.nih.gov/pubmed/26746458

Fluconazole, oral (pregnancy): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlii] Fluconazole, oral (breastfeeding): South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Fluconazole, oral (breastfeeding): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xliii] Liposomal amphotericin: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Liposomal Amphotericin B_ cryptococcal meningitis_Adults Review_Update_23 January 2024_final approved.

[xliv]Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Flucytosine for cryptococcal meningitis, 15 November 2018. https://www.knowledgehub.org.za/e-library

Flucytosine, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Health economic and budget impact analysis: Flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV infected adults, June 2019. https://www.knowledgehub.org.za/e-library

https://www.nejm.org/doi/full/10.1056/NEJMoa2111904

Flucytosine, oral: Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 25;7(7):CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Flucytosine, oral: Miot J, Leong T, Takuva S, Parrish A, Dawood H. Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa. BMC Health Serv Res. 2021 Apr 6;21(1):305. https://pubmed.ncbi.nlm.nih.gov/33823842/

[xlv]Fluconazole, oral: Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update

[xlvi]Fluconazole, oral (induction phase): Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I et al. Treatment for HIVassociated cryptococcal meningitis. Cochrane Database Syst Rev. 2018;7;CD005647. https://pubmed.ncbi.nlm.nih.gov/30045416/

Fluconazole, oral (induction phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (induction phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlvii]Fluconazole, oral (consolidation phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (consolidation phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlviii]Fluconazole, oral (maintenance phase): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Fluconazole, oral (maintenance phase): Bozzette SA, Larsen RA, Chiu J, Leal MA, Jacobsen J, Rothman P, Robinson P, Gilbert G, McCutchan JA, Tilles J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1991 Feb 28;324(9):580-4. https://pubmed.ncbi.nlm.nih.gov/1992319/

Fluconazole, oral (maintenance phase): Powderly WG, Saag MS, Cloud GA, Robinson P, Meyer RD, Jacobson JM, Graybill JR, Sugar AM, McAuliffe VJ, Follansbee SE, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. N Engl J Med. 1992 Mar 19;326(12):793-8. https://pubmed.ncbi.nlm.nih.gov/1538722/

Fluconazole, oral (maintenance phase): Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030. https://doi.org/10.4102/sajhivmed.v20i1.1030

[xlix] ART (delayed): Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis. 2010 Jun 1;50(11):1532-8.http://www.ncbi.nlm.nih.gov/pubmed/20415574

ART (delayed): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

[l]Steroids and HIV-associated Cryptococcal Meningitis Treatment: Beardsley J, Wolbers M, Kibengo FM, Ggayi AB, Kamali A, Cuc NT, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. N Engl J Med 2016;374:542-54. https://www.ncbi.nlm.nih.gov/pubmed/26863355

[li]Azithromycin: Dunne M, Fessel J, Kumar P, Dickenson G, Keiser P, Boulos M, Mogyros M, White Jr AC, Cahn P, O'Connor M, Lewi D, Green S, Tilles J, Hicks C, Bissett J, Schneider MM, Benner R. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with human immunodeficiency virus. Clin Infect Dis. 2000 Nov;31(5):1245-52. Erratum in: Clin Infect Dis 2001 May 1;32(9):1386. http://www.ncbi.nlm.nih.gov/pubmed/11073759

Azithromycin: Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. Clin Infect Dis. 1998 Nov;27(5):1278-85. http://www.ncbi.nlm.nih.gov/pubmed/9827282

[lii] Dolutegravir-based PEP regimen: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Dolutegravir-based PEP regimen: McAllister JW, Towns JM, McNulty A, Pierce AB, Foster R, Richardson R, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS. 2017;31(9):1291–5. https://www.ncbi.nlm.nih.gov/pubmed/28301425

Dolutegravir-based PEP regimen National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[liii]Protease-inhibitor- based PEP regimen: Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: A systematic review. Clinical Infectious Diseases. 2015;60 Suppl 3:S170–6. https://www.ncbi.nlm.nih.gov/pubmed/25972499

Protease-inhibitor- based PEP regimen: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[liv]Hepatitis B protocol (PEP): National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[lv]Monitoring in occupational exposures: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[lvi]Copper IUD (emergency contraception): Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

Copper IUD (emergency contraception): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/

[lvii]Levonorgestrel 1.5 mg oral (emergency contraception): Shen J, Che Y, Showell E, Chen K, Cheng L. Interventions for emergency contraception. Cochrane Database Syst Rev. 2019 Jan 20;1(1):CD001324. https://pubmed.ncbi.nlm.nih.gov/30661244/

[lviii]Levonorgesterol, oral - emergency contraception (double dose): Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and Efavirenz. Infect Dis Obstet Gynecol. 2012;2012:137192. http://www.ncbi.nlm.nih.gov/pubmed/22536010

Levonorgesterol, oral - emergency contraception (double dose): Tittle V, Bull L, Boffito M, Nwokolo N. Pharmacokinetic and pharmacodynamic drug interactions between antiretrovirals and oral contraceptives. ClinPharmacokinet. 2015 Jan;54(1):23-34. http://www.ncbi.nlm.nih.gov/pubmed/25331712

Levonorgesterol, oral - emergency contraception (double dose): Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874

Levonorgesterol, oral - emergency contraception (double dose): FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/

[lix] Metoclopramide, oral: National Department of Health, Essential Drugs Programme: Primary Health Care STGs and EML, 2020. http://www.health.gov.za/

[lx]STI prophylaxis: Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, Reno H, Zenilman JM, Bolan GA. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021 Jul 23;70(4):1-187. https://pubmed.ncbi.nlm.nih.gov/34292926/

[lxi]Non-occupational PEP: National Department of Health. National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
ADULT HOSPITAL CHAPTER 10: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

Note that the associated EML chapter has been subjected to subsequent clinical editing. These editorial amendments may not be reflected in the report below.

MEDICINE AMENDMENTS:

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
10 Antiretroviral therapy, adults and adolescents	Reference to national ART guidelines	Cross reference to national ART guidelines aligned to Paediatric EML
10.1 Antiretroviral therapy, adults - *Clinical indications for deferring ART initiation* *- Asymptomatic cryptococcal infection*	ART	Directions amended
10.1 Antiretroviral therapy, adults *- Treatment-naïve patients without TB*	TDF+3TC+DTG	Amended indication - expanded to ALL women
10.1 Antiretroviral therapy, adults *- Treatment-naïve patients with TB*	TDF +EFV+FTC	Retained
	Double-dosed DTG (TLD + DTG 50 mg)	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
10.1 Antiretroviral therapy, adults *- Contraindication to TDF*	ABC + 3TC+DTG	Amended as preferred treatment
	TAF+FTC+DTG	Added for PLHIV with chronic Hep B & RF
10.1 Antiretroviral therapy, adults *- Contraindication to TDF and ABC intolerance*	AZT+3TC with DTG	Amended as preferred treatment
10.1 Antiretroviral therapy, adults *- Recycling TDF in virological failure*	AZT	Deleted
	TDF	Added
10.1 Antiretroviral therapy, adults *- Switching existing clients to DTG-containing regimens*	DTG	New guidance added
	Clients with DTG resistance	Guidance added
10.1 Antiretroviral therapy, adults *- Rifampicin-based TB treatment (on DTG-regimen)*	DTG	Added
10.1 Antiretroviral therapy, adults *- Protease inhibitors (PI)*	LPV/r	Retained
	ATV/r	Indication expanded to preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (patients not on TB-rifampicin therapy)
10.1 Antiretroviral therapy, adults	Resistance testing	Retained, and emphasised
10.1 Antiretroviral therapy, adults *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
10.1 Antiretroviral therapy, adults *-Re-initiating ART in patients who have interrupted treatment*	Re-initiating ART	New guidance added
ART: Dosing and important adverse effects	3TC – renal adjusted dose	Amended
	FTC – renal adjusted dose	Amended
	TDF, ABC, 3TC, FTC, oral	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	DTG	Amended - weight-gain deleted
	DTG – serum creatinine	Guidance clarified
	Nevirapine, oral	Adverse effects and dosing information deleted
	Raltegravir, oral	Adverse effects and dosing information deleted
	TAF, oral – adverse effects	Added
Monitoring on ART *- At HIV diagnosis: CrAg screening*	CrAg screening	Amended
	Sputum screen for TB	Amended
	HIV viral load monitoring	Amended

	schedule	
10.1.1 Management of selected antiretroviral adverse drug reactions	Algorithm to manage drug-induced liver injury (DILI)	Amended
	Hypersensitivity	Guidance clarified
	Hyperlactataemia:	Guidance clarified
	Hepatitis in patients on ART and anti-tuberculosis therapy:	Guidance clarified
10.1.2 Immune reconstitution inflammatory syndrome (IRIS)	Paracetamol	Amended
10.2 Opportunistic Diseases		
10.2.1 Tuberculosis preventive therapy (TPT) *-Adult PLHIV initiated on ARVs*	TPT	Added as a therapeutic group
	Isoniazid (12H)	Retained as an example of class in the STG
	Rifapentine + isoniazid (3HP)	Guidance for EFV-based ART replaced with DTG-containing ART
	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
	Pregnant women	Guidance amended
10.2.2 Opportunistic infection prophylaxis, with cotrimoxazole	WHO clinical stage II	Deleted
10.2.3 Candidiasis of oesophagus/trachea/bronchi	Fluconazole, oral	Directions for use amended
10.2.4 Cryptococcosis	Algorithm for the prevention, diagnosis and management of cryptococcosis among PLHIV	Amended
10.2.4.1 Cryptococcosis, CSF CrAg negative	CrAg screening: CD4 threshold	Amended
	ART	Directions amended
10.2.4.2 Cryptococcal meningitis	Flucytosine, oral	Added
	Liposomal amphotericin B	Added
	Amphotericin B	Retained
	Fluconazole, oral	Retained
10.2.4.2 Symptomatic, non-meningeal cryptococcosis *(STG deleted)*	Fluconazole, oral	Deleted
	Amphotericin B	Deleted
	ART	Deleted
10.2.6 Cytomegalovirus (CMV) **-** *maintenance treatment*	Ganciclovir, parenteral	Deleted
	Valganciclovir, oral	Retained
10.2.9 Pneumocystis pneumonia	Primaquine, oral	Directions for access, added
10.5.1 Post-exposure prophylaxis, occupational	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- PEP regimens	TDF	Editorial amendments
	TDF-contraindicated	Guidance clarified
- *PEP for healthcare workers following hepatitis B exposure*	Hepatitis B Immunoglobulin	Amended
- Delay in obtaining HBsAb results	Time period of delay	Amended
10.5.2 Non occupational post exposure prophylaxis, sexual assault	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
	HIV PrEP	Added as a cross reference to the PHC STGs and EML (PrEP section)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)
- *Obese women*	Levonorgestrel, oral	Dose not amended
10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but included in therapeutic interchange database (not on TB-rifampicin therapy)
- Emergency contraception after pregnancy is excluded	Copper IUCD	Added (as first line option)
	Levonorgestrel, oral	Retained (as 2nd line option)

- *Obese women*	Levonorgestrel, oral	Dose not amended
	Description	Editorial amendment

ABC= Abacavir, ART=antiretroviral therapy, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, CSF=cerebrospinal fluid; CrAg=cryptococcal antigen, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, IUCD=intrauterine copper device, LPV/r=Lopinavir/ritonavir, PrEP=pre-exposure prophylaxis, TAF=tenofovir alafenamide, TDF = Tenofovir disoproxil fumarate

SUBSEQUENT UPDATES TO THE 2020-4 EDITION

Version no.	Section	Amendments
2.1	10.1 Drug interactions with dolutegravir	**Metformin** Guidance amended
2.1	10.2.4 Cryptococcus	**Erratum** Algorithm corrected

CROSS REFERENCE TO NATIONAL GUIDELINES

The cross reference to the National ART Guidelines 2023[1] has been amended and aligned to the PHC EML as tabulated below:

AMENDED FROM:
Consult the most recent HIV Guidelines from the National Department of Health. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants
AMENDED TO:
Comprehensive guidelines are available for ART and the care of adults and children with HIV infection in the 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

10.1 ANTIRETROVIRAL THERAPY

ASYMPTOMATIC CRYPTOCOCCAL INFECTION

ART: *Directions amended*

The STG text was aligned to the National ART Guidelines as tabulated below:

Positive cryptococcal antigen and no evidence for meningitis on LP:

AMENDED FROM:

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, defer ART until 2 weeks after initiating fluconazole.

AMENDED TO:

» In patients with positive cryptococcal antigen and no evidence for meningitis on LP, there is no need to delay. ART can be started immediately.

ART REGIMENS

Treatment-naïve patients without TB

Tenofovir + lamivudine + dolutegravir, oral: *amended indication to include all women*

Indication expanded from "≥6 weeks gestation" to "ALL women", see NEMLC recommendation as tabulated below. A copy of the full review[2] may be found at the end of this document or alternatively accessed on the NHI webpage.

[1] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

[2] NDoH Evidence Review. DTG in pregnancy. PHC-Adults Medicine review_17June2021_v2

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC 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 PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.					

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms
(Refer to appendix 2 for the evidence to decision framework)

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Monitoring and evaluation considerations

Research priorities

ART- TREATMENT-NAÏVE PATIENTS WITH TB

Tenofovir (TDF) + Efavirenz (EFV) + Emtricitabine (FTC) = (TEE): *retained*

Double-dosed dolutegravir (TLD + DTG 50 mg): *indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy*

Refer to the updated DTG in HIV-infected patients review with addendum, 21 July 2021 (second update of initial 26 January 2017 review). The NEMLC recommendation is tabulated below, a copy of the complete review[3] may be accessed at the end of this report or alternatively on the NHI webpage.

RECOMMENDATION
Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment..
Rationale: Randomised open-label INSPIRING study showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.
Level of evidence: Low certainty evidence

NEMLC MEETING 29 JULY 2021:
The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above and recommended that the report and review be circulated for external comment.

CONTRAINDICATION TO TDF

Abacavir + lamivudine + dolutegravir (ABC+3TC+DTG), oral: *Amended as preferred treatment*

Abacavir is preferred over zidovudine, as kidney disease is often progressive, resulting in anaemia.

[3] NDoH Evidence Review. NationalDeptOfHealth_EDP_Dolutegravir_HIV-Adults_Review Update_27 July 2021 with updated Addendum: DTG initiation_WithRifampicin_INSPIRINGstudy_PHC-Adults_Summary_27July2021

TAF+FTC+DTG, oral: *Added (for a select cohort)*

Tenofovir alafenamide (TAF):

An update to the TAF review was conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment.[4] TAF has been added to the EML as part of a fixed dose combination for PLHIV with chronic hepatitis B co-infection and renal impairment (eGFR 30-50mL/min). The updated recommendation is tabulated below. *(A subsequent update was made to the review in June 2024 to include an Addendum which details an evidence summary on the use of TAF for Hepatitis B in non-HIV co-infection*). A copy of the complete review may be found at the end of this report or alternatively accessible on the NHI webpage.

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.

CONTRAINDICATION TO TDF/TAF AND ABC INTOLERANCE/HYPERSENSITIVITY

Zidovudine + lamivudine with dolutegravir (AZT+3TC with DTG), oral: *amended as preferred treatment*

The following STG text was deleted:

~~Use of additional nephrotoxic drug e.g. aminoglycoside.~~

[4] Tenofovir alafenamide for HIV Adult Review Update_ 27 June 2024_v5_final

Aminoglycosides are no longer recommended for management of drug-resistant TB. However, available evidence did not show a significant increased risk of nephrotoxicity with TDF in DR-TB patients on kanamycin.[5] [6]

The STG has been amended in line with the above recommendations and aligned to the National ART Guidelines as tabulated below. Reference to 1st, 2nd and 3rd line regimens have been removed from the EML in alignment with the National ART Guidelines.

	AMENDED FROM:	**AMENDED TO:**
	1ST LINE ART	**INITIATING ART**
Treatment-naïve patients	» Men ≥35kg and ≥10 years of age » WOCP not actively wishing to conceive » Pregnant women ≥6 weeks gestation, and those who make an informed choice to use DTG TDF + 3TC + DTG <u>Patients with TB:</u> TDF + FTC + EFV <u>Pregnant women <6 weeks gestation or actively wanting to conceive:</u> TDF + FTC + EFV *(Also see section 6.7: HIV in pregnancy)*	<u>Individuals ≥30kg:</u> TDF + 3TC + DTG ("TLD") **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. <u>Patients on rifampicin-based TB treatment:</u> TDF + FTC + EFV **OR** TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later. The extra DTG dose can be stopped two weeks after completion of TB therapy. (Also see AH STG section 6.6: HIV in pregnancy)
Contraindications/ intolerance to DTG		TDF + 3TC/FTC + EFV
Contraindications and intolerance to EFV	TDF + 3TC + DTG » WOCP actively wanting to conceive and pregnant women <6 weeks gestation require adequate counselling to make an informed choice to use DTG.	
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + LPV/r	<u>Start protease inhibitor-based regimen:</u> TDF + 3TC/FTC + ATV/r **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r 800/200 mg 12-hourly. **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks (e.g. 600/150 mg and then 800/200 mg). The LPV/r can be switched back to ATV two weeks after completion of TB therapy.
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + LPV/r	
Contraindication to TDF » eGFR <50 mL/minute. » Use of additional nephrotoxic drug	Replace TDF + 3TC/FTC with either ABC+ 3TC **or** AZT + 3TC	<u>If chronic hepatitis B coinfection and eGFR 30-50 ml/min:</u> TAF + FTC + DTG. <u>Other scenarios:</u>

[5] Perumal R, Abdelghani N, Naidu N, Yende-Zuma N, Dawood H, Naidoo K, et al. Risk of nephrotoxicity in patients with drug-resistant tuberculosis treated With kanamycin/capreomycin with or without concomitant use of tenofovir-containing antiretroviral therapy. J Acquir Immune Defic Syndr. 2018;78: 536–542. https://pubmed.ncbi.nlm.nih.gov/29683992/

[6] Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Mengistu A, Mekonen TT, et al.. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents. Int J Tuberc Lung Dis. 2017;21: 1245–1250. https://pubmed.ncbi.nlm.nih.gov/29297444/

e.g. aminoglycoside.		ABC + 3TC + DTG
Contraindication to TDF and ABC intolerance	AZT+ 3TC with DTG **or** EFV	
Contraindication to TDF/TAF and ABC intolerance/hypersensitivity		AZT + 3TC with DTG
NOTE:	**Note:** In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, an alternative dual-therapy regimen may be used, e.g. DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) **or** EFV + LPV/r **or** DTG + LPV/r may be used. Consult a specialist.	**Note:** In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, the following alternative dual-therapy regimens may be used **after** consulting a specialist: • DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) • EFV + LPV/r • DTG+LPV/r
2ND LINE ART		
Management of viraemia on 1st line ART	<u>If plasma VL between 50–999 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL > 1000 copies/mL:</u> » Assess adherence, tolerability, medicine interactions & psychosocial factors. Repeat VL test 3 months later <u>If plasma VL 50-999 copies/mL:</u> » Continue enhanced adherence support. » Repeat VL test 6 months later. <u>If plasma VL remains at 50-999 copies/mL i.e. persistent low grade viraemia:</u> » Manage as virological failure below.	
Management of virological failure on 1st line ART	<u>If plasma VL confirmed ≥1000 copies/mL (on 2 tests), and adherence issues addressed:</u> » Change regimen to 2nd line therapy. **Note:** Always check hepatitis B surface antigen (HBsAg) before stopping TDF*:* » If patient has chronic hepatitis B, stopping TDF may lead to a fatal hepatitis flare. » If hepatitis B positive, TDF should be continued in the 2ndline regimen.	
		VIROLOGICAL FAILURE
Management of viraemia on TLD		<u>If plasma VL >50 copies/mL:</u> » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. <u>If plasma VL remains > 50:</u> » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time). » If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).
Failing a NNRTI-based 1st line regimen	AZT + 3TC + DTG. <u>If HBsAg positive:</u> TDF + 3TC + DTG	

(TDF+3TC/FTC+EFV/ NVP)	<u>If DTG contraindicated/ not tolerated:</u> AZT + 3TC +LPV/r (**PLUS** TDF, if HBsAg positive). <u>If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment):</u> ABC + 3TC + LPV/r	
Failing a DTG- based 1st line regimen for >2 years *(TDF+3TC+DTG)* » Resistance testing for adults and adolescents failing a DTG-based regimen and who meet the definition of confirmed virological failure may be authorized by an expert on a case-by-case basis.	AZT + 3TC +LPV/r <u>If HBsAg positive:</u> TDF + 3TC/FTC +LPV/r	
		CLIENTS WITH DTG RESISTANCE
Any DTG resistance shown on genotype authorised by HIV expert		Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available from TLART@health.gov.za or from https://www.righttocare.org/)
Dyslipidaemia requiring lipid-lowering therapy or diarrhoea associated with LPV/r	Switch LPV/r to ATV/r	
3RD LINE ART		
Failing any 2nd line regimen	Refer to a specialist. Resistance to LPV/r or ATV/r and/or DTG must be shown on genotype antiretroviral resistance test in order to qualify for 3rd line – this test is expensive and should only be done in patients with at least 2 years exposure to a PI and objective evidence of good adherence. Application for 3rd line using the standard motivation form is required (available from TLART@health.gov.za) –the regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure.	

RECYCLING TDF IN VIROLOGICAL FAILURE

<u>Zidovudine (AZT):</u> *deleted*

<u>Tenofovir disoproxil fumarate (TDF):</u> *added*

As the 96-weeks follow up data of the NADIA RCT[7] has been published in peer-review format, an update to the original evidence summary[8] was undertaken in May 2022, with the NEMLC recommendation tabulated below. A copy of the complete review[9] may be accessed at the end of this document or alternatively on the NHI webpage.

[7] 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. https://pubmed.ncbi.nlm.nih.gov/35460601/

[8] NDoH Evidence Summary. NDoH_EML_HIV_NADIA&ARTIST summary_30November2021_v1.0

[9] NDoH Evidence Summary. TDF-backbone as 2nd line in HIV_Adults_Evidence summary_19May2022_ v3.0

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					

The STG has been amended in line with the above recommendations and aligned to the National ART Guidelines as tabulated below:

STG AMENDED TO:

VIROLOGICAL FAILURE	
Management of viraemia on TLD	If plasma VL >50 copies/mL: » Address adherence, tolerability, medicine interactions & psychosocial factors. » Repeat VL test 3 months later. If plasma VL remains > 50: » Assess adherence, tolerability, medicine interactions & psychosocial factors again. » If on TLD <2 years, or persistent low-level viraemia (50-999 copies/mL), or adherence suboptimal, repeat VL at next scheduled visit (i.e. in 6 months' time). » If on TLD >2 years and ≥2 consecutive VL ≥1000 copies/mL (or 1 VL ≥1000 copies/mL plus CD4 <200 or opportunistic infection), discuss with an HIV expert* whether a resistance test is indicated (as a rule it is not, and efforts to resolve adherence issues should be intensified instead).

SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS

The STG has been amended to include guidance on switching existing clients to DTG-containing regimens as tabulated below:

SWITCHING EXISTING CLIENTS TO DTG-CONTAINING REGIMENS	
Patient on: » **TEE** » **ABC/3TC/EFV (or NVP)** » **AZT/3TC/EFV (or NVP)** » **AZT/3TC/DTG** » **Any LPV/r- or ATV/r-containing regimen for <2 years** » **Any LPV/r- or ATV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above.
Patient on: » **ATV/r or LPV/r regimen for >2 years and ≥2 consecutive VL ≥1000 copies/mL**	If adherence >80%, discuss with an HIV expert* to authorise and interpret a resistance test before switching. If adherence < 80%, switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as for first line above.

CLIENTS WITH DTG RESISTANCE
STG ADDITION:

CLIENTS WITH DTG RESISTANCE	
Any DTG resistance shown on genotype authorised by HIV expert	Discuss case with an HIV expert*. The regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure. Application for 3rd line using the standard motivation form may be required (available from TLART@health.gov.za or from https://www.righttocare.org/)

RIFAMPICIN-BASED TB TREATMENT (on DTG-regimen)
DTG: *added*
STG text was amended to align to the DTG evidence review (see details above):

If on DTG: DTG needs to be given at a dose of 50 mg 12-hourly (add DTG 50mg)

The STG has been aligned to the national HIV program guideline as tabulated below:
Amended to:

RIFAMPICIN-BASED TB TREATMENT	
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg 12 hours after TLD dose. If on ATV/r: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. LPV/r dose should be gradually titrated upward over 1-2 weeks. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy.

PROTEASE INHIBITORS
Lopinavir/ritonavir: *retained*
Atazanavir/ritonavir: *expanded to include all patients - preferred 2nd line PI*
A summary of the recommendation from the evidence review is included below. The complete evidence summary[10] may be found at the end of this document or alternatively accessed on the NHI webpage. The STG has been aligned to the National ART Guidelines.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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 PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy. *Rationale:* Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir, and is dosed once-daily. **Level of Evidence: Low to moderate certainty evidence**					
NEMLC MEETING 9 DECEMBER 2021: **NEMLC Recommendation:** The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e. DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.					
Monitoring and evaluation considerations					

Darunavir/ritonavir: *not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy*
A summary of the recommendation from the evidence review is included below. The complete evidence summary[11] may be found at the end of this document or alternatively accessed on the NHI webpage.

[10] NDoH evidence summary. ATV/r vs LPV/r_2 nd line adult HIV therapy_ AdultReview_18 November 2021
[11] NDoH evidence summary. DRV/r vs LPV/r as 2nd line adult HIV therapy_PHC-AdultsMedicineReview_27 July 2021.

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 DRV/r not be used in preference to LPV/r. *Rationale:* Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy. **Level of Evidence:** Moderate certainty of evidence **Review indicators:** Reduction in DRV/r price					
NEMLC MEETING 29 JULY 2021: The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.					
Monitoring and evaluation considerations					
Research priorities					

The therapeutic interchange database update as follows:

Indication	Medicine (INN)	Daily dosing	Therapeutic class	Therapeutic ATC
Adult 2nd line HIV management (patients not on rifampicin TB therapy)	Darunavir and ritonavir	800/100 mg	Protease inhibitors for HIV (combinations)	J05AR
	Lopinavir and ritonavir	800/200 mg	Protease inhibitors for HIV (combinations)	J05AR

RESISTANCE TESTING

Resistance testing: *emphasised*

The PHC/Adult Hospital Level Committee raised concerns regarding the emergence of DTG resistance in 4 NADIA participants, especially as DTG is used in second-line antiretroviral therapy in South Africa. Therefore, the statement in the STG, prompting consideration of resistance testing for patients failing DTG-containing antiretroviral therapy, was emphasised.

CURRENTLY AVAILABLE ARV FDC PREPARATIONS ON CONTRACT

ATV/r: *Added*

ABC + 3TC + DTG: *Added*

STG text was updated to reflect currently available fixed-dose combination antiretrovirals that are accessible on the current public sector tender.[12]

RE_INITIATING ART

Re-initiating ART in patients who have interrupted treatment: *New guidance added*

The STG was amended as tabulated below:

AMENDED FROM:

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Recommence previous regimen.

» Do VL, recommence ART regimen, repeat at 3-6 months.

» If VL does not to decrease to <1000 copies per mL at 6 months, manage virological failure according to the specific regiment (refer to ART regimens table).

AMENDED TO:

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Do VL, recommence ART regimen unless there is a clinical indication to defer ART, repeat VL at 3 months. Recommence previous regimen (unless patient would qualify for a switch to TLD anyway as per above, in which case start dolutegravir-based regimen, e.g. TLD)

» If VL does not to decrease to <1000 copies/mL at 3 months, manage as per virological failure above.

[12] Contract circular HP13-2022ARV http://www.health.gov.za/

ART: DOSING AND IMPORTANT ADVERSE EFFECTS

Lamivudine (3TC) – renal adjusted dose : *Amended*

The eGFR range was amended from 10-50mL/min to eGFR 10-30mL/min for which a dose of lamivudine 150mg daily is recommended. No changes were made for eGFR <10mL/min for which a dose of 50mg daily is recommended.

AMENDED FROM:	**AMENDED TO:**
CrCl 10-50 mL/min: 150 mg daily CrCl <10 mL/min: 50 mg daily	eGFR 10-30 mL/min: 150 mg daily eGFR <10 mL/min: 50 mg daily

Emtricitabine (FTC) – renal adjusted dose: *Amended*

As emtricitabine is only available in a fixed dose combination with TDF or TAF, dose adjustments in renal impairment would need to be guided by all components of the FDC formulation. TDF is contraindicated in patients with eGFR<50mL/min so these patients should be managed with a TAF-containing FDC. Amendments to the dosing guidance below is informed by the expert opinion based on pragmatic considerations of formulations available locally.

AMENDED FROM:	**AMENDED TO:**
eGFR 30-50 mL/min: 200 mg every 2 days eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days	eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days Note: FTC is not available as a single-ingredient formulation.

Tenofovir, abacavir, lamivudine, emtricitabine, oral: *Amended - very low risk, "Hyperlactataemia/ steatohepatitis" deleted*
Dolutegravir, oral: *Amended - weight-gain deleted*
Dolutegravir, oral – serum creatinine: *Guidance clarified*
Nevirapine, oral: *Adverse effects and dosing information deleted*
Raltegravir, oral: *Adverse effects and dosing information deleted*
Tenofovir alafenamide (TAF), oral: A*dded*

Dolutegravir (weight gain):

Refer to the NEMLC recommendation below for the use of dolutegravir (DTG) in pregnancy. *"Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant".* A copy of the complete review on the use of DTG in pregnancy[13], may be found at the end of this report, or alternatively on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC 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 PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.					

[13] NDoH evidence summary. DTG in pregnancy_PHC-Adults Medicine review_17June2021_v2

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant. Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance. Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens. A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide. Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks. **Level of Evidence: Moderate certainty of evidence** **Review indicator: New evidence of harms** *(Refer to appendix 2 for the evidence to decision framework)*
NEMLC MEETING OF 24 JUNE 2021: **NEMLC Recommendation:** The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme. It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.
Monitoring and evaluation considerations
Research priorities

Dolutegravir (serum creatinine):
An increase in serum creatinine is noted as an important adverse effect. The STG guidance has been clarified to indicate that an increase in serum creatinine of less than 30mmol/L is clinically insignificant[14]. Serum creatinine increases greater than 30mmol/L may warrant further workup.

Nevirapine, oral: The Information on the dosing and adverse effects of nevirapine was removed as long-term use of nevirapine has been removed from the National ART Guidelines.

Raltegravir, oral: Dosing and adverse effects information was deleted, as raltegravir has been removed from the 3rd line National ARV protocols.

Tenofovir alafenamide (TAF), oral: Adverse effects including acute kidney injury, Fanconi syndrome, reduced bone mineral density added.

ART: DRUG-DRUG INTERACTIONS
Drug Interactions with dolutegravir
Metformin: *Guidance amended*
Updates to the interaction between metformin and DTG were made in the STG (*Version 2.1*) in response to communication received by NELMC, from investigators who conducted a local South African cross-sectional study in 15 obese diabetic patients taking DTG 50mg daily and metformin 1000mg daily.[15] Findings from this pharmacokinetic study identified that metformin concentrations were half those seen in the healthy volunteer study by Song et al[16]. This raised concern that limiting metformin daily dosing to 1000 mg may result in sub-therapeutic concentrations and ineffective treatment in obese patients living with HIV and on concomitant DTG.

A brief literature search was undertaken to identify if there were any recent safety concerns with metformin - a summary of the findings is tabulated below:

Metformin safety Metformin is an old medicine for which we have extensive clinical and published outcome experience. Metformin is generally well-tolerated, and the dose can be titrated to a maximum of 2 550 mg daily[17] with the standard release formulation. It is worth noting that while metformin

[14] Mpofu R, Kawuma AN, Wasmann RE, et al. Determinants of early change in serum creatinine after initiation of dolutegravir-based antiretroviral therapy in South Africa. *Br J Clin Pharmacol*. 2024; 90(5): 1247-1257. doi:10.1111/bcp.16009
[15] Roland van Rensburg,1 Tracy Kellermann,1 Veshni Pillay-Fuentes Lorente,1 Christiena du Plessis,1 Catherine Orrell,2 Innocent Maposa,3 Gert van Zyl,4 Giovanni Schifitto,5 Eric Decloedt1. Reduced Metformin Concentrations in Obese Women with HIV Treated with Dolutegravir (pre-publication article shared with NEMLC)
[16] Song IH, Zong J, Borland J, Jerva F, Wynne B, Zamek-Gliszczynski MJ, Humphreys JE, Bowers GD, Choukour M. The Effect of Dolutegravir on the Pharmacokinetics of Metformin in Healthy Subjects. J Acquir Immune Defic Syndr. 2016 Aug 1;72(4):400-7. doi: 10.1097/QAI.0000000000000983. PMID: 26974526; PMCID: PMC4935531.
[17] Product Information. Glucophage. Merck (Pty) Ltd. Last renewed 4 Nov 2021. Accessed online https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/08/Glucophage-PI-approved-04.11.2021.pdf 14 Nov 2024

is a well-established therapy, a clear definition of its 'therapeutic concentration is lacking. In fact, a systematic review of therapeutic monitoring of metformin reported 65 different recommendations for therapeutic plasma concentrations or ranges with little consensus. Therapeutic monitoring of metformin concentrations was not included in the large longitudinal studies of metformin efficacy, and incidence of adverse events, and of lactic acidosis in particular, was not specified as an endpoint.[18,19]

Lactic acidosis

While lactic acidosis is noted as a caution in the product information[20], it has not translated into a significant concern in clinical practice. A Cochrane review, which pooled data from 347 comparative studies involving 96 295 participants followed for 125 941 patient years,[21] did not identify a single case of lactic acidosis in 70 490 metformin patient-years or among 55 451 non-metformin patient-years. The upper limit of the 95% confidence interval (95% CI) for their estimate of incidence of lactic acidosis per 100 000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the non-metformin group. The Cochrane reviewers thus concluded that there is no evidence that metformin is associated with an increased risk of lactic acidosis compared with other anti-hyperglycaemic therapies.

Cases of lactic acidosis in patients on metformin reported to the French pharmacovigilance centre were described in a case series. The metformin daily dose in these patients was high (mean daily dose >2.5 g), and more than 97% of patients in whom creatinine was reported, had renal impairment.")[22].

In view of the limited data on the clinical implications of the interaction between DTG and metformin and the high local prevalence of PLHIV with comorbid diabetes, many of whom are overweight or obese, a pragmatic approach to managing the potential interaction between metformin and DTG is warranted and the updated STG guidance is as tabulated below:

AMENDED FROM *(Version 2.0)*

DRUG INTERACTIONS WITH DOLUTEGRAVIR

Interacting medicine	Effect of co-administration	Recommendation
Metformin	Significant increase in metformin levels	Administer metformin to a maximum of 500 mg 12 hourly.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

AMENDED TO *(Version 2.1)*

DRUG INTERACTIONS WITH DOLUTEGRAVIR

Interacting medicine	Effect of co-administration	Recommendation
Metformin	May increase metformin concentration	*Metformin initiation:* Initiate metformin at a low dose (500-1000mg total daily dose), titrating up as needed. Do not exceed 2 g daily *DTG initiation:* If patient stabilised on metformin dose ≤ 2g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2g daily, reduce dose of metformin to ≤2g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30mL/min. See Appendix II for further guidance on patients with renal impairment.
Rifampicin	Significant reduction in concentration of DTG	Double DTG dose to 50 mg 12 hourly.

[18] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65. Erratum in: Lancet 1998 Nov 7;352(9139):1558. PMID: 9742977.

[19] Ekström N, Schiöler L, Svensson AM, Eeg-Olofsson K, Miao Jonasson J, Zethelius B, Cederholm J, Eliasson B, Gudbjörnsdottir S. Effectiveness and safety of metformin in 51 675 patients with type 2 diabetes and different levels of renal function: a cohort study from the Swedish National Diabetes Register. BMJ Open. 2012 Jul 13;2(4):e001076. doi: 10.1136/bmjopen-2012-001076. PMID: 22798258; PMCID: PMC3400073.

[20] Package Insert. Glucophage. Merck (Pty) Ltd. Date of first authorisation: 4 Nov 2021. Accessed online https://pi-pil-repository.sahpra.org.za/wp-content/uploads/2023/08/Glucophage-PI-approved-04.11.2021.pdf

[21] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2010; 4: CD002967.

[22] Boucaud-Maitre D, Ropers J, Porokhov B, Altman JJ, Bouhanick B, Doucet J, Girardin E, Kaloustian E, Lassmann Vague V, Emmerich J. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. Diabet Med. 2016 Nov;33(11):1536-1543. doi: 10.1111/dme.13098. Epub 2016 Mar 6. PMID: 26882092.

MONITORING ON ART

CrAg screening

CrAg screening - threshold*: Amended*

Reflex screening of Cryptococcal Antigen (CrAg) in PLHIV was amended to CD4<200 cells/mm^3. Current WHO guidelines states: "Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for PLHIV who have a CD4 count <100 cells/mm^3 (*strong recommendation, moderate certainty evidence*). This may be considered at a higher CD4 threshold of <200 cells/mm^3 (conditional recommendation, moderate certainty evidence)."[23] The cost per disability-adjusted life year saved was estimated as $21 (95% CI, $15-$32) for CrAg screening of PLHIV at CD4<100 cells/mm^3 with pre-emptive fluconazole treatment.[24] Ford et al's systematic review showed that Africa had the highest prevalence of CD4<100 cells/mm^3 and the authors suggest that "consideration should be given to screening at a higher CD4 count of ≤200 cells/mm^3 in settings where there are sufficient resources to implement such an approach, or where a simplified package of care for advanced disease is required based on a unified CD4 threshold."[25] The South African HIV Clinician Society Guideline[26] recommends reflex monitoring of CrAg at a CD4 ≤200 cells/mm^3. A NHLS technical report, based on a period where the CD4 threshold for CrAg testing was temporarily increased from 100 to 200 cells/mm^3 found that there was an increase of 36% in detected cryptococcal antigenaemia, with a prevalence of 2.6% in the 100-200 cell/mm^3 range which exceeded the previously-determined 0.6% threshold cut-off for cost-effectiveness. Following engagement with both the NHLS and the National HIV program guideline team, the NEMLC recommends that a threshold of CD4 ≤200 cells/mm^3 be applied, in view of the clinical value, and given that state facilities currently offer reflex testing at less than 100 cells/mm^3. The STG has been amended as tabulated below:

MONITORING ON ART

Baseline evaluation

- Confirm HIV positive result with second test.
- WHO staging.
- Check CD4 count.
- If CD4 <200 cells/mm^3:
  - Check cryptococcal antigen (if positive, perform LP regardless of whether symptoms are present or not).
  - Initiate cotrimoxazole prophylaxis (See Section 10.2.2: Cotrimoxazole prophylaxis).
  - Reflex CrAg testing is done on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately.

Sputum screening

Sputum screen for TB: *Amended*

As part of the baseline evaluation of all patients on ART, the EML has been amended to include sputum TB-NAAT screening in all patients who can produce sputum. The terminology has also been updated to the general term "TB-NAAT" to reflect a broadening of the diagnostic assays beyond the GeneXpert platform. The amendments have been aligned to the updated National ART Guidelines [27] and are as tabulated below:

Amended from:

- Screen for TB using the WHO screening questionnaire (any one of cough, fever, night sweats, or weight loss). If positive, investigate for TB with a sputum Xpert MTB/RIF Ultra ®. Also do urine LAM if severely ill or CD4 ≤100 cells/mm^3
- In pregnancy do sputum XpertMTB/RIF Ultra® in all.

Amended to:

- Sputum TB-NAAT* in all who can produce sputum, regardless of symptoms.
  *TB-NAAT: TB Nucleic Acid Amplification Tests (e.g. GeneXpert Ultra MTB/RIF)

Viral load monitoring

HIV viral load monitoring schedule: *Amended*

[23] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.

[24] Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, Kamya MR, Bohjanen PR, Boulware DR. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55.

[25] Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159.

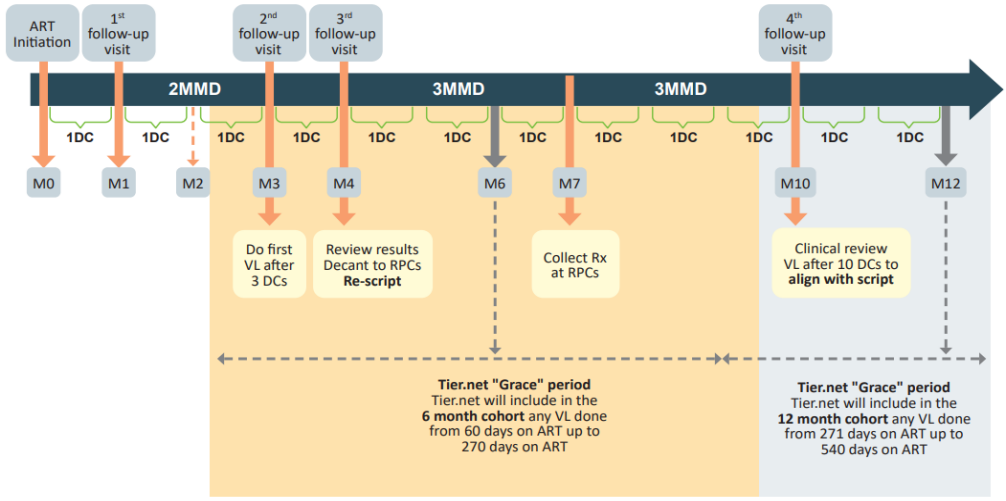
[26] Nel J, Meintjies G, Osih R et al. Southern African HIV Clinicians Society guidelines for antiretroviral therapy in adults: 2023 update. https://sahivsoc.org/Files/crypto%20guidelines.pdf

[27] NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

The HIV viral load monitoring schedule as illustrated in the national National ART Guideline has also been incorporated in the STG (figure 10.1).

HIV VIRAL LOAD MONITORING SCHEDULE

Routine VL monitoring	Intervention	Comments
First VL after ART initiation	Do 1st VL after **3 dispensing cycles**	• Allows for earlier detection of factors influencing viral suppression • Allows for earlier decanting for suppressed clients to minimise visits and promote continued engagement in care • This VL will form part of the **6 month VL completion cohort** in Tier.net
Second routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done from **10 dispensing cycles** but should be aligned with the clients scripting cycle	• This VL will form part of the **12 month VL completion cohort** in Tier.net
Third routine VL after ART initiation (in clients who remain virally suppressed)	This VL can be done **from 22 dispensing cycles**, but should be aligned with the clients scripting cycle	• This VL will form part of the 24 month **VL completion cohort** in Tier.net
Fourth and all subsequent VLs	VLs will be taken at intervals of 12 dispensing cycles for all clients who remain virally suppressed	
The timing of dispensing cycles, follow-up visits, and VL monitoring is illustrated in the diagram below		



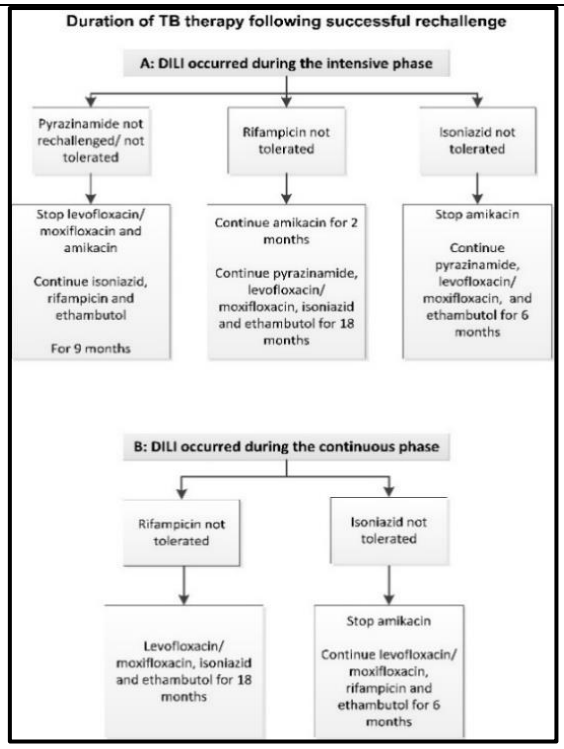
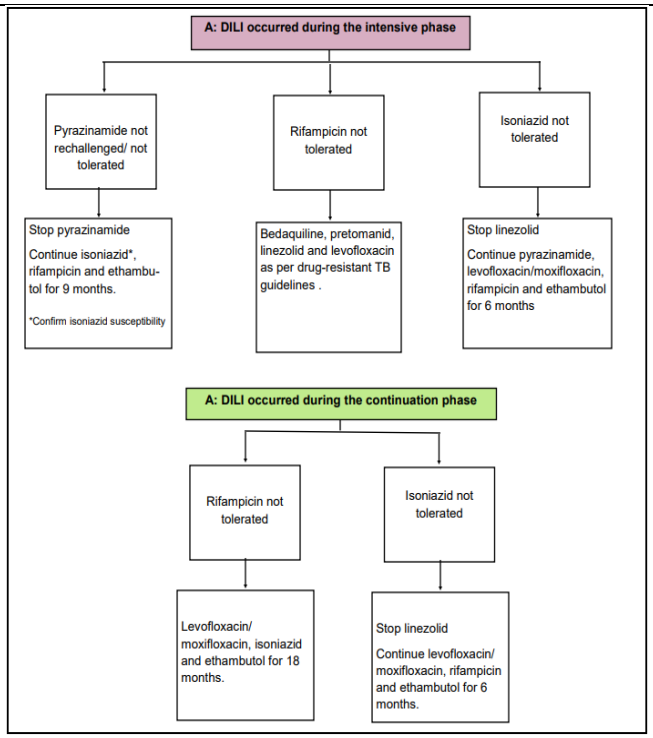
- For the 1st VL taken after 3 dispensing cycles, clients should be requested to return to the facility one DC later to review results and so that the client can be assessed for RPCs eligibility.
- For all subsequent VL monitoring (and other routine monitoring investigation) in clinically well clients: Clients should be rescripted at the same visit that their VL is taken. Clients should not be required to come back to the facility the following month for VL result review prior to rescript. Rather, recall to the facility only those clients with an elevated VL or other abnormal result.
- Facilities should ensure that results management processes are in place to ensure that results are reviewed by a clinician, that abnormal results are identified, and the client is appropriately actioned. The NHLS Results for Action (RfA) reports are a useful tool to facilitate the review of results.

! Breastfeeding women should have their VL monitored every 6 months starting from the time of delivery

10.1.1 MANAGEMENT OF SELECTED ANTIRETROVIRAL ADVERSE DRUG REACTIONS

Hepatotoxicity: *Amended*

Isolated hyperbilirubinaemia as a criterion for management of hepatotoxicity was removed, as this pattern is rare, and mostly of relevance to patients on ATV/r. ATV/r should only be stopped/switched if hyperbilirubinaemia was cosmetically unacceptable to the person. Treatment algorithm was amended:

AMENDED FROM:	AMENDED TO:
	

Hypersensitivity: *Guidance clarified*

The following editorial amendments were made to clarify that the features as detailed below are relevant specifically for EFV and not generally for all ARVs:

If any of the following features occur when a patient is on EFV, then EFV must be permanently discontinued:
- » Blistering
- » Lesions affecting mucous membranes (mouth, eyes, or genitals)
- » Fever.

Patients with lesions affecting the mucous membranes, or with significant blistering, likely have Stevens Johnson syndrome or toxic epidermal necrolysis, and will require admission.

With mild rashes EFV can be continued with careful observation and the rash will often subside.
If rash worsens or does not improve within a week discontinue EFV.

Hyperlactataemia**:** *Guidance clarified*

Editorial amendments as tabulated below were made for improved clarity. The Committee, however acknowledged that this guidance can be phased out of the STG in the next review cycle, given that treatment with AZT has been phased out.

AMENDED FROM:

A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated.

Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):
Therapy should be altered by selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
Stop the NRTIs.
If the patient is on a 1st line regimen, continue the EFV or DTG and add LPV/r.
If the patient is on the 2nd line regimen, consult with an HIV specialist.
If there is acidosis, then admission to a high care unit is recommended.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

AMENDED TO:
A high index of suspicion is necessary. Send blood for lactate levels (check with your local laboratory for specimen requirements for lactate). Alternatively, point of care finger prick lactate monitoring can be done. Check the serum bicarbonate level if lactate is elevated to confirm metabolic acidosis.

Patients with mild hyperlactataemia (lactate 2.5–5 mmol/L):
Alter therapy, selecting NRTIs that are less associated with hyperlactataemia.
Note: The resolution of hyperlactataemia may take a few months.

Patients with lactate levels > 5 mmol/L:
Stop the ART temporarily.
Consult with an HIV specialist regarding the: future ART plan.
Admission to a high care unit is recommended in patients with acidosis.

Lactic acidosis carries a poor prognosis. Treatment is largely supportive. It is essential to exclude other causes of lactic acidosis, especially sepsis. High dose vitamin B, especially riboflavin and thiamine, may have a role in therapy.

Hepatitis in patients on ART and anti-tuberculosis therapy: *Guidance clarified*

The management of patients on co-treatment with ARVs and TB therapy and who present with hepatitis has been amended as tabulated below. Amikacin should be considered as an alternative to linezolid if patients present with a Hb<8g/dL[28].

AMENDED FROM:
Management:
» Stop TB therapy and initiate background TB therapy and continue throughout rechallenge:
- Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative, but only for short term use).
- Moxifloxacin, oral, 400 mg daily or levofloxacin 750–1000 mg daily.
- Ethambutol, oral, 800–1200 mg daily.

» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

AMENDED TO:
Management:
» Stop TB therapy, initiate background TB therapy and continue throughout rechallenge:
- Linezolid, oral 600 mg daily (amikacin, IV/IM, 15 mg/kg daily is an alternative if Hb <8g/dL, but only for short term use).
- Levofloxacin, oral, 750–1000 mg daily or Moxifloxacin, oral, 400 mg daily.
- Ethambutol, oral, 800–1200 mg daily.

» Stop cotrimoxazole prophylaxis.
» Stop ART as described above.
» Repeat ALT and bilirubin in 2 days (inpatient) or 7 days (outpatient).
» When ALT is <100 IU/L and total bilirubin is less than twice the upper limit of normal, start TB medicine rechallenge as follows:

10.1.2 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Paracetamol: *dose amended*

The dose of paracetamol has been amended to align with updated guidance in the AH Chp 26 Pain chapter as tabulated below:

Pain:
- Paracetamol, oral, ~~1 g 4–6 hourly when required~~ 500mg-1 g, 4–6 hourly as required (to a maximum of 4g in 24 hours)
  - Maximum dose: 15 mg/kg/dose.

[28] Boyles T, Berhanu RH, Gogela N, Gunter H, Lovelock T, Mphothulo N, Parker A, Rabie H, Richards L, Sinxadi P, Wattrus C, Moosa MY. Management of drug-induced liver injury in people with HIV treated for tuberculosis: 2024 update. South Afr J HIV Med. 2024 Mar 30;25(1):1558. doi: 10.4102/sajhivmed.v25i1.1558. PMID: 38628909; PMCID: PMC11019071.

10.2 OPPORTUNISTIC DISEASES

10.2.1 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

ADULT PLHIV INITIATED IN ARVs

TB preventive therapy: *added as a therapeutic group*
Isoniazid (12H): *retained as an example of class in the STG*
Rifapentine + isoniazid (3HP): *added as a therapeutic alternative in the therapeutic interchange database*

During the previous review cycles, the NEMLC approved 12 months of daily isoniazid (12H) for PLHIV and not 3HP. Non-inferiority trials suggested that 3HP prophylaxis was not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H. Refer to the previous NEMLC-approved reviews for rifapentine in PLHIV (14 November 2019)[29] and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019)[30] which is accessible on the NHI webpage.

Rifapentine (3HP) as TPT in PLHIV 14 Nov 2019

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	☐	☐	☐	☐

Recommendation: Based on this evidence review, The Adult Hospital Level Committee recommended that a rifapentine-isoniazid regimen probably has similar efficacy and safety to the current INH recommendation and could be considered as an alternative TLTBI option in PLHIV on an efavirenz or raltegravir based ART regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Current evidence does not show superior efficacy of short course HP to 6-12H.
HP showed decreased adverse events when compared to 6-9H, the adverse event rates reported for INH in these populations are not consistent with the adverse event rates reported from other South African studies. The improved completion rates are already factored into the efficacy results for HP owing to MITT analysis, the improved rates shown did not translate into superior efficacy of HP over 6-9H.
Level of Evidence: I RCTs (moderate quality).

Review indicator: *Reduction in price*

Evidence of efficacy	Evidence of harm	Price reduction
x	x	X

VEN status:

Vital	Essential	Necessary

NEMLC MEETING OF 5 DECEMBER 2019
NEMLC accepted the proposal as reccomended by the Adult Hospital Level Committee, above. Until there is a reduction in price of rifapentine resulted in price parity between treatment regimens 12H and 3HP, rifapentine is considered unaffordable to include on the EML.

Monitoring and evaluation considerations:
- Completion rate in programmatic setting as a process indicator.
- Drug-drug interactions.
- TB incidence in PLHIV

Research priorities
- Results of ongoing trial looking at safety with dolutegravir.
- Durability of protective effect in high tuberculosis areas.
- Efficacy in persons on ART testing negative for LTBI.

[29] NDoH Evidence Summary. NDoH_EDP_Rifapentine_Adults Review Update_14November2019_v1.0
[30] NDoH Evidence Summary. NDoH_EML_Rifapentine_&_Dolutegravir_ TPT_AdultsReview_v1

Rifapentine in PLHIV on DTG-containing antiretroviral therapy

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[x]	☐	☐	☐	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee concludes that in patients with suppressed viral load on DTG, 3HP could be considered as an alternative TLTBI option in PLHIV that are virally suppressed on a DTG-containing regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Preliminary data, suggests that rifapentine has no impact on patients who are already virally suppressed. Co-administration of DTG and HP was well tolerated with no HP-related adverse effects of ≥ grade 3. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed and DTG can be co-administered with HP without dose-adjustment.

Level of Evidence: III Phase I/II study

Review indicator: *Reduction in price; evidence of efficacy and safety*

Evidence of efficacy	Evidence of harm	Price reduction
[x]	[x]	[X]

VEN status:

Vital	Essential	Necessary
☐	☐	☐

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as reccomended by the Adult Hospital Level Committee, above. Until there is a reduction in price of rifapentine resulted in price parity between treatment regimens 12H and 3HP, rifapentine is considered unaffordable to include on the EML.

Monitoring and evaluation considerations:

Therapeutic Interchange

3HP was recommended for inclusion to the therapeutic interchange database:

- 12H: Isoniazid, oral, 300 mg daily for 12 months
- 3HP: Isoniazid, oral 900 mg + Rifapentine, oral 900 mg weekly for 3 months (preferably as a FDC).

NEMLC MEETING OF 23 JUNE 2022:

NEMLC recommended that 3HP be included as a therapeutic alternative to 12H in PLHIV initiated on ART – however, for DTG-containing regimens, patients to be virally suppressed (this would promote competitive pricing).

However, as there is currently no available RCT evidence for concomitant use of rifapentine with viraemic patients on DTG, the following text was added to the STG:

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

The therapeutic interchange database update as follows:

Indication	Criteria	Medicine (INN)	Treatment course	Therapeutic class	Therapeutic ATC
TPT for ART-naïve HIV adult patients	n/a	Isoniazid	300 mg daily x 12 months	TPT	J04A
	• Initiated on TEE • Initiated on TLD BUT virally suppressed • NOT on a PI • Not on oral hormonal contraceptives	Isoniazid and rifapentine (FDC)	900/900 mg weekly x 3 months	TPT	J04A

FDC=fixed dose combination; TEE= TDF+EFV+FTC; TLD= TDF+3TC+DTG; TPT=TB preventive therapy; PI=protease inhibitor

In pregnant women, starting ART:

TPT in pregnant women: *Guidance amended*

The STG guidance on the use of TPT in pregnant women has been amended as tabulated below:

AMENDED FROM:

- In pregnant women, starting ART:

If CD4 >350 cells/mm^3.	If CD4 ≤350 cells/mm^3.
Defer TPT until after delivery.	Exclude active TB with symptom screen and TB-NAAT, then give TPT.

AMENDED TO:

NOTE: For pregnant women::

- Defer TPT until after delivery
- Ensure that routine screening against TB is conducted at each antenatal visit

Refer to the NDoH evidence summary Isoniazid Preventive Therapy in Pregnancy[31] for further details. A copy of the full review may be found at the end of this report or alternatively, accessed on the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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	

ERC Recommendation 9 November 2023: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 350 cells/mm^3 and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 350 cells/mm^3 and starting ART, IPT should be deferred to the post-partum period.

Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m^3(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher CD_4 counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence).

Level of Evidence:

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at CD_4 ≤ 350 cells/mm^3 (low certainty evidence from an observational study)

Review indicator: New high quality evidence of benefit or harm.

Multi stakeholder engagement meeting recommendation- 7 March 2024:

The consensus recommendation from a multi stakeholder engagement meeting, which included representatives from the NEMLC, NDOH TB and maternal healthcare programs and South African Medical Research Council (SAMRC) with reference to local feasibility considerations, is as follows:

- Initiation of IPT should be deferred in all pregnant patients until after delivery
- In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy must be emphasized.

Rationale: While the evidence in support of the ERC recommendation dated 9 November 2023 above was not in dispute, concern was expressed with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART. The consensus recommendation from the multi stakeholder group was therefore for a less complex recommendation to avoid IPT in pregnancy in all pregnant women, regardless of HIV status or CD4 count. It was noted at the meeting that screening for TB as part of routine antenatal care is already included in programmatic guidance, to identify pregnant women with tuberculosis disease timeously and initiate appropriate antituberculosis treatment.

NEMLC RECOMMENDATION (MEETING OF 14 March 2024): NEMLC supported the multi stakeholder recommendation that IPT be avoided during pregnancy.

Monitoring and evaluation considerations, and research priorities:

Pregnant women should be routinely screened for TB at every antenatal visit.

Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

[31] NdoH Evidence Summary. Evidence review: IPT in pregnancy_v1.2_15 April 2024_final approved

10.2.2 OPPORTUNISTIC INFECTION PROPHYLAXIS, WITH COTRIMOXAZOLE

Indications for primary prophylaxis - WHO clinical stage II: *Deleted*

The indications for primary prophylaxis against opportunistic infections with cotrimoxazole was amended to include WHO clinical stage III or IV i.e. WHO clinical stage II was removed from the STG. The STG has been aligned with the most recent WHO guidance[32] which has been amended from WHO stage II, III or IV in 2000[33] to stage III or IV only. Furthermore, as South Africa's CD4 threshold to stop cotrimoxazole prophylaxis has historically been lower than WHO's threshold (200 vs 350 cells/mm^3), the clinical stage thresholds are now better aligned with the CD4 count thresholds (a CD4 threshold of <200 cells/mm^3 correlates better with a clinical stage III or IV than with stage II).

10.2.3 CANDIDIASIS OF OESOPHAGUS/TRACHEA/BRONCHI

Fluconazole, oral: *directions for use amended*

The STG was editorially amended as follows:

- Fluconazole, IV/oral, 200 mg daily for 14 days.
  - The usual route is oral but give IV if patient unable to swallow or is vomiting.
  - An early relapse should be treated with a 4-week course of fluconazole, using a similar dose as above.
  - If no response to fluconazole, collect sample to confirm diagnosis of candidiasis (perform fungal MC&S).

10.2.4 CRYPTOCOCCOSIS

Algorithm for the prevention, diagnosis and management of cryptococcosis among PLHIV: *Amended*

ART (if CSF CrAg negative): *Directions for use amended (timing of initiation)*

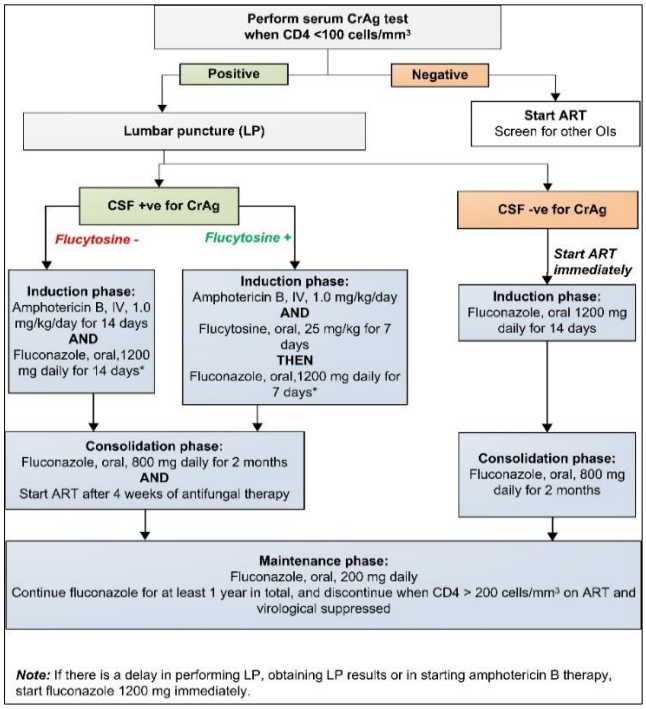
Treatment algorithm was amended for clarity purposes and correctness. It was noted that NEMLC had previously recommended that the SA HIV Clinicians Society algorithm be adapted, and the option to refuse a lumbar puncture be removed from the algorithm. Therefore, this section was delineated into management for i) CSF CrAg negative and ii) Cryptococcal meningitis, aligned with the most recent SA HIV Clinician Society algorithm[34], and section 10.2.4.2: Cryptococcal meningitis, below. Additionally, the algorithm also includes guidance for the use of a liposomal amphotericin regimen in combination with flucytosine. See Section 10.2.4.2 below for further details.

[32] https://www.ncbi.nlm.nih.gov/books/NBK298965/#:~:text=Co%2Dtrimoxazole%20prophylaxis%20is%20recommended,≤350%20cells%2Fmm3.]

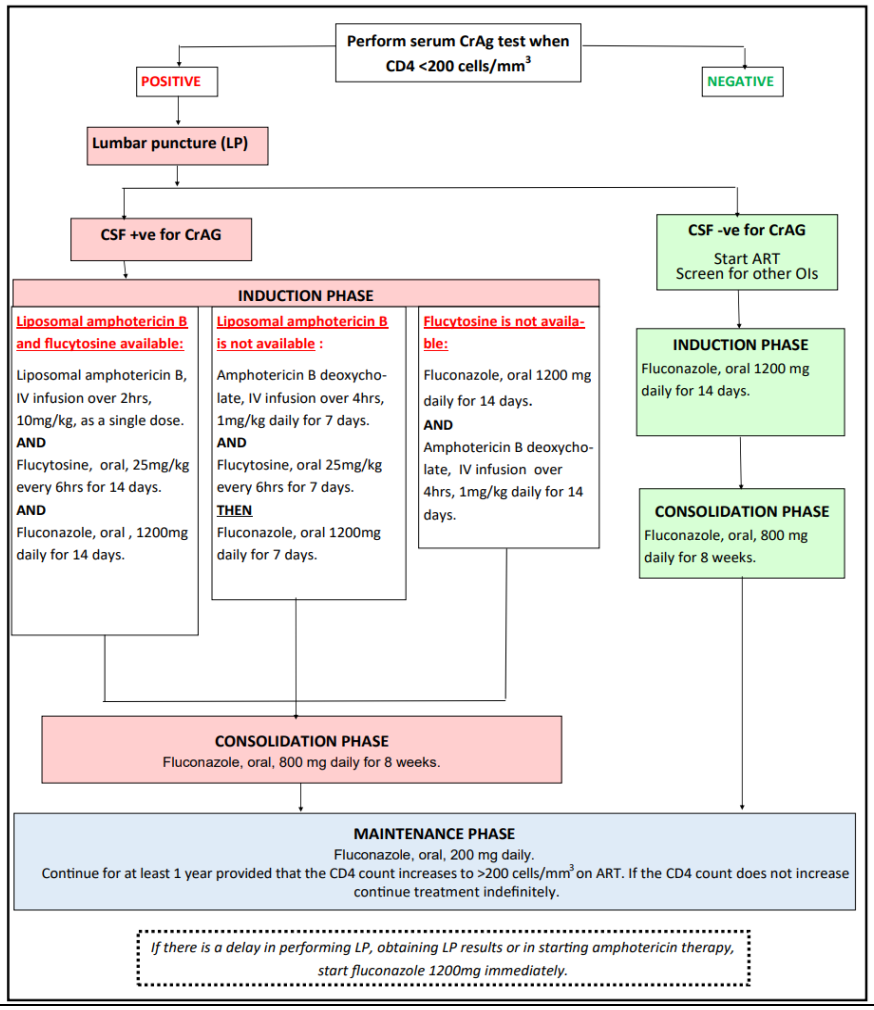
[33] Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa. Report 29/03/2000. Geneva: World Health Organization, 2000]

[34] Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. https://doi.org/10.4102/sajhivmed.v20i1.1030

AMENDED FROM:



AMENDED TO: *(V2.1 Erratum approved 28 Nov 2024)*



10.2.4.1 CRYPTOCOCCOSIS, CSF CRAG NEGATIVE

CrAg screening*: CD4 threshold amended*

Refer to discussion above – '*Monitoring on ART: CrAg screening at HIV diagnosis.'*

The description in the STG has been amended as tabulated below:

AMENDED FROM:

DESCRIPTION

All ART-naïve patients with CD4 <100 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a diagnosis of cryptococcal infection). If positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. The CSF should be tested for cryptococcal meningitis by CSF CrAg.

AMENDED TO:

DESCRIPTION

All ART-naïve patients with CD4 <200 cells/mm^3 should have cryptococcal antigen (CrAg) test done on serum, plasma or whole blood (unless they had a diagnosis of cryptococcal infection). This is performed as a reflex test on the patient's CD4 sample if it is <100 cells/mm^3. If the CD4 count is between 100 and 199, a separate sample should be sent for CrAg testing. If the CrAg test is positive, all patients should have a lumbar puncture, regardless of whether symptoms of meningitis are present, since asymptomatic cryptococcal meningitis may be present. The CSF should be tested for cryptococcal meningitis by CSF CrAg.

ART: *directions for use amended*

Aligned with section 10.1 Antiretroviral therapy, adults - Clinical indications for deferring ART initiation: Asymptomatic cryptococcal infection (refer to discussion above).

10.2.4.2 CRYPTOCOCCAL MENINGITIS

Flucytosine, oral: *Added*

Liposomal Amphotericin B*: Added*

Amphotericin B, IV*: Retained*

Fluconazole, oral: *Retained*

Flucytosine

NEMLC had previously recommended that flucytosine be considered for inclusion in the EML, once SAHPRA registered and if the price for the oral regimen was reduced by 42% (R2195 per pack of 500mg, 100 tablets). Refer to the medicine review (November 2018)[35], economic analysis (June 2019)[36] accessible on the NHI webpage for further details. Flucytosine was registered by SAHPRA in December 2021 and the STG has been updated as tabulated below.

[35] NDoH Evidence Summary. NDoH_EDP_Flucytosine_Adults Review_15Nov2018_v3.0

[36] Flucytosine Health Economic and Budget Impact Analysis – EML June 2019

Flucytosine for treatment of cryptococcal meningitis

Recommendation:

Based on the evidence review, the Adult Hospital Level Committee recommends the following, **pending SAHPRA registration:**

- One-week combination of Amphotericin B deoxycholate and Flucytosine be the preferred regimen for treatment of CM in the induction phase.
- As an alternative, where Amphotericin B is not available or intravenous therapy cannot be administered, two-week oral course of Flucytosine and Fluconazole should be the alternative regimen.

However, cost-effectiveness analysis and budget impact analysis need to be investigated to determine affordability.

Rationale: Meta-analysis evidence shows that 1-week Amphotericin B + Flucytosine is not inferior to 2 weeks Amphotericin B + Fluconazole. When flucytosine was added to amphotericin B in a large multicentre trial conducted in several African countries, flucytosine was associated with a 38% lower risk of death compared to fluconazole (4)

Level of Evidence: I Systematic Review

Review indicators: SAHPRA registration; Price

NEMLC Minutes of 11 July 2019:

Following the review of the health economics and budget impact analyses (accessible at: http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/411-hospital-level-adults-costings) , NEMLC recommended the following:

NEMLC Recommendation: Flucytosine be considered for inclusion to the EML, pending SAHPRA registration with a reduction in price.

Rationale: Simulation confirms that flucytosine is cost-effective as induction therapy for treatment of cryptococcal meningitis amongst HIV-infected. Incremental budget impact of flucytosine compared to current standard of care is an estimated R8 million per annum, but savings could be achieved with early discharge of patients (i.e. LOS 10 days or less).

A 60% reduction in price would result in a cost-neutral budget impact (R1500.00 per 100 flucytosine tablets) for the 1 week AmBd/5FC course and cost neutrality would be achieved at a price of R2195 per pack (42% price reduction) for the oral regimen. However, this is subject to uncertainty in the model, including the impact of reduction in LOS, uptake of flucytosine and use of different regimens and so a price reduction of around 40% is likely to be reasonable.

Level of Evidence: I RCT, Costing analyses, Expert opinion

Liposomal Amphotericin B

Following a reduction in the price of liposomal amphotericin B, the evidence summary and associated cost analysis for the use of liposomal amphotericin B was updated – NEMLC recommendation tabulated below. For a copy of the complete evidence review[37], refer to the end of this report or alternatively to the NHI webpage.

[37] Liposomal Amphotericin B_ cryptococcal meningitis_Adults Review_Update_23 January 2024_final approved

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)**
	☐	☐	☐	☒	☐

Recommendation: Based on the updated evidence review, the PHC/Adult Hospital Level Committee suggests the use of liposomal amphotericin B for treating patients with cryptococcal meningitis.
Liposomal amphotericin B is non-inferior to current standard of care in terms of efficacy and is safer. Liposomal amphotericin B has a similar or lower cost compared to current standard of care, at the latest price of R600 per 50mg vial taking length of hospital stay into account in the costing.
Rationale: The current evidence of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate.
Level of Evidence: Low to moderate certainty evidence
Review indicator: Price reduction

Evidence of efficacy	Evidence of harm	Price reduction
☐	☐	☒

VEN status: n/a

Vital	Essential	Necessary
☐	☐	☐

NEMLC MEETING OF 21 FEBRUARY 2019:
NEMLC ratified the medicine review and accepted the recommendation not to include liposomal amphotericin B in the Adult Hospital Level EML as although small and of moderate risk of bias, it shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, however it is currently not affordable.

NEMLC MEETING OF 23 JUNE 2022:
NEMLC upheld the previous recommendation not to include liposomal amphotericin B on the national EML, but amended the strength of recommendation from "strong" to "conditional", with a review indicator of "price reduction". The NEMLC further recommended that the proposed Gilead price of $16.25 per 50 mg vial be added as a threshold price.

NEMLC MEETING OF 30 NOVEMBER 2023: NEMLC supports the ERC's recommendation to include the use of liposomal amphotericin B on the EML for the management of cryptococcal meningitis in line with the treatment regimen included in the cost analysis (Addendum A). The Committee supported this recommendation on the basis of the better safety profile of liposomal amphotericin B compared to amphotericin B deoxycholate as well as the potentially lower overall cost with liposomal amphotericin B. The committee however, acknowledged the limitations of modelling the benefits of the better safety profile of liposomal amphotericin B in the cost analysis.

In line with the updated NEMLC recommendations as detailed above for liposomal amphotericin B, the STG has been updated as tabulated below:

AMENDED FROM:

10.2.4.2. CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Therapeutic lumbar puncture should be done daily until there is clinical improvement.

MEDICINE TREATMENT
Induction phase

If flucytosine is available:

- Flucytosine, oral 25 mg/kg for 7 days.

Weight	6 hourly dosing
30-39 kg	750 mg 6 hourly

AMENDED TO:

10.2.4.2. CRYPTOCOCCAL MENINGITIS

B20.5 + (B45.1 + G02.1*)

DESCRIPTION

Cryptococcal meningitis is the commonest manifestation of disseminated cryptococcosis in patients with advanced HIV. Severe headache is common due to raised intracranial pressure.

Diagnosis

Confirmed on lumbar puncture.

GENERAL MEASURES

Therapeutic lumbar puncture is indicated to lower pressure in symptomatic patients and should be done with pressure monitoring. Remove sufficient CSF (maximum 30 mL) to lower pressure to 50% of the opening pressure but not less than 20 cm H_2O.

Continue daily therapeutic lumbar puncture until there is clinical improvement.

MEDICINE TREATMENT
Induction phase

If liposomal amphotericin B and flucytosine are available:

- Liposomal amphotericin B, slow IV infusion over 2 hours, 10 mg/kg in dextrose 5%, single dose.

AND

40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

Note: Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

AND

- Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200mg daily for 7 days.

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND

- Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.

Note: Adjunctive corticosteroids have been shown to be detrimental.

REFERRAL

» Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.

» Persistent raised intracranial pressure despite daily therapeutic lumbar puncture.

- Flucytosine, oral 25 mg/kg 6 hourly for 14 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

AND

- Fluconazole, oral 1200mg daily for 14 days
  - Fluconazole requires dose adjustment in renal failure.

<u>If liposomal amphotericin B is not available:</u>

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 7 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

<u>AND</u>

- Flucytosine, oral 25 mg/kg 6 hourly for 7 days (see flucytosine weight-based dosing table below).
  - Flucytosine requires dose adjustment in renal failure (See Appendix II for preventing, monitoring and management of toxicity).

THEN (i.e. days 8-14 of induction phase):

- Fluconazole, oral 1200mg daily for 7 days.

<u>If flucytosine is not available:</u>

- Fluconazole, oral 1200 mg daily for 14 days.

AND

- Amphotericin B deoxycholate, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.
  - Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily.
  - Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm3 on ART. If the CD4 count does not increase continue treatment indefinitely.

- Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.

Note: Adjunctive corticosteroids have been shown to be detrimental.

Flucytosine weight-based dosing table:

Weight	6 hourly dosing
30-39 kg	750 mg 6 hourly
40-49 kg	1000 mg 6 hourly
50-59 kg	1250 mg 6 hourly
60-69 kg	1500 mg 6 hourly
70-79 kg	1750 mg 6 hourly

REFERRAL

- Focal neurological signs – CT scan required to exclude other pathology e.g. toxoplasmosis.
- Persistent raised intracranial pressure despite daily therapeutic lumbar puncture

Dosing in renal impairment has also been included in Appendix II for preventing, monitoring and management of toxicity, aligned with Guidelines *(note: Appendix II to be published with the final Adult Hospital Level STGs and EML, 2023 edition).* More specifically, an update has been made to drug monograph for amphotericin B deoxycholate (tabulated below).

AMENDED FROM:	**AMENDED TO:**
AMPHOTERICIN B, IV • Amphotericin B, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. ○ Reconstitue in 5% dextrose water only (as incompatibile with saline solution). ○ Administer over a period of 2–6 hours. ○ Ensure adequate hydration to minimise the risk of nephrotoxicity. ***Monitoring*** – Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week). – Monitor haemoglobin (baseline and weekly). – Careful attention to fluid monitoring of intake and output. – For management of hypokalaemia, see section 7.2.2: Hypokalaemia. ***Management of elevated creatinine*** If creatinine increases by ≥2 fold from baseline value, either omit an amphotericin B dose, or increase pre-hydration to 1 litre 8 hourly. – Once improved, restart at 0.7 mg/kg daily and consider alternate day amphotericin B. – If creatinine remains elevated i.e. ≥2 fold from baseline value, discontinue amphotericin B and continue with fluconazole, oral, 800 mg daily (for fungal infections known to be responsive to fluconazole, e.g. *Cryptococcus*). (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016]. http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf	**AMPHOTERICIN B DEOXYCHOLATE, IV** • Amphotericin B deoxycholate, IV, 0.7–1 mg/kg daily, dose and duration of therapy depend on indication for use and infecting organism. ○ Reconstitue in 5% dextrose only (as incompatibile with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion. ○ Administer over a period of 2–6 hours. ○ Ensure adequate hydration to minimise the risk of nephrotoxicity. ***Monitoring*** – Serum potassium, magnesium and creatinine (baseline and twice weekly). Monitoring of serum potassium and creatinine should occur more frequently in neutropenic patients (3 times a week). – Monitor haemoglobin (baseline and weekly). – Careful attention to fluid monitoring of intake and output. – For management of hypokalaemia, see section 7.2.2: Hypokalaemia. ***Management of elevated creatinine in cryptococcal meningitis*** If creatinine increases by ≥2 fold from baseline value, stop amphotericin B deoxycholate, increase pre-hydration to 1 litre 8 hourly (watch for fluid overload), and switch to fluconazole 600mg daily and flucytosine 25mg/kg (with the flucytosine dosing interval adjusted for eGFR). – Once improved, restart to complete 7 days amphotericin B deoxycholate in total (Adapted from: WHO. Rapid advice: diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children: Prevention, monitoring and management of amphotericin B toxicity. 2011 [Online] [Accessed March 2016] http://www.ncbi.nlm.nih.gov/books/NBK299520/pdf/Bookshelf_NBK299520.pdf

Additionally, new monographs added for flucytosine and liposomal amphotericin (as tabulated below) which will be added to Appendix II of the EML:

LIPOSOMAL AMPHOTERICIN B, IV ○ Liposomal amphotericin B, IV, 10 mg/kg single dose for cryptococcal meningitis – Reconstitute in 5% dextrose only (as incompatible with saline solution). Do not reconstitute or dilute with saline or administer through an intravenous line that has previously been used for saline unless first flushed with dextrose solution (5 %,10 % or 20 %) for infusion. – Administer over a period of 2 hours. – Liposomal amphotericin B contains soya oil. Patients allergic to peanut or soya should not be given liposomal amphotericin B. ***Monitoring in patients with cryptococcal meningitis***

- Anaphylaxis and anaphylactoid reactions have been reported in association with liposomal amphotericin B. If a severe anaphylactic/ anaphylactoid reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion.
- Monitor blood glucose levels in diabetic patients - each vial of liposomal amphotericin contains 900mg of sucrose. Furthermore, liposomal amphotericin B must be reconstituted with dextrose 5%.

FLUCYTOSINE, ORAL

- Flucytosine, oral, 25 mg/kg 6 hourly for 14 days for cryptococcal meningitis.

Monitoring

- Flucytosine is partially metabolised to 5-fluorouracil which is potentially teratogenic. Women of child-brearing age should be counselled on effective contraception during treatment and up to one month following discontinuation of treatment. Male patients should be counselled to use effective contraception during treatment and for 3 months following discontinuation of flucytosine treatment.

Management of elevated creatinine

Dosage adjustment is required in patients with renal impariment as tabulated below:

Creatinine Clearance	Single Dose	Dosing Interval
CrCl >40mL/min	25mg/kg	6 hourly
20 ≤ CrCl < 40mL/min	25mg/kg	12 hourly
10 ≤ CrCl < 20mL/min	25mg/kg	24 hourly
CrCl <10mL/min*	25mg/kg	48 hourly

***Adopted from:** Flucytosine | Johns Hopkins ABX Guide (hopkinsguides.com) https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540227/all/Flucytosine?q=flucytosine#3.2 and *Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030. https://pubmed.ncbi.nlm.nih.gov/32201629/ Source: The Sanford guide to antimicrobial therapy 2019 / editors, David N, Gilbert MD, George M, Eliopoulos MD, Henry F, Chambers MD et al. Sperryville, VA, USA: Antimicrobial Therapy, Inc., [2019]).*

10.2.4.2 SYMPTOMATIC, NON-MENINGEAL CRYPTOCOCCOSIS *(STG DELETED)*

Fluconazole, oral: *Deleted*

Amphotericin B, parenteral: *Deleted*

ART: *Deleted*

As all CrAg positive patients are recommended to have a lumbar puncture, regardless of whether symptoms of meningitis are present, this STG has been deleted - guidance has been included in section 10.2.4.1: Cryptococcosis, CSF CrAg negative.

~~**DESCRIPTION**~~

~~Cryptococcal infection confirmed on culture or serum CrAg positive with non-meningeal disease. Any anatomical site may be involved, but the lungs are the commonest site.~~

~~**MEDICINE TREATMENT**~~

~~**Induction phase**~~

- ~~Fluconazole, oral 1200 mg daily for 14 days.~~

~~**AND**~~

- ~~Amphotericin B, slow IV infusion, 1 mg/kg daily in dextrose 5 % over 4 hours for 14 days.~~
  - ~~Ensure adequate hydration to minimise nephrotoxicity. (See Appendix II for preventing, monitoring and management of toxicity).~~

~~**Consolidation phase**~~

~~Follow with:~~

- ~~Fluconazole, oral, 800 mg daily for 8 weeks.~~

~~**Maintenance phase**~~

- ~~Fluconazole, oral, 200 mg daily.~~
  - ~~Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase continue treatment indefinitely.~~
- ~~Commence ART 4–6 weeks after starting antifungal therapy. See section 10.1: Antiretroviral therapy.~~

10.2.6 CYTOMEGALOVIRUS (CMV)

Maintenance treatment

Ganciclovir, parenteral: *Deleted*

Valganciclovir, oral: *Retained*

The option to provide ganciclovir, IV, if valganciclovir, oral could not be tolerated for maintenance treatment of CMV was not considered to be a pragmatic option for public health sector, and was recommended for deletion.

Level of Evidence: IV Expert opinion

NEMLC MEETING OF 24 FEBRUARY 2022:

DISCUSSION:

Ganciclovir, parenteral: The proposal to remove ganciclovir, IV, for maintenance treatment of cytomegalovirus, was based on a value judgment, as it was more pragmatic to administer oral valganciclovir compared to parenteral ganciclovir (the latter requiring hospital admission). However, it is acknowledged that a standardised systematic framework for making value judgements is lacking.

Historically, ganciclovir, parenteral was cheaper than oral valganciclovir – the current price comparison estimated as follows (modelled on a 70kg adult and using UPFS 2020 tariffs for day patient administration of ganciclovir) favours use of oral valganciclovir:

Maintenance treatment regimen	Estimated cost for 30 days
Ganciclovir, IV, 5 mg/kg daily until CD4 count rises to >100 cells/mm3 on ART.	R724.50 + R1602 = R2326.50/day; 30 days **=R69 795.00**
Valganciclovir, oral, 900 mg daily until CD4 count rises to >100 cells/mm3 on ART.	**R 4973.75** (see discussion above)

References: Contract circulars Contract circular HP02-2021AI and HP02-2021AI/01; UPFS 2020 tariffs

10.2.9 PNEUMOCYSTIS PNEUMONIA

Primaquine, oral: *directions for access added*

The STG text was amended to include S21 access of primaquine.

Referral: *Editorial amendment*

The criteria for referral was amended editorially as tabulated below:

AMENDED FROM:

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to second line regimen.

AMENDED TO:

REFERRAL/CONSULTATION

Specialist or tertiary

Intolerance to all alternative regimens.

10.5.1 POST-EXPOSURE PROPHYLAXIS, OCCUPATIONAL

Darunavir/ritonavir: *not added*

An external comment was received to consider a darunavir/ritonavir (DRV/r)-containing PEP regimen if lopinavir/ritonavir or atazanavir/ritonavir is not tolerated. However, darunavir/ritonavir is salvage therapy, and not recommended for inclusion on the primary or secondary level EML. Therefore, the STG text was updated as follows:

Lopinavir/ritonavir often causes diarrhoea. If lopinavir/ritonavir is not tolerated switch to atazanavir/ritonavir. Atazanavir/ritonavir often causes unconjugated jaundice, which is benign but may not be tolerated, in which case switch to lopinavir/ritonavir. If both these protease-inhibitors are not well tolerated, consult a specialist.

PEP REGIMENS

Tenofovir disoproxil fumarate (TDF): *Editorial amendments*

TDF contraindicated: *Guidance clarified*

Amendments to the STG were made for improved clarity as tabulated below:

AMENDED FROM:

When PEP is indicated (administered preferably as a fixed-dose combination):

- Tenofovir, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

and

- Lamivudine, oral, 300 mg daily for 4 weeks

and

Dolutegravir, oral 50 mg once daily for 4 weeks.

If DTG is not tolerated:

- Tenofovir, oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

and

- Emtricitabine, oral, 200 mg daily for 4 weeks.

and

- Atazanavir/ritonavir 300/100 mg daily for 4 weeks.

Or

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If tenofovir is contraindicated or if source patient is known to be failing a tenofovir based regimen, replace tenofovir and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

and

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

AMENDED TO:

When PEP is indicated (administered preferably as a fixed-dose combination):

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute. Do not delay initiation of PEP while awaiting baseline eGFR. Re-assess TDF eligibility once results become available).

AND

- Lamivudine, oral, 300 mg daily for 4 weeks

AND

Dolutegravir, oral 50 mg daily for 4 weeks.

If DTG is not tolerated:

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily for 4 weeks (provided baseline eGFR is >50 mL/minute).

AND

- Emtricitabine, oral, 200 mg daily for 4 weeks.

AND

- Atazanavir/ritonavir 300/100 mg, 1 tablet, oral daily for 4 weeks.

OR

- Lopinavir/ritonavir 200/50 mg, oral, 2 tablets 12 hourly for 4 weeks.

If TDF is contraindicated or if source patient is known to be failing a TDF- based regimen, replace TDF and emtricitabine with:

- Zidovudine, oral, 300 mg 12 hourly for 4 weeks.

AND

- Lamivudine, oral, 150 mg 12 hourly for 4 weeks.

AND

- Continue third applicable drug (DTG or boosted PI – see above)

PEP is generally not well tolerated. Adverse effects occur in about half of cases and therapy is discontinued in about a third. Efavirenz is not recommended as it is very poorly tolerated in PEP.

PEP for healthcare workers following hepatitis B exposure

Hepatitis B Immunoglobulin: *Amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[38] - STG text was updated as follows:

Vaccination status and	Source patient			
	Vaccination status	**HBsAg positive**	**HbsAg negative**	**HBsAg unknown**
	Unvaccinated or	• HBIG, IM, 500 units* • Hep B vaccine	• Initiate Hep B vaccination	• HBIG, IM, 500 units* • Hep B vaccine

[38] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

antibody response status of HCW	vaccination incomplete	(3 doses at monthly intervals)	(month 0, 1 and 6)	(3 doses at monthly intervals)
	Vaccinated **AND** known to have HBsAb ≥ 10 units/mL[#]	No treatment	No treatment	No treatment
	Vaccinated **AND** HBsAb <10 units/mL or level unknown	• HBIG, IM, 500 units * • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)	No treatment	• HBIG, IM, 500 units* • If HBIG <10 units/mL, repeat HBIG at 1 month • Repeat Hep B vaccine (3 doses at monthly intervals)

* HBIG and first dose of vaccine to be given simultaneously, but at different sites.
[#] If the delay in obtaining HBsAb results is more than 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.
After vaccination ensure the health care worker has a HBsAb > 10 units/mL 1 – 2 months after the last vaccine dose.

Delay in obtaining HBsAb results

Time period of delay: *Amended*

Aligned with the National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020[39]- STG text was updated as follows:

If the delay in obtaining HBsAb results is more than ~~24 hours~~ 7 days initiate treatment as for vaccinated AND HBsAb < 10 units/mL.

10.5.2 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, SEXUAL ASSAULT

HIV PrEP: *Added as a cross reference to the PHC STGs and EML*

For patients at ongoing high risk of HIV acquisition, guidance was provided to transition from PEP to PrEP as follows:

HIV PrEP
If patient is at ongoing high risk of HIV acquisition, commence PrEP after PEP has been completed.
Perform HIV test 4-weeks after initiating PrEP.

Emergency contraception

Copper IUCD: A*dded (as first line option)*

Levonorgestrel, oral: *Retained (as 2nd line option)*

Copper IUCD placed as the first line option as this agent has less drug-drug interactions compared to oral levonorgestrel 1.5mg and is the agent of choice for obese women. Copper IUCD can also be used as a long-acting reversible contraceptive.[40] [41]

Emergency contraception for obese women

Levonorgestrel, oral: *Dose not amended*

An external comment was received that there is no need to double the dose of levonorgestrel for obese women for emergency contraception. Limited data suggests that obese women have an increased risk of pregnancy after use of levonorgestrel and ulipristal acetate emergency contraception compared to those who are not obese.[42] In a pharmacokinetic study with 10 participants, levonorgestrol Cmax in obese participants was half that achieved in participants with normal BMI, and doubling the levonorgestrol dose in obese participants resulted in a similar Cmax to that seen in those with normal BMI[43]. Faculty of Sexual & Reproductive Healthcare (FSRH) Overweight, Obesity and Contraception Guidelines of April 2019, therefore recommends "double-dose (3 mg) of levonorgestrel emergency contraception, if BMI >26 kg/m2 or weight >70 kg". However, the effectiveness of double-dosing in preventing

[39] National Clinical Guidelines of post-exposure prophylaxis (PEP) in occupational and non-occupational exposures, December 2020. https://www.knowledgehub.org.za/elibrary/national-clinical-guidelines-post-exposure-prophylaxis-pep-occupational-and-non

[40] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/

[41] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

[42] Jatlaoui TC and Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 94 (2016) 605–611. https://www.ncbi.nlm.nih.gov/pubmed/27234874

[43] Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception. 2016 Jul;94(1):52-7. https://pubmed.ncbi.nlm.nih.gov/27000996/

pregnancy is unknown.[44] In an randomised pharmacodynamic study with 70 obese participants, doubling the levonorgestrol dose did not result in improved inhibition of ovulation: proportion of women with no follicle rupture within 5 days of levonorgestrol administration was similar with standard and double dosing [45]. This suggests that doubling dose may not be sufficient to improve efficacy of oral levonorgestrol in obese women, although this study did not directly explore effect of double dosing on subsequent rates of pregnancy. Therefore, until new evidence emerges the recommendation of double-dosing of levonorgestrel amongst obese/overweight women will be retained, aligned with Guidelines.[5] Available evidence also suggests that the effectiveness of the copper IUCD is not affected by body weight or BMI. The copper IUCD is therefore the preferred method for emergency contraception in the obese.[46]
Level of Evidence: Guidelines

The caution box in the STG was amended as follows:

CAUTION
Emergency contraceptive tablets must be taken as soon as possible, preferably within 72 hours of unprotected intercourse, and not later than 5 days.
Enzyme inducers (including efavirenz and carbamazepine) cause a significant reduction in levonorgestrel concentrations.
Women on these medicines should preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.
Women > 80 kg or BMI ≥ 30 should also preferably have copper IUCD inserted or alternatively double the dose of levonorgestrel.

10.5.3 NON OCCUPATIONAL POST EXPOSURE PROPHYLAXIS, INADVERTENT NON-OCCUPATIONAL

Inadvertent (non-occupational) exposure: *Editorial amendment*
The list of examples pertaining to inadvertent, non-occupational exposure was transferred from Section 10.5.2 Non occupational post exposure prophylaxis, sexual assault to Section 10.5.3 Non occupational post exposure prophylaxis, inadvertent non-occupational as not relevant to sexual exposure. The following text was moved from Section 10.5.2 to Section 10.5.3:

Inadvertent (non-occupational) exposure to infectious material from HIV sero-positive persons often requires clinical judgement and includes:
» human bites (requires hepatitis B, but not HIV prophylaxis)
» sharing of needles during recreational drug use
» consensual sexual exposure, burst condoms
» contact sports with blood exposure

[44] FSRH Guideline (April 2019) Overweight, Obesity and Contraception. BMJ Sex Reprod Health. 2019 Apr;45(Suppl 2):1-69. https://pubmed.ncbi.nlm.nih.gov/31053605/
[45] Edelman, Alison B. MD, MPH; Hennebold, Jon D. PhD; Bond, Kise PSM; Lim, Jeong Y. PhD; Cherala, Ganesh PhD; Archer, David F. MD; Jensen, Jeffrey T. MD, MPH Double Dosing Levonorgestrel-Based Emergency Contraception for Individuals With Obesity, Obstetrics & Gynecology: June 9, 2022 - Volume - Issue - 10.1097/AOG.0000000000004717 doi: 10.1097/AOG.0000000000004717
[46] Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, Murphy PA. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception. 2014 Mar;89(3):222-8. https://pubmed.ncbi.nlm.nih.gov/24332433/

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

TITLE: DOLUTEGRAVIR IN PREGNANT WOMEN AND WOMEN OF CHILD-BEARING POTENTIAL (WOCP)

Date: 17 June 2021

Key findings

- This review is a second update of the 2017 review. In this update, we review evidence of safety and efficacy of dolutegravir (DTG) containing ART, compared with efavirenz (EFV) containing ART in women of child-bearing potential (WOCP) and pregnant women.
- The estimate of prevalence of neural tube defects (NTDs) in infants born to women on dolutegravir (DTG) has declined since the original safety signal from the Botswana Tsepamo study as more data in that cohort has accrued. The current estimate is approximately 2 NTDs per 1000 births.
  - In the July 2020 update from this study there were 7 NTDs in 3591 births with DTG exposure (0.19%; 95%CI 0.09% to 0.40%), and 8 NTDs in 10,958 births with EFV exposure from conception (0.07%; 95%CI 0.03% to 0.17%).
  - There was no significant difference in NTD prevalence between DTG and EFV at conception (difference 0.12%; 95%CI -0.001% to 0.33%).
  - In HIV-uninfected women there were 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)
- The Dolphin 2 study, randomised pregnant women of 28 or more weeks to DTG (n=129) or EFV (n=128)
  - HIV viral load < 50 copies/mL at delivery: DTG 74.2% vs EFV 42.7%
- A multicentre trial, including 643 pregnant women at 14-28 weeks gestation, randomised women to DTG/FTC/TAF (n=217), DTG/FTC/TDF (n=215) or EFV/FTC/ TDF (n=211).
  - At delivery, more participants were virally suppressed at in the combined DTG containing groups than the EFV group, 98% vs 91%, difference 6·5% (95% CI 2.0% to 10.7).
  - Neonatal mortality was highest in the EFV group: DTG/FTC/TAF group 1% vs DTG/FTC/TDF 2% vs EFV 5%.
  - Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion) was lower in the DTG/FTC/TAF group: DTG/FTC/TAF group 24% vs DTG/3TC/TDF 33% vs EFV 33%
  - Preterm deliveries were most common in the EFV group: DTG/FTC/TAF 6% vs DTG/3TC/TDF 9% vs EFV 12%.
  - Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.
- In a RCT comparing TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV, 10% of women were obese at baseline. At 48 weeks 20% of women on TAF/FTC/DTG , 11% on TDF/FTC/DTG 9% on TDF/FTC/EFV had new onset obesity.
- In an observational cohort study in Botswana including data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC, mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%). MTCT rates were similar when ART was started during pregnancy DTG 8/999 vs EFV 8/883 Risk difference 0.11% (95% CI -0.79 to 1.06%).

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC 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 PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms
(Refer to appendix 2 for the evidence to decision framework)

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Monitoring and evaluation considerations

Research priorities

BACKGROUND

The first review of dolutegravir (DTG) was conducted by the Primary Health Care (PHC) Expert Review Committee (ERC) in 2017, and was updated in 2019. In 2019 NEMLC recommended that DTG be included in South African antiretroviral therapy (ART) guidelines as a first-line agent, based on evidence of superior efficacy to efavirenz, and higher barrier to emergence of resistance. The paucity of evidence for use in pregnancy was noted, and NEMLC recommended that DTG should be avoided in early pregnancy and in women of child-bearing potential (WOCP) who are not on reliable contraception because of concerns regarding increased risk of neural tube defects (NTDs) with periconception and early first trimester exposure (Zash, Makhema, and Shapiro 2018).

A pooled sequence analysis found pretreatment HIV-1 Drug Resistance in less than 5% of antiretroviral therapy-naive adults in South Africa before 2009 (Chimukangara et al. 2019). By 2015 this had increased to 11·9% (95% confidence interval (CI) 9.2 to 15.0) in 2015. Pooled annual prevalence of non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance pre-therapy increased from below 5% in 2011 to 10.0% (95% CI 8.4 to 11.8) by 2014. In the 2017 national HIV household survey, 15 % of respondents not on ART, and 56% of ART defaulters had NNRTI resistance (Moyo et al. 2020) The increased prevalence of pre-treatment NNRTI resistance may put both antiretroviral naïve and previously ART exposed patients initiated on efavirenz at increased risk of treatment failure.

Phillips et al (2019) modelled risks and benefits of tenofovir (TDF), lamivudine (3TC), and DTG in sub-Saharan patients, including WOCP (Phillips et al. 2019). The model included drug resistance, efficacy in reducing viral load and clinical treatment outcomes, as well as potential for NTDs (based on the 12 times higher risk of NTD with DTG compared to non-DTG ART in the first Tsepamo report). In the model, benefits of averted disability adjusted life years (DALYs) of transitioning to a regimen of TDF, 3TC, and DTG for all people on ART, considerably outweighed the risks. The model projected that the reduction in risk of mother-to-child transmission was greater than the increased risk of NTD with the TDF, 3TC, and DTG for all on ART. Substantially more DALYs were averted with the TDF, 3TC, and DTG for all individuals on ART. Additionally, DTG for all on ART regimen was cost-effective in most (83% of setting scenarios) compared with the same regimen dependent on viral load suppression and intention to have more children (cost effective in <1% of setting scenarios). Dugdale *et al*., (2019) modelled three outcomes in South African women with HIV (age 15 to 49 years) starting or continuing first-line ART, and their children: (1) maternal and infant mortality, (2) sexual and pediatric HIV transmissions, and (3) NTDs (estimate of increased risk from 1st Tsepamo report) for three strategies i.e. (1) DTG for all, (2) EFV for all, or (3) EFV without contraception or DTG with contraception (WHO approach at the time)(Dugdale et al. 2019). Combined deaths among women and children were lowest with DTG (358,000) compared to the WHO approach (362,800) or EFV (367,300). DTG averted 13,700 women's deaths (0.44% decrease) compared to EFV. Over the 5-year time horizon DTG increased total pediatric deaths compared to EFV by 4,400 and WHO by 4,100 due to more NTDs. However, the combined maternal and infant mortality was more favorable for DTG compared to EFV because DTG resulted in 3.1-fold fewer deaths (13,700) among women. Clinical outcomes for woman were better in the DTG group than the EFV group (70,400 more women were virologically suppressed and 39,700 fewer severe opportunistic infections). DTG was superior to the WHO approach for all outcomes in woman. DTG resulted in fewer projected sexual transmissions to partners over five years compared with EFV or the WHO approach. Similarly, DTG averted more pediatric HIV transmissions compared to EFV and the WHO approach; 7,100 and 6,700 respectively. Compared to EFV, DTG resulted in 2,100 fewer non-NTD related deaths but 6,400 more projected NTDs. In the WHO approach most conceptions occurred among women on EFV resulting in the outcomes for WHO group being like the EFV group. Overall, in the DTG group, 3,000 more children were alive and HIV-free at five years. Both of these modelling analyses suggested considerable benefit from DTG containing ART, despite including a higher risk of NTD than more recent data suggests.

In 2019, the World Health Organisation updated its guidance to recommend DTG containing regimens as the preferred option for first line and second-line antiretroviral treatment for all populations, including pregnant women and WOCP(World Health Organization 2019).

This update focuses on use of DTG in women of childbearing potential, including pregnancy women, and reviews evidence that has emerged since the last NEMLC recommendation in 2019.**Error! Bookmark not defined.**

QUESTION: In pregnant woman and WOCP living with HIV taking first-line antiretroviral therapy, is dolutegravir more efficacious, better tolerated, and of similar safety compared to efavirenz?

METHODS

We updated the previous NEMLC DTG review (26 January 2017 (first update 11 February 2019). The original review and 2019 update included data on all adult patients. In this update, we focused on first-line treatment with DTG in pregnant woman and WOCP. We searched from June 2018, to give 6 months of overlap with the previous update. For the search strategy see Appendix 1. PubMed and the Clinical Trials.gov Register were systematically searched on 3 June 2021 (Appendix 1). Records retrieved from PubMed were extracted to Covidence while the Clinical Trials.gov results were extracted to Microsoft Excel. Screening of titles and abstracts were conducted in duplicate (ND, MR) with disagreement handled through discussion and a tie breaker (LF). Full texts were reviewed in duplicate (ND, LF) with disagreements handled by a tie breaker (KC). Records were excluded based on eligibility criteria. Data from relevant articles was extracted by 5 reviewers (KC, ND, RdW, LF, MR) into a narrative table of results.

Eligibility criteria for review

Population: Pregnant HIV positive women, WOCP

Intervention: DTG-containing ART

Comparators: EFV-containing ART

Outcomes: Viral suppression rates, mortality, development of resistance mutations, rates of perinatal transmission, adverse pregnancy outcomes (miscarriages, preterm delivery, small for gestational age, still birth, neonatal death), congenital anomalies, terminations for congenital anomalies, neural tube defects adverse events, adverse reactions.

Study designs:

- Efficacy: Systematic Reviews of Randomized Control Trials (RCTs), RCTs
- Harms: RCTs, prospective cohort studies, retrospective cohort studies, pregnancy registries, systematic reviews

RESULTS

RESULTS OF THE SEARCH

The search retrieved 134 PubMed records after removing duplicates. The Clinical Trials.gov search retrieved 13 records none of which were relevant as the studies did not meet the eligibility criteria, were ongoing or had already been retrieved in the PubMed search. After reviewing titles and abstracts in duplicate, we excluded 95 records, leaving 39 studies for full text review. After full text review, 18 reports met our inclusion criteria, of which 2 were already included in the 2019 update of this review. We also included an AIDS 2020 conference abstract and presentation which presented updated results for one of the included studies.

Table 1 reports the main characteristics and outcomes reported in the 16 study reports included in this update Table 2 summarizes the 2 papers reported initial findings from the Tsepamo study in Botswana (the previous update did not include summary tables for included studies of safety in pregnancy, so we have included these summaries to give context to the updates of this study data included in this review update). Table 3 outlines excluded studies with reasons for exclusion.

DESCRIPTION OF INCLUDED STUDIES

We included 3 RCTs comparing DTG and EFV-based ART initiated in pregnancy (Waitt et al. 2019; Kintu et al. 2020; Lockman et al. 2021).

We included 2 RCTs comparing DTG and EFV-based ART in non-pregnant adults, including WOCP (Venter et al. 2020; Venter et al. 2019; NAMSAL ANRS 12313 Study Group 2019).

We included data on pregnancy adverse outcomes from a network meta-analysis which included DTG and EFV-based ART(Kanters et al. 2020).

We included a cohort study comparing fetal biometry between DTG and EFV exposed pregnancies in Botswana(Banda et al. 2020), and a comparison of rates of gestational diabetes with DTG and EFV exposure from the same cohort(Mmasa et al. 2021)

We included two updates of the Tsepamo study analysis of prevalence neural tube defects (NTDs) with exposure to DTG and EFV at time of conception(Zash et al. 2019; Zash et al. 2020). We included a report of prospective surveillance for NTDs set up by the Botswana ministry of health in response to the initial Tsepamo signal (Raesima et al. 2019). We included an analysis of rates of NTDs within the Canadian perinatal HIV Surveillance programme (Money et al. 2019), and retrospective cohort analysis of prevalence of NTDs with DTG exposure conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021).

We included a cohort study comparing weight gain in pregnant women taking DTG and EFV(Caniglia et al. 2020).

We included an observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020).

Randomised controlled trials of DTG in pregnancy

The DolPHIN-1 study randomised HIV positive ART naive women in South Africa and Uganda at 28 to 36 weeks of gestation to DTG -containing ART (n=29) or EFV-containing ART (n=31) (Waitt et al. 2019). The primary endpoint was pharmacokinetics of DTG in women and breastfed infants.

- DTG resulted in significantly faster viral suppression compared to EFV, median time to viral load (VL)<50 copies/mL 32 vs 72 days.

The DolPHIN-2 study randomised HIV positive women of 28 weeks or more weeks gestation to DTG (n=129) or EFV based regimen (n=128) (Kintu et al. 2020) . Co-primary endpoints were virological suppression at 1st post-partum visit, and drug related adverse effects. Median duration of ART was 55 days (IQR 33 to 77)

Efficacy DTG vs EFV:

- HIV viral load < 50 copies/mL at delivery: 74.2% vs 42.7%
- Median time to VL < 50copies/mL: 28 days (95% CI 28–34) vs 82 days (55–97)
- Median time to VL < 1000 copies/ml: 7 days (7–20) vs 23 days (21–27)

Adverse events DTG vs EFV:

- Drug-related serious adverse event (SAE 0 in 1 (<1%) vs 0)
- Stillbirths: 3/124 (2·2%) vs 1/120 (<1%)
- No significant difference in proportion of preterm /late-preterm births
- Congenital abnormalities did not differ between groups. No NTDS in either arm
- 4/123 (3%) infant deaths vs 2/119 (2%)

Mother to child transmission:

- 3 transmissions in DTG group, zero in EFV group

Lockman et al (IMPAACT) randomised 643 pregnant women from 9 countries at 14 to 28 weeks gestation and with less than 14 days of ART exposure to DTG/ emtricitabine(FTC)/ tenofovir alafenamide (TAF) (n=217), DTG/FTC/ tenofovir dispoproxil fumerate (TDF) (n=215) or EFV/FTC/ TDF (n=211) (Lockman et al. 2021). The primary efficacy outcome was the proportion of participants with viral suppression, (HIV-1 VL< 200 copies per mL), at or within 14 days of delivery. VL available for 605 (94%) participants. Median weight was 63 kg (56 to 73) and median BMI was 25 (95% CI 22 to 28).

Efficacy

- 98% in the combined DTG-containing groups had VL suppression at delivery compared with 91% in the EFV group, estimated difference 6.5% (95% CI 2.0 to 10.7).

Adverse events

- Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion): DTG/FTC/TAF group 24% vs DTG/FTC/TDF 33% vs EFV/FTC/TDF 33%
- Preterm deliveries in DTG/FTC/TAF 6% vs DTG/FTC/TDF 9% vs EFV/FTC/TDF 12%.
  - Significant difference between DTG/FTC/TAF and EFV groups, difference –6·3% (95%CI –11·8 to –0·9)
- Neonatal mortality higher in EFV group: DTG/FTC/TAF 1% vs DTG/FTC/TDF 2% vs EFV/3TC/TDF 5%.

Weight gain

- Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.

RANDOMISED TRIALS THAT INCLUDED WOMEN OF CHILDBEARING POTENTIAL

Venter et al (ADVANCE study) randomised 1053 participants, 59% of them female, median age 32 years, to DTG plus emtricitabine (FTC) plus tenofovir dispoproxil fumerate (TDF) or DTG plus emtricitabine (FTC) plus tenofovir alafenamide (TAF) or TDF plus FTC plus EFV(Venter et al. 2019). EFV-based ART was standard of care in 2017 when the trial commenced. Primary end point was virological suppression (<50 copies/mL at week 48.

Efficacy

- HIV-1 viral load< 50 copies/mL at 48 weeks: 84% in the TAF-DTG group, 85% in the TDF-DTG group, and 79% in the EFV group (meeting non-inferiority definition). Efficacy results are not presented disaggregated by sex.

Safety

- Deaths: 1 in TAF-DTG, 1 in TDF-DTG, 2 in EFV
- Weight increase (both lean and fat mass) was greatest in the TAF-DTG group and among female patients. At 48 weeks 26/133 (20% of TAF-DTG group, 13/123 (11%) of the TDF-DTG group, and 9/104 (9%) of the EFV group had new onset obesity. 10% of women in the study were obese at baseline.
- 1 discontinuation in TAF-DTG group because of asymptomatic increase in aminotransferases.
- 8 EFV-linked discontinuations because of adverse reactions: 5 with liver dysfunction of which 2 symptomatic, 2 rash, 1 with neuropsychiatric adverse effects.
- No resistance to integrase inhibitors identified in patients failing the DTG-containing regimens. Four patients on EFV and 1 on DTG were found to have new NNRTI resistance.

Pregnancy outcomes

- There were 78 pregnancies (12.5% of included women), 50 on DTG-containing ART. There were no NTDs. There was 1 neonatal death (TAF/FTC/DTG arm) and 1 stillbirth in the EFV arm.

Week 96 of the IMPAACT study(Venter et al. 2020)

Efficacy

- Viral suppression to <50 copies/mL was 79%, 78%, and 74% in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- Two patients in the TDF-DTG group and 16 patients in the EFV group had resistance mutations (none to INSTIS).

Safety

- Amongst the 623 women in the study, 28%, 18%, and 12% developed obesity in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- By 96 weeks, there were 29, 25, and 34 pregnancies, with 6, 2, and 9 miscarriages in women on TAF-DTG, TDF-DTG, and EFV, respectively.

The NAMSAL study randomised 613 participants, 65.9% of them female, to DTG or EFV 400mg-based ART(NAMSAL ANRS 12313 Study Group 2019).

- Efficacy results are not presented disaggregated by sex. Primary end point was proportion of participants with VL<50 copies/mL at week 48. This was achieved in 74.5% of the DTG group and 69% of the EFV group, difference 5.5%, (95% CI -1.6 to 12.7).
- 6.2% of female participants fell pregnant during the trial, including 13 in the DTG group, all of whom were born live and without congenital anomalies.
- There was more weight gain in the DTG group than the EFV group overall.
  - Weight gain of 10% or more was observed in 147/379 (38.8%) of women vs 44/192 (22.9 %) of men.

ADVERSE PREGNANCY OUTCOMES AND CONGENITAL ANOMALIES

The Kanters et al network meta-analysis (which included data from Tsepamo and several smaller studies) found no significant differences between DTG and EFV in terms of rates of preterm birth, low birth weight, stillbirth, small for gestational age, or congenital anomalies.

A prospective cohort study (Tshilo Dikotla) in Botswana enrolled 469 pregnant women between 16 and 36 weeks gestation, including 182 on TDF.FTC/ DTG, 127 on TDF/FTC/ EFV based regimen and 160 who were HIV negative Banda et al. 2020). There was no difference in fetal biometry between the 3 groups (Banda et al. 2020).

RISK OF NEURAL TUBE DEFECTS

Tsepamo study

The risk period for neural tube defects (NTDs) is the first 28 days post-conception. Botswana transitioned to DTG in 2016. The Tsepamo cohort study in Botswana prospectively captured birth outcomes at 8 hospitals from August 2014. In 2018, they compared outcomes in women commencing DTG or non-DTG containing-ART prior to conception- this analysis was included in the 2019 update of this review. At that stage, 89,064 births had accrued of which 88,755 (99.7%) had a surface examination at birth.

- Prevalence of neural tube defects was higher in those exposed to DTG periconception than those on non-DTG containing ART: 4/426 (0.94%) versus 14/11300 (0.12%).
- At the time of this first analysis, there were no NTDs in 2812 women who started DTG during pregnancy.
- NTDs in 61 of 66057 (0.09%) infants born to HIV negative women (Zash, Makhema, and Shapiro 2018).

Tsepamo included 8 public hospital maternity wards from August 2014 to June 2018. Ten additional sites were added between July 2018 and March 2019, giving coverage of approximately 70% of births in Botswana.

Tsepamo 2019 update (Zash et al. 2019)

As at March 31, 2019 there were 119,477 deliveries, 119,033 (99.6% had an infant surface examination. This included 1683 on DTG from conception, 14792 on non-DTG ART from conception, of which 7959 were on EFV from conception, and 3840 who started DTG pregnancy. There was data from 89272 HIV negative mothers.

- There were 98 NTDs (0.08% of deliveries)
- The prevalence of NTDS remained slightly higher in association with DTG exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries).
  - 5 NTDs in 1683 deliveries in mothers taking DTG at conception, (0.30% of deliveries; 95% CI 0.13 – 0.69). (2 myelomeningocele, 1 anencephaly, 1 encephalocele, 1 iniencephaly)
  - 15 NTDs in 14792 women taking non DTG ART from conception (0.10%; 95% CI 0.06 – 0.17) infants. Prevalence difference was 0.20 (95% CI 0.01 – 0.59) vs the reference DTG from conception.
  - 3 NTDs in 7959 women taking EFV from Conception: (0.04%; 95% CI 0.01 – 0.11) infants. Prevalence Difference: 0.26 (95% CI 0.07 – 0.66) vs the reference DTG from conception
  - 1 NTD in 3840 women who commenced DTG during pregnancy (0.03%; 95% CI 0.00 – 0.15) infants. Prevalence Difference: 0.27 (95% CI 0.06 – 0.67) vs the reference DTG from conception
  - 70 NTDs in 89372 HIV negative women (0.08%; 95% CI 0.06– 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 – 0.62) vs the reference DTG from conception

Tsepamo 2020 update(Zash et al. 2020)

An update was presented at the AIDS conference in July 2020, including data from 39,200 additional births, which included 1908 additional DTG conception exposures.

- Since August 2014, 158,244 deliveries; 153,899 (97.2%) with infant surface exam
- 126 NTDs (0.08%, 95%CI 0.07%,0.09%)
- Prevalence of NTDs in infants born to women on DTG decline since the original safety signal. Prevalence estimate seems to be stabilizing at approximately 2 per 1000.
  - No significant difference between DTG and non-DTG- ART at conception (0.09% difference; 95%CI -0.03%, 0.30%).
  - No significant difference between DTG and EFV at conception (0.12% difference; 95%CI -0.001%, 0.33%).
  - DTG at conception, 7/3591 with NTD (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly
  - Non DTG-ART 21/19 with NTD,361 (0.11%; 95%CI 0.07%, 0.17%)
  - EFV from conception 8/10,958 with NTD (0.07%; 95%CI 0.03%, 0.17%)
  - DTG started in pregnancy 2/4,581 with NTD (0.04%; 95%CI 0.1%, 0.16%)
  - HIV-uninfected women 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)

In response to the signal from the Tsepamo study, the Botswana ministry of health expanded surveillance for NTDs to 22 non-Tsepamo facilities (Raesima et al. 2019). Midwives conducted surface examination of liveborn and stillborn infants.

- From October 2018- 31 March 2019 there were 3076 deliveries, of which 2328 (76%) HIV negative, 742 (24%) HIV positive, and 6 (<1%) HIV unknown.
- There were 544 (73% with ART exposure at conception, of which 152 (28%) were DTG exposed.
- There were 3 confirmed/probable NTDs, 1 in DTG exposed, 2 in HIV negative.

- NTD prevalence with DTG exposure was 0.66% (95%CI 0.02-3.69)
- NTD prevalence in babies born to HIV negative mothers was 0.09% (95% CI 0.01-0.31)
- Difference between DTG based ART and non-DTG based NTD prevalence was 0.66% (95% CI -0.48-3.63)

This study lacked power for precise estimate of NTD prevalence with DTG-exposure at conception.

The Canadian perinatal HIV Surveillance programme collects data on pregnant women living with HIV (WLWH), and their babies (Money et al. 2019).

- Between 2007 and 2017, 85 of 2423 WLWH (3.5%, 95% CI 2.85–4.36%) had non-chromosomal congenital anomalies.
- Rates of congenital anomalies were similar between women who were on ART in their first trimester (3.9%, CI 1.7–7.6%) and those without 1st trimester ART exposure (3.9%, 95% CI 2.6–5.6%)
- 4/80 (5.0%, 95% CI 1.4–12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies, none were neural tube defects (95% CI0.00–3.10%). There were very few first trimester DTG exposures and this study lacked power to detect rare events such as NTDs. The cohort included women on efavirenz, but rate of congenital anomalies not reported for EFV-containing ART.

A retrospective cohort analysis was conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021). Women with DTG exposure within 8 weeks of estimated conception between Jan 1, 2017, and May 31, 2018 were matched 3:1 with pregnant women exposed to EFV between Jan 1, 2015, and May 31, 2018. Primary outcomes were NTD and a composite measure of NTD, stillbirth, or miscarriage.

- 382/ 1427 were exposed to DTG within 8 weeks of estimated date of conception. During pregnancy, 183 (48%) of 382 DTG-exposed and 465 (44%) of 1045 EFV-exposed women received folic acid supplementation.
- There were no NTDs in either DTG-exposed (0, 95% CI 0–0.0010) or efavirenz-exposed groups (0, 95% CI 0–0·0036).
- There were 23 (6%) stillbirths or miscarriages in 384 DTG-exposed fetuses and 28 (3%) in the 1068 EFV-exposed fetuses (p=0·0037).
- After study closure, 2 NTDs in fetuses with periconception DTG exposure were reported to public health officials. Estimate of NTD incidence incorporating these cases and the estimated number of additional DTG-exposed pregnancies between Jan 1, 2015, and Feb 28, 2019, was 1.8 (95% CI 0·5–6·7) per 1000 DTG-exposed pregnancies.

MOTHER TO CHILD TRANSMISSION

An observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020). The analysis included data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC.

- Mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%).
- MTCT rates were similar when ART was started during pregnancy DTG 8/999 (0.80%, 95% CI 0.35 to 1.57%) vs EFV 8/883 (0.91, 95% CI 0.39 to 1.78%) Risk difference 0.11% (95% CI -0.79 to 1.06%).
- Most transmissions were in women starting ART <90 days before delivery: DTG 4/8 vs EFV 6/9.

ADVERSE EVENTS FROM NON-RANDOMISED STUDIES

<u>Weight gain in mothers during pregnancy</u>

Weight gain during pregnancy was explored in pregnant women commencing DTG or EFV-based ART before 17 weeks of gestation in the Tsepamo cohort in Botswana(Caniglia et al. 2020). The analysis included 1683 women on DTG, 1464 on EFV, and 21 917 HIV uninfected women.

- Women on DTG and EFV both gained less weight during pregnancy compared to uninfected people.
- DTG was associated with decreased risk of insufficient weight gain.
- EFV was associated with less risk of excessive weight gain.

<u>Gestational diabetes</u>

The Tshilo Dikotla prospective cohort in Botswana screened 468 pregnant women for gestational diabetes using a 75g oral glucose tolerance test, of which 486 were PLWHA(Mmasa et al. 2021). Women known to be diabetic were excluded.

- 8.4% of women had gestational diabetes, this was similar between PLWHA and HIV negative women.
- PLWHA taking DTG-containing ART had lower risk of gestational diabetes than those on EFV; 6.1% vs 13.5%.

- adjusted odds ratio 0.40, 95%CI 0.18 to 0.92), in a model including age, BMI, gravidity, CD4 count, and whether or not patient was on ART at the time of conception.

CONCLUSION

The Tsepamo study (Botswana) surveying birth outcomes in infants born to woman on DTG regimens provided the signal of harm (increased NTDs) in 2018(Zash et al. 2018). The updates in 2019 and 2020 have been reassuring - as more data has accrued the difference observed in the rate of NTDs between women taking DTG-based regimens at the time of conception compared to other antiretroviral drugs has shrunk, and is no longer significantly different(Zash et al. 2019; Zash et al. 2020). The current estimate of prevalence of NTDs in pregnancies with DTG exposure at time of conception in Botswana is 2 per 1000. The estimated prevalence in a recent retrospective cohort study in Brazil was similar (1.8 per 1000 DTG exposed pregnancies), but the study is underpowered and the estimate lacks precision(Pereira et al. 2021).

DTG causes more rapid viral load suppression in pregnancy than efavirenz. This could potentially reduce the risk of vertical HIV transmission in mothers who are initiated on DTG treatment in late pregnancy. However, rates of MTCT were similar for DTG and EFV-based ART in a cohort study in Botswana, and transmission event were rare(Davey et al. 2020).

In RCTS, both pregnant and non-pregnant women gained more weight in the DTG than the EFV arm(Venter et al. 2019; Venter et al. 2020; Lockman et al. 2021), especially in those on concomitant tenofovir alafenamide. The mechanism postulated for this difference is impaired weight gain in individuals taking EFV who have the slow metaboliser cytochrome P450 2B6 genotype, which is common in African patients(Griesel et al. 2020). Slow metabolizers have higher EFV concentrations than extensive metabolizers, which may result in increased mitochondrial toxicity from EFV. In the Tsepamo study, DTG in pregnancy was associated with decreased risk of insufficient weight gain and EFV was associated with less risk of excessive weight gain (Caniglia et al. 2020). However, women on either drug gained less weight than HIV negative women.

Based on the benefits to women in terms of viral suppression and reduced risk of drug resistance, and the fact that the risk of neural tube defects in infants exposed to dolutegravir in early pregnancy is no longer significantly different to those exposed to non-dolutegravir-based regimens, dolutegravir should form part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of childbearing potential, even if not on reliable contraception.

Reviewers: Karen Cohen, Natasha Davies, Lee Fairlie, Milli Reddy, Renee de Waal.

Declaration of interests: KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town), ND (Anova Health Institute), MR (Better Health Programme, South Africa), RdW (Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town) have nothing to declare in respect of dolutegravir in HIV. LF (WITS RHI) co-authored HIV publications of which some are included in this review, ND (Anova Health Institute) received a scholarship from Gilead to attend the International AIDS Society conference, in Mexico City in July 2019 and discloses involvement with Southern African HIV Clinicians' Society in development and updating of adult ART guidelines and statements pertaining to the use of dolutegravir in pregnant women and women of child-bearing potential following release of the Tsepamo data update July 2020.

Acknowledgements: Tamara Kredo and Joy Oliver (Cochrane South Africa) supported the systematic literature search. Trudy Leong (National Department of Health) provided support for this review.

Table 1. Characteristics of included publications

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Banda FM et al. 2020.	Design: Prospective cohort study (Tshilo DIkotla cohort), Botswana, August 2016-May 2019 Funding: National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (R01DK109881) COI: none declared	• Pregnant WLHIV and pregnant women without HIV • Between 16-36 weeks gestation • Women on TDF/FTC with DTG or EFV during pregnancy • 469 women enrolled • 182 on DTG based regimen • 127 EFV based regimen • 160 HIV negative Exclusions • Multiple gestations Fetal demise	**Exposures** TDF/FTC/DTG TDF/FTC/EFV	• Head circumference, Biparietal diameter, Abdominal circumference, Femoral length Z scores • Measurements taken during single ultrasound performed in second trimester • Association of in-utero HIV/ART exposure with each fetal biometric Z score	Median Age: EFV based: 32 years (older) DTG based 28 years p<0.01 HIV negative: 24 years Parity: EFV based: 3 DTG based 2 p<0.01 HIV negative: 1 Tertiary education: EFV based: 7.9% DTG based 14.3% p<0.01 HIV negative: 33.1% Gestational age: HIV positive: 28 weeks HIV negative: 26 weeks p<0.01 Viral load and CD4 values similar in both ART groups No significant differences in Z scores between groups, even with adjustments for maternal age, height, education level, parity, alcohol use in pregnancy	• No significant differences in fetal biometry between DTG exposed, EFV exposed and HIV unexposed fetuses Limitations: • Single study site • Small sample size • Single ultrasound (not longitudinal) • No birth follow up to confirm any congenital anomalies at birth Conclusion: • Reassuring results supporting safety of use of DTG in pregnancy.
Caniglia et al, 2020	National birth outcomes surveillance, Botswana (Tsepamo) Funding: NIH No COI declared	Inclusion: • Pregnant women • First time ART initiators • ART start before 17 weeks' gestation • DTG- or EFV-based regimens • HIV-uninfected group for comparison DTG: n=1 683 EFV: n=1 464 HIV-uninfected: n=21 917	EFV DTG HIV-uninfected	**Primary** • Weekly weight gain from 18±2 weeks' gestation to 36±2 weeks' gestation • Total weight gain over 18 weeks **Secondary** • Weight gain >0.59 kg/week • Weight gain <0.18 kg/week (above 2 categories based on Institute of Medicine recommendations) • Weight loss	**Weekly weight gain**, mean (SD) kg: EFV: 0.31 (0.23) DTG: 0.35 (0.22) HIV-uninfected: 0.44 (0.23) Adjusted mean difference versus EFV (95% CI) kg: DTG: 0.05 (0.03 to 0.07) HIV-uninfected: 0.12 (0.10 to 0.14) **Total weight gain**, mean (SD) kg: EFV: 5.3 (4.35) DTG: 6.27 (3.96) HIV-uninfected: 7.95 (4.11) Adjusted mean difference versus EFV (95% CI) kg: DTG: 1.05 (0.61 to 1.49) HIV-uninfected: 2.31 (1.85 to 2.77)	• HIV-uninfected women were more likely to be nulliparous and primigravid than HIV-infected women; women on DTG were less likely to have CD4 measured, had lower CD4 counts, and initiated ART earlier than those on EFV; other baseline characteristics were similar. • Analyses adjusted for age, CD4, employment, education, parity, gravidity, marital status, site, smoking, alcohol use, pre-pregnancy weight, baseline weight, gestational age at ART initiation, medical history (results very similar for crude analyses). • The authors state that the clinical significance of their findings is uncertain, but that lower weight gain is associated with increased risk of preterm birth and lower birth weight, and higher weight gain is associated with pregnancy and delivery complications. They also conclude that HIV and/or ART might impact weight gain.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					Weekly weight gain >0.59 kg, adjusted risk ratio versus EFV (95% CI): EFV: 9.1% DTG: 12.9%, 1.44 (1.11 to 1.87) HIV-uninfected: 23.1%, 2.41 (1.81 to 3.21) **Weekly weight gain <0.18 kg**, adjusted risk ratio versus EFV (95% CI): EFV: 27.7% DTG: 20.2%, 0.73 (0.63 to 0.86) HIV-uninfected: 11.1%, 0.48 (0.41 to 0.57) **Weight loss**, adjusted risk ratio versus EFV (95% CI): EFV: 9.4% DTG: 4.4%, 0.43 (0.28 to 0.67) HIV-uninfected: 2.2%, 0.30 (0.19 to 0.47)	
Crowell et al, 2020.	Prospective cohort study (22 sites in United States including Puerto Rico; from 2007 to 2017) Follow-up duration: Youth followed up to 18 years Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute of Dental and Craniofacial Research, the National Institute of Allergy and Infectious Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, Office of AIDS Research, the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism, through Cooperative agreements	Sample size: 3747 children - HIV-exposed but uninfected (CHEU) and exposed *in utero* to ARVs Two cohorts: • Static cohort (enrolled from 2007–2009; 1–12 years; participated in prior studies with available pregnancy and birth data) • Dynamic cohort (enrolled during gestation or within 1 week after birth) Patient characteristics: 48% girls 68% black and 31% Hispanic. Maternal tobacco use: 17% Maternal alcohol use: 8% Maternal marijuana use: 8% Maternal Cocaine/opiates use: 3% Inclusion criteria: CHEU enrolled by 1 April 2017 and had a study visit for neurologic trigger assessment by 1 August 2017 (triggers for potential neurologic diagnoses defined as a febrile or afebrile	Exposures: •ARVs (3747) •EFV vs control (166 vs 3487) •DTG vs control (94 vs 688)	**Primary outcome:** Neurological adverse event associated with ARVs (febrile or afebrile seizure, microcephaly, or other neurologic or ophthalmologic disorders)	**Primary outcome:** All ARVs • ***Neurological cases:*** ○ 231/3747 (6.2%, 95% CI 5.4% to 7.0%) over a median follow-up of 4.3 years (IQR: 1.4–7.0). • ***Neurologic diagnoses*** ○ Microcephaly: 25.1% ○ Febrile seizure: 17.6% ○ Eye-related abnormalities (esotropia, exotropia,strabismus, ptosis, nystagmus, ambylopia, and optic nerve abnormalities: 16.5% ○ Nonfebrile seizure:13.5% **Sub-analyses:** EFV vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), adjusted RR (aRR) 1.53 (95% CI 0.94 to 2.51), p=0.090 ○ At conception: aRR = 1.92 (95% CI 1.09 to 3.36) DTG vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), aRR 43 (95% CI 0.75 to 7.84), p=0.14 ○ At conception: aRR = 3.47 (95% CI 0.74 to 16.36) ○ At conception: aRR = 2.95 (95% CI 0.79 to 11.1)	• An observational study to determine neurological harms associated with ARVs • As models were restricted to children born after 2007 for darunavir and raltegravir, after 2011 for rilpivirine, and after 2013 for DTG and elvitegravir – due to drug approval dates, the study cohorts for DTG (n=94) was not comparable in size to EFV (n=166) • Of 3747 children enrolled, 94 lacked detailed ARV information and was excluded from the analysis – missing information for 2.5% of study population; some concern of selection bias • Maternal substance use was through self-reporting questionnaires that may have contributed to reporting bias at baseline. • Assessors in the panel that classified neurological triggers in CHEU, were blinded to the ARVs their mothers used. • Information on the controls are not clearly reported. • Sensitivity analyses were done to account for possible bias, adjusting for confounders such as maternal factors (age, race, ethnicity, chronic health conditions, obstetrical complications, and substance use), birth cohort (<2011, 2011–2014, 2015–2017), and family/household factors (socioeconomic status, household income level, and caregiver education level). • Adjusting for confounders, resulted in persistent association of EFV exposure with a risk for neurological adverse events.

<table>
<tr><th>Citation</th><th>Study design</th><th>Population</th><th>Exposures and control</th><th>Outcomes</th><th>Effect sizes</th><th>Comments</th></tr>
<tr><td></td><td>with the Harvard T.H. Chan School of Public Health and the Tulane University School of Medicine.

Declarations: E.G.C. holds stock in Abbot and AbbVie. All other authors report no conflicts of interest.</td><td>seizure, microcephaly, or other neurologic or ophthalmologic disorders)

Exclusion criteria:
Neurologic diagnoses determined to be secondary to events occurring after birth (e.g. postnatal meningitis, trauma)</td><td></td><td></td><td></td><td>• In utero DTG exposure was associated with an increased risk of a neurologic diagnosis but imprecision was high, due to the small number of exposed cases.</td></tr>
<tr><td>Davey et al, 2020</td><td>National surveillance, Botswana.
Early Infant Treatment Study screened infants for HIV at 20% of delivery facilities in the country; those in Tsepamo registry were linked to establish ART regimen

Funding: NIH
No COI declared</td><td>Total infants screened:
n=10 622

Liked to Tsepamo:
Exposed to DTG: n=1 235
Exposed to EFV: n= 2 411
Exposed to other ART: n=1 246
Exposed to multiple ART regimens: n=37
No ART exposure: n=135</td><td>DTG
EFV
Other regimens
No ART</td><td>MTCT rates</td><td>MTCT, n, % (95%CI):
Overall
DTG: 8/1 235, 0.64 (0.28 to 1.27)
EFV: 9/2 411, 0.37 (0.17 to 0.71)
Other regimens: 2/1283, 0.16 (0.02 to 0.56)
No ART: 6/135, 4.44 (1.65 to 9.24)

ART initiated before pregnancy
DTG: 0/213, 0 (0 to 1.72)
EFV: 1/1 497, 0.07 (0 to 0.37)

ART initiated during pregnancy
DTG: 8/999, 0.80 (0.35 to 1.57)
EFV: 8/883, 0.91 (0.39 to 1.78)
Risk difference: 0.11%, 95% CI -0.79 to 1.06</td><td>• Those on ‘other’ ART regimens were less likely to be diagnosed during pregnancy, less likely to start ART during pregnancy, and had a longer duration of ART exposure than those on EFV or DTG.</td></tr>
<tr><td>Kanters et al, 2020</td><td>Systematic review and network meta-analysis

Funding: WHO HIV department</td><td>For pregnancy outcomes the authors included 54 references from 35 studies. Studies included RCTs, comparative and non-comparative observational cohorts, and population-level surveillance or registries.</td><td>DTG
EFV</td><td>Preterm birth
Low birth weight
Small for gestational age
Congenital abnormalities
Still birth
Maternal death
Neonatal death
MTCT
NTDs</td><td>Pregnancies with pre- and post-conception exposures to DTG versus EFV
<table><tr><th>Outcome</th><th>Odds ratio</th><th>95% credible interval</th></tr><tr><td>Preterm</td><td>0.99</td><td>0.85 to 1.14</td></tr><tr><td>LBW</td><td>0.93</td><td>0.80 to 1.08</td></tr><tr><td>SGA</td><td>0.93</td><td>0.80 to 1.07</td></tr><tr><td>CA</td><td>1.06</td><td>0.40 to 2.86</td></tr><tr><td>Stillbirth</td><td>1.03</td><td>0.72 to 1.46</td></tr><tr><td>M. death</td><td>0.09</td><td>0.00 to 39.39</td></tr><tr><td>N. death</td><td>1.03</td><td>0.65 to 1.62</td></tr><tr><td>MTCT</td><td>6.87</td><td>0.74 to 39.10</td></tr></table>
Any adverse birth outcome
DTG: 33.2%
EFV: 35%

Neural tube defects
DTG: 6/1835
EFV: 3/8220
Risk difference 0.29% (95% CI 0.10 to 0.68)</td><td>• Most data on pregnancy outcomes is from Tsepamo (the other studies were relatively small in comparison).
• The NTD estimate is based on Tsepamo and the Raesima et al study only, because of variability in folic acid supplementation and background event rates. Tsepamo data up until March 2019 was included.
• Other outcomes (efficacy) were reported overall, and not for women separately.</td></tr>
</table>

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Kintu et al, 2020. DolPHIN-2 Study Group.	Randomised, open-label trail in Cape Town, South Africa (8 PHC facilities) and Kampala, Uganda (8 PHC antenatal facilities); from January to August 2018 Funding: Funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.	Sample size: 268 screened, 128 randomised to DTG (n=129) or EFV based regimen (n=128) Inclusion criteria: Woman≥ 18 yrs with untreated but confirmed HIV, positive pregnancy test, ± gestation of ≥28 weeks, provided consent. Exclusion Criteria: ART in the preceding year or ever received integrase inhibitors; documented virological failure of a non-nucleoside containing ART; previous EFV toxic events or clinical history precluding randomisation; estimated glomerular filtration rate <50 mL/min; haemoglobin <8.0 g/dL; decompensated liver disease or alanine aminotransferase > 5x upper limit of normal (ULN); or alanine aminotransferase >3x ULN and bilirubin >2x ULN (with >35% direct bilirubin); severe pre-eclampsia; medical, psychiatric, or obstetric condition that might affect participation; receiving any drugs significantly interacting with EFV or DTG within the preceding 2 weeks. *In June 2018, protocol amended to exclude patients with pretreatment HIV VL of < 50 copies/ml	**DTG (50 mg) or EFV** plus TDF (300 mg) plus FTC (200 mg) in South Africa or 3TC (300 mg) in Uganda) Both administered as single tablet once daily.	**Primary outcomes:** **Efficacy:** HIV viral load < 50 copies/mL at birth **Safety:** Frequency of drug-related adverse events. **Secondary Outcomes:** -viral load of <1000 copies/mL at birth, -occurrence of mother-to-child transmission -safety & tolerability of DTG in mothers and breastfed infants	**Primary outcomes:** *DTG Vs EFV :* **HIV viral load < 50 copies/mL @ birth (mothers):** 89/120 (74·2%) vs 50/117 (42·7%) **Median time to VL < 50copies/mL:** 28 days (95% CI 28–34) vs 82 days (55–97) **Median time to VL < 1000 copies/ml:** 7 days (7–20) vs 23 days (21–27) **Frequency of drug-related adverse events:** • ≥1 SAE: 30 (22%) vs 14 (11%) • ≥1 drug-related SAE 1 (<1%) vs 0 • ≥1 or immune reconstitution inflammatory syndrome (IRIS)-related SAE 1 (<1%) vs 0 **Secondary outcomes:** **Viral load of <1000 copies/mL at birth:** 112/120 (93%) vs 96/117 (82%) **Mother-to-child transmission:** 3 transmissions in DTG group **Safety & tolerability of DTG in mothers and breastfed infants:** Higher frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG vs EFV: • Stillbirths: 3/124 (2·2%) vs 1/120 (<1%). • 123 vs 119 live births • Median gestation at birth of 39 weeks (IQR 37·3–40·3) - both groups • No significant difference in proportion of preterm, late-preterm births, frequency of serious adverse events, infant birthweights • Congenital disorders (umbilical hernias, birth marks, skin dimples, acrochordon, heterochromia iridis, laryngomalacia, strabismus, talipes, cleft palate, and polydactyly) did not differ between groups • 0 neural tube defects • 4/123 (3%) infant deaths vs 2/119 (2%)	• Women on DTG regimen more likely to achieve VL< 50 copies per/ml / less likely to have a VL of ≥50 copies/mL) at time of birth (initiated in the third trimester) • Undisclosed ART unlikely - mothers with a VL < 50 copies/mL excluded at baseline • 7 & 28 day visit days used as a measure of time from randomization to viral load suppression which might have biased the true time of viral load suppression (but same in both groups) • For this population, peripartum HIV transmission strongly correlated with prevailing maternal VL therefore DTG regimens might reduce HIV transmission around birth & potentially during breastfeeding, compared with EFV regimens • 3 HIV-infected infants were likely to have had in-utero infections, but peripartum transmission cannot be excluded because infants not tested within 2 days of birth • Higher proportion of mothers who received DTG had serious adverse events Finding driven by a higher overall frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG, who had prolonged pregnancy beyond term. • 4 stillbirths - related to obstetric & severe maternal infection. • Sample size not large enough to study differences in infant transmissions, but powered to detect virological superiority before or at time of birth (best validated proxy for vertical HIV transmission) • Results were robust in sensitivity analysis. The DolPHIN-2 results strongly support global transition to DTG use in first-line ART
Kouafack et al, 2019. New Antiretroviral and Monitoring	Open-label, multicenter, randomized, phase 3 noninferiority trial (48 weeks – July 2016 – August 2017).	Sample size: N=613 Patient characteristics:	**Exposures:** •DTG regimen •EFV (400-mg) regimen	**Primary outcome:** •Proportion of participants with a VL of <50 copies/ml at week 48 **Secondary outcomes:**	**Patient Characteristics:** -Baseline values balanced between groups. Median age - 37 years. **65.9% (n=404) of the participants were women.** Median baseline VL - 5.3 log_{10} copies/ml. 66.4% -baseline VL of at least 100,000 copies/milliliter. Median CD4+ T-cell count	• Study included both men and women (no pregnant women) • Results showed noninferiority of DTG to EFV400 with regard to viral suppression at week 48.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Strategies in HIV-Infected Adults in Low-Income Countries **(NAMSAL)**	Study Setting: Cameroon Two Arms: -n=310 DTG -n=306 EFV -Randomization, 1:1 ratio, to receive DTG/EFV400 Follow-up duration: follow-up until week 96	Adults, **both males & females**, HIV – infected, HIV treatment naïve. 66.4% had a viral load (VL) of ≥100,000 copies/ml milliliter, & 30.7% had a viral load of ≥500,000 copies/ml) Inclusion criteria: ≥18 years of age, had not received ART, and had HIV-1 group M infection with a viral load of at least 1000 copies/ml. WOCP had to agree to use effective contraceptive methods. Exclusion criteria: Pregnant, breast-feeding, severe hepatic impairment, renal failure, severe psychiatric illness, & unstable tuberculosis coinfection Funding: Supported by Unitaid and the French National Agency for AIDS Research (ANRS 12313) Declarations: None		•VL with other thresholds: - VL <200 copies/ml; & virologic failure, defined by the WHO as VL>1000 copies/ml after reinforcement of adherence) at weeks 24 & 48 •Drug resistance. •Change from baseline in the CD4+ T-cell count at weeks 24 & 48 •Morbidity (WHO stage) •Adherence to treatment, -Safety, & Patient-reported outcomes (depression, anxiety, & stress; HIV treatment symptoms, including EFV related symptoms; & quality of life)	was 281/cubic mm. Adherence to treatment was similar in both groups. **Primary Outcome:** Efficacy: DTG vs EFV **(males and females)** Week 48, n=231/310 (74.5%) vs n=209/303 (69.0%) - viral load < 50copies/ml. Difference between treatment groups was 5.5 % points (95% confidence interval [CI], −1.6 to 12.7), meeting criterion for noninferiority (P<0.001) but not superiority (P = 0.13). **Results Reported for Women: DTG vs EFV Women & viral suppression:** (n=157/197 [79.7%] vs. n=147/207 [71.0%]; difference, 8.7 % points; 95% CI, 0.3 to 17.0) (favoring DTG). **Secondary Outcomes:** -25/404 (6.2%) women became pregnant - (13 DTG vs 12 EFV400) **Delivery:** 4 (30.7%) vs (66.7%) **Miscarriage:** 6 (42.2%) vs 4(33.3%) **Voluntary abortion:** 3 (23.1) vs (0 (0%) -All deliveries (n=12) born alive, without reported congenital abnormalities. Significantly > median increase in body weight in DTG group vs EFV group (5.0 kg [interquartile range, 1.0-8.0] vs. 3.0 kg [interquartile range, 0.0 - 7.0], P<0.001). Weight gain of at least 10% observed in > women vs men (147/379 [38.8%] vs. 44/192 [22.9%], P<0.001)	• Adherence to treatment was high on the basis of scores on a validated questionnaire but this measure has limitations. • The relationship between DTG and obesity as well as risks associated with childbearing potential need exploration
Lockman et al, 2021.	Design: Multicentre, phase 3, open-label, randomised controlled trial Recruitment: Jan 19, 2018, to Feb 8, 2019 Funding: National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health	Study population: Pregnant women gestation 14-28 weeks, less than 14 days of ART in sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe 643 pregnant women enrolled: 217 to the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate(TAF) group, 215 to the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (TDF) group, and 211 to the	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Primary efficacy outcome: proportion of participants with viral suppression (< 200 copies per mL, at or within 14 days of delivery prespecified non-inferiority margin of –10% in the combined dolutegravir-containing groups versus the efavirenz-containing group Primary safety outcomes: compared pairwise among treatment	Enrolment: • Median gestational age 21·9 weeks (IQR 18·3–25·3) • median HIV-1 RNA concentration 902·5 copies/mL (152·0–5182·5 • 181 [28%] of 643 participants HIV-1 VL <200 copies/mL) • Median CD4 count was 466 cells per µL (308–624) Delivery • VL available for 605 (94%) participants. • 395 (98%) of 405 participants in the combined dolutegravir containing groups had VL	• Study pause May 18 and Oct 12, 2018 due to NTD signal in Tsepamo • Direct comparison between DTG-based and EFV SOC-based ART in pregnancy, 14-28 weeks • Superior virological efficacy in DTG-containing regimen compared to efavirenz-containing regimen • DTG/DTC/TAF has lowest composite pregnancy outcomes • Efavirenz higher neonatal death

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		efavirenz, emtricitabine, and TDF group Inclusion criteria: • ≥18 years • 14-28 weeks gestation • HIV-1 infection Exclusion criteria • Previous ART (except 14 days for current pregnancy) • Psychiatric illness • Multiple pregnancy • Known fetal anomaly		groups, occurrence of a composite adverse pregnancy outcome (ie, either preterm delivery, the infant being born small for gestational age, stillbirth, or spontaneous abortion) in all participants with a pregnancy outcome, and the occurrence of grade 3 or higher maternal and infant adverse events in all randomised participants.	suppression at delivery compared with 182 (91%) of 200 participants in the efavirenz group (estimated difference 6·5% [95% CI 2·0 to 10·7], p=0·0052 • Slightly fewer women in DTG/FTC/TAF arm with composite adverse pregnancy outcomes (52 [24%] of 216) DTG/3TC/TDF (70 [33%] of 213; estimated difference –8·8% [95% CI –17·3 to –0·3], p=0·043) or the TEE group (69 [33%] of 211; –8·6% [–17·1 to –0·1], p=0·047) • Infants with grade 3 outcomes not different between groups • Preterm delivery lower in DTG/FTC/TAF group (12 [6%] of 208) compared to efavirenz group (25 [12%] of 207; –6·3% [–11·8 to –0·9] p=0·023) • Neonatal mortality significantly higher in efavirenz group (ten [5%] of 207 infants) DTG/FTC/TAF two [1%] of 208; p=0·019) DTG/3TC/TDF (three [2%] of 202; p=0·050)	
Money D, et al; 2019.	Canadian Perinatal (CPHSP) HIV Surveillance Programme Study Setting: 22 sites, 19 HIV referral health centres, 3 health departments from all Canadian provinces & territories). Captures ± 95% of all pregnancies in WLWH, and 100% where infant is infected with HIV Funding: No specific funding secured for the analysis. Public Health Agency of Canada (PHAC) had no role in this study's conduct and design; collection, management, analysis, or write up. Declarations: Data presented annually at the Canadian Conference on HIV/AIDS Research and other meetings.	Live-born infants born in Canada to WLWH between 2007 and 2017	ART (at conception & pregnancy)	Congenital anomalies	**From 2007 to 2017** **Patient Characteristics:** - 2591 live infants born to WLWH - 2423 had congenital anomaly data - 81.9% deliveries at term - Mean gestational age 38.2 weeks. - 2306 of the mothers had timing of HIV diagnosis known; 272 (11.8%) diagnosed with HIV during pregnancy, 40 (1.7%) at or after childbirth, 1994 (86.5%) before pregnancy. 4/80 (5.0%, 95% CI 1.4 to 12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies vs 3/46 (6.5%, 95% CI 1.4 to 17.9%) on EFV - Anomalies for DTG included urinary tract (n = 2), circulatory system (n = 1) & musculoskeletal system (isolated polydactyly, n = 1). -NTDs on DTG (0/117; 95% CI 0.00 to 3.10%) -3 cases of NTDs since 2007, overall incidence rate of 0.12% (95% CI 0.03 to 0.36%) – none on DTG or EFV	• Small sample size due to limited use of DTG in women of reproductive age in Canada • Looked at both DTG before conception and those initiated on DTG after conception • 5% of infants of Canadian women living with HIV on DTG at conception had congenital anomalies; none had neural tube defects

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Mmasa et al, 2021	Prospective cohort, Botswana Funding: NIH No COI declared	Pregnant women ≥18 years, 16-36 weeks' gestation, without diabetes n=486 DTG: 197 EFV: 126 HIV-uninfected: 163	DTG EFV HIV-uninfected	Gestational diabetes diagnosed on oral glucose tolerance test at 24-28 weeks' gestation, or earliest prenatal visit if after 28 weeks	**Gestational diabetes** DTG: 6.1% EFV: 13.5% aOR: 0.34 (95% CI 0.12 to 0.97), adjusted for age, BMI, gravidity, CD4, ART started before pregnancy aOR: 0.40 (95% CI 0.18 to 0.92), also adjusted for duration of ART exposure HIV-uninfected: 7.4% aOR versus HIV-infected on ART: 0.83 (95% CI 0.37 to 1.85), adjusted for age, education, BMI, and gravidity	• Those on EFV, compared to those on DTG, were older, were more likely to be on ART at conception, and had a longer duration of ART exposure; other baseline characteristics were similar

Pereira GFM, et al. 2021.	Design: retrospective, observational, national, cohort study
	
	Funding:
	Brazilian Ministry of Health and the United States' National Institutes of Health
	
	COI:
	BES, FM, CCMcG, and JLC declare receiving grants from the US National Institutes of Health. All other authors declare no competing interests.
		• 1468 women included
		• 382 any DTG exposure
		• 41 any RTG exposure
		• 1045 only EFV exposure All women with possible prenatal dolutegravir exposure from 1 Jan 2017 to 31 May 2018
		• All women potentially raltegravir exposed at conception (same timeline)
		• A pool of Efavirenz exposed women, geographically matched (comparative cohort)
		
		Inclusions:
		• Aall women with reported pregnancy and an immediately previous dolutegravir-based regimen
		• All women of childbearing age receiving dolutegravir who switched to a pregnancy-recommended regimen for unclear reasons
		• All women receiving dolutegravir who received injectable or oral solution zidovudine or nevirapine (or both) as an indication of a birth event.
		• Any DTG, EFV or RTG use at any point during the periconception window (8 weeks before or after
			Exposures:
			DTG
			RTG
			EFV
			
			Cases reviewed on 3:1 ratio for EFV:DTG
				Primary outcomes
				• NTD
				• Composite measure of NTD, stillbirth >22 weeks, miscarriage < 22 weeks
					Mean age:
					EFV only: 28.5 yrs
					DTG exposure: 26.6yrs
					
					CD4 count:
					EFV only: 604 cells/ml
					DTG exposure: 530 cells/ml
					
					Undetectable VL
					EFV only: 465 (75%)
					DTG exposure: 139 (36%)
					
					Primary Outcome:
					• No NTDs among birth outcomes of women periconceptionally exposed to DTG or EFV
					• Estimated NTD prevalence = 0
					• Composite outcomes (NTD+miscarriage+stillbirth):
					  ○ DTG-exposed: 25/384 = 7%, 95% CI 0.04 to 0.094
					  ○ EFV-exposed: 43/1068 = 4%, 95% CI 0.030 to 0.054
					• Miscarriages 6% vs 3% DTG vs EFV
					• No differences with sensitivity analyses and additional of prenatal variables for the composite outcome
					• 2 additional NTDs were reported just after the end of the study (May 2019).
					• This updated the incidence of NTD in DTG exposed women to 0.0018 - Equal to 1.8/1000 DTG exposed pregnancies (95% CI 0. To 6.7).
					
					Other outcomes:
					No significant differences in preterm labour, premature rupture of membranes, pre-eclampsia, diabetes/gestational diabetes, gestational
						• Sensitivity analyses conducted to see if any difference if women exposed to more than one ART during periconception period
						
						Conclusion
						• No occurrences of NTDs in Brazilian national cohort study of women with periconceptional DTG exposure
						• After inclusion of 2 NTDs reported after study close, incidence remained well below 1%
						• Increased rate of miscarriages in women exposed to DTG but finding inconclusive as attenuated once prenatal variables added to model
						
						Limitations:
						• Likely underpowered to detect difference in NTD risk because of rarity of event
						• Uncertainty of timing of conception relative to ART exposure
						• Many women received multiple ART regimens during periconception period
						• Retrospective analysis can introduce bias
						• Missing data for some women (birth outcome, ART exposure, timing of conception)

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		estimated date of conception) Exclusions: • Women found not pregnant, with unknown birth outcome or ART exposure and with no periconceptional exposure to DTG/RTG/EFV • Women whose estimated date of conception could not be calculated			hypertension or average weight gain per week between the groups	
Raesima MM et al. 2019.	National surveillance, Botswana	Inclusion: • All pregnancies with live-born or stillborn delivered beyond 24 weeks • 22 non-Tsepamo facilities • Delivered from October 2018- 31 March 2019 Population: • 22 sites, Botswana • 3076 deliveries • 2328 (76%) HIV negative • 742 (24%) HIV positive • 6 (<1%) HIV unknown • 544 (73%) ART exposed at conception • 152 (28%) DTG exposed	DTG-based regimen exposure Non-DTG based regimen exposure	Data collected: Surface examination (midwife) Maternal HIV status ART exposure at conception Folate exposure NOT collected Primary outcome: Estimated prevalence of NTD according to maternal HIV status and ART exposures, including DTG	• 3 confirmed/probable NTDs amongst all infants • 1 in DTG exposed, 2 in HIV negative • DTG prevalence 0.66% CI 0.02 to 3.69 • HIV negative prevalence 0.09% CI 0.01 to 0.31 • Difference between DTG based ART and non-DTG based NTD prevalence = 0.66% CI -0.48 to 3.63	• Slightly higher prevalence of NTDs among HIV positive mothers with DTG exposure at time of conception • Magnitude of NTD risk with DTG exposure at time of conception remains <1% Limitations • Short duration of study • NTD rare event, only 3 cases • Unstable prevalence estimates resulted from small sample size
Venter WDF et al. 2019.	Design: Phase 3, investigator-led, open-label, randomized trial Funding: U.S. Agency for International Development, Unitaid, and the South African Medical Research Council. Investigational drugs were donated by Gilead Sciences and ViiV Healthcare. COI: WDFV reports lecture fees and travel support from Roche, grant support,	Study population: South Africans ≥ 12 years Randomized to triple-therapy combination of emtricitabine (FTC) and DTG plus either of TAF (TAF-based group) or tenofovir disoproxil fumarate (TDF) (TDF-based group) — against the local standard-of-care regimen of TDF–FTC–efavirenz (standard-care group). Population 1053 patients randomised February 2017 through May 2018.	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Efficacy: The primary end point was the percentage of patients with a 48-week HIV-1 RNA level of less than 50 copies per milliliter, non-inferiority margin -10 percentage points Safety data at 48 weeks also reported	Baseline characteristics: • Mean age 32 years, mean CD4 count 337 cells/mm^3. Week 48: **Efficacy** • Percentage of patients with an HIV-1 RNA level of < 50 cps/ml 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group • DTG-containing regimens were noninferior to the standard-care/EFV regimen. • The number of patients who discontinued the trial regimen was higher in the standard-care group than in the other two groups.	• DTG-based regimens non-inferior to EFV-based SOC • TAF-based regimen less bone mineral and renal issues compared to TDF

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	advisory board fees, and provision of drugs from Gilead Sciences, advisory board fees from ViiV ealthcare, lecture fees from Merck and Adcock Ingram, and lecture fees and advisory board fees from Johnson & Johnson and Mylan; MM honoraria and conference attendance support from Johnson & Johnson, Cipla, and ViiV Healthcare, honoraria, advisory board fees, and conference attendance sponsorship from Gilead Sciences, advisory board fees from AbbVie, and conference attendance sponsorship from Merck; EA receiving advisory committee fees from ViiV Healthcare.	> 99% of the patients were Black, 59% female Inclusion criteria: • ≥12 years • no receipt of ART in the previous 6 months, • creatinine clearance of more than 60 ml per minute (>80 ml per minute in patients < 19 years • HIV-1 • VL ≥ 500 copies/ml Exclusion criteria: Pregnancy, current TB treatment			• In the per-protocol population, the standard-care regimen had equivalent potency to the other two regimens. **Safety** • The TAF-based regimen had less effect on bone density and renal function than the other regimens. • Weight increase (both lean and fat mass) was greatest in the TAF-based group and among female patients (mean increase, 6.4 kg in the TAF-based group, 3.2 kg in the TDF-based group, and 1.7 kg in the standard-care group). • No resistance to integrase inhibitors identified in patients receiving the DTG-containing regimens.	
Venter WDF, et al. 2020	ADVANCE study, as above. 96 week results	As above The trial included 623 women	As above	96-week outcomes reported separately for women: Viral suppression<50 copies/mL Obesity Pregnancy outcomes	**Women:** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 168/214 (79%) TDF/FTC/DTG: 154/208 (74%) TDF/FTC/EFV: 147/201 (73%) **Obesity** TAF/FTC/DTG: 42/151 (28%) TDF/FTC/DTG: 23/129 (18%) TDF/FTC/EFV: 15/125 (12%) **Pregnancy outcomes** TAF/FTC/DTG: 29 pregnancies in 26 women; 6 miscarriages (21%); 1 infant death TDF/FTC/DTG: 25 pregnancies in 24 women; 2 miscarriages (8%); 0 infant deaths TDF/FTC/EFV: 34 pregnancies in 32 women; 9 miscarriages; 0 infant deaths **Overall (all trial participants, not only women):** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 276/351 (79%)	• Subgroup analyses were presented for women overall, not necessarily only WOCP. The overall mean age of the study population was 32 years (range 13-62). • In the viral suppression results, patients with no viral load results were considered failures – the proportions with missing VL data weren't reported for women specifically, but were 18%, 18%, and 23% for the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV groups overall.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					TDF/FTC/DTG: 275/351 (78%) TDF/FTC/EFV: 258/351 (74%) **Drug discontinuation due to AE** TAF/FTC/DTG: 2 TDF/FTC/DTG: 1 TDF/FTC/EFV: 10 **Resistance mutations** In those with VF and a baseline and 96-week resistance data available, 2/16 patients in the TDF/EFV/DTG group had NRTI resistance mutations (M184V); and 13/21 patients in the EFV group had various mutations. No other resistance mutations were reported.	
Waitt et al, 2019.	Open – Label Randomized Control Trial (Uganda & South Africa between 9th March 2017 & 16th January 2018). Randomized 1:1 to DTG or EFV) containing ART until 2 weeks post-partum (2wPP). Study Setting: Mulago National Referral Hospital, Kampula, Uganda Gugulethu Community Health Care Centre, Cape Town Two Arms: -(n=29) pregnant women on DTG -(n=31) pregnant women on EFV Follow-up duration: 6 months until postpartum	Sample size: N=60 mothers initiating therapy in third trimester were randomised to receive EFV based (standard of care) or DTG regimen Patient characteristics: 100% Black African, HIV – infected treatment – ART treatment naïve pregnant women (28–36 weeks of gestation, age 26 (19–42), weight 67kg (45–119). Inclusion criteria: informed consent, comply with scheduled visits, treatment plans, other required study procedures, aged atleast 18 years, untreated HIV in late pregnancy, 28–36 weeks of gestation Exclusion criteria:Pregnant mothers who received ARVs in the previous 6 months, had ever received integrase inhibitors; anaemic (hb <than	Exposures: •DTG - ART (50mg) consisting of tenofovir disoproxil fumarate with either lamivudine/emtricitabine •EFV – ART (SOC) consisting of once daily EFV; tenofovir disoproxil fumarate with either lamivudine/ emtricitabine	Primary outcome: Pharmacokinetics of DTG in HIV infected women during the third trimester of pregnancy & after two weeks postpartum as defined by the area under the concentration-time curve of DTG between 0 & 24 hours (AUC_{0-24}). Secondary outcomes: Cord to maternal plasma DTG ratio (C:M ratio), maternal breast milk to plasma DTG ratio (M:P ratio), & infant DTG concentrations at maternal steady state & at 1, 3 & 3 days following discontinuation	DTG vs EFV No differences in baseline maternal age (median 27 vs 25 years), gestation (31 vs 30 weeks), weight (65 vs 68 Kg), obstetric history, viral load (4.5log10 copies/mL both arms) & CD4 count (343 vs 466 cells/mm^3). 28 DTG vs 31 EFV live births. Median (range) gestational age at delivery DTG 39 (35–43) weeks, vs EFV 38 (34–42) weeks. No significant differences for birth weight (3kg DTG) vs 3kg EFV) **Primary Outcome:** **Pharmacokinetic Data: Predose:** n=29 -intensive PK sampling. n=1 excluded - non – adherent due to undetectable DTG concentrations. n=28 in third trimester, Cmax, C_{24} & AUC_{0-24} (geometric mean, range) were 2435 (1462–3986) ng/mL, 642 (188–3088) ng/mL and 35322 (19196–67922) ng.h/mL respectively. **Pharmacokinectic Data: Post – Dose:** n=23 - intensive post-partum PK sampling following delivery; n=6 - sampling before 7 days postpartum excluded. n=17 sampled at a median of 10 (range 7–18) days following delivery, with C_{max}, C_{24} & AUC_{0-24} of 2899 (1397–4224) ng/mL, 777 (348–1210) ng/mL and 40127 (22795–59633) ng.h/mL respectively. No significant differences in the geometric mean ratios of C_{max}, C_{24} & AUC_{0-24} in 14	• DolPHIN-1 confirms that the superior virological responses observed with DTG-based combination therapy in non-pregnant adults is also seen in pregnancy. Differences show that DTG has a role in prevention of mother to child transmissions among women who are initiated on ART in the 3rd trimester. • Standard DTG dosing potentially safe & beneficial in late pregnancy. • High infant exposures to DTG in utero, & in first week of life, may offer additional prophylaxis against HIV transmission • **Discontinuations and Resistance:** n=1 participant in the DTG-ART arm discontinued for lack of efficacy after week 4 - undetectable DTG concentrations in 3rd trimester & admitted nonadherence. Another individual in the DTG-ART arm experienced resistance & had a viral load of 2217 copies/mL at the post-partum visit. Multi-class resistance demonstrated on baseline sample (M41L, L201W, T215Y, M184V, Y188L, M46I, I84V, I54V, V32I, V82A, L33F, K43T) & attained virological suppression after transition to a regimen containing DTG & ritonavir-boosted darunavir. The n=2 that discontinued prior to the post-partum visit for other reasons (1 in each arm) both had a VL <200 copies/mL at the point of discontinuation (4 weeks).

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	Funding: DolPHIN-1 was funded by ViiV Healthcare through an investigator-initiated study scheme https://www.viivhealthcare.com/en-gb/advancinghiv- science-and-rd/we-collaborate-to-innovate/, award number 205785 awarded to SK. CW is funded by a Wellcome Postdoctoral Training Fellowship for Clinicians WT104422MA https:// wellcome.ac.uk/funding/schemes/postdoctoralresearch-training-fellowships-clinicians. Declarations: ML declared research grants from ViiV, Janssen and personal fees from Mylan.	8 g/dL); had elevations in serum levels of alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or ALT >3xULN and bilirubin >2xULN (with >35% direct bilirubin); active hepatitis B; history/ clinical suspicion of unstable liver disease (presence of ascites, encephalopathy, coagulopathy, hyperbilirubinaemia, oesophageal/gastric varices/persistent jaundice); severe pre-eclampsia, or other pregnancy related events such as renal/ liver abnormalities (grade 2/ above proteinuria, elevation in serum creatinine (>2.5 x ULN), total bilirubin, ALT or AST); / clinical depression/ evidence of suicidal ideation.		of DTG. Viral load (VL) in at delivery & the change in VL over the first four weeks of therapy. Two approaches to hanndle missing VL data : 1) missing VL = failure [>50 copies/mL] (M = F) in which subjects with missing data at two weeks post-partum were assessed as experiencing failure, and 2) missing viral load equals excluded (M = X)	mothers who underwent sampling in the third trimester of pregnancy & at post-partum visit. **Cord & Maternal Blood Samples**: Paired cord & maternal blood samples available in 16 mother-infant pairs. 1 individual, both samples were < limit of quantitation (BLQ), & non-adherence was reported. n= 15 samples - median C:M ratio of 1.21 (range 0.51–2.11). **DTG levels in Breastmilk:** DTG detectable in breast milk with a BM_{max} of 84.6 (43.8–171) ng/mL and a BM_{trough} of 22.3 (3.0–64.3) ng/mL. DTG detectable in plasma of breastfed infants with an $Infant_{max}$ of 66.7 (21–654) ng/mL and an $Infant_{trough}$ of 60.9 (16.3–479) ng/mL - median of 10 (range 7–18) days of age. Infant plasma to maternal plasma (IP:MP) ratios were 0.03 (0.00–0.06) at $Infant_{max}$ and 0.08 (0.00–0.17) at $Infant_{trough}$. After discontinuation of maternal DTG, detectable in 100%, 80% and 80% breastfed infants at 48, 72 & 96 hrs after final maternal dose, respectively. **Secondary Outcomes** Safety: Both regimens tolerated, no significant differences with adverse effects. • DTG-ART - 25 (86.2%) - caesarean section & 4 (13.8%) normal delivery • EFV-ART -21 (67.7%) caesarean section & 10 (32.3%), normal delivery. **Adverse events**: n=3 **Serious adverse events**: n=1 -2 in the DTG arm: i) low HB - unrelated, & ii) hospitalisation due to maternal malaria & urinary tract infection with raised ALT, bilirubin, hypokalemia & hyponatremia. (The mother took herbal medications at onset of event). Stillbirth related to umbilical cord around neck – not DTG related. EFV arm - 1 SAE - preeclampsia - unrelated. No **congenital anomalies** in DTG arm vs 2 in EFV arm (n=1 syndactyly -unlikely to be related to EFV and n=1 with multiple skeletal, limb & cardiac malformations (possibly TARP [Talipes equinovarus, Atrial septal defect, Robin sequence,	• DTG showed superior virological suppression vs EFV among women commencing ART in late pregnancy • Two limitations: (1) related to the requirement to initiate immediate EFV-ART at HIV diagnosis, and the need to limit exposure of newborn and breastfed infants to what was not a recommended first-line regimen during the study period. Randomisation would have balanced effect in the two arms. • Some women attended postpartum visit earlier than the proposed 2 weeks, potentially minimising differences in DTG exposure as a result of late pregnancy.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					& Persistent left superior vena cava] syndrome) - not related EFV. n=1 infant in EFV arm - neonatal sepsis-not related to EFV, recovered **Virologic Response** **Proportion undetectable:** 69.0% (20/29) and 74.1% (20/27) DTG arm vs 38.7% (12/31) & 40.0% (12/30) EFV arm, in the M= F & M= X analyses, respectively. In analyses of log_{10} HIV RNA at 2wkPP, VL was significantly lower in the DTG arm vs EFV-ART (p = 0.007). n=3 discontinued prior to the 2-week post-partum visit (2 DTG-ART & 1 EFV-ART).	
Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, *et al*. 2019 Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. doi: 10.1056/NEJMoa1905230. Epub 2019 Jul 22. PMID: 31329379; PMCID: PMC6995896.	Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014 to June 2018, 10 adiitonal sites added between July 2018 and March 2019	Sample Size: From August 15, 2014, to March 31, 2019, 119,477 deliveries, 119,033 (99.6%) had an infant surface examination Patient Characteristics: Baseline characteristics (delivery site, history of epilepsy, diabetes, and weight during pregnancy) between ART exposures groups were negligible. Folate supplementation and timing similar across the treatment groups. Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Disclosures: Submitted with the publication	Exposures: •DTG from conception: (1683) •Any other non DTG ART from conception: (14792) •EFV from Conception (7959) •DTG started during pregnancy: (3840) HIV negative Mothers (89372)	**Primary Outcome:** Prevalence of neural-tube defects (NTDs) among infants	**Tsepamo Results from August 2014 to March 2019:** 98 NTDs (0.08%) **DTG from conception:** 5/1683 (0.30%; 95% CI 0.13 to 0.69) infants **Any other non DTG ART from conception:** 15/14792 (0.10%; 95% CI 0.06 to 0.17) infants. -Prevalence Difference: 0.20 (95% CI 0.01 to 0.59) vs the reference DTG from conception **EFV from Conception:** 3/7959(0.04%; 95% CI 0.01 to 0.11) infants. -Prevalence Difference: 0.26 (95% CI 0.07 to 0.66) vs the reference DTG from conception **DTG started during pregnancy**: 1/3840 (0.03%; 95% CI 0.00 to 0.15) infants. -Prevalence Difference: 0.27 (95% CI 0.06 to 0.67) vs the reference DTG from conception **HIV Negative:** 70/89372 (0.08%; 95% CI 0.06 to 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 to 0.62) vs the reference DTG from conception	• Prevalence of NTDs higher in association with DTG treatment at conception than with non DTG based ART at conception/ other types of ART.
Zash et al., 2020 Update on neural tube	Birth Outcomes Surveillance in government	Since August 2014 total of 158,244 deliveries; 153,899 (97.2%) had an evaluable infant surface exam, with	Exposures:	Prevalence of neural-tube defects (NTDs) among infants	**126 (0.08%, 95%CI 0.07%,0.09%) NTDs identified to date in cohort overall** **Cumulative results by group**	• After a decline since the original safety signal, the prevalence of NTD among infants born to women receiving DTG at conception seems to be stabilizing at approximately 0.2%.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
defects with antiretroviral. **This update from the Tsepamo study was presented at AIDS 2020. Abstract number OAXLB0102** ***Tsepamo Study*** https://www.natap.org/2020/IAC/IAC_112.htm	maternity sites, Botswana, since August 2014 August 2014 – July 2018 – 8 Sites (±45% of all births in Botswana) July 2018 to September 2018 – expanded to 18 surveillance sites (±72% of all births in Botswana) Since September 2019, maintained surveillance at 16 sites (±70% of all births in Botswana) Originally designed to assess NTD in infants whose mothers were exposed to exposed to EFV DTG was rolled out in Botswana in Mid 2016 Funding: National Institutes of Health &NICHD	1067 LATE BREAKER ABSTRACTS AUTHOR INDEX PUBLICATION ONLY ABSTRACTS	• DTG from conception: (1683) • Any other non DTG ART from conception: (14792) • EFV from Conception (7959) • DTG started during pregnancy: (3840) • HIV negative Mothers (89372)		**DTG at conception**, 7/3591 NTDs (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly. **Non DTG-ART** NTD in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) EFV from conception 8/10,958 (0.07%; 95%CI 0.03%, 0.17%) DTG started in pregnancy 2/4,581 (0.04%; 95%CI 0.1%, 0.16%) HIV-uninfected women. 87/119,630 (0.07%; 95%CI 0.06, 0.09%) Difference between DTG and non-DTG- ART at conception not different (0.09% difference; 95%CI -0.03%, 0.30%). **Tsepamo Results as at March 2019:** From May 2018 to March 2019 1 NTD/1275 adiitonal exposures to DTG at conception **Tsepamo Results through to 30th April 2020: 1 April 2019 to 30 April 2020** **Number of NTDs:** Total 28/39,200 (0.07%) **DTG from conception:** 2/1908 (0.1%) **Any other non DTG ART from conception:** 6/4569 (0.1%) **EFV from Conception:** 5/2999 (0.2%) **DTG started during pregnancy**: 1/741 (0.1%) **HIV Negative:** 17/30,258 (0.1%)	• Two Women (started on DTG at conception) who delivered infants with NTDs had no medical history, did not receive other medication, and did not receive pre-conception folate supplementation

Table 2: Tsepamo study reports included in the previous review update

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Zash *et al*. 2018 Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. 2018 Jul;6(7):e804-e810. doi: 10.1016/S2214-109X(18)30218-3. Epub 2018 Jun 4. PMID: 29880310; PMCID: PMC6071315.	Observational Study - Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014) Inclusion Criteria: DTG regimen started and delivery between Nov 1 2016 and Sep 3th 2017 for singleton pregnancy EFV regimen started and delivery between Aug 15th 2014 and Aug 15th 2016 for singleton pregnancy Exclusion criteria; births to mothers who switched ART regimens or stopped ART	Sample Size: Patient Characteristics: Age parity, socioeconomic indicators, timing of initiating of antenatal care and site of delivery were similar between EFV and DTG groups. HIV negative woman were younger, primiparous, higher education level compared to HIV positive woman. Similar timing of initiation and antenatal care for HIV infected and uninfected women. Funding: National Institutes of Health grants Disclosures: None declared	Exposures: •DTG based ART (1729) •EFV based ART (4593)	**Primary Outcome:** Combined endpoints of any adverse outcome **(**stillbirth, preterm birth (<37 weeks gestation), small for gestational age (SGA < 10th percentile of birthweight by gestational age) or neonatal death (withig 28 days of age) and very SGA (< 3rd percentile of birthweight by gestational age)	Aug 15th 2014 to Aug 15th 2016 n=11708 women with HIV delivered singletons -4593 (39%) on EFV based regimen after conception. Nov 1st 2016 to Sep 30th 2017, n=5418 women with HIV delivered singletons - 1729 (32%) began DTG regimen after conception. -51167 HIV negative woman had singleton pregnancies -total for both time periods Median CD4 count was similar between DTG and EFV group. Greater proportion of women in the EFV group had a CD4 count during pregnancy (2054 (44.7% vs 247 (14,2%) **Adverse outcomes**: -**Risk for any adverse outcome** among woman on DTG vs EFV was similar (n=574, 33·2% vs n=1606, 35·0%; aRR 0·95, 95% CI 0·88– 1·03), -**Risk of any severe birth outcome** was similar (n=185, 10·7% vs n=519, 11·3%; 0·94, 0·81–1·11). In 675 women (280 on DTG and 395 on EFV) with 1st trimester exposure to ART, 1 major congenital abnormality (skeletal dysplasia) in EFV exposed infant -No significant differences by regimen in individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA **HIV Negative Women** -134766 (28.9%) had any adverse birth outcomes -Severe adverse birth outcomes 5085 (9.9%) women	• Adverse birth outcomes were similar for DTG based ART vs FEV based ART during pregnancy • Sample size was large • Inability to fully evaluate CD4 cell count due to low number of woman in DTG group with CD4 reported (due to policy changes in testing) • Switch from EFV To DTG might put the data at historical bias (but short interval – 3 years) • Observational study – risk of confounding exists – however baseline characteristics of groups was similar, adjusted for confounding and conducted sensitivity analyses which were robust to changes • Unable to verify the data in medical records or validate gestational age dating (although any bias would be similar between the two treatment groups)
Zash R, et al, 2018. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018 Sep	Letter to the Editor outlining birth outcome surveillance (n=8 government hospitals, Botswana) Funding: National Institutes of Health (R01 HD080471-01 and K23 HD088230-01A1).	May 1, 2018 Sample Size: n=89,064 births included in surveillance n=88,755 (99.7%) had an infant surface examination	Exposures: •DTG from conception: (436) •Any other non DTG ART from conception: (11,300)	Prevalence of neural-tube defects (NTDs) among infants	**n=86 NTDs identified** (0.10% of births; 95% CI, 0.08 to 0.12) **Defects included:** -42 meningocele/myelomeningocele, 30 of anencephaly, 13 encephalocele, 1 of iniencephaly **DTG from conception:** 4/426 (0.94%; 95% CI 0.37–2.4) infants had a NTD (encephalocele, myelomeningocele (with	• Previously reported (2018) the risk of adverse birth outcomes or congenital abnormalities among women who started DTG based ART after conception (including therapy initiated during the first trimester of pregnancy) was not higher than the risk among women who started EFV based therapy after conception. • NTDs in DTG from conception: The 4 mothers delivered in 3 geographically separated hospitals over a 6-month period; none had epilepsy/diabetes/received folate supplementation at conception.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
6;379(10):979-981. doi: 10.1056/NEJMc1807653. Epub 2018 Jul 24. PMID: 30037297; PMCID: PMC6550482.	Declarations: Disclosure forms provided by authors		• DTG started during pregnancy: (2812) • HIV negative Mothers (66,065)		undescended testes), & iniencephaly (with major limb defect). **Any other non DTG ART from conception:** 14/11,300 (0.12%; 95% CI 0.07 – 0.21) infants -Prevalence Difference: -0.82 (95% CI, −0.24 to −2.3) vs the reference DTG from conception **DTG started during pregnancy**: 0 /2812 (0.00%; 95% CI 0.0 – 0.13) infants. Median gestational age at initiation of ART - 19 weeks (interquartile range, 14 to 25). 75 women started ART at gestational age < 6 weeks. -Prevalence Difference: -0.94 (95% CI, −0.35 to −2.4) vs the reference DTG from conception **HIV Negative:** 61/66,057 (0.09%; 95% CI 0.07– 0.12) infants -Prevalence Difference: -0.85 (95% CI, −0.27 to −2.3) vs the reference DTG from conception **7 additional infants with NTDs** -3 born to women who started non DTG ART during pregnancy -3 to (HIV)–infected women who did not receive ART during pregnancy -1 to a woman of unknown HIV infection status not on ART.	• Potential early signal for an increased prevalence of NTDs in association with DTG based ART from the time of conception. • Small number of events • Small difference in prevalence • Study is ongoing, and more data has since been collected which has refuted this signal

Table 3. List of excluded publications

No	Citation	Reason for Exclusion
1	Alhassan Y et al. Community acceptability of dolutegravir-based HIV treatment in women: a qualitative study in South Africa and Uganda. BMC Public Health. 2020 Dec 7;20(1):1883.	Wrong study design
2	Bollen P et al. Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women Network. The Effect of Pregnancy on the Pharmacokinetics of Total and Unbound Dolutegravir and Its Main Metabolite in Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021 Jan 23;72(1):121-127.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
3	Chandiwana NC et al. Unexpected interactions between dolutegravir and folate: randomized trial evidence from South Africa. AIDS. 2021 Feb 2;35(2):205-211.	Wrong outcomes
4	Chouchana L et al. Is There a Safety Signal for Dolutegravir and Integrase Inhibitors During Pregnancy? J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):481-486.	No comparison with EFV
5	Chouchana L et al. Dolutegravir and neural tube defects: a new insight. Lancet Infect Dis. 2020 Apr;20(4):405-406.	Analysis of spontaneous reports from Vigibase. This is a pharmacovigilance database of spontaneous adverse drug reaction reports, not a pregnancy registry – did not meet study design
6	Crawford M et al. Postmarketing Surveillance of Pregnancy Outcomes With Dolutegravir Use. J Acquir Immune Defic Syndr. 2020 Jan 1;83(1):e2-e5.	No comparison with EFV
7	Dickinson L et al. Infant exposure to dolutegravir through placental and breastmilk transfer: a population pharmacokinetic analysis of DolPHIN-1. Clin Infect Dis. 2020 Dec 21:ciaa1861.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
8	Grayhack C et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. AIDS. 2018 Sep 10;32(14):2017-2021.	No comparison to EFV-based ART
9	Hill A, Clayden P, Thorne C, Christie R, Zash R. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr 1;4(2):66-71.	Review looking at safety and pharmacokinetics of DTG. Only one of the safety studies included in the review (one of the early Tsepamo reports) met PICO, and was already included
10	Kreitchmann R et al. Two cases of neural tube defects with dolutegravir use at conception in south Brazil. Braz J Infect Dis. 2021 Mar-Apr;25(2):101572.	Wrong Study Design
11	Mulligan N et al.; IMPAACT P1026s Protocol Team. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. AIDS. 2018 Mar 27;32(6):729-737.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
12	Nguyen B et al.. Pharmacokinetics and Safety of the Integrase Inhibitors Elvitegravir and Dolutegravir in Pregnant Women With HIV. Ann Pharmacother. 2019 Aug;53(8):833-844.	Review looking at safety and pharmacokinetics of DTG. Relevant studies already included.
13	Podany AT et al. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors: An Updated Review. Clin Pharmacokinet. 2020 Sep;59(9):1085-1107.	NO - pharmacokinetic comparison between InSTIs
14	Rahangdale L et al; HOPES (HIV OB Pregnancy Education Study) Group. Integrase inhibitors in late pregnancy and rapid HIV viral load reduction. Am J Obstet Gynecol. 2016 Mar;214(3):385.e1-7.	Only 4 women on DTG
15	Reefhuis J et al. Neural Tube Defects in Pregnancies Among Women With Diagnosed HIV Infection - 15 Jurisdictions, 2013-2017. MMWR Morb Mortal Wkly Rep. 2020 Jan 10;69(1):1-5.	Wrong study design
16	Schomaker M et al. Assessing the risk of dolutegravir for women of childbearing potential. Lancet Glob Health. 2018 Sep;6(9):e958-e959.	Commentary
17	Slogrove AL et al. Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding. Curr Opin HIV AIDS. 2017 Jul;12(4):359-368.	Commentary /opinion piece
18	van De Ven NS et al. Analysis of Pharmacovigilance Databases for Dolutegravir Safety in Pregnancy. Clin Infect Dis. 2020 Jun 10;70(12):2599-2606.	No denominator to contribute to incidence of NTD with DTG vs EFV exposure
19	van der Galiën R et al. Pharmacokinetics of HIV-Integrase Inhibitors During Pregnancy: Mechanisms, Clinical Implications and Knowledge Gaps. Clin Pharmacokinet. 2019 Mar;58(3):309-323.	3 relevant studies already included / duplication
20	Vannappagari V, Thorne C; for APR and EPPICC. Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):371-378. doi: 10.1097/QAI.0000000000002035. PMID: 30939532; PMCID: PMC6905407.	No comparison with EFV
21	Zipursky J et al. Dolutegravir for pregnant women living with HIV. CMAJ. 2020 Mar 2;192(9):E217-E218.	Commentary

Appendix 1: Search strategy

Date searched for the updated review: 3 June 2021

Database: PubMed

Search Strategy

Search	Query	Results
#6	Search: (#1 AND #4) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	134
#5	Search: #1 AND #4 Sort by: Most Recent	136
#4	Search: #2 OR #3 Sort by: Most Recent	1,071,076
#3	Search: neural tube defects[mh] OR neural tube defect*[tiab] OR neurenteric cyst*[tiab] OR acrania*[tiab] OR craniorachischis*[tiab] OR diastematomyelia*[tiab] Sort by: Most Recent	31,975
#2	Search: pregnancy[mh] OR pregnant women[mh] OR pregnan*[tiab] Sort by: Most Recent	1,048,366
#1	Search: "dolutegravir" [Supplementary Concept] OR dolutegravir[tiab] Sort by: Most Recent	1,343

Number of studies: 134

Database: Clinical Trials.Gov

Search terms: dolutegravir AND (pregnancy OR pregnant women)

Records retrieved: 13

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: X Small: ☐ None: ☐ Uncertain: ☐	Compared with EFV, - viral suppression rates are non-inferior by 48 weeks; - viral suppression rates are superior by the time of delivery; - rates of vertical transmission are not significantly different, but event rates are very low with both regimens; - risk of insufficient weight gain in pregnancy is lower; and - risk of development of resistance mutations in those who fail first line regimens is lower.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: X Uncertain: ☐	Compared with EFV: - - Risk of NTD is not significantly different; -risk of other adverse pregnancy outcomes are not significantly different; - weight gain is higher, but the clinical significance of this is unknown (WLHIV on both regimens had less weight gain in pregnancy than HIV-uninfected women
BENEFITS & HARMS	**Do desirable effects outweigh undesirable harms?** Favours intervention: x Favours control: ☐ Intervention = Control *or* Uncertain: ☐	
QUALITY OF EVIDENCE	**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	RCT data for efficacy, resistance, and some adverse events (eg weight). Observational data for NTDs is consistent.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: X No: ☐ Uncertain: ☐	
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: X Uncertain: ☐	Price of medicines/ 28 days: **Medicine** | **Price** TDF+FTC+EFV (TEE) | R104.56 TDF+3TC+DTG (TLD) | R 98.18 Contract circular RT71-2019ARV
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: X Major: ☐ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: X No: ☐ Uncertain: ☐	Standardised first line regimens for all adults and adolescents living with HIV is likely to be valued by prescribers. Access to DTG for WOCP has been advocated for by patient advocacy groups.
EQUITY	**Would there be an impact on health inequity?** Yes: x No: ☐ Uncertain: ☐	There is likely to be a positive effect in terms of reducing health inequity.

REFERENCES

- Banda, F. M., K. M. Powis, S. Sun, J. Makhema, G. Masasa, L. M. Yee, and J. Jao. 2020. 'Fetal biometry following in-utero exposure to dolutegravir-based or efavirenz-based antiretroviral therapy', *AIDS*, 34: 2336-37.
- Caniglia, Ellen C., Roger Shapiro, Modiegi Diseko, Blair J. Wylie, Chloe Zera, Sonya Davey, Arielle Isaacson, Gloria Mayondi, Judith Mabuta, Rebecca Luckett, Joseph Makhema, Mompati Mmalane, Shahin Lockman, and Rebecca Zash. 2020. 'Weight gain during pregnancy among women initiating dolutegravir in Botswana', *EClinicalMedicine*, 29.
- Chimukangara, B., R. J. Lessells, S. Y. Rhee, J. Giandhari, A. B. M. Kharsany, K. Naidoo, L. Lewis, C. Cawood, D. Khanyile, K. A. Ayalew, K. Diallo, R. Samuel, G. Hunt, A. Vandormael, B. Stray-Pedersen, M. Gordon, T. Makadzange, P. Kiepiela, G. Ramjee, J. Ledwaba, M. Kalimashe, L. Morris, U. M. Parikh, J. W. Mellors, R. W. Shafer, D. Katzenstein, P. Moodley, R. K. Gupta, D. Pillay, S. S. Abdool Karim, and T. de Oliveira. 2019. 'Trends in Pretreatment HIV-1 Drug Resistance in Antiretroviral Therapy-naive Adults in South Africa, 2000-2016: A Pooled Sequence Analysis', *EClinicalMedicine*, 9: 26-34.
- Davey, S., G. Ajibola, K. Maswabi, M. Sakoi, K. Bennett, M. D. Hughes, A. Isaacson, M. Diseko, R. Zash, O. Batlang, S. Moyo, S. Lockman, M. Lichterfeld, D. R. Kuritzkes, J. Makhema, and R. Shapiro. 2020. 'Mother-to-Child HIV Transmission With In Utero Dolutegravir vs. Efavirenz in Botswana', *J Acquir Immune Defic Syndr*, 84: 235-41.
- Dugdale, C. M., A. L. Ciaranello, L. G. Bekker, M. E. Stern, L. Myer, R. Wood, P. E. Sax, E. J. Abrams, K. A. Freedberg, and R. P. Walensky. 2019. 'Risks and Benefits of Dolutegravir- and Efavirenz-Based Strategies for South African Women With HIV of Child-Bearing Potential: A Modeling Study', *Ann Intern Med*, 170: 614-25.
- Griesel, Rulan, Gary Maartens, Maxwell Chirehwa, Simiso Sokhela, Godspower Akpomiemie, Michelle Moorhouse, Francois Venter, and Phumla Sinxadi. 2020. 'CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz', *Clinical Infectious Diseases*.
- Kanters, Steve, Marco Vitoria, Michael Zoratti, Meg Doherty, Martina Penazzato, Ajay Rangaraj, Nathan Ford, Kristian Thorlund, Prof Aslam H. Anis, Mohammad Ehsanul Karim, Lynne Mofenson, Rebecca Zash, Alexandra Calmy, Tamara Kredo, and Nick Bansback. 2020. 'Comparative efficacy, tolerability and safety of dolutegravir and efavirenz 400mg among antiretroviral therapies for first-line HIV treatment: A systematic literature review and network meta-analysis', *EClinicalMedicine*, 28.
- Kintu, Kenneth, Thokozile R. Malaba, Jesca Nakibuka, Christiana Papamichael, Angela Colbers, Kelly Byrne, Kay Seden, Eva Maria Hodel, Tao Chen, Adelline Twimukye, Josaphat Byamugisha, Helen Reynolds, Victoria Watson, David Burger, Duolao Wang, Catriona Waitt, Miriam Taegtmeyer, Catherine Orrell, Mohammed Lamorde, Landon Myer, and Saye Khoo. 2020. 'Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial', *The Lancet HIV*, 7: e332-e39.
- Lockman, S., S. S. Brummel, L. Ziemba, L. Stranix-Chibanda, K. McCarthy, A. Coletti, P. Jean-Philippe, B. Johnston, C. Krotje, L. Fairlie, R. M. Hoffman, P. E. Sax, S. Moyo, N. Chakhtoura, J. S. Stringer, G. Masheto, V. Korutaro, H. Cassim, B. T. Mmbaga, E. João, S. Hanley, L. Purdue, L. B. Holmes, J. D. Momper, R. L. Shapiro, N. K. Thoofer, J. F. Rooney, L. M. Frenkel, K. R. Amico, L. Chinula, and J. Currier. 2021. 'Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial', *Lancet*, 397: 1276-92.
- Mmasa, K. N., K. Powis, S. Sun, J. Makhema, M. Mmalane, S. Kgole, G. Masasa, S. Moyo, M. Gerschenson, T. Mohammed, J. Legbedze, E. J. Abrams, I. J. Kurland, M. E. Geffner, and J. Jao. 2021. 'Gestational diabetes in women living with HIV in Botswana: lower rates with dolutegravir- than with efavirenz-based antiretroviral therapy', *HIV Med*.
- Money, D., T. Lee, C. O'Brien, J. Brophy, A. Bitnun, F. Kakkar, I. Boucoiran, A. Alimenti, W. Vaudry, J. Singer, and L. J. Sauve. 2019. 'Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study', *Bjog*.
- Moyo, S., G. Hunt, K. Zuma, M. Zungu, E. Marinda, M. Mabaso, V. Kana, M. Kalimashe, J. Ledwaba, I. Naidoo, S. Takatshana, T. Matjokotja, C. Dietrich, E. Raizes, K. Diallo, G. Kindra, L. Mugore, and T. Rehle. 2020. 'HIV drug resistance profile in South Africa: Findings and implications from the 2017 national HIV household survey', *PLoS One*, 15: e0241071.
- NAMSAL ANRS 12313 Study Group. 2019. 'Dolutegravir-Based or Low-Dose Efavirenz–Based Regimen for the Treatment of HIV-1', *New England Journal of Medicine*, 381: 816-26.
- Pereira, Gerson Fernando Mendes, Ahra Kim, Emilia M. Jalil, Fernanda Fernandes Fonseca, Bryan E. Shepherd, Valdilea G. Veloso, Fernanda Rick, Rachel Ribeiro, Maria Cristina Pimenta, Andrea Beber, Renato Girade Corrêa, Renato Lima, Fernanda Maruri, Catherine C. McGowan, Adele Schwartz Benzaken, Beatriz Grinsztejn, and Jessica L. Castilho. 2021. 'Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study', *The Lancet HIV*, 8: e33-e41.
- Phillips, T. K., P. Sinxadi, E. J. Abrams, A. Zerbe, C. Orrell, N. C. Hu, K. Brittain, Y. Gomba, J. Norman, L. Wiesner, L. Myer, and G. Maartens. 2019. 'A Comparison of Plasma Efavirenz and Tenofovir, Dried Blood Spot Tenofovir-Diphosphate, and Self-Reported Adherence to Predict Virologic Suppression Among South African Women', *J Acquir Immune Defic Syndr*, 81: 311-18.
- Raesima, Mmakgomo M., Chibuike M. Ogbuabo, Vasavi Thomas, Sara E. Forhan, Gadzikanani Gokatweng, Eldah Dintwa, Chipo Petlo, Catherine Motswere-Chirwa, Elizabeth M. Rabold, Sarah C. Tinker, Shifawu Odunsi, Sifelani Malima, Omphemetse Mmunyane, Thusoetsile Modise, Kelame Kefitlhile, Kunle Dare, Mpho Letebele, Michelle E. Roland, Cynthia A. Moore, Surbhi Modi, and Dhelia M. Williamson. 2019. 'Dolutegravir Use at Conception — Additional Surveillance Data from Botswana', *New England Journal of Medicine*, 381: 885-87.
- Venter, W. D. F., M. Moorhouse, S. Sokhela, L. Fairlie, N. Mashabane, M. Masenya, C. Serenata, G. Akpomiemie, A. Qavi, N. Chandiwana, S. Norris, M. Chersich, P. Clayden, E. Abrams, N. Arulappan, A. Vos, K. McCann, B. Simmons, and A. Hill. 2019. 'Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV', *N Engl J Med*.
- Venter, W. D. F., S. Sokhela, B. Simmons, M. Moorhouse, L. Fairlie, N. Mashabane, C. Serenata, G. Akpomiemie, M. Masenya, A. Qavi, N. Chandiwana, K. McCann, S. Norris, M. Chersich, G. Maartens, S. Lalla-Edward, A. Vos, P. Clayden, E. Abrams, N. Arulappan, and A. Hill. 2020. 'Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial', *Lancet HIV*, 7: e666-e76.
- Waitt, C., C. Orrell, S. Walimbwa, Y. Singh, K. Kintu, B. Simmons, J. Kaboggoza, M. Sihlangu, J. A. Coombs, T. Malaba, J. Byamugisha, A. Amara, J. Gini, L. Else, C. Heiburg, E. M. Hodel, H. Reynolds, U. Mehta, P. Byakika-Kibwika, A. Hill, L. Myer, M. Lamorde, and S. Khoo. 2019. 'Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DolPHIN-1 study)', *PLoS Med*, 16: e1002895.

- World Health Organization. 2019. *WHO recommends dolutegravir as preferred HIV treatment option in all populations. https://www.who.int/news/item/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all populations. Accessed 3 June 2021*.
- Zash, R., L. Holmes, M. Diseko, D. Jacobson, G. Mayondi, Isaacson A., S. Davey, J. Mabuta, Mmalane M., Gaolathe T., Lockman S., Makhema J., and Shapiro R. 2020. "Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. Late Breaker abstract number OAXB0102." In *23rd international AIDS Conference*. Virtual Conference.
- Zash, R., D. L. Jacobson, M. Diseko, G. Mayondi, M. Mmalane, M. Essex, T. Gaolethe, C. Petlo, S. Lockman, L. B. Holmes, J. Makhema, and R. L. Shapiro. 2018. 'Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study', *Lancet Glob Health*, 6: e804-e10.
- Zash, R., J. Makhema, and R. L. Shapiro. 2018. 'Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception', *N Engl J Med*, 379: 979-81.
- Zash, Rebecca, Lewis Holmes, Modiegi Diseko, Denise L. Jacobson, Sean Brummel, Gloria Mayondi, Arielle Isaacson, Sonya Davey, Judith Mabuta, Mompati Mmalane, Tendani Gaolathe, M. Essex, Shahin Lockman, Joseph Makhema, and Roger L. Shapiro. 2019. 'Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana', *New England Journal of Medicine*.

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

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: 27 July 2021 (second update of initial review of 26 January 2017) – see addendum
Medicine (INN): Dolutegravir
Medicine (ATC): J05AX12
Indication (ICD10 code): B24
Patient population: HIV-infected patients commencing first-line antiretroviral therapy (ART)
Prevalence of HIV infection: South African general population: 13.1%; women in their reproductive ages (15–49 years): 20%; youth aged 15–24:5.5% *(Statistics South Africa, Mid-year population estimates 2018).*
Level of Care: Primary
Prescriber Level: Nursing practitioner or medical doctor
Current standard of care: Efavirenz (EFV) in combination with two nucleoside/nucleotide reverse transcriptase inhibitors (tenofovir + lamivudine/emtricitabine)
Efficacy estimates: (preferably NNT) Viral suppression to <50 copies/mL at 96 weeks, RR 1.12 (95% confidence interval 1.04 to 1.21, I2=0%) of DTG-based vs EFV-based regimens i.e. 376/465 vs 338/469 events of undetectable viral load; ARR 8.79%, NNT 12.
(Rutheford et al, 2016)
Motivator/reviewer name(s): Michelle Moorhouse; Karen Cohen
PTC affiliation: N/A

2. **Name of author(s)/motivator(s)**

Michelle Moorhouse *
Karen Cohen**

3. **Author affiliation and conflict of interest details**

* Wits Reproductive Health and HIV Institute.

Dr Moorhouse has received speaker fees and honoraria from Gilead Sciences, ViiV Healthcare, AbbVie, Cipla and HIV Virology, and has previously received conference sponsorship from Gilead, Merck, Dr Reddy, Cipla and Mylan. Wits RHI is part of optimisation collaborations – grants to improve testing, new drug regimens, linkage to care and has received drug donations for studies. This includes the ADVANCE study (RCT comparing three regimens in patients eligible for first-line ART: DTG/TAF/FTC versus DTG/TDF/FTC versus EFV/TDF/FTC)[i] in which DTG has been donated by ViiV Healthcare and TAF/FTC by Gilead Sciences.

Note: Dr Moorhouse was recused from the decision-making process regarding a recommendation.

** Division of Clinical Pharmacology, Department of Medicine; no conflicts of interest declared.

4. Introduction/ Background

The PHC ERC prepared a technical review of dolutegravir (DTG) in 2017. At that time NEMLC decided not to add DTG to the EML as an option for first line ART, pending availability of further evidence, particularly in pregnant women and patients on concomitant rifampicin. Further evidence is now available, and the NDoH HIV directorate is considering adding DTG to national ART guidelines. The DTG technical review has now been updated to inform NEMLC comment on the proposed ART guidelines and to inform NEMLC decision regarding including DTG on the EML.

Since the START and TEMPRANO studies, which demonstrated that ART should be started irrespective of CD4 count[ii iii], the WHO recommended that everyone infected with HIV should start ART[iv], doubling those eligible for ART, with significant programmatic and financial implications. In September 2016, this recommendation was implemented in South Africa.

While there is evidence of benefit of ART, even at high baseline CD4 counts, for those with earlier stage disease, benefits are modest, and need to be weighed up against the potential harms, including side effects result in poor adherence and resistance, with wider public health consequences[v]. Current first-line ART in SA is a fixed dose combination (FDC) of efavirenz (EFV) with two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs), usually tenofovir (TDF) with lamivudine (3TC) or emtricitabine (FTC). For those patients in whom EFV is contra-indicated or poorly tolerated, nevirapine (NVP) or boosted lopinavir (LPV/r) are alternatives, depending on the CD4 count of the patient when initiating ART.

Current first-line treatment in South Africa has several challenges:

- **Tolerability:** Current first-line ART has side effects, resulting in non-adherence or discontinuation. Improved safety profiles would keep patients on first-line longer
- **Cost**: The cost of ARVs consumes a significant portion of the programme budget. Current cost is unlikely to decrease significantly[i]
- **Robustness/Resistance:** NNRTI-based regimens are vulnerable to resistance. Data on the number of first-line failures in South Africa are still elusive but a study looking at several programmes suggested just over 2% of patients migrate across to second-line annually (a larger percentage are lost to follow-up)[vi]. Finding a first-line regimen that is more robust and durable will limit transition to expensive and less well tolerated second- and third-line regimens
- **Pill size:** The currently used fixed dose combinations are large pills which some patients find difficult to swallow. The size of the pill has other effects as well, such as packaging and storage space requirements[i].

Dolutegravir (DTG), an integrase inhibitor, has been shown to be efficacious when used in both salvage and first-line ART. We reviewed the evidence forthe efficacy and safety of DTG compared with EFV, the current standard of care. We also summarised the evidence for its use in pregnancy, and with concomitant TB treatment.

5. Purpose/Objective i.e. PICO question[comparison to current standard of care for a specific indication]:

-P *(patient/population):* Adult patients commencing first-line ART
-I *(intervention):* Dolutegravir plus two nucleoside/nucleotide reverse transcriptase inhibitors (N (t) RTIs)
-C *(comparator):* Efavirenz plus two N (t) RTIs
-O *(outcome):*1. Efficacy (virological suppression) 2. Adverse effects 3. Neuropsychiatric adverse effects

Question: Amongst adult patients on first-line combination ART, is the integrase inhibitor dolutegravir more efficacious and/or better tolerated than the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz?

6. **Methods:**
   a. **Data** sources: PubMed

   b. **Search strategy**
   ("dolutegravir"[MeSH Terms] OR "dolutegravir"[All Fields]) AND ("efavirenz"[MeSH Terms] OR "efavirenz"[All Fields]).

We ran the search on 20 January 2017 using the search terms above. We identified 63 abstracts, from which we selected 12 for further review(Hill, Mitchell et al. 2018).

These 12 abstracts describe the following:

- Systematic reviews (6 publications)[vii] [viii] [ix] [x] [xi] [xii]
- RCT (6 publications) [xiii] [xiv] [xv] [xvi] [xvii] [xviii]

In addition, we ran two searches for information on use in two patient groups: patients requiring concomitant TB treatment, and DTG in pregnant women.

- We ran a search for information regarding use of DTG with rifampicin-containing tuberculosis (TB) treatment. (In our setting concomitant TB treatment and ART are frequently required):
  - Search terms “dolutegravir” AND “(rifampicin OR rifampin.). This search identified six abstracts, of which one was relevant to our question: we identified one phase 1 healthy volunteer pharmacokinetic study, regarding the interaction between DTG and rifampicin (and rifabutin) [xix].
- We ran a search on DTG in pregnancy:
  - We conducted a search in Pubmed using the terms “dolutegravir” AND “pregnancy”. We retrieved 12 abstracts, none of which included data on safety of dolutegravir in pregnancy.
  - We also reviewed information in the antiretroviral pregnancy registry to date [xx].

<u>Update February 2019</u>

We ran the same searches above in Pubmed on 2 Feb 2019 and reviewed the abstracts with a 6 month overlap (i.e. June 2016 to 2 Feb 2019).

- For the main search identified 99 abstracts. We selected two abstracts not previously retrieved for review (Fettiplace, Stainsby et al. 2017[xxi], Hill, Mitchell et al. 2018[xxii])

<u>Pregnancy:</u>

- We used the same search terms as the previous search. We identified 42 abstracts. We retrieved seven for further review (Mounce, Pontiggia et al. 2017[xxiii], Bornhede, Soeria-Atmadja et al. 2018[xxiv], Grayhack, Sheth et al. 2018[xxv], Hill, Clayden et al. 2018[xxvi], Mulligan, Best et al. 2018[xxvii], Zash, Jacobson et al.

2018[xxviii], Zash, Makhema et al. 2018[xxix]). In addition, we reviewed the most recent version of the antiretroviral pregnancy registry (Committee 2018[xxx])

Tuberculosis

- We used the same search terms as the previous search. We identified 12 abstracts. We retrieved 2 for further review (Cevik and McGann 2018[xxxi], Pena, Chueca et al. 2019[xxxii]). In addition, we reviewed a CROI conference presentation(Dooley, Kaplan et al. 2018[xxxiii])

7. Summary of included and excluded studies

a. Excluded studies:

Author, date	***Type of study***	***Reason for exclusion***
You J, 2016 [viii]	Systematic review and meta-analysis of RCTs, non-RCT clinical trials, case-control studies, cohort studies, case reports (n > 10)	Compares various integrase inhibitors (InSTIs)(EFV is an NNRTI)
Jiang J, 2016 [xii]	Meta-analysis of RCTs	Compares various InSTIs (EFV is a NNRTI)
Raffi F, 2015 [viii]	Cross comparison of key subpopulations across different DTG studies in ARV-naïve subjects	Third drug used differs in each study – the studies included use EFV (SINGLE), raltegravir (SPRING-2) or darunavir (FLAMINGO). RAL and DRV not relevant to this medicine review and PICO

b. Included studies

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Kanters S, 2016 [vii]	Systematic review and network meta-analysis of RCTs	31 404 patients	ART-naive adults and adolescents (aged 12 years or older)	154 treatment groups, pertaining to 16 'third drugs' incl EFV and DTG	Viral suppression, mortality, AIDS-defining illnesses, discontinuations, discontinuations due to adverse events, and serious adverse events	Effect [OR (95% CI)] of DTG relative to EFV is 1·87(1·34–2·64)for viral suppression at 48 weeks and 1·90(1·40–2·59)at 96 weeks; 0·26(0·14–0·47) for treatment discontinuations; 0·84(0·49–1·43) for treatment emergent SAEs (NSS)	DTG was significantly better than EFV at 48 weeks and at96 weeks. InSTIs tended to be protective of discontinuations due to adverse events relative to standard-dose EFV. The most protective effect relative to EFV was that of DTG, followed by low-dose EFV.
Rutherford GW, 2016 [ix]	Systematic review and meta-analysis of RCTs	465 patients on DTG and 469 on EFV	ART-naïve adults	DTG-based regimens compared to EFV-based regimens (first-line)	Viral suppression to < 50 copies/mL at 48, 96 and 144 weeks	RR = 1.10(95% CI 1.04–1.16) at 48 weeks; RR = 1.12(95% CI1.04–1.21)at 96 weeks and RR = 1.13(95% CI 1.02–1.24) at 144 weeks	DTG-containing regimens were superior to EFV-containing regimens. No difference in risk of death between the two regimens (RR = 0.26, 95% CI 0.01–4.20). One study reported discontinuation of initial ART regimen due to AEs or death at 96 and 144 weeks. At both time points, the DTG regimens were superior to the EFV regimens (RR = 0.27, 95%CI 0.15–0.50 at 96 weeks and RR = 0.28, 95% CI 0.16–0.48 at 144 weeks). Risk of SAEs was similar in each regimen at 96 weeks (RR = 1.15, 95% CI 0.80–1.63) and 144 weeks (RR = 0.93, 95% CI 0.68–1.29).
Ford N, 2015 [x]	Systematic review of RCTs and quasi	8466 patients on EFV and	ARV-naïve HIV-infected adults	EFV-based ART versus non-EFV	Drug discontinuation as a result of an	RR of discontinuation was greater for	No statistically significant difference in risk of SAEs. Absolute risk of severe lab AEs was higher comparing EFV with

	randomised trials	9631 on comparator drug	(children included in theory but no paed studies met inclusion criteria)	based ART (NVP in 9; ritonavir-boosted lopinavir in 7, rilpivirine in 4, DTG in 2)	adverse event (AE)	EFV compared to DTG(RR: 4.3, 95% CI: 2.2-8.3) but absolute risks were not significantly different	DTG (2.8, 95% CI: 0.2 to 5.3), but relative differences were not significant. Severe neuropsychiatric AEs were more common for EFV compared to DTG (RR: 16.7, 95% CI: 2.0 to 137.8; RD: 3.0,95% CI: 1.4 to 4.6)
Patel DA, 2014 [xi]	Systematic review and network meta-analysis of phase 3/4 RCTs	17 000	ART-naive patients with HIV-1infection; aged ≥ 13 years	DTG, EFV, ATV/r, DRV/r, EVG/c, LPV/r, RAL, or RPV	Not clearly stated. Virologic suppression <50 copies/mL	Mean odds of virologic suppression were significantly higher for DTG than EFV. OR = 1.85 (1.34, 2.50)	Virologic suppression = HIV RNA<50 copies/mL. DTG had significantly lower associated TC, HDL, and LDL increases than EFV. Odds of experiencing an AE were significantly lower for DTG Compared to EFV:0.57 (0.38, 0.81). Odds of discontinuation due to AEs were lower for DTG relative to EFV: 0.26 (0.14, 0.43).
SPRING-1 Van Lunzen J, 2012 [xiii]; Stellbrink H, 2013 [xvii]	RCT (phase 2b)	205	ARV-naïve HIV-infected adults	DTG 10/25/50 mg versus EFV 600 mg (in combination with TDF/FTC orABC/3TC)	Proportion with VL < 50 copies/mL at week 16	Week 16 response rates were 93% (144/155) for all doses of DTG (with little difference between dose groups) and 60% (30/50) for EFV(no CI/p-values provided)	Week 48 response rates were 90% (139/155) for all doses of DTG and 82% (41/50) for EFV (no CI/p-values provided).At week 96, the proportion with VL < 50 copies/mL was 79, 78, and 88% for DTG 10, 25, and 50 mg, respectively, compared with 72% for EFV. 6 participants withdrew due to AEs: two on DTG (grade 2 dyspepsia in the 25 mg group and grade 4 Burkitt's lymphoma in the 50 mg group) and 4on EFV(one each of drug intolerance, drug hypersensitivity, abnormal dreams, and suicide attempt).At 96 weeks, fewer of DTG group withdrew due to AEs (3%) compared with EFV group (10%). No SAEs due to DTG. More in EFV group had drug-related AEs of moderate or higher severity (10 [20%]

							/50) than those in the combined DTG groups (13 [8%] /155). Across all DTG doses, but not EFV, small non-progressive mean increases in creatinine concentrations from baseline at week 1 remained constant to about week 16 (0.10 mg/dL [SD 0.108] DTG overall vs 0.01 [0.079] EFV; p<0.0001 with *post-hoc* t test); values gradually returned to baseline over 48 weeks. The increases happened across both NRTI backbones. 4 participants who received DTG 25 mg had treatment-emergent grade 1 increases in creatinine concentration, and one had a grade 2 increase; no other graded creatinine abnormalities. More participants in the DTG groups (21 participants; 14%) than in the EFV group (1; 2%) had treatment-emergent increases in dipstick urine protein (≥1), which were neither time nor dose dependent.
SINGLE study Walmsley S, 2013 [xiv]; Walmsley S, 2015 [xv]	RCT phase 3 Double blind, double dummy	833	ARV-naïve HIV-infected adults	DTG 50 mg with ABC/3TC versus EFV/TDF/FTC	Proportion with VL < 50 copies/mL at week 48	At week 48, the proportion with VL < 50 copies/mL significantly higher in DTG arm than in EFV arm: 88% vs. 81%, P = 0.003.This met criterion for superiority	At 144 weeks, 71% on DTG and 63% on EFV maintained VL < 50 copies/mL. DTG arm had shorter median time to viral suppression than the EFV arm (28 vs. 84 days, P<0.001). Discontinuations due to AEs on DTG less than EFV 3% vs. 11% at 144 weeks. Rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) significantly more common with EFV, whereas insomnia reported more frequently with DTG.

							No participants on DTG developed integrase or nucleoside resistance through 144 weeks.
Sub analysis of SINGLE [xvi]	RCT phase 3	833	ARV-naïve HIV-infected adults	DTG 50 mg with ABC/3TC versus EFV/TDF/FTC	Sub analysis assessed long-term bone turnover biomarker effects over144 weeks	Relative to baseline, CTx, osteocalcin, BSAP, and P1NP increased; vitamin D decreased in both groups at weeks48, 96, and 144. Changes from baseline typically peaked at weeks 48 or 96 and for the four analytes, excl vitamin D, with the EFV/FTC/TDF group having significantly greater changes from baseline at all time points.	The sub analysis evaluated vitamin D serum levels and bone turnover markers (BTMs), including type 1 collagen cross-linked C-telopeptide(CTx), osteocalcin, bone-specific alkaline phosphatase (BSAP), and procollagentype 1 N-terminal propeptide (P1NP), at baseline and weeks 48, 96, and 144. Changes described are likely attributable to the different NRTI backbones used in the two arms of the study, and unlikely to be related to the third drugs used in either arm, namely DTG or EFV.
Risk of CVS or CNS AEs and IRIS: Meta-analysis of randomised trials(Hill, Mitchell et al. 2018 [xxii])	Systematic review of RCTs both non-switch and switching	8 published trials + 1 trial presented at IAS 20187	Patients on DTG containing ART dose 50mg	Control arm on other ARV	Number of "key adverse events and SAES. cardiac disorders, suicide-related disorders, insomnia, IRIS	<u>Serious cardiac events</u> :(SINGLE to 144 week) DTG 4/414 vs EFV 2/419 <u>Suicidality SAES</u> (SINGLE and SPRING-1) DTG 5/465 (1.1%) vs EFV 6/469(1.3%) DTG vs any other ARV RR1.21 (0.59 to 2.47) <u>Insomnia all grades</u> DTG 165/2716	No break down grades of insomnia RCTS excluded CDC stage C patients who are at more risk of IRIS Limitation-quality of AE data in published papers

						(6.1%) vs any other ARV 124/2727 (4.5%) RR 1.30 (1.03 to 1.63) IRIS: few events and no difference SINGLE DTG 1/414 vs EFV 2/419 (studies excluded CDC grade C)	
Fettiplace et al. (Fettiplace, Stainsby et al. 2017 [xxi])	Review of psychiatric symptoms reported in 5 phase 3 clinical trials, the OPERA observational cohort, and spontaneous reports. Industry funded (ViiV). (Only RCT data is presented in this table)	5 phase 3 RCTs, of which one DTG vs EFV	ARV-naïve HIV-infected adults	Control arm on other ARV	RCTS:"Psychiatric symptoms" (PS): Insomnia, anxiety, depression and suicidality ("Company safety physician"grouped related MedDRA terms)	More EFV treated patients with withdrawal due to PS than other drugs EFV 15/419 (4%) vs DTB 4/1672 (0.2%) SINGLE study- more insomnia with DTG than EFv: 71/414 vs 52/419; 3 vs 0 Gr3/4, 1 vs 4 withdraw as a result	

8. Evidence synthesis

Efficacy

The SINGLE trial compared DTG/abacavir (ABC)/3TC to EFV/TDF/FTC in ART-naïve adults [xiv]. At week 48, the DTG arm was superior to the EFV arm: 88% of participants in the DTG arm had HIV viral load <50 copies/mL versus 81% in the EFV arm. The difference was driven by the superior tolerability of the DTG arm, with 2% on DTG vs 10% on EFV discontinuing study drug due to an adverse event [xiv]. A systematic review of RCTs showed that DTG was superior to EFV in terms of viral suppression to <50 copies/mL:RR = 1.10(95% CI 1.04–1.16) at 48 weeks; RR = 1.12(95% CI1.04–1.21) at 96 weeks and RR = 1.13 (95% CI 1.02–1.24) at 144 weeks [ix].

Tolerability

A systematic review including 42 randomised control trials showed that the relative risk for discontinuations due to adverse effects was higher for EFV compared with most other first-line options, including DTG [x]. The systematic review demonstrated that neuropsychiatric adverse events were common with EFV, affecting close to 30% of patients (29.6%; 95% CI: 21.9% to 37.3%), of which 6.1% (95% CI: 4.3% to 7.9%) were severe. Dizziness and abnormal dreams were the most commonly reported neuropsychiatric adverse events experienced by patients treated with EFV [x]. Notably, most of the studies included were conducted among predominantly white populations and therefore would not account for differences in metabolism of EFV in African populations, which may result in more frequent neuropsychiatric adverse effects. There is a high prevalence of EFV slow metaboliser genotypes in South Africa (17% versus 3% in Caucasian groups)[xxxiv].

A systematic review compared reported cardiovascular and central nervous adverse events, as well as incidence of the immune reconstitution inflammatory syndrome (IRIS), in patients initiating DTG-containing ART and patients switching to DTG-containing ART (Hill, Mitchell et al. 2018 [xxii]).

There was significantly more insomnia in patients treated with DTG vs efavirenz. There was no significant difference in cardiovascular events (rare events, therefore underpowered to show difference). No difference in suicidality when compared with efavirenz; 1% of participants in both arms. There was no difference in incidence of IRIS, but exclusion of patients with more advanced HIV disease (CDC stage C) from the phase 3 studies is a limitation, as this is the group at highest risk of IRIS (see table of included studies).

A manufacturer funded review of psychiatric symptoms in patients receiving DTG versus non-DTG containing regimens found that more patients on efavirenz withdrew from phase 3 studies because of psychiatric symptoms than those on regimens with DTG or other drug as backbone (Fettiplace, Stainsby et al. 2017 [xxi]).

DTG in pregnancy

There was very little data on use of DTG at the time when this medicine review was first compiled. Since then, data from a prospective cohort study have been published which suggest increased risk of neural tube defects in infants born to women taking DTG at the time of conception, relative to other antiretrovirals. This has led WHO to recommend that DTG be avoided in women of child-bearing potential who are not on reliable contraception.

Preclinical toxicity studies for DTG in pregnancy did not reveal any significant concerns, and DTG was classified as FDA pregnancy category B, prior to the removal of this classification from use.

The Botswana cohort study prospectively captured birth outcomes at 8 hospitals from 2014. Botswana moved to first-line use of DTG in 2016. The risk period for neural tube defects is the first 28 days post-conception. The Botswana group analysed outcomes in women commencing DTG or non-DTG containing-ART prior to conception, and found a higher prevalence of neural tube defects in those exposed to DTG: 4/426 (0.94%) versus 14/11300 (0.12%). Defects in the DTG group were anencephaly, encephalocele, myelomeningocele with undescended testes, and iniencephaly with a major limb defect. None of the 4 on DTG were epileptic or diabetic, none received folate supplementation. At the time of the first analysis, there were no neural tube defects in 2812 women who started DTG during pregnancy. There were neural tube defects in 61 of 66057 (0.09%) infants born to HIV negative women (Zash, Makhema et al. 2018 [xxix]). This is a safety signal of concern.

The investigators presented an updated analysis at the AIDS conference 2018, at which time there had been 2 further neural tube defects: one myelomeningocele in an infant exposed to DTG starting in the 7th week of pregnancy, and one in infant with an HIV negative mother. Updated prevalence in the group with DTG exposure at the time of conception is 4/596 (0.67%, 95%CI 0.26% to 1.7%)(Zash, Holmes et al. 2018[xxxv]). The next planned analysis is March 2019.

In another analysis in the same cohort the Botswana group compared birth outcomes between 1729 women who initiated DTG during pregnancy and 4593 who initiated efavirenz based ART; median gestational age at ART initiation 19 weeks (IQR 14 to 25) and 21 (IQR 16 to 27) respectively. Risk of adverse outcome (stillbirth, preterm <37wk, small for gestational age <10th percentile, neonatal death) and severe adverse outcome (stillbirth, neonatal death, very preterm <32 wk.) were similar: DTG versus efavirenz 33.2% vs 35.5%, aRR 0.95 (95% CI 0.88 to 1.03) and 10.7% vs 11.3% aRR 0.94 (95% CI 0.81 to 1.11) respectively. There were no differences in those individual outcomes. This study is limited in that data on congenital anomalies is based on surface examination at birth, with results for 675 first trimester exposures only (280 exposures to DTG and 395 to efavirenz); they reported one major congenital anomaly (skeletal dysplasia in an efavirenz-exposed infant) and six cases of postaxial polydactyly type B (Zash, Jacobson et al. 2018 [xxviii]).

In registration trials and Compassionate Use programmes, among 38 pregnancies, 1 congenital anomaly, 18 live births without any anomalies, 9 elective terminations without any anomalies, 13 spontaneous

abortions without any anomalies, and 3 ectopic pregnancies were described. In post marketing surveillance, 74 pregnancies were reported as of 16 January 2016, with 18 live births without any anomalies, 2 live births with congenital anomalies, 4 spontaneous abortions without anomaly, 1 spontaneous abortion with anomaly, 1 stillbirth without anomaly and 39 pregnancies ongoing or lost to follow-up[xxxvi]. In the 2018 Antiretroviral pregnancy registry update, no neural tube defects had been observed in 688 periconception integrase stand transferase inhibitor (InSTI) exposures reported to the registry; this includes 201 DTG exposures (Committee 2018 [xxx]). To date there have been 401 DTG exposures reported and 12 defects: in 6 of 201 patients with exposure at conception, 2 of 61 with first trimester exposure, and 4 of 139 with 2nd/3rd trimester exposure. The current estimate of prevalence of birth defects with first trimester DTG exposure is 3.5% (95% CI 1.5 to 6.8) (Committee 2018 [xxx]).

A study from IMPAACT 1026 of pharmacokinetics of DTG in pregnancy (presented at CROI in 2016, and now published) in 29 mother-infant pairs, reported seven infant abnormalities at birth: total anomalous pulmonary venous return (1 case, mother started DTG at 16 weeks, assessed as unrelated to drug exposure); renal anomalies in 2 infants which were both assessed as possibly related to drug exposure (1 isolated renal cyst and 1 multicystic dysplastic kidney); congenital chin tremor (1 case) which resolved; congenital filum terminale lipoma (1 case); 2 vessel umbilical cord (1 case); supernumerary digit (1 case) (Mulligan, Best et al. 2018 [xxvii]).

A systematic review of studies reporting birth outcomes and congenital anomalies in DTG-exposed pregnancies included 1200 pregnancies with DTG exposed pregnancies and compared these to controls from 5 historical studies. The largest contributor of DTG exposures to this systematic review was the Botswana cohort; the systematic review included data from a conference proceeding for this cohort. (Those data were later published (Zash, Jacobson et al. 2018 [xxviii])). There was no difference in pregnancy outcomes (stillbirth, preterm birth (<37 wk.), or small for gestation age between DTG exposed pregnancies and historical controls. Percentage with congenital anomalies ranged widely, between 0% in Botswana study (n=845) and the IMPAACT P1026 study- the systematic review reports a prevalence of 13.3% in this study based on the conference abstract; in the peer reviewed publication 7/29 (24%) has defects, of which 2 were thought to be possibly caused by DTG as described above (Mulligan, Best et al. 2018 [xxvii]).

A retrospective cohort analysis from 2 urban clinics in the USA reported outcomes in 66 DTG exposed pregnancies, of which 57 delivered. There were 2 birth defects (non-immune hydrops fetalis and a cardiac defect: endocardial fibroelastosis versus ventricular septal defect); 31.6 were born prematurely and 15.8% were small for gestational age (Grayhack, Sheth et al. 2018 [xxv]). A small retrospective cohort analysis of 36 DTG exposed pregnancies (14 commenced DTG before pregnancy and 22 during pregnancy) in Stockholm reported 4 early spontaneous abortions, 1 late termination and 1 loss to follow up. There was 1 preterm delivery for maternal indication, and no malformations (Bornhede, Soeria-Atmadja et al. 2018 [xxiv]). A very small retrospective cohort study compared 7 patients with InSTI exposure to 14 patients taking protease inhibitors and found similar outcomes; this study only included one patient exposed to DTG and outcomes are not disaggregated by drug (Mounce, Pontiggia et al. 2017 [xxiii]).

Background prevalence of birth defects in South Africa and risks of birth defects with efavirenz

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

There were previously concerns about efavirenz exposure during pregnancy, in particular regarding neurodevelopmental defects but data on efavirenz exposure in pregnancy has not shown increased prevalence of birth defects with efavirenz exposure *in utero*. In a systematic review of observational cohort studies (16 studies; 1256 efavirenz-exposed live births) incidence of overall birth defects in infants with first trimester efavirenz exposure was 2.9% (95% confidence interval 2.1 to 4%). One neural tube defect was seen with first trimester efavirenz exposure, giving a prevalence of 0.08% (95% CI 0.002-0.44%). Relative risk of birth defect in efavirenz exposed women compared with those on other regimens was 0.87 (95% confidence interval 0.61 to 1.24)[xxxix].

Rifampicin-containing tuberculosis treatment

DTG metabolism (primarily by UGT1A1 with CYP3A as minor route) is induced by concomitant rifampicin. In a phase 1 pharmacokinetic drug interaction conducted in healthy volunteers (n=12) DTG concentrations were similar when dosed at 50mg daily without rifampicin and at 50 mg 12 hourly with rifampicin 600mg daily: geometric mean ratio (GMR) for the 24-hour area under the time-concentration curve (AUC_{0-24}) was 1.33 [90% confidence interval (CI): 1.14 to 1.53], and the GMR for the trough (C_{tau}) was 1.22 (90% CI: 1.01 to 1.48) [xix]. Based on this pharmacokinetic study, 12 hourly dosing of DTG is recommended with rifampicin-based TB treatment [xix].

An interim analysis of a trial which randomised ARV naïve patients on rifampicin-containing TB treatment commencing ART to efavirenz (44 patients) or DTG 50mg 12 hourly (69 patients) found that 39/44 (89%) and 56/69 (81%) respectively had VL<50 copies/mL at 24 weeks (Dooley, Kaplan et al. 2018). DTG 50 mg 12 hourly was well tolerated. There were 2 discontinuations for adverse events, both on efavirenz. This RCT was presented at a conference (CROI 2018 [xxxiii]) and has not yet been published in a peer-reviewed journal. A case series of 10 patients treated with DTG 50 mg 12 hourly over 3 years in the UK reported virological suppression at 24 weeks of 9/10, and no severe side effects (Cevik and McGann 2018 [xxxi]). There was a case report of subtherapeutic DTG concentrations, virological failure, and emergence of virological resistance in a woman treated with rifampicin (for a staphylococcal infection) and commenced on DTG-containing ART, despite 12 hourly DTG dosing and directly observed medicine intake (Pena, Chueca et al. 2019 [xxxii]).

9. Other potential considerations

Barrier to resistance

DTG appears to have a high resistance barrier, with no cases of DTG resistance documented in ARV-naive patients in high-income countries where the drug has been used for over three years. Switching to DTG-based first-line ART might limit the number of patients transitioning to more expensive, less tolerable and less convenient second-line regimens, resulting in direct and indirect cost savings.

Renal function effects

DTG inhibits tubular creatinine excretion resulting in modest plasma creatinine elevations and corresponding reductions in creatinine clearance/eGFR. These changes typically manifest within 2–4 weeks and are non-progressive with no associated with haematuria, proteinuria or glycosuria. This change in eGFR does not reflect clinically significant kidney injury [xl]. However this might need to be taken into account in renal function monitoring guidelines especially if DTG is used in combination with tenofovir.

Potential cost savings

DTG requires a smaller dose than EFV (50 mg versus 600 mg). Low dose drugs require smaller amounts of Active Pharmaceutical Ingredients (API), which lowers manufacturers' costs. Moving from EFV-based first-line to DTG could result in significant cost savings once volumes are met [i].

Drug interactions

There are interactions between dolutegravir and other medicines. The interaction with rifampicin is dealt with in this medicine review, above. There are other clinically relevant drug interactions e.g. with anticonvulsants (phenytoin, phenobarbitone, carbamazepine, valproate), metformin, aluminium and magnesium containing antacids, calcium supplements, iron supplements.

For drug interactions and recommendations regarding implications for management, please refer to the following:

1. University of Liverpool drug interactions website: https://www.hiv-druginteractions.org/checker
2. The Medicines Information Center ARV/EML Drug interaction booklet.

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

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?
Confident [x] Not confident [ ] Uncertain [ ]</td><td>See evidence synthesis table</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [x]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

References:</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 [x] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Price of medicines/ month:
<table><tr><th>Medicine</th><th>Price (R)</th></tr><tr><td>DTG (50mg)+ABC (600mg)+3TC (300mg), 30 tabs</td><td>R 507.04*</td></tr><tr><td>DTG (50mg), 30 tabs</td><td>R 423.46**</td></tr><tr><td>EFV (600mg), 28 tabs</td><td>R 49.36**</td></tr><tr><td>EFV (600mg)+FTC (200mg)+TDF (200 mg), 28 tabs</td><td>R 125.34**</td></tr><tr><td>DTG (50mg)+3TC (300mg)+TDF (200 mg), 28 tabs</td><td>R 85.03***</td></tr></table>*SEP Database 21 Dec 2018 - currently MCC registered products (average price)
Note: DTG is not currently listed on the MSH International Medical Products Price Guide. http://mshpriceguide.org/en/home/
**Contract circular HP13-2015ARV (weighted average price)
***Contract circular RT71-2019, wef 1 July2019 (weighted average price)

Additional resources:
Venter WDF, Kaiser B, Pillay Y, Conradie F, Gomez GB, Clayden P, Matsolo M, Amole C, Rutter L, Abdullah F, Abrams EJ, Casas CP, Barnhart M, Pillay A, Pozniak A, Hill A, Fairlie L, Boffito M, Moorhouse M, Chersich M, Seranata C, Quevedo J, Loots G. Cutting the cost of South African antiretroviral therapy using newer, safer drugs. SAMJ 2017;107(1):28-30.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]</td><td></td></tr>
</table>

FEASIBILITY	Is the implementation of this recommendation feasible? Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[ ]	[ ]	[ ]	[X]	[ ]

Recommendation: After the first iteration of this review, the Primary Healthcare expert review committee (ERC) recommendation was as follows:
Based on the appraisal of the evidence presented in this technical review, the Primary Healthcare ERC recommends that dolutegravir be introduced into the first-line antiretroviral regimen (in combination with 2 N(t)RTIs) for HIV-infected adult patients commencing ART.
However, in response to the neural tube defect signal, DTG is not recommended for use in early pregnancy and DTG should be avoided in women of child-bearing potential who are not on reliable contraception.
Patients requiring concomitant rifampicin-containing TB therapy would require DTG dose adjustment. Alternatively switching to efavirenz-based ART for the duration of the TB therapy could be considered.
Rationale: Evidence of superior efficacy and potenitally superior barrier to resistance of dolutegravir compared with efavirenz; though there is limited evidence for use in pregnancy. Pharmacokinetic data indicate dose adjustment is necessary with concomitant rifampicin (rifampicin is a strong inducer of UGTIA3 and CYP3A4, and reduces DTG concentrations).

Level of Evidence: I Systematic review, RCT

NEMLC MEETING OF 21 FEBRUARY 2019:

- NEMLC accepted the above-mentioned reccomendation at the meeting of 21 February 2019, noting the caution to avoid DTG in women of childbearing potential who are not on reliable contraception.
- NEMLC recommended that respective DTG drug-drug interactions would require to be appropiately documented (probably as guidance in the STGs).

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[x]	[ ]

VEN status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

Monitoring and evaluation considerations

Research priorities: Clinical outcomes with TB treatment and in pregnancy

ANNEXURE A

Potential DTG-containing regimens

A FDC (fixed dose combination) would be preferred. Regimen options include:

1. DTG + TDF + FTC
2. DTG + TDF + 3TC
3. DTG + ABC + 3TC
1. DTG + TAF* + FTC
2. DTG + TAF* + 3TC

*not yet approved by the Medicines Control Council, South Africa

Abbreviations

DTG	Dolutegravir
TDF	Tenofovir disoproxil fumarate
FTC	Emtricitabine
3TC	Lamivudine
ABC	Abacavir
TAF	Tenofovir alafenamide fumarate

REFERENCES

[i] Venter WDF, Kaiser B, Pillay Y, Conradie F, et al. Cutting the cost of South African antiretroviral therapy using newer , safer drugs. SAMJ 2017;107(1):28–30.

[ii] INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med [Internet]. 2015;373(9):795–807. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26192873%5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4569751

[iii] TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med [Internet]. 2015;373(9):808–22. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1507198

[iv] National Department of Health HIV Consolidated Guidelines , 2013;(June).

[v] Al-Dakkak I, Patel S, McCann E, Gadkari A, Prajapati G, Maiese EM. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. AIDS Care [Internet]. 2013;25(4):400–14. Available from: http://www.tandfonline.com/doi/abs/10.1080/09540121.2012.712667

[vi] ART-LINC of IeDEA Study Group., Keiser O, Tweya H, Boulle A, Braitstein P,Schecter M, et al. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. AIDS. 2009 Sep 10;23(14):1867-74

[vii] Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV [Internet]. 2016 Sep 28; Available from: http://dx.doi.org/10.1016/S2352-3018(16)30091-1

[viii] You J, Wang H, Huang X, Qin Z, Deng Z, Luo J. Therapy-Emergent Drug Resistance to Integrase Strand Transfer Inhibitors in HIV-1 Patients : A Subgroup Meta-Analysis of Clinical Trials. PlosOne 2016;1–19.

[ix] Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV : A Systematic Review. PlosOne 2016;1–13.

[x] Ford N, Shubber Z, Pozniak A, Vitoria M, Doherty M, Kirby C, et al. Comparative Safety and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials. J Acquir Immune Defic Syndr [Internet]. 2015;69(4):422–9. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-900000000-97607%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/25850607

[xi] atel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R, et al. 48-Week Efficacy and Safety of Dolutegravir Relative to Commonly Used Third Agents in Treatment-Naive HIV-1 – Infected Patients : A Systematic Review and Network. Plos One 2014;9(9):1–10.

[xii] Jiang J, Xu X, Guo W, Su J, Huang J, Liang B, et al. Dolutegravir (DTG , S / GSK1349572) combined with other ARTs is superior to RAL - or EFV - based regimens for treatment of HIV - 1 infection : a meta - analysis of randomized controlled trials. AIDS Res Ther 2016;1–10.

[xiii] Lunzen J Van, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S / GSK1349572) in combination therapy in antiretroviral-naive adults with HIV : planned interim 48 week results from SPRING-1 , a dose-ranging , randomised , phase 2b trial. Lancet Infect Dis [Internet]. 12(2):111–8. Available from: http://dx.doi.org/10.1016/S1473-3099(11)70290-0

[xiv] Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med [Internet]. 2013;369(19):1807–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24195548

[xv] Walmsley S, Baumgarten A, Berenguer J, Felizarta F, Florence E, Khuong-josses M, et al. Dolutegravir Plus Abacavir / Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients : Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. N Engl J Med 2015;70(5):1–3.

[xvi] Tebas P, Kumar P, Hicks C, Granier C, Wynne B, Min S, et al. Greater change in bone turnover markers for efavirenz / emtricitabine / tenofovir disoproxil fumarate versus dolutegravir R abacavir / lamivudine in antiretroviral therapy-naive adults over 144 weeks. AIDS 2015;(April):2459–64.

[xvii] Stellbrink H-J, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1 : 96-week results from a randomized dose-ranging study. AIDS 2013;(March) 27:1771–1778.

[xviii] Raffi F, Rachlis A, Brinson C, Arasteh K, Brennan C, Pappa K, et al. Dolutegravir efficacy at 48 weeks in key subgroups of treatment-naive HIV-infected individuals in three randomized trials Franc. AIDS 2015;167–74.

[xix] Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety , Tolerability , and Pharmacokinetics of the HIV Integrase Inhibitor Dolutegravir Given Twice Daily With Rifampin or Once Daily With Rifabutin : Results of a Phase 1 Study Among Healthy Subjects. J Acquir Immune Defic Syndr 2013;62(1):21–7.

[xx] Report I. THE ANTIRETROVIRAL PREGNANCY REGISTRY [Internet]. Vol. Dec 2016. 2016. Available from: http://www.apregistry.com/forms/interim_report.pdf

[xxi] Fettiplace, A., C. Stainsby, A. Winston, N. Givens, S. Puccini, V. Vannappagari, R. Hsu, J. Fusco, R. Quercia, M. Aboud and L. Curtis (2017). "Psychiatric Symptoms in Patients Receiving Dolutegravir." J Acquir Immune Defic Syndr **74**(4): 423-431.

[xxii] Hill, A. M., N. Mitchell, S. Hughes and A. L. Pozniak (2018). "Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomized trials." Curr Opin HIV AIDS **13**(2): 102-111.

[xxiii] Mounce, M. L., L. Pontiggia and J. L. Adams (2017). "A Single-Center Retrospective Cohort Analysis of Maternal and Infant Outcomes in HIV-Infected Mothers Treated with Integrase Inhibitors During Pregnancy." Infect Dis Ther **6**(4): 531-544.

[xxiv] Bornhede, R., S. Soeria-Atmadja, K. Westling, K. Pettersson and L. Naver (2018). "Dolutegravir in pregnancy-effects on HIV-positive women and their infants." Eur J Clin Microbiol Infect Dis **37**(3): 495-500.

[xxv] Grayhack, C., A. Sheth, O. Kirby, J. Davis, K. Sibliss, H. Nkwihoreze, E. Aaron, G. Alleyne, R. Laguerre, A. Rana, M. Badell and F. Momplaisir (2018). "Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy." AIDS **32**(14): 2017-2021.

[xxvi] Hill, A., P. Clayden, C. Thorne, R. Christie and R. Zash (2018). "Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review." J Virus Erad **4**(2): 66-71.

[xxvii] Mulligan, N., B. M. Best, J. Wang, E. V. Capparelli, A. Stek, E. Barr, S. L. Buschur, E. P. Acosta, E. Smith, N. Chakhtoura, S. Burchett and M. Mirochnick (2018). "Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV." Aids **32**(6): 729-737.
[xxviii] Zash, R., D. L. Jacobson, M. Diseko, G. Mayondi, M. Mmalane, M. Essex, T. Gaolethe, C. Petlo, S. Lockman, L. B. Holmes, J. Makhema and R. L. Shapiro (2018). "Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study." Lancet Glob Health **6**(7): e804-e810.
[xxix]Zash, R., J. Makhema and R. L. Shapiro (2018). "Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception." N Engl J Med **379**(10): 979-981.
[xxx] Committee, A. P. R. S. (2018). THE ANTIRETROVIRAL PREGNANCY REGISTRY INTERIM REPORT December 2018 : http://www.apregistry.com/forms/interim_report.pdf. Wilmington, NC, Registry Coordinating Center.
[xxxi] Cevik, M. and H. McGann (2018). "Dolutegravir use in combination with rifampicin-based tuberculosis therapy: 3 years of real-world experience in a large UK teaching hospital." Sex Transm Infect **94**(6): 420.
[xxxii] Pena, M. J., N. Chueca, A. D'Avolio, J. M. Zarzalejos and F. Garcia (2019). "Virological Failure in HIV to Triple Therapy With Dolutegravir-Based Firstline Treatment: Rare but Possible." Open Forum Infect Dis **6**(1): ofy332.
[xxxiii] Dooley, K., R. Kaplan, N. Mwelase, B. Grinsztejn, E. Ticona, M. Lacerda, P. Cahn, E. Belonosova, M. Ait-Khaled, Angelis, K., D. Brown, R. Singh, C. Talarico, A. Tenorio and M. Aboud (2018). SAFETY AND EFFICACY OF DOLUTEGRAVIR-BASED ART IN TB/HIV COINFECTED ADULTS AT WEEK 24 Abstract 33. Conference of Retroviruses and Opportunistic Infections. Boston, Massachusetts.
[xxxiv] Sinxadi PZ, Leger PD, McIlleron HM, Smith PJ, Dave JA, Levitt NS, et al. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. Br J Clin Pharmacol. 2015;80(1):146–56.
[xxxv] Zash, R., L. Holmes, J. Makhema, D. Diseko, D. L. Jacobsen, G. Mayondi, M. M., L. Mofenson, T. Gaolathe, C. Petlo, M. Essex, S. Lockman and R. L. Shapiro (2018). Surveillance for neural tube defects following antiretroviral exposure from conception- symposium presentation (Safety of Dolutegravir in pregnancy). AIDS. Amsterdam.
[xxxvi] Clayden BP, Collins S, Frick M, Harrington M, Horn T, Jefferys R, et al. 2016 PIPELINE REPORT.
[xxxvii] Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa , 2000 DifJ. 2010;93(9).
[xxxviii] Dheda M, Mhlongo O, Van Schalkwyk C, Maharaj N, Moran N, Naidoo P, et al. Birth outcomes following antiretroviral exposure during pregnancy: Results from the first year of the South African pregnancy exposure registry and birth defect surveillance system WEPEC162. In 2016. p. 361–2
[xxxix] Ford N, Mofenson L, Shubber Z, Calmy A, Andrieux-meyer I, Vitoria M, et al. Safety of efavirenz in the first trimester of pregnancy : an updated systematic review and meta-analysis. AIDS. 2014 Mar;28 Suppl 2:S123-31.
[xl] Yombi JC, Pozniak A, Boffito M, Jones R, Khoo S, Levy J, et al. Antiretrovirals and the kidney in current clinical practice : renal pharmacokinetics , alterations of renal function and renal toxicity. AIDS. 2014 Mar 13;28(5):621-32

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

ADDENDUM

Title: Initiating dolutegravir-containing antiretroviral therapy in patients receiving rifampicin-containing TB treatment

Date: 21 July 2021

Reviewer: Karen Cohen

Affiliation and declaration of interests: KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) has no interests to declare with respect to dolutegravir.

Background: Dolutegravir (DTG) in people living with HIV and AIDs (PLWHA) commencing antiretroviral therapy was reviewed in January 2017, and the review updated in February 2019. This document is an addendum to the 2019 medicine review update, focussing on initiation of DTG in patients receiving rifampicin-containing TB treatment.

Dolutegravir-rifampicin interaction: Dolutegravir (DTG) metabolism is induced by concomitant rifampicin. In a phase 1 pharmacokinetic drug interaction conducted in healthy volunteers (n=12) DTG concentrations were similar when dosed at 50mg daily without rifampicin and at 50 mg 12 hourly with rifampicin 600mg daily: geometric mean ratio (GMR) for the 24-hour area under the time-concentration curve (AUC_{0-24}) 1.33 [90% confidence interval (CI): 1.14 to 1.53], GMR for the trough (C_{tau}) 1.22 (90% CI: 1.01 to 1.48)[1]. Based on this pharmacokinetic study, which was included in the 2019 review update, 12 hourly dosing of DTG is recommended with rifampicin-based TB treatment in the current Essential Medicines List (EML) standard treatment guidelines (STGs), for patients who start rifampicin-containing TB treatment when already taking DTG-containing ART. However, for patients starting antiretroviral therapy during TB treatment, efavirenz-containing ART was recommended for the duration of TB treatment, with switch to DTG on completion of TB treatment. The rationale for that recommendation was that at the time of STG compilation, there was very limited clinical outcome data on patients treated with concomitant DTG and efavirenz. In addition, efavirenz does not require dose adjustment with concomitant rifampicin.

INSPIRING study: Since formulation of the STGs, results of a randomised "non-comparative" trial assessing efficacy and safety of DTG in patients initiating DTG-containing ART while on rifampicin containing TB treatment, the "INSPIRING" study have been published[2]. This open label study randomised HIV-1–infected antiretroviral therapy–naive adults (CD4+ ≥50 cells/mm3) on rifampicin-based tuberculosis treatment for ≤8 weeks to receive DTG 50 mg twice daily both during and 2 weeks after tuberculosis therapy, then 50 mg once daily (n=69) or efavirenz 600 mg daily (n=44). Both interventions were given with 2 nucleoside reverse transcriptase inhibitors, and participants were followed up for 52 weeks. The primary endpoint was the proportion of DTG-arm participants with plasma HIV-1-RNA <50 copies/mL (responders) by the Food and Drug Administration Snapshot algorithm (intent-to-treat exposed population i.e., all participants who received at least 1 dose of study drug) at Week 48. The trial was not powered to show a difference between study arms and no formal statistical hypothesis was tested. Participants were randomised to 3:2 to DTG and efavirenz to increase precision of estimates for DTG group. A sample size of 66 to 72 participants in the DTG arm was estimated to have >85% power to detect a response rate of greater than 70%, assuming an 85% response rate at Week 48.

Results:

- Week 48 response rates: 75% virologically suppressed (52/69, 95% confidence interval [CI] 65–86%) for DTG and 82% (36/44, 95% CI 70–93%) for efavirenz. The DTG "nonresponses" were driven by non–treatment related discontinuations (10 were lost to follow-up in the DTG arm before week 48, most after completion of TB treatment).
- No deaths or study drug switches.

- Two discontinuations for toxicity, both in the efavirenz arm.
- Three protocol-defined virological failures (confirmed viral load>400 copies per mL at or beyond 24 weeks on treatment), 2 in the DTG arm, neither of which had acquired resistance, and 1 in the efavirenz arm with emergent resistance to nucleoside reverse transcriptase inhibitors and nonnucleoside reverse transcriptase inhibitors.

***Conclusions**:* The INSPIRING randomised trial was not powered to compare outcomes between DTG and efavirenz. However, it demonstrated that DTG-containing ART with DTG double dosing is well tolerated. Virological outcomes for efavirenz and DTG were similar.

Currently, the STG include double dosing of DTG during TB treatment for patients diagnosed with TB on DTG. However, for the patients initiating ART while on TB treatment, the only option in the STGs currently is efavirenz-based ART for the duration of TB treatment. Switch to DTG after TB treatment is then required.

There is to date no randomised data on standard dose DTG with rifampicin-containing TB treatment- but a trial is under way (NCT03851588. Standard Versus Double Dose Dolutegravir in Patients With HIV-associated Tuberculosis-RADIANT-TB). Efavirenz has the advantage of not requiring any dose adjustment, but regimen switches increase programmatic complexity, and TEE may become less readily available as it is no longer the preferred option for WOCP. In addition, efavirenz is not tolerated by all patients.

RECOMMENDATION

Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment.. *Rationale:* Randomised open-label INSPIRING study showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.

Level of evidence: Low certainty evidence

NEMLC MEETING 29 JULY 2021:

The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above and recommended that the report and review be circulated for external comment.

References

1. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr* 2013; 62(1):21-27.

2. Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. *Clin Infect Dis* 2020; 70(4):549-556.

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
1) Department of Health, North West Province, South Africa.
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
1) Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand

Prof K Cohen
No applicable conflicts of interest to declare
1) Department of Clinical Pharmacology, University of Cape Town

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

References

1. Johnson LF, Chiu C, Myer L, Davies MA, Dorrington RE, Bekker LG, et al. Prospects for HIV control in South Africa: a model-based analysis. Glob Health Action. 2016 Jan;9(1):30314.

2. National Department of Health. The South African Antiretroviral Treatment Guidelines. 2010.

3. Franey C, Knott D, Barnighausen T, Dedicoat M, Adam A, Lessells RJ, et al. Renal impairment in a rural African antiretroviral programme. BMC Infect Dis. 2009 Aug;9:143.

4. Brennan A, Evans D, Maskew M, Naicker S, Ive P, Sanne I, et al. Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir. AIDS. 2011 Aug;25(13):1603–9.

5. Seedat F, Martinson N, Motlhaoleng K, Abraham P, Mancama D, Naicker S, et al. Acute Kidney Injury, Risk Factors, and Prognosis in Hospitalized HIV-Infected Adults in South Africa, Compared by Tenofovir Exposure. AIDS Res Hum Retroviruses. 2017 Jan;33(1):33–40.

6. Le MP, Landman R, Koulla-Shiro S, Charpentier C, Sow PS, Diallo MB, et al. Tenofovir plasma concentrations related to estimated glomerular filtration rate changes in first-line regimens in African HIV-infected patients: ANRS 12115 DAYANA substudy. J Antimicrob Chemother. 2015 May;70(5):1517–21.

7. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007 Jun;21(10):1273–81.

8. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis. 2010 Sep;51(5):496–505.

9. Woodward CLN, Hall AM, Williams IG, Madge S, Copas A, Nair D, et al. Tenofovir-associated renal and bone toxicity. HIV Med. 2009 Sep;10(8):482–7.

10. Kamkuemah M, Kaplan R, Bekker LG, Little F, Myer L. Renal impairment in HIV-infected patients initiating tenofovir-containing antiretroviral therapy regimens in a Primary Healthcare Setting in South Africa. Trop Med Int Health. 2015 Apr;20(4):518–26.

11. De Waal R, Cohen K, Fox MP, Stinson K, Maartens G, Boulle A, et al. Changes in estimated glomerular filtration rate over time in South African HIV-1-infected patients receiving tenofovir: a retrospective cohort study. J Int AIDS Soc. 2017 Apr;20(1):1–8.

12. G B. HIV-related renal disease: a clinical and practical approach in the South African context. South Africa Medical Journal. 2003;(Feb):11–4.

13. Franceschini N, Napravnik S, Eron JJJ, Szczech LA, Finn WF. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. Kidney Int. 2005 Apr;67(4):1526–31.

14. Matovu FK, Wattanachanya L, Beksinska M, Pettifor JM, Ruxrungtham K. Bone health and HIV in resource-limited settings: a scoping review. Curr Opin HIV AIDS. 2016 May;11(3):306–25.

15. Shiau S, Broun EC, Arpadi SM, Yin MT. Incident fractures in HIV-infected individuals: a systematic review and meta-analysis. AIDS. 2013 Jul;27(12):1949–57.

16. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis. 2010 Oct;51(8):963–72.

17. Grant PM, Cotter AG. Tenofovir and bone health. Curr Opin HIV AIDS. 2016 May;11(3):326–32.

18. Bedimo RJ, Drechsler H, Jain M, Cutrell J, Zhang S, Li X, et al. The RADAR study: week 48 safety and efficacy of RAltegravir combined with boosted DARunavir compared to tenofovir/emtricitabine combined with boosted darunavir in antiretroviral-naive patients. Impact on bone health. PLoS One. 2014;9(8):e106221.

19. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JMAH, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004 Jul;292(2):191–201.

20. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACT. J Infect Dis. 2011 Jun;203(12):1791–801.

21. Orkin C, DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV. 2017 May;4(5):e195–204.

22. Gotham D, Hill A, Pozniak AL. Candidates for inclusion in a universal antiretroviral regimen: tenofovir alafenamide. Curr Opin HIV AIDS. 2017 Apr;

23. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr. 2014 Sep;67(1):52–8.

24. Gallant JE, Daar ES, Raffi F, Brinson C, Ruane P, DeJesus E, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, activ. Lancet HIV. 2016 Apr;3(4):e158-65.

25. Arribas JR, Thompson M, Sax PE, Haas B, McDonald C, Wohl DA, et al. Brief Report: Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results. J Acquir Immune Defic Syndr. 2017 Jun;75(2):211–8.

26. Wohl D, Oka S, Clumeck N, Clarke A, Brinson C, Stephens J, et al. Brief Report: A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results. J Acquir Immune Defic Syndr. 2016 May;72(1):58–64.

27. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with

HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis. 2016 Jan;16(1):43–52.

28. Sax PE, Wohl D, Yin MT, Post F, DeJesus E, Saag M, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015 Jun;385(9987):2606–15.

29. Pozniak A, Arribas JR, Gathe J, Gupta SK, Post FA, Bloch M, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J Acquir Immune Defic Syndr. 2016 Apr;71(5):530–7.

30. Cerrone M, Alfarisi O, Neary M, Marzinke MA, Parsons TL, Owen A, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. Journal of Antimicrobial Chemotherapy. 2019 Jun 1;74(6):1670–8.

31. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, et al. Tenofovir Alafenamide for Drug-Resistant Hepatitis B: A Randomized Trial for Switching From Tenofovir Disoproxil Fumarate. Clinical Gastroenterology and Hepatology. 2022 Feb;20(2):427-437.e5.

32. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018 Apr;68(4):672–81.

33. Chinula L, Ziemba L, Brummel S, McCarthy K, Coletti A, Krotje C, et al. Efficacy and safety of three antiretroviral therapy regimens started in pregnancy up to 50 weeks post partum: a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet HIV. 2023 Jun;10(6):e363–74.

34. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, et al. Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials. Clinical Infectious Diseases. 2021 Oct 20;73(8):1440–51.

35. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020 Oct;7(10):e666–76.

36. Venter WDF, Sokhela S, Simmons B, Moorhouse M, Fairlie L, Mashabane N, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV. 2020 Oct;7(10):e666–76.

37. Tao X, Lu Y, Zhou Y, Zhang L, Chen Y. Efficacy and safety of the regimens containing tenofovir alafenamide versus tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection: A meta-analysis of randomized controlled trials. International Journal of Infectious Diseases. 2020 Apr;93:108–17.

38. Tao X, Lu Y, Zhou Y, Huang Y, Chen Y. Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens: A meta-analysis of randomized controlled trials. International Journal of Infectious Diseases. 2019 Oct;87:43–53.

39. Tamuzi JL. Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate: Systematic Review and Meta-Analysis. International Journal of Pulmonary & Respiratory Sciences. 2018 Mar 19;2(5).

40. Vitoria M, Ford N, Clayden P, Pozniak AL, Hill AM. When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO Think Tank. Curr Opin HIV AIDS. 2017 Apr;

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:
[1.] Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand,
[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

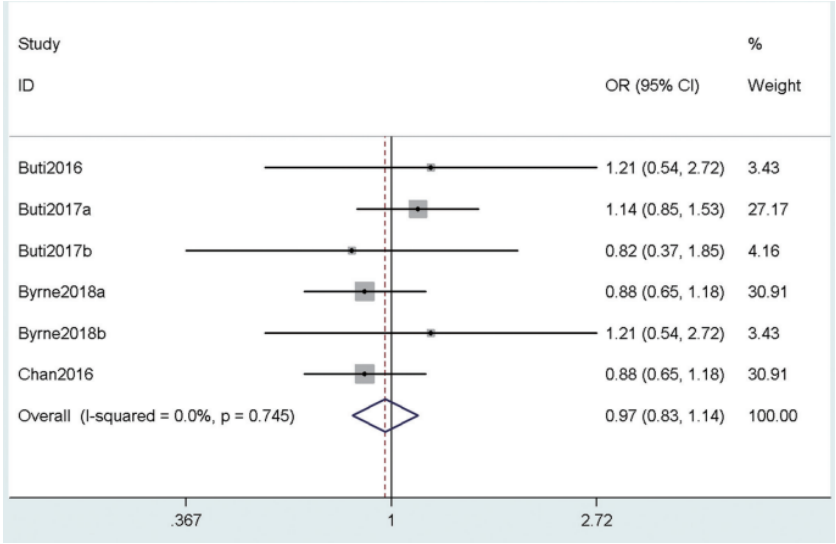


Fig 1: Pooled OR of virological response in TAF-treated vs. TDF-treated CHB patients after 48 weeks of treatment

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%).

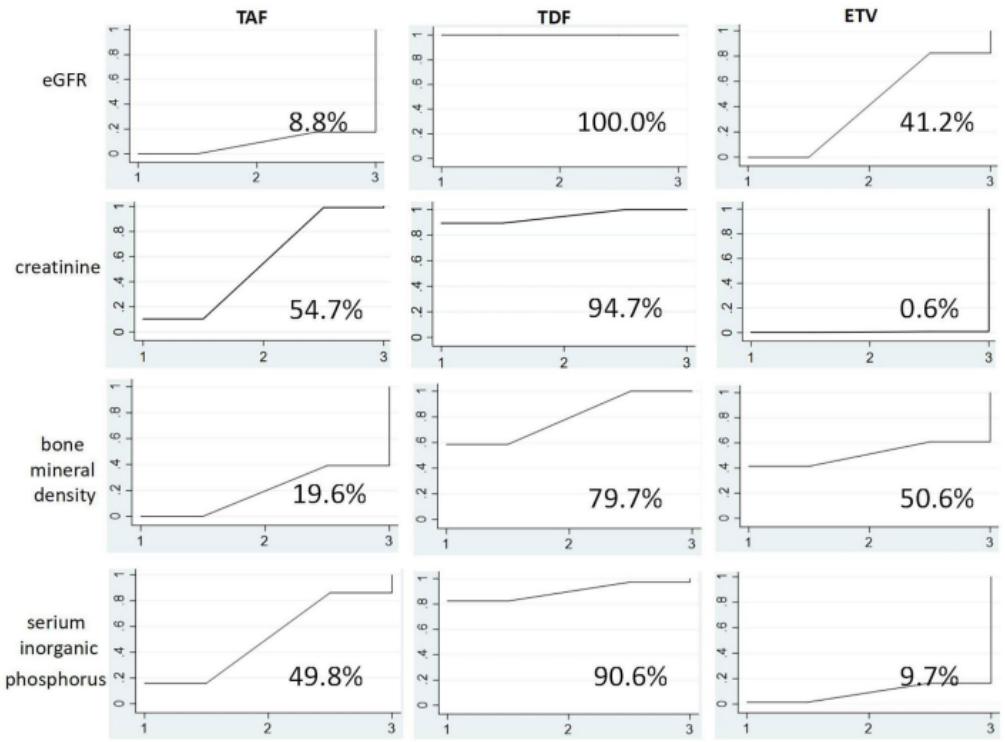


Figure 2: SUCRA diagram of side effects. The figure shows the probability of the effects of three drugs on eGFR, creatinine, bone mineral density, and blood phosphorus before and after medication. According to the level of area under the curve (SUCRA), the larger the area, the greater the index change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

REFERENCES

Chen L et al. (n.d.). Comparison of the Effects of Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) on Liver Function in Patients with Hepatitis B: A Meta-analysis. *Altern Ther Health Med [E-PUB AHEAD OF PRINT]*.

Hwang EG et al. (2023). Risk of dyslipidemia in chronic hepatitis B patients taking tenofovir alafenamide: a systematic review and meta-analysis. *Hepatology International* , :860–869.

Liu Z et al. (2023). 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 . *BMC Gastroenterology* .

Ma X, Liu S et al. (2021). Tenofovir Alafenamide Fumarate, Tenofovir Disoproxil Fumarate and Entecavir: Which is the Most Effective Drug for Chronic Hepatitis B? A Systematic Review and Meta-analysis. *Journal of Clinical and Translational Hepatology*, 335-344.

Maepa MB et al. (2022). Hepatitis B Virus Research in South Africa. *Viruses*.

Scherer de Fraga R et al. (2020). Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review. *J Gastroenterol*, 496-514.

Spearman CWN et al. (2013). South African guideline for the management of chronic hepatitis B: 2013. *SAMJ*.

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

APPENDIX

Pubmed search History

History and Search Details

Download Delete

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

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.

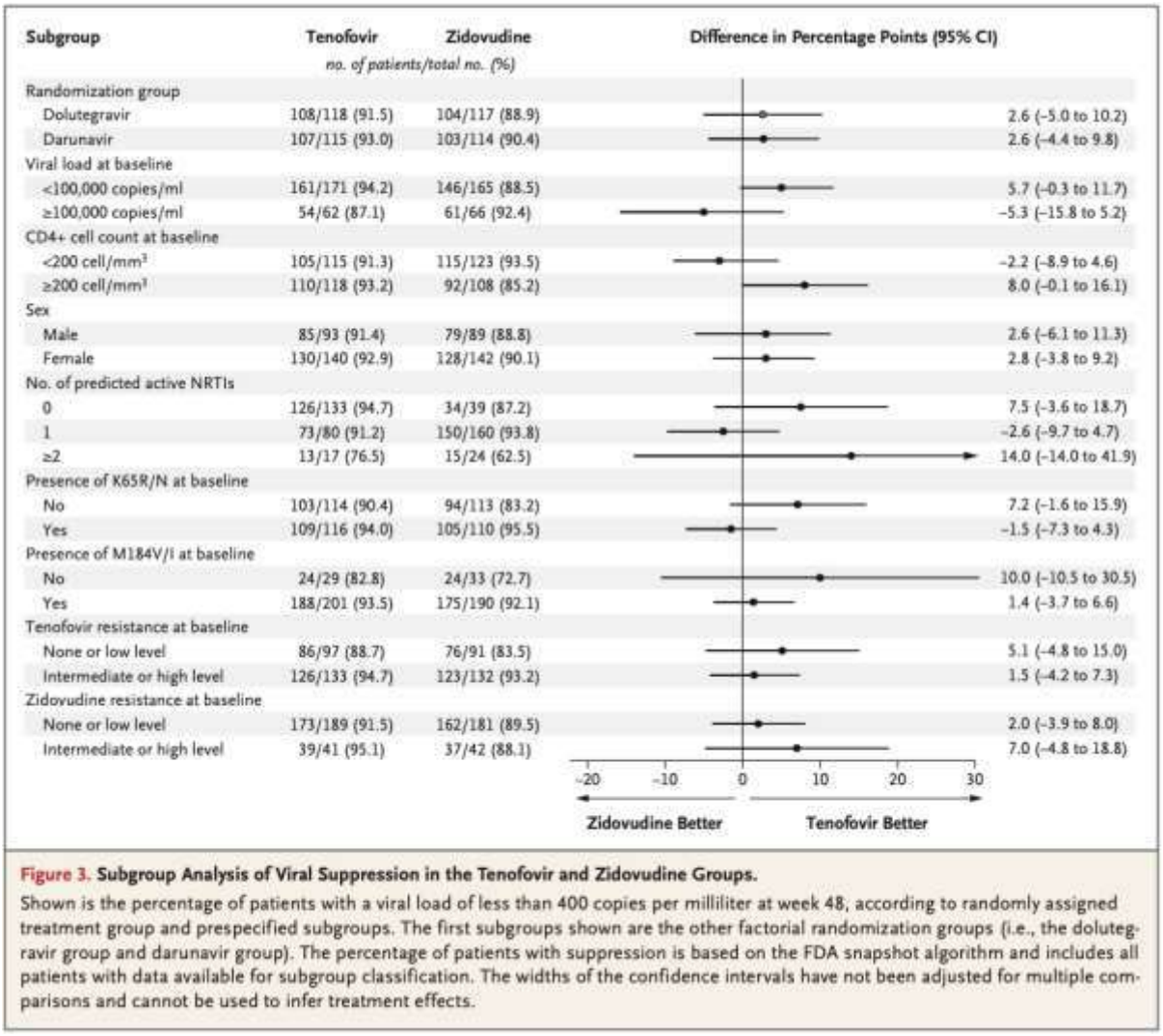


Figure 3. Subgroup Analysis of Viral Suppression in the Tenofovir and Zidovudine Groups.

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:

1. National Department of Health. National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission2019 16 August 2021. Available from: https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants.
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.
4. Paton NI, Kityo C, Thompson J, Nankya I, Bagenda L, Hoppe A, et al. Nucleoside reverse-transcriptase inhibitor cross-resistance and outcomes from second-line antiretroviral therapy in the public health approach: an observational analysis within the randomised, open-label, EARNEST trial. Lancet HIV. 2017;4(8):e341-e8.
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.

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

MEDICINE REVIEW:

TITLE: ATAZANAVIR/RITONAVIR vs LOPINAVIR/RITONAVIR FOR ADULT HIV PATIENTS

DATE: 18 November 2021

Key findings

- We conducted a review of ritonavir-boosted atazanavir (ATV/r) compared with ritonavir-boosted lopinavir (LPV/r) in protease inhibitor naïve adult people living with HIV (PLHIV).
- We included 3 randomised controlled trials and conducted meta-analyses for important clinical outcomes.
- The proportion of patients with viral load <50 copies/mL at 48 and 96 weeks was slightly higher (about 10%) with ATV/r than LPV/r; 48 weeks: relative risk (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.18 (3 studies, n=1105, moderate certainty evidence) and 96 weeks: RR 1.09, 95%CI 1.01 to 1.19 (2 studies, n=1045, moderate certainty evidence). Number needed to treat to achieve 1 additional viral load < 50: 12 (95% CI 8 to 30) and 16 (95% CI 9 to 190) at 48 and 96 weeks respectively.
- The proportion of patients who died by 48 and 96 weeks was not significantly different between ATV/r and LPV/r; 48 weeks: RR 1.01, 95% CI 0.25 to 4.00 (3 studies, n=942, moderate certainty evidence) and 96 weeks: RR 1.55, 95% CI 0.53 to 4.51 (2 studies, n=1045, moderate certainty evidence).
- The proportion of patients with grade 2 to 4 treatment related adverse events (AE) at 48 and 96 weeks was numerically lower with ATV/r than LPV/r, but this was not statistically significant; 48 weeks: RR 0.88, 95% CI 0.73 to 1.06 (3 studies, n=937, moderate certainty evidence) and 96 weeks: RR 0.88, 95% CI 0.73 to 1.06 (2 studies, n=1045, moderate certainty evidence).
- The proportion of patients with treatment discontinuations due to AEs at 48 and 96 weeks was numerically lower with ATV/r than LPV/r, but this was not statistically significant; 48 weeks: RR 0.65, 95%CI 0.37 to 1.15 (3 studies, n=1104, moderate certainty evidence) and 96 weeks: RR 0.54, 95%CI 0.29 to 1.00 (2 studies, n=1045, moderate certainty evidence).

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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 PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy.
Rationale: Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir, and is dosed once-daily.
Level of Evidence: Low to moderate certainty evidence

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e. DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.

Monitoring and evaluation considerations

Research priorities

1. EXECUTIVE SUMMARY

Date: 18 November 2021
Medicine (INN): Atazanavir, boosted with ritonavir
Medicine (ATC): J05AR23
Indication (ICD10 code): B24
Patient population: PLHIV who are protease inhibitor-naive
Prevalence of condition: Adult population of PLHIV in South Africa, estimated at 14.0% (95% CI: 13.1–15.0).(1)
Level of Care: Primary and Adult Hospital Level
Prescriber Level: Nurse practitioner, Medical Doctor, Specialist
Current standard of Care: Lopinavir based PI therapy
Efficacy estimates: Viral suppression <50 copies/mL at 48 weeks: relative risk (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.18. Number needed to treat to prevent 1 patient with viral load ≥50: 12 (95% CI 3 to 13).
Budget estimates: Refer to the evidence to decision framework.
Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:

- Cost of LPV/r for one year: R 675 442 893
- Cost of ATV/r for one year: R 763 833 470

Motivator/reviewer name(s): Simba Takuva, Renee de Waal

2. REVIEWERS AND ACKNOWLEDGEMENTS

Reviewers: Simba Takuva, Renee de Waal.

Declaration of interests: ST (Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand and School of Health Systems and Public Health, Faculty of Health Sciences, University of Pretoria and RdW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town) have no interests to declare related to atazanavir/ritonavir or lopinavir/ritonavir.

Acknowledgements: T Leong (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) assisted with the review and the costing, and the following assisted with the literature searches and screening of records: T Kredo (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), J Oliver (Cochrane South Africa, South African Medical Research Council), A Brandt (Stellenbosch University, SA GRADE Network), VD Ngah (Stellenbosch University), E Pienaar (Cochrane South Africa, South African Medical Research Council).

3. INTRODUCTION/ BACKGROUND

Protease inhibitors (PI) are potent inhibitors of HIV-1 protease. In current South African National guidelines, lopinavir in combination with ritonavir (LPV/r) is the recommended PI for second-line antiretroviral therapy (ART) in adult PLHIV who received dolutegravir-based first-line regimens, and in those who received NNRTI-based first-line regimens who have a contraindication to dolutegravir. However, LPV/r is associated with high pill burden which may negatively impact adherence, poor gastrointestinal tolerability (diarrhoeal side effects are an established risk factor of treatment failure), adverse effects such as hyperlipidaemia, and the need to double dose during TB therapy.(2,3) Patients who experience adverse effects on LPV/r, may be switched to ATV/r.

ATV has a high genetic barrier to resistance, is generally better tolerated than LPV and can be taken once daily.(4,5) Several ATV/r fixed dose combinations are now registered locally. A pitfall of ATV is reduced

absorption with acid-lowering drugs like proton-pump inhibitors.(6) ATV causes a non-clinically significant unconjugated hyperbilirubinemia that manifests as jaundice in a small proportion of patients leading to a need to substitute the drug for cosmetic reasons.(7) Genetic variants of UGT1A1 have been found to predispose to more severe jaundice on ATV (8) and in a recent study, one third of people sampled in KwaZulu Natal had variant alleles in UGT1A1.(9)

The purpose of this review is to evaluate if ATV can be used as the preferred PI for PI-naïve adult PLHIV in South African national guidelines.

4. OBJECTIVE

Review question: Should atazanavir/ritonavir (ATV/r) be used as the preferred protease inhibitor in place of lopinavir/ritonavir for second-line antiretroviral therapy in HIV positive adults who are PI-naive.

Table 1. PICO framework of the technical review

Population	PLHIV who are PI-naive
Intervention/s and comparisons	Atazanavir/ritonavir (ATV/r) – based combination antiretroviral therapy Lopinavir/ritonavir (LPV/r) – based combination antiretroviral therapy
Outcomes	**Efficacy:** Viral suppression rates, Mortality, Development of resistance mutations **Safety:** Adverse events, Discontinuation rates, Lipid profile
Study designs	Systematic reviews of randomized controlled clinical trials in humans Randomized controlled clinical trials in humans (eligible trials not included in systematic reviews identified)

5. METHODS

PubMed, the Cochrane Database of Systematic Reviews, Epistemonikos databases were searched up to 25 July 2021 and references of systematic reviews were scanned. There was no restriction on date, language, or publication status. The search strategy is shown in Appendix A. Included were systematic reviews of randomized controlled clinical trials in humans and randomized controlled clinical trials. Excluded were none head-to-head comparison trials, observational studies, case reports, case series, case reports and narrative reviews. Trials of PI-treatment experienced patients were also excluded.

The search produced 440 studies; 334 were removed for either being duplicates, non-human, non RCTs or systematic reviews. The remaining 110 records were screened (abstracts and title) and 20 records were identified for full text review. Three systematic reviews, two network meta-analysis and 12 RCTs were identified. After full-text screening and review of the bibliography of systematic reviews, three of the seven RCTs included in the Tigabu et al systematic review(10) were eligible. The Prisma flow diagram for the search output including reasons for exclusion is shown below (Figure 1).

Risk of bias was assessed using the modified Cochrane Collaboration risk of bias tool (Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook. Outcomes from individual studies were pooled using the fixed-effects

model in Revman 5.3. Heterogeneity as evaluated by the i^2 statistic was low hence the fixed effects approach is appropriate. The summary of findings table was computed in GRADEPro.

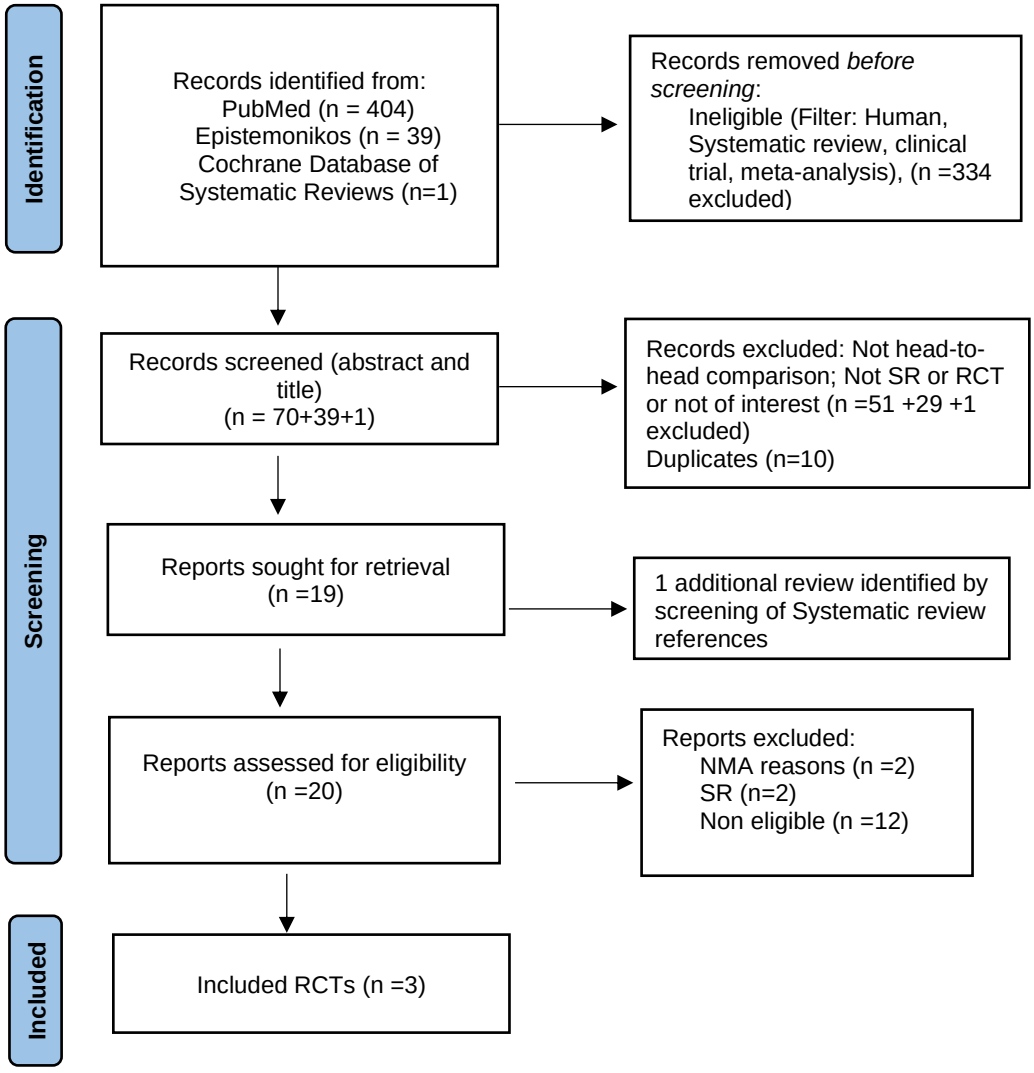


Figure 1. PRISMA flow-chart detailing study selection

6. RESULTS

The three included studies are summarised in Table 2, and the summary of findings is shown in Table 3, illustrating the effect sizes of the different outcomes evaluated. Table 3 shows the excluded studies from the Tigabu et al(10) systematic review and reasons for exclusion.

In the open label study by Andersson et al(11), 243 ART naïve HIV positive patients in 29 sites in Sweden and Norway were randomized to receive combination ART consisting of either EFV 600 mg once daily, ATV/r 300 mg/100 mg once daily or LPV/r 400 mg/100 mg twice daily. The primary endpoint was proportion with virologic suppression < 50 copies/ml at 48 and 144 weeks. This was a small under-powered study not designed to demonstrate non-inferiority or equivalence. NRTI backbone was heterogenous and not defined by the protocol and choice of NRTI may have confounded the findings. Genotypic resistance data was not available from this study.

The CASTLE study(12,13) was a 96 week open label non-inferiority trial that examined once-daily ATV/r and twice-daily LPV/r, both given in combination with once-daily, fixed dose tenofovir (TDF) and emtricitabine (FTC), in 883 treatment-naive HIV-1-infected patients from 134 centres in 29 countries. Primary endpoint was proportion of patients achieving virologic suppression of <50 copies/ml at 48 weeks. Outcomes at 96 weeks were also subsequently reported.

The Advanz-3 trial(14) was an open label multi-centre study that randomized 89 HIV positive ART naïve patients to receive either EFV 600 mg once daily, ATV/r 300 mg/100 mg once daily or LPV/R 400 mg/100 mg combined with FTC/TDF. Primary endpoint was median increase in CD4 cell count and secondary endpoints included patients achieving virologic suppression < 50 copies/ml at 48 weeks. This was a small study with insufficient power to detect differences in secondary outcomes across the three arms (including differences in virologic suppression).

Viral suppression

Viral suppression (<50 copies/ml) was evaluated at 48 weeks (three studies)(11,12,14) or 96 weeks (two studies)(11,13). Where suppression rates were not available for the two time points, the longest follow-up period was evaluated. After 48 weeks of ART, there was a 11% statistically significant increased likelihood of achieving virological suppression in the ATV/r arm (453/551) compared to the LPV/r arm (410/554), pooled Relative Risk: 1.11; 95% CI 1.04 – 1.18 (fixed effects model). Similarly, when the studies reporting virological suppression over 96 weeks were pooled, there was a marginal higher chance of suppression while on an ATV/r regimen (374/521) compared to a LPV/r regimen (344/524), pooled RR 1.09; 95%CI 1.01 -1.19. Figure 2 illustrates the forest plots reproduced using the data from these studies.

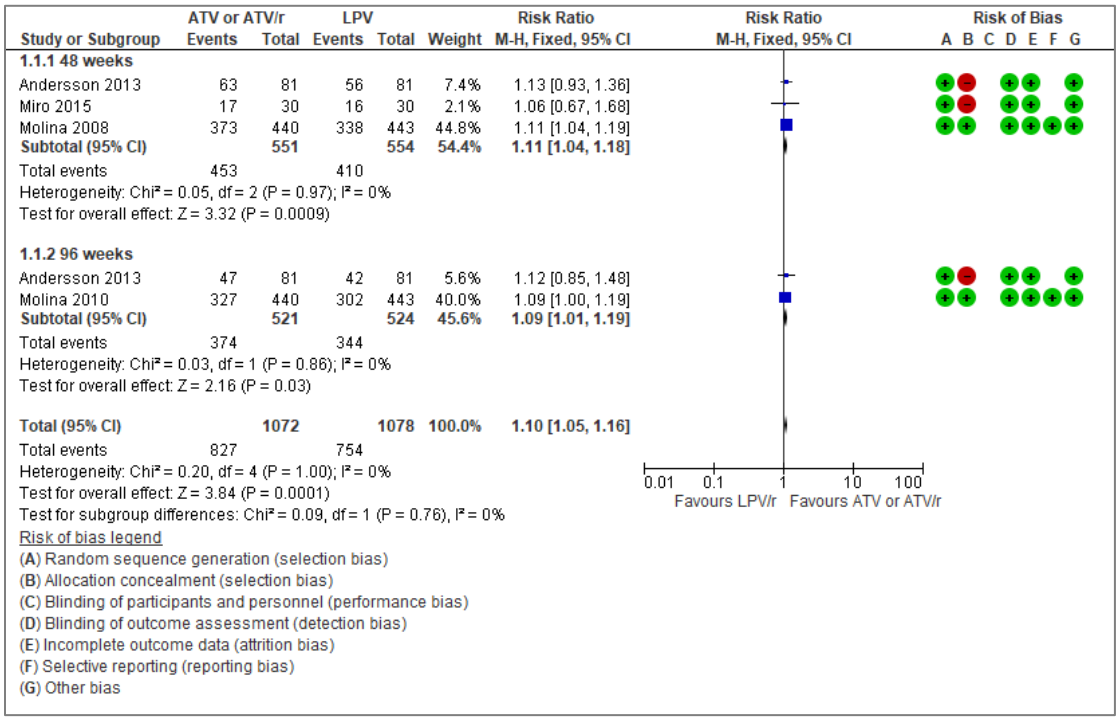


Figure 2. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (virological failure <50 copies/ml)

Development of resistance mutations

In the CASTLE study(13) rates of development of resistance to PIs were low, with only a single patient in each treatment arm with virologic failure at 96 weeks developing phenotypic resistance to a study PI. The emergence of NRTI substitutions was also low, with 5 patients in each treatment group developing phenotypic resistance to emtricitabine and 2 patients on lopinavir/ritonavir with phenotypic resistance to tenofovir disoproxil fumarate. None of the other included studies conducted genotypic resistance testing.

Mortality

Mortality was generally low across the included studies. The proportion of patients who died by 48 and 96 weeks was not significantly different between ATV/r and LPV/r; 48 weeks: RR 1.01, 95% CI 0.25 to 4.00 (3 studies, n=942, moderate certainty evidence) and 96 weeks: RR 1.55, 95% CI 0.53 to 4.51 (2 studies, n=1045, moderate certainty evidence). None of the deaths were considered related to treatment (see Figure 3, below).

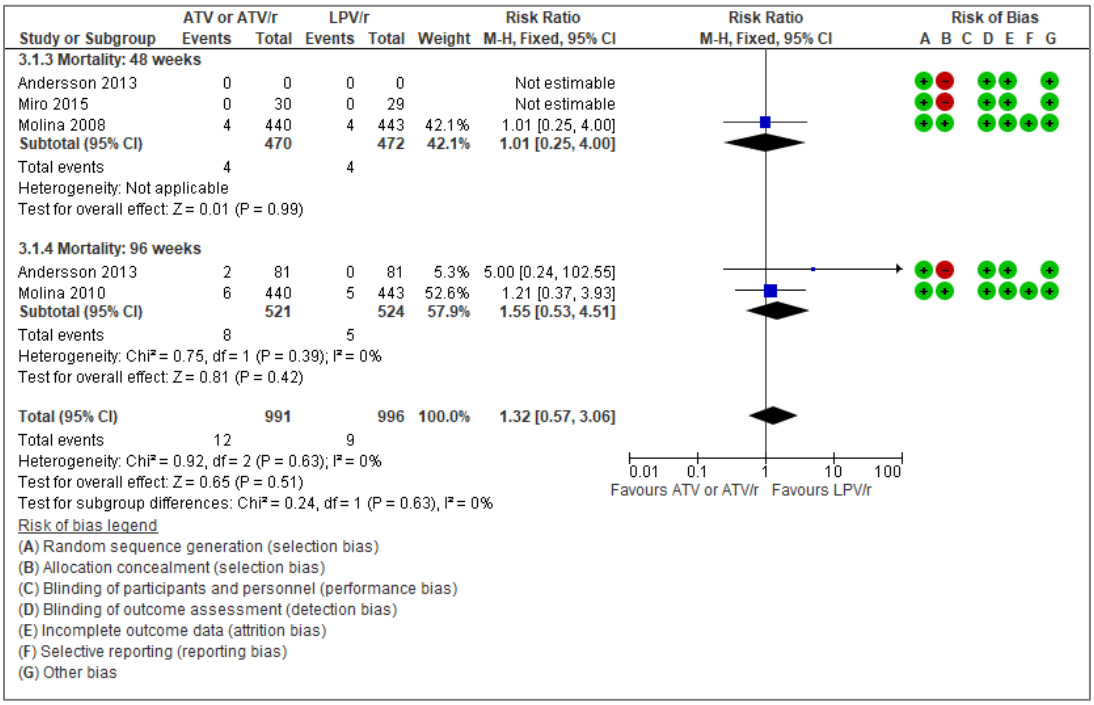


Figure 3. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Mortality)

Adverse events

Patients in the ATV/r arm had lower risk of occurrence of treatment related of grade 2-4 adverse events compared to those in the LPV/r arm, this was consistently seen across studies evaluated, pooled RR 0.88; 95% CI 0.77 – 1.00.(11–14) See Figure 4. Diarrhoeal events were much more common in the LPV/r arm vs. ATV/r arm and required use of anti-diarrhoeal events i.e., 24% vs. 12% in the CASTLE study.

Hepatobiliary adverse events were significantly more in the ATV/r arm than the LPV/r arm. In the CASTLE study, three patients discontinued due to jaundice/ hyperbilirubinemia through week 48 with no additional discontinuations due to hyperbilirubinemia occurring between weeks 48 and 96. In pooled estimated across all included studies, RR 80.44; 95% CI 31.90 – 202.85. See Figure 5.

Serious adverse events (SAEs) were numerically higher in the ATV/r arm than the LPV arm across the three studies, overall, 78 in ATV/r arm vs. 57 in LPV/r am, pooled RR 1.24; 95%CI 0.97 – 1.57. Few of these serious adverse events were deemed related to the study treatment. See Figure 6.

Patients on the ATV/r regimen had significantly lower levels of total cholesterol and fasting triglycerides than those on LPV/r regimens after 48 weeks of treatment.(12–14) After 96 weeks of treatment and above, mean percentage changes in total cholesterol and triglycerides was significantly higher in LPV/r than ATV/r based regimens (all p<0.01).(11,13)

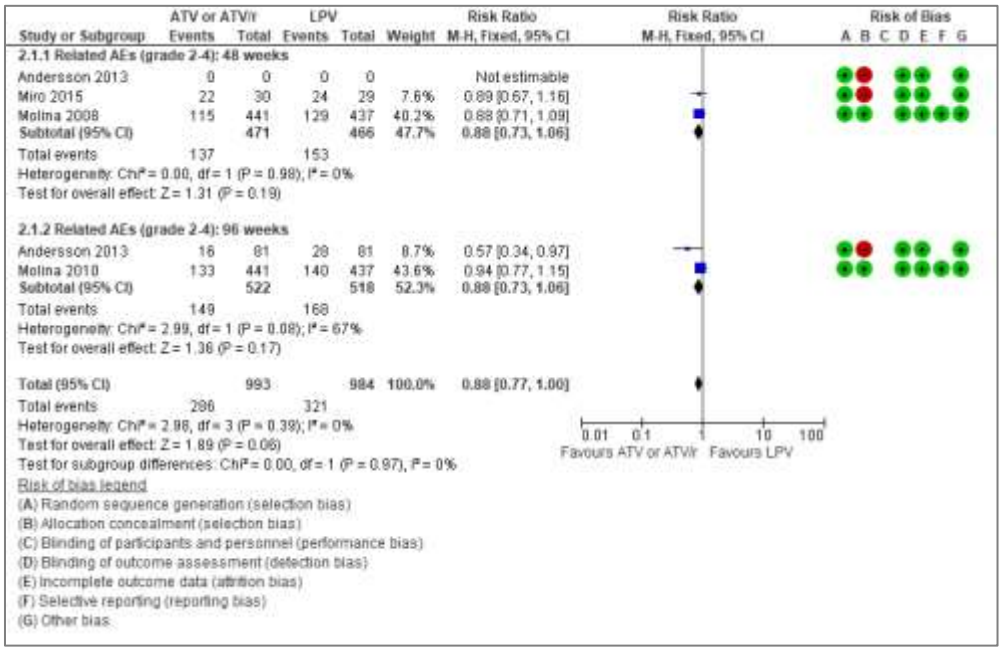


Figure 4. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (treatment related adverse events)

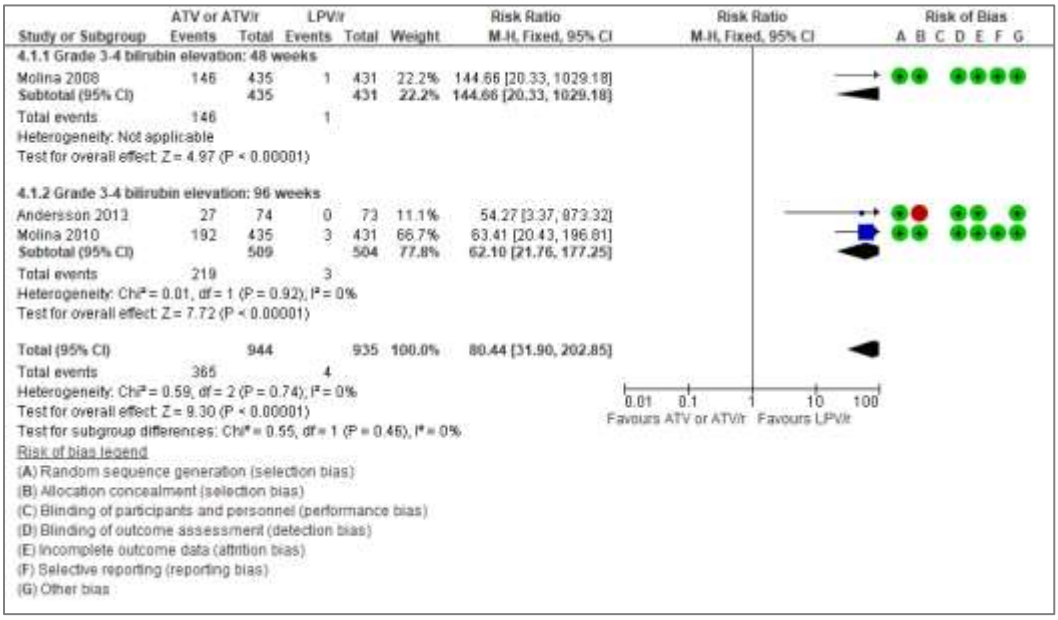


Figure 5. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Bilirubin levels)

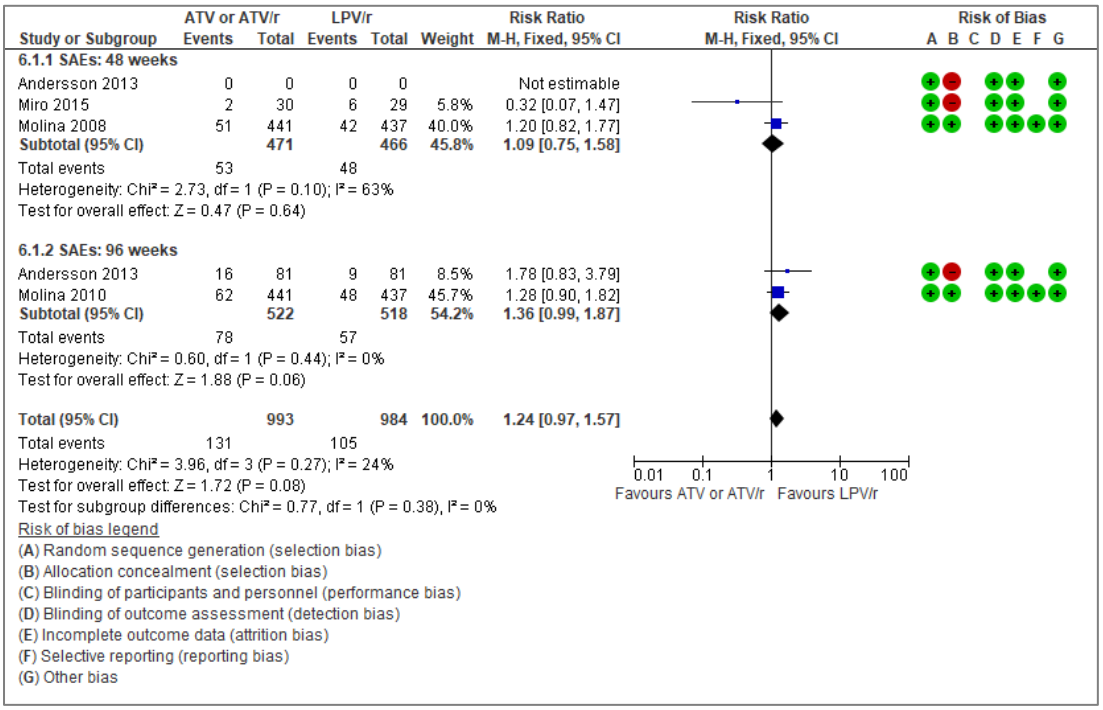


Figure 6. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Serious adverse events)

Discontinuation rates

Across the included studies, through 144 weeks, treatment discontinuation rates were significantly lower in the ATV/r arm (total 34) than the LPV/r arm (total 57), pooled RR 0.60; 95%CI 0.40 – 0.90. Gastrointestinal toxicities resulted in many discontinuations in the LPV/r arm. See Figure 7, below.

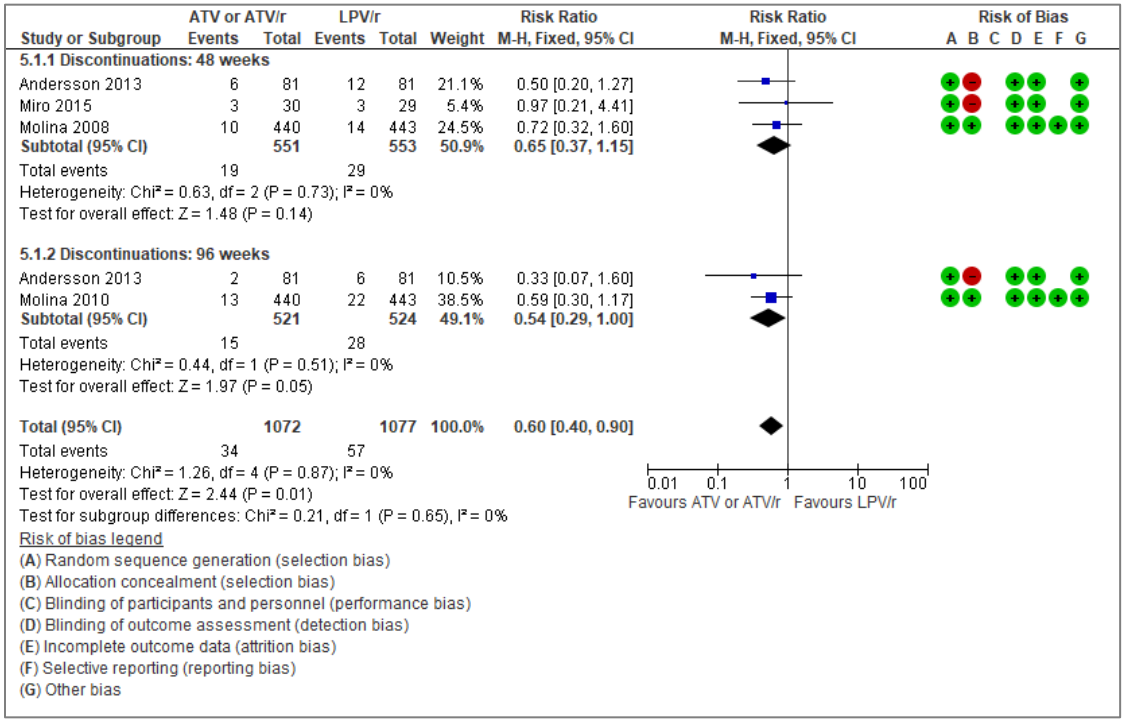


Figure 7. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (discontinuations due to adverse events)

CONCLUSIONS

Overall, ATV/r is reported to be noninferior to LPV/r, but with improved tolerance in terms of gastrointestinal side-effects, once-daily administration, and importantly, a better lipid profile than LPV/r in treatment-naive patients. As a result of the lower incidence of diarrhoea and favourable lipid parameters among patients receiving ATV/r, significantly less use of concomitant medications such as either anti-diarrhoeal or lipid-lowering agents was observed in clinical studies.(11–14)

However, ATV/r has the following limitations, it cannot be used with rifampicin-based TB treatment and has important drug interactions leading to reduced absorption with acid-lowering drugs like proton-pump inhibitors; use also leads reversible indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevation. Discontinuations were reported in studies due to the negative cosmetic effects of the jaundice. Local data regarding the prevalence of hyperbilirubinemia associated with ATV/r is limited. However, Naidoo *et al.* extrapolated that about 1/3 of patients taking ATV/r would have a genetic polymorphism that may result in hyperbilirubinemia, but the proportion of patients that would develop cosmetically distressing hyperbilirubinaemia resulting in non-compliance is unknown.(16)

Based on the review, the balance of benefits vs harms favours ATV/r as an alternative PI to LPV/r.

Table 2. Characteristics of included studies

Citation	Study design	Population	Intervention and Comparisons	Main findings (ATV/r versus LPV/r)
Molina, JM. et al(15) 48 weeks FU	RCT open label	Adults aged 18 years or older, naive to ART VL≥5000 copies/ml Up to 96 weeks follow up 134 sites in 29 countries (n=883)	ATV/r 300 mg/100 mg OD, or LPV/r 133/33·3 mg BD NRTI backbone: TDF/FTC 300/200 mg OD	**Efficacy**: VL Difference estimates, 1·7% (95%CI –3·8 to 7·1) **Mortality:** 4/440 ATV/r and 4/443 LPV/r **Adverse events:** Grade 2-4 related AEs: 115 (26%) ATV vs. 129 (30%) LPV/r **Grade 2/3-4 bilirubin**: 146/435 ATV/r vs. 1/431 LPV/r **SAEs:** 51 (12%) ATV vs. 42 (10%) **Lipids**: Total cholesterol (≥240 mg/dL) - 30/434 (7%) ATV/r vs. 77/428 (18%) LPV/r; Triglycerides (≥751 mg/dL) - 2/434 (<1%) ATV vs. 15/428 (4%) LPV/r **Discontinuations**: 10/440 (ATV/r) vs. 14/443 (LPV/r)
Molina, JM. et al(13) 96 weeks FU				**Efficacy**: VL Difference estimates, 1.8% (-2.6% to 6.3%) **Mortality** – 4/440 ATV/r and 4/443 LPV/r **Grade 2-4 related AEs**: 133 (30%) ATV vs. 140 (32%) LPV/r **Grade 2/3-4 bilirubin**: 146/435 ATV/r vs. 1/431 LPV/r **SAEs** – 62 (14%) ATV vs. 48 (11%) **Lipids**: Total cholesterol (≥240 mg/dL) - 47/434 (11%) ATV/r vs. 108/428 (25%) LPV/r; Triglycerides (≥751 mg/dL) - 3/434 (<1%) ATV vs. 18/428 (4%) LPV/r **Discontinuations**: 13/440 (ATV/r) vs. 22/443 (LPV/r)
Andersson, LM. Et al(11) 144 weeks FU	RCT open label	Antiretroviral-naïve adults 29 sites in Sweden and Norway (n=243)	EFV 600 mg OD, or ATV/r 300 mg/100 mg OD, or LPV/r 400 mg/100 mg twice OD	**Efficacy**: Week 48 HIV-1 RNA < 50 copies/ml – 86 (78–94)% EFV arm, 78 (69–87)% in ATV/r arm and, 69 (59–78)% in LPV/r arm Week 144 - 61 (50–72)% EFV arm, 58 (47–69)%, in ATV/r arm, and 51 (41–63)% in LPV/r arm **Mortality:** over 144 weeks - 0 in LPV/r vs. 2 in ATV/r (not related) **Grade 2-4 related AEs**: over 144 weeks – 16 ATV/r vs. 28 LPV/r **Grade 2/3-4 bilirubin**: over 144 weeks – 27/74 ATV/r vs. 0/73 LPV/r **SAEs**: over 144 weeks – 16 ATV/r vs. 9 LPV/r **Lipids**: over 144 weeks – median % change in fasting TC and TG from baseline through week 144 was higher in the LPV/r arm than the AZV/r arm (all p<0.05) **Discontinuations**: over 48 weeks – 6 ATV/r vs. 12 LPV/r and over 144 weeks – 2 ATV/r vs. 6 LPV/r
Miro, JM. et al(14) 48 weeks FU	RCT open label	Adults aged 18 years or older Antiretroviral naïve 5 sites in Spain (n=89)	EFV 600mg OD, ATV/r 300mg/100mg OD or LPV/r 400mg/100mg BD NRTI backbone	**Efficacy**: VL <50 copies/ml: 64.3% (45.8 to 79.3) EFV, 56.7% (39.2 to 72.6) ATV, 51.7% (34.4 to 68.6) LPV/r, p=0.63 **Mortality**: 0 **Grade 2-4 related AEs**: 13/28 EFV vs. 11/30 ATV/r vs. 14/29 LPV/r **Grade 2/3-4 bilirubin**: 0 EFV vs. 2/30 ATV vs. 0 **SAEs**: 2/28 EFV vs. 6/30 ATV vs. 6/29 LPV/r **Lipids**: Trend towards lower lipids for ATV arm than EFV arm

Citation	Study design	Population	Intervention and Comparisons	Main findings (ATV/r versus LPV/r)
				Discontinuations: 1/28 EFV vs. 3/30 ATV vs. 3/29

Table 3. Excluded reviews / RCTs: Reasons for exclusion

Excluded RCT studies		Reasons
1	Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS. 2006 Mar 21;20(5):711-8. doi: 10.1097/01.aids.0000216371.76689.63. PMID: 16514301.	Previous failure to PI
2	Kanters S, Socias ME, Paton NI, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV [Internet]. 2017;4(10):e433–41. Available from: http://dx.doi.org/10.1016/S2352-3018(17)30109-1	No ATV/r RCT was included. Study included was prospective observational study.
3	Atazanavir Versus Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Not Had Success With Protease Inhibitor-Containing HAART Regimen(s). NCT00028301	Previous failure to PI
4	Tigabu BM, Agide FD, Mohraz M, Nikfar S. Atazanavir / ritonavir versus lopinavir / ritonavir-based combined antiretroviral therapy (cART) for HIV-1 infection: A systematic review and meta-analysis. Afr Health Sci. 2020;20(1):91–101.	Three studies out of seven from this review were included.
7	Ferrer E, del Rio L, Martínez E, et al. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. AIDS Res Hum Retroviruses. 2011 Oct;27(10):1061-5. doi: 10.1089/AID.2010.0254. Epub 2011 Jan 15. PMID: 21166602.	Switch study, not PI naïve.
8	Randomised, multicentre, open clinical trial assessing the effectiveness and safety of simplification to atazanavir + ritonavir versus continuation of a stable antiretroviral regimen on lopinavir/ritonavir, Sponsor not yet defined (Spain)	Switch study, not PI naïve
9	Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS. 2005 Apr 29;19(7):685-94. doi: 10.1097/01.aids.0000166091.39317.99. PMID: 15821394.	Not PI naïve
10	Ribera E, Azuaje C, Lopez RM, et al A. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. AIDS. 2006 May 12;20(8):1131-9. doi: 10.1097/01.aids.0000226953.56976.ad. PMID: 16691064.	Not PI naive
11	Menshawy A, Ismail A, Abushouk AI, , et al. Efficacy and safety of atazanavir/ritonavir-based antiretroviral therapy for HIV-1 infected subjects: a systematic review and meta-analysis. Archives of Virology. 2017:1-10.	Three out of ten included studies in this review met eligibility for the current review
12	Efficacy and safety of switching suppressed patients with elevated triglycerides from lopinavir/ritonavir or fosamprenavir/ritonavir to atazanavir/ritonavir or darunavir/ritonavir based therapy: the LARD study," Skiest, DJ	Switch study of patients tolerating LPV/r and suppressed on it. Patients not PI naïve.
13	Edén A, Andersson LM, Andersson Ö, et al. Differential effects of efavirenz, lopinavir/r, and atazanavir/r on the initial viral decay rate in treatment naïve HIV-1-infected patients. AIDS Research and Human Retroviruses. 2010;26(5):533-40.	Very short 28 day study
14	Mallolas J, Podzamczer D, Milinkovic A, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. Journal of Acquired Immune Deficiency Syndromes (1999). 2009;51(1):29-36.	Switch study for patients stable on LPV/r
15	Study of HIV Patients With Undetectable Viral Load and Abnormal Lipids Switching to Atazanavir/Ritonavir. NCT00120393	Switch study, not PI naïve.
16	Soriano V, Garcia-Gasco P, Vispo E, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. The Journal of Antimicrobial Chemotherapy. 2008;61(1):200-5.	Switch study for patients stable on LPV/r

Table 3. Summary of Findings: ATV/r compared to LPV/r for treatment of HIV positive adults

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with LPV/r	Risk difference with ATV/r
Virological suppression (<50 copies/ml) - 48 weeks	1105 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.11** (1.04 TO 1.18)	740 per 1,000	**81 more per 1,000** (30 more to 133 more)
Virological suppression (<50 copies/ml) - 96 weeks	1045 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.09** (1.01 to 1.19)	656 per 1,000	**59 more per 1,000** (7 more to 125 more)
Related AEs (grade 2-4): 48 weeks	937 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.88** (0.73 to 1.06)	328 per 1,000	**39 fewer per 1,000** (89 fewer to 20 more)
Related AEs (grade 2-4): 96 weeks	1040 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.88** (0.73 to 1.06)	324 per 1,000	**39 fewer per 1,000** (88 fewer to 19 more)
Mortality: 48 weeks	942 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.01** (0.25 to 4.00)	8 per 1,000	**0 fewer per 1,000** (6 fewer to 25 more)
Mortality: 96 weeks	1045 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 1.55** (0.53 to 4.51)	10 per 1,000	**5 more per 1,000** (4 fewer to 33 more)
Grade 3-4 bilirubin elevation: 48 weeks	866 (1 RCT)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 144.66** (20.33 to 1029.18)	2 per 1,000	**333 more per 1,000** (45 more to 2,386 more)
Grade 3-4 bilirubin elevation: 96 weeks	1013 (2 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 62.10** (21.76 to 177.25)	6 per 1,000	**364 more per 1,000** (124 more to 1,049 more)
Discontinuations: 48 weeks	1104 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c,d]	**RR 0.65** (0.37 to 1.15)	52 per 1,000	**18 fewer per 1,000** (33 fewer to 8 more)
Discontinuations: 96 weeks	1045 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 0.54** (0.29 to 1.00)	53 per 1,000	**25 fewer per 1,000** (38 fewer to 0 fewer)
Serious adverse events: 48 weeks	937 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 1.09** (0.75 to 1.58)	103 per 1,000	**9 more per 1,000** (26 fewer to 60 more)
Serious adverse events: 96 weeks	1040 (2 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]	**RR 1.36** (0.99 to 1.87)	110 per 1,000	**40 more per 1,000** (1 fewer to 96 more)

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. All included trials were open label studies with no blinding of participants and researchers. Open label studies are susceptible to numerous biases. However measurement bias is minimal for an outcome like virological suppression as this is a hardcore laboratory endpoint. While randomization methods and sequences were clearly described, allocation concealment is not clearly illustrated in Andersson and Miro (potential issues of selection and confounding bias). Attrition was good across all studies (<10%). Selective reporting was not assessed as there was no access to the study protocols. Overall Risk Of Bias classified as moderate as only one domain of risk was highlighted as serious bias resulting in downgrade.

b. Inconsistency across studies was negligible
c. Indirectness is assessed as not serious as the included studies were head-to-head comparisons of ATV/r versus LPV/r. However, none of the studies evaluated patients who had failed first-line therapy. The review question specifically seeks to inform use of ATV/r vs. LPV/r in patients who switch to second line therapy.
d. The sample size for two of the studies is quite small i.e. 81 per arm in the Andersson et al study and taking into consideration some of the small event occurrences this may have affected study power. The 95% CIs are quite wide in some of the studies. Two papers from the CASTLE study present larger sample size (about 440 per arm) and the precision is quite improved in these studies.

7. 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	**Overall certainty:** Low to moderate, due to open-label design, imprecision (as wide CIs) and modest sample sizes and event rate. The following outcomes were considered critical: ***Viral suppression rates***: moderate certainty evidence ***Mortality:*** moderate certainty evidence **Discontinuation rates**: moderate certainty evidence
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	**ATV/r versus LPV/r (reference)** **Viral suppression rates**: 48 weeks – RR 1.11, 95%CI 1.04 – 1.18 and 96 weeks: RR 1.09, 95%CI 1.01 – 1.19 **Mortality**: 48 weeks -RR1.01, 95%CI 0.25 – 4.00 and 96 weeks: RR 1.55, 95%CI 0.53 – 4.51 **Treatment related grade 2-4 adverse events**: 48 weeks – 0.88, 95%CI 0.73 – 1.06 and RR 0.88, 95%CI 0.73 -1.06 **AE related discontinuations**: 48 weeks – RR 0.65, 95%CI 0.37 – 1.15 and 96 weeks: RR 0.54, 95%CI 0.29 – 1.00
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	**Overall certainty:** moderate **Adverse events including laboratory abnormality AEs**: moderate certainty evidence **Serious adverse events**: moderate certainty evidence **Grade 3-4 bilirubin elevation**: moderate certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☒ Small ☐ None ☐	Elevated bilirubin from the ATV/r group was observed in significantly higher rates, however this was deemed not harmful. Serious advents events were largely similar across the two arms. **ATV/r versus LPV/r (ref)** **Serious adverse events**: 48 weeks – RR 1.09, 95%CI 0.79 – 1.58 and 96 weeks: RR 1.36, RR 0.99 – 1.87 **Grade 3-4 bilirubin elevation**: 48 weeks – RR 144.66, 95%CI 20.33 – 1029.18 and 96 weeks: RR 62.10, 95%CI 21.76 – 177.25
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favour's intervention ☒ Favour's control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	List the members of the group: DRV/r Specific exclusion from the group: n/a

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?

Yes [x] No [ ] Uncertain [ ]</td><td>Already included in the National essential medicine list.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [x] Uncertain [ ]</td><td>
Price of medicines:
<table>
<tr><th>Medicine</th><th>Price (ZAR)</th></tr>
<tr><td>LPV/r 200/50 mg, 112 tablets</td><td>233.45*</td></tr>
<tr><td>ATV/r 300/100 mg, 30 tablets</td><td>264.00**</td></tr>
</table>
*Contract circular RT71-2019ARV
**NDoH notice, reference 2020/11/03/EDP/01, quotation price from Mylan/Emcure

<u>A: ESTIMATED INCREMENTAL BUDGET IMPACT FOR ATV/R-CONTAINING REGIMEN:</u>

<u>Assumptions:</u>
• Utilisation data of LPV/r 200/50 mg formulation of 247 000 for 2020 comparable to 2021 [1]
• Annual incidence of TB among people living with HIV 2506 per 100,000 (2.5%)[2]
• 95.4% of TB cases are rifampicin-sensitive [3], and therefore can't be switched from LPV/r to ATV/r as rifampicin based therapy is required.
<u>Model inputs:</u>
Estimated population:
• Number of patients on LPV/r estimated as 247 000/ annum.
• Estimation of patients on LPV/r with HIV/TB co-morbidity per annum = 6175
• Estimation of patients on LPV/r who would require rifampicin-based therapy = 5891
• Estimation of patients on LPV/r with either no TB, or with rifampicin-resistant TB, who could switch to ATV/r = 241109
Medicine price:
• Price of 30-day supply of LPV/r 200/50mg tablets (120) = R250.13 [4]
• Price of 30-day supply of ATV/r 300/100mg tablets (60) = R264.00 [5]

<u>Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:</u>
• Cost of LPV/r for one year: R 675 442 893
• Cost of ATV/r for one year: R 763 833 470

<u>Incremental budget impact for one year, using ATV/r = R 88 390 578</u>

<u>Sensitivity analysis:</u>
<table>
<tr><th>Incidence of TB among patients on PI-based regimen</th><th>Incremental annual budget impact</th></tr>
<tr><td>1%</td><td>R 89 686 351</td></tr>
<tr><td>10%</td><td>R 8 911 711</td></tr>
</table>
<u>B: NON-COMPLIANCE DUE TO HYPERBILIRUBINAEMIA WITH ATV/R:</u>
Assumption: Approximately 30% non-compliance on ATV/r-regimen due to hyperbilirubinaemia may occur after ±1 year.

<u>Amended estimated model inputs:</u>
• 30% non-compliant on ATV/r = 241109 x 30% = 72 333 patients and approximately 168 776 patients compliant on ATV/r)
</td></tr>
</table>

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td></td><td></td><td>
30% switching to LPV/r = 72 333 patients
<u>Estimated annual cost of protease inhibitor consumption for PLHIV factoring in non-compliance due to hyperbilirubinaemia:</u>
Cost of ATV/r for one year: R 534 683 318
Cost of LPV/r for one year: R 202 632 826
Total: R 737 316 144
<u>Incremental budget impact for one year, using ATV/r = R 61 873 392</u>
<u>Sensitivity analysis:</u>
<table>
<tr><th>Incidence of TB among patients on PI-based regimen</th><th>Incremental annual budget impact</th></tr>
<tr><td>15%</td><td>R 75 131 975</td></tr>
<tr><td>40%</td><td>R 53 034 336</td></tr>
</table>
References.
1. NDoH data on file
2. UNAIDS 2019 report: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf
3. Ismail NA, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018 Jul;18(7):779-787. doi: 10.1016/S1473-3099(18)30222-6. doi: 10.1016/S1473-3099(18)30222-6
4. Contract circular RT71-2019ARV
5. NDoH notice – reference 2020/11/03/EDP/01 – quotation price from Mylan
6. Naidoo A, et al Hyperbilirubinemia in atazanavir-treated human immunodeficiency virus-infected patients: the impact of the UGT1A1*28 allele. Pharmgenomics Pers Med. 2017 Aug 23;10:233-234.
Other resources: LPV/r use requires monitoring of lipid profiles.
</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>
Is there important uncertainty or variability about how much people value the options?
Minor [x] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]
</td><td>No local survey data could be sourced but the Committee considered that that ATV/r would be acceptable to patients and healthcare workers as ATV/r would offer a better tolerated regimen compared to LPV/r, with better compliance of a once-daily regimen, compared to 12-hourly dosing for LPV/r-based regimens.

However, ATV would not be able to be used with rifampicin-based TB treatment.</td></tr>
<tr><td>EQUITY</td><td>
Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]
</td><td></td></tr>
</table>

REFERENCES

1. Simbayi LC, Zuma K, Zungu N, Moyo S, Marinda E, Jooste S MM, Ramlagan S, North A, van Zyl J, Mohlabane N, Dietrich C NI and the SVT. AIDS statistics. [Internet]. South African national HIV prevalence, incidence and behaviour survey, 2017. Cape Town; 2019. Available from: http://www.hsrc.ac.za/uploads/pageContent/10779/SABSSM V.pdf
2. Vogel M, Rockstroh JK. Safety of lopinavir/ritonavir for the treatment of HIV-infection. Expert Opin Drug Saf. 2005 May;4(3):403–20.
3. Kaplan SS, Hicks CB. Safety and antiviral activity of lopinavir/ritonavir-based therapy in human immunodeficiency virus type 1 (HIV-1) infection. J Antimicrob Chemother. 2005 Aug;56(2):273–6.
4. Bentué-Ferrer D, Arvieux C, Tribut O, Ruffault A, Bellissant E. Clinical pharmacology, efficacy and safety of atazanavir: a review. Expert Opin Drug Metab Toxicol. 2009 Nov;5(11):1455–68.
5. Kanters S, Socias ME, Paton NI, Vitoria M, Doherty M, Ayers D, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV [Internet]. 2017;4(10):e433–41. Available from: http://dx.doi.org/10.1016/S2352-3018(17)30109-1
6. Klein CE, Chiu Y-L, Cai Y, Beck K, King KR, Causemaker SJ, et al. Effects of acid-reducing agents on the pharmacokinetics of lopinavir/ritonavir and ritonavir-boosted atazanavir. J Clin Pharmacol. 2008 May;48(5):553–62.
7. McDonald C, Uy J, Hu W, Wirtz V, Juethner S, Butcher D, et al. Clinical significance of hyperbilirubinemia among HIV-1-infected patients treated with atazanavir/ritonavir through 96 weeks in the CASTLE study. AIDS Patient Care STDS. 2012 May;26(5):259–64.
8. Culley CL, Kiang TKL, Gilchrist SE, Ensom MHH. Effect of the UGT1A1*28 allele on unconjugated hyperbilirubinemia in HIV-positive patients receiving Atazanavir: a systematic review. Ann Pharmacother. 2013 Apr;47(4):561–72.
9. Naidoo A, Naidoo K, Ramsuran V, Reddy M, Padayatchi N. Hyperbilirubinemia in atazanavir-treated human immunodeficiency virus-infected patients: the impact of the UGT1A1*28 allele. Pharmgenomics Pers Med. 2017;10:233–4.
10. Tigabu BM, Agide FD, Mohraz M, Nikfar S. Atazanavir / ritonavir versus lopinavir / ritonavir-based combined antiretroviral therapy (cART) for HIV-1 infection: A systematic review and meta-analysis. Afr Health Sci. 2020;20(1):91–101.
11. Andersson L-M, Vesterbacka J, Blaxhult A, Flamholc L, Nilsson S, Ormaasen V, et al. Lopinavir/ritonavir, atazanavir/ritonavir, and efavirenz in antiretroviral-naïve HIV-1-infected individuals over 144 weeks: an open-label randomized controlled trial. Scand J Infect Dis. 2013 Jul;45(7):543–51.
12. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet. 2008;372(9639):646–55.
13. Molina J-M, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. J Acquir Immune Defic Syndr. 2010 Mar;53(3):323–32.
14. Miro JM, Manzardo C, Ferrer E, Loncà M, Guardo AC, Podzamczer D, et al. Immune Reconstitution in Severely Immunosuppressed Antiretroviral-Naive HIV-1-Infected Patients Starting Efavirenz, Lopinavir-Ritonavir, or Atazanavir-Ritonavir Plus Tenofovir/Emtricitabine: Final 48-Week Results (The Advanz-3 Trial). J Acquir Immune Defic Syndr. 2015 Jun;69(2):206–15.
15. Molina J-M, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet (London, England). 2008 Aug;372(9639):646–55.
16. Naidoo A, Naidoo K, Ramsuran V, Reddy M, Padayatchi N. Hyperbilirubinemia in atazanavir-treated human immunodeficiency virus-infected patients: the impact of the UGT1A1*28 allele. Pharmgenomics Pers Med. 2017 Aug 23;10:233-234.

APPENDIX A: SEARCH STRATEGY

Database: PubMed

Date: 25 July 2021

Search	Query	Results
#1	HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab]))	422,178
#2	antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab])	207,971
#3	(Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab])	1,923
#4	("lopinavir*"[mh] OR "abt 378"[tiab] OR "abt 378"[tiab] OR ("lopinavir"[mh] OR "lopinavir"[tiab] OR "abt378"[tiab])) AND ("ritonavir*"[tiab] OR ("ritonavir"[mh] OR "ritonavir"[tiab] OR "novir"[mh] OR "norvir"[tiab]))	3,187
#5	((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome"))	183,992
#5	#1 AND (#2 AND #3 AND #4) NOT #5	404
#6	Filters: Clinical Trial, Meta-Analysis, Systematic Review, Humans Sort by: Most Recent	70

Database: Epistemonikos

Date: 25 July 2021

(Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND ("lopinavir*"[mh] OR "abt 378"[tiab] OR "abt 378"[tiab] OR ("lopinavir"[mh] OR "lopinavir"[tiab] OR "abt378"[tiab])) AND ("ritonavir*"[tiab] OR ("ritonavir"[mh] OR "ritonavir"[tiab] OR "novir"[mh] OR "norvir"[tiab])) NOT ((coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome" OR "mers-cov" OR "mers cov" OR "middle east respiratory syndrome" OR "middle-east respiratory syndrome"))
No of records retrieved: 39

Database: Cochrane Library

Date: 25 July 2021

Atazanavir sulphate[mh] OR Atazanavir sulfate[mh] OR atazanavir[tiab] OR reyataz[tiab]

No of records retrieved: 1

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

MEDICINE REVIEW:

TITLE: DARUNAVIR/RITONAVIR vs LOPINAVIR/RITONAVIR FOR ADULT HIV PATIENTS

Date: 27 July 2021

Key findings

- We reviewed the evidence for darunavir/ritonavir versus lopinavir/ritonavir in patients; requiring a protease inhibitor-based regimen, who were treatment naïve to both drugs.
- We included two randomised controlled trials: the TITAN trial, for which published results were available for the 48- and 96- week period, and the ARTEMIS trial, for which 48-, 96-, and 192-week data were included. We also included a single systematic review and network meta-analysis, which did not include the TITAN or ARTEMIS trials, but included one additional randomised controlled trial.
- Darunavir/ritonavir (DRV/r)-based regimens are overall associated with a higher rate of **virological suppression** than lopinavir/ritonavir (LPV/r)-based regimens (moderate certainty of evidence). The absolute difference in rate of viral suppression to <50 copies/mL seen in the TITAN and ARTEMIS trials was 8.7% [95% CI 0.8-16.6] and 11.6% respectively [95% CI 4.4-18.8%]. This equates to a NNT of 9 and 13, respectively, for each additional patient with virological suppression).
- The rates of drug-associated **adverse events** are lower with DRV/r than LPV/r (absolute difference 3.9% and 7.8% in TITAN and ARTEMIS respectively, moderate certainty of evidence). This is partly driven by a significantly lower rate of gastrointestinal side-effects (~15% for LPV vs ~8% for DRV in both the TITAN and ARTEMIS trials)
- Patients on DRV/r-containing regimens may be less likely to develop **drug resistance-associated mutations** than those on LPV/r-containing regimens (9.3-15% for DRV/r vs 15.8-33% for PI-mutations, p <0.05) (low certainty of evidence due to limited and potentially biased sampling).
- Unlike LPV/r, DRV/r cannot be given with **rifampicin-based tuberculosis regimens**. Furthermore, a switch to DRV/r as the second-line protease inhibitor of choice may limit the third-line antiretroviral regimen options that are available to patients who require them.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE 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)**
Type of recommendation		X			

Recommendation: The Committee suggests that DRV/r not be used in preference to LPV/r.
Rationale: Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy.
Level of Evidence: Moderate certainty of evidence
Review indicators: Reduction in DRV/r price

NEMLC MEETING 29 JULY 2021:
The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.

Monitoring and evaluation considerations

Research priorities

Executive summary:

Date: 26 July 2021
Medicine (INN): Darunavir/ritonavir (as a fixed dose combination)
Medicine (ATC): J05AR26
Indication (ICD10 code): B20
Patient population: HIV positive adults requiring a protease-inhibitor-based antiretroviral therapy regimen.
Prevalence of condition: 7.5 million South Africans living with HIV (2019 estimate)
Level of Care: Primary Healthcare and Adult Hospital Level of care
Prescriber Level: Primary health care nurses and doctors
Current standard of Care: Lopinavir/ritonavir
Efficacy estimates: (preferably NNT) For virological suppression, NNT = 9-13
Reviewer name(s): Jeremy Nel, Shelley McGee
PTC affiliation: JN: Helen Joseph Hospital PTC

Background

Protease inhibitors (PIs) are a class of agents that, as their name suggest, inhibit the protease enzyme of HIV. Protease's normal function is to cleave the translated polyproteins into HIV's final protein products, and inhibition of this step results in immature, non-infectious virions being produced instead.

There are three available protease inhibitor combinations available in South Africa: lopinavir (LPV), atazanavir (ATV) and darunavir (DRV), each given with low-dose ritonavir (r). The role of ritonavir is to act as a pharmacokinetic booster; by inhibiting CYP3A4, higher PI drug levels are achieved, permitting less frequent dosing.

PIs are generally used as second-line ART drugs, following first-line virological failure, or intolerance to first-line drugs. South Africa's move to a dolutegravir (DTG)-based first line regimen will likely reduce the number of patients requiring 2nd-line drugs, owing chiefly to a higher virological barrier to resistance compared to efavirenz (EFV). However, there will still be a need for PI-based therapy for some of those patients already on a PI-based regimen, for patients who fail first-line therapy, and for patients who are intolerant of certain 1st line drugs.

Historically, South Africa has utilised LPV/r as its PI-combination of choice, owing chiefly to its lower price. The current public sector price for DRV/r is more expensive than for LPV/r.

Boosted DRV is an important agent for use in treatment-experienced patients owing to a high barrier to resistance and darunavir's ability to maintain virologic activity despite multiple PI mutations.[1, 2]

Review Question:
For HIV-positive adults requiring protease inhibitor-based antiretroviral therapy (ART), how does darunavir/ritonavir-based therapy compare to lopinavir/ritonavir-based therapy?

Methods:

A rapid review of the evidence was conducted by searching selected electronic databases (PubMed, Epistemonikos and the Cochrane Library) on 14 June 2021. The search strategy is shown in Appendix 1. Retrieved records were screened against the eligibility criteria in the Covidence platform; the titles and abstracts were first screened in duplicate, followed by the screening of relevant full text papers in duplicate, with conflicts resolved by consensus. Data extraction from the included studies was done independently, with results reviewed and checked by a second reviewer. Table 1 lists the excluded studies and provides the rationale for exclusion.

Eligibility criteria

-P (patient/population): PLHIV who are darunavir and lopinavir naïve.
-I (intervention): Darunavir/ritonavir-based combination antiretroviral therapy.
-C (comparator): Lopinavir/ritonavir-based combination antiretroviral therapy.
-O (outcomes)*: mortality, viral suppression rates, adverse events, discontinuation rates, lipid profile, and development of resistance mutations.

** considered to be critical outcomes*

Only randomised control trials and systematic reviews of randomised control trials were included.

Results

Search

The search produced 663 studies; 135 were duplicates and were removed. Of the remaining 528 records, 501 were excluded in screening as they were not applicable to the PICO. The full test of the 27 remaining articles were assessed for eligibility. 21 of these were excluded, for reasons given in table 1. 6 studies were included in the qualitative analysis. The included studies are summarised in table 2.

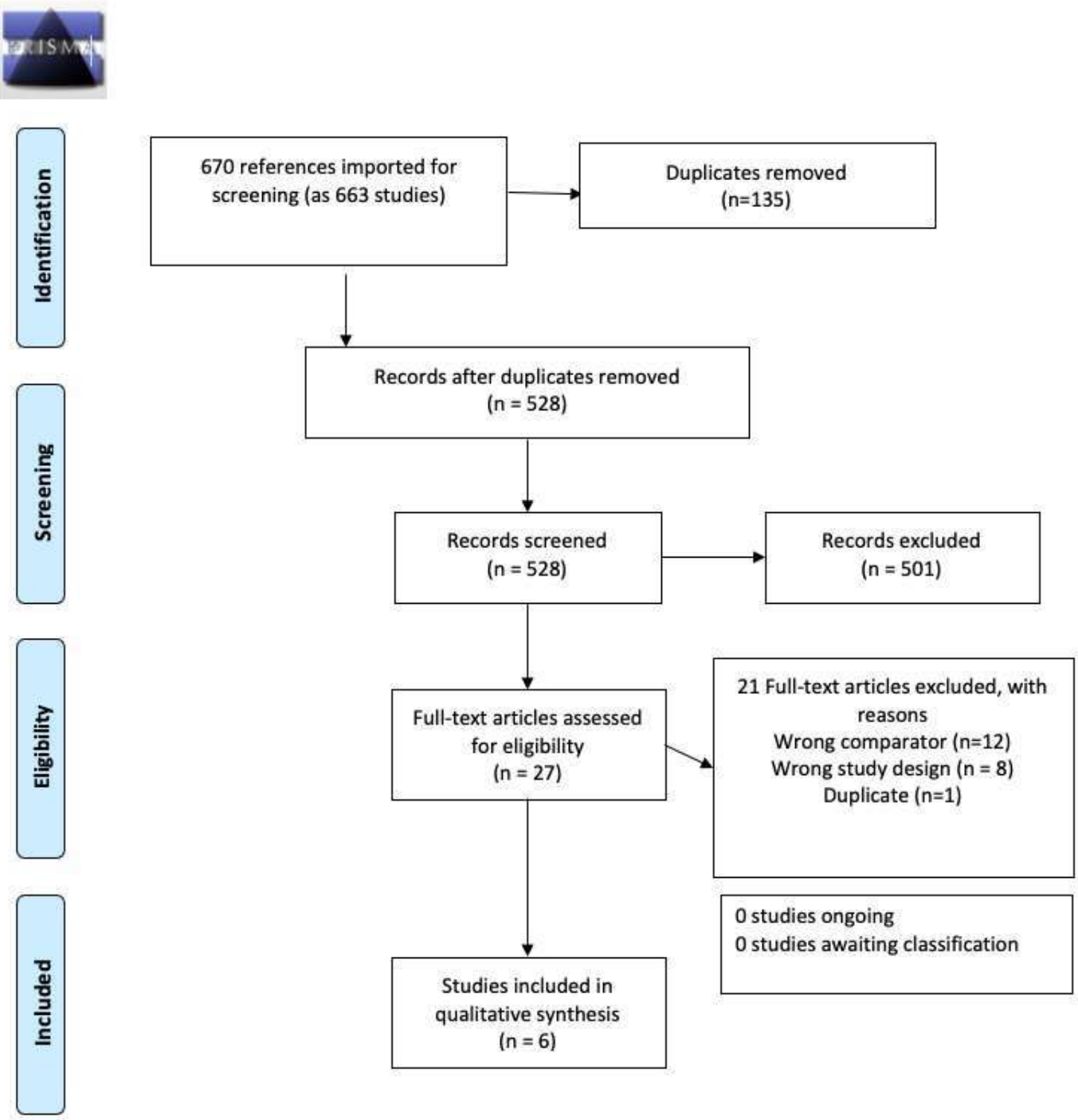
The TITAN study was a randomised, controlled, phase III trial to compare efficacy and safety of darunavir-ritonavir with that of lopinavir-ritonavir in treatment-experienced, lopinavir-naive patients. Patients received optimised background regimen plus non-blinded treatment with darunavir-ritonavir 600/100 mg twice daily or lopinavir-ritonavir 400/100 mg twice daily. For the TITAN study, both 48- and 96-week results were available in separate articles (by Madruga and Bánhegyi et al. respectively).[3, 4]

The ARTEMIS trial was a randomized, open-label phase III trial in treatment-naïve HIV-1-infected adults. Patients were stratified by baseline HIV-1 RNA and CD4 count, and randomized to once-daily DRV/r 800/100 mg or LPV/r 800/200 mg total daily dose (either once or twice daily) plus tenofovir/emtricitabine. Similarly, for the ARTEMIS trial, 48-, 96-, and 192- week data were available (Ortiz, Mills, and Orkin).[5-7]

So as to incorporate all data, all articles that included the two TITAN papers are discussed together as a group, as are the three ARTEMIS trial articles.

A single systematic review and network meta-analysis was also included that evaluated outcomes in treatment-experienced adults living with HIV who switched ART regimen after failure of a WHO-recommended first-line NNRTI-based regimen.[7] Only one study included in this meta-analysis was relevant to the review question. This was a 3-arm phase 3 open label randomised controlled trial of 454 patients of 48-week study duration, comparing tenofovir/emtricitabine + LPV/r (control group) to either abacavir + didanosine + LPV/r or tenofovir/emtricitabine + DRV/r regimens.[8]

Figure 1: Process for searching and selecting studies for inclusion



Results

Viral suppression rates

In the open label TITAN randomised control trial, treatment-experienced LPV- and DRV-naïve patients with HIV were randomised to either DRV/r or LPV/r, both in conjunction with an optimised background regimen consisting of 2 or more NRTIs and/or NNRTIs. At 48 weeks, more patients on DRV/r attained a viral load <400 copies in the intention to treat population: 77% vs 67% respectively (95% CI 2-17, p<0.0001). A similar gap in viral suppression was seen in the per protocol analysis (77% vs 68% respectively, 95% CI 2-16) and when a threshold of <50 copies/mL was used (71% vs 60% respectively).[3] After 96 weeks, a similar pattern was seen: more patients on DRV/r attained a viral load <400 copies/mL (66.8% vs 58.9%, difference 8.7% [95% CI 0.7-16.7), p=0.034) and a suppressed viral load (<50 copies/mL; non-virological failure censored population

80.0% vs 71.3%, difference 8.7% [95% CI 0.8-16.6, p=0.03]).[4] The TITAN trial was marked by a large discontinuation rate, but the main reason for discontinuation was due to adverse events (and thus is relevant), and the per protocol analyses were very similar to the intention-to-treat analyses in any case. Of note, when the efficacy results were analysed with reference to pre-existing PI resistance, DRV/r retained its efficacy even in the face of several major baseline PI mutations, whereas LPV/r did not.[1] The open label TITAN RCT was assessed as moderate certainty evidence due to imprecision (wide CIs) and a high rate of attrition.

In the ARTEMIS trial of first line PI-based therapies, a higher proportion of patients in the DRV/r arm obtained viral suppression at the 192-week mark (as they had at the 48 and 92 week marks in previous work). The rate of suppression at the 192-week mark was 68.8% in the DRV/r arm vs 57.2% in the LPV/r arm (difference 11.6%, 95% CI 4.4-18.8%, p=0.002). A similar sized difference was seen whether DRV was compared to a daily or 12-hourly LPV/r dosing schedule. At the 48- and 96-week marks, the suppression rates with DRV/r vs LPV/r were 84% vs 78% and 79% vs 71% respectively (p<0.001 in both instance). Thus the efficacy gap widened with time.

By contrast, the Kanter et al. fixed-effect network meta-analysis of second-line therapies in people with HIV with previous NNRTI-based ART failure, failed to find any significant difference in viral suppression rate with LPV/r + 2 NRTIs vs DRV/r + 2 NRTIs: OR 1.16 (95% CI 0.76 to 1.74) - , moderate certainty evidence due to imprecision. The network meta-analysis only reported on one RCT comparing LPV/r-containing regimen to DRV/r-containing regimen (neither the ARTEMIS nor TITAN trials were included), and did not include the DRV/r-containing regimen in the only league table described that allows for ranking of the interventions, comparing the relative effect between pairs of protease inhibitor interventions for the change from baseline in CD4 cell count.

Mortality

There were numerically fewer deaths in the DRV arm (2, 0.7%) than in the LPV arm (4, 1.3%) in the TITAN study by 96 weeks, although this difference was not statistically significant.

In the ARTEMIS trial, there were a lower proportion of deaths in the DRV arm at 192-weeks (1.2%) than the LPV/r arm (2.0%), but the absolute number of events was again very small (4 vs 7; total 11).

In the meta-analysis by Kanter et al., there was no significant mortality difference seen in those who, after failing first line therapy, switched to LPV/r with 2 NRTIs compared to DRV/r with 2 NRTIs: OR 0.53 (95% CI 0.11-3.13).

Adverse events, including lipid profiles

In the TITAN study's 96 week results, there were more grade 2-4 adverse events possibly related to the protease inhibitor in the LPV arm vs the DRV arm (44.8% vs 40.9%), and more serious adverse advents overall in the LPV arm vs the DRV arm (16.5% vs 13.8%). However, the rate of discontinuation due to adverse events was identical in each arm (8.1%). The total cholesterol and LDL were raised in similar percentage of cases between DRV and LPV. DRV was associated with a lower rate of grade 2-4 diarrhoea compared with LPV (8.1% versus 15.2%).

The ARTEMIS trial similarly suggested that DRV/r was better tolerated than LPV/r (in each case with TDF/FTC as a backbone). At 192-weeks, serious adverse events, regardless of causality, were less frequent in the DRV arm (16% vs 21%, p=0.116). Grade 2-4 adverse events related to the drug were similarly in the favour of DRV/r (28% vs 35.8%, p=0.028) as were adverse events of any grade (56.6% vs 74.9%, p<0.001). Those on

DRV/r were less likely to have an elevated total cholesterol (24.3% vs 32.7%, p=0.018), though the proportion with an elevated LDL were similar. Results were consistent at the 48-, 96-, and 192- week marks.

The Kanter et al. meta-analysis found a higher rate of serious adverse events in patients on LPV/r with 2 NRTIs vs those on DRV/r with 2 NRTIs. The OR calculated was 4.17, though the confidence interval narrowly crossed unity: 0.93-33.33.

Discontinuations

In the Kanter et al. meta-analysis, those on LPV/r-containing regimens were more likely to discontinue therapy (OR 1.26, 95% CI 0.49-3.71) and to discontinue therapy specifically due to adverse events (OR 2.56, 95% CI 0.24-100), although in both cases the confidence intervals around these point estimates were too wide for any firm conclusion to be drawn.

The ARTEMIS trial's data were more definitive. At 192-weeks, discontinuations due to adverse events had been significantly less frequent with DRV/r than they were with LPV/r (7.6% vs 14.5%, p=0.005).

In the TITAN trial, by 96 weeks, the rate of discontinuation overall was greater in the LPV/r arm (37.0%) than in the DRV/r arm (27.5%, p=0.01), although the rate of discontinuation due to adverse events was identical (8.1%). Similar results were seen at the 48-week mark - discontinuation due to adverse events was 7% in each arm (moderate certainty evidence).

Development of drug resistance mutations

In the TITAN study, fewer patients on DRV developed PI resistance (15% vs 33%) or NRTI mutations (8% vs 26%) at 96 weeks. This was statistically significant, with a p-value of <0.05.

In the ARTEMIS study, of those with paired baseline/endpoint genotypes, 9.3% in DRV/r arm vs 15.8% in LPV/r developed PI-resistance mutations (p=0.01). However, only ~15% of patients had paired baseline/endpoint genotypes done, putting this finding at high risk of bias.

Conclusion

The RCT evidence of follow-up > 48 weeks DRV/r-based antiretroviral regimens achieved higher rates of virological suppression than are LPV/r-base regimens. This absolute difference seen was clinically significant: 8.7% (95% CI 0.8-16.6) in the TITAN trial at 96 weeks, and 11.6% (95% CI 4.4-18.8%) in the ARTEMIS trial at 192 weeks, with a tendency for the differences to enlarge as the trials progressed. Whether this translates into fewer deaths is unclear, as relatively well patients were enrolled, and consequently the absolute differences in the small number of deaths were not statistically significant.

DRV/r-based antiretroviral regimens were better tolerated than LPV/r-based ones. This appears to be true of both severe adverse events and adverse events specifically thought to be related to the drugs. Some of this difference is driven by a consistently lower proportion of gastrointestinal events in the DRV/r-based arms, such as diarrhoea and vomiting. DRV/r-based therapy was also associated with a lower rate of therapy discontinuation due to adverse events in the ARTEMIS trial, but not in the TITAN trial.

There is some evidence that DRV/r-based therapy may be more virologically robust than LPV/r, with a lower rate of incident drug resistance-associated mutations. Furthermore, DRV maintains its virological activity better than LPV does in the face of baseline PI mutations.[1]

In evaluating DRV/r vs LPV/r, there are other programmatic considerations that are relevant to the South African context. Importantly, DRV/r cannot be co-administered with rifampicin-based tuberculosis treatment regimens. Furthermore, third line regimens in South Africa have traditionally been based on DRV/r and/or dolutegravir. The switch to dolutegravir in first line regimens, combined with a switch to DRV/r in second line regimens, could create challenges for the relatively small number of patients who would require third line therapy.

Table 1. Characteristics of excluded studies

Excluded studies		Reasons
1	Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Wirtz V, Rightmire A, Odeshoo L, McLaren C. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS. 2006 Mar 21;20(5):711-8. doi: 10.1097/01.aids.0000216371.76689.63. PMID: 16514301.	Atazanavir, not darunavir
2	Santos JR, Llibre JM, Bravo I, García-Rosado D, Cañadas MP, Pérez-Álvarez N, Paredes R, Clotet B, Moltó J. Short Communication: Efficacy and Safety of Treatment Simplification to Lopinavir/Ritonavir or Darunavir/Ritonavir Monotherapy: A Randomized Clinical Trial. AIDS Res Hum Retroviruses. 2016 May;32(5):452-5. doi: 10.1089/AID.2015.0248. Epub 2016 Feb 11. PMID: 26781004.	Monotherapy, not combination therapy.
3	Atazanavir Versus Lopinavir/Ritonavir (LPV/RTV) in Patients Who Have Not Had Success With Protease Inhibitor-Containing HAART Regimen(s). NCT00028301	Atazanavir, not darunavir
4	Sax PE. Meeting notes from the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment. Atazanavir in treatment-experienced patients. AIDS Clin Care. 2003 Sep;15(9):78. PMID: 14666914.	Atazanavir, not darunavir.
5	Venter WDF, Moorhouse M, Sokhela S, Serenata C, Akpomiemie G, Qavi A, Mashabane N, Arulappan N, Sim JW, Sinxadi PZ, Wiesner L, Maharaj E, Wallis C, Boyles T, Ripin D, Stacey S, Chitauri G, Hill A. Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial. Lancet HIV. 2019 Jul;6(7):e428-e437. doi: 10.1016/S2352-3018(19)30081-5. Epub 2019 Jun 12. PMID: 31202690.	Switch study in patients already suppressed and tolerating LPV/r. Patients not PI-naïve.
6	Brogan A, Mauskopf J, Talbird SE, Smets E. US cost effectiveness of darunavir/ritonavir 600/100 mg bid in treatment-experienced, HIV-infected adults with evidence of protease inhibitor resistance included in the TITAN Trial. Pharmacoeconomics. 2010;28 Suppl 1:129-46. doi: 10.2165/11587490-000000000-00000. PMID: 21182348.	Cost-effectiveness study.
7	Ferrer E, del Rio L, Martínez E, Curto J, Domingo P, Ribera E, Negredo E, Rosales J, Saumoy M, Ordóñez J, Gatell JM, Podzamczer D. Impact of switching from lopinavir/ritonavir to atazanavir/ritonavir on body fat redistribution in virologically suppressed HIV-infected adults. AIDS Res Hum Retroviruses. 2011 Oct;27(10):1061-5. doi: 10.1089/AID.2010.0254. Epub 2011 Jan 15. PMID: 21166602.	Atazanavir, not darunavir. Switch study, not PI naïve.
8	Randomised, multicentre, open clinical trial assessing the effectiveness and safety of simplification to atazanavir + ritonavir versus continuation of a stable antiretroviral regimen on lopinavir/ritonavir,Sponsor not yet defined (Spain)	Atazanavir, not darunavir
9	Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, Lichtenstein K, Rightmire A, Sankoh S, Wilber R. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS. 2005 Apr 29;19(7):685-94. doi: 10.1097/01.aids.0000166091.39317.99. PMID: 15821394.	Atazanavir not darunavir
10	Ribera E, Azuaje C, Lopez RM, Diaz M, Feijoo M, Pou L, Crespo M, Curran A, Ocaña I, Pahissa A. Atazanavir and lopinavir/ritonavir: pharmacokinetics, safety and efficacy of a promising double-boosted protease inhibitor regimen. AIDS. 2006 May 12;20(8):1131-9. doi: 10.1097/01.aids.0000226953.56976.ad. PMID: 16691064.	Atazanavir not darunavir
11	A Multicentre Trial of Second-line Antiretroviral Treatment Strategies in African Adults Using Atazanavir or Lopinavir/Ritonavir," NCT01255371"	Duplicate
12	Efficacy and safety of switching suppressed patients with elevated triglycerides from lopinavir/ritonavir or fosamprenavir/ritonavir to atazanavir/ritonavir or darunavir/ritonavir based therapy: the LARD study," Skiest, DJ	Switch study of patients tolerating LPV/r and suppressed on it. Patients not PI naïve.
13	Hill A. Atazanavir/ritonavir versus lopinavir/ritonavir: equivalent or different efficacy profiles? AIDS. 2005 Nov 18;19(17):2054-5. doi: 10.1097/01.aids.0000194137.73876.d5. PMID: 16260922.	Atazanavir, not darunavir.
14	Johnson M. Response to "Atazanavir/ritonavir versus lopinavir/ritonavir: equivalent or different efficacy profiles?" by Hill. AIDS. 2006 Oct 3;20(15):1987. doi: 10.1097/01.aids.0000247125.42753.63. PMID: 16988525.	Atazanavir, not darunavir. Journal letter.
15	Study of HIV Patients With Undetectable Viral Load and Abnormal Lipids Switching to Atazanavir/Ritonavir. NCT00120393	Switch study, not PI naïve. Atazanavir, not darunavir.
16	Randomised and Prospective Clinical Study to Evaluate the Efficacy and Safety of Lopinavir/ritonavir Monotherapy Vs Darunavir/ritonavir Monotherapies as Simplification Switching Strategies of PI/NNRTI-triple Therapy Based-regimens," EUCTR2009-013287-39-ES,"	Monotherapy, not combination therapy
17	Cochrane Central Register of Controlled Trials. A 96 Week Phase IIIB Study Comparing the Antiviral Efficacy and Safety of Atazanavir/ritonavir ATV/RTV with Lopinavir/ritonavir LPV/RTV , Each in Combination with Fixed Dose Tenofovir-Emtricitabine in HIV-1 infected treatment naive	Atazanavir not darunavir

	subjects. – Castle. EUCTR2005-001895-11. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2005-001895-11-IT, 2006 | added to CENTRAL: 31 March 2019 | 2019 Issue 3	
18	Perry CM. Emtricitabine/tenofovir disoproxil fumarate: in combination with a protease inhibitor in HIV-1 infection. Drugs. 2009;69(7):843-57. doi: 10.2165/00003495-200969070-00005. PMID: 19441871.	Narrative review of tenofovir + lamotrigine + dolutegravir
19	Evaluation of inflammatory immune parameters predicting cardiovascular risk in HIV-1-infected antiretroviral therapy naive patients treated with atazanavir/ritonavir versus lopinavir/ritonavir based regimens. - CRISTAL," EUCTR2008-006644-19-IT,"	Atazanavir not darunavir
20	Simpson KN, Baran RW, Collomb D, Beck EJ, Van de Steen O, Dietz B. Economic and health-related quality-of-life (HRQoL) comparison of lopinavir/ritonavir (LPV/r) and atazanavir plus ritonavir (ATV+RTV) based regimens for antiretroviral therapy (ART)-naïve and -experienced United Kingdom patients in 2011. J Med Econ. 2012;15(4):796-806. doi: 10.3111/13696998.2012.691927. Epub 2012 Jun 7. PMID: 22563716.	Atazanavir vs LPV/r
21	De Meyer S, Hill A, Picchio G, DeMasi R, De Paepe E, dr Béthune, MP. Influence of Baseline Protease Inhibitor Resistance on the Efficacy of Darunavir/Ritonavir or Lopinavir/Ritonavir in the TITAN trial. J Acquir Immune Defic Syndr. 49(5):563-564	Discussion of TITAN outcomes relating to baseline resistance. Excluded as not an RCT or systematic review, but included in discussion.

Table 2. Included studies

Author, date	Type of study	Intervention	Population	Comparators	Primary outcome	Effect sizes	Comments
Bánhegyi D et al., 2012[4] (TITAN trial) – 96 week results	RCT	Darunavir/ritonavir 600/100mg 12-hourly, plus optimised background regimen.	Treatment experienced, LPV-and DRV-naïve, HIV-positive adults with HIV viral load >1000 copies/mL, who had been on ART for ≥12 weeks. Multicentre, across 27 countries. n=604.	Lopinavir/ritonavir 400/100mg 12-hourly, plus optimised background regimen	Proportion with HIV viral load <400 copies/mL at 96 weeks.	For VL <400 copies/mL, viral suppression (ITT population): 66.8% (DRV) vs 58.9% (LPV), difference 8.7% (CI 0.7-16.7), p=0.034 Per protocol: 67.5% vs 59.5%: difference 8.7%, p<0.001. Using VL <50 copies/mL as threshold, non-viral failure censored population had similar findings: 80% vs 71.3%; difference 8.7%, 95% CI 0.8-16.6, p=0.03	High rate of treatment discontinuation: 81/298 for DRV, and 110/297 for LPV/r. However, much of the discontinuation was due to drug side-effects, and thus relevant. Also per protocol analysis similar to ITT analysis for primary outcome. Open label study Some patients not PI-naïve, though all were LPV and DRV naïve. Baseline PI mutations could have exacerbated the difference between LPV and DRV.

Madruga et al.[3] (TITAN trial – 48 week results)	RCT, 48-week follow up – see Bánhegyi et al. for 96-week results	Darunavir/ritonavir 600/100mg 12-hourly, plus optimised background regimen.	Treatment experienced, LPV-and DRV-naïve, HIV-positive adults with HIV viral load >1000 copies/mL, who had been on ART for ≥12 weeks. Multicentre, across 27 countries. n=604.	Lopinavir/ritonavir 400/100mg 12-hourly, plus optimised background regimen	Proportion with HIV viral load <400 copies/mL at 96 weeks.	ITT population: 77% with VL <400 copies in DRV/r group vs 67% in LPV/r group (95% CI 2-17, p<0.0001). Per-protocol population: 77% (DRV) vs 68% (LPV), 95% CI 2-16.	48-week results from TITAN trial. See Bánhegyi et al. above for 96 week results. High rate of treatment discontinuation: 62/298 for DRV, and 86/297 for LPV/r. However, much of the discontinuation was due to drug side-effects, and thus relevant. Also per protocol analysis similar to ITT analysis for primary outcome. Open label study For VL<50 copies, similar pattern: 71% (DRV) vs 60% (LPV), with gap widening as trial progressed. Some patients not PI-naïve, though all were LPV and DRV naïve. Baseline PI mutations could have exacerbated the difference between LPV and DRV.
Kanters S et al., 2017[9]	Systematic review and network meta-analysis	Multiple comparisons between LPV/r, ATV/r and DRV/r, with or without other companion drugs.	HIV positive adults and adolescents who were failing first-line NNRTI-based therapy	[See intervention]	Viral suppression, mortality, AIDS-defining illnesses or WHO stage 3-4 disease, discontinuations, discontinuations due to adverse events, and serious adverse events.	Relating to LPV + 2 NRTIS vs DRV + 2 NRTIS – fixed-effect network meta-analysis: • Viral suppression at 48 weeks: OR 1.16 (95% CI 0.76-1.74, NS) • Mortality: OR 0.53 (95% CI 0.11-3.13, NS). • Discontinuations: OR 1.26 (0.49-3.71)	Multiple comparisons computed in the paper; LPV + 2 NRTIs vs DRV + 2 NRTIs extracted, since this is most representative of real-world clinical practice. GRADE evaluation for quality of evidence for this subset for 48-week viral suppression: MODERATE.

						• Discontinuations due to severe AE: OR 2.56 (0.24-100). • Serious AEs: OR 4.17 (0.93-33.33)	
Orkin C et al., 2012[6] (ARTEMIS trial – 192 week results)	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 68.8% in DRV/r arm vs 57.2% in LPV/r arm; difference 11.6% (95% CI 4.4-18.8%), p=0.002. Resistance: Of those with paired baseline/endpoint genotypes, 9.3% in DRV/r arm vs 15.8% in LPV/r developed PI-resistance mutations. Discontinuation due to AE: Less frequent in DRV/r arm (7.6%) vs LPV/r arm (14.5%, p=0.005). Serious AEs (regardless of causality): 16% of DRV/r arm vs 21% in LPV/r arm. Grade 2-4 AEs (at least possibly related to drug): 28% DRV/r vs 35.8% LPV/r (p=0.028). Total cholesterol higher in DRV/r arm (p=0.018) but LDL difference not statistically significant.	Treatment naïve patients only. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression. Paired baseline/endpoint genotypes only available for a small minority of cases (risk of selection bias).

Mills et al. 2009. (ARTEMIS trial – 96 week results)[5]	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 79% (DRV) vs 71% (LPV). 95% CI for difference 1.9-14.8, p<0.001.	Treatment naïve patients. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression.
Ortiz et al. 2008. (ARTEMIS trial – 48 week results)[7]	RCT, phase 3.	DRV/r 800/100 daily with TDF/FTC.	HIV-positive adults, treatment-naïve with viral load ≥5000 copies. N=689.	LPV/r 800/200 (either daily or divided 12-hourly), with TDF/FTC	Viral suppression <50 copies/mL at week 192 in ITT population.	Viral suppression in 84% (DRV) vs 78% (LPV(. 95% CI for difference -0.1-11%, p<0.001.	Treatment naïve patients. 2 different LPV/r regimens, but in subgroup analyses, DRV/r was superior to both daily and 12-hourly LPV/r re: virological suppression.

Reviewers: JS Nel, S McGee
Declaration of interests: JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand) has previously received lecture fees from Abbvie, and is a member of the HIV Clinicians' Society Adult ART Guidelines committee. SM (Ophathlmolgical Society of South Africa, which receives sponsorships, grants and support for CPD activities, conferences, meetings and registry activities from various companies including Genop, Bayer, Roche, Alcon, Zeiss, and Oculate).

Acknowledgements: T Leong (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) assisted with the review and the costing, M Reddy (Better Health Programme – South Africa) assisted with the review and the following assisted with the literature searches and screening of records: T Kredo (Cochrane South Africa, South African Medical Research Council, SA GRADE Network), J Oliver (Cochrane South Africa, South African Medical Research Council), A Brandt (Stellenbosch University, SA GRADE Network), VD Ngah (Stellenbosch University), E Pienaar (Cochrane South Africa, South African Medical Research Council).

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence? N/a** 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	The following critical outcomes were assessed: • ***Viral suppression rates***: moderate certainty evidence • ***Discontinuation rates:*** moderate certainty evidence Randomised controlled trials and systematic review, but downgraded to "moderate" certainty due to imprecision (wide CIs) and a high rate of attrition in TITAN trial.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ Moderate ☐ Small ☐ None ☐	***Viral suppression rates***: large – absolute difference in rate of viral suppression to <50 copies/mL seen in the TITAN and ARTEMIS trials was 8.7% (NNT=9) and 11.6% respectively (NNT= 13). ***Discontinuation rates***: large – absolute difference of 6.9% lower in ARTEMIS trial (at 192 weeks) with DRV/r; NNT=11 and 9.5% lower in TITAN trial (at 96 weeks); NNT=15
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence? n/a** 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	Moderate certainty evidence – randomised controlled trials and systematic review, but downgraded to "moderate" certainty due to imprecision and a high rate of attrition in TITAN trial.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes? n/a** Large ☐ Moderate ☐ Small ☐ None ☒	DRV/r is better tolerated. The rates of drug-associated adverse events are lower with DRV/r than LPV/r (absolute difference 3.9% and 7.8% in TITAN and ARTEMIS respectively), driven mostly by a difference in gastrointestinal side-effects, particularly drug-induced diarrhoea.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☒ No ☐	List the members of the group: Atazanavir/ritonavir List specific exclusion from the group: n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain ☒	Single supplier – may pose supply chain challenges. Additional challenge for those on concurrent rifampicin for tuberculosis treatment as darunavir is contraindicated for use with rifampicin.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive [X] Less intensive [ ] Uncertain [ ]	**Price of medicines:** | Medicine	Price (ZAR) | |---|---| | LPV/r 200/50 mg, 112 tablets | 233.45* | | DRV/r 400/50 mg, 60 tablets | 647.62** | *Contract circular RT71-2019ARV **NDoH notice – reference 2020/11/03/EDP/01 – quotation price from Mylan **Estimated incremental budget impact for DRV/r-containing regimen:** *Assumptions:* • Utilisation data of LPV/r 200/50 mg formulation of 247 000 for 2020 comparable to 2021 [1] • Annual incidence of TB among people living with HIV 2506 per 100,000 (2.5%)[2] • 95.4% of TB cases are rifampicin-sensitive [3], and therefore can't be switched from LPV/r to DRV/r as rifampicin based therapy is required. *Model inputs:* *Estimated population:* • Number of patients on LPV/r estimated as 247 000/ annum. • Estimation of patients on LPV/r with HIV/TB co-morbidity per annum = 6175 • Estimation of patients on LPV/r who would require rifampicin-based therapy = 5891 • Estimation of patients on LPV/r with either no TB, or with rifampicin-resistant TB, who could switch to DRV/r = 241109 *Medicine price:* • Price of 30-day supply of LPV/r 200/50mg tablets (120) = R250.13 [4] • Price of 30-day supply of DRV/r 400/50mg tablets (60) = R647.62 [5] *Estimated annual cost of protease inhibitor consumption for PLHIV without co-morbid TB:* • Cost of LPV/r for one year: R 723 730 000 • Cost of DRV/r for one year: R 1 873 765 000 **Incremental budget impact for one year, using DRV/r = R 1 150 061 235** *Sensitivity analysis:* | Incidence of TB among patients on PI-based regimen	Incremental annual budget impact | |---|---| | 1% | R 1 166 921 000 | | 10% | R 1 065 764 000 | **References.** 1. NDoH data on file 2. UNAIDS 2019 report: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf 3. Ismail NA, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018 Jul;18(7):779-787. doi: 10.1016/S1473-3099(18)30222-6. doi: 10.1016/S1473-3099(18)30222-6 4. Contract circular RT71-2019ARV 5. NDoH notice – reference 2020/11/03/EDP/01 – quotation price from Mylan **Other resources:** n/a
VALUE	**Is there important uncertainty or variability about how much people value the options?**	No local survey data could be sourced but the Committee considered that that DRV/r would be acceptable to patients and healthcare workers

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	as DRV/r would offer a better tolerated regimen compared to LPV/r, with better compliance of a once-daily regimen, compared to 12-hourly dosing for LPV/r-based regimens. However, DRV would not be able to be used with rifampicin-based TB treatment.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Would be more equitable, since patients in private care are more readily offered alterative, better-tolerated PIs other than LPV/r, such as ATV/r and DRV/r.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	27 July 2021	JN, SM	DRV/r not be recommended for inclusion in the national EML, but be added as an alternative to LPV/r and ATV/r in ART-regimen in PLHIV not on concomitant rifampicin-containing TB therapy. Review indicator is DRV/r's price.

Appendix 1 – search strategy details

Database: PubMed

Date: 9 June 2021

Search	Query	Results
#13	Search: #10 AND #12 Sort by: Most Recent	414
#12	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	5,094,658
#11	Search: #3 AND #6 AND #9 Filters: Systematic Review Sort by: Most Recent	11
#10	Search: #3 AND #6 AND #9 Sort by: Most Recent	521
#9	Search: #7 OR #8 Sort by: Most Recent	3,184
#8	Search: (lopinavir[mh] OR lopinavir[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	3,128
#7	Search: "lopinavir-ritonavir drug combination" [Supplementary Concept] OR kaletra[tiab] OR lopimune[tiab] OR alluvia[tiab] Sort by: Most Recent	497
#6	Search: #4 OR #5 Sort by: Most Recent	1,861
#5	Search: (Atazanavir sulphate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,112
#4	Search: (Darunavir[mh] OR darunavir[tiab] OR prezista[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,010
#3	Search: #1 AND #2 Sort by: Most Recent	127,157
#2	Search: antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immunodeficiency[tiab])) OR ((anti[tiab]) AND (acquired immuno-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immune-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency[tiab])) Sort by: Most Recent	206,302
#1	Search: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) Sort by: Most Recent	420,176

Search	Query	Results
#9	Search: #6 AND #8 Sort by: Most Recent	180
#8	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	5,094,658
#7	Search: #3 AND #4 AND #5 Filters: Systematic Review Sort by: Most Recent	8
#6	Search: #3 AND #4 AND #5 Sort by: Most Recent	239
#5	Search: (Atazanavir sulphate[mh] OR atazanavir[tiab] OR reyataz[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,112
#4	Search: (Darunavir[mh] OR darunavir[tiab] OR prezista[tiab]) AND (ritonavir[mh] OR ritonavir[tiab] OR norvir[tiab]) Sort by: Most Recent	1,010
#3	Search: #1 AND #2 Sort by: Most Recent	127,157
#2	Search: antiretroviral therapy, highly active[MeSH] OR anti-retroviral agents[MeSH] OR antiviral agents[MeSH:NoExp] OR ((anti[tiab]) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti[tiab]) AND (retroviral*[tiab])) OR HAART[tiab] OR ((anti[tiab]) AND (acquired immunodeficiency[tiab])) OR ((anti[tiab]) AND (acquired immuno-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immune-deficiency[tiab])) OR ((anti[tiab]) AND (acquired immun*[tiab]) AND (deficiency[tiab])) Sort by: Most Recent	206,302
#1	Search: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) Sort by: Most Recent	420,176

Database: EPISTEMONIKOS
Date: 14 June 2021
No. of records retrieved: 13
(darunavir AND atazanavir)

(title:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome") OR abstract:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome")) AND (title:((darunavir OR prezista) AND (ritonavir OR norvir)) OR abstract:((darunavir OR prezista) AND (ritonavir OR norvir))) AND (title:((atazanavir OR reyataz) AND (ritonavir OR norvir)) OR abstract:((atazanavir OR reyataz) AND (ritonavir OR norvir)))

Database: EPISTEMONIKOS
Date: 14 June 2021
No. of records retrieved: 38
(darunavir OR atazanavir)

(title:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome") OR abstract:(hiv* OR hiv-1 OR hiv-2 OR hiv1 OR hiv2 OR "human immunodeficiency virus" OR "human immuno-deficiency virus" OR "human immuno-deficiency virus" OR "human immunedeficiency virus" OR "human immune-deficiency virus" OR "human immune-deficiency virus" OR "acquired immunodeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immuno-deficiency syndrome")) AND (title:((lopinavir OR kaletra OR lopimune OR alluvia) AND (ritonavir OR norvir)) OR abstract:((lopinavir OR kaletra OR lopimune OR alluvia) AND (ritonavir OR norvir))) AND (title:(((darunavir OR prezista) AND (ritonavir OR norvir)) OR ((atazanavir OR reyataz) AND (ritonavir OR norvir))) OR abstract:(((darunavir OR prezista) AND (ritonavir OR norvir)) OR ((atazanavir OR reyataz) AND (ritonavir OR norvir))))

Database: CLIB, Issue 6 of 12, June 2021
Date: 14 June 2021
(darunavir OR atazanavir)

ID	Search	Hits
#1	MeSH descriptor: [HIV Infections] explode all trees	12861
#2	MeSH descriptor: [HIV] explode all trees	3134
#3	hiv* or hiv-1 or hiv-2 or hiv1 or hiv2 or (hiv near infect*) or (human immunodeficiency virus) or (human immunedeficiency virus) or (human immune-deficiency virus) or (human immuno-deficiency virus) or (human immune deficiency virus) or (human immuno deficiency virus) or (acquired immunodeficiency syndrome) or (acquired immunedeficiency syndrome) or (acquired immuno-deficiency syndrome) or (acquired immune-deficiency syndrome) or (acquired immun* next deficiency syndrome) (Word variations have been searched)	30926
#4	MeSH descriptor: [Lymphoma, AIDS-Related] this term only	22
#5	MeSH descriptor: [Sexually Transmitted Diseases, Viral] this term only	29
#6	#1 or #2 or #3 or #4 or #5	30868
#7	MeSH descriptor: [Antiretroviral Therapy, Highly Active] this term only	1230
#8	MeSH descriptor: [Anti-HIV Agents] explode all trees	3576
#9	MeSH descriptor: [Antiviral Agents] this term only	4033
#10	MeSH descriptor: [AIDS Vaccines] this term only	444
#11	(anti hiv) or antiretroviral* or (anti near retroviral*) or (aids near vaccin*) (Word variations have been searched)	13008
#12	#7 or #8 or #9 or #10 or #11	17035
#13	#6 and #12 (Word variations have been searched)	13485
#14	([mh Darunavir] or darunavir:ti,ab,kw or prezista:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	563
#15	([mh "Atazanavir sulphate"] or atazanavir:ti,ab,kw or reyataz:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	651
#16	#14 or #15	1056
#17	([mh lopinavir] or lopinavir:ti,ab,kw or kaletra:ti,ab,kw or lopimune:ti,ab,kw or alluvia:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	1305
#18	#13 and #16 and #17 in Cochrane Reviews	1

#19	#13 and #16 and #17 in Trials	204

Database: CLIB, Issue 6 of 12, June 2021
Date: 14 June 2021
(darunavir AND atazanavir)

ID	Search	Hits
#1	MeSH descriptor: [HIV Infections] explode all trees	12861
#2	MeSH descriptor: [HIV] explode all trees	3134
#3	hiv* or hiv-1 or hiv-2 or hiv1 or hiv2 or (hiv near infect*) or (human immunodeficiency virus) or (human immunedeficiency virus) or (human immune-deficiency virus) or (human immuno-deficiency virus) or (human immune deficiency virus) or (human immuno deficiency virus) or (acquired immunodeficiency syndrome) or (acquired immunedeficiency syndrome) or (acquired immuno-deficiency syndrome) or (acquired immune-deficiency syndrome) or (acquired immun* next deficiency syndrome) (Word variations have been searched)	30926
#4	MeSH descriptor: [Lymphoma, AIDS-Related] this term only	22
#5	MeSH descriptor: [Sexually Transmitted Diseases, Viral] this term only	29
#6	#1 or #2 or #3 or #4 or #5	30868
#7	MeSH descriptor: [Antiretroviral Therapy, Highly Active] this term only	1230
#8	MeSH descriptor: [Anti-HIV Agents] explode all trees	3576
#9	MeSH descriptor: [Antiviral Agents] this term only	4033
#10	MeSH descriptor: [AIDS Vaccines] this term only	444
#11	(anti hiv) or antiretroviral* or (anti near retroviral*) or (aids near vaccin*) (Word variations have been searched)	13008
#12	#7 or #8 or #9 or #10 or #11	17035
#13	#6 and #12 (Word variations have been searched)	13485
#14	([mh Darunavir] or darunavir:ti,ab,kw or prezista:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	563
#15	([mh "Atazanavir sulphate"] or atazanavir:ti,ab,kw or reyataz:ti,ab,kw) and ([mh ritonavir] or ritonavir:ti,ab,kw or norvir:ti,ab,kw) (Word variations have been searched)	651
#16	#13 and #14 and #15 in Cochrane Reviews	0
#17	#13 and #14 and #15 in Trials	125

References

1. De Meyer S, Hill A, Picchio G, DeMasi R, De Paepe E, de Bethune MP. Influence of baseline protease inhibitor resistance on the efficacy of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. J Acquir Immune Defic Syndr. 2008;49(5):563-4.
2. Moorhouse MA, Carmona S, Davies N, Dlamini S, van Vuuren C, Manzini T, et al. Appropriate clinical use of darunavir 800 mg. South Afr J HIV Med. 2018;19(1):918.
3. Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet. 2007;370(9581):49-58.
4. Banhegyi D, Katlama C, da Cunha CA, Schneider S, Rachlis A, Workman C, et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. Curr HIV Res. 2012;10(2):171-81.
5. Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard PM, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS. 2009;23(13):1679-88.
6. Orkin C, DeJesus E, Khanlou H, Stoehr A, Supparatpinyo K, Lathouwers E, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. HIV Med. 2013;14(1):49-59.
7. Ortiz R, Dejesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS. 2008;22(12):1389-97.
8. Ciaffi L, Koulla-Shiro S, Sawadogo A, le Moing V, Eymard-Duvernay S, Izard S, et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. AIDS. 2015;29(12):1473-81.
9. Kanters S, Socias ME, Paton NI, Vitoria M, Doherty M, Ayers D, et al. Comparative efficacy and safety of second-line antiretroviral therapy for treatment of HIV/AIDS: a systematic review and network meta-analysis. Lancet HIV. 2017;4(10):e433-e41.

PHC/Adult Hospital Expert Review Committee: Evidence Summary Isoniazid Preventive Therapy in Pregnancy

Date: 9 November 2023
Reviewer(s): Dr Jessica Taylor, Prof. Karen Cohen
Affiliation: University of Cape Town, Groote Schuur Hospital
Author affiliation and conflict of interest details: JT and KC have no interests pertaining to isoniazid. KC is a co-author on the paper by Kalk et al.

Secretariat Support: Zahiera Adam

Research Question: What is the efficacy and safety of isoniazid preventive therapy in pregnant women?

1. Background and history of current recommendations

Tuberculosis disease during pregnancy and the post-partum period is associated with adverse maternal, pregnancy, infant outcomes.(1) There is consensus regarding the benefit of treating active tuberculosis disease during pregnancy. Additionally, there is consensus regarding the benefit of isoniazid preventive therapy (IPT) in non-pregnant people living with HIV (PLWHIV) to prevent tuberculosis disease.(1)

In PLWHIV not on ART, tuberculosis preventive therapy is reported to reduce the risk of tuberculosis disease by 33% (RR 0.67; 95% CI 0.51 to 0.87), with the reduction in risk reaching 64% in those with proven latent tuberculosis infection on skin testing (RR 0.36; 95% CI 0.22 to 0.61)(2). In a South African study of PLWHIV who were predominantly on ART, 12 months of IPT was associated with 37% reduction in risk of tuberculosis (3226.5 person-years of follow up; HR 0.63; 95% CI 0.41 to 0.94). This protective effect was demonstrated even in those with negative tuberculin skin tests (TST)(aHR 0.43; 95% 0.21 to 0.86) or interferon gamma release assays (IGRA)(aHR 0.43; 95% CI 0.20 to 0.96). However, no difference in all-cause mortality was reported (IPT 0.9 per 100 person-years vs. placebo 1.2 per 100 person-years; HR 0.72; 95% CI 0.34 to 1.34; p = 0.32).(3) The 2018 NEMLC medicine review titled "Isoniazid Preventive Therapy" reported a number needed to treat (NNT) to avert 1 case of tuberculosis disease of 33 in non-pregnant PLWHIV.(4) Additionally, this review indicated that IPT is associated with a mortality benefit in a long-term follow-up study across all CD_4 counts and irrespective of baseline latent tuberculosis infection (aHR 0.61; 95% CI 0.39 to 0.94; NNT 57).(4, 5) However, there remains a lack of consensus regarding the safety and efficacy of IPT in pregnant women living with HIV. Safety is of particular importance in the setting of prophylactic treatment, where the acceptable threshold for potential harm is much lower.

In the 2014 primary healthcare (PHC) standard treatment guidelines (STG), IPT was recommended for all PLWHIV. The duration of IPT recommended, ranged from 6 – 36 months depending on the results and availability of TST and whether or not the patient was taking highly active antiretroviral therapy (HAART). In addition, 12 months of IPT was recommend for all HIV positive pregnant women.(6)

In 2018, the decision was taken to simplify this recommendation to 12 months of IPT for all PLWHIV regardless of TST testing or HAART, based on the results of the locally conducted clinical trial of IPT versus placebo in participants on ART mentioned previously.(3) In the same year preliminary data from the TB APPRISE randomized controlled trial (RCT) reported increased adverse pregnancy outcomes associated with IPT use during pregnancy as compared to the post-partum period, and no difference in tuberculosis disease or mortality. As a result, NEMLC recommended that a caution be added to the STG regarding the use of IPT in pregnant women living with HIV with high CD_4 counts. (1)

After further deliberation, based on the evidence of potential harm associated with IPT use in pregnancy, and after consideration of the potential benefit of IPT in the high tuberculosis prevalence setting of South Africa, a CD_4 cut off for IPT initiation in pregnancy was recommended. The recommendation was that IPT be deferred until after delivery in women living with HIV with CD_4 counts of < 100 cells/mm^3. This CD_4 count was extrapolated from the REALITY RCT, which showed an association between IPT and a reduction in incident tuberculosis disease in non-pregnant patients with advanced HIV (CD_4 < 100 cells/mm^3) starting ART. (7)

Following this, data emerged from a locally conducted, retrospective cohort study in the Western Cape, which reported the benefit of antenatal IPT in preventing incident tuberculosis in women living with HIV with CD_4 counts ≤ 350 cells/mm^3, as well as encouraging safety data, leading to a change in the previously recommended CD_4 count criteria. In the Adult Hospital HIV Chapter (2017 – 2019) and the Primary Healthcare HIV Chapter (2020), it was recommended that pregnant women living with HIV and with a CD_4 count cells/mm^3 < 350 receive 12 months of IPT, while in those with CD_4 counts ≥ 350 cells/mm^3, IPT be deferred till after delivery (see textbox 1). (8)

Textbox 1: Current NEMLC Recommendation (2017-2019 review cycle)

NEMLC Recommendation: *IPT deferral if CD4 ≥350 in pregnant women; whilst where CD4<350, active TB to be excluded with symptom screen and then IPT given.*

Rationale:
A RCT of immediate versus delayed IPT initiation in pregnant woman found that isoniazid exposure in pregnancy was associated with increased risk of adverse pregnancy outcome (fetal demise, low birth weight, preterm delivery and congenital anomaly). Isoniazid should therefore be deferred until after delivery, except in women who are severely immunocompromised and have low CD4s. Subsequently, a local retrospective cohort study[31] (n= 43 971) showed that antenatal IPT is safe with greatest benefit against active TB when CD4 ≤350 cells/mm3.

Level of Evidence: II Cohort Study

Currently, in high tuberculosis incidence settings, the World Health Organisation (WHO) recommends 36 months of IPT in PLWHIV with unknown or positive TST, irrespective of CD_4 count, history of previous treatment for tuberculosis or pregnancy (conditional recommendation, low quality evidence).(9) This recommendation is based on data from non-pregnant population.

In February 2023, the South African Tuberculosis programme released national guidelines for the treatment of tuberculosis infection, recommending 12 months of IPT for all HIV positive pregnant women, irrespective of CD_4 count. Additionally in these programmatic guidelines, in HIV negative pregnant women, with a history of close contact with a person with active tuberculosis disease, a 3-month treatment regimen consisting of isoniazid and rifampicin is recommended. (10)

Subsequently, new evidence relating to the safety and efficacy of IPT in pregnancy has been published. This document aims to summarize this new evidence as well as the data previously considered by the NEMLC and the Adult Hospital/Primary Healthcare Evidence Review Committee (AH/PHC ERC) to inform further recommendations and decision-making.

2. Literature Search

A rapid review of the literature was conducted. PubMed was searched with the following search terms:

("isoniazid"[MeSH Terms] OR "isoniazid"[All Fields] OR "isoniazide"[All Fields]) AND ("prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR ("preventive"[All Fields] AND "therapy"[All Fields]) OR "preventive therapy"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])

One hundred and thirty-two articles were identified in the initial search. Systematic reviews, randomized clinical trials, and observational studies with comparator groups, published in English, were eligible for inclusion. Furthermore, studies were required to compare isoniazid monotherapy in pregnant women to placebo/no treatment/delayed treatment, and report on safety (adverse pregnancy outcomes, infant outcomes, hepatotoxicity) and/or efficacy (tuberculosis disease and mortality), to be included.

In the screening stage, only 3 studies conducted in HIV-negative populations were identified. Two of these were single-arm retrospective cohort studies comparing outcomes to historical cohorts only, and were therefore not eligible for inclusion.(11, 12) The third study conducted in HIV-negative women examined pregnancy outcomes in women who became pregnant in RCT's that compared weekly rifapentine-isoniazid (3-HP) to IPT, or self-administered 3-HP to directly observed 3-HP. In this study, rates of fetal loss in IPT and 3-HP exposed pregnancies were compared to each other, and overall, to a historical American cohort.(11) This study was also not considered for further inclusion.

Therefore, after screening of the titles and abstracts, 8 studies were identified, none of which were conducted in pregnant women without HIV.

The relevant studies identified for inclusion are summarized in table 1.

Table 1.

	Study Name/Author	Study Type	Name of Publication	Year of Publication
1.	Hamada et al.	Systematic Review	The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis(13)	2020
2.	Gupta et al. (TB-APPRISE)	Randomized Controlled Trial	Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women(1)	2019
2.1	Theron et al. (TB-APPRISE)	Randomized Controlled Trial	Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living with Human Immunodeficiency Virus(14)	2020
2.2	Cherkos et al. (TB-APPRISE)	Randomized Controlled Trial	Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial(15)	2023
3.	Taylor et al.	Prospective cohort study nested in randomized controlled trial.	Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy(16)	2013
4.	Gupta et al. (BRIEF-TB)	Prospective cohort study nested in randomized controlled trial.	Adverse Pregnancy Outcomes Among Women with Human Immunodeficiency Virus Taking Isoniazid Preventive Therapy During the First Trimester(17)	2023
5.	Salazar-Austin et al. (TSHEPISO)	Prospective cohort study	Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living with Human Immunodeficiency Virus in the Tshepiso Cohort (18)	2020
6.	Kalk et al.	Retrospective cohort study	Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data(8)	2020

3. Evidence Summary

3.1 TB-APPRISE(1, 14, 15)

TB-APPRISE was a multicenter, double-blind, placebo controlled non-inferiority trial that enrolled pregnant women living with HIV between 14 – 34 weeks' gestation. All women were enrolled from high tuberculosis prevalence countries, defined as ≥ 60 cases per 100 000. However, only 20% of participants were enrolled from South Africa, which has twice the tuberculosis prevalence than some of the other countries of enrollment. Women were randomized to receive either IPT immediately for 28 weeks followed by placebo, or placebo immediately followed by IPT initiated from 12-weeks post-partum. Women with a recent exposure to a close contact with active tuberculosis, and therefore at higher risk of progression to tuberculosis disease, were excluded.

A total of 956 women were enrolled in the study with 477 randomized to the immediate IPT group and 479 to the deferred IPT group. The median CD_4 count was 493 cells/mm^3 and all but one of the participants were receiving HAART[1]. The HAART regimen included efavirenz in 85.1% of all participants and 63.1% of participants had an undetectable HIV viral load at enrollment. Thirty percent of the enrolled study participants had positive IGRA results indicative of latent tuberculosis infection.

A relatively high attrition rate was reported with 171 women (17.9%) discontinuing the trial prematurely, 88 in the immediate IPT group and 83 in the deferred IPT group. No significant difference in patient-reported adherence or by assessment of pill count were noted between the immediate and deferred groups.

Approximately, one third of participants were exposed to IPT or placebo from the second trimester into the third trimester. The remaining two thirds of participants were exposed to IPT or placebo in third trimester only.

The primary outcome was a composite safety outcome of maternal adverse events of grade 3 or higher that were possibly, probably, or related to isoniazid or placebo or permanent discontinuation of the trial due to toxic effects. The primary outcome event occurred at an incidence rate of 15.03 events per 100 person-years in the immediate IPT group as compared to 14.93 events per 100 person-years in the deferred group (rate difference 0.10; 95% CI -4.77 to 4.98). The predefined noninferiority criterion was met for the primary outcome event.

In terms of efficacy, only 6 cases of incident tuberculosis were reported throughout the trial, 3 cases in each arm. As a result, no significant difference in incident tuberculosis between the immediate IPT and the deferred group was reported (incidence rate: 0.60 vs. 0.59 per 100 person-years; rate difference 0.01; 95% CI -0.94 to 0.96). Six deaths occurred during the trial, 2 in the immediate IPT group and 4 in the deferred group. A large proportion of the deaths occurred due to liver failure (66.67%). No significant difference in mortality rate between the immediate IPT group and the deferred group was reported (incidence rate 0.40 vs. 0.78 per 100 person-years; rate difference -0.39; 95% CI -1.33 to 0.5).

Of the 956 women enrolled in the study, 926 women had pregnancy outcome data. The composite adverse pregnancy outcome included stillbirth (fetal death ≥ 20 weeks' gestation), spontaneous abortion (pregnancy loss <20 weeks' gestation), low birth weight (<2500 g), preterm delivery (delivery < 37 weeks' gestation), or major congenital anomalies in an infant. The composite adverse pregnancy outcome occurred more frequently in the immediate IPT group as compared to the deferred group (23.6% vs. 17.0%; risk difference 6.7 percentage points; 95% CI 0.8 to 11.9; p = 0.01). Individually, the outcomes of stillbirth, spontaneous abortion, and low birth weight infant occurred more frequently in the immediate IPT group than in the deferred group, but the between group differences failed to reach statistical significance.

Theron et al. conducted a secondary analysis of the pregnancy outcome data from 925 mother-infant pairs[2] from the TB-APPRISE study.(14) Important covariates adjusted for in the multivariable logistic regression models included maternal age at delivery, CD_4 quartile, suppressed HIV viral load, timing of ART initiation, HBsAg status,

[1] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[2] 926 women with pregnancy outcome and excluding 1 induced abortion. Therefore, 925 women who had at least 1 live birth or fetal demise were analysed.

maternal mid upper arm circumference (MUAC), IGRA status, noninfectious pregnancy complications, infectious pregnancy complications, twin versus singleton pregnancy, current smoking status, and hospitalization.

The study reported that the adjusted odds of a composite of fetal demise, preterm delivery, low birth weight infant or congenital anomaly were 1.63 times higher among women randomized to immediate IPT arm (23.6% vs. 17.0%; aOR 1.63; 95% CI 1.15 to 2.31; p = 0.007; NNTH 16) (refer Table 2). Immediate IPT was also associated with increase odds of composite adverse outcomes that included neonatal death (composite 2) and early neonatal death (composite 3). When examining the individual components of the composite outcomes, no association was detected between IPT study arm and perinatal mortality or preterm delivery. However, after adjusting for other covariates, immediate IPT was associated with a 58% increase in the odds of a low-birth-weight infant (14.4% vs. 10.3%; aOR 1.58; 95% CI 1.02 to 2.46; p = 0.041; NNTH 25).

Table 2. Summary of Composite Adverse Pregnancy Outcomes by Treatment Group and Adjusted Odds Ratio Estimates from Theron et al.

Outcome	Immediate INH, n/N (%)	Deferred INH, n/N (%)	Unadjusted OR (95% CI), by study arm	Adjusted OR (95% CI), by study arm
Composite 1: fetal demise, PTD, LBW, or congenital anomaly	106/449 (23.6)	78/460 (17.0)	1.51 (1.09–2.10)	1.63 (1.15–2.31)
Composite 2: fetal demise, PTD, LBW, or neonatal death (<28 days)	105/450 (23.3)	78/459 (17.0)	1.48 (1.07–2.06)	1.62 (1.14–2.30)
Composite 3: fetal demise, PTD, LBW, or early neonatal death (<7 days)	105/450 (23.3)	73/459 (15.9)	1.61 (1.15–2.24)	1.74 (1.22–2.49)
Perinatal death 1: fetal demise or neonatal death	23/459 (5.0)	20/466 (4.3)	1.18 (.64–2.17)	1.32 (.69–2.53)
Perinatal death 2: fetal demise or early neonatal death	21/459 (4.6)	13/466 (2.8)	1.67 (.83–3.38)	1.84 (.87–3.85)
LBW: <2500 grams at birth	62/430 (14.4)	46/446 (10.3)	1.46 (.97–2.20)	1.58 (1.02–2.46)
PTD: <37 weeks gestation at delivery	48/442 (10.9)	40/458 (8.7)	1.27 (.82–1.98)	1.35 (.85–2.15)

Multivariable model for composite outcomes by study arm.

Abbreviations: CI, confidence interval; LBW, low birth weight; OR, odds ratio; PTD, preterm delivery.

Cherkos et al. conducted a post hoc analysis of data from the TB APPRISE RCT, analyzing only 898 HIV-exposed but uninfected live born babies with at least one follow-up after birth.(15) After adjusting for maternal BMI, maternal age, HAART regimen, HIV viral load, CD_4 count, level of education, and household food security, they reported that infants born to mothers randomized to the immediate IPT arm had a 1.60 times greater risk of low birth weight than infants born to mothers in the deferred IPT arm (aRR 1.60; 95% CI 1.07 to 2.41). No significant association between treatment arm and preterm birth (aRR 1.31; 95% CI 0.87 to 1.97) or small-for-gestational-age was reported (aRR 0.97; 95% CI 0.71 to 1.32). Additionally, infants born to mothers randomized to immediate IPT experienced a 47% increased risk of becoming underweight in the first 12 weeks of life (aHR 1.47; 95% CI 1.06 to 2.03), and a 34% increased risk of becoming underweight in the first 48 weeks of life (aHR 1.34; 95% CI 1.01 to 1.78). No association between IPT treatment arm and stunting or wasting was reported. These findings were particularly pronounced in male infants, suggesting modification of the effect of antenatal IPT by sex.

Pertinent results from all 3 publications arising from the TB-APPRISE RCT are summarized in Table 3 below.

Table 3. Summary of all publications arising from TB-APPRISE RCT

Efficacy(1)	Maternal Adverse Events(1)	Adverse pregnancy outcomes(1, 14)	Infant Growth(15)
INCIDENT TB: IG 0.60 vs. DG 0.59 Rate difference: 0.01 per 100 person-years (95% CI -0.94 to 0.96) **MORTALITY:** IG 0.40 vs. DG 0.78 Rate difference: -0.39 per 100 person-years (95% -1.33 to 0.56)	**≥ GRADE 3 AE OR AE LEADING TO TREATMENT DISCONTINUATION:** IG 15.03 vs. DG 14.93 Rate difference: 0.10 per 100 person-years (95% CI -4.77 to 4.98)	**STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, CONGENTIAL ANOMALIES** IG 23.6% vs DG 17% Risk difference: 6.7 (95% CI 0.8 to 11.9) aOR 1.63 (95% CI 1.15 to 2.31)	**LBW:** aRR 1.60 (95% CI 1.07 to 2.41) **PRETERM:** aRR 1.31 (95% CI 0.87 to 1.97) **SGA:** aRR 0.97 (95% CI 0.71 to 1.32) **UNDERWEIGHT by 12 weeks:** aHR 1.47 (95% CI 1.06 to 2.03)

		STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (28 days): aOR 1.62 (95% CI 1.14 to 2.30) **STILLBIRTH, SPONT. ABORTION, LBW, PRETERM, NEONATAL DEATH (7 days):** aOR 1.74 (95% CI 1.22 to 2.49)	**UNDERWEIGHT by 48 weeks:** aHR 1.34 (95% CI 1.01 to 1.78)
IG – immediate group; DG – deferred group; SGA – small for gestational age; LBW – birth weight < 2.5kg; SGA –small for gestational age or weight < 10th percentile for gestational age; aOR – adjusted odds ratio; CI – confidence interval			

3.2. Taylor et al. (16)

Taylor et al. conducted a nested cohort study of women living with HIV who became pregnant while enrolled in a double-blind, randomized, placebo-controlled tuberculosis prevention trial. In the trial, conducted in Botswana, all participants received 6 months of IPT, after which they were randomized to either continue IPT or changed to placebo for a further 30 months. Women, not yet on HAART[3], who became pregnant during the trial with CD_4 counts of > 200 cells/mm^3 received zidovudine prophylaxis from 34 weeks' gestation. Whereas those who became pregnant CD_4 counts ≤ 200 cells/mm^3 were referred to initiate HAART.

One hundred and ninety-six pregnancies occurred during the trial, of which 103 pregnancies[4] were exposed to isoniazid (52.6%) and 93 were not. Almost all (99%) of IPT-exposed pregnancies were exposed from the first trimester, with only 68% of women having ongoing exposure throughout the pregnancy. Thirty seven percent of pregnant women received HAART during pregnancy, with the remainder receiving only zidovudine-based prophylaxis. The median CD_4 count at baseline for women who became pregnant during the trial was 368 cells/mm^3. Approximately 16% of the cohort had CD_4 counts below 200 cells/mm^3. No statistical comparison of the baseline characteristics of the pregnancies exposed to IPT compared to those unexposed was provided.

In this study, adverse pregnancy outcome was defined as preterm delivery (≤ 37 weeks' gestation), low birth weight (<2500g), stillbirth (delivery of an infant with no signs of life at ≥ 28 weeks' gestation), spontaneous abortion (spontaneous termination of pregnancy < 24 weeks' gestation), neonatal mortality (death of a term infant within 28 days of delivery), or any noted congenital abnormality. Isoniazid exposure during pregnancy was not associated with increased odds of an adverse pregnancy outcome (aOR 0.6; 95% CI 0.3 to 1.1), after adjusting for ART regimen, maternal CD_4 count, maternal age, and BMI. Furthermore, no maternal deaths, isoniazid-associated hepatitis or other severe isoniazid-associated events were reported in the 103 women who were exposed to IPT in pregnancy during the trial.

3.3. Gupta et al. (BRIEF-TB trial)(17)

BRIEF-TB was an open-label, randomized, non-inferiority trial, comparing a weight-based 1-month isoniazid plus rifapentine regimen (1HP) with the standard 9-month IPT for tuberculosis prevention among PLWHIV. The trial was conducted from 2012 to 2017, and enrolled participants from ten high tuberculosis prevalence countries[5] (including South Africa). All those who were randomized to receive IPT and became pregnant during the trial were analysed as part of the planned secondary analysis by Gupta et al. Pregnancies were classified as being unexposed[6] (n = 89) or exposed to IPT (possibly or definitely)(n = 39)[7]. Based on the study definition of exposure, all pregnancies exposed to IPT were conceived while taking IPT, with fewer women having ongoing exposure in the second and third trimesters. To note, although the data that informed this study was collected prospectively under trial conditions, which pregnancies were exposed or not exposed to IPT was not determined by randomization.

[3] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.
[4] In 103 women
[5] High tuberculosis prevalence defined as ≥ 60 cases per 100 000 population.
[6] Pregnancies were classified as IPT unexposed if pregnancy outcome occurred > 45 weeks after the final isoniazid dose.
[7] Pregnancies were classified as definitely exposed to IPT if the positive pregnancy test, pregnancy outcome, or estimated date of conception based on gestational age at birth occurred on or before the date of last dose of isoniazid.

Once again a composite adverse pregnancy outcome of spontaneous abortion (fetal demise before 20 weeks' gestation), ectopic pregnancy, or stillbirth (fetal demise at or beyond 20 weeks' gestation) was defined. For live births, low birth weight (< 2500 g) and preterm delivery (delivery before 37 weeks gestational age) were outcomes of interest. Analyses were adjusted for maternal CD_4 count, ART use, hepatitis B surface antigen positivity, age, and latent tuberculosis infection. However, other important confounders associated with poor pregnancy outcomes such as maternal smoking status, BMI or obstetric history were not measured or adjusted for. The median CD_4 count for the cohort was 534 cells/$mm^{3.}$ Thirty eight percent of the IPT-exposed women were receiving HAART at enrolment, increasing to 79% by pregnancy outcome. Thirty four percent of the unexposed women were receiving HAART at enrolment, increasing to 96% at pregnancy outcome. The difference in proportion of women receiving HAART at pregnancy outcome by IPT exposure was statistically significant (79% vs. 96%; p = 0.007).

A total of 29 pregnancies ended in an adverse pregnancy outcome: 25 spontaneous abortions, 2 stillbirths and 2 ectopic pregnancies. The composite pregnancy outcome occurred in 33% of pregnancies exposed to IPT and 18% of pregnancies not exposed to IPT. Crudely, the proportion of spontaneous abortions and stillbirths was 2-fold higher in the pregnancies exposed to IPT as compared to those unexposed. When adjusted for baseline covariates mentioned previously, IPT exposure in pregnancy was associated with an almost 2-fold increased risk of the adverse composite outcome (aRR 1.90; 95% CI 1.01 to 3.54; p = 0.04)(Refer Table 4). In an analysis adjusted for the same covariates, but measured closest to the pregnancy outcome, the association was no longer statistically significant (aRR 1.45; 95% CI 0.75 to 2.80; p = 0.27). No association was reported between IPT exposure in pregnancy and low birth weight (RR 1.01; 95% CI 0.29 to 3.56) or preterm delivery (RR 0.87; 95% CI 0.32 to 2.42).

Table 4. Results from Regression Model of Relative Risk of Adverse Pregnancy Outcome by IPT exposure from Gupta et al. 2023.

	No./Total N (%)		Unadjusted		Adjusted for Covariates Measured at Enrollment		Adjusted for Covariates Measured at Pregnancy Outcome	
Outcome	IPT-exposed	Unexposed	RR (95% CI)	*P*	aRR (95% CI)	*P*	aRR (95% CI)	*P*
Composite adverse outcome[a] (excludes induced abortion as adverse outcome)								
Primary analysis (n = 128)	13/39 (33)	16/89 (18)	1.85 (.99, 3.47)	.05	1.90 (1.01, 3.54)	.04	1.45 (.75, 2.80)	.27
Restricted risk set analysis (n = 122[b])	13/36 (36)	16/86 (19)	1.94 (1.04, 3.61)	.04	1.98 (1.08, 3.65)	.03	1.52 (.83, 2.81)	.18
Extended composite adverse outcome (includes induced abortion as adverse outcome)	16/39 (41)	19/89 (21)	1.92 (1.11, 3.33)	.02	1.98 (1.15, 3.41)	.01	1.47 (.84, 2.55)	.18
Preterm delivery <37 wks gestational age (n = 68[c])	4/20 (20)	11/48 (23)	0.87 (.32, 2.42)	.80	…	…	…	…
Low birth weight <2500 g (n = 74[c])	3/22 (14)	7/52 (13)	1.01 (.29, 3.56)	.98	…	…	…	…

Models adjusted for maternal age, CD4 count, antiretroviral use and latent tuberculosis status.

Abbreviations: aRR, adjusted relative risk; CI, confidence interval; IPT, isoniazid prevention therapy; RR, relative risk.

[a]Any event resulting in a non-live birth, other than induced abortion; individual component outcomes were spontaneous abortion (<20 wks), stillbirth (≥20 wks), and ectopic pregnancy.

[b]Excluded six pregnancies that ended in induced abortion (3 in each exposure group).

[c]Assessed among live births for which data were available; adjusted analyses not undertaken because of small number of events.

3.4. Salazar- Austin et al. TSHEPISO Cohort(18)

Salazar-Austin et al. conducted a secondary analysis of data collected prospectively from a cohort of pregnant women living with HIV in Soweto (TSHEPISO cohort), between 2011 and 2014. The study enrolled pregnant women of at least 18 years of age living with HIV, and of at least 13 weeks' gestation. As part of the study, enrolled women who were investigated for and identified as having tuberculosis disease were subsequently matched to 2 pregnant women living with HIV but without tuberculosis. All pregnant women enrolled without tuberculosis disease were offered IPT. In this study, maternal, pregnancy, and infant outcomes among those women living with HIV without tuberculosis disease, who did or did not use IPT for tuberculosis prevention during pregnancy, were analyzed.

All outcomes assessed in the study were self-reported but confirmed using clinic and hospital records or the road-to-health-chart where available. A participant was considered exposed to IPT if she self-reported use of isoniazid for tuberculosis prevention for any duration while pregnant. A large proportion of the study was conducted during the

time when according to South African guidelines pregnant women were only eligible for efavirenz-based HAART if their CD_4 count was less than 350 cells/mm^3.

The study enrolled 155 women without tuberculosis disease, and 71 were considered IPT exposed (46%) and 84 (54%) unexposed. Pregnancy outcomes were available for 69 of the women exposed to IPT (97%) and 82 (98%) of women unexposed to IPT. Significantly less long-term outcome data, relating to tuberculosis disease and mortality, were available for women unexposed to IPT (76%), as compared to the IPT exposed group (92%), and only a complete case analysis was performed.

Baseline characteristics were similar between the two groups. The CD_4 count at enrollment for the IPT exposed participants was 373 cells/mm^3 compared to 364 cells/mm^3 in the unexposed group. Approximately 26.49% of the cohort received zidovudine with or without single dose nevirapine at delivery for prevention of mother to child transmission. In the unexposed group, 87% were receiving HAART at delivery, compared to only 65% of the IPT exposed group (although this difference was not statistically significantly). As a result, only 39% of the IPT exposed group were virally suppressed, as compared to 55% of the unexposed group, prior to delivery. Almost all participants initiated IPT in the second or third trimester, with only 2 participants reporting initiation in the first trimester. No participants were taking IPT at the time of conception.

In this study the composite adverse pregnancy outcome consisted of fetal demise (spontaneous abortion < 28 weeks or stillbirth ≥ 28 weeks gestational age), low birth weight (< 2500g), prematurity (<37 weeks) and/or major congenital abnormality). Crudely, this outcome occurred less frequently in the IPT-exposed pregnancies, but the difference was not statistically significant (IPT exposed 16% vs. unexposed 28%; p = 0.08). The absolute increase in the composite adverse pregnancy outcome in the unexposed group was driven by preterm delivery (IPT exposed 10% vs. unexposed 22%, p = 0.06).

There was no difference in the composite outcome consisting of maternal, fetal, or infant death, or tuberculosis disease occurring within 1 year of delivery between those exposed to IPT and those unexposed (IPT exposed 3% vs. unexposed 4%; p = 1.0). In the adjusted logistic regression, women unexposed to IPT had 2.5-fold greater odds of having an adverse pregnancy outcome after controlling for CD_4 count at baseline, ARV regimen, HIV viral load, maternal age, BMI, and anemia (aOR 2.5; 95% CI 1.0 to 6.5; p = 0.048).

In this non-randomized study, it is possible that women who opted to take IPT were healthier with better health-seeking behavior than those who declined IPT, impacting on the association of IPT with decreased adverse pregnancy outcomes. This is illustrated by the greater proportion of missing outcome events for the unexposed group, and the larger number of participants in the unexposed group qualifying for HAART at the time. Additional, important confounders of adverse pregnancy outcomes such as maternal smoking status, alcohol use, and obstetric history and risk factors were not measured or adjusted for. Additionally, the self-reported measure of exposure to IPT does not exclude participants prescribed IPT, who did not take the treatment, contributing to misclassification bias.

3.5 Kalk et al.

Kalk et al. conducted a large retrospective cohort study in the Western Cape, using routine electronic health data from the public sector. The cohort comprised 43 971 pregnant women living with HIV who initiated ART during or prior to a pregnancy between 1 January 2015 and 31 December 2017. The objective of the study was to analyze differences in tuberculosis incidence, mortality, and pregnancy outcomes between those women who received IPT during pregnancy and those who did not, over 12 months of post pregnancy outcome follow-up. At the time, South African guidelines recommended 12 months of IPT for all PLWHIV regardless of CD_4 count and including pregnant women. Additionally, all pregnant women living with HIV were eligible for HAART.

IPT was dispensed during pregnancy in 16.6% of the cohort. The median CD_4 count for the cohort was 422, with only 9.7% of the cohort having CD_4 counts <200. At antenatal presentation, there were noteworthy and statistically significant differences in the characteristics of women by antenatal IPT exposure. More women exposed to antenatal IPT group were receiving HAART prior to falling pregnant (77.9% vs 71.6%; p < 0.001). A larger proportion of women exposed to antenatal IPT group had CD_4 counts greater than 500 cells/mm^3 compared to those who were not exposed to IPT (29.1% vs 26.7%). Similarly, a greater proportion of the antenatal IPT exposed group were virologically

suppressed (63.9% vs. 56.1%; p < 0.001). A history of previous tuberculosis disease was also less common in the IPT exposed women (10.6% vs. 13.0%; p < 0.001). These differences may indicate that the cohort that received IPT antenatally was more clinically stable, healthier, or at lower risk of tuberculosis disease than those who did not.

Tuberculosis developed in 1 002 (2.3%) women across the cohort. Only 1% of the women that received antenatal IPT developed tuberculosis, compared to 2.5% of the women who did not receive IPT (Risk difference -1 518 cases per 100 000; 95% CI -1 799 to -1 238 per 100 000). Furthermore, antenatal IPT was associated with a 29% reduction in risk of tuberculosis (aHR 0.71; 95% CI 0.63 to 0.81) after adjusting for maternal age, CD_4 count, history of tuberculosis disease, HIV viral load, and duration of HAART prior to delivery. When stratified by CD_4 count, the benefit of IPT in terms of reduction in incident tuberculosis was greatest in those with $CD_4 \leq 350$ cells/mm^3 (aHR 0.51; 95% CI 0.41 to 0.63), with no reduction in risk of tuberculosis in those with $CD_4 > 350$ cells/mm^3 (aHR 0.93; 95% CI 0.76 to 1.13). Additionally, the reduction in tuberculosis risk persisted even when IPT was started after 14 weeks gestation compared to no IPT (aHR 0.63; 95% CI 0.54 to 0.74). In 75.7% of those that developed tuberculosis during the study, the diagnosis occurred close to the time of the pregnancy outcome or soon thereafter, with 35.6% occurring within 3 months following the pregnancy outcome. After adjustment for covariates listed previously, IPT was not associated with a reduction in maternal mortality (aHR 0.75; 95% CI 0.46 to 1.22) but was associated with severe liver injury (aHR 1.51; 95% CI 1.18 to 1.93).

In the study, the composite adverse pregnancy outcome included miscarriage (loss of products of conception before 27 weeks' gestation), stillbirth (delivery of a fetus with no signs of life after 27 completed weeks' gestation), neonatal death (death of an infant within 28 days of birth), or low birth weight (< 2500 g). Antenatal IPT exposure was associated with a 17% reduction in the odds of adverse pregnancy outcome in the adjusted analysis (aOR 0.83; 95% CI 0.78 to 0.87). The mechanism of this protective effect is postulated to be related to the reduction in tuberculosis disease. However, other important confounders of adverse pregnancy outcomes, such as maternal BMI, smoking status, alcohol use and obstetric history were not adjusted for. When components of the composite outcome were examined individually, stillbirth (aOR 0.80; 95% CI 0.63 to 1.00) and miscarriage (aOR 0.83; 95% CI 0.68 to 1.00) appeared to be largely responsible for the effect.

When analyzed by timing of IPT exposure in pregnancy, IPT exposure starting after 14 weeks gestation was associated with reduced adverse pregnancy outcomes as compared to no IPT exposure (refer Table 5). This effect was driven largely by the reduction in miscarriage, with much smaller reductions in low birth weight and stillbirth.

Table 5. Multivariable analysis for individual pregnancy outcomes by timing of IPT exposure in pregnancy from Kalk et al.

	aOR (95% CI) IPT < 14 weeks versus none	aOR (95% CI) IPT > 14 weeks versus none	aOR (95% CI) IPT < 14weeks versus IPT > 14weeks (<14weeks=ref)
Poor outcome composite	1.04 (0.94 – 1.16)	0.71 (0.65 – 0.79)	0.64 (0.55 – 0.75)
Misc	1.39 (1.11 – 1.75)	0.33 (0.22 – 0.48)	0.21 (0.13 – 0.35)
SB	0.97 (0.68 – 1.37)	0.71 (0.53 – 0.94)	0.73 (0.44 – 1.19)
NND	1.16 (0.76 – 1.77)	0.83 (0.56 – 1.21)	0.84 (0.45 – 1.56)
LBW (livebirths)	1.10 (0.97 – 1.18)	0.90 (0.83 – 0.98)	0.91 (0.79 – 1.04)

IPT – INH preventive therapy; LBW – Low birth weight < 2500g; Misc – miscarriage; NND – neonatal death; SB – stillbirth

Adjusted for maternal age, first recorded pregnancy, ART prior to pregnancy, history of TB disease, CD category, VL suppression category, booking and/or delivery in primary care.

IPT exposure from after 14 weeks of gestation compared to IPT exposure prior 14 weeks gestation was also associated with a reduction in odds of an adverse pregnancy outcome (aOR 0.64; 95% CI 0.55 to 0.75). Again, this reduction in adverse outcome was driven by the reduction in miscarriage (refer Table 5). However, although the study defined any loss before 27 weeks as a miscarriage, risk of miscarriage decreases significantly with advancing gestation. (19) Therefore, survival bias is introduced in the cohort of women exposed to IPT after 14 weeks of gestation. For any women to be classified as IPT exposed after 14 weeks gestation, the pregnancy must have been viable and survived

until 14 weeks gestation. These pregnancies would have therefore, already passed the period of greatest risk, explaining the apparent reduction in miscarriage events reported when compared to no IPT or IPT initiated prior to 14 weeks.

In those exposed to IPT prior to 14 weeks gestation compared to no IPT exposure, no significant difference in the composite adverse pregnancy outcome were reported (aOR 1.04; 95% CI 0.94 to 1.16)(refer Table 3). However, examination of the individual components of the composite outcome, reveal a statistically significantly increased odds of miscarriage associated with first trimester exposure to IPT (aOR 1.39; 95% CI 1.11 to 1.75).

3.6. Hamada et al.

Hamada et al. conducted a systematic review and meta-analysis of the safety of IPT in pregnancy. Randomized and non-randomized studies of pregnant or postpartum women, regardless of HIV status, where the intervention was preventive treatment with daily isoniazid alone for 6 months or longer, and the comparator was another preventive treatment regimen or no preventive treatment (including deferred provision until postpartum in the comparison group) were included. Additionally, to be included, studies needed to have reported on the following outcomes: permanent drug discontinuation due to adverse drug reaction; grade 3 or grade 4 drug related toxic effects; death from any cause; hepatotoxicity; in utero fetal death; neonatal death; preterm delivery/prematurity; intrauterine growth restriction; low birth weight or congenital anomalies. In the systematic review, randomized and non-randomized studies, including those without a comparator group were eligible for inclusion.

The systematic review was assessed as "low quality", using the AMSTAR 2 appraisal tool as the description of the included studies did not contain adequate detail (e.g. duration of follow up), as sources of funding for studies included in the review were not reported, and as they did not provide a list of excluded studies (although the reasons for exclusion were described).

Databases were searched from inception until 15 May 2019. Nine studies were included after full text review(1, 11, 12, 16, 18, 20-23), of which only 1 study was a randomized controlled trial.(1) This RCT was assessed to have some concern for bias due to missing outcome data, and is previously summarized in section 3.1. The outcomes from this RCT relating to infant growth emerged after this systematic review was conducted, and were not included in this analysis. (15)

Of the 8 non-randomized studies included, three had no control/comparator arm and did not contribute to any of the pooled analyses.(12, 21, 23) Another 2 non-randomized studies conducted comparisons between IPT and other preventive regimens, rather than placebo/no treatment/deferred treatment, and are not summarized further here. (11, 20). The three remaining non-randomized studies were considered to be at serious risk of bias, specifically related to confounding.(8, 16, 18) These three studies are summarized in sections 3.2, 3.4 and 3.5 above. Notably, the data included in the systematic review from the study by Kalk et al. was derived from the analysis of the same cohort data published in 2020, but from a conference abstract presented in 2018.(8, 22) Furthermore, the analysis of the BRIEF-TB trial is not included in this systematic review as it was published in 2023. (17)

Due to significant heterogeneity between study types, data from the RCT and non-randomized studies could not be pooled for the outcome hepatotoxicity. Similarly, for maternal death, the RCT by Gupta et al. and pooled analysis of 2 non-randomized studies by Kalk et al. and Salazar-Austin et al. are reported separately and indicated no association with IPT use in pregnancy (Refer Table 6).

Table 6. Summary of evidence regarding IPT use in pregnant women living with HIV with GRADE assessment by Hamada et al.[8]

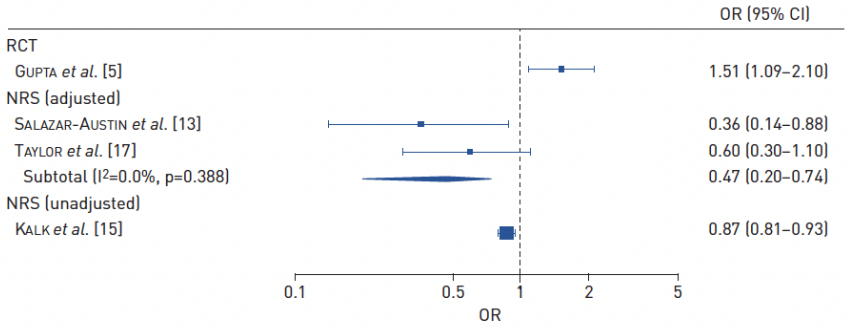
[8] The table contains a correction of an error detected in the review process and confirmed with the primary author of the systematic review.

Outcomes	Studies	Anticipated absolute effects (95% CI)[¶¶]		Relative effect (95% CI)	Participants	Certainty of the evidence (GRADE)
		Risk with no IPT or a placebo	Risk with IPT			
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, or congenital anomaly	One RCT: Gupta *et al.* [5]	170 per 1000	236 per 1000 (182 300)	OR 1.51 (1.09 2.10)	909	⊕⊕⊕◯ (Moderate)[#]
Composite pregnancy outcomes (low birth weight, preterm delivery, spontaneous abortion, stillbirth, neonatal mortality, or congenital anomaly)	Two observational studies: Salazar Austin *et al.* [13] Taylor *et al.* [17]	360 per 1000	209 per 1000 (101 294)	OR 0.471 (0.199 0.742)	347	⊕◯◯◯ (Very low)[#,¶]
Maternal death	One RCT: Gupta *et al.* [5]	6 per 1000	2 per 1000 (0 20)	Risk ratio 0.33 (0.03 3.21)	956	⊕⊕◯◯ (Low)[+]
Maternal death	Two observational studies: Salazar Austin *et al.* [13] Kalk et al. [15]	3 per 1000	2 per 1000 (1 3)	Risk ratio 0.65 (0.39 1.07)	52097	⊕⊕◯◯ (Low)[¶]
Grade 3 or 4 AEs related to study treatment	One RCT: Gupta *et al.* [5]	46 per 1000	71 per 1000 (42 120)	Risk ratio 1.55 (0.92 2.61)	956	⊕⊕⊕◯ (Moderate)[#]
Hepatotoxicity	One RCT: Gupta *et al.* [5]	23 per 1000	38 per 1000 (18 79)	Risk ratio 1.64 (0.78 3.44)	956	⊕⊕⊕◯ (Moderate)[#,§]
Hepatotoxicity	One observational study: Kalk *et al.* [15]	3 per 1000	3 per 1000 (2 4)	Risk ratio 1.01 (0.68 1.51)	58242	⊕⊕◯◯ (Low)[f,##]
Discontinuation of study drug due to toxicity	One RCT: Gupta *et al.* [5]	17 per 1000	23 per 1000 (9 57)	Risk ratio 1.38 (0.56 3.40)	956	⊕⊕⊕◯ (Moderate)[§]

CI: confidence interval; RCT: randomised controlled trial; OR: odds ratio; AE: adverse event. [#]: optimal information size was not met; [¶]: bias due to confounding was considered serious (important confounders were not fully accounted for); [+]: large CI, including both appreciable benefits and harms, and very few events; [§]: CI included both appreciable benefits and harms; [f]: confounding was not accounted for and bias due to measurement of hepatotoxicity was considered serious (since liver function tests were performed only if clinically indicated, which was likely to be influenced by knowledge of the receipt of IPT); [##]: very large sample size and CI of absolute effect was very narrow; [¶¶]: the risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

The results for adverse pregnancy outcomes were inconsistent across the included studies. Once again, due to significant heterogeneity, data from the RCT could not be pooled with the non-randomized studies. However, the adjusted estimates from the studies by Taylor et al. and Salazar-Austin et al. were pooled, and suggested that IPT use in pregnancy is associated with a reduction in adverse pregnancy outcomes (OR 0.47; 95% CI 0.20 to 0.74).(16, 18) The estimates from the study by Kalk et al. were unadjusted and could not be pooled with the other non-randomized studies, but suggested the same direction of effect (Refer figure 1 and table 6).

Figure 1. Forest plot for composite adverse pregnancy outcomes in pregnant women with HIV by IPT exposure from Hamada et al.



A summary of evidence for the safety of IPT use in pregnant women with HIV is presented in Table 6 with accompanying GRADE certainty of evidence assessment.

4 Summary of Evidence

Important differences in study design, population and tuberculosis prevalence between the studies discussed are summarized in Table 7. Key points to note from the evidence

- There is a signal of increased spontaneous miscarriage after first trimester exposure to IPT, compared to no exposure in pregnant women living with HIV on HAART, with relatively high CD_4 counts, in some observational studies. (8, 17)
- In an RCT, there was an association between IPT exposure in second and third trimester and low birth weight (<2500g), that may continue to impact infant growth at week 12 and week 48 of life in pregnant women living with HIV on HAART and with relatively high CD_4 counts.(1, 14, 15)
- In an RCT of women living with HIV on ART, with high CD_4 counts, and without recent close contact to an active tuberculosis case, the risk of developing tuberculosis is similar when IPT is given antenatally versus delayed to 12 weeks post-partum.(1)
- In observational data from a high TB prevalence setting, there is a reduction in incident tuberculosis disease in pregnant women on ART with CD_4 counts ≤ 350 cells/mm^3 who received IPT during pregnancy, but not for those with CD4 counts >350 cells//mm^3. (8)
- Antenatal IPT did not reduce in maternal mortality in the RCT or observational studies.(1, 8, 18)
- Risk of IPT-associated hepatotoxicity may be higher during pregnancy and the postpartum period than in non-pregnant woman (1).
- The reduction in tuberculosis disease seen with antenatal IPT use in women with low CD_4 counts may be an explanation for the better pregnancy outcomes seen in observational studies. None of the observational studies were adjusted for important confounders of adverse pregnancy outcomes. (8, 16, 18)
- All the above data were from women living with HIV, and the majority of those on ART were on efavirenz containing regimens.
- We found no comparative data exploring benefits and risks of IPT in HIV-negative pregnant women.

5. Feasibility considerations

Following engagement with the NDoH program guideline team and other stakeholders on the 7th March 2024, the following matters were raised for local consideration:

- The TB program team raised concerns with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART.
    - Especially considering the number of pregnant women starting ART below various CD4 thresholds has not yet been determined.
    - A simplified recommendation applicable to all pregnant patients with HIV would be preferred for ease of implementation.
- It was noted that the evidence of benefit in terms of reduction of TB disease was demonstrated in low-quality observational data from South Africa. But that there was no difference in reduction of TB disease between antenatal IPT and IPT deferred to the postpartum period in data from an RCT. However, it was highlighted that the median CD4 from this RCT was 500, which is much higher than what is observed locally
- The strong signals of harm highlighted by the review were noted.

In light of the above, the group proposed that the following recommendation be considered by NEMLC:

- Initiation of IPT should be deferred in all pregnant patients until after delivery
- In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy was emphasized.

Table 7. Summary of important differences between studies reviewed.

Study Author, Study Type	N	% on HAART on entry into study	Median CD4 (cells/mm^3)	% Viral Load Suppressed	% on efavirenz based HAART	% participants confirmed with latent TB infection	TB Prevalence by Geographic Location of enrolment	% participants initiated on IPT by trimester	Effect
Gupta et al. Randomized controlled trial	956	100%	493	62.83%	85.1%	30% positive IGRA	Zimbabwe: 33.37% (344 per 100 000) (24) South Africa: 19% (681 per 100 000)(8) Uganda 17.36% (401 per 100 000)(24) Botswana: 12.55% (305 per 100 000)(25)	No 1st trimester IPT initiation. IPT initiation between 14 – 24 weeks: 33.6% IPT initiation >24 weeks: 66.4%	Increased adverse pregnancy outcome, specifically low birth weight, after second/third trimester exposure. Increased risk of underweight for infant exposed antenatally.
Kalk et al. Retrospective cohort study	43 971	76.8%	422 CD_4 < 200: 9.7%	57.4%	Not reported	Not reported.	South Africa: 100% (681 per 100 000)(8)	IPT initiation < 14 weeks: 36.2% IPT initiation ≥ 14 weeks: 63.8%	Decreased adverse pregnancy outcomes. IPT < 14 weeks associated with increased miscarriage compared to no IPT.
Taylor et al. Nested prospective cohort study	196	(Pre-universal ART) 37%	368 CD_4< 200: 16%	Not reported	Not reported	Not reported.	Botswana: 100% (305 per 100 000)(25)	1st trimester IPT initiation: 99%	No association.
Gupta et al. 2023 Nested prospective cohort study	128	(Pre-universal ART) 35%	534	Not reported	64% in IPT exposed group at pregnancy outcome 87% in unexposed group at pregnancy outcome.	20% positive TST (but testing limited by shortage of reagents)	South Africa: 28.12% (681 per 100 000)(8) Botswana: 26.56% (305 per 100 000)(25) Haiti: 18.75% (254 per 100 000)(26) Kenya: 10.16% (558 per 100 000)(24)	1st trimester IPT initiation: 100% (All IPT exposed pregnancies were conceived while taking isoniazid.)	Increased adverse pregnancy outcomes, specifically miscarriage, after first trimester exposure.
Salazar Austin et al. Prospective cohort study	155	71.52% on HAART	364 - 373 (No IPT vs. IPT)	47.68%	60.26 %	Not reported.	South Africa: 100% (681 per 100 000)(8)	1st trimester IPT initiation: 3% 2nd trimester IPT initiation: 48% 3rd trimester IPT initiation: 49%	Decreased adverse pregnancy outcomes.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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	

ERC Recommendation 9 November 2023: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 350 cells/mm^3 and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 350 cells/mm^3 and starting ART, IPT should be deferred to the post-partum period.

Rationale: The benefit of IPT in preventing tuberculosis disease at CD4 counts ≤ 350 cells/m^3(low certainty evidence) outweighs the increased risk of adverse pregnancy outcomes. However, in pregnant women with higher CD_4 counts, the increased risk of miscarriage after first trimester IPT exposure (low certainty evidence) and increased risk of low birth weight and underweight for age after second trimester IPT exposure (moderate certainty evidence) outweighs any potential benefit (moderate certainty evidence).

Level of Evidence:

Risk of adverse pregnancy outcomes after first trimester exposure (low certainty evidence from observational studies and cohort studies nested in randomised controlled trials)

Risk of adverse pregnancy outcomes after second trimester exposure (moderate certainty evidence from a randomized controlled trial)

Evidence of benefit at CD_4 ≤ 350 cells/mm^3 (low certainty evidence from an observational study)

Review indicator: New high quality evidence of benefit or harm.

Multi stakeholder engagement meeting recommendation- 7 March 2024:

The consensus recommendation from a multi stakeholder engagement meeting, which included representatives from the NEMLC, NDOH TB and maternal healthcare programs and South African Medical Research Council (SAMRC) with reference to local feasibility considerations, is as follows:

- Initiation of IPT should be deferred in all pregnant patients until after delivery
- In the absence of IPT initiation, the importance of ART and continued active screening for TB throughout pregnancy must be emphasized.

Rationale: While the evidence in support of the ERC recommendation dated 9 November 2023 above was not in dispute, concern was expressed with the complexity of multiple guidance for pregnant women at various CD4 counts initiating ART and for pregnant women already established on ART. The consensus recommendation from the multi stakeholder group was therefore for a less complex recommendation to avoid IPT in pregnancy in all pregnant women, regardless of HIV status or CD4 count. It was noted at the meeting that screening for TB as part of routine antenatal care is already included in programmatic guidance, to identify pregnant women with tuberculosis disease timeously and initiate appropriate antituberculosis treatment.

NEMLC RECOMMENDATION (MEETING OF 14 March 2024): NEMLC supported the multi stakeholder recommendation that IPT be avoided during pregnancy.

Monitoring and evaluation considerations, and research priorities:

Pregnant women should be routinely screened for TB at every antenatal visit.

Strenthening of pharmacovigilance systems, with implementaiton of measures for identifying signals of drug-related harm in pregnant women.

References

1. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019;381(14):1333-46. 10.1056/NEJMoa1813060.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews. 2010(1). 10.1002/14651858.CD000171.pub3. https://doi.org//10.1002/14651858.CD000171.pub3.
3. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682-90. 10.1016/s0140-6736(14)60162-8.
4. Black A, Dawood H. NEMLC. Adult Hospital level Medication Review Process. Isoniazid Preventive Therapy. . 2018.
5. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Health. 2017;5(11):e1080-e9. 10.1016/s2214-109x(17)30372-8.
6. South African National Department Of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa. Primary Health Care Level 2014.
7. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. New England Journal of Medicine. 2017;377(3):233-45. 10.1056/NEJMoa1615822. https://www.nejm.org/doi/full/10.1056/NEJMoa1615822.
8. Kalk E, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, et al. Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data. Clin Infect Dis. 2020;71(8):e351-e8. 10.1093/cid/ciz1224.
9. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2020.
10. South African National Department of Health. National Guidelines on the Treatment of Tuberculosis Infection. 2023. https://knowledgehub.health.gov.za/elibrary/national-guidelines-treatment-tuberculosis-infection.
11. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, et al. Exposure to Latent Tuberculosis Treatment during Pregnancy. The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018;15(5):570-80. 10.1513/AnnalsATS.201704-326OC. https://www.ncbi.nlm.nih.gov/pubmed/29393655.
12. Franks AL, Binkin NJ, Snider DE , Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep. 1989;104(2):151-5.
13. Hamada Y., Figueroa C., Martín-Sánchez M., Falzon D., Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. Eur Respir J. 2020;55(3). 10.1183/13993003.01967-2019.
14. Theron G., Montepiedra G., Aaron L., McCarthy K., Chakhtoura N., Jean-Philippe P., et al. Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021;72(11):e784-e90. 10.1093/cid/ciaa1482.
15. Cherkos A. S., LaCourse S. M., Enquobahrie D. A., Richardson B. A., Bradford S., Montepiedra G., et al. Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial. EClinicalMedicine. 2023;58:101912. 10.1016/j.eclinm.2023.101912. https://www.ncbi.nlm.nih.gov/pubmed/36969345.
16. Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, et al. Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy. Infectious Diseases in Obstetrics and Gynecology. 2013;2013:195637. 10.1155/2013/195637. https://doi.org/10.1155/2013/195637.
17. Gupta A., Hughes M. D., Cruz J. L., Avihingsanon A., Mwelase N., Severe P., et al. Adverse Pregnancy Outcomes among HIV-infected Women Taking Isoniazid Preventive Therapy During the First Trimester. Clin Infect Dis. 2023. 10.1093/cid/ciad583. https://www.ncbi.nlm.nih.gov/pubmed/37768207.
18. Salazar-Austin N, Cohn S, Lala S, Waja Z, Dooley KE, Hoffmann CJ, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living With Human Immunodeficiency Virus in the Tshepiso Cohort. Clin Infect Dis. 2020;71(6):1419-26. 10.1093/cid/ciz1024.
19. Tong S, Kaur A, Walker SP, Bryant V, Onwude JL, Permezel M. Miscarriage risk for asymptomatic women after a normal first-trimester prenatal visit. Obstet Gynecol. 2008;111(3):710-4. 10.1097/AOG.0b013e318163747c.
20. Singh P, Moulton LH, Barnes GL, Gupta A, Msandiwa R, Chaisson RE, et al. Pregnancy in Women With HIV in a Tuberculosis Preventive Therapy Trial. J Acquir Immune Defic Syndr. 2022;91(4):397-402. 10.1097/QAI.0000000000003078. https://www.ncbi.nlm.nih.gov/pubmed/36000934.
21. Tiam A, Machekano R, Gounder CR, Maama-Maime LB, Ntene-Sealiete K, Sahu M, et al. Preventing tuberculosis among HIV-infected pregnant women in Lesotho: the case for rolling out active case finding and isoniazid preventive therapy. J Acquir Immune Defic Syndr. 2014;67(1):e5-e11. 10.1097/qai.0000000000000209.
22. Kalk EK, Heekes A, Mehta U. Programmatic review of safety and effectiveness of isoniazid preventive

therapy in HIV infected pregnant women on ART in routine care. Reproductive Toxicology. 2018; 80: 155.
23. Chang AH, Polesky A, Bhatia G. House calls by community health workers and public health nurses to improve adherence to isoniazid monotherapy for latent tuberculosis infection: a retrospective study. BMC Public Health. 2013;13(1):894. 10.1186/1471-2458-13-894. https://doi.org/10.1186/1471-2458-13-894.
24. Law I, Floyd K, The African TB Prevalence Survey Group. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308-27. https://doi.org/10.1111/tmi.13485. https://onlinelibrary.wiley.com/doi/abs/10.1111/tmi.13485.
25. Tembo BP, Malangu NG. Prevalence and factors associated with multidrug/rifampicin resistant tuberculosis among suspected drug resistant tuberculosis patients in Botswana. BMC Infectious Diseases. 2019;19(1):779. 10.1186/s12879-019-4375-7. https://doi.org/10.1186/s12879-019-4375-7.
26. Delva GJ, Francois I, Claassen CW, Dorestan D, Bastien B, Medina-Moreno S, et al. Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs. Tuberc Res Treat. 2016;2016:8020745. 10.1155/2016/8020745.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

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

MEDICINE REVIEW:

1. Executive Summary

Date: 26 October 2023 (Update of initial review of 28 November 2018)
Medicine (INN): Liposomal amphotericin B
Medicine (ATC): J02AA01
Indication (ICD10 code): Cryptococcal meningitis - B20.5 + (B45.1 + G02.1*)
Patient population: Immunocompromised patients with cryptococcal meningitis.
Prevalence of condition: In 2014, an estimated 223,100 incident cases and 181,100 deaths occurred globally, and cryptococcal meningitis is estimated to cause up to 15% of HIV-related deaths (Rajasingham 2017).
Level of Care: Adult Hospital Level
Prescriber Level: Medical officer
Current standard of Care: Amphotericin B deoxycholate
Efficacy estimates: (preferably NNT)
Nov 2018 summary
Regarding efficacy the trial by Hamill et al. gives the most informative findings and has the lowest risk of bias. Looking at mycological success at 2 weeks the NNT for benefit with liposomal amphotericin B 3 mg/kg/day over amphotericin B deoxycholate is 9 patients. Regarding mycological success at 2 weeks for liposomal amphotericin B 6 mg/kg/day versus amphotericin B deoxycholate, the **NNT is 200** patients. Looking at therapeutic success at 10 weeks the **NNT for benefit is 13** patients with amphotericin B deoxycholate versus liposomal amphotericin B 3 mg/kg/day, and for liposomal amphotericin B 6 mg/kg/day **NNT is 56** patients (note the inversion of comparison here). These findings did however not show statistical significance and the conclusions from the trial were the non-inferiority of liposomal amphotericin B versus amphotericin B deoxycholate.
The only safety outcomes available that were directly related to the review question also came from the RCT by Hamill et al. Regarding nephrotoxicity (creatinine level of 2 times baseline and >1.2 mg/dL), liposomal amphotericin B 3 mg/kg/day had an NNT for benefit of 5 patients versus amphotericin B deoxycholate. Similarly, for benefit with liposomal amphotericin B 6 mg/kg/day, **NNT was 8** patients versus amphotericin B deoxycholate. Hypokalaemia and anaemia were only significantly improved when using liposomal amphotericin B 3 mg/kg/day versus amphotericin B deoxycholate with an **NTT for benefit of 5** patients for both outcomes
May 2022 update
Authors of a phase III non-inferiority study (Jarvis 2022) comparing a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1 plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control) in patients with cryptococcal meningitis, reported that the 10-week mortality was 24.8% (95% confidence interval [CI], 20.7 to 29.3) in the liposomal amphotericin B group (101 of 407 participants had died) and 28.7% (95% CI, 24.4 to 33.4) in the control group (117 of 407 participants had died), based on their intention to treat analysis. The authors concluded that single-dose liposomal amphotericin B combined with flucytosine and fluconazole was non-inferior to the control (P<0.001 for non-inferiority) and was associated with fewer adverse events.
Motivator/reviewer name(s): *Initial review* (28 November 2022) - Dr R Griesel; Updated review (19 May 2022) – Dr H Dawood
PTC affiliation: RG: Groote Schuur Hospital

2. Name of author(s)/motivator(s)

Original document: Dr R Griesel, Dr H Dawood
August 2023 Update: Dr J Nel, Dr J Miot, Ms Z Adam

3. Author affiliation and conflict of interest details

RG: University of Cape Town, Pharmacology Department; Adult Hospital Level Committee (2017-2018); HD: Greys hospital and Caprisa, University of KwaZulu-Natal. RG and HD have no conflicts of interest pertaining to liposomal amphotericin B.

JM: Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand. JN: Helen Joseph Hospital, Faculty of Health Sciences, University of the Witwatersrand. ZA: Consultant, Right to Care. The reviewers have no conflicts to declare.

4. Introduction/ Background

Cryptococcal meningitis is a severe fungal infection primarily seen in people with compromised cell-mediated immunity. Most cases occur in the context of advanced HIV disease with the risk increasing with decreasing CD4 cell count (Tenforde 2018). In 2014, an estimated 223,100 incident cases and 181,100 deaths occurred globally, and cryptococcal meningitis is estimated to cause up to 15% of HIV-related deaths (Rajasingham 2017). Approximately 73% of cases are estimated to occur in sub-Saharan Africa.

The World Health Organization (WHO) guidelines in 2018 recommend a 1-week course of amphotericin B plus flucytosine as the preferred regimen for the induction phase in the treatment of cryptococcal meningitis (WHO 2018). Flucytosine has historically not been freely available in South Africa and local guidelines still recommend a 2-week induction phase course of amphotericin B followed by fluconazole.

Conventional amphotericin B deoxycholate is a broad-spectrum antifungal that has been used as standard therapy for treatment of many invasive fungal infections since it was introduced to clinical practice in the 1950s (Bassetti 2011). The significant dose-limiting toxicity of amphotericin B deoxycholate (most notably nephrotoxicity and infusion-related reactions) provided the impetus to develop new less toxic formulations. Liposomal amphotericin B is a unique lipid formulation of amphotericin B that has been used for nearly 20 years to treat a broad range of fungal infections. While the antifungal activity of amphotericin B is retained following its incorporation into a liposome bilayer, its toxicity is significantly reduced (Bassetti 2011). This is due to the fact that when the liposome reaches the fungal cell, it is disrupted, and the drug is released into the fungal cell membrane where it binds to the ergosterol. The liposome keeps its integrity in the presence of mammalian cells resulting in minimal toxicity (Adler-Moore 2002).

This review will focus on the comparison of liposomal amphotericin B versus amphotericin B deoxycholate, specifically assessing efficacy and safety outcomes. This review may inform resource allocation decisions for liposomal amphotericin B use, particularly in our resource-limited setting.

Document History:

The original evidence review prepared in Nov 2018 was updated in May 2022 to include results from the Jarvis et al publication (March 2022) which concluded that the liposomal amphotericin B regimen was non-inferior to the control group (amphotericin B deoxycholate regimen) in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid. The study had a standardized 7-day inpatient monitoring in both arms, with some indication that liposomal amphotericin B could shorten hospital length of stay (LoS). However as liposomal amphotericin B was significantly more expensive than amphotericin B deoxycholate, the NEMLC did not support the inclusion of liposomal amphotericin B on the EML.

Following the announcement of a reduction in price of liposomal amphotericin B (R600 per 50mg vial)[1] in 2023, the cost analysis (Addendum A) has subsequently been updated and a revised recommendation was tabled at NEMLC on the 30th November 2023 for consideration. Furthermore, flucytosine is also now available on tender (NDoH contract HP02-2023AI). The updates to the cost analysis and recommendation are as detailed below.

[1] NDoH Communication Ref HP02-2023AI

5. Purpose/Objective i.e. PICO

Efficacy: *Is liposomal amphotericin B non-inferior to amphotericin B deoxycholate for the treatment of cryptococcal meningitis?*

Safety: *Is liposomal amphotericin B superior to amphotericin B deoxycholate for the treatment of cryptococcal meningitis?*

Population: Adult patients treated for cryptococcal meningitis with impaired renal function (defined as eGFR <60ml/L) at the onset of therapy, or those who develop intractable renal impairment or electrolyte disturbances (K^+) on amphotericin B deoxycholate.

Intervention: Initiate liposomal amphotericin B or substitute conventional amphotericin B deoxycholate with liposomal amphotericin B

Comparator: Amphotericin B deoxycholate. An advantage of the comparator is cost. Disadvantages are related to severe thrombophlebitis and infusion related reactions, nephrotoxicity, electrolyte disturbances, and anaemia.

Outcome:

Efficacy: Mortality benefit or rate of clearance of CSF (surrogate marker)

Safety:

- Renal impairment (decrease in estimated glomerular filtration or increase in serum creatinine)
- Infusion related reactions
- Electrolyte disturbances (K^+)
- Anaemia

6. Methods:

a. Data sources Medline (PubMed) and Cochrane database

b. Search strategy

(((("amphotericin b"[MeSH Terms] OR "amphotericin b"[All Fields]) OR ("amphotericin B, deoxycholate drug combination"[Supplementary Concept] OR "amphotericin B, deoxycholate drug combination"[All Fields] OR "amphotericin b deoxycholate"[All Fields])) AND (("cryptococcus"[MeSH Terms] OR "cryptococcus"[All Fields]) OR ("meningitis, cryptococcal"[MeSH Terms] OR ("meningitis"[All Fields] AND "cryptococcal"[All Fields]) OR "cryptococcal meningitis"[All Fields] OR ("cryptococcal"[All Fields] AND "meningitis"[All Fields])))) AND ("liposomal amphotericin B"[Supplementary Concept] OR "liposomal amphotericin B"[All Fields] OR "liposomal amphotericin b"[All Fields]) AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

The search revealed 9 publications. Going through these individually to check for applicability, 2 systematic reviews and meta-analyses were relevant. Two applicable randomised control trials (RTCs) were isolated. Both RCTs were included in the systematic reviews and meta-analyses. No new RCTs had been published since the publication of the systematic reviews and meta-analyses.

c. Excluded studies:

Four publications from the literature search was excluded (see below).

Author, date	***Type of study***	***Reason for exclusion***
Hadley 2009	RCT	Wrong indication and wrong intervention and comparator
Jadhav 2010	RCT	Wrong comparison
Luke 1998	RCT	Wrong intervention
Sharkey 1996	RCT	Wrong intervention
Coker 1993	Observational	Non-comparative study

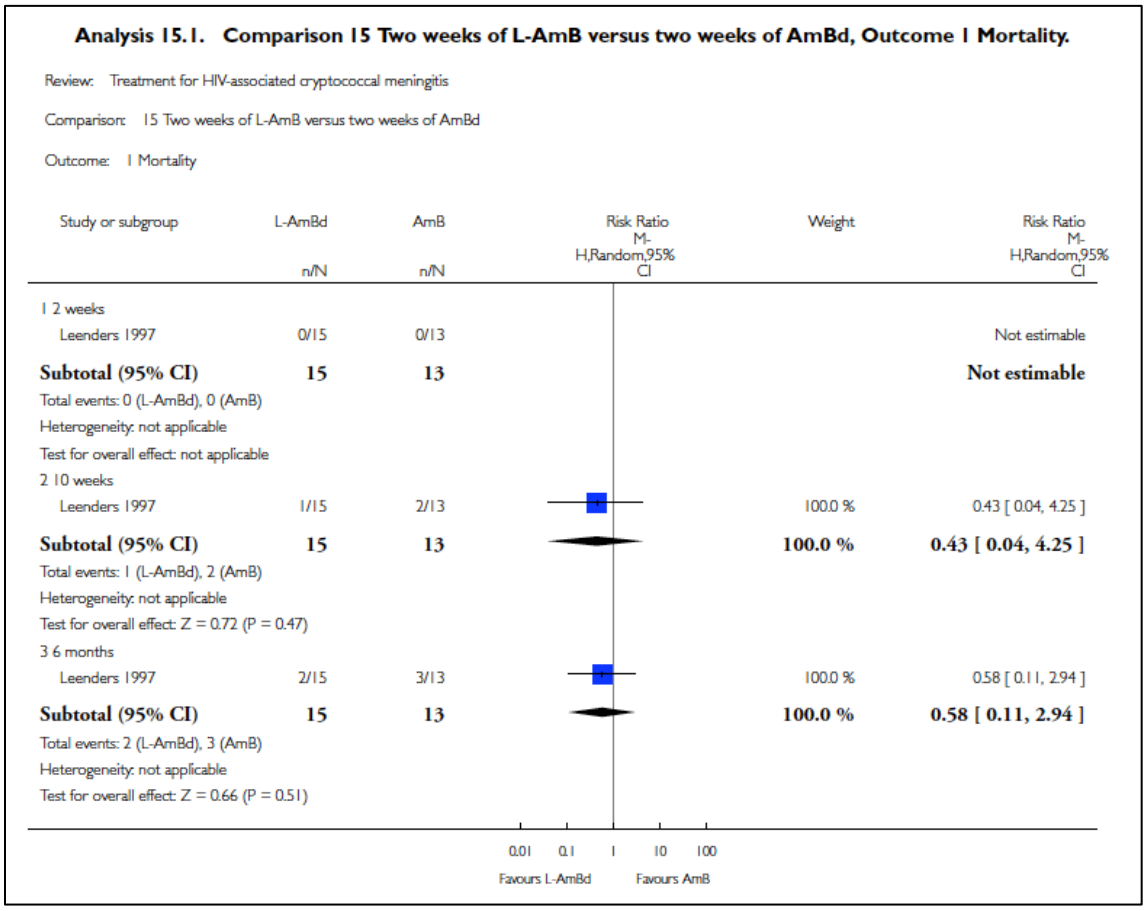
7. Evidence synthesis:

Assessing the treatment of cryptococcal meningitis in HIV-infected patients, Tenforde et al. (Tenforde 2018) specifically assessed the comparison of 2 weeks treatment with liposomal amphotericin B versus 2 weeks treatment with amphotericin B deoxycholate.

Only 1 RCT by Leenders et al. compared a lipid-based amphotericin B preparation to conventional amphotericin B (Leenders 1997). They assessed the outcome of mortality at 10 weeks (primary outcome) and 6 months (secondary

outcome) between the treatment of liposomal amphotericin B for 3 weeks and amphotericin B deoxycholate for 3 weeks (Table 1). The evidence from this RCT was classified as very low by the GRADE classification. There was no significant difference in either of these outcomes (10 weeks: RR 0.43, 95% CI 0.04 to 4.25; 6 months: RR 0.58, 95% CI 0.11 to 2.94), however the trend was toward a benefit (Figure 1). No clinical relapses were observed during the 10-week study period. No proven clinical relapses occurred during the 6-month or further follow-up.

Figure 1



Regarding mycological outcomes, liposomal amphotericin B resulted in a CSF culture conversion within 7 days in 6 out of 15 patients versus 1 out of 12 for amphotericin B deoxycholate (P = 0.09). Within 21 days 11 out of 15 patients treated with liposomal amphotericin B versus 3 out of 8 patients treated with amphotericin B deoxycholate had responded mycologically (P = 0.18). When Kaplan–Meier estimates were used to compare time to CSF culture conversion, liposomal amphotericin B was significantly more effective than for amphotericin B deoxycholate (P < 0.05) (Figure 2). The median time to CSF culture conversion was between 7 and 14 days for liposomal amphotericin B versus > 21 days for amphotericin B deoxycholate. A significant correlation was found between the time to CSF culture conversion and the time to clinical response (r = 0.63; P < 0.001) (Figure 3).

Both treatment regimens were well tolerated. Concerning nephrotoxicity, when increases from baseline of serum creatinine (SCr) levels at the various timepoints were analysed with repeated measurements ANOVA, it was found that this increase was on average a factor of 1.37 (P = 0.003) greater in the amphotericin B deoxycholate treated patients. Three patients treated with liposomal amphotericin B and four patients treated with amphotericin B deoxycholate experienced hypokalaemia, but none of these patients had to discontinue therapy for this reason.

The systematic review and meta-analysis by Botero Aguirre et al. (Botero Aguirre 2015) looked at the benefit of using liposomal amphotericin B, as compared to conventional amphotericin B regarding a two-fold increase in SCr from baseline (Table 1). In this systematic review and meta-analysis comparisons were made using all indications for the use of amphotericin B (Table 1). The risk was significantly reduced (RR 0.49, 95% CI 0.40 – 0.59) with a moderate quality of evidence (GRADE classification). The number needed to treat for this benefit (NNTB) is 6 patients (Figure 4).

Figure 2

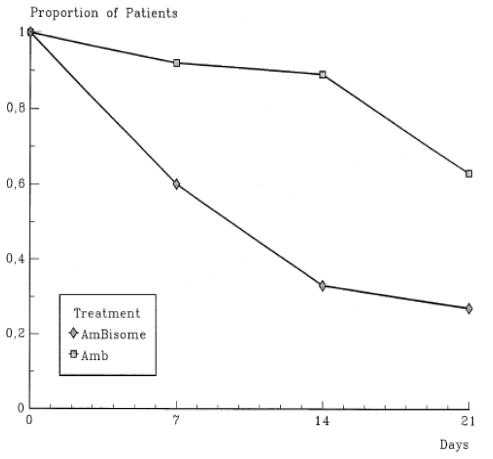


Fig. 1. Kaplan–Meier estimates of the proportion of patients who had positive cerebrospinal fluid cultures during the first 3 weeks of treatment, according to treatment group.

Figure 3

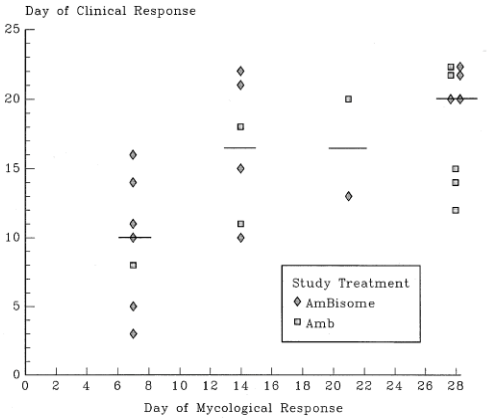


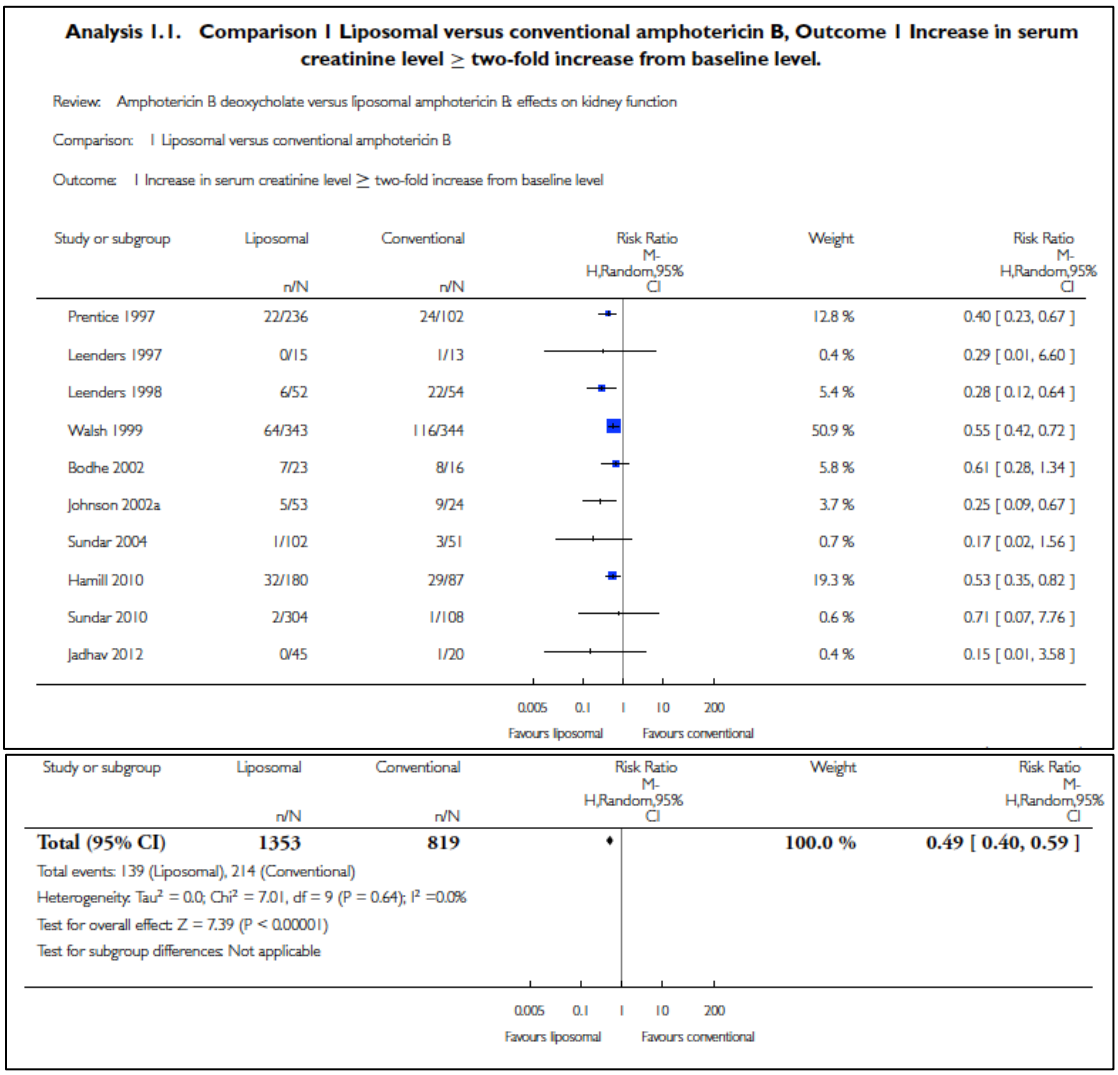
Fig. 2. Correlation between the time to mycological response and the time to clinical response. The times to mycological and clinical response show a significant correlation in AIDS patients with crytococcal meningitis treated with AmBisome or amphotericin B (P = 0.0009 by Spearman rank correlation test).

Nine RCTs included in the systematic review and meta-analysis by Botero Aguirre et al. (Botero Aguirre 2015) assessed infusion related reactions between liposomal amphotericin B and conventional amphotericin B (sodium deoxycholate). There was significant decrease in all infusion-related reactions in the liposomal group compared with the conventional amphotericin B group (Figure 5).

The RCT by Leenders et al. was included in this systematic review and meta-analysis. Only one other included RCT specifically looked at efficacy and safety outcomes in comparing liposomal amphotericin B with amphotericin B deoxycholate for the management of cryptococcal meningitis (Hamill 2010) (Table 1).

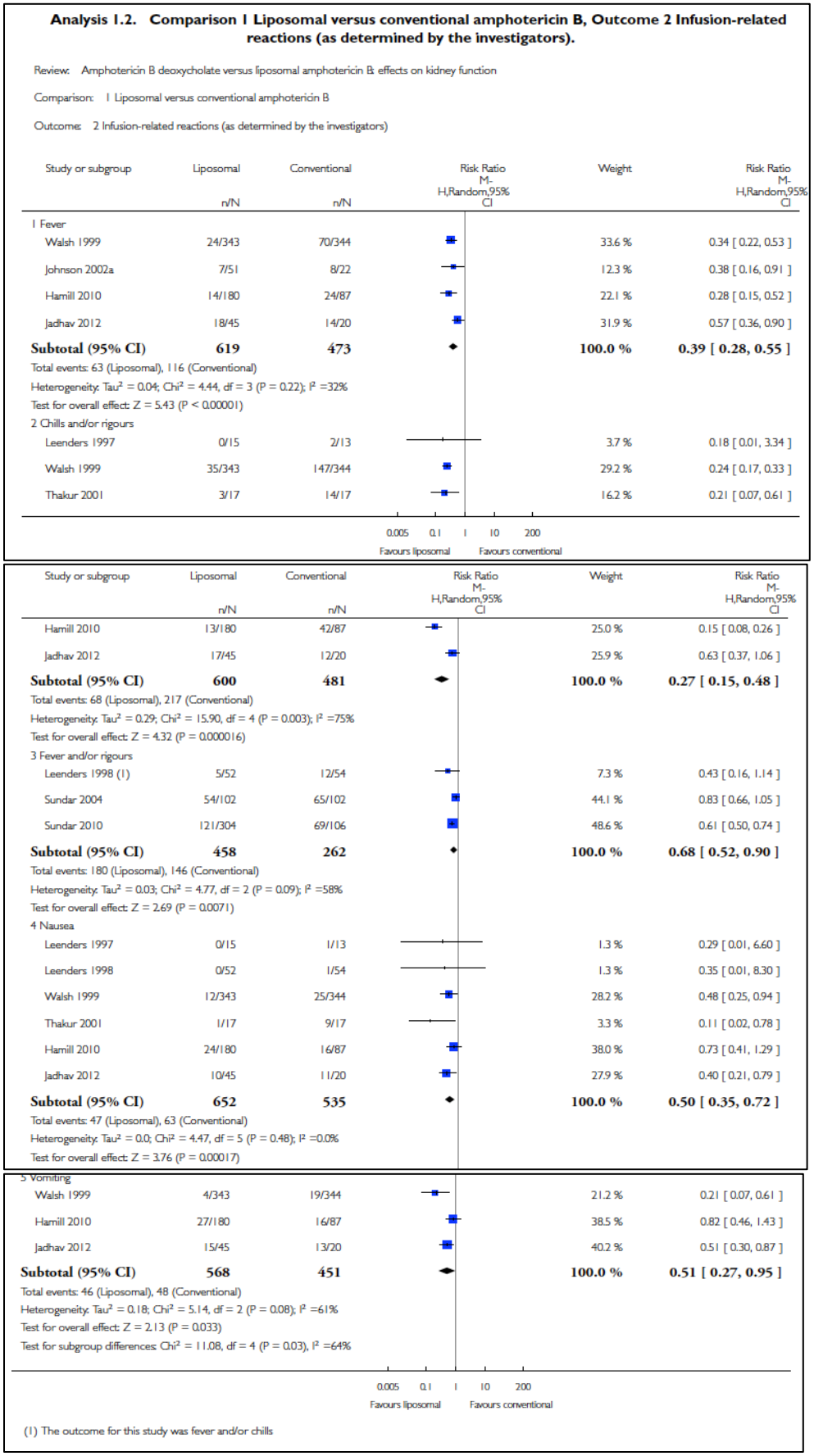
Table 2 reports the primary efficacy end point for the comparison of liposomal amphotericin B versus amphotericin B deoxycholate from Hamill et al. CSF culture results were negative at 2 weeks in 47.5% of patients who received amphotericin B deoxycholate, in 58.3% of those who received liposomal amphotericin B 3 mg/kg/day and in 48.0% of those who received liposomal amphotericin B 6 mg/kg/day. None of these differences among the groups were statistically significant. The lower bounds of the 95% CIs for the treatment differences (liposomal amphotericin B versus amphotericin B deoxycholate) were all greater than -20% but not greater than 0. Consequently, liposomal amphotericin B (combined, 3 and 6 mg/kg/day) was at least as effective as, but not superior to, amphotericin B deoxycholate with regard to mycological success at week 2.

Figure 4



The incidence of infusion-related reactions, as well as the individual frequencies of fever, chills or rigors and respiratory events, were significantly lower for patients administered either dose of liposomal amphotericin B compared with amphotericin B deoxycholate (Table 3). Significant anaemia, as indicated by a hemoglobin concentration <8 g/dL, occurred less frequently in the liposomal amphotericin B 3 mg/kg/day arm (Table 4). Significantly fewer patients who received liposomal amphotericin B 3 mg/kg/day developed nephrotoxicity, as indicated by a doubling of the SCr level (P = 0.04) (Table 4); the difference for liposomal amphotericin B 6 mg/kg/day was not significant, although there was a trend towards less nephrotoxicity (P = 0.066). Significantly fewer patients in the liposomal amphotericin B 3 mg/kg/day arm developed serum potassium values <3 mmol/L than in the other 2 arms (Table 4).

Figure 5


Analysis 1.2. Comparison 1 Liposomal versus conventional amphotericin B, Outcome 2 Infusion-related reactions (as determined by the investigators).
Review: Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function
Comparison: 1 Liposomal versus conventional amphotericin B
Outcome: 2 Infusion-related reactions (as determined by the investigators)
Study or subgroup
Liposomal n/N
Conventional n/N
Risk Ratio M-H,Random,95% CI
Weight
Risk Ratio M-H,Random,95% CI
1 Fever
Walsh 1999 24/343 70/344 33.6 % 0.34 [0.22, 0.53]
Johnson 2002a 7/51 8/22 12.3 % 0.38 [0.16, 0.91]
Hamill 2010 14/180 24/87 22.1 % 0.28 [0.15, 0.52]
Jadhav 2012 18/45 14/20 31.9 % 0.57 [0.36, 0.90]
Subtotal (95% CI) 619 473 100.0 % 0.39 [0.28, 0.55]
Total events: 63 (Liposomal), 116 (Conventional)
Heterogeneity: Tau² = 0.04; Chi² = 4.44, df = 3 (P = 0.22); I² =32%
Test for overall effect: Z = 5.43 (P < 0.00001)
2 Chills and/or rigours
Leenders 1997 0/15 2/13 3.7 % 0.18 [0.01, 3.34]
Walsh 1999 35/343 147/344 29.2 % 0.24 [0.17, 0.33]
Thakur 2001 3/17 14/17 16.2 % 0.21 [0.07, 0.61]
0.005 0.1 1 10 200
Favours liposomal
Favours conventional
Hamill 2010 13/180 42/87 25.0 % 0.15 [0.08, 0.26]
Jadhav 2012 17/45 12/20 25.9 % 0.63 [0.37, 1.06]
Subtotal (95% CI) 600 481 100.0 % 0.27 [0.15, 0.48]
Total events: 68 (Liposomal), 217 (Conventional)
Heterogeneity: Tau² = 0.29; Chi² = 15.90, df = 4 (P = 0.003); I² =75%
Test for overall effect: Z = 4.32 (P = 0.000016)
3 Fever and/or rigours
Leenders 1998 (1) 5/52 12/54 7.3 % 0.43 [0.16, 1.14]
Sundar 2004 54/102 65/102 44.1 % 0.83 [0.66, 1.05]
Sundar 2010 121/304 69/106 48.6 % 0.61 [0.50, 0.74]
Subtotal (95% CI) 458 262 100.0 % 0.68 [0.52, 0.90]
Total events: 180 (Liposomal), 146 (Conventional)
Heterogeneity: Tau² = 0.03; Chi² = 4.77, df = 2 (P = 0.09); I² =58%
Test for overall effect: Z = 2.69 (P = 0.0071)
4 Nausea
Leenders 1997 0/15 1/13 1.3 % 0.29 [0.01, 6.60]
Leenders 1998 0/52 1/54 1.3 % 0.35 [0.01, 8.30]
Walsh 1999 12/343 25/344 28.2 % 0.48 [0.25, 0.94]
Thakur 2001 1/17 9/17 3.3 % 0.11 [0.02, 0.78]
Hamill 2010 24/180 16/87 38.0 % 0.73 [0.41, 1.29]
Jadhav 2012 10/45 11/20 27.9 % 0.40 [0.21, 0.79]
Subtotal (95% CI) 652 535 100.0 % 0.50 [0.35, 0.72]
Total events: 47 (Liposomal), 63 (Conventional)
Heterogeneity: Tau² = 0.0; Chi² = 4.47, df = 5 (P = 0.48); I² =0.0%
Test for overall effect: Z = 3.76 (P = 0.00017)
5 Vomiting
Walsh 1999 4/343 19/344 21.2 % 0.21 [0.07, 0.61]
Hamill 2010 27/180 16/87 38.5 % 0.82 [0.46, 1.43]
Jadhav 2012 15/45 13/20 40.2 % 0.51 [0.30, 0.87]
Subtotal (95% CI) 568 451 100.0 % 0.51 [0.27, 0.95]
Total events: 46 (Liposomal), 48 (Conventional)
Heterogeneity: Tau² = 0.18; Chi² = 5.14, df = 2 (P = 0.08); I² =61%
Test for overall effect: Z = 2.13 (P = 0.033)
Test for subgroup differences: Chi² = 11.08, df = 4 (P = 0.03), I² =64%
0.005 0.1 1 10 200
Favours liposomal
Favours conventional
(1) The outcome for this study was fever and/or chills

REVIEW UPDATE (19 MAY 2022)

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis.

Background: A recent publication (Jarvis et al, March 2022) of single dose of liposomal amphotericin B for the treatment of cryptococcal meningitis was reviewed.

The phase 3 trial evaluated the efficacy and safety of a single dose of liposomal amphotericin B (10mg/kg), followed by 14 days of flucytosine (100mg/kg/day) and fluconazole (1200mg/day) compared to a control treatment of amphotericin B deoxycholate (1mg/kg/day) plus flucytosine (100mg/kg/day) for 7 days, followed by 1 week of fluconazole (1200mg/day). This was followed with fluconazole at 800mg/day for 8 weeks, then 200mg/day fluconazole in all patients. The study was conducted in five African countries (8 hospitals).

814 participants with cryptococcal meningitis were included in the intention-to-treat analysis. Those who previously received more than two doses of fluconazole or amphotericin B, pregnancy or breastfeeding, history of adverse reaction to study drugs, elevated alanine aminotransferase, leukopenia, and thrombocytopenia were excluded. All were treated in hospital for at least 7 days.

The mortality rate was 24.8% for the intervention group (95% CI, 20.7 to 29.3) and 28.7% (95% CI, 24.4 to 33.4) for the control group at 10 weeks and the fungal clearance in CSF was similar. Grade 3 or 4 adverse events within the first 21 days of treatment was 50.0% vs 62.3% in the liposomal amphotericin B group compared to the control group. Similarly adverse events such as anaemia, creatinine elevation, and thrombophlebitis were less prevalent in the intervention group.

Conclusion: The liposomal amphotericin B regimen was non-inferior to the control group in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid. The study had a standardized 7-day inpatient monitoring in both arms. The study authors indicated that there may be potential to shorten length of hospital stay with liposomal amphotericin B.

Table 1

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Botero Aguirre 2015	Cochrane systematic review and meta-analyses	2298 participants (2172 participants included in the meta-analysis)	Patients diagnosed with proven, probable or possible invasive fungal infection were included, as well as those with documented or suspected neutropenia (absolute neutrophil count < 500 cells/ mm^3), those considered at high risk for developing invasive fungal infection by investigators, and those with other infectious diseases where amphotericin B is used as primary treatment.	Conventional amphotericin B deoxycholate	<u>Primary outcomes:</u> • Increase in serum creatinine (SCr) level ≥ than two-fold from baseline. <u>Secondary outcomes:</u> • 50% increase in SCr occurring at any time during the study period • Discontinuation of amphotericin B therapy due to nephrotoxicity as determined by the investigators • Increase in SCr > 2 mg/dL at any time during the study period • Change in creatinine clearance (CrCl) from beginning to end of the study • Infusion-related reactions as determined by the investigators.	<u>Increase in serum creatinine:</u> There was a significant increase in SCr level: ≥ two-fold from baseline level with conventional amphotericin B compared to liposomal amphotericin B (10 studies, 2172 participants): RR 0.49, 95% CI 0.40 - 0.59; I2 = 0%). <u>Infusion-related reactions:</u> There was significant decrease in all infusion-related reactions in the liposomal group compared with the conventional group (Analysis 1.2): fever (4 studies, 1092 participants): RR 0.39, 95% CI 0.28 to 0.55; I2 = 32%); chills and/or rigours (5 studies, 1081 participants): RR 0.27, 95% CI 0.15 to 0.48; I2 = 75%); fever and/or rigours (2 studies, 720 participants): RR 0.68, 95% CI 0.52 to 0.90; I2 = 58%); nausea (6 studies, 1187 participants): RR 0.50, 95% CI 0.35 to 0.72; I2 = 0%); and vomiting (3 studies, 1019 participants): RR 0.51, 95% CI 0.27 to 0.95; I2 = 61%).	Overall, risk of bias in included studies was low or unclear for most domains. However, blinding of participants and personnel, blinding of outcome assessment and other bias (funding) tended to have a high risk of bias. Summary of findings for the main comparison provides a concise overview and synthesis of the volume and quality of the evidence for the comparison between liposomal and conventional amphotericin B respect to the increase in SCr level ≥ two-fold from baseline level. Publication bias was not detected and several sensitivity analyses were performed to check the robustness of the effect estimate.
Leenders 1997	Unblinded RCT	30 (2 excluded after randomization including	Inclusion criteria: HIV infected; ≥18 years of age;	3 weeks of conventional amphotericin B deoxycholate	<u>Primary outcome</u> • Clinical and mycological response at the completion of 10 weeks (including	10-week mortality RR 0.43 (95% CI 0.04 – 4.25) and 6-month mortality RR 0.58 (95% CI 0.11 – 2.94)	Certainty of evidence for this trial was classified as GRADE very low (the true effect is likely to be different from the estimate of effect).

		comatose patient without written informed consent from family and patient with negative CSF culture)	positive CSF India ink or CrAg with confirmation by positive CSF culture or CSF CrAg with positive blood culture Exclusion criteria: previous cryptococcal meningitis; SCr >250 µmol/L	vs 3 weeks of liposomal amphotericin B Consolidation: fluconazole 400 mg/day up to 10 weeks, then 200 mg/day maintenance dose	mortality and sterile CSF culture) <u>Secondary outcomes</u> • Mortality up to 6 months		

Table 2

Efficacy of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Parameter	No. (%) of patients, by regimen			Treatment difference, % (95% CI)[a]	
	L-AmB 3	L-AmB 6)	AmB	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Mycological success[b]					
Week 2	35 (58.3)	36 (48)	29 (47.5)	10.8 (−6.9 to 28.5)	0.5 (−16.4 to 17.3)
Week 10	36 (60)	53 (70.7)	48 (78.7)		
Therapeutic success:[c] week 10	27 (67.5)	42 (73.7)	40 (75.5)	−8.0 (−26.5 to 10.6)	−1.8 (−18.1 to 14.5)
Clinical success					
Week 2[d]	48 (65.8)	64 (75.3)	50 (65.8)	…	…
Week 10[e]	31 (70.5)	43 (72.9)	44 (81.5)	…	…
Survival:[f] week 10	74 (86)	85 (90.4)	77 (88.5)	…	…

NOTE. CI, confidence interval; L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

[a] Treatment difference for 1° end point for incidence of mycological success at week 2.

[b] All randomized patients who received ≥1 dose of study drug, had a positive baseline culture result, and underwent ≥1 follow-up culture.

[c] All randomized patients who received ≥1 dose of study drug, had a positive baseline culture result, and underwent ≥1 follow-up culture (ie, mycological evaluable patients) and who completed therapy or died during weeks 2–10.

[d] All randomized patients who received ≥1 dose of study drug and had a positive baseline culture result.

[e] All randomized patients who received ≥1 dose of study drug and had a positive baseline culture result who completed therapy or died during weeks 2–10.

[f] Among the modified intent-to-treat population, the Kaplan-Meier estimate of patient survival was 83.6% (95% CI, 75.7%–91.6%) for the combined liposomal amphotericin B groups and 87% (95% CI, 79.5%–95.6%) for the amphotericin B group.

Table 3

Table 3. Incidence of Infusion-Related Reactions among Recipients of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Infusion-related reaction	No. (%) of patients, by regimen			*P*[a]	
	L-AmB 3 (*n* = 86)	L-AmB 6 (*n* = 94)	AmB (*n* = 87)	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Increase in temperature ≥1.0°C	6 (7)	8 (8.5)	24 (27.6)	<.001	<.001
Chills and/or rigors	5 (5.8)	8 (8.5)	42 (48.3)	<.001	<.001
Nausea	11 (12.8)	13 (13.8)	18 (20.7)	.222	.241
Vomiting	14 (16.3)	13 (13.8)	16 (18.4)	.841	.425
Respiratory system (any adverse event)	0 (0)	1 (1.1)	8 (9.2)	.007	.015
Overall	27 (31.4)	35 (37.2)	58 (66.7)	<.001	<.001

NOTE. AE, adverse event; L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

[a] Determined using the Fisher exact test.

Table 4

Table 4. Adverse Events among Recipients of Liposomal Amphotericin B and Conventional Amphotericin B Deoxycholate (AmB)

Adverse event	No. (%) of patients, by regimen			*P*	
	L-AmB 3	L-AmB 6	AmB	L-AmB 3 vs AmB	L-AmB 6 vs AmB
Creatinine level of 2.0 times baseline and >1.2 mg/dL	12 (14.9)	20 (21.3)	29 (33.3)	.004	.066
Serum potassium level, <3.0 mmol/L	8 (9.3)	33 (35.1)	26 (29.9)	.001	.529
Hemoglobin concentration, ≤8 g/dL	20 (23.3)	39 (41.5)	38 (43.7)	.006	.650

NOTE. L-AmB 3, liposomal amphotericin at 3.0 mg/kg/day; L-AmB 6, liposomal amphotericin at 6.0 mg/kg/day.

a. Evidence quality:

The quality of evidence from the RCT by Leenders et al. was classified as very low by the GRADE classification in the Cochrane systematic review. Hamill et al. was classified as a low risk of bias in the Cochrane systematic review.

8. Alternative agents:

None

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [x] Uncertain: [ ]	Very few trials available that looked at this specific treatment comparison of liposomal amphotericin B versus amphotericin B deoxycholate for the management of cryptococcal meningitis. The available evidence is moderate regarding risk of bias. The recent RCT by Jarvis et al (2022) likewise considered to be of moderate risk of bias.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	The benefits of using liposomal amphotericin B outweigh the risks, specifically regarding safety outcomes: nephrotoxicity, infusion related reactions, electrolyte disturbances, and anaemia. Jarvis et al (2022) found liposomal amphotericin B regimen to be non-inferior to the control group (amphotericin B deoxycholate regimen) in terms of mortality outcomes and cryptococcal clearance from cerebrospinal fluid - mortality rate of 24.8% (95% CI, 20.7 to 29.3) vs 28.7% (95% CI, 24.4 to 33.4) at 10 weeks and the fungal clearance in CSF was similar. Grade 3 or 4 adverse events within the first 21 days of treatment was 50.0% vs 62.3% in the liposomal amphotericin B group compared to the control group. Similarly adverse events such as anaemia, creatinine elevation, and thrombophlebitis were less prevalent in the intervention group.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes: [ ] No: [x]	There are no other alternatives available in South Africa for Amphotericin B in the management of cryptococcal meningitis.
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: [x] No: [ ] Uncertain: [ ]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [x*] Uncertain: [ ] *Similar or less intensive costs with Liposomal amphotericin B compared to current standard of care.	Cost of medicines/unit: **Medicine** / **SEP (ZAR)*** / **MHPL**** AmpB deoxylate 50 mg inj / 155.02 / n/a AmpB liposomal 50 mg inj / 3078.83 / 600 *SEP database, 14 August 2023 ** MHPL 1 Dec 2023 **Induction phase** / **Cost (ZAR)*** 1 week AmpBd/Flucytosine / 5,156 2 week Liposomal AmpB (single dose) Flucytosine/fluconazole / 10,487 **Additional resources:** Refer to cost analysis (Addendum A)
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [x]	Significantly higher cost of liposomal amphotericin B could impact health equity.

FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Implementation is feasible, particularly if restricted to specific patients that will benefit from the improved safety benefits of this agents.

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 the updated evidence review, the PHC/Adult Hospital Level Committee suggests the use of liposomal amphotericin B for treating patients with cryptococcal meningitis.

Liposomal amphotericin B is non-inferior to current standard of care in terms of efficacy and is safer. Liposomal amphotericin B has a similar or lower cost compared to current standard of care, at the latest price of R600 per 50mg vial taking length of hospital stay into account in the costing.

Rationale: The current evidence of moderate risk of bias, shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate.

Level of Evidence: Low to moderate certainty evidence

Review indicator: Price reduction

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[ ]	[X]

VEN status: n/a

Vital	Essential	Necessary
[ ]	[ ]	[ ]

NEMLC MEETING OF 21 FEBRUARY 2019:

NEMLC ratified the medicine review and accepted the recommendation not to include liposomal amphotericin B in the Adult Hospital Level EML as although small and of moderate risk of bias, it shows that liposomal amphoteracin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis, however it is currently not affordable.

NEMLC MEETING OF 23 JUNE 2022:

NEMLC upheld the previous recommendation not to include liposomal amphotericin B on the national EML, but amended the strength of recommendation from “strong” to “conditional”, with a review indicator of “price reduction”. The NEMLC further recommended that the proposed Gilead price of $16.25 per 50 mg vial be added as a threshold price.

NEMLC MEETING OF 30 NOVEMBER 2023: NEMLC supports the ERC’s recommendation to include the use of liposomal amphotericin B on the EML for the management of cryptococcal meningitis in line with the treatment regimen included in the cost analysis (Addendum A). The Committee supported this recommendation on the basis of the better safety profile of liposomal amphotericin B compared to amphotericin B deoxycholate as well as the potentially lower overall cost with liposomal amphotericin B. The committee however, acknowledged the limitations of modelling the benefits of the better safety profile of liposomal amphotericin B in the cost analysis.

Monitoring and evaluation considerations

Need for restriction and monitoring if allowed for use in patients that require it.

Research priorities

None

References:

Adler-Moore 2002

Adler-Moore J, Proffitt RT. AmBisome: liposomal formulation, structure, mechanism of action and preclinical experience. Journal of Antimicrobial Chemotherapy 2002;49 Suppl 1:21–30.

Bassetti 2011

Bassetti M, Aversa F, Ballerini F, Benedetti F, Busca A, Cascavilla N, et al. Amphotericin B lipid complex in the management of invasive fungal infections in immunocompromised patients. Clinical Drug Investigation 2011;31(11):745–58.

Botero Aguirre 2015

Botero Aguirre JP, Restrepo Hamid AM. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD010481.

Hamill 2010

Hamill RJ, Sobel JD, El-Sadr W, Johnson PC, Graybill JR, Javaly K, Barker DE. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. Clin Infect Dis. 2010 Jul 15;51(2):225-32.

Johansen 2014

Johansen HK, Gøtzsche PC. Amphotericin B lipid soluble formulations versus amphotericin B in cancer patients with neutropenia. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD000969.

Leenders 1997

Leenders AC, Reiss P, Portegies P, Clezy K, Hop WC, Hoy J, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 1997;11(12):1463–71.

Rajasingham 2017

Rajasingham R, Smith RM, Bark BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV associated cryptococcal meningitis: an updated analysis. Lancet Infectious Diseases 2017;17(8):873–81.

Tenforde 2018

Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, Ford N. Treatment for HIV-associated cryptococcal meningitis. Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD005647.

WHO 2018

World Health Organization. Diagnosis, Prevention and Management of Cryptococcal Disease HIV-infected Adults, Adolescents and Children: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. March 2018. Licence: CC BY-NC-SA 3.0 IGO.

Jarvis 2022

Jarvis JN, Lawrence DS, Meya DB, Kagimu E, Kasibante J, Mpoza E, et al.; Ambition Study Group. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

Mashau 2022

Mashau, R., Meiring, S., Quan, V., Nel, J., et al.; Outcomes of flucytosine-containing combination treatment for cryptococcal meningitis in a South African national access programme: a cross-sectional observational study. The Lancet Infectious Diseases, Volume 22, Issue 9, 1365 - 1373

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	28 Nov 2018	RG and HD	
V3.0	29 may 2022	JM	Updated Jarvis et al, March 2022 and BIA
V4.0	26 October 2023	JM	BIA updated with reduced price of Liposomal amphotericin B and hospitalisation costs

ADDENDUM A:

Liposomal amphotericin B cost analysis

Date of Update: 19 October 2023

Authors: Jacqui Miot, Trudy Leong, Lise Jamieson, Danleen Hongoro

Affiliation(s) and declaration: JM, LJ and DH (Health Economics and Epidemiology Research Office (HE^2RO), University of Witwatersrand) and TL (Essential Drugs Programme, National Department of Health) have no interests pertaining to liposomal amphotericin B.

A cost analysis was conducted based on the data available from the Jarvis et al. publication. A single dose of Liposomal amphotericin B (10mg/kg) followed by 14 days of flucytosine 100mg/kg/day and fluconazole 1200mg/day (Lipo AmB/5FC/Flu) was compared to 1 week of amphotericin B (1mg/kg/day) and flucytosine 100mg/kg/day (1wk AmBd/5FC) followed by 1 week of fluconazole (1200mg/day). This was followed with fluconazole at 800mg/day for 8 weeks, then 200mg/day fluconazole in all patients. The model also presents data from other treatment regimens used in cryptococcal meningitis in South Africa, however, these are simply cost comparisons and not cost-effectiveness analyses (i.e. they don't take into account any differences in clinical benefits).

The model has been updated to reflect recent price changes. Flucytosine is now available on SEP at R1,764.89 per pack of 100 x 500mg tablets, Amphotericin B is available at an SEP of R155.02 per vial and Liposomal amphotericin B was recently awarded on tender at R600 per 50mg vial. Each treatment arm included the cost of the medicines, administration, and infusion costs, consumables, supportive medicines, laboratory monitoring, and hospital stays. In the Jarvis paper, patients in each treatment arm stayed in the hospital for 7 days. Since amphotericin B is given as an infusion, it is necessary for the patients to remain in the hospital in the treatment arm for at least 1 week with flucytosine. In a local cross-sectional observational study of patients with CM, those on flucytosine regimens were compared to other regimens the majority of which was a combination of amphotericin B deoxycholate and fluconazole (Mashau 2022). In this study patients on the flucytosine regimens (of which the majority were flucytosine plus amphotericin B) the median length of stay was 10 days compared to 14 days in the other regimens. Therefore, it is reasonable to assume that in South Africa, the 1-week AmBd/5FC treatment cohort would have a LOS of 10 days. It is possible that patients in the Liposomal amphotericin B arm would be able to leave the hospital sooner and be treated at home, however given the severity of the nature of cryptococcal meningitis this is unlikely to be less than 7 days and so the baseline LOS was assumed to be 7 days.

Medicines costs assumed a patient weight of 60kg and also included pre-emptive hydration and potassium and magnesium supplements in the amphotericin B arm. The medicine and consumable costs were mostly obtained from the Master Health Products Price list (April 2022). Hospital, laboratory, blood transfusion and administration costs were taken from the relevant price lists of 2018 and inflation-adjusted to 2023. We further present two scenarios of costing hospital costs, procedures, supportive medicines: 1) using costs from the Uniform Patient Fee Schedule (UPFS), and 2) using the expenditure per patient day equivalent (PDE) to represent the hospital costs. The PDE hospital cost is a top-down average and therefore includes any consultations, supporting medicines, consumables etc. so these were removed from the PDE analysis.

Table 1: Total medicine Costs

1 week AmBd/5FC									
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**	
Induction phase	Amphotericin B	7	1mg/kg daily	310.04	1.00	310.04	2170.28		
	Dextrose 5%	7	1litre	12.71	1.00	12.71	88.97		
	Flucytosine	7	100mg/kg daily	211.79	1.00	211.79	1482.51		
	Infusions	7		202.00	1.00	202.00	1414.00	**5155.76**	week 1
	Fluconazole	7	1200mg daily	2.25	3.00	6.74	47.18	**47.18**	week 2
Consolidation phase	Fluconazole	56	800mg daily	2.25	2.00	4.49	251.60	**251.60**	**Total**
Maintenance phase	Fluconazole	294	200mg daily	1.12	1.00	1.12	330.23	**330.23**	**R 5,784.76**

2 week 5FC/Flu with single dose Liposomal amphotericin B									
Drug costs		**Number of days**	**Dose**	**Dose cost**	**Frequency per day**	**Cost per day**	**Cost per phase**	**Total cost (includes intial treatment phase)**	
Induction phase	Liposomal AmB	1	10mg/kg daily	7200.00	1.00	7,200.00	7200.00		
	Dextrose 5%	1	1litre	12.71	1.00	12.71	12.71		
	Flucytosine	14	100mg/kg daily	211.79	1.00	211.79	2965.01		
	Infusions	1		215.37	1.00	215.37	215.37	**10487.44**	
	Fluconazole	14	1200mg daily	2.25	3.00	6.74	94.35		week 2
Consolidation phase	Fluconazole	56	800mg daily	2.25	2.00	4.49	251.60	**251.60**	**Total**
Maintenance phase	Fluconazole	294	200mg daily	1.12	1.00	1.12	330.23	**330.23**	**R 11,069.26**

Total medicine cost for the full regimen including maintenance phase fluconazole was R5,784.76 per patient for the 1-week AmBd/5FC regimen compared to R11,069.26 per patient for the liposomal AmB/5FC regimen.

Table 2: Total Costs Summary

Total Costs Summary (ZAR)				
	UPFS-based		**Expenditure per PDE**	
Per Patient	**2wk 5FC LipAmB**	**1wk AmBd/5FC**	**2wk 5FC LipAmB**	**1wk AmBd/5FC**
Medicine Costs				
Induction (week 1)	10487	5156	10487	5156
Induction (week 2)	-	47	-	47
Consolidation	252	252	252	252
Maintenance	330	330	330	330
ART costs	3319	3319	3319	3319
Total Medicine Costs	**14388**	**9103**	***14388***	***9103***
Hospital Costs				
Secondary level	8433	12048	25816	36881
Other costs				
Supportive Medicines	0	212		
Laboratory Costs (Monitoring)	1675	1675	1675	1675
Lumbar puncture	1570	1570		
ADR Costs				
Blood transfusions	186	442		
Antibiotics	93	75		
Total ADR costs	**280**	**517**		
Total Costs (per patient)	**R26,346**	**R25,125**	**R41,879**	**R47,659**

In our cost analysis, we employed two distinct methodologies, UPFS-based and PDE-based, to assess the overall cost of Liposomal amphotericin B in comparison to two alternative treatments: the 1-week AmBd/5FC course and the standard

2-week AmBd/Flu regimen. When evaluated from the UPFS-based perspective, the total cost analysis, which considered laboratory monitoring, adverse drug reactions (ADRs), hospitalization, and other relevant costs, revealed that Liposomal amphotericin B tends to be relatively more expensive per patient, with a per-patient cost of R26,346 in comparison to the 1-week AmBd/5FC course (R25,125) and the standard 2-week AmBd/Flu treatment (R31,670) (Table 3a). Conversely, when we considered the PDE-Based perspective, the total cost analysis indicated that Liposomal amphotericin B presents as a less expensive choice (R41,879) when contrasted with the 1-week AmBd/5FC course (R47,659) and the standard 2-week AmBd/Flu treatment (R63,753) (Table 3b). Adverse drug reactions that were considered were anaemia requiring blood transfusions and antibiotics for neutropaenia and thrombophlebitis. Dosing and the likelihood of these specific ADRs were sourced from the Jarvis et al. publication. For comprehensive insights into the cost breakdowns for the 1-week AmBd/5FC and 2-week AmBd/5FC (SC) courses, refer to the economic analysis of flucytosine.[2]

The model was sensitive to the LOS. In the UPFS-based costing, where a difference of one day LOS (either 6 days in LipAmB/5FC or 11 days in AmBd/5FC) brought the total costs to neutral (i.e. no cost difference). In the PDE-based costing, if the LOS of LipAmB/5FC increased beyond 8 days (compared to 10 days in the AmBd/5FC arm) or the AmBd/5FC LOS decreased below 8 days (compared to 7 days in the LipAmB/5FC) then the model was no longer cost-neutral and the Liposomal amphotericin B arm because more expensive.

Table 3a: Cost analysis (using UPFS cost for hospital and procedures)

Total Costs (ZAR)	2wk 5FC LipAmB	1wk AmBd/5FC	1wk AmBd/Flu	2wk AmBd/Flu (SC)	Oral
Per pt costs (at 1 year)					
Medicine costs	14,388	9,103	7,548	11,163	6,960
Hospital costs	8,433	12,048	16,867	16,867	20,481
Lumbar puncture	1,570	1,570	734	1,570	1,570
Laboratory costs	1,675	1,675	1,675	957	535
Supportive medicines	0	212	212	225	0
ADR treatment costs	280	517	675	888	396
Total	**26,346**	**25,125**	**27,711**	**31,670**	**29,942**

Table 3b: Cost analysis (using expenditure per PDE for hospital and procedures)

Total Costs (ZAR)	2wk 5FC LipAmB	1wk AmBd/5FC	1wk AmBd/Flu	2wk AmBd/Flu (SC)	Oral
Per pt costs (at 1 year)					
Medicine costs	14,388	9,103	7,548	11,163	6,960
Hospital costs	25,816	36,881	51,633	51,633	62,697
Laboratory costs	1,675	1,675	1,675	957	535
Total	**41,879**	**47,659**	**60,855**	**63,753**	**70,192**

[2] Miot J, Leong T, Takuva S, Parrish A, Dawood H. Cost-effectiveness analysis of flucytosine as induction therapy in the treatment of cryptococcal meningitis in HIV-infected adults in South Africa. BMC Health Serv Res. 2021 Apr 6;21(1):305. https://pubmed.ncbi.nlm.nih.gov/33823842/