PHC Chapter 11: Human immunodeficiency virus and acquired immune deficiency syndrome (HIV AND AIDS)

HIV infection in adults and adolescents (10-19 years old)

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.[1]

HIV INFECTION IN ADULTS AND ADOLESCENTS (10-19 YEARS OLD)

DESCRIPTION

HIV replicates in CD4 lymphocytes and monocytes, leading to progressive destruction of CD4 lymphocytes and impaired immunity.

Primary infection is characterised by:

- glandular fever-type illness
- maculopapular rash
- small orogenital ulcers

After primary infection, patients may have generalised lymphadenopathy and are usually asymptomatic for several years. Subsequently, if untreated, inflammatory skin conditions and an increased frequency of minor infections occur, followed by more severe infections (especially tuberculosis), weight loss and/or chronic diarrhoea. Eventually, severe opportunistic infections, HIV-associated cancers, or other severe HIV manifestations develop, known as the Acquired Immune Deficiency Syndrome (AIDS).

DIAGNOSIS

- Provide adequate pre- and post-test counselling.
- Ensure patient confidentiality.
- A positive rapid HIV test in adults must be confirmed with a 2nd rapid test from a different manufacturer. If the screening and confirmation rapid test result differ, repeat the tests. If the repeated test series differ, do a laboratory test (usually ELISA).
- HIV antibodies are not detected during the 1st few weeks after infection. This is known as the window period.

PROGNOSIS

- HIV disease progression is variable. The CD4 lymphocyte count and clinical features of immune suppression (see WHO staging below) both provide independent information on prognosis. Patients may be asymptomatic with very low CD4 counts or have severe clinical features with well-preserved CD4 counts. CD4 counts < 200 cells/mm^3 indicate severe immune suppression. All HIV-infected patients must have a CD4 count and WHO clinical staging done at diagnosis.
- All PLHIV are eligible for ART, irrespective of CD4 count or WHO stage. Patients should be counselled about the benefits and risks of early ART initiation, and encouraged to initiate ART as soon as feasible. However, should a patient elect to defer ART, the CD4 count should be repeated every 6 months until ART can be initiated.

South African modified WHO staging of HIV/AIDS for adults and adolescents

Clinical Staging	Clinical Features
Stage 1	• Asymptomatic. • Persistent generalised lymphadenopathy.
Stage 2	• Unexplained moderate weight loss (< 10% of presumed or measured body weight). • Recurrent respiratory tract infections (sinusitis, otitis media and pharyngitis). • Herpes zoster (shingles). • Angular stomatitis. • Recurrent oral ulceration. • Papular pruritic eruption. • Seborrhoeic dermatitis. • Fungal nail infections.
Stage 3	• Unexplained severe weight loss (> 10% of presumed or measured body weight). • Unexplained chronic diarrhoea for > 1 month. • Unexplained persistent fever (> 37.5°C intermittent or constant for > 1 month). • Persistent oral candidiasis (thrush). • Oral hairy leukoplakia. • Pulmonary TB. • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteraemia). • Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis. • Unexplained anaemia (< 8 g/dL), neutropaenia (< 0.5×10^9/L) and/or chronic thrombocytopaenia (< 50×10^9/L).
Stage 4	• HIV wasting syndrome. • Extrapulmonary tuberculosis. • Pneumocystis pneumonia. • Recurrent severe bacterial pneumonia. • Chronic herpes simplex infection (orolabial, genital or anorectal of > 1 month duration or visceral at any site). • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs). • Kaposi's sarcoma. • Cytomegalovirus infection (retinitis or infection of other organs). • Central nervous system toxoplasmosis. • HIV encephalopathy. • Extrapulmonary cryptococcosis including meningitis. • Disseminated non-tuberculous mycobacterial infection. • Progressive multifocal leukoencephalopathy. • Chronic cryptosporidiosis.

Clinical Staging	Clinical Features
	• Chronic isosporiasis. • Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis). • Recurrent septicaemia (including non-typhoidal Salmonella). • Lymphoma (cerebral or B cell non-Hodgkin). • Invasive cervical carcinoma. • Atypical disseminated leishmaniasis. • Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy.

GENERAL MEASURES

- Encourage patients and their families to join support or peer groups.
- Counsel patients on methods to reduce the spread of HIV:
  - Use condoms during sexual intercourse
  - ART in HIV-infected. See Section 11.1: Antiretroviral therapy.
  - PrEP where indicated. See Section 11.11: Pre-exposure prophylaxis (PrEP)
  - Seek early treatment for sexually transmitted infections. See Chapter 12: Sexually transmitted infections.
  - Safe handling of blood spills.

11.1 ANTIRETROVIRAL THERAPY, ADULTS AND ADOLESCENTS (10-19 YEARS OLD)

B24

DESCRIPTION

Antiretroviral therapy (ART) suppresses viral replication (measured with the viral load test), increases the CD4 count and reduces HIV-associated diseases and death. ART guidelines are regularly updated, so it is important to consult the current National Guidelines.

ELIGIBILITY FOR ART

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

Timing of ART initiation: *LoE: Ia*[2]

ART may be started on the day of diagnosis if the patient has no clinical contraindication, and the patient is willing to start after receiving pre-ART counselling. For clinical indications for deferring ART initiation, see below.

Immediate initiation:

Initiate ART immediately in pregnancy and during breastfeeding if the patient has no clinical contraindication. *LoE:IIa*[3]

Clinical indications for deferring ART initiation:
Early ART initiation increases the risk of the immune reconstitution inflammatory syndrome (IRIS) (see Section 11.13.1: Immune Reconstitution Inflammatory Syndrome (IRIS)). Defer ART in patients with cryptococcal meningitis (see Adult Hospital EML Section 10.2.4.3 Cryptococcal meningitis) or TB meningitis (see Section 10.17: Tuberculosis, extrapulmonary) as there is increased risk of mortality due to IRIS with early ART initiation (see below for timing).

TB co-infection:

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

LoE:Ia[4]

TB meningitis co-infection:

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

LoE:IIIa[5]

Cryptococcal meningitis co-infection:

- Defer ART until 4–6 weeks after starting antifungal therapy (earlier initiation has been shown to increase the risk of death).

LoE:IIIa[6]

Positive cryptococcal antigen and no evidence for meningitis on LP:

- No need to delay ART. ART can be started immediately.

LoE:IVb[7]

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. Give 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/alcohol is an impediment to adherence and, where possible, should be addressed before initiating ART.

LoE:IIIb[8]

ART REGIMENS

INITIATING ART	
Treatment-naïve patients	Individuals ≥30kg and ≥10 years TDF + 3TC + DTG ("TLD") *LoE:IIa*[9] **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential.

	LoE:IIa[10] <u>Patients on rifampicin-based TB treatment:</u> 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 stopping rifampicin. *LoE:IIIb*[11] (Also see PHC STG Section 6.8: HIV in pregnancy)
Contraindications/ intolerance to DTG	TDF + 3TC/FTC + EFV
Contraindications to EFV and DTG	<u>Start protease inhibitor-based regimen:</u> TDF + 3TC/FTC + ATV/r *LoE:IIb*[12] **Note:** if patient requires rifampicin-based TB treatment, substitute ATV/r with LPV/r at 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/r two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	<u>If chronic hepatitis B coinfection and eGFR 30-50 ml/min:</u> TAF + FTC + DTG. *LoE:IIb*[13] <u>Other scenarios:</u> ABC + 3TC + DTG *LoE:IIb*[14]
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*[15]
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).
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") (*Refer to Figure 11.1 below*). If contraindications to DTG or TDF, use alternative regimen as in "Initiating ART" section above. *LoE:IIb*[16]
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.* Provide individualised regimen as recommended by HIV expert. If adherence < 80%. switch to DTG-containing regimen:

	TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as per "Initiating ART" section above. *LoE:IIb*[17]
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. If on ATV/r: *LoE:IIIb*[18] 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 11.1: 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.
» If HBsAg positive, TDF should be incorporated as part of the ART regimen.

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 100 mg
- ABC 600 mg + 3TC 300 mg + DTG 50 mg

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

Switching existing clients to DTG-containing regimens

Non VL-dependent regimen switches
Regimens where the VL result will not influence nor delay the decision to switch to DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
Switching regardless of VL result	**TEE** **ABC/3TC/EFV** **AZT/3TC/EFV** **AZT/3TC/DTG** **Any LPV/r or ATV/r regimen for less than 2 years**	**Switch all to a DTG-containing regimen, regardless of VL result** Review VL in last 12 months. If VL in last 12 months was not suppressed, continue to switch same day, but do ABCDE assessment and provide enhanced adherence counselling (EAC) if needed. If VL was not done in last 12 months, do it at this visit, but do not wait for results to switch.	**TLD** Provided no renal dysfunction and age > 10 years and weight > 30 kg If client does not quality for TDF **ABC[1]/3TC/DTG** If client does not quality for TDF and has ABC hypersensitivity **AZT/3TC/DTG**

VL-dependent regimen switches
Relevant to all clients who have been on PI-based regimens for more than two years: their VL result in the last 12 months will influence the decision of how and when to switch to a DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
VL < 1000 c/mL	**Any LPV/r or ATV/r regimen for more than 2 years**	**Switch all to a DTG-containing regimen** If VL in last 12 months was not < 50 c/mL, continue to switch same day, but do ABCDE assessment and provide EAC if needed.	**TLD** provided no renal dysfunction and age > 10 years and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
[2]Two or more VLs ≥ 1000 c/mL taken two or more years after starting PI regimen	Adult or adolescent on any **LPV/r or ATV/r** regimen and adherence **less than 80%[3]**	**Switch all to a DTG-containing regimen** **Do not do a resistance test** These clients are unlikely to have PI resistance mutations. Rather switch to a more tolerable once daily FDC regimen which is likely to support adherence.	**TLD** provided no renal dysfunction and age > 10 yrs and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
	Adult or adolescent on any **LPV/r or ATV/r regimen and adherence more than 80%[3]**	Clients who meet the definition of confirmed virological failure despite confirmed adherence more than 80% may need a resistance test. **These clients do not qualify for a same-day switch.** Discuss with an HIV expert[4] to authorise and interpret a resistance test. Provide individualised regimen as recommended by HIV expert.	
	Child < 10 years, or weight < 30 kg on any **LPV/r or ATV/r regimen**	These clients do not yet qualify for TLD and may require a resistance test. Refer to algorithm **"Switching children on PI-containing regimens to DTG-containing regimens"**	

1. If clients are not eligible to use TDF and they have ABC hypersensitivity, use AZT/3TC/DTG.
2. Confirmed virological failure is defined as two or more VLs ≥ 1000 c/mL taken two or more years after starting a DTG or PI containing regimen, despite adherence > 80% by objective measurement. A patient who has only 1 VL > 1000 after 2 years on a PI-based regimen should have an ABCDE assessment, EAC if applicable, and their VL repeated in 3 months. The result of the repeat VL will allow the patient to be grouped into one of the categories in the table above and will inform the further course of action.
3. Objective measures of good adherence include at least one of:
   - Pharmacy refills > 80% in the last 6-12 months (if this is known).
   - Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known).
   - Detection of current antiretroviral drug/s in the client's blood or urine, if available.

   Note: Self-reported adherence is not considered a reliable measure of good adherence.
4. For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

Figure 11.1: Switching existing clients to DTG-containing regimens (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

Re-initating ART in patients who have interrupted treatment

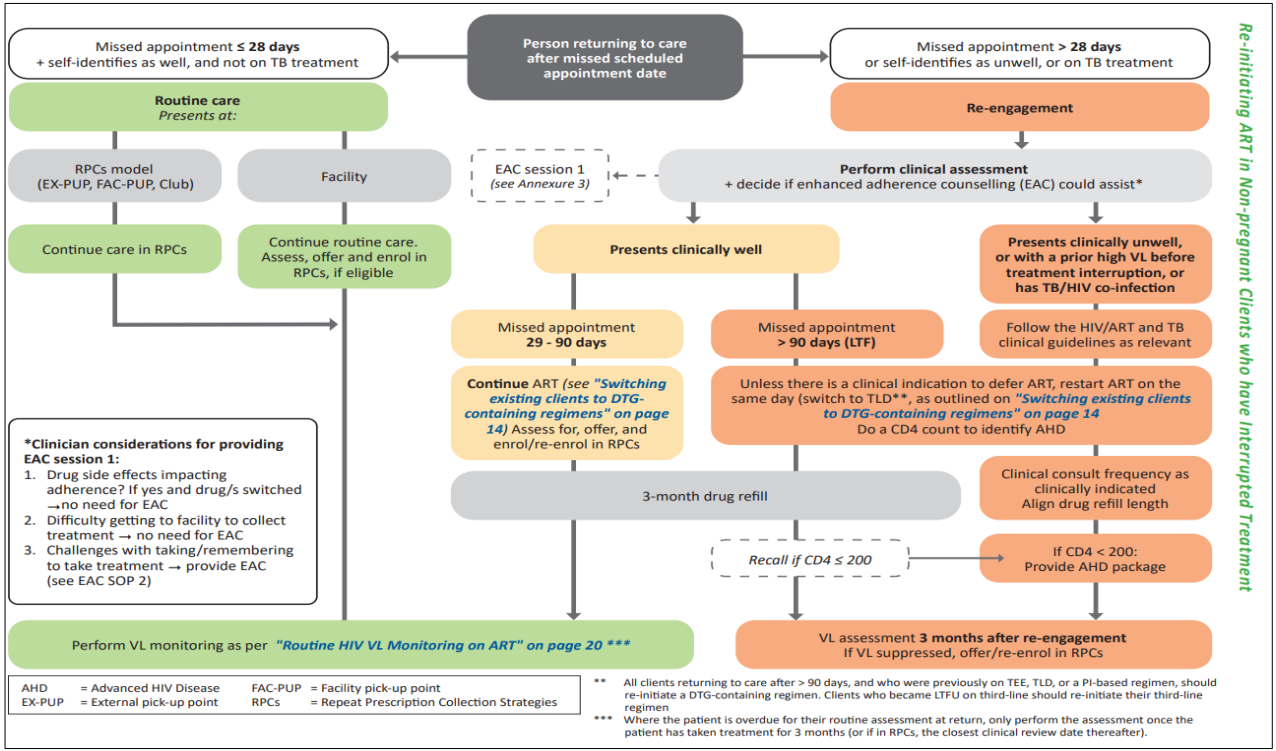


Figure 11.2: Management algorithm of a patient who returns to care after interrupting treatment. Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

MONITORING ON ART	

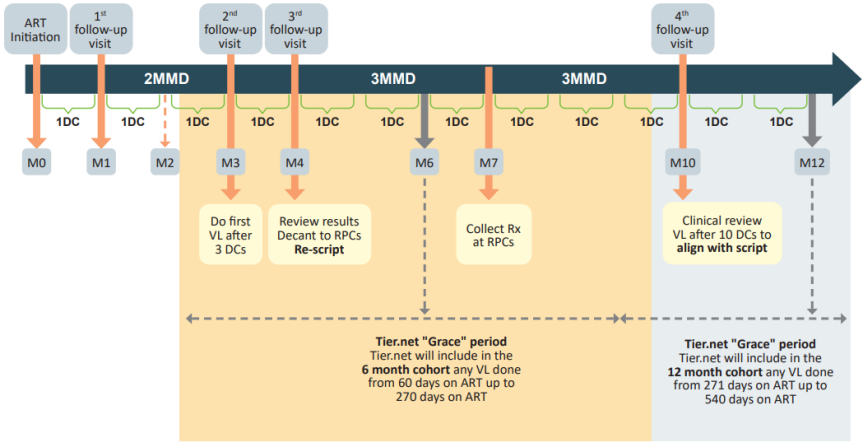
Baseline evaluation	» WHO staging (See table above).
	» Check CD4 count.
	» <u>If CD4 <200 cells/mm^3:</u>
	  » Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). CrAg testing is done reflexly on the CD4 sample if CD4 <100 cells/mm^3. If patient's CD4 is 100-199, a serum CrAg test must be ordered separately.
	  » Initiate cotrimoxazole prophylaxis (See Section 11.2.1: Cotrimoxazole prophylaxis). *LoE:IVb*[19]
	» 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*[20]
	» Check HBsAg (if positive, TDF should form part of the regimen).
	» Cervical cancer screening *LoE:IIb*[21]
	
	*TB-NAAT: TB Nucleic Acid Amplification Test (e.g. GeneXpert Ultra MTB/RIF)

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/re-commenced. 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 11.2: 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

Figure 11.3: Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.
DC: Dispensing cycle; MMD: Multi-month dispensing; RPCs: Repeat prescription collection strategies

ART: DOSING AND IMPORTANT ADVERSE EFFECTS				
Generic name	**Class**	**Usual dose**	**Renal adjusted dose**	**Important adverse drug reactions and timing**
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.
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 eGFR <10 mL/min: 50 mg daily	» Anaemia due to pure red cell aplasia (rare).
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*[22]

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 (rare - weeks to months). » Decline in eGFR (months to years) » Fanconi syndrome (rare – months to years) » Reduced bone mineral density (months to years).
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). » Rash (1 to 6 weeks). *LoE:IVb*[23] » Hepatitis (weeks to months) » Gynaecomastia.
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 taken 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).

Table 11.3: 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. InSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

LoE:IIIb[24]

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

- https://www.hiv-druginteractionslite.org/checker
- http://www.mic.uct.ac.za/ and 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 (INH) which also inhibits EFV metabolism).	No dose adjustment required (600 mg at night).
InSTI	DTG	Significant reduction in concentration of DTG	Increased dose frequency to 50 mg 12 hourly. **Note:** Continue increased dose for 2 weeks after rifampicin is stopped, then decrease to usual dose.
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. Increase dose gradually 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.

Table 11.4: ART interactions with rifampicin and dose-adjustment recommendations

LoE:IIIb[25]

In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with rifabutin (doctor prescribed) – see Adult Hospital Level STGs and EML, Section 10.1: Antiretroviral therapy.

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 DTG concentration	Avoid co-administration if possible. Consider valproate or lamotrigine. *For carbamazepine:* Double DTG dose to 50 mg 12 hourly.
Metformin	Significant increase in metformin concentration	Administer metformin to a maximum of 500 mg 12 hourly.
Rifampicin	Significant reduction in DTG concentration	Double DTG dose to 50 mg 12 hourly.

Table 11.5: Drug interactions with DTG *LoE:IIIb*[26]

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 benzodiazepines)	Significant increase in concentrations of CYP3A4 substrates	Avoid co-administration or use lower doses of CYP3A4 substrates (always consult interaction resources)
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of PI	Avoid co-administration. Consider valproate or lamotrigine.
Proton pump inhibitors	Significant reduction in ATV concentration	Avoid co-administration. *LoE:IIIb*[27]
Rifampicin	Significant reduction in PI concentration	Double LPV/r 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 (e.g. 600/150 mg and then 800/200 mg). Adjusted dose of LPV/r should be continued for 2 weeks after rifampicin is stopped. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy. If ATV/r or DVR/r is required, rifampicin must be replaced with dose-adjusted rifabutin (doctor prescribed) - see AH STG Section 10.1: Antiretroviral therapy.

Table 11.6: Drug interactions with boosted PIs.

REFERRAL

Dolutegravir resistance demonstrated on resistance testing.

11.2 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN ADULTS

11.2.1 COTRIMOXAZOLE PROPHYLAXIS

Z29.2 + (B24)

DESCRIPTION

Primary prophylaxis reduces the probability of developing many infections, e.g.:

- pneumocystis pneumonia
- toxoplasmosis
- bacterial pneumonia
- bacteraemia
- cystoisosporiasis

Indications for primary prophylaxis:

- WHO Clinical stage 3 or 4.
- CD4 count < 200 cells/mm^3.

LoE:IIIb[28]

MEDICINE TREATMENT

Prophylaxis

- Cotrimoxazole, oral, 160/800 mg daily.

LoE:IIb[29]

Note:

- Once the CD4 >200 cells/mm^3 discontinue prophylaxis. If the CD4 count was >200 cells/mm^3 when cotrimoxazole was commenced (e.g. patients with TB) continue for 6 months (See Section 17.3.4.2.4: Pneumocystis pneumonia, for secondary prophylaxis).
- Cotrimoxazole hypersensitivity is common and usually presents as a maculopapular rash. If there are systemic features or mucosal involvement associated with the use of cotrimoxazole, stop the medicine immediately and permanently, and refer the patient to hospital.

LoE:IIIb[30]

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Z29.2 + (B24)

PLHIV, at any CD4 count, are more susceptible to TB infection than HIV-uninfected people. TPT is an effective intervention for reducing the incidence of TB in PLHIV.

Eligibility

All adult PLHIV, irrespective of CD4 count and ART status.

Exclusions

- suspected or confirmed TB
- liver disease
- previous MDR- or XDR-TB
- painful peripheral neuropathy
- alcohol use disorder

Note:

- Exclude TB before initiating TPT by screening for the following:
  - cough (any duration)
  - cever
  - weight loss
  - night sweats

- Do not start TPT if any of the above symptoms are present. These patients require further investigation for active TB.
- Start TPT together with ARVs.

LoE:IIb[31]

- TPT, e.g.:
- Isoniazid, oral, 300 mg daily for 12 months.

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 used.
  - 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*].
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

ADD

LoE:IIb[32]

- 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.
  - Follow patients up monthly for the first 3 months.

NOTE: For pregnant women:

LoE:IIb[33]

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

11.3 OPPORTUNISTIC INFECTIONS, TREATMENT IN ADULTS

11.3.1 APHTHOUS ULCERS IN HIV INFECTION

K12.0 + (B24)

DESCRIPTION

Painful ulcers in the mouth, except the gums, hard palate and dorsum of the tongue.
Minor ulcers (< 1 cm diameter) usually heal within 2 weeks.
Major ulcers (> 1 cm diameter) are very painful, often very deep, and persistant. Major ulcers generally resolve rapidly on ART.
Herpes simplex, histoplasmosis and mycobacteria may also present with major mucosal ulcers.

MEDICINE TREATMENT

Minor aphthous ulcers:

- Tetracaine 0.5 %, oral, topical, applied every 6 hours.
  - Apply a thin layer on the affected areas only.

REFERRAL

Major aphthous ulcers for further diagnostic evaluation.

11.3.2 CANDIDIASIS, ORAL

B20.4

See Section 1.2: Candidiasis, oral (thrush).

- Commence ART.

11.3.3 CANDIDIASIS, OESOPHAGEAL

B20.4

DESCRIPTION

Infection of the oesophagus with candida, a fungus that causes oral thrush.

Patients with oral thrush who also have pain or difficulty on swallowing may have oesophageal candidiasis. See Section 1.2: Candidiasis, oral (thrush).

GENERAL MEASURES

Maintain hydration.

MEDICINE TREATMENT

- Fluconazole, oral, 200 mg daily for 14 days. *LoE:IIIb*[34]

REFERRAL

- Inability to swallow.
- Frequent relapses.
- Poor response to fluconazole.

11.3.4 CRYPTOCOCCOSIS

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

DESCRIPTION

A life-threatening fungal infection caused by the fungus *Cryptococcus*. The fungi remain inactive unless a person's immune system is weakened, such as in transplant recipients or persons with untreated HIV.

INVESTIGATIONS

- All ART-naïve adults and adolescents with CD4 < 200 cells/mm^3 should have a serum cryptococcal antigen (CrAg) test done (unless confirmed 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 cell count is between 100 and 199, a separate sample should be sent for CrAg testing.
- All patients with a positive serum CrAg test should have a lumbar puncture (LP) to exclude cryptococcal meningitis. The CSF is tested for cryptococcal meningitis by CSF CrAg.

LoE:IIa[35]

MEDICINE TREATMENT

If CSF CrAg positive:

Refer for liposomal amphotericin B, IV (induction phase) and monitoring of intracranial pressure symptoms - See Adult Hospital STGs and EML, Section 10.2.4: Cryptococcosis. Patients may be down referred for consolidation and maintenance phase therapy; see below.

If there is any delay in performing LP, start oral fluconazole therapy:

- Adults: Fluconazole, oral, 1200 mg immediately. *LoE:IVb*[36]
- Children: 12 mg/kg to a maximum dose of 800 mg immediately

No symptoms present and CSF CrAg negative (LP):

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days. *LoE:IIIb*[37]

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.**

LoE:IIIb[38]

- Commence ART: See Section 11.1: Antiretroviral therapy.
  - Cryptococcal meningitis: 4–6 weeks after starting antifungal therapy.
  - Asymptomatic cryptococcosis: No need to delay ART. ART can be started immediately.

LoE:IIIb[39]

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*[40]
- 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. Even for higher doses, the benefits will likely outweigh the risks, though this can be discussed with a specialist. *LoE:IVb*[41]

REFERRAL

- If LP unavailable: Refer all serum CrAg positive patients to a facility where LP is available.
- If LP available:
  - Refer all patients that are CSF CrAg positive (cryptococcal meningitis).
  - Refer all symptomatic patients that are CSF CrAg negative (non-meningeal cryptococcosis).
- All patients with complications.

11.3.5 DIARRHOEA, HIV-ASSOCIATED

B20.8 + (A07.2-3)

DESCRIPTION

Diarrhoea that persists for > 2 weeks.
Often associated with wasting.
Diarrhoea persisting for 4 weeks is a WHO stage 3 condition (if there is weight loss or fever it is stage 4).
Send stool sample to look for ova, cysts and parasites in all cases.
Note: A negative stool specimen does not exclude *Cryptosporidium*. If *Cryptosporidium* infection is suspected, request specific laboratory testing for the parasite.

MEDICINE TREATMENT

If stool is negative for parasites or shows *Cryptosporidium*:

- Loperamide, oral, 2 mg as required.
  - Maximum 8 mg daily.
- Commence ART.

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 single strength (80/400 mg) tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 single strength (80/400 mg tablets) daily until CD4 > 200 cells/mm^3 on ART.
- Commence ART.

REFERRAL

Stool contains blood or mucus.

11.3.6 ECZEMA, SEBORRHOEIC

See Section 5.8.3: Dermatitis, seborrhoeic.

11.3.7 FUNGAL NAIL INFECTIONS

B20.5 + B35.1

This is common in PLHIV and can involve multiple nails. Treatment is not generally recommended because it is mostly of only cosmetic importance and therefore the risk of systemic therapy is not warranted. It generally resolves when patient is on ART.

11.3.8 FUNGAL SKIN INFECTIONS

B20.5

See Section 5.5: Fungal infections of the skin.

11.3.9 GINGIVITIS, ACUTE NECROTISING ULCERATIVE

See Section 1.3.3: Necrotising periodontitis.

11.3.10 HERPES SIMPLEX ULCERS, CHRONIC

B20.3 + (B00.1-2)

DESCRIPTION

Painful ulcers due to herpes simplex virus, involving the skin around the anogenital area or in and around the mouth and nostrils in patients with advanced HIV infection. Ulcers persist for weeks and may be several centimetres in diameter.

GENERAL MEASURES

Keep affected areas clean with soap and water or diluted antiseptic solution.

MEDICINE TREATMENT

- Antiviral (active against herpes simplex) e.g.: *LoE: IIIb*[42]
- Aciclovir, oral, 400 mg 8 hourly for 7 days.
- Commence ART.

Pain:

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

REFERRAL

- No response to therapy.
- Frequent recurrences.

11.3.11 HERPES ZOSTER (SHINGLES)

B20.3 + (B02.0-3/B02.7-9)

DESCRIPTION

Painful vesicular rash in a dermatomal distribution, usually presenting as a band on one side of the body, due to recrudescence of the varicella-zoster virus that causes chickenpox. The surrounding skin is inflamed and the vesicles often contain cloudy fluid. Secondary bacterial infection is very uncommon.
The elderly and PLHIV are most affected.
Severe pain can occur after shingles has healed (post-herpetic neuralgia).
Shingles is less infectious than varicella (chickenpox) and isolation is not warranted.

MEDICINE TREATMENT

If fresh vesicles are present:

- Antiviral (active against herpes zoster) e.g.:
- Aciclovir, oral, 800 mg five times daily for 7 days (4 hourly missing the middle of the night dose). *LoE:IIa*[43]

If secondary infection is present:

ADD

- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

Pain:

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

If inadequate pain relief:

ADD

- Tramadol, oral, 50 mg 6 hourly (Doctor prescribed).

For prolonged pain occurring after shingles has healed (post-herpetic neuralgia), or if pain not responding to paracetamol and tramadol:

- Amitriptyline, oral, 25 mg at night.
  - Increase dose to 50 mg after two weeks if needed.
  - Increase to 75 mg after a further two weeks if needed.

REFERRAL

- Involvement of the eye.
- Disseminated disease (many vesicles extending beyond the main area).
- Features of meningitis (headache and neck stiffness).
- Severe post-herpetic neuralgia not responding to amitriptyline.

11.3.12 PAPULAR PRURITIC ERUPTION

L29.8

DESCRIPTION

Itchy inflamed papules at different stages of evolution. Healed lesions are often hyperpigmented. The itch is difficult to manage. May flare after starting ART, but generally improves as the CD4 count increases. It is essential to exclude scabies.

GENERAL MEASURES

Minimise exposure to insect bites, e.g. by regularly dipping pets.

MEDICINE TREATMENT

- Cetirizine, oral, 10 mg daily.
- Hydrocortisone 1%, topical cream, applied twice daily for 7 days.
  - Apply sparingly to the face.

11.3.13 PNEUMONIA, BACTERIAL

See Section 17.3: Respiratory infections.

11.3.14 PNEUMONIA, PNEUMOCYSTIS

See Section 17.3.4.2.4: Pneumocystis pneumonia.

11.3.15 TOXOPLASMOSIS

B58 + (B20.8)

DESCRIPTION

Initial diagnosis should only be made at hospital level.

MEDICINE TREATMENT

- Cotrimoxazole, oral, 320/1600 mg 12 hourly for 4 weeks.
  - Then 160/800 mg 12 hourly for 12 weeks.

Secondary prophylaxis

- Cotrimoxazole, oral 160/800 mg daily.
  - Continue until the CD4 count has risen to >200 cells/mm^3 on ART.
- Commence ART.

REFERRAL

Patients with suspected toxoplasmosis infection requiring further investigation to confirm diagnosis.

11.3.16 TUBERCULOSIS (TB)

See Section 17.4: Pulmonary tuberculosis (TB).

11.4 HIV AND KIDNEY DISEASE

N04.9/N05.9/N17.9 + (B24)

DESCRIPTION

Various forms of kidney disorders are described among PLHIV.
Early detection of HIV kidney disease may be beneficial in an attempt to protect the kidney from further disease progression and for adjusting the dose of relevant medicines (See Table 11.3: Dosing and important adverse effects associated with ART).
Screen all patients for renal disease at time of HIV diagnosis.
Patients at high risk or susceptible for HIV renal disease include:

- CD4 count < 200 cells/mm^3.
- History of nephrotoxic medications.
- Comorbidity such as diabetes mellitus, hypertension, or hepatitis C virus co-infection.

Screening for renal disease in HIV

- Tests should include:
  - Urine dipstix for haematuria and proteinuria.
  - Serum creatinine and eGFR.
- If there is no evidence of kidney disease at the initial evaluation, repeat screening annually.

- Monitor creatinine/eGFR on initiation and at months 3, 6, 12 and then 12 monthly for patients receiving tenofovir.

REFERRAL

- Patients with persistent significant proteinuria (1+ or more).
- Unexplained haematuria on 2 consecutive visits
- Estimated eGFR < 60 mL/min.

HIV INFECTION IN CHILDREN (<10 YEARS OLD)

DESCRIPTION

HIV is a retrovirus affecting immune cells, especially CD4 T-lymphocytes. In advanced HIV disease the body loses its ability to fight infections and this is characterised by organ damage, opportunistic infections, malignancies and very low CD4 counts.

In infants and children, most infection is transmitted from mother to child. In adolescents and adults sexual spread is the usual cause.

Infants born of HIV-infected mothers may be:

- HIV-infected,
- HIV-exposed uninfected, or
- HIV-exposed, unknown infection status (at risk of becoming HIV-infected).

For the purpose of the ART guidelines:

- Children <10 years of age: follow the paediatric antiretroviral therapy (ART) guidelines.
- Adolescents (10–19 years of age): follow the adult ART guidelines. *LoE:IIIb*[44]

DIAGNOSIS IN CHILDREN

Testing must be done with counselling of parent/legal guardian/primary caregiver and, where appropriate, the child. The appropriate consent/assent should be obtained.

HIV TESTING IN CHILDREN

Age	Test	Note
HIV-exposed		
Birth	HIV PCR	If the HIV PCR is positive at any time, confirm with a second HIV PCR
10 weeks	HIV PCR	
6 months	HIV PCR	
6 weeks post-cessation of breastfeeding	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Universal screening		
18 months	HIV rapid/ELISA	Perform on all children, unless known to be HIV infected
HIV infected confirmatory test (any child with positive HIV test)		
<24 months	HIV PCR	Between 18 and 24 months, the initial test will be HIV rapid/ELISA, but is confirmed with an HIV PCR
≥24 month	HIV rapid/ELISA	Perform the second test on a different blood specimen with a test kit from a different manufacturer

Possible/suspected symptomatic HIV infection		
Any age if IMCI classification of: • Pneumonia • Ear discharge (ever) • Persistent diarrhoea in past 3 months • Not growing well, moderate acute malnutrition (MAM) or severe acute malnutrition (SAM). • ≥ 2 enlarged glands of: neck, axilla or groin. • Oral thrush. • Parotid enlargement	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Other situations		
• Parents request testing • Breastfed infant of a newly diagnosed HIV infected mother • Suspicion of sexual assault • Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later). • Children considered for adoption or fostering.	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	

If an HIV PCR test is indeterminate or discordant, refer to the National Department of Health Guidelines for prevention of Mother to Child Transmission of Communicable Infections, 2023.

Table 11.7 HIV testing in children

WHO clinical staging of HIV and AIDS for infants and children

https://iris.who.int/bitstream/handle/10665/69058/WHO_HIV_2005.02.pdf

Adapted WHO clinical staging of HIV and AIDS for infants and children For persons ≤15 years of age with confirmed laboratory evidence of HIV infection
Clinical Stage 1 • asymptomatic • persistent generalised lymphadenopathy (PGL)
Clinical Stage 2

- unexplained persistent weight loss
- hepatosplenomegaly
- papular pruritic eruptions
- extensive human papilloma virus infection
- extensive molluscum contagiosum
- fungal nail infections
- recurrent oral ulcerations
- lineal gingival erythema (LGE)
- unexplained persistent parotid enlargement
- herpes zoster
- recurrent or chronic RTIs, i.e.
- otitis media
- otorrhoea
- sinusitis

Clinical Stage 3

- moderate unexplained malnutrition (not adequately responding to standard therapy)
- unexplained persistent diarrhoea (14 days or more)
- unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month)
- persistent oral candidiasis (after first 6-8 weeks of life)
- oral hairy leukoplakia
- acute necrotising ulcerative gingivitis/periodontitis
- lymph node TB
- pulmonary TB
- severe recurrent bacterial pneumonia
- chronic HIV-associated lung disease including bronchiectasis
- symptomatic lymphoid interstitial pneumonitis (LIP)
- unexplained anaemia (< 8 g/dL), and or neutropaenia (< 500/mm^3) and/or thrombocytopaenia (< 50 000/mm^3) for more than one month

Clinical Stage 4

- unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy
- pneumocystis pneumonia
- recurrent severe presumed bacterial infections, e.g.
  - empyema
  - bone or joint infection
  - pyomyositis
  - meningitis
- *but* excluding pneumonia
- chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- extrapulmonary TB
- Kaposi's sarcoma
- oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- CNS toxoplasmosis (outside the neonatal period)
- HIV encephalopathy
- CMV infection (CMV retinitis or infections of organs other than liver, spleen or lymph nodes; onset at age one month of more)
- extrapulmonary cryptococcosis including meningitis
- any disseminated endemic mycosis, e.g.
- extrapulmonary histoplasmosis
- coccidiomycosis

- chronic cryptosporidiosis
- chronic isosporiasis
- disseminated non-tuberculous mycobacteria infection
- HIV associated recto-vaginal fistula
- cerebral or B cell non-Hodgkin lymphoma
- progressive multifocal leukoencephalopathy (PML)
- HIV-associated cardiomyopathy or HIV-associated nephropathy

Table 11.8: WHO clinical staging for infants and children

11.5 THE HIV-EXPOSED INFANT

Z20.6

DESCRIPTION

An HIV-exposed infant or child is one born to a mother living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding.

Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving post-exposure prophylaxis to the infant, a strategy now known as Vertical Transmission Prevention (VTP; formerly termed Prevention of Mother to Child Transmission).

The risk of transmission from breast milk is low when the mother is virally suppressed. Ensure maternal VL monitoring is done every 6 months while breastfeeding and offer enhanced adherence counselling to ensure viral suppression is achieved and maintained.

When to test HIV-exposed children

- Birth (HIV PCR).
- For recommendations on when to perform additional tests, refer to the guidance on "HIV Testing in Children" (See section above: HIV infection in children).

Feeding advice

- It is strongly recommended that exclusive breastfeeding be initiated within 1 hour of birth and continued for the first 6 months of life, after which the child's nutritional requirements will require the introduction of complementary foods in addition to breastfeeding.
- Women living with HIV should be fully supported for ART adherence during the breastfeeding period and thereafter.
- Women with a VL > 50 copies/mL on TLD1 should continue breastfeeding while every effort is made to regain viral suppression. Their infants should receive high-risk prophylaxis during breastfeeding.
- The following may be indications to discontinue breastfeeding:
  - » Infants of mothers who are failing TLD2.
  - » Infants of mothers who are failing third-line PI-based treatment.

- Discuss appropriate feeding practices with the mother regarding the risks and benefits of continuing breastfeeding vs replacement feeding.
- The use of flash pasteurisation or 'Pretoria' pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved. For instance, it can be used as an interim measure during maternal mastitis.

  NOTE: For the above,
  - » TLD1 = TLD as a first line ART regimen.
  - » TLD2 = TLD in patient who has failed a previous ART regimen.

MEDICINE TREATMENT

Mother

The VTP plan starts with initiation of ART in the mother (either pre or post conception). See Section 6.8: HIV in pregnancy.

Infant

Thereafter, the HIV-exposed infant may be classified into one of the following categories which determines the appropriate infant prophylaxis regimen:

- Low risk.
- High risk.
- Unknown risk, e.g. abandoned infant (manage as high risk). *LoE:IIa*[45]

Maternal VL	Risk profile	Prophylaxis	Comment
Maternal delivery VL as yet unknown at discharge from labour ward (results pending).	High-risk (until maternal delivery VL results become available)	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	All HIV-exposed infants will be considered high-risk until the final risk profile can be determined by the maternal delivery VL. If the maternal delivery VL result is not available at discharge from labour ward, review result at the 3– 6 day postnatal visit and reclassify the infant accordingly. Dispense a full 6 weeks supply of dual prophylaxis. Ask the mother to return with all medication at the

Maternal VL	Risk profile	Prophylaxis	Comment
			3–6 day postnatal visit
Maternal delivery VL ≥ 50 copies/mL in a breastfeeding mother	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency. Stop infant NVP only after confirmation of maternal VL being < 50 copies/mL, or until 4 weeks after cessation of all breastfeeding
Maternal delivery VL ≥ 50 copies/mL in a mother who is exclusively formula feeding her infant from birth.*	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for 6 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency
Maternal delivery VL < 50 copies/mL regardless of feeding choice.	Re-classify as low risk.	Change to low risk prophylaxis: NVP at birth and then daily for 6 weeks	Affirm and encourage good adherence. Repeat maternal VL 6-monthly during breastfeeding.

*Non-breastfeeding mother diagnosed HIV-positive > 72 hours after delivery: Do not start the infant on prophylaxis. Start maternal ART. Perform an HIV PCR test on the infant and, if positive, initiate ART. If negative, continue to monitor HIV risk and perform HIV testing as above.

Table 11.9: Risk categories for HIV-exposed infants

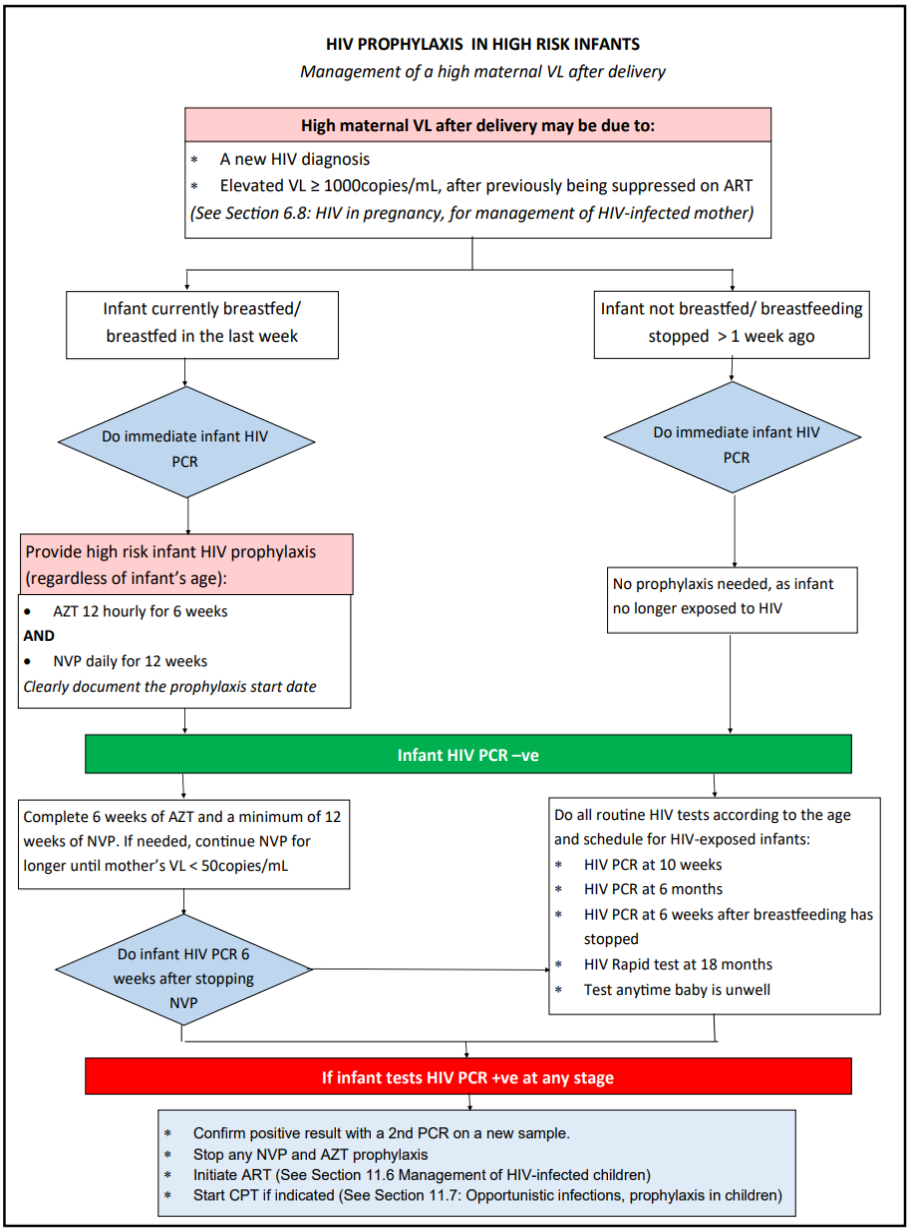


Figure 11.4: HIV prophylaxis in HIV-exposed infant at high risk after delivery *LoE:IIIb*[46]

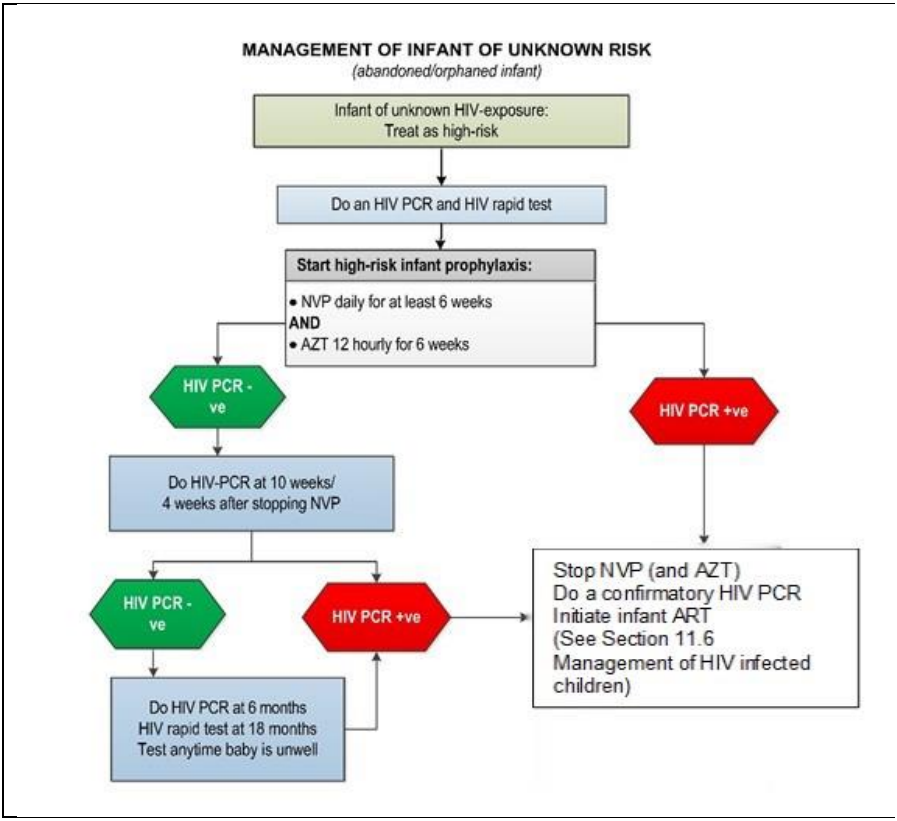


Figure 11.5: Management of HIV-exposed infant of unknown risk

LoE:IIIb[47]

Non-breastfeeding mother diagnosed HIV positive > 72 hours after delivery:
Do not start NVP. Perform an HIV PCR on infant and if positive initiate ART.

Infant VTP dosages:
Daily prophylaxis for 6 or 12 weeks administered to infants, as indicated above:

- Give 1st dose as soon as possible after birth.
- If baby vomits: Repeat dose once only.
- If infant HIV PCR is positive at any time, stop prophylactic ARV, confirm with 2nd PCR and initiate/refer for ART, while awaiting 2nd PCR result.
- Continue normal breastfeeding .

Nevirapine (NVP) and Zidovudine (AZT) doses for infant on VTP:

LoE:IIb[48]

Newborns and infants:

- Nevirapine, oral, 4 mg/kg daily.
- Zidovudine, oral, 4mg/kg/dose 12 hourly.

	Birth–6 weeks			6 weeks – 6 months	6 – 9 months	9 – 24 months
	1.5-1.9 kg	2.0– 2.49 kg	≥ 2.5 kg			
NVP (Daily)	0.35 mL (0.35 mg) for 2 weeks THEN 0.6 mL (0.6 mg)	1 mL (10 mg) daily	1.5 mL (15 mg) daily	2 mL (20 mg) daily	3 mL (30 mg) daily	4 mL (40 mg) daily
AZT (Twice daily)	2mg/kg for 2 weeks THEN 3mg/kg for 2 weeks THEN 4mg/kg	1 mL (10 mg) twice daily	1.5 mL (15 mg) twice daily	6 mL (60 mg) twice daily	Children > 6 months of age requiring AZT prophylaxis should use treatment doses.	

Table 11.10: Dose bands for NVP and AZT in VTP.

REFERRAL
Mother declines infant ARV prophylaxis.

11.6 MANAGEMENT OF HIV-INFECTED CHILDREN (<10 YEARS)
B24

DESCRIPTION
HIV-infected child: An infant/child in whom HIV infection has been confirmed with two age-appropriate tests. See Section 11.5: The HIV-exposed infant.

GENERAL AND SUPPORTIVE MEASURES
- Identify a caregiver who can supervise the child's treatment.
- Link the HIV interventions to the regular well infant visits/nutritional care. Ensure the road to health booklet is correctly completed and used to reflect and guide care.
- Counselling is a vital part of the successful care of children with HIV infection and their families. Specific matters requiring attention are:
  - The implications of the disease to the family.
  - Implications of treatment and understanding of the condition and its care.
  - The disclosure process within the family and extended family should be encouraged. Besides the caregiver, help from the family is often useful.
- Disclosure to the child as appropriate to age and maturity, with the parents' support.
  - Find out what the child understands of their illness and what they would like to know.
  - Disclosure should be child-led in terms of information required, language used and educational/emotional readiness.
  - Anticipate the effects of disclosure on the child, family and other contacts such as friends and school colleagues.

- Ensure that in disclosure, the child is constantly reassured of the parents'/caregivers' love.

Treatment of mothers, caregivers and other family members:

- Always ask about the caregiver's health, and the health of other family members.
- Ensure that mothers and other family members have timeous access to medical care including ART.
- Encourage breastfeeding in all mothers with HIV-infected children, with introduction of complementary foods from 6 months of age.
- At every visit ask about TB contacts and symptoms in children and their caregivers.

STANDARDISED NATIONAL MONITORING FOR INFANTS & CHILDREN WITH HIV

AT INITIAL DIAGNOSIS OF HIV	PURPOSE
Verify HIV status.	To ensure that national testing algorithm has been followed.
Document weight, height, head circumference (< 2 years of age) and development.	To monitor growth and development.
Screen for TB symptoms.	To identify TB and HIV co-infection
Do CD4 count.	Determine eligibility for cotrimoxazole prophylaxis (CPT): < 1 year: CPT irrespective of CD4 count. 1–5 years: CPT if CD4 count < 25% or WHO Stage 3 and 4. > 5 Years: CPT if CD4 count < 200 cells/mm3 or WHO Stage 3 and 4.
Hb or FBC if available.	To detect anaemia or neutropaenia.
AT INITIATION OF ART (BASELINE)	**PURPOSE**
Hb or FBC.	If < 8 g/dL: Manage appropriately.
CD4 count (if not performed in last 6 months).	Baseline assessment.
ALT (If jaundiced or on TB treatment).	To detect liver dysfunction.
ON ART	**PURPOSE**
Height, weight, head circumference (if child < 2 years) and development.	To monitor growth and development. Adjust dosing at each visit according to weight gain.
Clinical assessment including medicine-related adverse events.	To monitor response to ART and detect adverse effects.
CD4: At 1 year on ART, and then every 6 months until meets criteria to stop cotrimoxazole. Thereafter stop CD4 count monitoring if patient remains virologically supressed. If not virologically supressed monitor CD4 count every 6 months.	To monitor response to ART. Stop cotrimoxazole prophylaxis if indicated.
Viral load: At month 3 on ART, after 12 months on ART, then every 12 months if virologically suppressed.	To monitor viral response to ART. To identify treatment failure and adherence problems.

More frequent monitoring (3–6 monthly) recommended in patients with treatment failure.	For management of an elevated VL, see algorithm, below: Monitoring and management of viral loads.
Hb or FBC at months 3 and 6 if on AZT. Thereafter, repeat if clinically indicated	To identify AZT-related anaemia.
If on PI-based regimen: Cholesterol + triglyceride at month 3. If above acceptable range, do fasting cholesterol and TGs; and if still above acceptable range consult with doctor/specialist.	To monitor for PI-related metabolic side effects.

Table 11.11: Monitoring for infants and children with HIV on ART *LoE:IIIb*[49]

MEDICINE TREATMENT

Prophylaxis for opportunistic infections

See Section 11.7 Opportunistic infections, prophylaxis in children

Immunisation, deworming and vitamin A programme

- Continue deworming and vitamin A programme as in the HIV-uninfected child.
- Continue immunisation as per the SA-EPI (See Section 13.3). If signs of HIV infection present, defer the BCG vaccination

Nutritional support

Treat specific nutritional deficiencies appropriately.

Antiretroviral therapy

Initiation of ART in well infants shown to be PCR-positive should be carried out at PHC level.

The preparation of the child and family to start ART is critical to the success of the treatment. Failure to achieve adherence and understanding may lead to resistance and adversely affect the prognosis of the child.

Eligibility for ART

Clinical criteria

- Confirmation of diagnosis of HIV infection, irrespective of CD4 count/percentage or WHO clinical stage. *LoE:IIIb*[50]

AND

- No indications for deferral (e.g. major organ dysfunction). If medical contraindications are present, refer to hospital for rapid review and planning.

Social issues that must be addressed to ensure successful treatment

These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.

- Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social

circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.

- Adherence:
  - High levels of adherence are required for adequate virological response and prevention of viral resistance. This can be achieved with regular education and support.
  - All efforts to encourage this level of adherence should be made.
  - Viral load measurements are useful for monitoring adherence.
  - Sensitive, age-appropriate disclosure facilitates adherence.
- Mother and other family members should be assessed and treated.

Counselling before ART is initiated

The health care worker should ensure the caregiver/s understanding of HIV, ART and the importance of virological suppression and train caregivers on practical skills to adhere to ART.

ART regimens

- Treatment regimens are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.
- Adjust the dosage of ART according to weight during follow up visits. Assess weight gain and need for adjustment at each visit.
- Do not change regimens or move to an alternative regimen, without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Address adherence problems thoroughly before switching to an alternative regimen.
- Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ART.

First-line ART regimens for infants and children:

ALD1: Clients on a DTG-containing regimen, having never failed a previous regimen (old 'first-line' terminology).

ALD2: Clients on a DTG-containing regimen, who have failed a previous regimen (old 'second- line' terminology).

ALD: abacavir, lamivudine, dolutegravir.

General ART comments

- Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.
- Fixed-dose combinations are preferred to single agents.
- If available, use once daily dose regimens.

Side effects:

In patients being considered for an AZT-containing regimen, monitor for anaemia prior to initiation of ART.

A small proportion of patients initiated on ABC are at risk of abacavir hypersensitivity reaction, which presents with fever, rash and gastrointestinal disturbances. If this reaction is suspected, consult an expert.

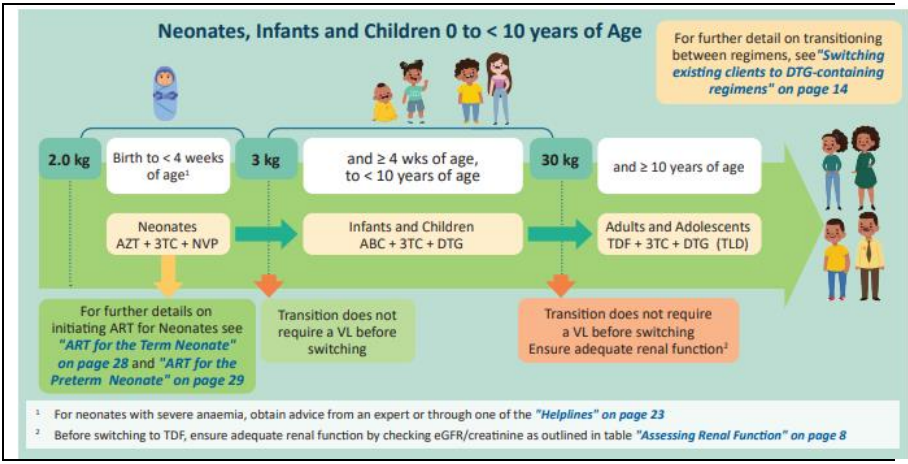


Figure 11.6: First-line paediatric ART-switching algorithm for neonates/infants/children (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

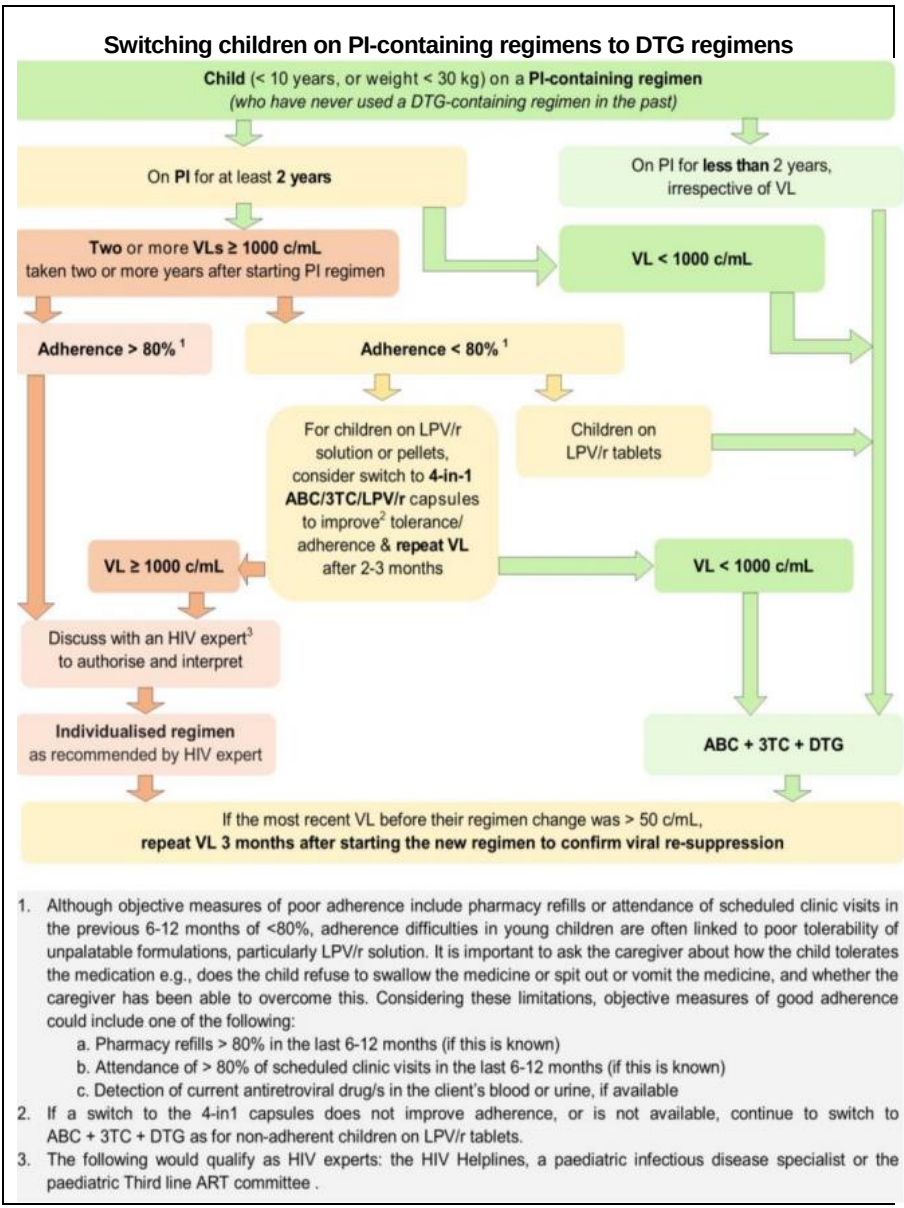
LoE:IIIb[51]

Transition from ABC/3TC/LPV/r to DTG based regimens

- Children < 10 years or weight < 30 kg
  - On PI based regimen for < 2 years: switch to DTG based regimen (no VL required)
  - On PI based regimen for ≥ 2 years: review VL results, manage as per algorithm in figure 11.7.

For patients not eligible for transition to DTG based regimen

- Consider switching to ABC/3TC/LPV/r 4-in-1 formulation and repeating HIV VL in 3 months. If HIV VL < 1000 copies/mL, change to ABC/3TC/DTG and if > 1000 copies/mL, perform an HIV drug resistance test (DR).
- Perform an HIV DR if 4-in-1 formulation not available.
- If NRTI mutations on the HIV DR show:
  - No mutations or only M184V – switch to ABC/3TC/DTG.
  - M184V + other mutations – discuss with an experienced practitioner in child ARV medicine.



1. Although objective measures of poor adherence include pharmacy refills or attendance of scheduled clinic visits in the previous 6-12 months of <80%, adherence difficulties in young children are often linked to poor tolerability of unpalatable formulations, particularly LPV/r solution. It is important to ask the caregiver about how the child tolerates the medication e.g., does the child refuse to swallow the medicine or spit out or vomit the medicine, and whether the caregiver has been able to overcome this. Considering these limitations, objective measures of good adherence could include one of the following:
    a. Pharmacy refills > 80% in the last 6-12 months (if this is known)
    b. Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known)
    c. Detection of current antiretroviral drug/s in the client's blood or urine, if available
2. If a switch to the 4-in1 capsules does not improve adherence, or is not available, continue to switch to ABC + 3TC + DTG as for non-adherent children on LPV/r tablets.
3. The following would qualify as HIV experts: the HIV Helplines, a paediatric infectious disease specialist or the paediatric Third line ART committee .

Figure 11.7: Switching children on PI-containing regimens to DTG regimens (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

Treatment failure

The HIV viral load is the most sensitive method to detect failure of response to ART.

Virological failure can be defined as a measurable viral load despite optimal adherence and dosage over 4 months. Treatment failure is primarily defined by viral loads, as waiting for clinical or immunological failure increases the chances of increasing viral resistance to other available antiretroviral agents.

Poor adherence is the most common cause of treatment failure. Adherence issues should be assessed and then implement strategies to improve adherence.

*For guidance on the step-up adherence package, refer to the National adherence guidelines. https://www.nacosa.org.za/wp-content/uploads/2016/11/Integrated-Adherence-Guidelines-NDOH.pdf

Third-line (patients failing ALD2)

Discuss with expert

» Application forms for third-line antiretroviral therapy (patients failing ALD2) can be accessed at the following link: http://www.sahivsoc.org/Files/Application%20for%20Third%20Line%20Antiretrovirals_2017.pdf

» Important information to assist in applying for third-line antiretrovirals can be found at www.righttocare.org/what-we-do/third-line-art/

Applications can be emailed to TLART@health.gov.za

LoE:IIIb[52]

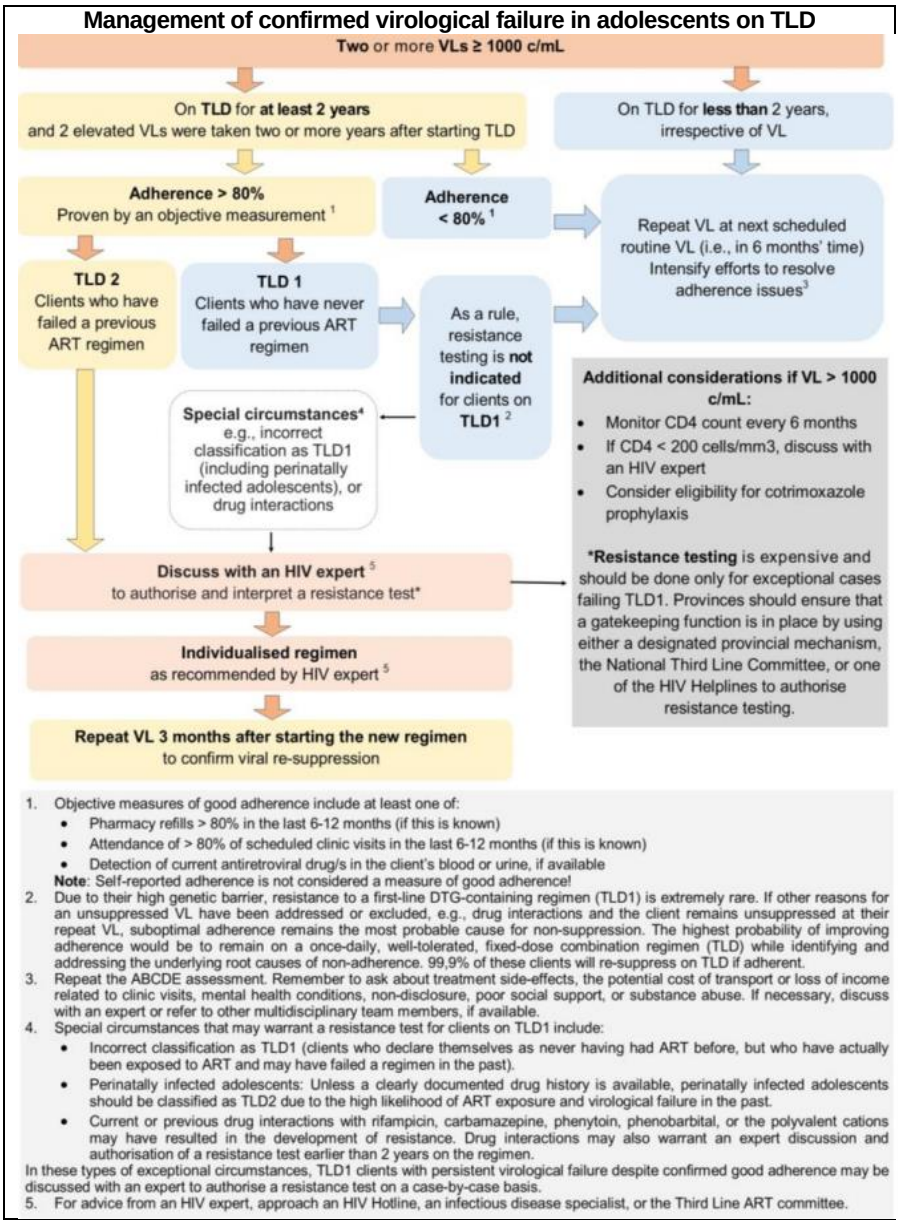
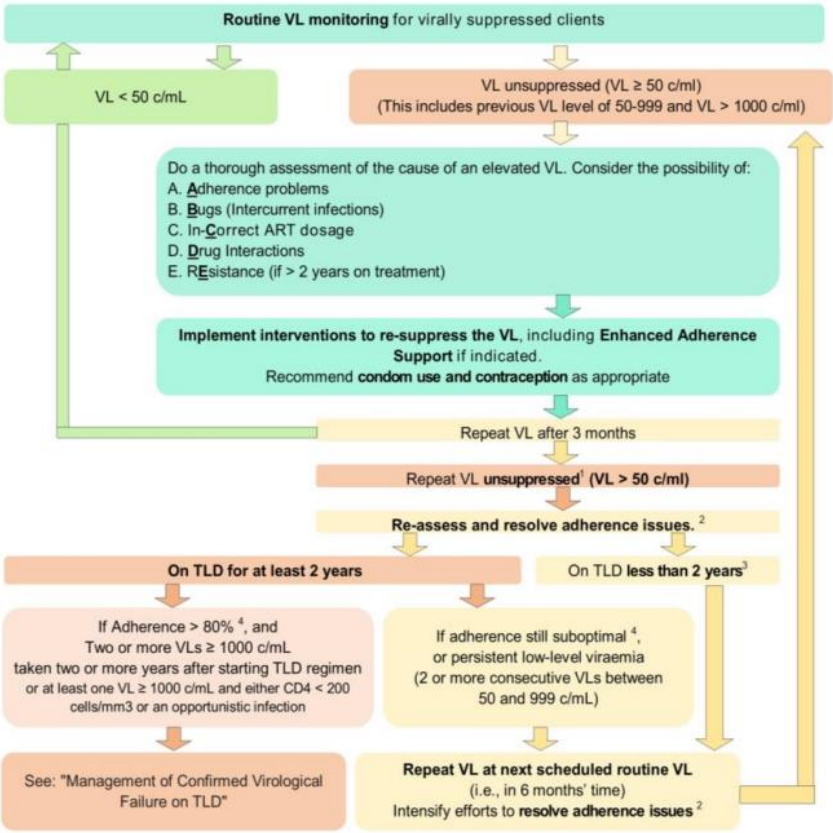


Figure 11.8: Management of confirmed virological failure in adolescents on TLD (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).TLD1 = TLD as a first line ART regimen and TLD2 = TLD in patient who has failed a previous ART regimen

Viral Load Monitoring for clients on TLD



1. Due to their high genetic barrier, resistance to a first-line DTG-containing (TLD1) regimen is extremely rare. If other reasons for an unsuppressed VL have been addressed or excluded, e.g., drug interactions, and the client remains unsuppressed at their repeat VL, suboptimal adherence remains the most probable cause for non-suppression. The highest probability of improving adherence would be to remain on a once-daily, well-tolerated, fixed-dose combination regimen (TLD) while identifying and addressing the underlying root causes of non-adherence. 99,9% of these clients will re-suppress on TLD if adherent!
2. Repeat ABCDE assessment as outlined on "ABCDE assessment of an Elevated Viral Load" on page 20. Remember to ask about treatment side-effects, the potential cost of transport or loss of income related to clinic visits, non-disclosure, gender-based violence (GBV), and current or prior drug interactions. Current or previous drug interactions with rifampicin, carbamazepine, phenytoin, phenobarbital, or the polyvalent cations may have resulted in the development of resistance.
3. Drug interactions may also warrant an expert discussion and authorisation of a resistance test earlier than 2 years on the regimen. If necessary, discuss with an expert
4. Objective measures of good adherence include at least one of:
   a. Pharmacy refills > 80% in the last 6-12 months (if this is known)
   b. Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known)
   c. Detection of current antiretroviral drug/s in the client's blood or urine, if available

Note: Self-reported adherence is not considered a measure of good adherence.

Figure 11.9: Viral load monitoring for clients on TLD (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

ART dosing tables for infants and children

	Abacavir (ABC)	Lamivudine (3TC)	Abacavir + Lamivudine (ABC + 3TC)	Dolutegravir (DTG)	Dolutegravir when on rifampicin
Target dose	8 mg/kg **TWICE daily** **OR** If ≥ 10 kg: 16 mg/kg **ONCE daily**	4 mg/kg **TWICE daily** **OR** If ≥ 10 kg: 8 mg/kg **ONCE daily**	As for individual medications **ONCE daily**	By weight band **ONCE daily**	By weight band **TWICE daily**
Available formulations	Sol. 20 mg/mL Tabs 60 mg (scored, dispersible), 300 mg (not scored)	Sol. 10 mg/mL, Tabs 150 mg (scored)	Dispersible tablets (FDC): ABC/3TC 120/60 mg Tablet FDC: ABC/3TC 600/300 mg ABC/3TC/DTG 600/300/50 mg	Dispersible tabs (DT) 10 mg, film coated (FC) tabs 50 mg, FDC: TLD 300/300/50 mg **OR** ABC/3TC/DTG 600/300/50 mg **DT AND FC TABLETS ARE NOT BIOEQUIVALENT**	Dispersible tabs (DT) 10 mg, film coated (FC) tabs 50 mg, FDC: TLD 300/300/50 mg **OR** ABC/3TC/DTG 600/300/50 mg **DT AND FC TABLETS ARE NOT BIOEQUIVALENT**
Weight (kg)	Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg.				
3–5.9	3 mL 12 hourly **OR** 1 x 60 mg tab 12 hourly	3 mL 12 hourly	1 x 120/60 mg tab daily	0.5 x 10 mg DT daily	0.5 x 10 mg DT 12 hourly
6-9.9	4 mL 12 hourly **OR** 1.5 x 60 mg tabs 12 hourly	4 mL 12 hourly	1.5 x 120/60 mg tabs daily	1.5 x 10 mg DT daily	1.5 x 10 mg DT 12 hourly
10–13.9	4 x 60 mg tabs daily **OR** 12 mL daily	12 mL daily	2 x 120/60 mg tabs daily	2 x 10 mg DT daily	2 x 10 mg DT 12 hourly

Table 11.12: ART dosing tables for infants and children (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

<table>
<tr><th></th><th>Abacavir (ABC)</th><th>Lamivudine (3TC)</th><th>Abacavir + Lamivudine (ABC + 3TC)</th><th>Dolutegravir (DTG)</th><th>Dolutegravir when on rifampicin</th></tr>
<tr><td>14–19.9</td><td>5 x 60 mg tabs daily
OR
1 x 300 mg tab daily</td><td>1 x 150 mg tab daily</td><td>2.5 x 120/60 mg tabs daily</td><td>2.5 x 10 mg DT daily</td><td>2.5 x 10 mg DT 12 hourly</td></tr>
<tr><td>20–24.9</td><td>1 x 300 mg tab
PLUS
1 x 60 mg tab daily
OR
6 x 60 mg tabs daily</td><td rowspan="4">2 x 150 mg tabs daily</td><td rowspan="4">1 x ABC/3TC 600/300 mg tab daily
OR
ABC/3TC/DTG FDC (600/300/50 mg) if eligible, daily</td><td>3 x 10 mg DT daily
OR
1 x 50 mg FC tab daily</td><td>3 x 10 mg DT 12 hourly
OR
1 x 50 mg FC tab 12 hourly</td></tr>
<tr><td>25–29.9</td><td rowspan="3">2 x 300 mg tabs daily</td><td>1 x 50 mg tab daily
OR
FDC: ABC/3TC/DTG 600/300/50 mg tab daily</td><td>1 x 50 mg tab 12 hourly
OR
FDC: ABC/3TC/DTG 600/300/50 mg tab 12 hourly</td></tr>
<tr><td>30–39.9</td><td rowspan="2">1 x 50 mg FC tab daily
OR
FDC: TLD if eligible daily
OR
FDC: ABC/3TC/DTG if eligible daily</td><td rowspan="2">1 x 50 mg FC tab 12 hourly
OR
FDC: TLD if eligible daily + 50 mg DTG FC tab 12 hours later
OR
FDC: ABC/3TC/DTG if eligible daily + 50 mg DTG FC tab 12 hours later</td></tr>
<tr><td>≥ 40</td></tr>
</table>

Table 11.12: ART dosing tables for infants and children (continued) (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

	Lopinavir/ritonavir (LPV/RTV)	Abacavir + Lamivudine + Lopinavir/ ritonavir	Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin) *Choose one of the 2 options below as appropriate*		#Atazanavir (ATV) + ritonavir (RTV)	Efavirenz (EFV)	Zidovudine (AZT)
Target dose	300/75 mg/m^2/dose LPV/RTV **TWICE daily**	By weight band **TWICE daily**	LPV/RTV std dose + super-boosting with ritonavir (RTV) powder **TWICE daily** (≥ 0.75 x LPV dose 12 hourly)	Double-dose LPV/RTV tabs ONLY if able to swallow whole LPV/RTV tabs **TWICE daily**	By weight band **ONCE daily**	By weight band **ONCE daily**	180–240 mg/m^2/dose **TWICE daily**
Available formulations	Sol. 80/20 mg/mL Adult tabs 200/50 mg, Paed tabs 100/25 mg **TABLETS MUST BE SWALLOWED WHOLE** Pellets 40/10 mg per capsule **ONLY FOR USE IF NOT TOLERATING LPV/RTV SOLUTION. CAPSULES ARE NOT RECOMMENDED < 6 MONTHS OF AGE**	Caps 30/15/ 40/10 mg **IF PATIENT IS ON RIFAMPICIN TB TREATMENT, ADD RTV POWDER** (next column)	Oral powder 100 mg per packet	Adult tabs 200/50 mg, Paed tabs 100/25 mg	ATV caps 150, 200 mg: RTV tabs 100 mg; FDC: ATV/RTV 300/100 mg; **RTV TABLETS AND ATV/R FDC TABLETS MUST BE SWALLOWED WHOLE**	Caps/tabs 50, 200, 600 mg; FDC: TEE 300/200/600 mg; **TABLETS MUST BE SWALLOWED WHOLE**	Sol. 10 mg/mL Tabs 100 mg, 300 mg (not scored), AZT/3TC 300/150 mg
Weight (kg)	Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg.						

Table 11.12: ART dosing tables for infants and children (continued) (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

<table>
<tr><th></th><th>Lopinavir/ritonavir (LPV/RTV)</th><th>Abacavir + Lamivudine + Lopinavir/ ritonavir</th><th colspan="2">Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin)
Choose one of the 2 options below as appropriate</th><th>#Atazanavir (ATV) + ritonavir (RTV)</th><th>Efavirenz (EFV)</th><th>Zidovudine (AZT)</th></tr>
<tr><td>3–5.9</td><td>*1 mL 12 hourly
OR
2 capsules 12 hourly</td><td>2 capsules
12 hourly</td><td rowspan="2">LPV/RTV std dose
PLUS
oral RTV powder 100 mg (1 packet)
12 hourly</td><td rowspan="2">Do not use double-dose LPV/RTV tabs</td><td rowspan="2">Not recommended</td><td rowspan="2">Not recommended</td><td>6 mL 12 hourly</td></tr>
<tr><td>6–9.9</td><td>*1.5 mL 12 hourly
OR
3 capsules 12 hourly</td><td>3 capsules
12 hourly</td><td>9 mL 12 hourly</td></tr>
<tr><td>10–13.9</td><td>2 mL 12 hourly
OR
4 capsules 12 hourly
OR
2 x 100/25 mg paed tabs in morning PLUS
1 x 100/25 mg paed tab at night</td><td>4 capsules
12 hourly</td><td rowspan="2">LPV/RTV std dose
PLUS
oral RTV powder 200 mg (2 packets)
12 hourly</td><td>3 x 100/25 mg tabs
12 hourly</td><td rowspan="2">ATV 1 x 200 mg cap daily
PLUS
RTV 1 x 100 mg tab or 100 mg oral powder (1 packet) daily</td><td>1 x 200 mg cap/tab at night</td><td>12 mL
12 hourly
OR
1 x 100 mg tab 12 hourly</td></tr>
<tr><td>14–19.9</td><td>2.5 mL 12 hourly
OR
5 capsules 12 hourly
OR
2 x 100/25 mg paed tabs 12 hourly
OR
1 x 200/50 mg adult tab 12 hourly</td><td>5 capsules
12 hourly</td><td>4 x 100/25 mg paed tabs 12 hourly
OR
2 x 200/50 mg adult tabs 12 hourly</td><td>1 x 200 mg cap/tab + 2 x 50 mg caps/tabs at night</td><td>2 x 100 mg tab in morning
PLUS
1 x 100 mg tab at night
OR
15 mL 12 hourly</td></tr>
</table>

Table 11.12: ART dosing tables for infants and children (continued) (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

<table>
<tr><th></th><th>Lopinavir/ritonavir (LPV/RTV)</th><th>Abacavir + Lamivudine + Lopinavir/ ritonavir</th><th colspan="2">Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin)
Choose one of the 2 options below as appropriate</th><th>#Atazanavir (ATV) + ritonavir (RTV)</th><th>Efavirenz (EFV)</th><th>Zidovudine (AZT)</th></tr>
<tr><td>20–24.9</td><td>3 mL 12 hourly
OR
6 capsules 12 hourly
OR
2 x 100/25 mg paed tabs 12 hourly
OR
1 x 200/50 mg adult tab 12 hourly</td><td>6 capsules 12 hourly</td><td></td><td></td><td></td><td></td><td>2 x 100 mg tabs 12 hourly
OR
20 mL 12 hourly</td></tr>
<tr><td>25–29.9</td><td>3.5 mL 12 hourly
OR
7 capsules 12 hourly
OR
3 x 100/25 mg paed tabs 12 hourly
OR
1 x 200/50 mg adult tab 12 hourly PLUS 1 x 100/25 mg paed tab 12 hourly</td><td rowspan="3">Not recommended</td><td rowspan="3">LPV/RTV std dose
PLUS
oral RTV powder 300 mg (3 packets) 12 hourly</td><td>6 x 100/25 mg paed tabs 12 hourly
OR
3 x 200/50 mg adult tabs 12 hourly</td><td rowspan="3">1 x ATV/RTV 300/100 mg FDC daily
OR
ATV 2 x 150 mg caps daily
PLUS
RTV 1 x 100 mg tab or 100 mg oral powder (1 packet) daily</td><td rowspan="2">2 x 200 mg caps/tabs at night</td><td rowspan="3">1 x 300 mg tab 12 hourly
OR
1 x AZT/3TC 300/150 mg tab 12 hourly</td></tr>
<tr><td>30–39.9</td><td rowspan="2">5 mL 12 hourly
OR
10 capsules 12 hourly
OR
4 x 100/25 mg paed tabs 12 hourly</td><td>8 x 100/25 mg paed tabs 12 hourly
OR</td></tr>
<tr><td>≥ 40</td><td>2 x 200 mg caps/tabs at night
OR</td></tr>
</table>

Table 11.12: ART dosing tables for infants and children (continued) (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

	Lopinavir/ritonavir (LPV/RTV)	Abacavir + Lamivudine + Lopinavir/ ritonavir	Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin) *Choose one of the 2 options below as appropriate*		#Atazanavir (ATV) + ritonavir (RTV)	Efavirenz (EFV)	Zidovudine (AZT)
	OR 2 x 200/50 mg adult tabs 12 hourly			4 x 200/50 mg adult tabs 12 hourly		FDC: TEE if eligible, daily	

*Avoid LVP/r solution in any full-term infant < 14 days of age and any preterm infant < 42 weeks post conceptual age (corrected gestational age) or obtain expert advice.
Children weighing 25 to 29.9 kg may also be dosed with LPV/r 200/50 mg adult tabs: 2 tablets in the morning and 1 tablet at night.
#Atazanavir plus ritonavir should not be used in children/adolescents on treatment with rifampicin, obtain expert advice.
No dosage adjustments are required for children receiving treatment with efavirenz and rifampicin.

Table 11.12: ART dosing tables for infants and children (continued) (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

Instructions to administer LPV/r pellets to children are:

- Hold the capsule at both ends and, twisting in opposite directions, pull apart to pour out the pellets inside the capsule.
- Add the pellets (from the required number of capsules) to a spoonful of food a little at a time. For example, porridge can be used (must be at room temperature)
- Do not stir, crush, or dissolve the pellets: rather sprinkle over the food.
- Use only a small amount of food, to ensure child can consume all the pellets. Discard food with pellets after 2 hours.
- The capsule can be discarded with usual waste.

LoE:IIIb[53]

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Z29.2 + (B24)

Cotrimoxazole prophylaxis

Initiation *LoE:IIIb*[54]

- All HIV-infected infants (< 1 year), starting from 6 weeks of age.
- Any child 1–5 years of age with CD4 < 25%, or WHO stage 3 and 4
- Any child > 5 years of age with CD4 count < 200 cells/mm^3, or WHO stage 3 and 4.

• Cotrimoxazole (sulfamethoxazole/trimethoprim), oral, once daily.

Recommended daily dosage by weight band	Dose of sulfamethoxazole/ trimethoprim	Suspension (200/40 mg per 5 mL)	Single strength tablet (400/80 mg)	Double strength tablet (800/160 mg)
3 to 5.9 kg	100/20 mg	2.5 mL	¼ tablet	-
6 to 13.9 kg	200/40 mg	5 mL	½ tablet	-
14 to 24.9 kg	400/80 mg	10 mL	1 tablet	½ tablet
25 kg	800/160 mg	-	2 tablets	1 tablet

Table 11.13: Dose bands for cotrimoxazole

Discontinuation

Prophylaxis may be discontinued if the immune system is fully reconstituted on ART i.e. Child > 1 year of age*, AND* immune system shows signs of full reconstitution on two CD4 tests at least 3-6 months apart (regardless of clinical stage), i.e.:

Child 1-5 years of age: CD4 > 25%

Child > 5 years of age: CD4 > 200 cells/mm^3

TB prophylaxis

See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Immunisation

Continue immunisation as per the SA-EPI (See Section 13.3). If signs of HIV infection present, defer the BCG vaccination.

11.8 OPPORTUNISTIC INFECTIONS, TREATMENT IN CHILDREN

11.8.1 CANDIDIASIS, ORAL (THRUSH), RECURRENT

B20.4

MEDICINE TREATMENT

- Nystatin suspension, oral, 100 000 IU/mL, 0.5 mL after each feed.
  - Keep in contact with the affected area for as long as possible prior to swallowing.
  - In the older child, ask child to swirl in the mouth, prior to swallowing.
  - In the infant, advise caregiver to apply to front of the mouth and spread over the oral mucosa with a clean finger.
  - Continue for 48 hours after resolution of symptoms.

If there is oral candidiasis and the child cannot swallow, this indicates the presence of oesophageal candidiasis. See Section 11.8.2: Candidiasis, oesophageal.

11.8.2 CANDIDIASIS, OESOPHAGEAL

B20.4

MEDICINE TREATMENT

- Fluconazole, oral, 6 mg/kg once daily for 21 days. See dosing table, pg 23.5.

11.8.3 DIARRHOEA, HIV-ASSOCIATED

See Section 2.9: Diarrhoea.

11.8.4 PNEUMONIA

See Section 17.2: Respiratory infections.

11.8.5 MEASLES AND CHICKENPOX

Refer all patients.

11.8.6 SKIN CONDITIONS

These are common and include scabies, seborrhoeic eczema and others.
See Chapter 5: Skin conditions.
If no response to care as directed in the chapter, refer.

11.8.7 TUBERCULOSIS (TB)

A15.0-6/A15.7-9/A16.0-5/A16.7-9/A17.0-1/A17.8-9/A18.0-8/A19.0-2/A19.8-9 + B20.0

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.

Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.

TB should be considered early in non-resolving pneumonias. At every follow up visit, ask about symptoms of cough, night sweats, fever, TB contacts and check for failure to thrive.

Refer early for diagnostic evaluation. If TB is suspected:

- Chest radiograph (CXR)
- GeneXpert on any relevant specimen including stool
- Culture on respiratory or appropriate specimen
- Urine-LAM. If no sample obtained, continue evaluation

MEDICINE TREATMENT

TB prophylaxis Z29.2 + (B24)

Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

- Exposed to a close contact with infectious pulmonary TB or
- TST-positive (this test is only reliable the first time TPT is given).
- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
  - Maximum dose: 300 mg daily.
  - See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.

Refer if patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment.

TB treatment

If the child is not yet on ART:

» TB treatment and ART can be started at the same time, with the exception of children with TB meningitis – start ART at 4 weeks regardless of CD4 count to avoid IRIS.
» Assess the child for possible disseminated TB disease.
» Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:

» Commence TB treatment, considering possible drug interactions and the need for ART dosage adaptations.

If the child needs to take concomitant ART and rifampicin-containing treatment:

- Dolutegravir: use dolutegravir twice daily.
- Efavirenz: use the normal recommended dosage as per the dosing table.
- Abacavir and lamivudine: no adjustment of dosages.

- Lopinavir/ritonavir: refer to the dosage table for the ritonavir boosting doses.
  - Avoid using double-dose lopinavir/ritonavir solution in young children. If ritonavir powder is not available, consult an expert.
- Give pyridoxine (vitamin B6) to all children on TB treatment and ART, to avoid development of peripheral neuropathy.

11.9 DEVELOPMENTAL DELAY OR DETERIORATION

GENERAL MEASURES

Refer children with cognitive (learning problems) and motor delays for assesment and neurodevelopmental rehabilitation.

11.10 ANAEMIA

See Section 3.1: Anaemia

HIV PREVENTION

11.11 PRE-EXPOSURE PROPHYLAXIS (PREP)

Z20.6 + Z29.2

Consult the most recent National Department of Health Guideline for PrEP eligibility criteria.

DESCRIPTION

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medicines by HIV-negative individuals before potential exposure to HIV to prevent them from acquiring HIV infection. PrEP only protects against HIV infection; it does not offer protection against other STIs or pregnancy.

PrEP should be used as part of a package that also includes condoms; lubricants for anal sex; STI management; screening and management of intimate partner violence; sexual and reproductive health services; medical male circumcision; and HIV services, including counseling and testing, HIV management, ART, and PEP.

All individuals requesting PrEP should be assessed and initiated if elgible.

Individuals initiated on PrEP must meet the following criteria:

- HIV-negative.
- At substantial risk of HIV infection.
- Willing and able to adhere to PrEP.
- Prepared to come for repeat HIV testing every 3 months.
- No contra-indications to tenofovir or emtricitabine.
- No suspicion of acute HIV-infection (see clinical features, below).

Clinical features of acute HIV infection

Symptoms	Signs
Malaise, anorexia, myalgia, headache, sore throat, sore glands, rash	Fever, sweating, viral meningitis, generalised lymphadenopathy, hepatosplenomegaly, pharyngitis, truncal rash, orogenital herpetiform ulceration, oral/oesophageal candidiasis, cervical adenopathy

CONTRAINDICATIONS TO PrEP

- Pre-existing HIV infection.
- Estimated creatinine clearance or eGFR < 60 mL/min.
- Use of nephrotoxic medicines e.g. aminoglycosides.
- Young women/men < 35 kg or < 15 years of age who are not Tanner stage 3 (sexual maturity) or greater.
- Unwilling or unable to adhere to daily PrEP.

ORAL PREP REGIMEN

A fixed dose combination formulation of:

- Tenofovir disoproxil fumarate (TDF), oral, 300 mg daily.

AND

- Emtricitabine, oral, 200 mg daily. *LoE:Ia*[55]

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required. Individuals should be counselled that additional barrier protection should be used until therapeutic levels achieved. *LoE:IIIb*[56]

Screening investigations before starting PrEP

Investigation	Purpose	Action
HIV test (using algorithm in the HTS guidelines*)	Assessment of HIV status.	If HIV-negative, consider PrEP If HIV-positive: Link to treatment and care services.
Estimated creatinine clearance (eGFR)	To identify pre-existing renal disease.	Do not initiate PrEP if creatinine clearance/eGFR < 60 mL/min. Repeat creatinine clearance after two weeks. If renal function returns to normal and other PrEP criteria are met, PrEP may be initiated. Refer for further investigation if renal function remains abnormal.
Hepatitis B surface antigen (HBsAg)	To diagnose chronic hepatitis B infection. To identify those eligible for vaccination against hepatitis B.	Assess eligibility for vaccination if available (see table below).. If HBsAg-positive, do ALT prior to PrEP initiation.
ALT if HBsAg-positive		If ALT persistently elevated or other abnormal liver function tests, refer for assessment.
Urine pregnancy test	To identify if pregnant.	Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP.
RPR	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	To diagnose and treat STI.	Manage according to STI guidelines.

Table 11.13: Screening investigations before starting PrEP

*HIV Testing Services guidelines

Note:

- If symptoms or signs of acute HIV infection are present, PrEP should be postponed until symptoms subside and a repeat rapid HIV test after 4 weeks remains negative.
- TDF + FTC is active against hepatitis B (HBV) infection. HBV infection is not a contra-indication to PrEP, but will require LFT monitoring. Discontinuation of TDF + FTC in patients with HBV requires referral to a specialist because of a risk of a hepatitis flare.

Hepatitis B immune status and PrEP eligibility

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP. Vaccinate concurrently if available
Negative (-)	Positive (+)	Start PrEP. No vaccine needed
Positive (+)	N/A	Refer for evaluation, if ALT > 2 times upper limit of normal.

Table 11.14: PrEP eligibility determined by hepatitis B immune status

Note:

- PrEP users with chronic hepatitis B infection who develop abnormal liver function tests should be referred for assessment.

PrEP follow up and monitoring

Activity	Frequency
Confirmation of HIV-negative status	At 1 month, then every 3 months
Address side effects	Every visit
Adherence counseling	Every visit
Estimated creatinine clearance	Frequency dependant on pregnancy status, age and co-morbidity: *LoE:IVb*[57]
STI screening and treatment	Every visit
PrEP dispensing	1 month supply, then 3 monthly supply
Behavioural sexual risk reduction counseling	Every visit

Age/ pregnant	Co-morbidity	Creatinine
< 30 years	None	n/a
30–49 years	None	Baseline
< 49 years	Diabetes/ hypertension	Baseline, annually
≥ 50 years	None	Baseline
≥ 50 years	Diabetes/ hypertension	Baseline, annually
Pregnant	n/a	Baseline, 3 & 6 months

Table 11.15: Monitoring of person(s) on PrEP

PREP SAFETY

Relevant medicine interaction information

Medicine	Interaction information	Advise
Standard TB medicines	No interaction	No need for dose adjustments
Hormonal contraception	No interaction	Hormonal contraception does not affect PrEP effectiveness, nor does PrEP affect hormonal contraceptive effectiveness
Nephrotoxic medicines	Increase risk of renal side effects	Avoid PrEP. Advise other prevention methods

Table 11.16: Oral PrEP drug interactions

Side effects of TDF + FTC combination

Major	Renal toxicity, decreased bone mineral density, extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
Minor	Gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss

Table 11.17: Side effects of oral PrEP

Note:

- Minor side effects are relatively common (approximately 1 in 10 individuals in the first 1-2 months).
- Mild and self-limiting; do not require discontinuation.
- Renal toxicity and decreased bone mineral density usually reversible upon stopping PrEP.

STOPPING PREP

PrEP should be stopped if:

- Tests HIV-positive.
- Renal disease develops.
- Non-adherent to PrEP.
- Does not need or want PrEP.
- No longer meets eligibility criteria.
- There are safety concerns where the risks of PrEP use outweigh potential benefit.

Continue PrEP for 7 days after the last potential HIV exposure. *LoE:IVb*[58]

Note: Patients with chronic HBV may experience a hepatitis flare on discontinuation of PrEP.

REFERRAL

- HBsAg-positive, with abnormal ALT.
- Discontinuation of TDF + FTC in patients with HBV.

PREP INITIATION ALGORITHM

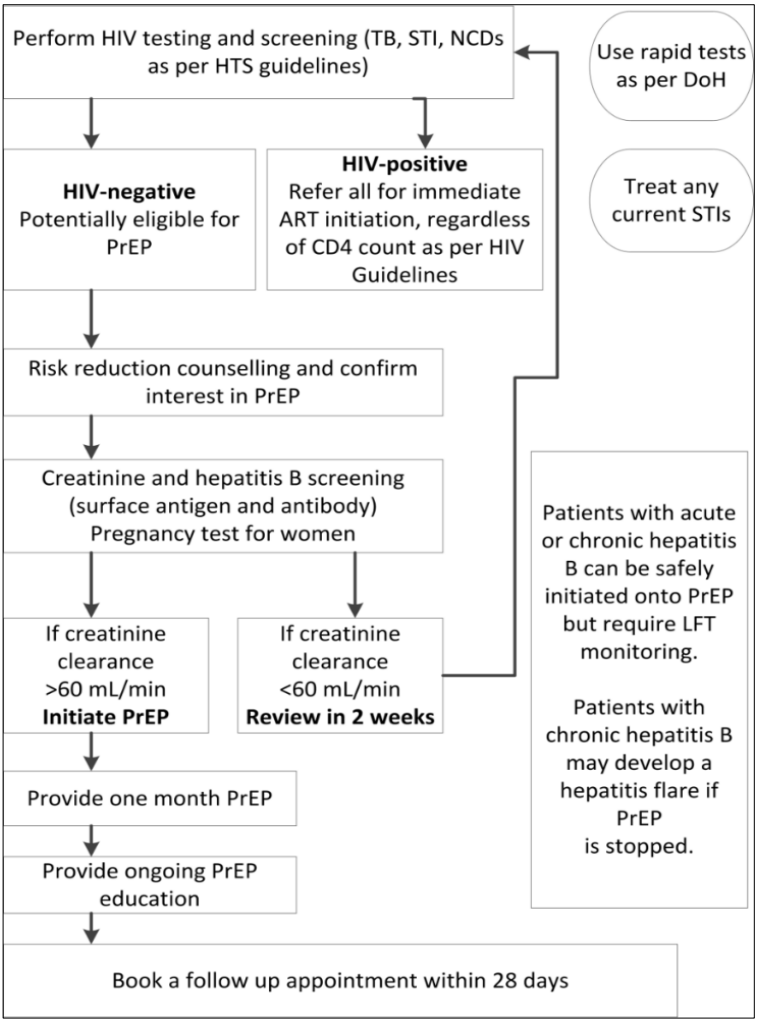


Figure 11.10: PrEP initiation algorithm

NOTE: In patients with Chronic Kidney Disease (CKD) with eGFR < 60mL/min, PrEP is contraindicated.

11.12 POST EXPOSURE PROPHYLAXIS

See Section 21.3.6: Post exposure Prophylaxis (PEP).

11.13 SIDE EFFECTS AND COMPLICATIONS OF ART

Refer to the Adult Hospital Level STGs and EML: Section 10.1.1 Management of selected antiretroviral adverse drug reactions, and consult with an infectious disease specialist as required.

11.13.1 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

D89.3 + (Y41.5 + B24)

DESCRIPTION

Clinical deterioration can occur after starting ART due an improvement in the immune system response to organisms already causing infection, e.g.

- M.Bovis (BCG)
- M. tuberculosis (MTB)

There are 2 types of IRIS:

1. Unmasking: when a previously unsuspected condition becomes manifest.
2. Paradoxical: known condition on appropriate treatment becomes worse.

DIAGNOSTIC CRITERIA

- Exclude other active or inadequately treated diseases (including DR-TB).
- Presentation:
  - Usually during the first 6 weeks after starting ART.
  - Depends on the causative organism and the organ system involved, e.g. TB presents with fever, lymphadenopathy, worsening of the original tuberculous lesion, and/or deteriorating chest radiographic manifestations such as miliary pattern or pleural effusion.

REFERRAL

All patients.

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Chapter 12

SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
PRIMARY HEALTH CARE CHAPTER 11: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -24 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
	Reference to national ART guidelines	Cross reference to national ART guidelines aligned to Paediatric EML
A: HIV INFECTION IN ADULTS		
11.1 Antiretroviral therapy, adults and adolescents		
- TB co-infection	ART	Directions amended
- TB meningitis co-infection	ART	Directions amended
- Asymptomatic cryptococcal infection	ART	Directions amended
11.1 Antiretroviral therapy, adults and adolescents *- Treatment-naïve patients without TB*	TDF +EFV+FTC	Retained
	TDF +3TC + DTG	Indication expanded from ≥6 weeks gestation to ALL women
	TAF	Added for patients with chronic hepatitis B coinfection and RF
11.1 Antiretroviral therapy, adults and adolescents *- Treatment-naïve patients with TB*	TDF + EFV + FTC (TEE)	Retained
	Double-dosed DTG	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
11.1 Antiretroviral therapy, adults and adolescents *- Contraindication to TDF*	TAF as (TAF+FTC+DTG):	Added for select cohort of patients
	ABC + 3TC+DTG	Amended as preferred treatment
11.1 Antiretroviral therapy, adults and adolescents *- Contraindication to TDF/TAF and ABC intolerance*	AZT+3TC with DTG	Amended as preferred treatment
	Aminoglycoside nephrotoxicity caution	Deleted
11.1 Antiretroviral therapy, adults and adolescents *- Recycling TDF in virological failure*	AZT	Deleted
	TDF	Added
11.1 Antiretroviral therapy, adults and adolescents *DTG contra-indicated/not tolerated/failing*	LPV/r	Retained
	ATV/r	Expanded to include all patients - preferred 2nd line PI
	DRV/r	Not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy
11.1 Antiretroviral therapy, adults and adolescents – ART Regimens *- DTG resistance*	Resistance testing	Retained, and emphasised
11.1 Antiretroviral therapy, adults and adolescents *- Rifampicin-based TB treatment (already on DTG-regimen)*	DTG	Added
11.1 Antiretroviral therapy, adults and adolescents *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
Re-initiating ART in patients who have interrupted treatment	Guidance	Amended
Monitoring on ART *- Baseline evaluation*	CrAg screening	Amended
	Sputum screen for TB	Amended
	HIV viral load monitoring schedule	Amended
ART: Dosing and important adverse effects	3TC	Amended
	FTC	Amended

	TDF, ABC, 3TC, FTC	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	Dolutegravir, oral – 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
	TAF, oral	Added
ART interactions with rifampicin and recommendations for administration	Rifabutin, oral	Not added
Drug interactions with boosted PIs	Rifampicin	Guidance amended
Referral	Criteria	Amended
11.2 Opportunistic Infections, Prophylaxis in adults		
11.2.1 Cotrimoxazole prophylaxis	WHO clinical stage II	Deleted
11.2.2 Tuberculosis preventive therapy (TPT)	TPT	Added as a therapeutic group
-Adult PLHIV initiated on ARVs	Isoniazid (12H)	Retained as an example of class in the STG
	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
	Pregnant women	Guidance amended
11.3.3 Candidiasis, oesophageal	Fluconazole	Guidance amended
11.3.4 Cryptococcosis	CrAg screening	Guidance clarified
	CrAg screening – CD4 threshold	Amended
	Fluconazole, oral	Dose for children added
	Fluconazole, oral	Caution updated
	Flucytosine, oral	Not added
-Asymptomatic cryptococcosis	ART initiation	Amended
-Referral	Criteria	Amended
11.3.5 Diarrhoea, HIV associated	Cotrimoxazole dosing	Guidance clarified
11.3.11 Herpes Zoster (shingles)	Paracetamol	Amended
11.4 HIV and kidney disease	Routine screening for renal disease	Retained
B: HIV INFECTION IN CHILDREN (<10 YEARS OLD)		
Diagnosis in children	Testing in children	Amended
Clinical staging of HIV and AIDS	WHO clinical staging	Editorial update
11.5 The HIV exposed infant	Description	Amended
	Feeding advice	Aligned to Paediatric EML
	Terminology - PMTCT	Amended
	Medicine treatment	Aligned to Paediatric EML
	NVP & AZT – infacts on VTP	Dosing guidance amended
	Cotrimoxazole, oral	Prophylaxis in high risk infants - amended
	HIV prophylaxis in high risk infants	Flow diagram - amended
11.6 Management of HIV-infected children (<10 years)	Viral load monitoring	Amended
	Cotrimoxazole prophylaxis	Amended to include WHO clinical stages
	BCG immunisation	Amended
	Social issues for successful treatment	Amended
	Counselling guidance	Editorial amendments
	Side effects of ARVs	Amended
	ART regimens - DTG	Added
	Guidance on ART regimens	Amended
-Transition from ABC/3TC/LPV/r to DTG based regimens	Guidance	Added
-Treatment failure	Guidance	Amended
-Confirmed virological failure in adolescents on TLD	Guidance	Added
-Viral load monitoring for clients on TLD	Guidance	Added
-ART dosing	Dosing tables	Added
11.7 Opportunistic infections, prophylaxis in children	Cotrimoxazole, oral	Directions for use amended
	Cotrimoxazole, oral- WHO clinical staging	Added

	Immunisation	Aligned with Section 11.6
11.8.7 Tuberculosis (TB)	Description	Amended
C: HIV PREVENTION		
11.11 Pre-exposure prophylaxis (PrEP)		
-Contraindications to PrEP	eGFR	Guidance clarified
- Oral PrEP regimen	TDF + FTC	Duration of therapy amended
-Screening investigations before starting PrEP	HBsAg screening	Guidance clarified
-PrEP Initiation	Algorithm	Guidance clarified
- Oral PrEP follow up and monitoring	Estimated creatinine clearance	Monitoring updated
-Medicine interaction information	MDR-TB guidance	Deleted
- Stopping oral PrEP	TDF + FTC	Duration of therapy amended
- Other PrEP agents	Dapivirine vaginal ring	Not added
	Cabotegravir	Not added
D: SIDE EFFECTS AND COMPLICATIONS OF ART		
11.14 Lactic acidosis	STG	Deleted

ABC= Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, LPV/r=Lopinavir/ritonavir, PrEP=Pre-exposure prophylaxis; TAF=tenofovir alafenamide, TDF = Tenofovir disoproxil fumarate

The cross reference to the national ART guidelines 20231 has been amended and aligned to the Paediatric 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.

A. HIV INFECTION IN ADULTS & ADOLESCENTS (10-19 YEARS OLD)

11.1 ANTIRETROVIRAL THERAPY, ADULTS & ADOLESCENTS (10-19 YEARS OLD)

TB co-infection

STG text was aligned to the Adult Hospital Level STG.

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):

- CD4 counts < 50 cells/mm^3: start ART within 2 weeks of starting TB treatment.
- CD4 count ≥ 50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, which does not increase the risk of mortality and reduces the risk of deterioration due to the immune reconstitution inflammatory syndrome (IRIS).

TB meningitis co-infection

STG text was aligned to the Adult Hospital Level STG.

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

Positive cryptococcal antigen and no evidence for meningitis on LP:

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

Positive cryptococcal antigen and no evidence for meningitis on LP:

[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.

Amended from:

- Defer ART until 2 weeks after initiating fluconazole

Amended to:

- No need to delay ART. ART can be started immediately.

Treatment-naïve patients without TB

TDF +EFV+FTC: *Retained*

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.

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					

Tenofovir alafenamide (TAF): *Added (for a select cohort)*

An update to the TAF review was conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment.[3] 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.

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

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

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.

ART-treatment naïve patients with TB

Tenofovir + Efavirenz + Emtricitabine (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[4] may be accessed at the end of this report or alternatively on the NHI webpage.

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

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

Tenofovir alafenamide + emtricitabine + dolutegravir (TAF+FTC+DTG): *added (select cohort)*

TAF has been added to the EML for patients with chronic hepatitis B co-infection and eGFR 30-50ml/min. Refer to the TAF review conducted in March 2024 for PLHIV with chronic Hepatitis B co-infection and renal impairment,[5] which may be found at the end of this report or alternatively accessed on the NHI webpage.

Abacavir + lamivudine + dolutegravir (ABC+3TC+DTG), oral: *amended*

(ABC+3TC+DTG)amended as the preferred treatment for patients other than those with, chronic hepatitis B coinfection and renal impairment (as for TAF+FTC+DTG above).

Contraindication to TDF/TAF and ABC intolerance

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

Aminoglycoside nephrotoxicity caution: *deleted*

The following STG text was deleted:

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

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.[6] [7]

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 Patients with TB: • TDF + FTC + EFV Pregnant women <6 weeks gestation or actively wanting to conceive: • TDF + FTC + EFV *(Also see section 6.7: HIV in pregnancy)*	Individuals ≥30kg and ≥10 years TDF + 3TC + DTG ("TLD") **Note***:* DTG-based regimens are now recommended as first line ART in all women of childbearing potential. Patients on rifampicin-based TB treatment: TDF + FTC + EFV **OR** TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later.

[5] Tenofovir alafenamide for HIV Adult Review Update_ 27 June 2024_v5_final
[6] 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/
[7] 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/

		The extra DTG dose can be stopped two weeks after completion of TB therapy. (Also see section PHC STG 6.8: 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 and then 800/200mg). 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.	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> 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

Recycling TDF in virological failure

<u>Zidovudine:</u> *deleted*

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

As the 96-weeks follow up data of the NADIA RCT[8] has been published in peer-review format, an update to the original evidence summary[9] was undertaken in May 2022, with the NEMLC recommendation tabulated below. A copy of the complete review[10] may be accessed at the end of this document or alternatively 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: 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:

	AMENDED FROM:	**AMENDED TO:**
	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>

[8] 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/

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

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

		» 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 *(TDF+3TC/FTC+EFV/NVP)*	AZT + 3TC + DTG. If HBsAg positive: TDF + 3TC + DTG If DTG contraindicated/ not tolerated: AZT + 3TC +LPV/r (**PLUS** TDF, if HBsAg positive). If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment): 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 If HBsAg positive: 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.	

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: » **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 ARV/r-containing regimen with latest VL <1000 copies/mL**	Switch to DTG-containing regimen regardless of VL result: TDF + 3TC + DTG ("TLD") (*Refer to Figure 11.1 below*). If contraindications to DTG or TDF, use alternative regimen as in "Initiating ART" section 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.* Provide individualised regimen as recommended by HIV expert. If adherence < 80%. switch to DTG-containing regimen: TDF + 3TC + DTG ("TLD") If contraindications to DTG or TDF, use alternative regimen as per "Initiating ART" section above.

The treatment pathway for switching existing clients to DTG-containing regimens as illustrated below, has been adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

Non VL-dependent regimen switches
Regimens where the VL result will not influence nor delay the decision to switch to DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
Switching regardless of VL result	TEE	Switch all to a DTG-containing regimen, regardless of VL result Review VL in last 12 months. If VL in last 12 months was not suppressed, continue to switch same day, but do ABCDE assessment and provide enhanced adherence counselling (EAC) if needed. If VL was not done in last 12 months, do it at this visit, but do not wait for results to switch.	**TLD** Provided no renal dysfunction and age > 10 years and weight > 30 kg If client does not quality for TDF **ABC[1]/3TC/DTG** If client does not quality for TDF and has ABC hypersensitivity **AZT/3TC/DTG**
	ABC/3TC/EFV		
	AZT/3TC/EFV		
	AZT/3TC/DTG		
	Any LPV/r or ATV/r regimen for less than 2 years		

VL-dependent regimen switches
Relevant to all clients who have been on PI-based regimens for more than two years: their VL result in the last 12 months will influence the decision of how and when to switch to a DTG-containing regimen

VL considerations	Current Regimen	Criteria for switch	Regimen if change indicated
VL < 1000 c/mL	Any LPV/r or ATV/r regimen for more than 2 years	Switch all to a DTG-containing regimen If VL in last 12 months was not < 50 c/mL, continue to switch same day, but do ABCDE assessment and provide EAC if needed.	**TLD** provided no renal dysfunction and age > 10 years and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
[2]Two or more VLs ≥ 1000 c/mL taken two or more years after starting PI regimen	Adult or adolescent on any **LPV/r or ATV/r** regimen and adherence **less than 80%[3]**	Switch all to a DTG-containing regimen **Do not do a resistance test** These clients are unlikely to have PI resistance mutations. Rather switch to a more tolerable once daily FDC regimen which is likely to support adherence.	**TLD** provided no renal dysfunction and age > 10 yrs and weight > 30 kg If clients does not qualify for TDF **ABC[1]/3TC/DTG**
	Adult or adolescent on any **LPV/r or ATV/r regimen and adherence more than 80%[3]**	Clients who meet the definition of confirmed virological failure despite confirmed adherence more than 80% may need a resistance test. **These clients do not qualify for a same-day switch.** Discuss with an HIV expert[4] to authorise and interpret a resistance test. Provide individualised regimen as recommended by HIV expert.	
	Child < 10 years, or weight < 30 kg on any **LPV/r or ATV/r regimen**	These clients do not yet qualify for TLD and may require a resistance test. Refer to algorithm **"Switching children on PI-containing regimens to DTG-containing regimens"**	

1. If clients are not eligible to use TDF and they have ABC hypersensitivity, use AZT/3TC/DTG.
2. Confirmed virological failure is defined as two or more VLs ≥ 1000 c/mL taken two or more years after starting a DTG or PI containing regimen, despite adherence > 80% by objective measurement. A patient who has only 1 VL > 1000 after 2 years on a PI-based regimen should have an ABCDE assessment, EAC if applicable, and their VL repeated in 3 months. The result of the repeat VL will allow the patient to be grouped into one of the categories in the table above and will inform the further course of action.
3. Objective measures of good adherence include at least one of:
   - Pharmacy refills > 80% in the last 6-12 months (if this is known).
   - Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known).
   - Detection of current antiretroviral drug/s in the client's blood or urine, if available.

   Note: Self-reported adherence is not considered a reliable measure of good adherence.
4. For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

DTG CONTRAINDICATED/ NOT TOLERATED/FAILING

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[11] may be found at the end of this document 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	

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

[11] NDoH evidence summary. ATV/r vs LPV/r_2 nd line adult HIV therapy_ AdultReview_18 November 2021

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[12] may be found at the end of this document or alternatively accessed 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 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 STG has been aligned to the national HIV program guideline as tabulated below:

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/)

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.

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

Rifampicin-based TB treatment (on DTG-regimen)

DTG: *added*

STG text was amended to align with the previously reviewed addendum to the DTG 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:

RIFAMPICIN-BASED TB TREATMENT		
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg 12 hours after TLD dose. If on ATV/r:	*LoE:IIIb*

[12] NDoH evidence summary. DRV/r vs LPV/r as 2nd line adult HIV therapy_PHC-AdultsMedicineReview_27 July 2021.

	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.

Currently available FDC preparations on contract

ATV/r: *added*

ABC + 3TC + DTG: *added*

STG text was updated to reflect currently available fixed-dose combination ARVs that are accessible on the current public sector tender.[13]

Re-Initiating ART in patients who have interrupted treatment

Previous EML guidance as tabulated below has been removed and replaced with Figure 11.1 Algorithm of a patient who returns to care after interrupting treatment, as adapted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

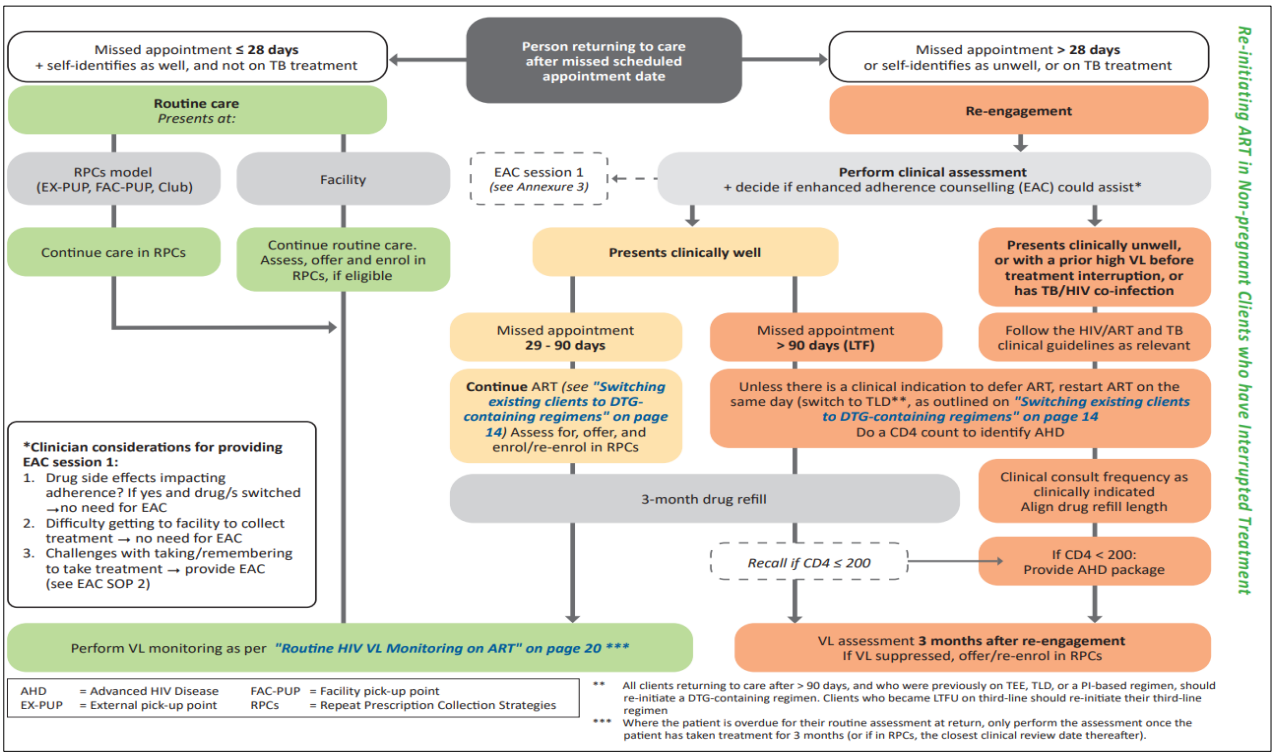
AMENDED FROM:

» 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.

AMENDED TO:

Management algorithm of a patient who returns to care after interrupting treatment. Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. (*Refer to the EML Section 11.1 Antiretroviral therapy, adults and adolescents (10-19 years old*).



MONITORING ON ART

CrAg Screening

CrAg screening - threshold*: Amended*

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

The CD4 threshold for screening for 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*).[14] This may be considered at a higher CD4 threshold of <200 cells/mm^3 (conditional recommendation, moderate certainty evidence)." 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.[15] 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."[16] The South African HIV Clinician Society Guideline[17] 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 CrAg testing at less than 100 cells/mm^3. The STG has been amended as tabulated below:

MONITORING ON ART

Baseline evaluation

» WHO staging.

» Check CD4 count.

» CD4 <200 cells/mm^3:
Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). 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[18] 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*

The HIV viral load monitoring schedule as illustrated in the national ART guideline has also been incorporated in the EML as tabulated below:

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

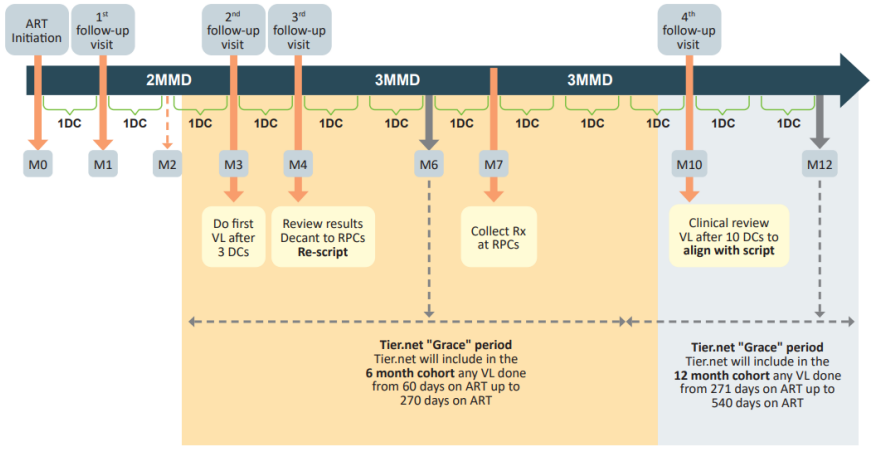
[15] Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, Kamya MR, Bohjanen PR, Boulware DR. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited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

[16] 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.

[17] 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

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

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

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:

CrCl 10-50 mL/min:
150 mg daily
CrCl <10 mL/min:
50 mg daily

AMENDED TO:

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:

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

AMENDED TO:

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: *added*

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[19], 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.					
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					

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

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[20]. 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 Guideline.

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 INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION
Rifabutin, oral: *not added*
Rifabutin, oral was not added as an essential medicine for primary level of care, as the medicine which has a sole supplier with intermittent supply constraints, and is already included on the Adult Hospital Level EML. However, a cross-reference to the respective Adult Hospital STG was added, as follows:

Patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with rifabutin (doctor prescribed) – see Adult Hospital Level STGs and EML. section 10.1: Antiretroviral therapy.

Drug Interactions with boosted PIs
Rifampicin: *Guidance amended*
Dosing guidance for the use of double dose LPV/r added to the STG as tabulated below:

DRUG INTERACTIONS WITH BOOSTED PIs:

Interacting medicine	Effect of co-administration	Recommendation
Rifampicin	Significant reduction in PI concentration	Double LPV/r 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 (e.g. 600/150 mg and then 800/200 mg). Adjusted dose of LPV/r should be continued for 2 weeks after rifampicin is stopped. The LPV/r can be switched back to ATV/r two weeks after completion of TB therapy. If ATV/r or DVR/r is required, rifampicin must be replaced with dose-adjusted rifabutin (doctor prescribed) - see AH STG Section 10.1: Antiretroviral therapy.

REFERRAL
Reference to second line ART regimens has been removed from the STG.

Amended from: **Referral** Second-line ART regimen failures **Amended to:** **Referral** Dolutegravir resistance demonstrated on resistance testing.

[20] 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

11.2 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN ADULTS

11.2.1 COTRIMOXAZOLE PROPHYLAXIS

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[21] which has been amended from WHO stage II, III or IV in 2000[22] 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).

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Adult PLHIV initiated on 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)[23] and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019)[24] which is accessible on the NHI webpage.

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:

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 used.
  - 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*].
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant) associated with TPT.

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.
  - Follow patients up monthly for the first 3 months.

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

[22] 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]

[23] NDoH Evidence Summary. NDoH_EDP_Rifapentine_Adults Review Update_14November2019_v1.0

[24] NDoH Evidence Summary. NDoH_EML_Rifapentine_&_Dolutegravir_ TPT_AdultsReview_v1

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.

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).

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/mm³.	If CD4 ≤350 cells/mm³.
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[25] 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.					

11.3.3 CANDIASIS, OESOPHAGEAL

Medicine treatment - fluconazole*: guidance amended*

Guidance on the initiation of ART has been removed to align with amendments in Section 11.1 above.

MEDICINE TREATMENT

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

~~Commence ART within 7 days (unless patient has cryptococcal or TB meningitis). See section: 11.1 Antiretroviral therapy, adults~~

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

11.3.4 CRYPTOCOCCOSIS

CrAg screening*: amended to clarify that guidance applicable to adults and adolescents*
CrAg screening*: CD4 threshold amended*
Fluconazole oral: *dose for children added*

The following statements as tabulated below were amended to clarify that the STG guidance is applicable to both adults and adolescents. Dosing guidance for the use of fluconazole in children has been added. Updates to the CD4 threshold for CrAg screening have been included in line with Section 11.1 above. The guidance not to delay the initiation of ART in asymptomatic cryptococcosis has also been aligned to Section 11.1 as detailed above.

INVESTIGATIONS

All ART-naïve adults and adolescents with CD4 < 200 cells/mm^3 should have a serum cryptococcal antigen (CrAg) test done (unless confirmed 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 cell count is between 100 and 199, a separate sample should be sent for CrAg testing.

MEDICINE TREATMENT

If CSF CrAg positive:
Refer for liposomal amphotericin B, IV (induction phase) and monitoring of intracranial pressure symptoms - See Adult Hospital STGs and EML, Section 10.2.4: Cryptococcosis.
Patients may be down referred for ~~secondary prophylaxis~~ consolidation and maintenance phase therapy; see below.

If there is any delay in performing LP, start oral fluconazole therapy:

- Adults: Fluconazole, oral, 1200 mg immediately.
- Children: 12mg/kg to a maximum dose of 800mg immediately

Commence ART: See section 10.1: Antiretroviral therapy.
Cryptococcal meningitis: 4–6 weeks after starting antifungal therapy.
Asymptomatic cryptococcosis: ~~After completion of the induction phase i.e. at 2 weeks after starting antifungal therapy~~. No need to delay ART. ART can be started immediately.

Fluconazole, oral: *caution updated*
The fluconazole caution box was updated to align with the amended Adult Hospital Level STG and EML, with the inclusion of the following text:

» 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.

CSF CrAg positive

Flucytosine, oral: *not added*
External comment received regarding flucytosine, oral as induction therapy in this clinical setting was noted. Though, flucytosine, oral is included in the respective Adult Hospital Level STG.

Asymptomatic cryptococcosis

ART initiation: *Amended*
The STG has been amended to align with the national ART guideline as tabulated below:

Amended from:
Asymptomatic cryptococcosis: After completion of the induction phase i.e. at 2 weeks after starting antifungal therapy

Amended to:
Asymptomatic cryptococcosis: No need to delay ART. ART can be started immediately.

Referral

Criteria: *Amended*
The following statement has been amended to clarify that patients should be referred to facilities where there is access to lumbar puncture: *'If LP unavailable: Refer all serum CrAg positive patients ~~for~~ to a facility where LP is available.'*

11.3.5 DIARRHOEA, HIV-ASSOCIATED

Medicine treatment – cotrimoxazole dosing: *Guidance clarified*

Dosing guidance for the management of *Isospora belli* infection has been amended as tabulated below, to clarify that the recommended dose of cotrimoxazole 320/1600mg is equivalent to 4 single strength tablets of the 80/400mg adult tablet formulation and is currently available on tender. This clarification is to avoid any potential confusion with the double strength formulation, cotrimoxazole 160/800mg tablets which is also available locally although not on tender.

AMENDED FROM:

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 tablets) daily until CD4 > 200 cells/mm3 on ART.
- Commence ART.

AMENDED TO:

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 single strength (80/400 mg) tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 single strength (80/400 mg) tablets) daily until CD4 > 200 cells/mm^3 on ART.
- Commence ART.

11.3.11 HERPES ZOSTER (SHINGLES)

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 (maximum of 4g in 24 hours)
  - Maximum dose: 15 mg/kg/dose.

11.4 HIV AND KIDNEY DISEASE

Routine screening for renal disease: *retained*

An external comment was received regarding annual screening for renal disease, despite use of ARVs that did not include tenofovir. However, HIV was considered a risk factor for chronic kidney disease.[26]

[26] Wyatt CM. Kidney Disease and HIV Infection. Top Antivir Med. 2017 Feb/Mar;25(1):13-16. https://pubmed.ncbi.nlm.nih.gov/28402929/

B. HIV INFECTION IN CHILDREN (<10 YEARS OLD)

Diagnosis in children: *guidance amended*

STG guidance amended to align with the national HIV program guideline as tabulated below:

AMENDED FROM:

WHEN AND HOW TO TEST IN CHILDREN

Which test

Child <18 months of age

HIV PCR test: Always confirm with 2nd HIV PCR test if the first test is positive. Do not delay ART initiation; start ART with the first positive result.

Child ≥ 18 months of age

HIV rapid or ELISA test: If 1st rapid test is positive, confirm the result with:

A HIV PCR test if infant between 18-24 months

A second rapid test using a kit of a different manufacturer, and preferably on a different blood specimen if infant is > 24 months.

HIV rapid tests may be less reliable in children with advanced disease. If clinical findings suggest HIV infection but the rapid test is negative, send a further specimen of blood to the laboratory for HIV ELISA testing. If HIV status is still unclear, do an HIV PCR test.

When to test HIV-exposed children (See section: 11.5 The HIV-exposed infant).

Birth (HIV PCR).

Repeat at 10-week visit (HIV PCR).

Repeat at 6-month visit (HIV PCR)

At any time when clinical signs indicate possible HIV infection.

6 weeks after breastfeeding has stopped.

Do Universal HIV rapid/ELISA test at 18 months (HIV rapid test for ALL children regardless of HIV exposure, except in those who previously tested HIV positive and are on ART).

LoE:IIIb

Also perform PCR testing AT BIRTH on:

Infants born to mothers who were on TB treatment for active TB during their pregnancy.

Infants with congenital pneumonia.

Infants with clinical features suggestive of HIV infection.

High risk infants requiring urgent HIV diagnosis.

If the HIV PCR result is not available at discharge, the mother must return within 1 week for the result.

If the HIV PCR result is negative, repeat at 10 weeks:

- If HIV PCR result at 10–18 weeks, or an age-appropriate test 6 weeks after breastfeeding has stopped, is still negative, perform HIV rapid test at 18 months of age.
- If positive at any time, start infant ART.

Note:

Negative tests do not exclude HIV infection until 10-18 weeks after birth and 6 weeks after exposure to other risk of HIV infection (including breastfeeding).

Discuss children with discordant HIV test results with an expert.

Do not repeat HIV rapid/ELISA tests in children on established ART.

Also perform age-appropriate testing at any time:

Parental request to test the child.

HIV-infected father or sibling.

Death of mother, father or sibling.

Mother's HIV status and her whereabouts are unknown.

Clinical features suggest HIV infection.

Infant has acute severe illness.

Breastfed infant of newly diagnosed HIV-infected breastfeeding mother.

IMCI classification of SUSPECTED SYMPTOMATIC HIV INFECTION or POSSIBLE HIV INFECTION (see below).

TB diagnosis, history of TB treatment or new TB exposure.

Suspicion of sexual assault.

Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later).

Children considered for adoption or fostering.

Newborn child whose mother is of unknown HIV status, has died or is not available due to abandonment or other reasons:

Perform both infant HIV PCR and HIV rapid tests. Initiate PMTCT as for high risk exposure.

Perform age-appropriate HIV testing in an HIV-uninfected child at any other time if clinical symptoms suggest HIV infection.

Clinical indications that HIV infection should be considered in a child are:

If the mother is HIV-infected or if the mother's HIV status is not known.

If the child was HIV PCR-negative but was subsequently breastfed.

If a child has any of the following features:

- Rapid breathing or chest indrawing now ("Pneumonia").

- Persistent diarrhoea now or in the past.
- Ear discharge now or in the past.
- Low weight for age/height or unsatisfactory weight gain.
- ≥ 2 enlarged glands of: neck, axilla or groin.
- Oral thrush.
- Parotid enlargement.

All infants/children accessing care should have their HIV exposure status (recent maternal HIV status) and/or HIV status determined.
Women who previously tested HIV-positive should not be retested.
Where mothers tested negative in pregnancy, maternal HIV status should be determined 3-monthly whilst breastfeeding.

AMENDED TO:

HIV TESTING IN CHILDREN

Age	Test	Note
HIV-exposed		
Birth	HIV PCR	If the HIV PCR is positive at any time, confirm with a second HIV PCR
10 weeks	HIV PCR	
6 months	HIV PCR	
6 weeks post-cessation of breastfeeding	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Universal screening		
18 months	HIV rapid/ELISA	Perform on all children, unless known to be HIV infected
HIV infected confirmatory test (any child with positive HIV test)		
<24 months	HIV PCR	Between 18 and 24 months, the initial test will be HIV rapid/ELISA, but is confirmed with an HIV PCR
≥24 month	HIV rapid/ELISA	Perform the second test on a different blood specimen with a test kit from a different manufacturer
Possible/suspected symptomatic HIV infection		
Any age if IMCI classification of: Pneumonia Ear discharge (ever) Persistent diarrhoea in past 3 months Not growing well, moderate acute malnutrition (MAM) or severe acute malnutrition (SAM). ≥ 2 enlarged glands of: neck, axilla or groin. Oral thrush. Parotid enlargement	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	
Other situations		
Parents request testing Breastfed infant of a newly diagnosed HIV infected mother Suspicion of sexual assault Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later). Children considered for adoption or fostering	Age appropriate testing: <18 months: HIV PCR ≥18 months: HIV rapid/ELISA	

If an HIV PCR test is indeterminate or discordant, refer to the National Department of Health Guideline for Vertical Transmission Prevention of Communicable Infections, 2023[27].

[27] NDoH. Vertical Transmission Prevention Guideline 2023. Accessible : https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-09/2023%20Vertical%20Transmission%20Prevention%20Guideline%2004092023%20signed%20WEB_1.pdf

Clinical staging of HIV and AIDs for infants and children

WHO clinical staging guidance: *Editorial update*

The hyperlink to the interim *WHO clinical staging of HIV/AIDS case definitions for surveillance (Africa Region)*[28] has been added to the EML. The Committee acknowledged that the WHO clinical staging of HIV and AIDs for infants and children has become less relevant as CD4 counts are readily available. The WHO clinical staging is however still a consideration for cotrimoxazole prophylaxis and has been retained in the EML. Consideration will be given to removing the WHO clinical staging table from the EML in the next review cycle.

11.5 THE HIV-EXPOSED INFANT

Description: *amended editorially*

The description has been amended editorially for improved clarity as tabulated below:

AMENDED FROM:

DESCRIPTION

An infant whose mother is HIV-infected, or in whom HIV infection has not been confirmed or excluded.
Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving ARVs to the infant.
If the mother's VL is not suppressed the risk of breast milk transmission remains significant.

AMENDED TO:

DESCRIPTION

An HIV-exposed infant or child is one born to a mother living with HIV, until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding.

Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving post-exposure prophylaxis to the infant, a strategy now known as Vertical Transmission Prevention (VTP; formerly termed Prevention of Mother to Child Transmission).

The risk of transmission from breast milk is low when the mother is virally suppressed. Ensure maternal VL monitoring is done every 6 months while breastfeeding and offer enhanced adherence counselling to ensure viral suppression is achieved and maintained.

Feeding advice: *aligned to Paediatric EML*

Feeding advice has been aligned to the Paediatric EML as tabulated below:

AMENDED FROM:

Feeding advice

- Exclusive breastfeeding is strongly recommended for the 1st first 6 months, after which the nutritional needs of the child will require the introduction of complementary foods, while breastfeeding continues
- Mothers whose 2nd or 3rd line regimens are failing TLD2 should not breastfeed. However, a sustainable supply of formula must be provided.
- If women are switched from 1st to 2nd line therapy during pregnancy or breastfeeding, consult with a practitioner experienced and knowledgeable of the factors informing the feeding option decision.
- Mothers on effective ART should be encouraged to breastfeed as the advantages of breastfeeding exceed the risks of HIV transmission.
- Use of flash pasteurisation or Pretoria pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved.

AMENDED TO:

Feeding advice

- It is strongly recommended that exclusive breastfeeding be initiated within 1 hour of birth and continued for the first 6 months of life, after which the child's nutritional requirements will require the introduction of complementary foods in addition to breastfeeding.
- Women living with HIV should be fully supported for ART adherence during the breastfeeding period and thereafter.
- Women with a VL > 50 copies/mL on TLD1 should continue breastfeeding while every effort is made to regain viral suppression. Their infants should receive high-risk prophylaxis during breastfeeding.
- The following may be indications to discontinue breastfeeding:
  > Infants of mothers who are failing TLD2.

[28] https://iris.who.int/bitstream/handle/10665/69058/WHO_HIV_2005.02.pdf

> Infants of mothers who are failing third-line PI-based treatment.

- Discuss appropriate feeding practices with the mother regarding the risks and benefits of continuing breastfeeding vs replacement feeding.
- The use of flash pasteurisation or 'Pretoria' pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved. For instance, it can be used as an interim measure during maternal mastitis.

NOTE: For the above,

» TLD1 = TLD as a first line ART regimen.

» TLD2 = TLD in patient who has failed a previous ART regimen.

Terminology – PMTCT: *Amended*

Historical reference to PMTCT (prevention of mother to child transmission), has been replaced throughout the chapter with VTP (vertical transmission prevention) in line with the national clinical guideline[29].

Medicine treatment: *aligned to Paediatric EML*

Guidance on medicine treatment has been aligned to the Paediatric EML as tabulated below:

AMENDED FROM:

Situation	Comment
Low Risk (at birth) • **NVP** at birth and then daily for 6 weeks.	
Mother is on lifelong ART, and VL <1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL <1000 copies/ml *at delivery*	» HIV testing* – Do HIV PCR at birth. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months. – Do infant HIV testing 6 weeks' post-cessation of breastfeeding (either HIV PCR or ELISA depending on age). » Encourage maternal ART adherence.
High Risk (at birth) • **NVP daily for at least 12 weeks (until maternal VL< 1000 copies/mL) and AZT 12 hourly for 6 weeks.**** ○ (initiate as soon as possible) *LoE:IIIa*	
Mother is on lifelong ART, and VL >1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL >1000 copies/ml at delivery. **or** Mother with no VL result in the last 12 weeks. **or** Mother not on ART.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » HIV testing* – Do infant HIV PCR at birth/ immediately, if infant tests HIV PCR+, do repeat HIV PCR test and initiate ART immediately. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months. – Do infant HIV testing 6 weeks post-cessation of breastfeeding (either HIV PCR or rapid test depending on age). » Encourage maternal ART adherence. » If maternal VL ≥ 1000 copies/ml continue infant NVP prophylaxis.
High Risk (during breastfeeding) **NVP daily for at least 12 weeks (until maternal VL<1000 copies/mL) and AZT 12 hourly for 6 weeks.** ○ Initiate as soon as possible.	
Breastfeeding mother newly diagnosed HIV positive > 72 hours after delivery. Mother on ART with latest VL > 1000 copies/ml during breastfeeding.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to re-suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » Do immediate infant HIV PCR*. » If infant currently breastfeeding, or has breastfed in the last week: provide high-risk infant prophylaxis. » If breastfeeding never started or stopped > 1 week ago: no prophylaxis needed. » Repeat HIV PCR 6 weeks after stopping NVP » Do all other routine HIV tests according to the age and schedule for HIV exposed infants*. » See algorithm below: Management of high maternal VL after delivery.
UNKNOWN RISK (abandoned/orphaned infant) • **NVP daily for 6 weeks and AZT 12 hourly for 6 weeks.** ○ Initiate as soon as possible. *LoE:IIa*	
Unknown maternal status because orphaned or abandoned. (Treat all as high-risk HIV-exposed infants)	» Do an HIV PCR* and HIV rapid test » Start high risk infant prophylaxis for 6 weeks. » Repeat HIV PCR at 10 weeks of age, or 4 weeks after stopping NVP* » Do all other routine HIV tests according to the age and schedule for HIV-exposed infants*.

[29] NDoH. Vertical Transmission Prevention Guideline 2023. Accessible : https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-09/2023%20Vertical%20Transmission%20Prevention%20Guideline%2004092023%20signed%20WEB_1.pdf

	» See algorithm below: Management of infant of unknown risk (abandoned infant).

Note:

* If infant tests HIV-positive at any stage, confirm positive result, stop any ART prophylaxis, and initiate ART. See Section 11.6: Management of HIV-infected children.
**High-risk infants who are exclusively formula fed from birth: give NVP daily for 6 weeks and AZT 12 hourly for 6 weeks.

LoE:IIIb

Table 11.8: Infant prophylaxis for HIV

AMENDED TO:

Maternal VL	Risk profile	Prophylaxis	Comment
Maternal delivery VL as yet unknown at discharge from labour ward (results pending).	High-risk (until maternal delivery VL results become available)	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	All HIV-exposed infants will be considered high-risk until the final risk profile can be determined by the maternal delivery VL. If the maternal delivery VL result is not available at discharge from labour ward, review result at the 3– 6 day postnatal visit and reclassify the infant accordingly. Dispense a full 6 weeks supply of dual prophylaxis. Ask the mother to return with all medication at the 3–6 day postnatal visit
Maternal delivery VL ≥ 50 copies/mL in a breastfeeding mother	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for a minimum of 12 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency. Stop infant NVP only after confirmation of maternal VL being < 50 copies/mL, or until 4 weeks after cessation of all breastfeeding
Maternal delivery VL ≥ 50 copies/mL in a mother who is exclusively formula feeding her infant from birth.*	High-risk	Provide dual prophylaxis: AZT at birth and then twice daily for 6 weeks. NVP at birth and then daily for 6 weeks.	Do an ABCDE assessment and get the mother's VL resuppressed as a matter of urgency
Maternal delivery VL < 50 copies/mL regardless of feeding choice.	Re-classify as low risk.	Change to low risk prophylaxis: NVP at birth and then daily for 6 weeks	Affirm and encourage good adherence. Repeat maternal VL 6- monthly during breastfeeding.

*Non-breastfeeding mother diagnosed HIV-positive > 72 hours after delivery: Do not start the infant on prophylaxis. Start maternal ART. Perform an HIV PCR test on the infant and, if positive, initiate ART, if negative, continue to monitor HIV risk and perform HIV testing as above.

Nevirapine (NVP) and Zidovudine (AZT) doses for infant on VTP

Dosing guidance: *Amended*

The table detailing dosing guidance for NVP and AZT in children from birth to 24 months of age has been amended to accommodate for infants weighing less than 2kg that may be managed at the PHC level of care. Dosing guidance for children up to the age of 24 months has been included in the dosing table. Amendments to the terminology PMTCT (Prevention of mother to Child Transmission) to the alternative, VTP (Vertical Transmission Prevention)[30] have also been made in line with changes to national guidance. Amendments are as tabulated below.

AMENDED FROM:

Nevirapine (NVP) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Nevirapine, oral, 4 mg/kg daily.

Weight kg	Dose mg	Syrup 10 mg/mL	Age Months
2–2.5 kg	10 mg	1 mL	Birth–6 weeks
> 2.5 kg	15 mg	1.5 mL	
> 2.5–7 kg	20 mg	2 mL	> 6 weeks–6 months

Children >6 months of age requiring prophylaxis should use treatment doses. See the Paediatric Hospital STGs and EML, section 9.1.3 The HIV Infected Infant/Child.

Zidovudine (AZT) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Zidovudine, oral, 4mg/kg/dose 12 hourly.

Weight	Dose	Syrup	Age

[30] NDoH Guideline. Guideline for the Prevention of Vertical Transmission of Communicable Infections 2023

kg	mg	10 mg/mL	Months
2–2.499kg	10mg	1 mL	Birth–6 weeks
≥ 2.5 kg	15 mg	1.5 mL	
≥ 2.5–7 kg	60 mg	6 mL	> 6 weeks–6 months

AMENDED TO:

Nevirapine (NVP) and Zidovudine (AZT) doses for infant on VTP:

Newborns and infants:

- Nevirapine, oral, 4 mg/kg daily.
- Zidovudine, oral, 4mg/kg/dose 12 hourly.

	Birth–6 weeks			6 weeks – 6 months	6 – 9 months	9 – 24 months
	1.5-1.9 kg	2.0– 2.49 kg	≥ 2.5 kg			
NVP (Daily)	0.35 mL (0.35 mg) for 2 weeks THEN 0.6 mL (0.6 mg)	1 mL (10 mg) daily	1.5 mL (15 mg) daily	2 mL (20 mg) daily	3 mL (30 mg) daily	4 mL (40 mg) daily
AZT (Twice daily)	2mg/kg for 2 weeks THEN 3mg/kg for 2 weeks THEN 4mg/kg	1 mL (10 mg) twice daily	1.5 mL (15 mg) twice daily	6 mL (60 mg) twice daily	Children > 6 months of age requiring AZT prophylaxis should use treatment doses.	

Cotrimoxazole prophylaxis in high risk infants: *Amended*

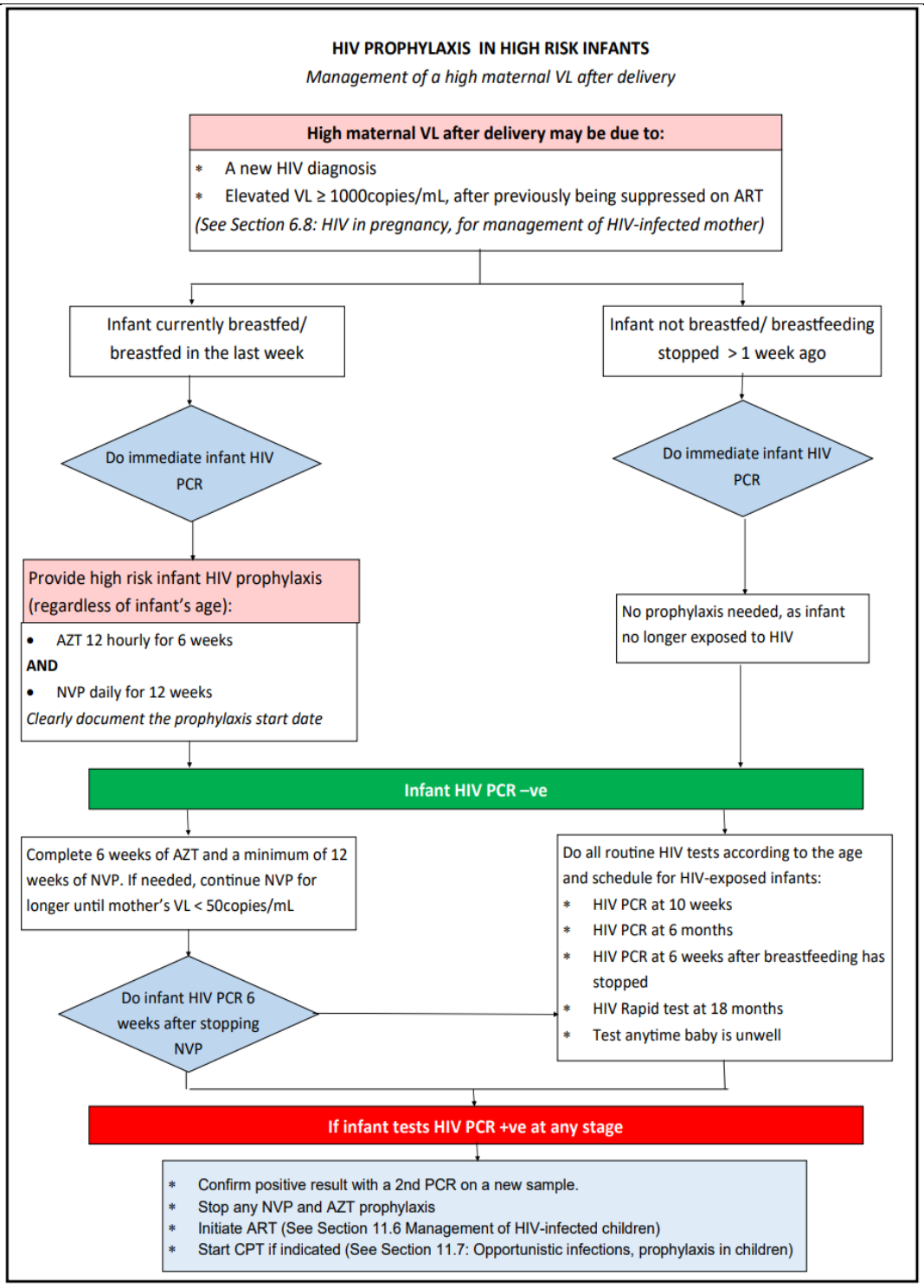
Cotrimoxazole prophylaxis is no longer recommended for high-risk infants older than 6 weeks of age, and this has been removed from the EML, in line with the national ART guideline[31] recommendations. Cotrimoxazole prophylaxis is now only recommended for children confirmed to be HIV positive.

HIV Prophylaxis in high-risk infants: *flow diagram updated*

The flow diagram detailing HIV prophylaxis in high-risk infants has been updated to reflect a lower threshold of VL<50 copies/cell as a measure of viral suppression. Recommendation on cotrimoxazole prophylaxis has been aligned as detailed above (i.e. high-risk infants > 6 weeks of age no longer require cotrimoxazole prophylaxis). This guidance has been aligned to the National ART guideline.[32] The updated flow diagram is as tabulated below:

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

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



11.6 MANAGEMENT OF HIV-INFECTED CHILDREN (<10 YEARS)

Monitoring for infants and children with HIV

Viral load: amended

Guidance for viral load monitoring in children on ART aligned to the national ART guideline as tabulated below:

Viral load: At month 3 on ART, after 12 months on ART, then every 12 months if virologically suppressed. More frequent monitoring (3–6 monthly) recommended in patients with treatment failure. ~~At month 6 on ART, after 12 months on ART, then every 12 months~~.

Eligibility for cotrimoxazole prophylaxis (CPT) – WHO staging: *amended*
Amended in line with Section 11.7 below.

Medicine treatment
Immunisation, deworming and vitamin A programme
BCG immunization: *guidance amended*
The STG has been amended for clarification as tabulated below:

Amended from:

Immunisation, deworming and vitamin A programme

- Continue deworming and vitamin A programme as in the HIV-uninfected child.
- Continue immunisation as in the HIV-uninfected child (See Section 13.3: Vaccines for routine administration), except do not give birth BCG vaccine.

Amended to:

Immunisation, deworming and vitamin A programme

- Continue deworming and vitamin A programme as in the HIV-uninfected child.
- Continue immunisation as per the SA-EPI (See section 13.3). If signs of HIV infection present, defer the BCG vaccination.

Social issues that must be addressed to ensure successful treatment
Adherence**:** *aligned to Paediatric Hospital EML*
The STG has been amended editorially as tabulated below in alignment with the Paediatric Hospital EML and national ART guideline.

AMENDED FROM:
Social issues that must be addressed to ensure successful treatment
These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Adherence to treatment must at least be considered probable. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.
Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.

AMENDED TO:
Social issues that must be addressed to ensure successful treatment
These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.
Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.

Counselling before ART is initiated
Counselling guidance: *Editorial amendments*
Guidance for counselling caregivers before ART is initiated in children has been amended as tabulated below:

AMENDED FROM:
Requirements before ART is initiated:
The child's family (parents, caregivers) should understand:
» ART is life-long.
» The prognosis of the condition (treated and untreated).
» Medicines' adverse effects and modes of action, and the risk and implications of developing resistance, if incorrectly used.
» That all medicines should be given - if two ARVs are missing from the medicine regimen, stop treatment until they are all available again.

AMENDED TO:
Counselling before ART is initiated:
The health care worker should ensure the caregiver/s understanding of HIV, ART and the importance of virological suppression and should train caregivers on practical skills to adhere to ART.

ART Regimens

Dolutegravir: *added*

ARV regimen aligned to the Paediatric EML and national ART guideline recommendations.

Guidance on ART regimens for infants and children: *Amended*

The STG guidance on ART regimens for infants and children has been amended to align with the updated National ARV guidelines. Amendments are as tabulated below:

AMENDED FROM

ART regimens

Are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.

Adjust the dosage of ART according to weight, during follow up visits.

Do not change regimens or move to 2nd line therapy without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Adherence problems need to be addressed thoroughly before switching to a 2nd or 3rd line regimen.

Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ARV medicine.

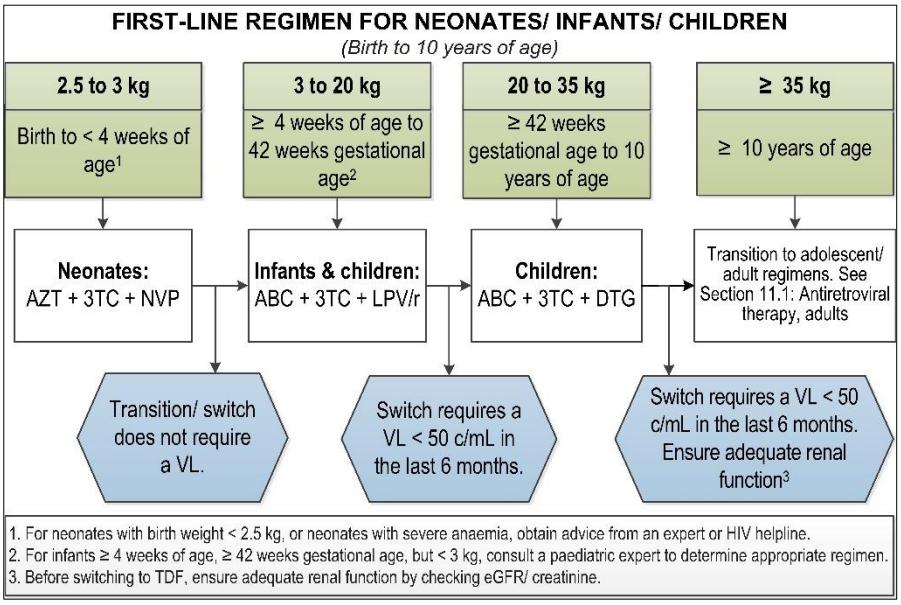
FIRST-LINE REGIMEN	
Infants < 4 weeks or < 3 kg: Consult paediatric expert on treatment regimen and dosage, or refer.	
If weight 3–19.9 kg, and child ≥ 4 weeks of age and ≥ 42 weeks gestational age:	ABC + 3TC + LPV/r.
If weight ≥ 20 to < 35 kg or < 10 years of age:	ABC + 3TC + DTG.
If weight ≥ 35 kg AND ≥10 years of age	TDF + 3TC + DTG

General ART comments

Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.

Fixed-dose combinations are preferred to single agents.

If available, use daily dose regimens.



Initiating ART in children (the 6 steps/IMCI child NIMART)

(These steps that were taken from the IMCI nursing protocol were removed from the EML as no longer relevant)

Side effects:

(The table detailing side effects of ARVs was removed as no longer relevant to the updated ARV treatment guidance.)

AMENDED TO:

ART regimens

- Treatment regimens are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.
- Adjust the dosage of ART according to weight during follow up visits. Assess weight gain and need for adjustment at each visit.
- Do not change regimens or move to an alternative regimen, without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Address adherence problems thoroughly before switching to an alternative regimen.

- Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ART.

First-line ART regimens for infants and children:
ALD1: Clients on a DTG-containing regimen, having never failed a previous regimen (old 'first-line' terminology).
ALD2: Clients on a DTG-containing regimen, who have failed a previous regimen (old 'second- line' terminology).

ALD: abacavir, lamivudine, dolutegravir.

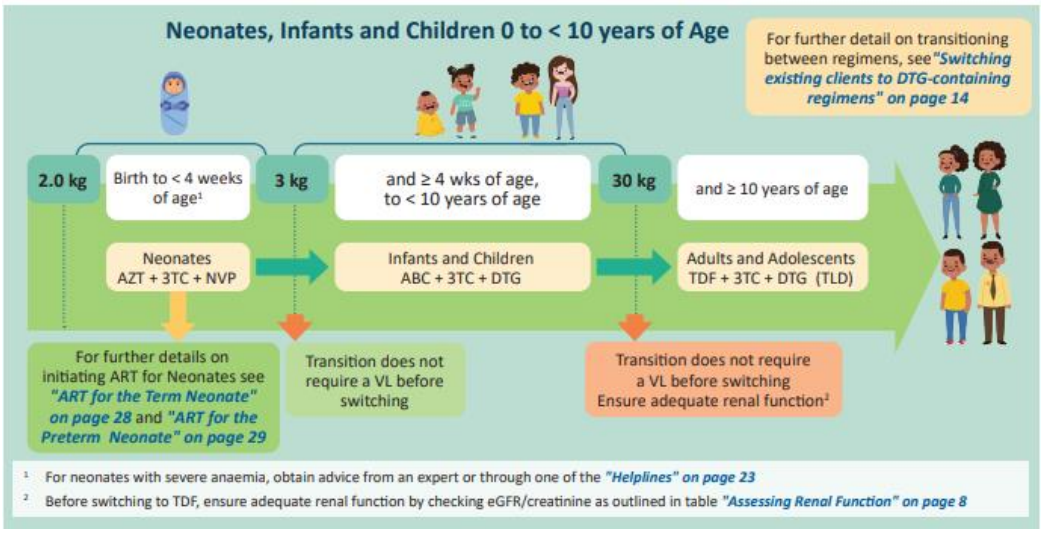
General ART comments

- Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.
- Fixed-dose combinations are preferred to single agents.
- If available, use once daily dose regimens.

Side effects:

In patients being considered for an AZT-containing regimen, monitor for anaemia prior to initiation of ART.

A small proportion of patients initiated on ABC are at risk of abacavir hypersensitivity reaction, which presents with fever, rash and gastrointestinal disturbances. If this reaction is suspected, consult an expert.



Transition from ABC/3TC/LPV/r to DTG based regimens

Guidance to transition from ABC/3TC/LPV/r to DTG based regimens**:** *Added*

New STG guidance on transitioning to DTG based ART regimens for infants and children has been added to align with the updated National ARV guidelines with adoption of the flow diagram. Guidance for patients not eligible to transition to a DTG based regimen is also included. Additions to the STG are as tabulated below:

Transition from ABC/3TC/LPV/r to DTG based regimens

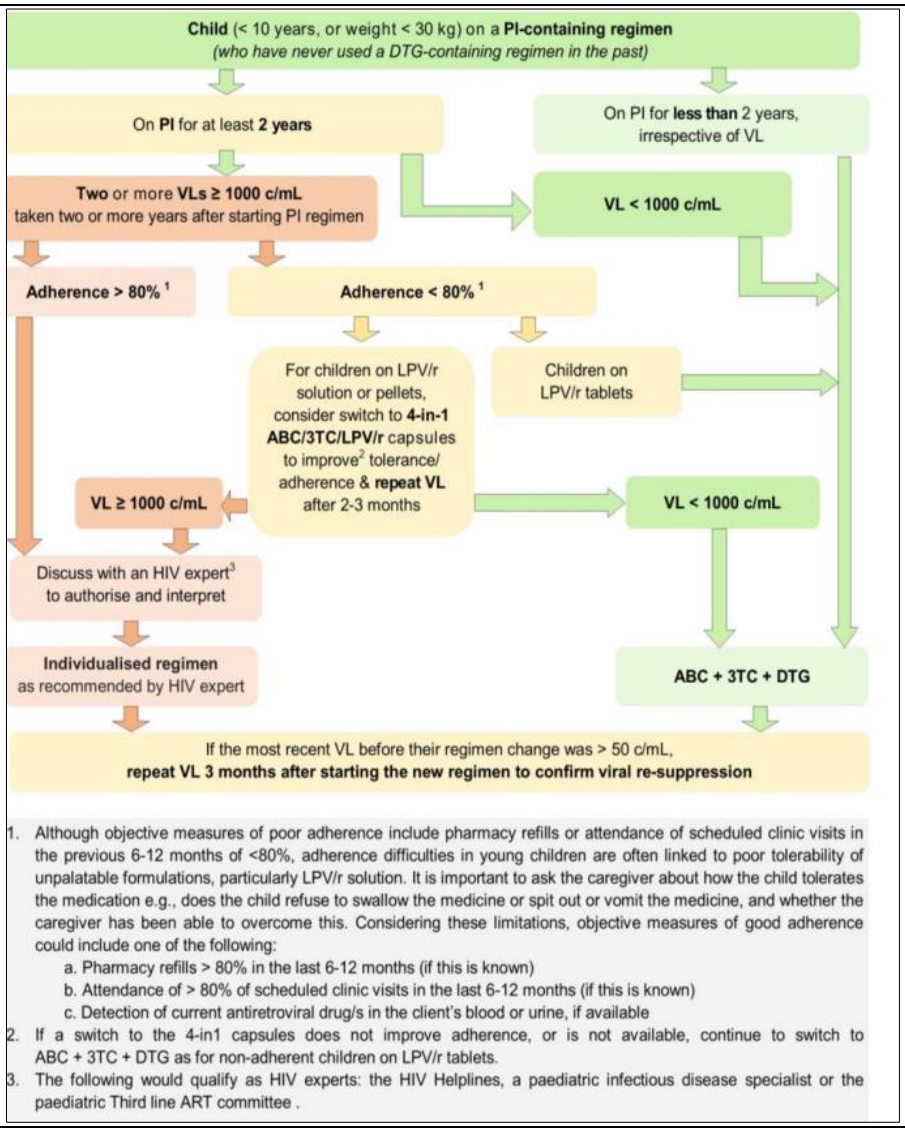
Children < 10 years or weight < 30 kg

- On PI based regimen for < 2 years: switch to DTG based regimen (no VL required)
- On PI based regimen for ≥ 2 years: review VL results, manage as per algorithm in figure 11.6

For patients not eligible for transition to DTG based regimen

- Consider switching to ABC/3TC/LPV/r 4-in-1 formulation and repeating HIV VL in 3 months. If HIV VL < 1000 copies/mL, change to ABC/3TC/DTG and if > 1000 copies/mL, perform an HIV drug resistance test (DR).
- Perform an HIV DR if 4-in-1 formulation not available.
- If NRTI mutations on the HIV DR show:
  - No mutations or only M184V – switch to ABC/3TC/DTG.
  - M184V + other mutations – discuss with an experienced practitioner in child ARV medicine.

Switching children on PI-containing regimens to DTG regimens



Treatment failure

Guidance on managing treatment failure: *Amended*

STG guidance on managing treatment failure in infants and children has been amended to align with the updated National ARV guidelines. Amendments are as tabulated below:

AMENDED FROM:

Treatment failure

- VL is the most sensitive method to detect failure of response to ART.
- Virological failure can be defined as a measurable viral load, despite optimal adherence and optimal dosing over a 4-month period. Clinical and immunological deterioration are late features of ART failure.
- The most common cause of treatment failure is poor adherence. Adherence has to be addressed, before switching to 2nd-line therapy.

AMENDED TO:

Treatment failure

The HIV viral load is the most sensitive method to detect failure of response to ART.

Virological failure can be defined as a measurable viral load despite optimal adherence and dosage over 4 months. Treatment failure is primarily defined by viral loads, as waiting for clinical or immunological failure increases the chances of increasing viral resistance to other available antiretroviral agents.

Poor adherence is the most common cause of treatment failure. Adherence issues should be assessed and then implement strategies to improve adherence.

*For guidance on the step-up adherence package, refer to the National adherence guidelines. https://www.nacosa.org.za/wp-content/uploads/2016/11/Integrated-Adherence-Guidelines-NDOH.pdf

Third-line (patients failing ALD2)

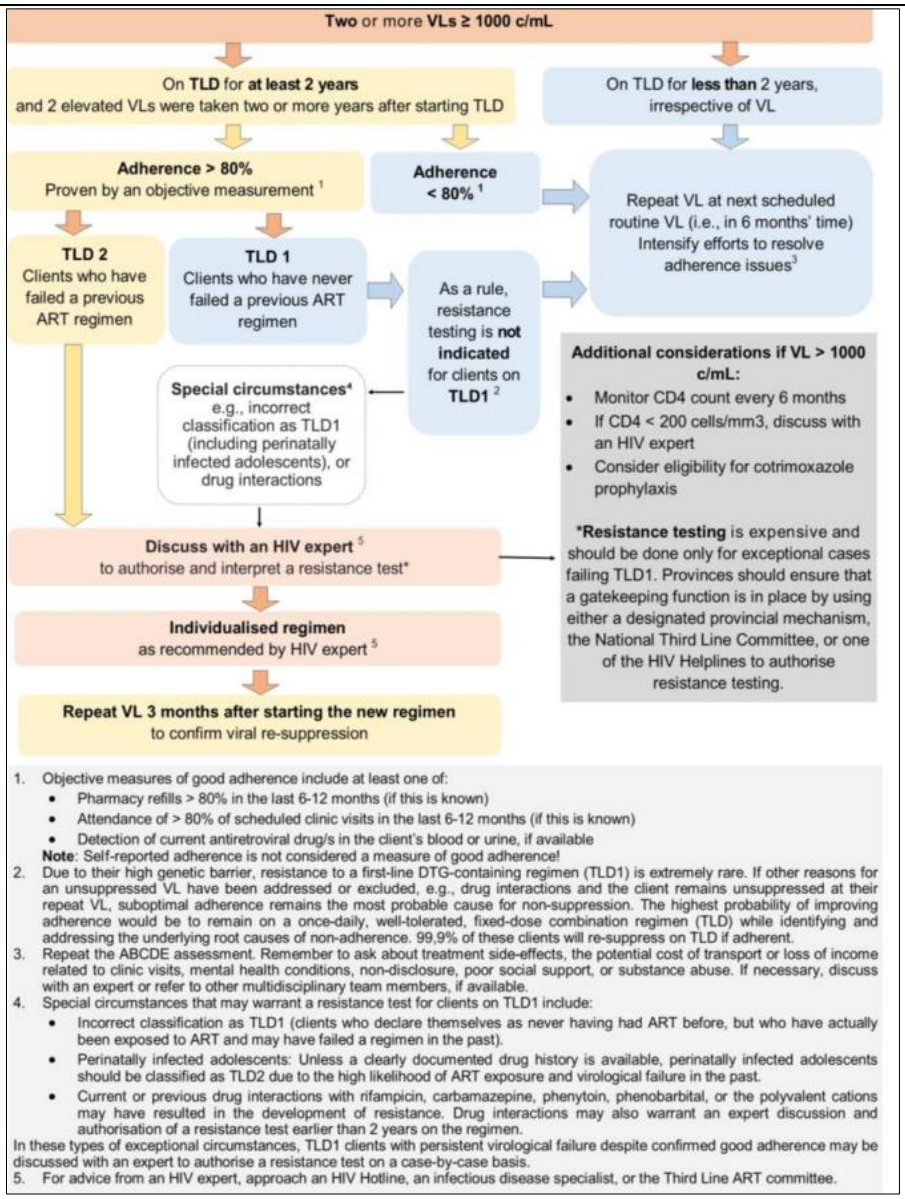
Discuss with expert

» Application forms for third-line antiretroviral therapy (patients failing ALD2) can be accessed at the following link: http://www.sahivsoc.org/Files/Application%20for%20Third%20Line%20Antiretrovirals_2017.pdf
» Important information to assist in applying for third-line antiretrovirals can be found at www.righttocare.org/what-we-do/third-line-art/
Applications can be emailed to TLART@health.gov.za

Management of confirmed virological failure in adolescents on TLD

Guidance on virological failure in adolescents on TLD: *Added*

The flow diagram on the management of confirmed virological failure in adolescents on TLD has been adopted from the National ARV guidelines as tabulated below:

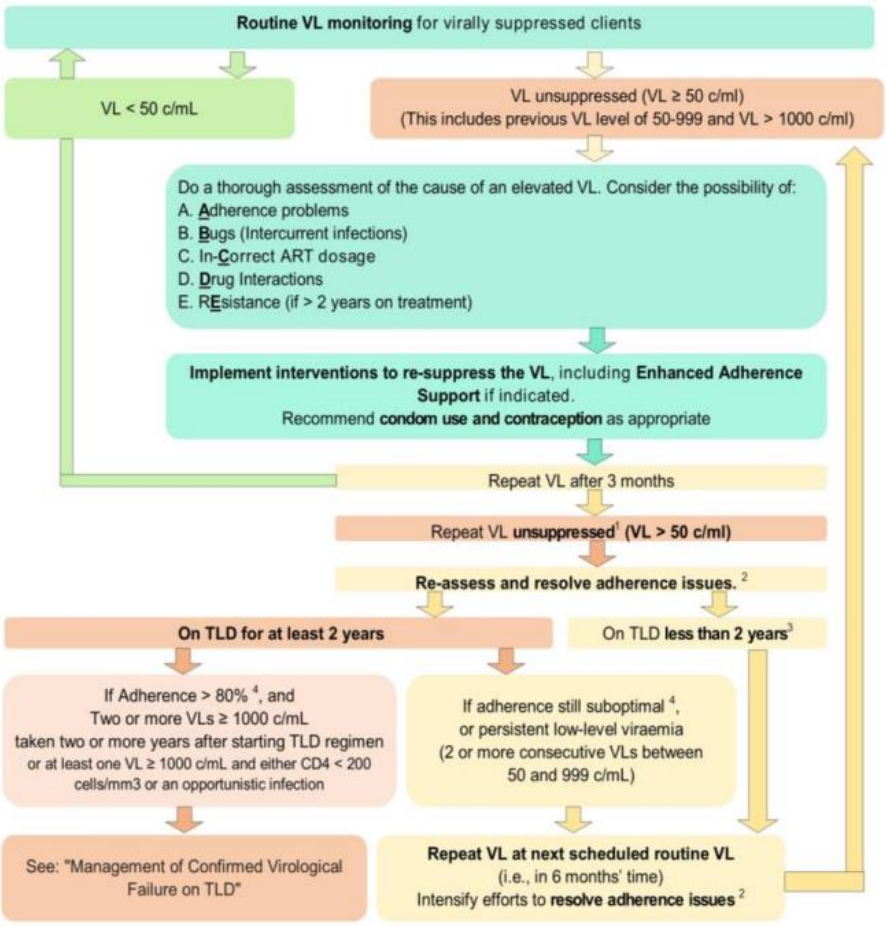


NOTE:
TLD1 = TLD as a first line ART regimen.
TLD2 = TLD in patient who has failed a previous ART regimen.

Viral Load Monitoring for clients on TLD

Guidance on viral load monitoring while on TLD: *Added*

The flow diagram guiding on viral load monitoring while on TLD therapy, has been adopted from the National ARV guidelines as tabulated below:



1. Due to their high genetic barrier, resistance to a first-line DTG-containing (TLD1) regimen is extremely rare. If other reasons for an unsuppressed VL have been addressed or excluded, e.g., drug interactions, and the client remains unsuppressed at their repeat VL, suboptimal adherence remains the most probable cause for non-suppression. The highest probability of improving adherence would be to remain on a once-daily, well-tolerated, fixed-dose combination regimen (TLD) while identifying and addressing the underlying root causes of non-adherence. 99,9% of these clients will re-suppress on TLD if adherent!
2. Repeat ABCDE assessment as outlined on "ABCDE assessment of an Elevated Viral Load" on page 20. Remember to ask about treatment side-effects, the potential cost of transport or loss of income related to clinic visits, non-disclosure, gender-based violence (GBV), and current or prior drug interactions. Current or previous drug interactions with rifampicin, carbamazepine, phenytoin, phenobarbital, or the polyvalent cations may have resulted in the development of resistance.
3. Drug interactions may also warrant an expert discussion and authorisation of a resistance test earlier than 2 years on the regimen. If necessary, discuss with an expert
4. Objective measures of good adherence include at least one of:
   a. Pharmacy refills > 80% in the last 6-12 months (if this is known)
   b. Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known)
   c. Detection of current antiretroviral drug/s in the client's blood or urine, if available

Note: Self-reported adherence is not considered a measure of good adherence.

ART dosing tables for infants and children

Dosing tables: *aligned to the national ART guideline*

The ARV dosing tables from the national ART guideline have replaced previous ARV dosing tables (refer to tables 11.12 included in the EML).

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Cotrimoxazole prophylaxis (CPT), oral: *directions for use amended*

Aligned with the Paediatric Hospital Level HIV chapter (2021) based on the benefit:risk assessment of CPT in HIV exposed, uninfected (HEU) infants at low- and high-risk of HIV infection through vertical mother-to-child transmission (MTCT).

Evidence: There is strong evidence that CPT significantly reduces mortality and infectious morbidity amongst HIV-infected adults and children; and CPT has been shown to be beneficial in HEU infants living in malaria endemic areas. However, a recent appraisal of the evidence by the World Health Organization included two Sub-Saharan studies (n= 2848 and n=1219, respectively), which showed that CPT did not improve survival amongst HEUs with low risk for MTCT,

in areas unaffected by malaria. CPT also was shown not to have an effect on hospitalisation, or the incidence of grade 3 or 4 common childhood illnesses (pneumonia or diarrhoea) compared to no CPT. However, harms such as more grade 3/4 neutropaenia as well as cotrimoxazole resistance was more prominent amongst HEUs on CPT.
Broad-spectrum CPT has also been shown to select for antimicrobial resistance of other non-sulfonamide antimicrobials, by decreasing gut microbiome diversity and increasing antibiotic resistance. Powis et al. showed that HEUs on CPT had commensal gastrointestinal bacteria that were more resistant to cotrimoxazole and amoxicillin compared to the placebo group.[9]
Therefore, targeted CPT rather than global CPT for HEU infants has been proposed in order to minimise unnecessary selection of antimicrobial resistance and unnecessary adverse effects, especially amongst HEUs who are at low risk of MTCT of HIV.

Cotrimoxazole prophylaxis (CPT) – WHO clinical staging : *Added*
The WHO clinical stage 3 and 4 has been added as criteria for consideration for the initiation of cotrimoxazole prophylaxis in children over the age of 1 year[33]. Amendments to the STG are detailed below:

AMENDED FROM:

Cotrimoxazole prophylaxis

Initiation

- All HIV-infected infants (< 1 year), starting from 6 weeks of age.
- Any child 1–5 years of age with CD4% < 25%.
- Any child > 5 years of age with CD4 count < 200 cells/mm3.
- Cotrimoxazole, oral, once daily (everyday). See dosing table, pg 23.4.

Discontinuation

- HIV-infected child > 1 year of age whose immune system is fully reconstituted on ART (i.e. 1–5 year: CD4% > 25% or > 5 years: CD4 count > 200 cells/mm^3 on two tests at least 3–6 months apart).
- Child is HIV-infected with PJP infection: after treatment, continue cotrimoxazole prophylaxis until 5 years of age.

AMENDED TO

Cotrimoxazole prophylaxis

Initiation

- All HIV-infected infants (< 1 year), starting from 6 weeks of age.
- Any child 1–5 years of age with CD4 < 25%, or WHO stage 3 and 4
- Any child > 5 years of age with CD4 count < 200 cells/mm^3, or WHO stage 3 and 4.

• Cotrimoxazole (sulfamethoxazole/trimethoprim), oral, once daily.

Recommended daily dosage by weight band	Dose of sulfamethoxazole/ trimethoprim	Suspension (200/40 mg per 5 mL)	Single strength tablet (400/80 mg)	Double strength tablet (800/160 mg)
3 to 5.9 kg	100/20 mg	2.5 mL	¼ tablet	-
6 to 13.9 kg	200/40 mg	5 mL	½ tablet	-
14 to 24.9 kg	400/80 mg	10 mL	1 tablet	½ tablet
25 kg	800/160 mg	-	2 tablets	1 tablet

Discontinuation
Prophylaxis may be discontinued if the immune system is fully reconstituted on ART i.e.
Child > 1 year of age, *AND* immune system shows signs of full reconstitution on two CD4 tests at least 3-6 months apart (regardless of clinical stage), i.e.:
Child 1-5 years of age: CD4 > 25%
Child > 5 years of age: CD4 > 200 cells/mm^3

Immunisation
Amended to align with Section 11.6 above as follows: *'Continue immunisation as per the SA-EPI (See section 13.3). If signs of HIV infection present, defer the BCG vaccination.'*

[33] Temporal Trends in Co-trimoxazole Use Among Children on Antiretroviral Therapy and the Impact of Co-trimoxazole on Mortality Rates in Children Without Severe Immunodeficiency | Journal of the Pediatric Infectious Diseases Society | Oxford Academic (oup.com)

11.8.7 TUBERCULOSIS (TB)

Description: *amended for improved clarity*

The STG has been amended as tabulated below for improved clarity:

AMENDED FROM:

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.
Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.
TB should be considered early in non-resolving pneumonias.
Tuberculin tests are often not reliable and a negative test does not exclude TB.
If TB is suspected but cannot be proven, refer early for diagnostic evaluation

TB prophylaxis Z29.2 + (B24)

Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

- » Exposed to a close contact with infectious pulmonary TB or
- » TST-positive (only the 1st time a positive TST is shown).
  - Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
    - Maximum dose 300 mg daily.
    - See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.

If patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment, refer.

TB treatment

If the child is not yet on ART:
Commence TB treatment first. Follow with ART, usually after 2–8 weeks:

- 2 weeks if CD4 < 50 cells/mm3
- 8 weeks if CD4 > 50 cells/mm3

- » Check ALT before commencing ART. If the ALT is raised, discuss this with an expert as it may not be an absolute contra-indication to treatment.
- » Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:

- » Commence TB treatment taking into consideration possible medicine interactions.

If the child needs to take concomitant ART and rifampicin:

- » Dolutegravir: use DTG 12 hourly.
- » Efavirenz: use the normal recommended dosage as per dosing table on pg 23.4.
- » Abacavir and lamivudine: no dose adjustment required.
- » Lopinavir/ritonavir: Add additional ritonavir to ensure an equal dose in mg of lopinavir and ritonavir while on rifampicin. For example, for each mL of LPV/r solution (80/20 mg/mL), add 0.75 mL of ritonavir solution (80 mg/mL). See dosing table, pg 23.9.
- » Give pyridoxine (vitamin B6) to all children on TB and ART, to avoid development of peripheral neuropathy.

AMENDED TO:

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.
Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.
TB should be considered early in non-resolving pneumonias. At every follow up visit, ask about symptoms of cough, night sweats, fever, TB contacts and check for failure to thrive.

Refer early for diagnostic evaluation. If TB is suspected:

- Chest radiograph (CXR)
- GeneXpert on any relevant specimen including stool
- Culture on respiratory or appropriate specimen
- Urine-LAM. If no sample obtained, continue evaluation

TB prophylaxis Z29.2 + (B24)
Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

- Exposed to a close contact with infectious pulmonary TB or
- TST-positive (this test is only reliable the first time TPT is given).
- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
  Maximum dose: 300 mg daily.

See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.
Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.
Refer if patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment.

TB treatment
If the child is not yet on ART:
- » TB treatment and ART can be started at the same time, with the exception of children with TB meningitis – start ART at 4 weeks regardless of CD4 count to avoid IRIS.
- » Assess the child for possible disseminated TB disease.
- » Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:
- » Commence TB treatment, considering possible drug interactions and the need for ART dosage adaptations.

If the child needs to take concomitant ART and rifampicin-containing treatment:
- Dolutegravir: use dolutegravir twice daily.
- Efavirenz: use the normal recommended dosage as per the dosing table.
- Abacavir and lamivudine: no adjustment of dosages.
- Lopinavir/ritonavir: refer to the dosage table for the ritonavir boosting doses.
  - Avoid using double-dose lopinavir/ritonavir solution in young children. If ritonavir powder is not available, consult an expert.
- Give pyridoxine (vitamin B6) to all children on TB treatment and ART, to avoid development of peripheral neuropathy.

C. HIV PREVENTION

11.11 PRE-EXPOSURE PROPHYLAXIS (PREP)

Note: Oral PrEP is now available at all primary level facilities in the public sector.

Contraindications to PrEP

The following was amended for clarity purposes:

» Estimated creatinine clearance or eGFR < 60 mL/min.

Oral PrEP Regimen

Tenofovir + emtricitabine: *duration of therapy amended*

To reach adequate protective levels in tissue, guidance is provided to continue oral PrEP for 7 days for all sexual practices, aligned with the 2021 updated National Department of Health PrEP guidelines[34]. Additional guidance to use barrier protection until therapeutic drug concentrations are attained also added.

STG text was amended as follows:

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required ~~for anal sex and 20 days for vaginal sex.~~ Individuals should be counselled that additional barrier protection should be used until therapeutic levels achieved.

Level of Evidence: III Guidelines[35]

Screening investigations before starting PrEP

Hepatitis B surface antigen (HBsAg) screening: *Guidance clarified*

STG guidance for hepatitis B vaccination has been clarified to ensure that patients are assessed for eligibility in line with the eligibility criteria included in table 11.14: PrEP eligibility determined by hepatitis B immune status.

PrEP Initiation

PrEP Initiation algorithm: *Guidance clarified*

Prep is contraindicated in patients with chronic kidney disease (CKD) and a eGFR <60mL/min. This caution has been added as a footnote to the algorithm on PrEP initiation as tabulated below:

NOTE: In patients with Chronic Kidney Disease (CKD) with eGFR < 60mL/min, PrEP is contraindicated.

Oral PrEP follow up and monitoring

Estimated creatinine clearance: *monitoring updated*

Aligned with 2021 updated National Department of Health PrEP guidelines,[36] and STG text was updated as follows:

Activity	Frequency		
Estimated creatinine clearance	**Frequency dependant on pregnancy status, age and co-morbidity:**		
	Age/ pregnant	**Co-morbidity**	**Creatinine**
	< 30 years	None	n/a
	30–49 years	None	Baseline
	< 49 years	Diabetes/ hypertension	Baseline, annually
	≥ 50 years	None	Baseline
	≥ 50 years	Diabetes/ hypertension	Baseline, annually
	Pregnant	n/a	Baseline, 3 & 6 months

Relevant medicine interaction information

MDR-TB Guidance: *Deleted*

Interactions with MDR-TB medicines have been removed from table 11.16: Oral PrEP drug interactions, as this is no longer relevant with the newly introduced BPaL regimen for the management of MDR-TB.

[34] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[35] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[36] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.

Stopping oral PrEP

Tenofovir + emtricitabine**:** *duration of therapy amended*

The following was amended, aligned with 2021 updated National Department of Health PrEP guidelines.[37]

Continue oral PrEP for ~~28~~ 7 days after the last potential HIV exposure.

Other PrEP agents:

Dapivirine vaginal ring: *not added*

A summary of the NEMLC recommendation is included below. A copy of the medicine review[38] and economic analysis[39] may be included 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: Based on this evidence review, the PHC/Adult hospital level committee suggests not to use the dapivirine ring as an additional option for prevention of HIV acquisition in women. *Rationale:* Available evidence for the dapivirine ring is restricted to placebo-controlled data, with no studies comparing dapivirine to oral tenofovir plus emtricitabine, the current standard of care in South Africa. There is currently no data for efficacy in adolescents. The dapivirine ring cannot be used in pregnancy. There is sub-group of women who cannot use tenofovir plus emtricitabine for whom the dapivirine ring may be an option. However, at the current proposed price, dapivirine is unaffordable. The estimated threshold price for reviewing this recommendation is R52.00 per ring. **Level of Evidence:** Moderate quality of evidence **Review indicator: Reduction in price**					
NEMLC RECOMMENDATION (23 JUNE 2022): The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation with amendments to the review indicator (added, uptake and social harms), as follows: **Review indicator: Reduction in price; Uptake of all PrEP; Social harms of all PrEP**					
Monitoring and evaluation considerations: see review indicators above					
Research priorities: see review indicators above					

Cabotegravir: *Not added*

A summary of the NEMLC recommendation is included below. A copy of the medicine review[40] and economic analysis[41] may be included at the end of this report or alternatively, accessible on the NHI webpage. NEMLC has also engaged with representatives from the NDoH and the program regarding receipt of donated stock of injectable cabotegravir - refer to the evidence review document for a summary of the NEMLC's deliberations regarding this donated stock.

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: Although the efficacy of CAB is high, and the safety profile acceptable, the PHC/Adult Hospital Level Committee suggests not to use CAB as PrEP for HIV, until such time as the price becomes known, and the evidence of efficacy for regimens that do not include an oral lead-in phase are available. *Rationale:* Two phase 3 RCTs both found that PrEP with long-acting injectable CAB had greater efficacy than oral tenofovir plus emtricitabine. A model to assess budgetary impact and cost-effectiveness analysis has been developed, however until a price is confirmed, a final recommendation cannot be made. **Level of Evidence: High certainty evidence** **Review indicator:** Evidence of efficacy in regimens that do not require oral lead-in doses, information on cost.					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): Accepted **UPDATED NEMLC RECOMMENDATION (e-ratified, 30 MARCH 2023):** Updated recommendation following completion of the budget impact analysis (March 2023) ratified by NEMLC, as above.					
Monitoring and evaluation considerations					
Research priorities					

[37] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[38] NDoH evidence summary. DapivirineRingForPrEP_PHC-Review_9June2022_v5
[39] NDoH Cost effectiveness Analysis Report. DapvirineRingForPrEP_CEA and costing report_23May2022_v2
[40] NDoH evidence summary. CABForPrEP_PHC-Review_13 Sep 2024_v5.1
[41] NDoH Cost effectiveness Analysis and BIA Report. Cabotegravir (CAB-LA) cost effectiveness and budget impact analysis_Final_23 February 2023

D: SIDE EFFECTS AND COMPLICATIONS OF ART

11.14 LACTIC ACIDOSIS

Lactic acidosis STG: *deleted*

An external comment was received querying why guidance was provided for lactic acidosis only and why not other adverse effects. Therefore, section 11.14: Lactic acidosis was deleted and a cross-reference was made to the Adult Hospital Level STGs and EML for detailed information on adverse effects associated with ARVs.

The following was added to the STG text:

Refer to the Adult Hospital Level STGs and EML: Section 10.1.1Management of selected antiretroviral adverse drug reactions, and consult with an infectious disease specialist as required.

And the following was deleted:

~~**11.14 LACTIC ACIDOSIS**~~

~~E87.2 + (Y41.5 + B24)~~

~~**Description**~~

~~All nucleoside analogues have been associated with lactic acidosis, which is rare but life-threatening. Initial symptoms vary and occur between 1–20 months (median 4 months) after starting therapy. The risk is highest with stavudine, followed by didanosine and then zidovudine.~~

~~**Diagnostic criteria**~~

~~*Clinical*~~

~~Clinical prodromal syndrome:~~

~~» Generalised fatigue~~

~~» Weakness and myalgia~~

~~» Gastrointestinal symptoms:~~

~~- nausea - vague abdominal pain~~

~~- vomiting - hepatomegaly~~

~~- diarrhoea - anorexia~~

~~- unexplained weight loss~~

~~» Respiratory symptoms: tachypnoea and dyspnoea.~~

~~» Neurologic symptoms, including motor weakness.~~

~~*Investigations*~~

~~» Laboratory abnormalities:~~

~~- Hyperlactataemia~~

~~Raised: 2.1–5 mmol/L~~

~~Severely raised : > 5 mmol/L~~

~~- Lactic acidosis, defined by:~~

~~Lactate: > 5 mmol/L~~

~~Bicarbonate: < 20 mmol/L~~

~~Severe acidosis i.e. pH < 7.3~~

~~Increased anion gap i.e. > 15 mEq/L~~

~~**Referral**~~

~~All urgently.~~

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.

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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.

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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

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APPENDIX 1: CHARACTERISTICS OF INCLUDED STUDIES

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

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	were sponsored by Gilead Sciences. COI: Authors reported on fees/grants/honoraria with multiple pharma companies including Gilead Sciences.	n= 7316	Control: Continue stable baseline regimen (SBR) (n=3150) *Boosted and unboosted regimens were included*	• ART on weight gain	**Demographic factors**: younger age and lower baseline body mass index were associated with any or ≥10% weight gain Clinical factors: Absolute values and changes in cholesterol components and systolic blood pressure were similar between switch and SBR participants who experienced ≥10% weight gain, with small reductions in HDL noted in this group. **ART**: By week 48, 4.6% gained ≥10% weight (6.4% of switch and 2.2% of SBR), the greatest risk was with switch from efavirenz (EFV) to rilpivirine (RPV) or elvitegravir/cobicistat and switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF). Switch from abacavir to TAF was associated with less weight gain than switch from TDF to TAF and was not associated with increased risk for ≥10% weight gain.	Baseline ART was a predictor of post-switch weight gain; participants who switched off of EFV and TDF had the greatest weight gain. The biological mechanisms that underlie the differential effects of switching ART agents on weight and associated clinical implications require further study"
Venter et al 2020 ADVANCE trial -96 week data	RCT: open-label, non-inferiority phase 3 trial based across 2 sites in S.Africa. 96 week data Funding source: Unitaid, USAID, Gilead Sciences, and ViiV Healthcare contributed to study design. COI: Authors reported on multiple pharma and non-phrama-related interests.	PLHIV aged 12 years or older weighing >/= 40kg, with no ARV exposure in the previous 6 months, CrCl > 60 mL/min (>80 mL per min in individuals aged <19yrs) and HIV-1 RNA concentration >/= 500 copies/mL. (n=1053)	Random assignment (1:1:1) to one of three oral regimens: 1. DTG/ emtricitabine, and TAF (n=351) 2.DTG emtricitabine, and TDF (n=351) or 3.efavirenz, emtricitabine, and TDF (n=351)	Primary Endpoint: Proportion of participants who had a plasma HIV-1 RNA concentration of less than 50 copies per mL at week 48 Secondary endpoint Plasma HIV-1 RNA concentration of less than 50 copies per mL at the week 96 visit	Secondary endpoint – 96 week data **% of participants reaching plasma HIV-1 RNA concentration of less than 50 copies per mL:** DTG/emtricitabine/TAF = 79% DTG/emtricitabine/TDF = 78% Efavirenz/emtricitabine/TDF = 74% Non-inferiority established and no significant treatment effects noted. Sub-group analysis **Virological failure** DTG/emtricitabine/TAF = 18% DTG/emtricitabine/TDF = 19% Efavirenz/emtricitabine/TDF =14% **Emergent diabetes** DTG/emtricitabine/TAF = 2% DTG/emtricitabine/TDF = 1% Efavirenz/emtricitabine/TDF = <1% **Weight gain (where data available among participants), mean weight gain which was higher in females**: DTG/emtricitabine/TAF = 7.1kg DTG/emtricitabine/TDF = 4.3kg Efavirenz/emtricitabine/TDF = 2.3kg **Treatment-realted discontinuation (within 48 weeks)** DTG/emtricitabine/TAF = nil DTG/emtricitabine/TDF = nil Efavirenz/emtricitabine/TDF = 3% liver dysfunction (n=4), rash (n=3), renal dysfunction (n=2), neuropsychiatric (n=1).	**EFFICACY & SAFETY** **Study conclusion:** "Medium-term and long-term metabolic and clinical consequences of the considerable increase in bodyweight observed in participants given these antiretroviral regimens and the trajectory of this weight gain over time, especially among women, require further study." **NOTES** Isoniazid prophylaxis was routinely used in participants, according to local guidelines. Women who became pregnant and participants who developed tuberculosis were allowed to continue on adapted regimens. Genotyping not done before initiating ART. There were differences in pill burden between groups.
Tao X, et al. 2020	Design: Meta-analysis - 7 RCTs including: • one-phase 1/2 trial	n=6269	Experimental: TAF containing regimen	***Efficacy outcomes:***	**Virologic suppression:** Rates were similar: (RR, 1.02; 95% CI, 1.00-1.04; p > 0.05) at week 24 (94.0% vs. 94.2%,), week 48 (90.7% vs. 89.5%), and week 96 (86.2% vs. 84.8%).	**EFFICACY & SAFETY (Non-inferiority)** **Study Conclusions:**

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	• two-phase 2 trials • four-phase 3 trials Funding Source: Grants from National Major Scientific and Technological Special Project and the Chongqing Municipal Health and Family Planning Commission Medical Research Projects COI: Authors declared that there were none		Control: TDF containing regimen	• Virologic suppression • CD4 Cell Count • Virologic Failure • Adherence *Safety outcomes:* • Adverse events • Discontinuation due to adverse events • Grade 3 or 4 adverse events • Fractures • Bone Outcomes • Renal outcomes Lipid Profile	**CD4 Cell Count:** No significant improvement in CD4 cell count in TAF vs TDF regiments for antiretroviral-naive patients (SMD, 0.05; 95% CI, -0.08 to 0.19; $p > 0.05$) **Virologic Failure:** No significant difference in treatment-naive patients between the two groups during weeks 48 and 96 (RR, 1.25; 95% CI, 0.85–1.84; $p > 0.05$) **Adherence**: To the end of weeks 24, 48, and 96, expressed as the median cumulative adherence change in the treatment-naive patients from baseline. Measured by pill count : 91.61% in the TAF vs 88.22% in the TDF-containing regimens. Four RCTS: No significant difference for the Treatment-naive patients between the two groups (RR, 1.01; 95CI, 0.99–1.03; $p > 0.05$). **Adverse Events:** Both treatments were safe and well-tolerated, and most adverse events were similar as mild to moderate in severity. **Discontinuation due to adverse events:** Six RCTs: discontinuations because of adverse events. 1.54% TAF- vs 2.66% TDF-containing regimens. Prevalence of discontinuation due to adverse events in TAF group was significantly lower than those of the TDF-containing regimens (RR, 0.55; 95CI, 0.37–0.82; $p < 0.05$). **Grade 3 or 4 adverse events:** Six RCTs - between 48 weeks and 96 weeks of follow-up, similar adverse events for TAF and TDF (18.49% vs. 17.64%), and there was no significant difference between TAF vs TDF regimens (RR, 1.07; 95CI, 0.96–1.20; $p > 0.05$). **Fractures:** Five RCTs: including 0.35% TAF-vs 0.82% patients who received TDF-containing regimens, - with no significant difference between the two groups at weeks 48 and 96 (RR, 0.48; 95CI, 0.12–2.00; $p > 0.05$). **Bone Outcomes:** Compared with the TDF-containing regimens, the TAF-containing regimens in patients had significantly smaller reductions in both hip (RR, 0.33; 95CI, 0.29-0.39; $p < 0.05$) and spine (RR, 0.58; 95CI, 0.51-0.65; $p < 0.05$). **Renal Outcomes:** TAF-containing regimens in patients had significantly fewer increases for renal events than those of the TDF-containing regimens through 48 weeks (0.31; 95% CI, 0.18-0.55; $p < 0.05$). **Lipid Profile:** Significant differences in the median changes between the TAF-containing regimens and the TDF-containing regimens, which included total cholesterol (30.87 vs. 11.63, $p < 0.05$), low-density lipoprotein (LDL) cholesterol (17.47 vs. 5.40, $p < 0.05$), high density lipoprotein (HDL) cholesterol (6.12 vs. 2.67, $p < 0.05$) and triglycerides (22.86 vs. 7.48, $p < 0.05$), whereas the total cholesterol/HDL cholesterol ratio remained unchanged (median increases 0.14 vs. 0.03, $p > 0.05$) for the treatment-naive patients at week 48.	"Our meta-analysis indicated that efficacy, safety, and tolerability of TAF-containing regimens were non-inferior in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection. Furthermore, compared with those receiving the TDF-containing regimens, patients on the TAFcontaining regimens had significant advantages in renal function, bone parameters, and lipid profile for the naive patients."

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Tao,. Et al 2019	Design: Meta-analysis - 8 RCTs including: randomized, actively controlled, multicenter, phase 3 trials Funding Source: Grants from National Major Scientific and Technological Special Project and the Chongqing Municipal Health and Family Planning Commission Medical Research Projects COI: Authors declared that there were no conflict of interests	n=7613 patients recruited. n=4434 were participants switching from TDF-containing regimens to TAF-containing regimens n= 3179 participants received TDF-containing regimens.	Switching from TDF-containing regimens to TAF-containing regimens TDF-containing regimens.	**Efficacy Analysis:** • Virologic response • CD4+ cell counts • Virologic failure **Safety analysis:** • Adverse Events • Discontinuation due to adverse events • Grade 3 or 4 adverse events • Fractures • Bone Outcomes • Renal Outcomes • Lipid Profile	***Efficacy:*** **Viral Suppression:** Switch to TAF-containing regimens had significantly better viral suppression than those continuing TDF-containing regimens at weeks 48 and 96 (RR, 1.02; 95CI, 1.00-1.03), but no significant difference in the per-protocol (PP) analysis (RR, 1.00; 95CI, 0.99-1.01). **CD4 Cell Counts:** Virologically suppressed HIV-infected patients on the TAF-containing regimens had significant increases in CD4 cell counts vs those receiving the TDF-containing regimens, (SMD, 0.12; 95CI, 0.08 to 0.17). **Virologic Failure:** n=55 patients (from 7 RCTS) had virologic failure after 48 and 96 weeks of treatment, 31 (0.84%; N=3671) participants who received TAF-containing regimens had virologic failure with resistance. For the combined effect size of virologic failure, no significant difference was found in the ART-experienced patients between the two groups at week 48 (RR, 1.04; 95% CI, 0.44– 2.47; p > 0.05). ***Safety:*** **Adverse Events;** n=6181 patients (from 6 RCTs), reported adverse events (AEs) during 48 and 96 weeks of therapy. Safety profiles of TAF vs TDF-containing regimens were similar (72.16% vs. 70.99%) reporting any treatment-emergent adverse events. **Discontinuation due to adverse events:** Number of AEs leading to study drug discontinuation was similar n=66 (1.49%) in the TAF-containing regimens and n=50 (1.68%) in TDF-containing regimens. **Grade 3 or 4 adverse events:** After 48 and 96 weeks of therapy, 709 (18.82%) of 3767 participants in the TAF-containing regimens vs 452 (18.76%) of 2410 participants in the TDF-containing regimens had grade 3 or 4 laboratory abnormalities **Fractures:** Uncommon, non-significant (32 [0.72%] of 4434 in the TAF vs. 22 [0.72%] of 3073 in the TDF-containing regimens), (RR, 1.08; 95CI, 0.60–1.93; p > 0.05). **Secondary Outcomes** **Bone Outcomes:** At weeks 24, 48, 72 and 96, no significant improvements in bone mineral density in the hip (RR, 1.00; 95CI, 0.98–1.01; p > 0.05)) and spine (RR,1.11; 95CI, 0.98–1.01; p > 0.05) among ART-experienced patients after switching to TAF- containing regimens vs continuing TDF-containing regimens. **Renal Outcomes:** Renal AEs were reported from 6 RCTs which occurred in 34 (0.92%) of 3680 participants in the TAF-containing regimens group vs. 32 (1.38%) of 2323 participants in the TDF-containing regimens group. Fewer patients had significant renal AEs in the TAF-containing	**EFFICACY & SAFETY** Study conclusion: "Virologically suppressed HIV-infected patients on TDF-containing regimens significantly benefit from switching to TAF-containing regimens, resulting in better viral suppression, better immune reconstruction, and less bone and renal problems."

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					regimens group than in the TDF-containing regimens group through 48 and 96 weeks (RR, 0.50; 95CI, 0.27–0.94; p < 0.05) **Lipid Profile:** 5.2% of all TAF-containing regimen patients vs 3.8% TDF-containing patients started lipid-lowering drugs. No statistical differences were found between the two groups after 48 weeks and 96 weeks of treatment (RR, 1.27; 95%CI, 0.94–1.71)	
Tamuzi., et al 2018	Design: Meta-analysis -18 RCTs included Funding Source: Not declared COI: The authors have not declared any conflict of interests.	HIV-infected adult patients.	Intervention = TAF contained regimens Control = TDF contained regimens	**Primary Outcomes:** • Viral load • Serum clearance creatinine • Proteinuria • HBV DNA • HBsAg **Secondary Outcomes:** • Bone mineral density • CD4 count • Hepatic transminases • Adverse events	**Virological failure (48 to 144 weeks):** 5RCTs: TAF less likely to treatment failure vs TDF group (OR 0.92, 95% CI 0.65 to 1.29). **Creatinine Clearance rate(ml/min) (48 to 144 weeks):** 10 RCT: s Random-effects meta-analysis of glomerular filtration rate yielded a pooled MD estimate of -3.94(95% CI -6.07 to-1.81, P P<0.000001) with I2=100%. Not statistically significant (P=0.63). **Proteinuria (48 to 144 weeks):** Proteinuria was higher in TDF group OR 1.11 (95% CI 0.8 1 to 1.54, P=0.03). **HBV DNA: After 96 weeks:** 4 RCTs: Significant in one study - OR 1.29 (95%CI 1.05 to 1.59, P=0.02). 3 studies reported a non-significant increase of HBV DNA odds. **Mean percentage change Spine BMD (%) (48 to 144 weeks):** 11 RCTs All statistically significant with random effect model. Transforming from fixed to random effect, the overall results decreased to 1.6%. The mean difference of percentage change spine BMD was decreased in TFD compared to TAF -1.77 (-1.97 to -1.58) with P=0.001 **CD4 count (cells/µl) (48 to 144 weeks):** TDF group had a low MD of CD4 count than TAF group (MD -18.99, 95% CI -19.61,- 18.37, <00001). **ALT above ULN (96 weeks):** ALT above ULN reached the lowest odds in TAF group compared to TDF group (OR 0.75, 0.57 to 0.98), 2 studies included in this meta-analysis were not statistically. **Any adverse events (96 weeks):** TAF vs TDF on any adverse event was not statistically significant with OR 1.09 (95% CI 0.95 to 1.25, 7 studies, P=0.21), **Serious adverse events (48 to 144 week):** Balanced in TAF and TDF groups.	**RENAL TOXICITY.** **EFFICACY IN HIV/HEP B CO-INFECTION** **Study Conclusion:** "Evidence suggests that use of TAF is more protective and effective than either TDF. Improving renal and hepatic related comorbidities in HIV-infected population, TAF may be beneficial in public health policy, specifically in high HIV epidemic regions."
Gotham et al 2017	Design: Meta-analysis -10 RCTs included. Funding Source: Not declared COI: Nothing to declare *(Reviewers have declared consultancy*	HIV-1 (n=5671 in 8/10 RCTs) and chronic hepatitis B (CHB) (n= 6969)	TAF (n=4000) versus TDF (n=2969) Dose of TAF 10mg in HIV	Efficacy and Safety	**Efficacy** **Virological effects:** No significant difference noted for both treatment-naïve and treatment-experienced groups. **Resistance**: No significant difference in rates of emergent primary genotypic resistance. **Safety** No significant differences in the estimated effect of TAF compared to TDF, across measures of any adverse event (experienced by 83% of	RCTs included predominantly white, male participants around 40 years of age, with a baseline CD4+ count greater than 350. Boosted TDF may have resulted in supratherapeutic levels of TDF as doses not adjusted.

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

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

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

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

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

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

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

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

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

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

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

PICO

The following eligibility criteria was approved for the review.

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

Literature search

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

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

Summary of Evidence

EFFICACY

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

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

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

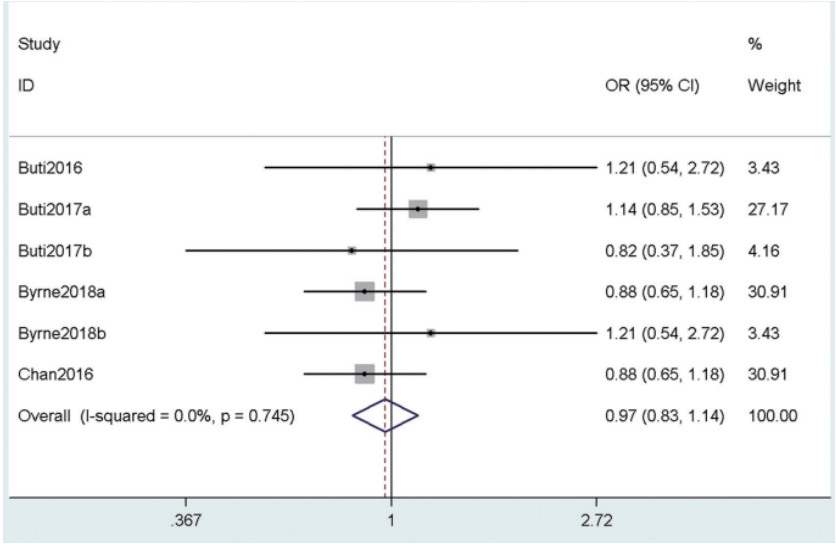

Fig 1: Pooled OR of virological response in TAF-treated vs. TDF-treated CHB patients after 48 weeks of treatment

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

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

ADVERSE EFFECTS

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

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

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

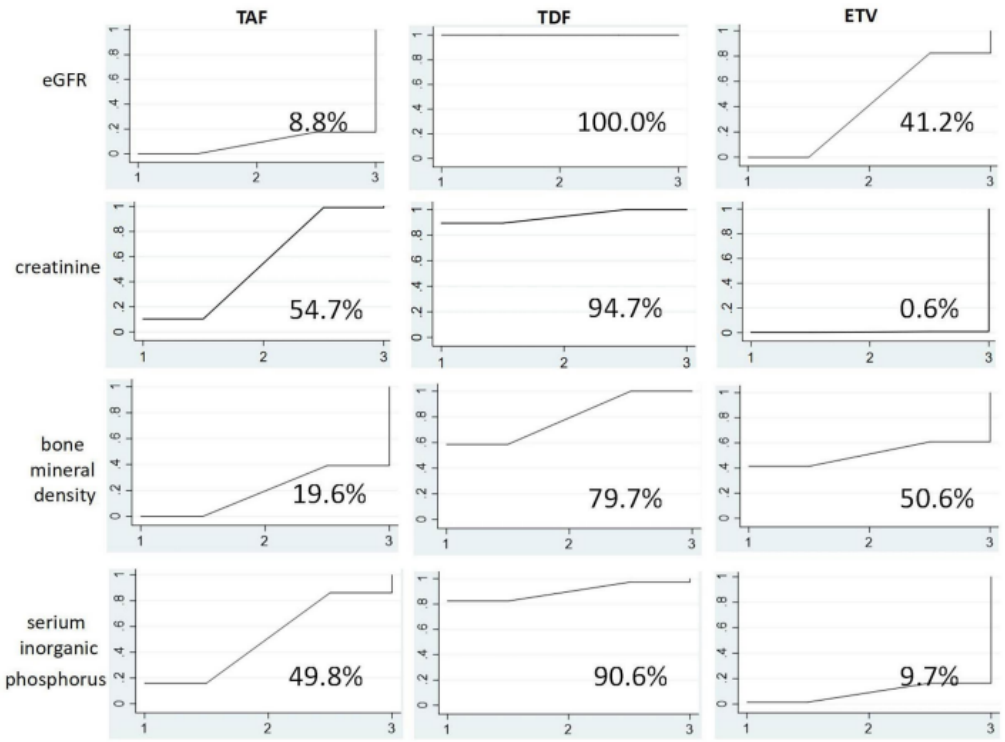

Figure 2: SUCRA diagram of side effects. The figure shows the probability of the effects of three drugs on eGFR, creatinine, bone mineral density, and blood phosphorus before and after medication. According to the level of area under the curve (SUCRA), the larger the area, the greater the index change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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Recommendation*

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

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

- Tenofovir alafenamide, oral, 25 mg daily.

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

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APPENDIX

Pubmed search History

History and Search Details

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 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

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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.

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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.

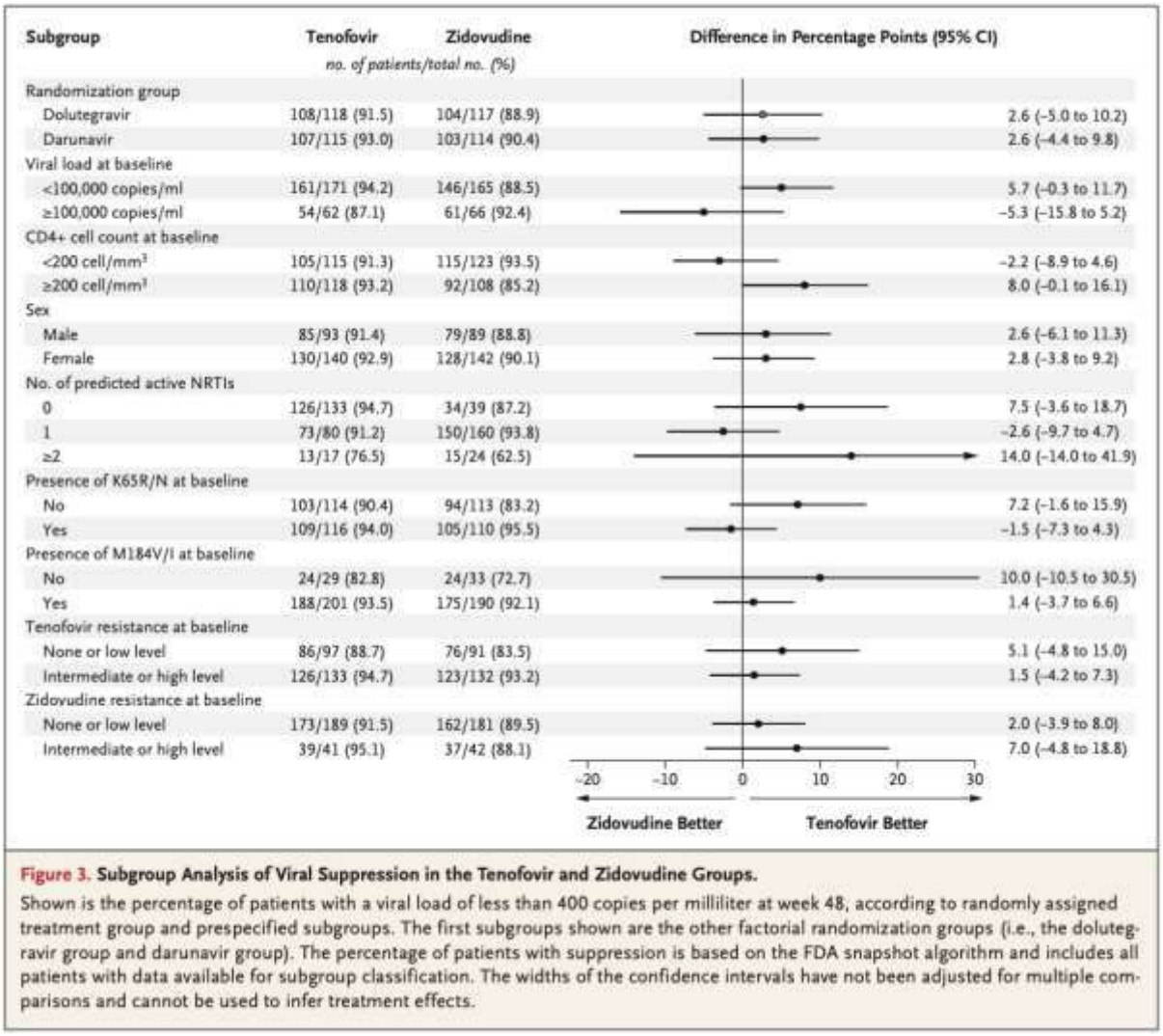

Figure 3. Subgroup Analysis of Viral Suppression in the Tenofovir and Zidovudine Groups.

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.

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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.

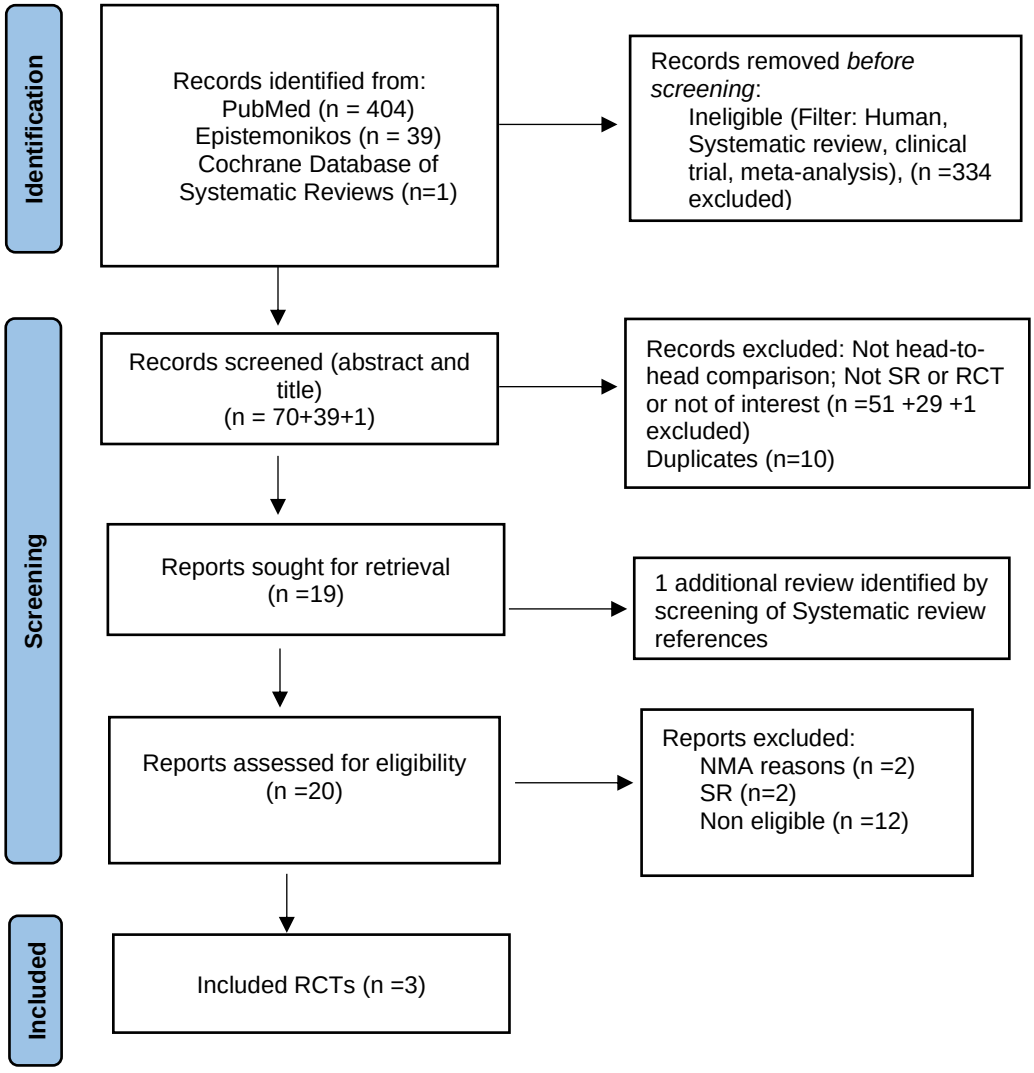

Figure 1. PRISMA flow-chart detailing study selection

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.

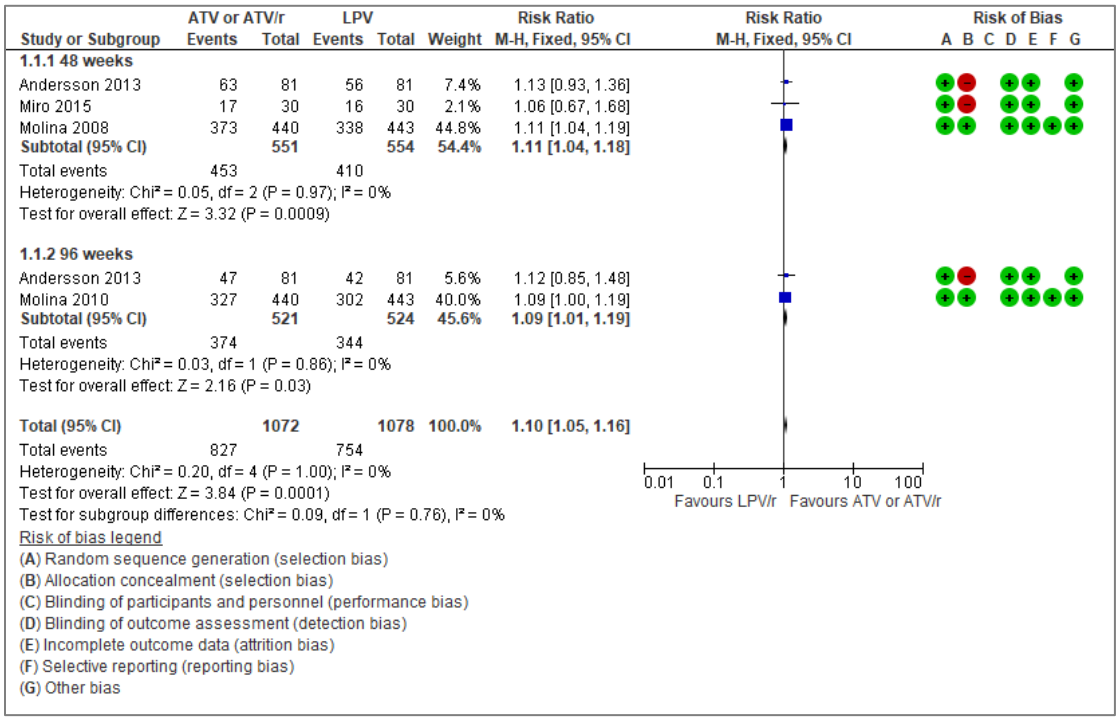

Figure 2. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (virological failure <50 copies/ml)

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).

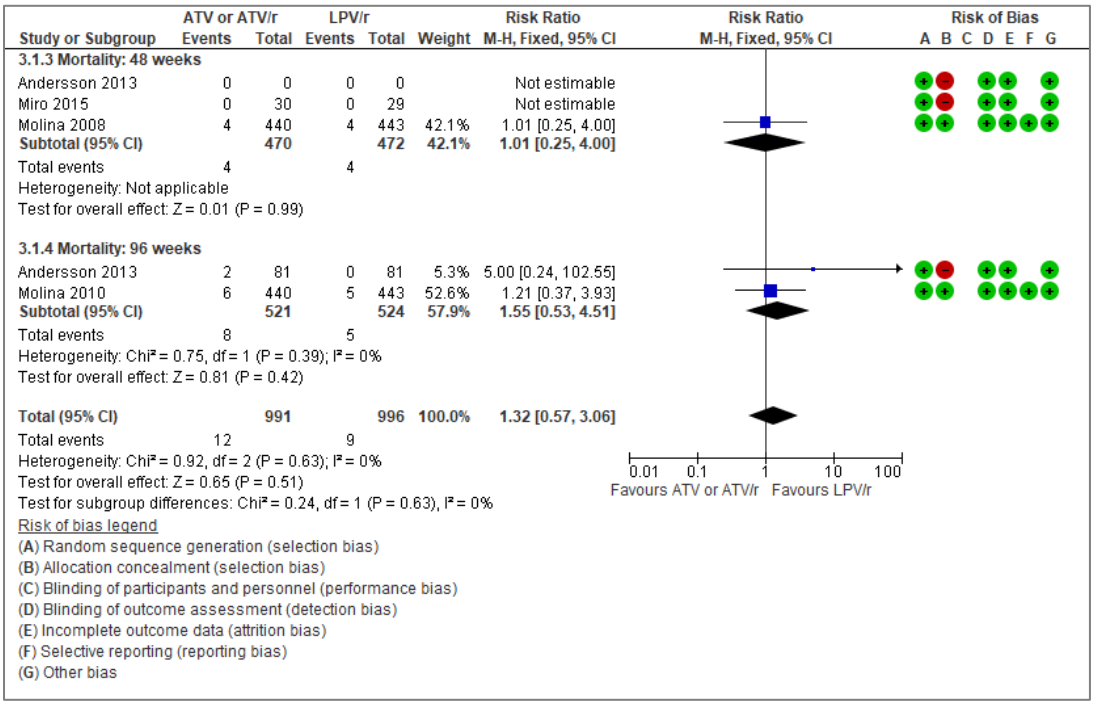

Figure 3. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Mortality)

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)

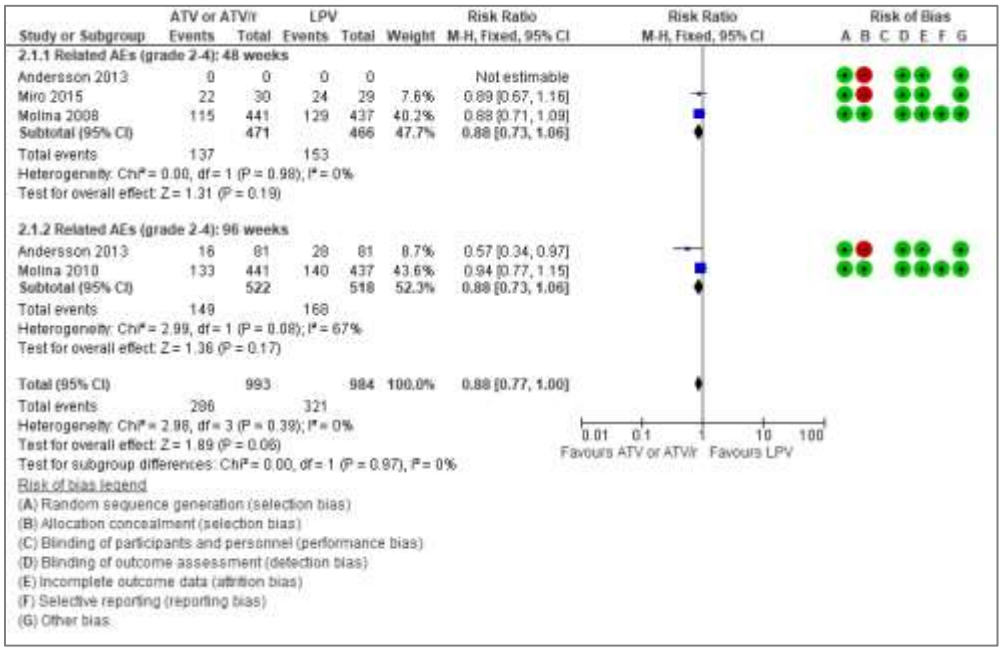

Figure 4. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (treatment related adverse events)

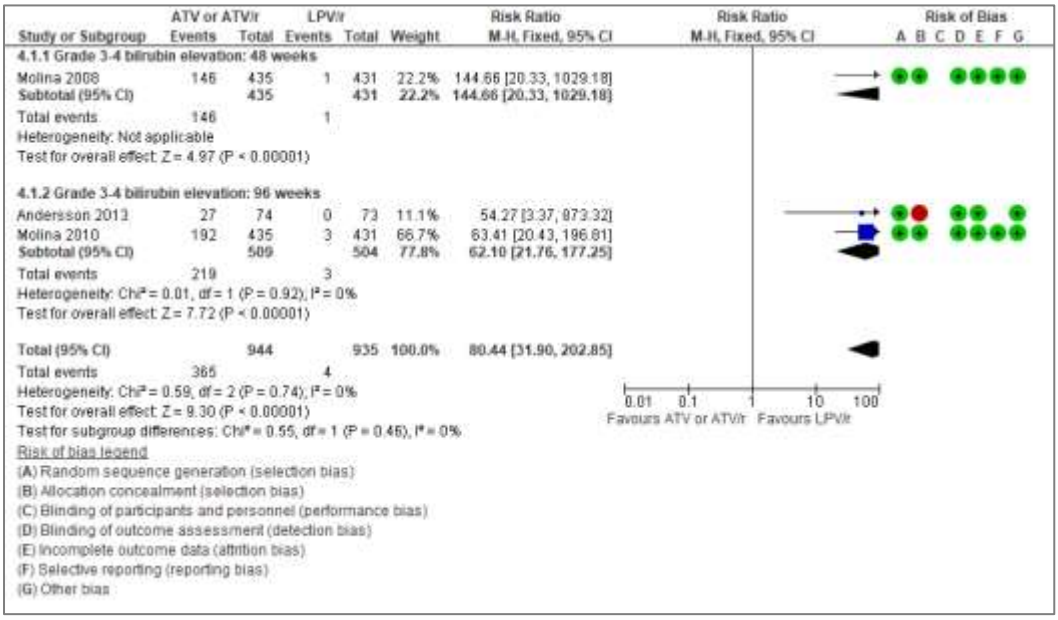

Figure 5. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Bilirubin levels)

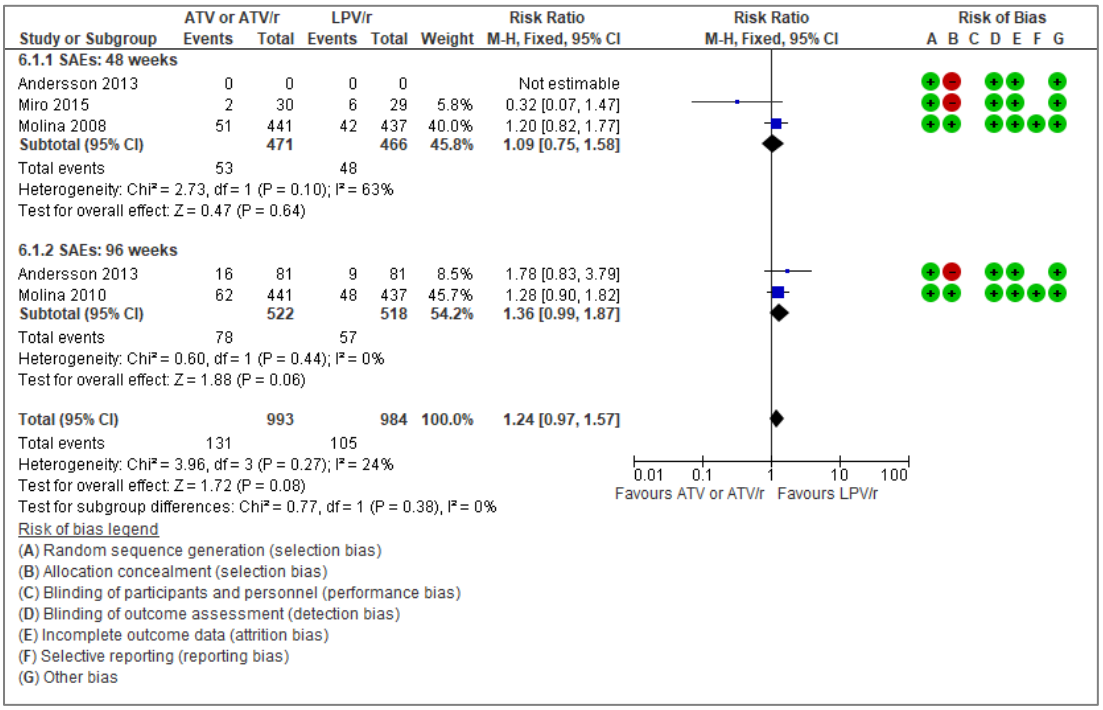

Figure 6. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (Serious adverse events)

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.

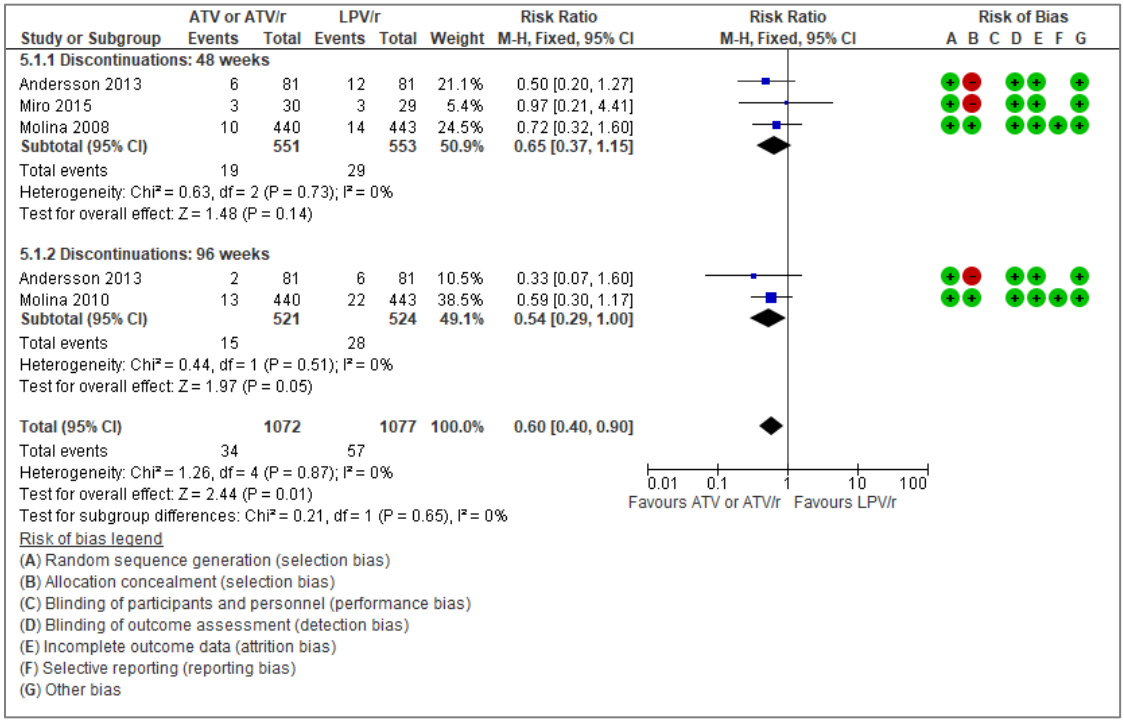

Figure 7. Forest plots for the comparison of ATV/r vs LPV/r for the treatment of PLHIV (discontinuations due to adverse events)

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>

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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.

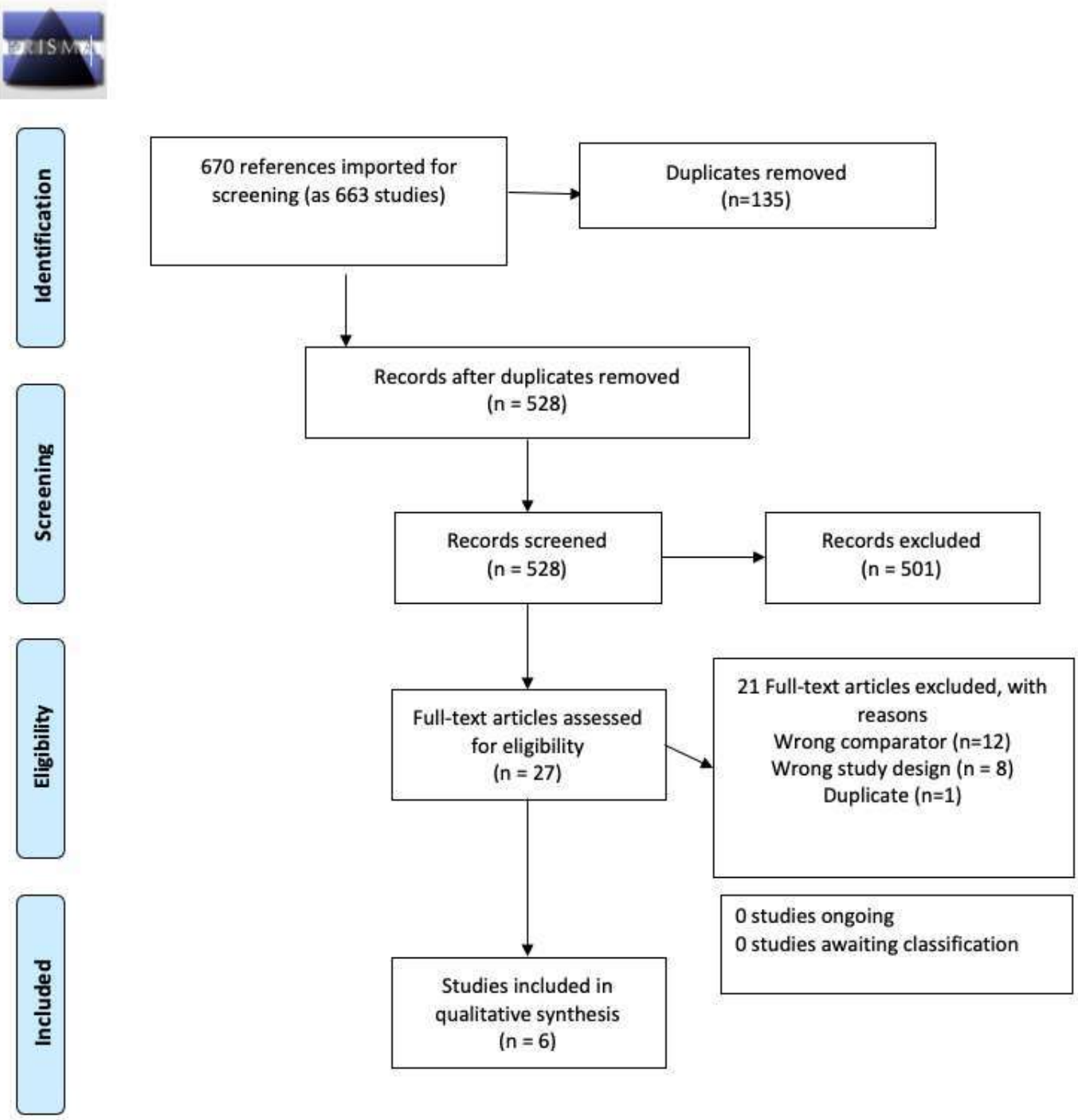
The TITAN study was a randomised, controlled, phase III trial to compare efficacy and safety of darunavir-ritonavir with that of lopinavir-ritonavir in treatment-experienced, lopinavir-naive patients. Patients received optimised background regimen plus non-blinded treatment with darunavir-ritonavir 600/100 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).

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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

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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]

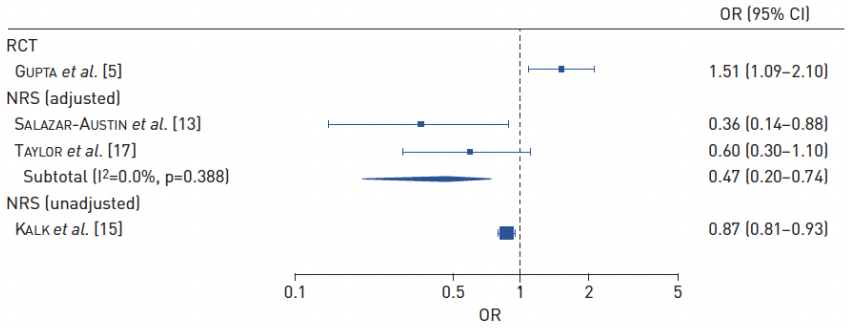
[8] The table contains a correction of an error detected in the review process and confirmed with the primary author of the systematic review.

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.

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South African National Essential Medicine List
Primary Healthcare Medication Review process
Component: HIV and AIDS

EVIDENCE REVIEW

Title: To determine if the dapivirine eluting vaginal ring (dapivirine) is safe and effective in preventing HIV acquisition in women at substantial risk of HIV infection

Date: 9 June 2022

Key findings

- We conducted a search for systematic reviews of randomized controlled trials, and guidelines to determine whether the dapivirine eluting vaginal ring is safe and effective in preventing HIV acquisition in women at substantial risk of HIV infection.
- We identified two systematic reviews– both pooled data from two randomised controlled trials (RCTS) of dapivirine versus placebo – the Ring and ASPIRE studies.
- Data from the two placebo controlled RCTs informed the 2021 World Health Organization (WHO) Guideline recommendations for use of dapivirine vaginal ring in HIV prevention. On AGREE assessment, the 2021 WHO guidelines scored favourably (6/7), and GRADE-adolopment was performed.
- Use of the dapivirine ring may reduce HIV incidence compared to non-use (23 fewer HIV acquisitions per 1000 patient, 95% CI 10-34 fewer acquisitions, moderate quality evidence), and is not associated with an increase in adverse events (RR 1.02, 95% CI 0.98-1.06).However one RCT found 94 instances of social harm in 4680 person-years of follow-up, of which 93% were partner-related.
- We found no RCTS comparing dapivirine to tenofovir plus emtricitabine, which is the current standard of care for prevention of HIV acquisition in South Africa.

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 suggests not to use the dapivirine ring as an additional option for prevention of HIV acquisition in women.
Rationale: Available evidence for the dapivirine ring is restricted to placebo-controlled data, with no studies comparing dapivirine to oral tenofovir plus emtricitabine, the current standard of care in South Africa. There is currently no data for efficacy in adolescents. The dapivirine ring cannot be used in pregnancy. There is sub-group of women who cannot use tenofovir plus emtricitabine for whom the dapivirine ring may be an option. However, at the current proposed price, dapivirine is unaffordable. The estimated threshold price for reviewing this recommendation is R52.00 per ring.
Level of Evidence: Moderate quality of evidence
Review indicator: Reduction in price

NEMLC RECOMMENDATION (23 JUNE 2022):
The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation with amendments to the review indicator (added, uptake and social harms), as follows:
Review indicator: Reduction in price; Uptake of all PrEP; Social harms of all PrEP

Monitoring and evaluation considerations: see review indicators above

Research priorities: see review indicators above

(Refer to Appendix 2 for the Evidence to decision framework)

1. Executive Summary

Date: 6 June 2022
Medicine (INN): Dapivirine vaginal ring
Medicine (ATC): G01AX17
Indication (ICD10 code): Z29.2
Patient population: Women > 18 years of age
Incidence: Estimated 140 000 new infections in women aged 15 and over in South Africa. The HIV incidence per 1000 population is 7.79 (UNAIDS country factsheet, South Africa). Incidence in women has decreased between 2014 and 2017 from 4.9 to 3.1 seroconversion events per 100 person-years but remains high (Vandormael).
Level of Care: Primary healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: Oral tenofovir plus emtricitabine
Efficacy estimates: A meta-analysis of 2 phase III placebo-controlled trials of 4588 women found a 29% reduction of HIV acquisition risk (95% CI 11 to 43%; I^2 = 0%; moderate certainty evidence). 23 fewer women per 1000 using the dapivirine vaginal ring would acquire HIV infection compared to placebo (95% CI: from 34 fewer to 10 fewer), NNT 48 (95% CI 28 to 160) (Obiero).
Motivator/reviewer name(s): Regina Osih, Jeremy Nel, Halima Dawood, Hasina Subedar, Lise Jamieson, Trudy Leong
PTC affiliation: Jeremy Nel - Helen Joseph Hospital PTC; Halima Dawood – KZN Provincial PTC

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4) Hasina Subedar – PrEP Programme Manager, National Department of Health
5) Lise Jamieson – Health Economics and Epidemiology Research Office (HE^2RO), University of Witwatersrand
6) Trudy Leong – Essential Drugs Programme, National Department of Health

RO, JN, HD, HS, LJ and TL have no interests to declare pertaining to dapivirine vaginal ring.

3. Introduction/ Background

South Africa has one of the world's highest prevalence and incidence of HIV. There were 230,000 newly infected adults with HIV in 2020, of which 140,000 were women aged 15 and over. The HIV incidence per year per 1000 population in adults aged 15-49 was estimated at 7.79. Women aged 15-49 were estimated to have a prevalence of 24.7% and women aged 15-24 a prevalence of 10.4% (range 4.0-16.4). While combination prevention modalities such as oral PrEP are available, accessibility to additional prevention modalities may assist in reducing HIV acquisition, particularly in adolescent young girls and women.

The dapivirine vaginal ring is a microbicide that inhibits HIV replication. Duration of action is 3 months. Dapivirine acts locally in the reproductive tract mucosa to prevent HIV replication (Baeten).

There are no head-to-head comparisons of dapivirine to oral PrEP (fixed-dose combination of tenofovir plus emtricitabine). Oral PrEP is the current standard of care recommended for those at high risk of acquiring HIV (PHC STGs and EML, 2020). Compared to placebo/ no PrEP, oral PrEP reduces risk of HIV infection by 51% (95% CI 33% to 73%) (Fonner). Poor adherence resulted in decreased effectiveness of oral PrEP. When stratified by mode of acquisition, oral PrEP showed similar effectiveness across groups: Oral PrEP vs placebo RR of 0.34 (95%CI 0.15 to 0.80) for rectal exposure and RR of 0.54 (95% CI 0.32 to 0.90) for penile/vaginal exposure. Notably, oral PrEP had decreased efficacy in individuals <25 years old, which may be the result of poorer adherence: RR 0.71 (95%CI 0.47 to 1.06). Emergence of tenofovir or emtricitabine resistance was low, and there was no evidence for oral PrEP resulting in risk compensating behavior (NEMLC report, 2017-9 review).

Comparing direct medicine prices, dapivirine is more expensive than oral PrEP, at a proposed price of $14.96/ R213.11 (Direct communication from NDoH Programme) and from a local public sector perspective, the service delivery would

generally be the same for both interventions. However, cost-effectiveness analyses suggest that dapivirine is cost-effective compared to oral PrEP – the latter requiring HIV, creatinine clearance and hepatitis B surface antigen tests; whilst the dapivirine vaginal ring only requires HIV-testing (Smith, WHO July 2021). South African studies found that amongst female sex workers in KwaZulu-Natal, dapivirine would be cost-saving (Glabius) and that the dapivirine vaginal ring could have a modest impact on the HIV epidemic and be a cost-effective intervention, despite low efficacy, if uniform coverage across all high-risk groups was achieved (Reidy).

Furthermore, a systematic review found that the use of dapivirine was highly acceptable, and the vast majority of participants across studies reported that the rings are easy to insert and remove (Griffin).

Pregnant and postpartum women, in particular, have higher rates of HIV acquisition compared with non-pregnant women (Drake, Kinuthia, Thomson), but there are no published studies in pregnant women to date. Two studies will provide more data on the dapivirine ring in pregnancy and breastfeeding mothers: B-PROTECTED (MTN-043) has completed follow-up and results are awaited, the DELIVER study is currently underway (MTN-042).

In March 2022, the South African Health Products Regulatory Authority approved the use of the dapivirine ring in women aged 18 years and above. Thus, an evidence review was conducted to inform a recommendation by the National Essential Medicines List Committee.

4. Purpose/Objective:
Should the dapivirine vaginal ring be used for HIV prevention among women at substantial risk of HIV infection?

PICO eligibility criteria*(Adapted from PICO question 1, "Should the dapivirine vaginal ring vs. non-use of the dapivirine vaginal ring be used for HIV prevention among women at substantial risk of HIV infection?", that informed the WHO Guidelines, July 2021):*

Population	Women at substantial risk of HIV infection (defined as HIV incidence of >3 per 100 person–years in the absence of PrEP
Intervention	Dapivirine vaginal ring
Comparator	No intervention
Outcome	HIV infection; Any adverse event; Any grade 3/4 adverse event; Drug resistance; Contraceptive effectiveness; Pregnancy-related adverse events; Therapeutic/elective abortion; Number of sexual partners , measured pre- to post-intervention; Condom use at last sex act , measured pre- to post-intervention
Studies	Systematic reviews of randomised controlled trials.

Note: The WHO guideline development PICO did not include oral PrEP tenofovir plus emtricitabine as comparator

5. Methods:
We sourced World Health Organization (WHO) guidelines and appraised these using the AGREE 2 tool (Brouwers - https://www.agreetrust.org/agree-ii/), to determine if the GRADE-adolpment approach could be used for efficiency purposes. This approach to guideline production combines adoption, adaptation, and, as needed, de novo development of recommendations (Schünemann), using the WHO Clinical Guidelines' Panel's evidence to decision framework.

TL also conducted a search for systematic reviews of randomised controlled trials in two databases on 4 May 2022 to determine if there was any new evidence that had not been included in the WHO guidelines.

a. Data sources: Epistemonikos and PUBMED were searched.

b. Search strategy: See appendix I.

6. Results:
Guidelines:
The recent WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach of July 2021 was identified as providing updated guidance on the

dapivirine vaginal ring as a prevention option (WHO, July 2021). These guidelines were appraised using the AGREE2 instrument (Brouwers). Refer to appendix 2, for the AGREE2 assessment conducted by JN and TL (See appendix 2).

WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach, July 2021.

Citation (date published)	Recommendation (pg)	AGREE II appraisal
WHO Consolidated guidelines on HIV prevention, testing, Treatment, service Delivery and monitoring: Recommendations for a Public Health approach, July 2021.	Pg 6. The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk[a] of HIV infection as part of combination prevention approaches. ***(Conditional recommendation, moderate certainty evidence)*** a. Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP.	**6/7**

Appendix 3 describes the evidence profile (GRADE tables for the dapivirine ring review of evidence, 17 September 2020) that informed the WHO Guideline recommendations.

Systematic reviews:

A search for systematic reviews in two databases was conducted to identify additional evidence that was not included in the July 2021 WHO guidelines. The same 4 systematic reviews (Musekiwa, Obiero, Lokken, Ridgeway) was retrieved from both databases. These systematic reviews were screened by one reviewer (TL) and three were excluded for synthesis – see table 1 for the list of excluded studies. One systematic review was selected for inclusion in this review (Obiero) confirmed by another reviewer (RO). Table 2 describes the details of the selected Cochrane review (Obiero).Two RCTs included in that systematic review informed the WHO guidelines –the Ring Study (IPM-027) (Nel) and ASPIRE (MTN-020) (Baeten) trials.

Effects of intervention

- *Risk of acquiring HIV infection*

The Cochrane review included 12 RCTs of various microbicides for the prevention of sexually transmitted infection with 32,464 participants, conducted in Sub-Saharan Africa, of which two compared dapivirine to placebo. The review found that dapivirine reduces the risk of acquiring HIV infection (55 HIV acquisitions per 1000 women) compared to placebo (78 per 1000), risk ratio (RR) 0.71, (95% confidence interval (CI) 0.57 to 0.89, I^2 = 0%, 2 trials, 4588 women; *moderate-certainty evidence*. Overall, the two included RCTs investigating dapivirine ring were assessed as low risk of bias (using the Cochrane 'Risk of bias' tool), but the quality of evidence was downgraded by one level for imprecision, due to lack of optimal information size. Similarly, the risk of publication bias could not be evaluated, as there were too few trials.

An age-stratified analysis of the ASPIRE study (Baeten) found that the dapivirine ring did not reduce HIV incidence among women aged <25 years (10%, 95% CI -41 to 43) and reduced HIV incidence by 61% (95% CI 32 to 77) among women aged ≥ 25 years. The age stratified analysis in the Ring Study (Nel) found no significant difference in efficacy of the dapivirine ring amongst women aged ≤21 years [Hazard ratio (HR) 0.85; 95% CI 0.45 to 1.60] compared to women >21 years (HR 0.63; 95% CI, 0.41 to 0.97).

- *Serious adverse events*

The review found no difference between dapivirine ring and placebo in terms of serious adverse events (288/2620 vs 216/1968, RR 1.12 (95% CI 0.94 to 1.32); I^2 = 87%; *low certainty evidence.* Quality of the evidence was assessed as low due to imprecision, lack of optimal information size as well as inconsistency.

- *Adverse event – social harm*

The ASPIRE RCT reported on study-related social harm, defined as "non-medical adverse consequences of dapivirine vaginal ring use or of trial participation more generally" (Palanee-Philips). They found 94 instances of social harm with 4680 person-years of follow-up, of which 93% (n=87) were partner-related. 61% (n=85) had disclosed study participation to their primary partners. 40% of the cases of social harm were categorized as having a more than

minimal impact on the quality of life. Younger women (18–26 years) were more than twice as likely to experience social harm than older women, resulting in decreased product adherence.

Conclusion

The WHO Guidelines (WHO, July 2021) recommends inclusion of dapivirine as part of a comprehensive combination prevention approach, providing women the choice between oral PrEP (TE) and dapivirine ring options. Moderate certainty evidence suggests that there will be 23 fewer HIV acquisitions per 1000 patient using dapivirine ring compared to no ring, 95% CI 10-34 fewer acquisitions. However, there is concern that the ring might not be as effective in younger women (<25 years), a key demographic in South Africa. Further research will be required to determine if the low efficacy seen in younger women is due to lower adherence or additional factors.

There are no head-to-head comparisons of the dapivirine ring to oral PrEP. However, a larger reduction in HIV acquisition was seen for oral PrEP compared to placebo than has been seen with dapivirine (Obiero, Fonner).

Table 1: List of excluded studies

Study		Reason for exclusion
1	Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Health. 2020 Jul;25(7):790-802. doi: 10.1111/tmi.13401	Duplicate of Cochrane review (Obiero, 2021)
2	Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, et al. Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front Reprod Health. 2021;3:672446.	PICO eligibility criteria not met
3	4. Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33.	PICO eligibility criteria not met (may be relevant when assessing the evidence to decision framework criteria)

Table 2: Characteristics of the included study

Citation	Study design	Population	Intervention vs comparator	Outcomes	Effect sizes	Comments
• ***Systematic review:***						
Obiero J et al, 2021. Topical microbicides for preventing sexually transmitted infections (Review). Cochrane Database Syst Rev. 2021 Mar 13;3(3):CD007961. [8]	Systematic Review and Meta-Analysis	12 studies; 32 464 participants (12 trials conducted in sub-Saharan Africa, with one having a study site in the USA, and another a site in India) **Note: The population specific to the dapivirine vaginal ring was 4 588 women from 2 RCTs.** Eligible participants were sexually active non-pregnant heterosexual women.	**Intervention:** Dapivirine (2 RCTs, n=4588), **Comparator:** Placebo	**Primary outcomes:** • Risk of acquiring HIV infection – incidence of laboratory-confirmed HIV • Serious adverse events	**Dapivirine vs placebo:** *Risk of acquiring HIV infection:* 55 per 1000 vs 78 per 1000; RR 0.71 (95% CI 0.57 to 0.89); I^2=0%; NNT *(moderate certainty evidence)* *Serious adverse events:* There was no clear evidence of a difference between dapivirine vaginal ring vs placebo: 288/2620 vs 216/1968; RR 1.12 (95% CI 0.94 to 1.32); I^2 = 87% *(low certainty evidence)* No studies assessed the acceptability of the intervention.	• There is a concern that only two RCTs have to date assessed dapivirine vaginal ring. Thus, the certainty of evidence for risk of acquiring HIV infection was downgraded one level, from high to moderate certainty for imprecision, due to lack of optimal information size. • *Risk of bias:* Overall assessment described in the Cochrane review – **LOW RISK** ○ Random sequence generation (selection bias) – **LOW RISK** ○ Allocation concealment (selection bias) – **LOW RISK** ○ Blinding of participants and personnel (performance bias) – **LOW RISK** ○ Blinding of outcome assessment (detection bias) – **LOW RISK** ○ Incomplete outcome data (attrition bias) – **LOW RISK** ○ Selective reporting (reporting bias) – **LOW RISK** ○ Other bias – **LOW RISK**

Table 3: WHO Guideline Panel's GRADE tables for the dapivirine ring review of evidence (17 September 2020)

Author(s): Fonner V. & Dalglish S.
Question: The dapivirine vaginal ring compared to non-use of the dapivirine vaginal ring for HIV prevention among women at substantial risk of HIV infection
Setting: Global
Bibliography: One phase II placebo-controlled RCT, two phase III placebo-controlled RCTs, two open-lapel extension studies (see references for detailed information)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DVR	No DVR	Relative (95% CI)	Absolute (95% CI)		
HIV infection (RCTs) (follow up: 24 months)												
2	RCTs[a,b]	serious[c]	not serious	not serious	not serious	none	151/2610 (5.8%)	155/1952 (7.9%)	RR 0.71 (0.57 to 0.88)	**23 fewer per 1,000** (from 34 fewer to 10 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
HIV infection (DREAM) (follow up: 12 months)												
1	Observational study[d]	serious[e]	not serious	not serious	serious[b]	dose response gradient[f]	1.8 per 100 person years (95% CI: 1.1-2.9)g	4.7 per 100 person years (95% CI: 3.7-5.8)h	reduction in incidence 0.62 (-- to --) [i]	not estimable	⊕⊕⊕◯ Moderate	CRITICAL
HIV infection (HOPE) (follow up: 12 months)												
1	Observational study[j]	not serious[k]	not serious	not serious	not serious	dose response gradient[f]	2.7 per 100 person years (95% CI: 1.9-3.8)[l]	4.4 per 100 person years (95% CI: 3.2-5.8)[m]	reduction in incidence 0.39 (0.14 to 0.65)	not estimable	⊕⊕⊕◯ Moderate	CRITICAL
Any adverse event (RCTs) (follow up: 24 months)												
1	RCT[a]	serious[n]	not serious	not serious	not serious	none	1322/2619 (50.5%) [o]	739/1968 (37.6%) [o]	RR 1.02 (0.98 to 1.06)	**8 more per 1,000** (from 8 fewer to 23 more)	⊕⊕⊕◯ Moderate	IMPORTANT
Any adverse event (safety study) (follow up: 12 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DVR	No DVR	Relative (95% CI)	Absolute (95% CI)		
1	RCT	not serious	not serious	not serious	not serious	none	114/140 (81.4%) [p]	121/140 (86.4%) [p]	RR 0.9 (0.9 to 1.0)	**86 fewer per 1,000** (from 86 fewer to 0 fewer)	⨁⨁⨁⨁ High	IMPORTANT
Any grade 3/4 adverse event (RCTs) (follow up: 24 months)												
2	RCTs[a]	serious[n]	serious[q]	not serious	not serious	none	236/2619 (9.0%)	204/1968 (10.4%)	RR 1.19 (0.68 to 2.05)	**20 more per 1,000** (from 33 fewer to 109 more)	⨁⨁◯◯ Low	CRITICAL
Drug resistance (RCTs) (follow up: 24 months)												
2	RCTs[a]	serious[b]	not serious	not serious	serious[r]	none	22/145 (15.2%) [s]	19/152 (12.5%) [s]	RR 1.13 (0.64 to 2.01)	**16 more per 1,000** (from 45 fewer to 126 more)	⨁⨁◯◯ Low	CRITICAL
Pregnancy-related adverse events (in ASPIRE and The Ring Study) (follow up: 24 months)[u]												
2	RCTs	serious[b]	not serious	serious[v]	very serious[r]	none	Range of effects [w]		not estimable	not estimable	⨁⨁⨁◯ Very low	CRITICAL
Number of sexual partners (self-reporting ≥2 sexual partners), measured pre- to post-intervention (follow up: 24 months)[x]												
1	RCT	not serious	not serious	not serious	serious[r]	none	64/107 (59.8%) [y]	74/132 (56.1%) [y]	**p**-value comparing pre to post 0.814 (-- to --)	not estimable	⨁⨁⨁◯ Moderate	IMPORTANT
Condom use at last sex act (self-reported), measured pre- to post-intervention (follow up: 24 months)[x]												
1	RCT	not serious	not serious	not serious	serious[r]	none	37/107 (34.6%) [z]	46/132 (34.8%) [z]	not estimable	not estimable	⨁⨁⨁◯ Moderate	IMPORTANT

CI=Confidence interval; RCT= randomised controlled trial; RR= risk ratio

Explanations

a. Pooled effect size from two Phase III RCTs (ASPIRE and the Ring Study), random effects meta-analysis.

b. Both ASPIRE and The Ring Study identified sites with lower than anticipated participant adherence to the study product. In ASPIRE, the sample size was recalibrated to allow for a fully-powered analysis

excluding individuals from the two sites with lower than expected adherence. Enrollment at the two sites was stopped but participants already enrolled were allowed to continue in follow-up. Results for the primary endpoint—HIV infection—are presented with and without data from the two sites. For this outcome, we included results inclusive of all sites (i.e., the more conservative estimate). In The Ring Study, three sites were identified with high levels of protocol noncompliance and low adherence. As a result, prior to unblinding all participants from these sites were withdrawn from the study, resulting in approximately 20% attrition. For these reasons we have downgraded for potential risk of bias.

c. Outcomes from one Phase I/II safety study included (Nel et al., 2016). Intent-to-treat analysis.

d. DREAM was a Phase IIIB multicenter follow-on open-label extension study (prospective cohort design). Participants included those who had completed the Ring Study and were HIV-negative at enrollment. In DREAM, willingness to use the dapivirine vaginal ring (DVR) was a requirement for study participation.

e. HIV-1 incidence in DREAM was compared descriptively with the incidence rate obtained from bootstrap sampling in the placebo group of The Ring Study (i.e., a simulated control group was used to estimate incidence among those not receiving the DVR). Although the lack of a true control is a limitation of the study design, this was not considered a serious risk of bias, thus results were not downgraded.

f. Both open-label extension studies, HOPE and DREAM, found significantly higher DVR adherence (as measured objectively through levels of residual dapivirine in used rings) as compared with the placebo-controlled RCTs that preceded them (ASPIRE and the Ring Study, respectively). Additionally, both OLEs found higher effectiveness than in the RCTs. Given that we have not downgraded the evidence for any other reason, and both studies found a dose-response relationship, we have upgraded the evidence one-level.

g. 18 HIV infections occurred in the study cohort among participants using DVR in the modified intent to treat analysis (n=938). Of note, 26 HIV infections occurred overall, but only 18 were included in analysis (3 were excluded due to HIV infection at baseline; 3 had positive HIV-1 antibody tests at the exit visit but were HIV-1 RNA negative at the last product visit (LPUV, thus considered to have become infected after DVR discontinuation; one participant with HIV-1 seroconversion at the exit visit had an HIV-1 RNA result below the limit of detection (<40 copies/mL) at the LPUV, and an undetectable result when retested. The remaining participant seroconverted after prolonger non-DVR use (5 months). A sensitivity analysis including the participant who seroconverted after prolonged non-DVR use and the participant with an HIV-1 RNA result below the limit of detection at LPUV, demonstrated an incidence rate of 2·0 (95% CI: 1.1-2.9 per 100 person years), a 57% reduction in incidence.

h. This simulated incidence rate was calculated from bootstrap sampling of participants in the placebo group of The Ring Study, matched for research center, age, and presence of sexually transmitted infections (STIs) at enrolment.

i. Confidence interval not provided.

j. HOPE was a Phase IIIB multicenter follow-on open-label extension study (prospective cohort design). Participants included those who had completed the ASPIRE study and were HIV-negative at enrollment. In HOPE, ring use was optional (women could choose at every visit whether or not to accept the ring).

k. HIV-1 incidence in HOPE was compared descriptively with the incidence rate obtained from bootstrap sampling in the placebo group of ASPIRE (i.e., a simulated control group was used to estimate incidence among those not receiving the DVR). Although the lack of a true control is a limitation of the study design, this was not considered a serious risk of bias, thus we did not downgrade the results.

l. Overall 35 HIV infections occurred out of 1456 participants.

m. This simulated incidence rate was calculated from bootstrap sampling of participants in the placebo group of ASPIRE, matched for research center, age, and presence of a curable sexually transmitted infections (STIs) at baseline.

n. Both ASPIRE and The Ring Study identified sites with lower than anticipated participant adherence to the study product. In ASPIRE, the sample size was recalibrated to allow for a fully-powered analysis excluding individuals from the two sites with lower than expected adherence. Enrollment at the two sites was stopped but participants already enrolled were allowed to continue in follow-up. In The Ring Study, three sites were identified with high levels of protocol noncompliance and low adherence. As a result, prior to unblinding all participants from these sites were withdrawn from the study, resulting in approximately 30% attrition. For these reasons we have downgraded for potential risk of bias.

o. Outcomes reported as treatment emergent adverse events for the Ring Study (defined as adverse events that occurred/worsened after the first insertion of IP, up to 6 weeks after last ring use)(Nel et al., 2016). For ASPIRE (Baeten et al., 2016), outcome reported as “primary safety endpoint” defined as “any serious adverse event, any grade 3 or 4 adverse event, and any grade 2 adverse event”. Analysis includes results from all 15 sites, including those with low adherence.

p. Outcome reported as treatment-emerge adverse events (defined as AEs which occurred/worsened after the first insertion of IP, up to 6 weeks after last ring use)

q. Within the random effects meta-analysis, heterogeneity was high (I-squared=76.55%); reasons for the high heterogeneity are unknown, so the evidence was downgraded once for inconsistency.

r. Downgraded for imprecision due to the small number of events

s. Defined as any non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations

t. Of 2629 women enrolled, 2310 women returned for follow-up and reported using a hormonal contraceptive method at any point during study participation (1139 in the dapivirine arm, 1171 in the placebo arm). A total of 117 pregnancies occurred among 114 participants during use of a hormonal contraceptive method (63 pregnancies in the dapivirine ring arm and 54 in the placebo arm). Pregnancy incidence in the dapivirine arm versus placebo among women using injectable depot medroxyprogesterone acetate was 0.43% vs. 0.54%, among women using injectable norethisterone enanthate was 1.15% vs. 0%, among women using hormonal implants was 0.22% vs. 0.69%, and among women using oral contraceptive pills was 32.26% vs. 28.01%. Pregnancy incidence did not differ by study arm for any of the hormonal

contraceptive methods (individual hazard ratios for each contraception method are presented in Table 2 of Balkus et al., 2017).
u. Includes results from entire ASPIRE trial and site-specific results from The Ring Study (only site in South Western Uganda reporting results)
v. Downgraded for indirectness because outcomes were measured among women who were only exposed to the study product for a brief period during early pregnancy (all participants were regularly screened for pregnancy and study product was immediately discontinued once pregnancy was detected). Therefore, these results may be different if women had been exposed to the study product for the entire duration of their pregnancies.
w. A range of varying pregnancy outcomes were reported for ASPIRE and one research site in The Ring Study. These results are summarized in Table 7 of the report. Across studies, no significant differences in adverse pregnancy events were found, although women were only exposed to DVR in early pregnancy (see comment on indirectness).
x. Measured only in one research site (in South Western Uganda)
y. These numbers represents the total number of participants (recruited specifically from the research site in South West Uganda) reporting ≥2 sexual partners (time period not specified) at baseline (non-use of DVR) and 104 weeks follow-up (DVR). The p-value comparing baseline to follow-up rates of condom use at last sex was 0.814 (chi-square test).
z. These numbers represents the total number of participants (recruited specifically from the research site in South West Uganda) reporting condom use at last sex act at baseline (non-use of DVR) and 104 weeks followup (DVR). The p-value comparing baseline to follow-up rates of condom use at last sex was 0.706 (chi-square test).

Appendix 1 – Search strategy

Database: **Epistemonikos**
Date: **4 May 2022**

Search: (title:(dapivirine) OR abstract:(dapivirine))
Restricted to systematic reviews

4 records retrieved.

Database: **PubMed**
Date: **4 May 2022**

Search	Query	Results
#3	Search: (("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])) AND (meta-analysis[Filter] OR systematicreview[Filter])	4
#2	Search: (("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])) AND (systematicreview[Filter])	4
#1	Search: ("dapivirine"[Supplementary Concept] OR "dapivirine"[All Fields] OR "dapivirine"[All Fields]) AND ("hiv"[MeSH Terms] OR "hiv"[All Fields]) AND ("prevent"[All Fields] OR "preventability"[All Fields] OR "preventable"[All Fields] OR "preventative"[All Fields] OR "preventatively"[All Fields] OR "preventatives"[All Fields] OR "prevented"[All Fields] OR "preventing"[All Fields] OR "prevention and control"[MeSH Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields] OR "prevention s"[All Fields] OR "preventions"[All Fields] OR "preventive"[All Fields] OR "preventively"[All Fields] OR "preventives"[All Fields] OR "prevents"[All Fields])	176

4 records retrieved, all duplicates of Epistemonikos search.

Appendix 2: Adaptation of the WHO 2020 TPT Guidelines Evidence to decision framework

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	• More than half of all new HIV infections globally are among women and girls.[1] • Approximately 7,000 young women aged 15–24 years become infected with HIV each week.[2] • 20.1 million women and girls are currently living with HIV.[1] • Young women aged 15–24 years are twice as likely to be living with HIV than men. • HIV is the global leading cause of death for women (15-49 years).[2] • Recent results from ECHO trial in sub-Saharan Africa demonstrate continued high HIV incidence among women (3.81 per 100 woman years (95% CI 3·45 to 4·21)), despite the availability of existing HIV prevention options, including oral pre-exposure prophylaxis (PrEP)).[3] • There are challenges with uptake and continued use of a daily pill i.e. oral PrEP among women. Alternatives to daily oral PrEP are needed. Having expanded options for PrEP would address users differing needs and preferences.[4 5] • This evidence demonstrates that additional HIV prevention options are needed for women and girls	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> South Africa has one of the world's highest prevalence and incidence of HIV. There were approximately 230,000 newly infected adults with HIV in 2020, of which 140,000 were women aged 15 and over. The HIV incidence per 1000 population in adults aged 15-49 is estimated at 7.79 Women aged 15-49 are estimated to have a prevalence rate of 24.7 with young women aged 15-24 having a prevalence of 10.4.	

[1] UNAIDS, . 20.1 million girls and women living with HIV. 2020.

[2] UNAIDS, . Women and HIV: A spotlight on adolescent girls and young women. 2019.

[3] Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet. 2019 Jul 27;394(10195):303-313. doi: 10.1016/S0140-6736(19)31288-7. Epub 2019 Jun 13. Erratum in: Lancet. 2019 Jul 27;394(10195):302.

[4] van der Straten A, Agot K, Ahmed K, Weinrib R, Browne EN, Manenzhe K, et al; TRIO Study Team. The Tablets, Ring, Injections as Options (TRIO) study: what young African women chose and used for future HIV and pregnancy prevention. J Int AIDS Soc. 2018 Mar;21(3):e25094. doi: 10.1002/jia2.25094.

[5] Montgomery ET, Beksinska M, Mgodi N, Schwartz J, Weinrib R, Browne EN, et al. End-user preference for and choice of four vaginally delivered HIV prevention methods among young women in South Africa and Zimbabwe: the Quatro Clinical Crossover Study. J Int AIDS Soc. 2019 May;22(5):e25283. doi: 10.1002/jia2.25283.

	Furthermore, pregnant and postpartum women, in particular, have higher rates of HIV acquisition compared with non-pregnant women.[6] [7] [8] As pregnant women are excluded from clinical trials, a systematic review by Lokken et al[9] demonstrated the background prevalence of adverse neonatal and pregnancy outcomes (Malawi, South Africa, Uganda, Zimbabwe). The outcomes with the highest pooled prevalence were preterm birth (12.7%, 95%CI 11.2–14.3), LBW (11.7%, 95%CI 10.6–12.9), and gestational hypertension (11.4%, 95%CI 7.8–15.7). Among the outcomes with the lowest pooled prevalence estimates were neonatal mortality (1.7%, 95%CI 1.4–2.1), pregnancy loss [1.9%, 95%CI 1.1–2.8, predominately studies (23/29) assessing losses occurring after the first trimester], PPROM (2.2%, 95%CI 1.5–3.2), and stillbirth (2.5%, 95%CI 2.2–2.7). The data would assist in investigating use of dapivirine ring in pregnancy	

Desirable effects: How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
WHO Guideline panel		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	HIV infection •Pooled results from two phase III placebo-controlled randomized trials (ASPIRE[10] and the Ring Study[11]) **demonstrated a significant reduction in HIV incidence (29%, 95% CI: 11%-43%)** comparing women randomized to receive the dapivirine ring (DVR) vs. those randomized to receive a placebo ring. •An age-stratified analysis from one of the two placebo-controlled randomized trials (ASPIRE) found that **the dapivirine ring did not reduce HIV incidence among women aged <25 years and reduced HIV incidence by 61% among women aged ≥ 25 years**. The age stratified analysis in the Ring Study found **no difference in reduction in HIV incidence comparing women aged ≤21 years vs. >21 years.** •However, when results across the tool trials were pooled, **HIV-1 risk reduction was significantly higher in participants older than 21 years; no risk reduction was observed in participants 21 years or younger.[12]** •An analysis from ASPIRE assessed the relationship of product adherence, as measured by residual levels of dapivirine in returned study rings, and **found a significant relationship between adherence and efficacy.** Medium to high levels of adherence (defined as <22mg of residual dapivirine) was associated with a 65% relative reduction in HIV risk (95% CI: 22	DVR is not expected to prevent HIV from non-vaginal routes of HIV transmission, such as receptive anal intercourse (RAI) and parenteral transmission. One sub-analysis of data from ASPIRE found that RAI comprised only 1.5% of all sex acts reported over a three-month period. In the adjusted analysis, RAI was not associated with reduced HIV-1 protection from the ring.[15]

[6] Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during pregnancy and postpartum and risk of mother-to-child HIV transmission: a systematic review and meta-analysis. PLoS Med. (2014) 11:e1001608. doi: 10.1371/journal.pmed.1001608

[7] Kinuthia J, Drake AL, Matemo D, Richardson BA, Zeh C, Osborn L, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics: a cohort study. AIDS. (2015) 29:2025–33. doi: 10.1097/QAD.0000000000000793

[8]Thomson K, Hughes J, Baeten J, John-Stewart G, Celum C, Cohen C, et al. Increased risk of HIV acquisition among women throughout pregnancy and during the postpartum period: a prospective per-coital-act analysis among women with HIV-infected partners. J Infect Dis. (2018) 218:16–25. doi: 10.1093/infdis/jiy113

[9] Lokken EM, Mathur A, Bunge KE, Fairlie L, Makanani B, Beigi R, Noguchi L, Balkus JE. Pooled Prevalence of Adverse Pregnancy and Neonatal Outcomes in Malawi, South Africa, Uganda, and Zimbabwe: Results From a Systematic Review and Meta-Analyses to Inform Trials of Novel HIV Prevention Interventions During Pregnancy. Front Reprod Health. 2021;3:672446. doi: 10.3389/frph.2021.672446.

[10] Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al.; MTN-020–ASPIRE Study Team. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. N Engl J Med. 2016 Dec 1;375(22):2121-2132. doi: 10.1056/NEJMoa1506110.

[11] Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, et al.; Ring Study Team. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. N Engl J Med. 2016 Dec 1;375(22):2133-2143. doi: 10.1056/NEJMoa1602046.

[12] Rosenberg, Z, Nel, A, van Niekerk, N, Van Baelen, B, Van Roey, J, Palanee-Phillips, T, Brown, E, Soto-Torres, L, Hillier, S, Baeten, J, Teams, IPM,027/The,Ring,Study,and,MTN-020/ASPIRE,Study, , , , . Pooled Efficacy Analysis of Two Phase III Trials of Dapivirine Vaginal Ring for the Reduction of HIV-1 Infection Risk in HIV-Uninfected Women in Sub-Saharan Africa . 2017

[15] Peebles K, van der Straten A, Palanee-Phillips T, Reddy K, Hillier SL, Hendrix CW, Harkoo I, Gati Mirembe B, Jeenarain N, Baeten JM, Brown ER; MTN-020/ASPIRE Study Team. Brief Report: Anal Intercourse, HIV-1 Risk, and Efficacy in a Trial of a Dapivirine Vaginal Ring for HIV-1 Prevention. J Acquir Immune Defic Syndr. 2020 Mar 1;83(3):197-201. doi: 10.1097/QAI.0000000000002253.

	to 84, p=0.01), low to high adherence levels (defined as <23.5mg of residual dapivirine) was associated with a relative risk reduction of 56% (95%CI: 20-76, p=0.007). Non-adherence (defined as ≥23.5 mg residual dapivirine) was not associated with a significant reduction in risk. • Results from two open-label extension projects (OLEs), HOPE and DREAM, which included women who participated in ASPIRE and the Ring Study, **demonstrated a range of effectiveness from 39% to 62% reduction in HIV incidence**, comparing HIV incidence among participants to a simulated control involving women randomized to the placebo arm of the prior randomized controlled trial, matched for STI, matched for research center, age, and presence of STIs at enrolment.[13] [14] **Both open-label extension projects noted increased adherence to DVR as compared with adherence to DVR measured during the randomized controlled trials.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> Furthermore, retrieved systematic reviews[16] [17] similarly pooled data from ASPIRE[6] and the Ring[7] RCTs showing that dapivirine ring significantly reduced HIV incidence (55 per 1000) compared to placebo (78 per 1000); RR 0.71 (95% CI 0.57 to 0.89, I^2 = 0%, n=4588 women; *moderate-certainty evidence*). Dapivirine vaginal ring was studied compared to placebo. Placebo-controlled oral PrEP (TE) studies suggest that oral PrEP may be more efficacious than the dapivirine ring: RR 0.49 (95% CI 0.33 to 0.73) but there are no head- to head comparative trials.	
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	**Adverse Events** • Results from a phase IIa safety study (n=140) **showed no increased risk of adverse events** comparing women randomized to the dapivirine ring vs. placebo ring.[18] • Pooled results from the two phase III trials, demonstrated **no increased risk for any adverse events** comparing women randomized to the dapivirine ring vs. placebo (relative risk= 1.02, 95% CI: 0.98 to 1.06) and **no increased risk for any grade 3 or 4 adverse event** comparing women randomized to the dapivirine ring vs. placebo (relative risk= 1.19, 95% CI: 0.68 to 2.05).[9, 10]	Given the vaginal ring provides a local delivery mechanism (i.e., dapivirine is delivered directly to the vaginal tissue), risk of systemic exposure is much lower than for oral therapies, thus reducing the potential for systemic toxicities (e.g., side effects and foetal complications).

[13] Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, et al.; MTN-025/HOPE Study Team. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e87-e95. doi: 10.1016/S2352-3018(20)30304-0.

[14] Nel, A., van Niekerk, N., Van Baelen, B., Malherbe, M., Mans, W., Carter, A. , al., et. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. Lancet HIV. 2021 Feb;8(2):e77-e86. doi: 10.1016/S2352-3018(20)30300-3.

[16] Musekiwa A, Fernando NB, Abariga SA. Effectiveness of vaginal microbicides in preventing HIV transmission. Trop Med Int Health. 2020 Jul;25(7):790-802. doi: 10.1111/tmi.13401.

[17] Obiero J, Ogongo P, Mwethera PG, Wiysonge CS. Topical microbicides for preventing sexually transmitted infections. Cochrane Database Syst Rev. 2021 Mar 13;3(3):CD007961. doi: 10.1002/14651858.CD007961.pub3.

[18] Nel A, Bekker LG, Bukusi E, Hellström E, Kotze P, Louw C, et al. Safety, Acceptability and Adherence of Dapivirine Vaginal Ring in a Microbicide Clinical Trial Conducted in Multiple Countries in Sub-Saharan Africa. PLoS One. 2016 Mar 10;11(3):e0147743. doi: 10.1371/journal.pone.0147743.

	• One randomized controlled trial (ASPIRE) reporting on social harms (defined as "nonmedical adverse consequences of DVR use or of trial participation more generally") found **3% of women experienced a social harm during the trial.**[19] Younger women (aged 18-26) were over twice as likely to experience a social harm as compared to older women, and reporting a social harm was associated with short-term decreased product adherence. **Drug Resistance** • Across the two placebo-controlled trials, there was **no difference in the number of NNRTI mutations found among seroconverters comparing those randomized to DVR vs. placebo** (relative risk= 1.13, 95% CI: 0.64 to 2.01). [9, 10] **Contraceptive effectiveness and pregnancy outcomes** • **Note:** Use of effective contraception was part of the eligibility criteria across included studies. Additionally, women were tested for pregnancy at study visits, and use of study product was discontinued immediately following detection of pregnancy. • One analysis from ASPIRE evaluated contraceptive effectiveness, and **found no difference in pregnancy incidence comparing DVR to placebo arms, across all hormonal contraceptive methods.**[20] • Analyses from ASPIRE and The Ring Study (data from one specific research site) found **no significant differences in adverse pregnancy related events comparing DVR to placebo arms.** [21, 22] **Behavioral outcomes** • One research site from The Ring Study reported on condom use and sexual behavior (n=132) and **found no significant change in reports of non-condom use at last sex as reported at week 4 and week 104** (64% and 68%, respectively, p=0.71), and **no significant change in reports of 2 or more sexual partners comparing baseline and completion (week 104), p=0.81.**[23] • Studies found relatively high rates of curable STI incidence during the trials (at baseline and post-intervention) but **found no substantive differences comparing rates among those randomized to DVR vs. placebo.**[10] One sub-analysis from one research site in the Ring Study found significant decreases in diagnoses of Trichomonas vaginalis and Neisseria gonorrhea from baseline to 104 weeks followup. [17]	The reduced possibility for side effects and unlikely foetal toxicity might make DVR more acceptable to adolescent girls and young women. In comparison, oral PrEP has been associated with issues pertaining to bone mineral density, renal functioning, and a "startup syndrome" with associated gastrointestinal symptoms. None of these issues have been found with DVR.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Large ○ Moderate ○ Small ○ Trivial	As per WHO Guideline panel's rationale above.	

[19] Palanee-Phillips T, Roberts ST, Reddy K, Govender V, Naidoo L, Siva S, et al. Impact of Partner-Related Social Harms on Women's Adherence to the Dapivirine Vaginal Ring During a Phase III Trial. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):580-589. doi: 10.1097/QAI.0000000000001866.

[20] Balkus JE, Palanee-Phillips T, Reddy K, Siva S, Harkoo I, Nakabiito C, et al.. Brief Report: Dapivirine Vaginal Ring Use Does Not Diminish the Effectiveness of Hormonal Contraception. J Acquir Immune Defic Syndr. 2017 Oct 1;76(2):e47-e51. doi: 10.1097/QAI.0000000000001455.

[21] Kusemererwa, S., Abaasa, A.. Pregnancy incidence and outcomes among women using dapivirine vaginal ring for HIV prevention in a phase III clinical trial in south western Uganda. AIDS Research and Human Retroviruses; 2018.

[22] Makanani B, Balkus JE, Jiao Y, Noguchi LM, Palanee-Phillips T, Mbilizi Y, Moodley J, Kintu K, Reddy K, Kabwigu S, Jeenariain N, Harkoo I, Mgodi N, Piper J, Rees H, Scheckter R, Beigi R, Baeten JM. Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy. J Acquir Immune Defic Syndr. 2018 Dec 15;79(5):566-572. doi: 10.1097/QAI.0000000000001861.

[23] Kusemererwa, S., Abaasa, A.. Does the use of the dapivirine vaginal ring result in change in risk sexual behavior?. AIDS Research and Human Retroviruses; 2018.

○ Varies ○ Don't know		
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	• Mostly moderate certainty of evidence for HIV infection, adverse event outcomes, contraceptive effectiveness, and sexual behaviour outcomes. Mostly low certainty of evidence for outcomes related to drug resistance and adverse pregnancy-related outcomes. • Data available from 5 studies, including 3 RCTs and 2 observational studies. • RCTs had some risk of bias due to censoring of data at trial sites with low adherence. • OLEs used simulated controls, drawn from the placebo arm of the prior randomized studies, to estimate HIV incidence in the absence of ring use. • Approximately 5,000 participants across studies • Few absolute events for drug resistance and reproductive health outcomes (women taken off study product once pregnancy was known) • Data only available for women aged ≥18 years	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> All of the studies included South African sites. Follow-up studies exploring feasibility and acceptability and the open label extension study also took place in South Africa. However, it is unclear what efficacy is in women under 25, especially in a real-life setting that lacks the incentives and controls associated with clinical trials. **Note:** There is no available studies comparing dapivirine ring to oral PrEP (TE).	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	• HIV prevention and ring safety are highly valued across all stakeholders. • Women value having a discrete prevention option that they can choose to divulge to partners or not. • Any increase in drug resistance due to ring use would be an important consideration for population-level impact on treatment. However, due to the local delivery of dapivirine directly into vaginal tissue, risk of drug resistance for DVR appears to be less than for other PrEP delivery systems (i.e., oral PrEP) • There has been no noted behavioral risk compensation for oral PrEP among adolescent girls and young women. We do not know for certain if this will be the same for DVR use. However, we do know that many women who choose to use oral PrEP products also have difficulty using condoms consistently.	

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> A systematic review[24]found favorable acceptability pooled prevalence of 85.6% (95%CI 81.3, 89.0). European (90.6%; 95%CI 83.9, 94.7), Asian (97.1%; 95%CI 92.0, 99.0), and multi-region studies (93.5%; 95%CI 84.6, 97.4) reported more favorable acceptability compared to African studies (59.4%; 95%CI 38.3, 77.5).	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	• Results from the systematic review and meta-analysis show that **the dapivirine ring has promising benefits regarding HIV prevention among women and few undesirable clinical effects.** • Results identified **no safety concerns of DVR, no evidence of increased drug resistance among seroconverters exposed to DVR, and no evidence of behavioral risk compensation.** Low levels of partner-specific social harms associated with ring use or trial participation were reported in one phase III RCT (ASPIRE). • **More research is needed to understand the use of and adherence to DVR among adolescent women and girls**, given that a pooled analysis of results from the two phase III placebo-controlled RCTs found no protective benefit of DVR among younger women aged ≤21 years. • **More research is needed to understand the effects of DVR among pregnant and lactating women** as DVR use within the reviewed studies was discontinued immediately following pregnancy detection and did not resume use until pregnancy and lactation had ceased. **A system is needed to capture adverse maternal and foetal/infant outcomes among pregnant and lactating women exposed to DVR** through links with pregnancy and anti-retroviral (ARV) registries.	Importantly, implementation of DVR across all trials was offered in the context of a comprehensive package of prevention services, including periodic HIV testing and counselling, risk reduction counselling, testing and treatment of sexually transmitted infections, antiretroviral treatment for HIV positive persons, access to free condoms, etc.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention *(compared to placebo)* ○ Favors the intervention ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. Compared to placebo, dapivirine ring shown to prevent HIV acquisition (RR 0.71; 95% CI 0.57 to 0.88). There are no head-to-head evidence for dapivirine ring. Oral PrEP appears to be more efficacious when compared to placebo in preventing HIV acquisition (RR 0.49; 95% CI 0.33 to 0.73). Of note, is that ASPIRE[19] reported on social harms (defined as "nonmedical adverse consequences of DVR use or of trial participation more generally") found 3% of women experienced a social harm during the trial. Younger women (aged 18-26) were over twice as likely to experience a social harm as compared to older women, and reporting a social harm was associated with short-term decreased product adherence.	There were no safety concerns, however, no benefit was found in women under 21 years which warrants further study.

[24] Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33. doi: 10.1016/j.contraception.2021.10.001.

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**Medicine costs:** • According to the International Partnership for Microbicides, the **current cost of goods is $8 per ring**, with a total annual cost (12 rings) of $96. • Different modelling studies have estimated the total annual cost of DVR (inclusive of drug, laboratory costs and service delivery) is between $107-$115, with variation in cost by target group [25]; $131 (19); and between $152-$189(20), with variation by country. **Service delivery costs:** • Service delivery costs for ring use include routine HIV testing. A modeling study estimated the cost of HIV testing (assuming a negative result) to be $12 in the South African context.[26] Therefore, testing on a quarterly basis would involve a total cost of $48 annually, although this amount would vary by setting. • **DVR is expected to require fewer health system resources than oral PrEP**, as the only associated cost is HIV testing. Unlike oral PrEP, no creatinine monitoring or Hepatitis B testing is required for the dapivirine ring. Additionally, DVR may be suitable for delivery outside of clinic settings, such as using pharmacy, community, and self-care delivery models.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	As per WHO Guideline panel's rationale above. Additional contextual information: According to the International Partnership for Microbicides, the **current cost of goods is $14.59 (per ring,** for the South African market (Communication from the NDoH Programme). Furthermore, the NDoH Programme considers that from a local public sector perspective, the service delivery would generally be the same for both dapivirine vaginal ring and oral PrEP. **Note:** The NDoH Programme advised that IPM provided an updated price of **$15.31** as of June 2022. Analysis conducted by the Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand, Johannesburg, using methods similar to their previous work on the costing of oral PrEP[27,28], **estimated the cost of provision of DVR at $130/woman initiated** (inclusive of drug, laboratory costs and service delivery), under the assumption that a	

[25] Smith J, Harris K, Garnett G, Van Damme L, Hallett, T. Cost-effectiveness of the intravaginal dapivirine ring: A modeling analysis. Topics in Antiviral Medicine; 2016.

[26] Glaubius R, Ding Y, Penrose KJ, Hood G, Engquist E, Mellors JW, Parikh UM, Abbas UL. Dapivirine vaginal ring for HIV prevention: modelling health outcomes, drug resistance and cost-effectiveness. J Int AIDS Soc. 2019 May;22(5):e25282. doi: 10.1002/jia2.25282.

[27] Jamieson L, Gomez GB, Rebe K, et al (2020) The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa. AIDS 34:883–891. https://doi.org/10.1097/QAD.0000000000002486

[28] Jamieson L, Johnson LF, Nichols BE, et al (2022) The Relative Cost-Effectiveness of Long-Acting Injectable Cabotegravir Versus Oral Pre-Exposure Prophylaxis: A Modelled Economic Evaluation and Threshold Analysis in South Africa Based on the HPTN 083 and 084 Trials. SSRN Journal. https://doi.org/10.2139/ssrn.4047136

	DVR client remains on the program for an average duration 5 months after initiation and the current cost of goods is $14.59/ring. Assuming a **coverage of 5% for 15 to 49-year-old women (coverage rates estimated based on the oral PrEP programme)**, we can expect a total of 528,000 to 575,000 women to take up DVR at a total cost of R999 to-R1,088 million (or $468-75 million) per year, over 2023 to 2027, assuming the cost of the ring remains at $14.59 per ring. The estimated threshold price for DVR to be as cost-effective as oral PrEP, was estimated as R52.00 per ring. **Refer to the short-report: Cost-effectiveness of dapivirine ring compared to oral PrEP, 23 May 2022.**	

Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o Very low o Low o Moderate o High o No included studies	Cost of resource requirements would vary by setting.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o Very low o **Low** o Moderate o High o No included studies	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> Resource requirements would depend significantly on both the cost of the dapivirine ring and eventual uptake once rolled out. Though the assumed coverage/uptake was 5%, this was based on uptake seen in the oral PrEP programme. Uptake of the dapivirine ring, once available, remains uncertain.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention	Our review identified three studies related to the cost-effectiveness of the dapivirine vaginal ring: • Smith et al., 2018 (modeling study based in the South African context): **DVR would be a cost-effective intervention**, even with low efficacy, if its use was highly targeted to those at greatest risk (sex workers, young women and those with multiple partners). Glaubius et al., 2017 (modeling study based in the South African context): **DVR would be a cost-saving intervention for KwaZulu Natal if the intervention were prioritized for female sex workers.**	Prioritizing ring use for women at substantial risk of HIV infection will be critical. Attention on how to identify women at substantial risk, generate demand for DVR, and support adherence will be of utmost importance.

○ Varies ○ No included studies	• Reidy et al., 2019[29] (modeling study based on scenarios in Kenya, South Africa, Uganda, Zimbabwe): Use of the GOALS model found the **impact of DVR on HIV epidemics to be highly variable** and dependent on many factors, such as treatment coverage and potential intervention cost. **The cost per HIV infection averted varied between $13,000 and $121,000 within the South African context.** • Studies highlighted uncertainty regarding **adherence to DVR and demand for/uptake of DVR** as critical aspects of determining cost effectiveness and impact.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ **Favors the comparison** *(compared to SOC: oral PrEP - TE)* ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studie	**Contextual information** **DVR compared to oral daily Prep (TE):** Over a 20-year time horizon (2023-2042), **daily oral PrEP is estimated to be more cost effective compared to DVR**, over a baseline with no PrEP: at $13,445/HIV infection averted (oral PrEP), versus both DVR effectiveness assumptions (29%: $60,707/HIV infection averted and 62%: $26,549/HIV infection averted). For DVR to be similarly cost-effective to oral PrEP**, the cost of the ring will need to be lower at approximately $4/ring** (assuming 29% effectiveness of DVR) **and up to $8.80/ring** (assuming 62% effectiveness of DVR). This is based on analysis conducted by HE^{2}RO comparing the cost-effectiveness of scaling up DVR vs daily oral PrEP, modelling the impact of each intervention in a HIV transmission model, and assessing incremental cost per HIV infection averted. Main assumptions included the same target population (women aged 15-49 and female sex workers), the same target coverage (5%), and the same average duration of use (5 months), for both DVR and oral PrEP. They modelled two scenarios for effectiveness for DVR protection against HIV infection: 1) 29%, and 2) an upper limit of 62%. In comparison the effectiveness of oral PrEP is estimated at 65% [30].	

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	• DVR offers an **additional, discrete, woman-controlled biomedical HIV prevention option.** • Expanding PrEP options through offering DVR in addition to oral PrEP **could help meet the diverse needs and preferences of women**. • Evidence from the field of contraception has demonstrated an association between increased contraceptive choice and increased contraceptive use among women. **Increasing biomedical HIV prevention options could have a similar effect (i.e., increased options may lead to increased use).**[31] • Access to the dapivirine ring for women could also provide **additional opportunities for sexual and reproductive health services**.	It is possible that offering DVR in addition to oral PrEP would replace oral PrEP use (e.g., oral PrEP users would switch to DVR or vice versa), but is also possible that offering DVR in addition to oral PrEP would expand PrEP use more generally by providing options and allowing preferable selection.

[29] Reidy M, Gardiner E, Pretorius C, Glaubius R, Torjesen K, Kripke K. Evaluating the potential impact and cost-effectiveness of dapivirine vaginal ring pre-exposure prophylaxis for HIV prevention. PLoS One. 2019 Jun 26;14(6):e0218710. doi: 10.1371/journal.pone.0218710.
[30] Fonner VA, Dalglish SL, Kennedy CE, et al (2016) Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS 30:1973–1983. https://doi.org/10.1097/QAD.0000000000001145
[31] Ross J, Stover J. Use of modern contraception increases when more methods become available: analysis of evidence from 1982-2009. Glob Health Sci Pract. 2013 Jul 26;1(2):203-12. doi: 10.9745/GHSP-D-13-00010.

	• **Cost of dapivirine ring and clinic visits could prevent some people from gaining access**. However, current cost estimates suggest PrEP delivered through a vaginal ring would cost less than oral PrEP. • **Preventing HIV in high incidence female populations will reduce future treatment cost.** • **Preventing HIV infection among women will help sustain their health and that of their sexual partners.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ **Varies** ○ Don't know	As per WHO Guideline panel's rationale above. <u>Additional contextual information:</u> For those women who cannot use SOC (TE), accessing dapivirine ring will promote equity for PrEP. Current cost estimates reviewed by the WHO Guideline panel suggests that PrEP delivered through a vaginal ring would cost less than oral PrEP. However, comparing direct medicine prices, dapivirine is more expensive than oral PrEP, at a proposed price of $15.31 (Direct communication from NDoH Programme) and from a local public sector perspective, the service delivery would generally be the same for both interventions.	

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	A comprehensive systematic review and meta-analysis assessing global acceptability of vaginal rings (agnostic to active pharmacological ingredient) found that rings were highly acceptable. **The overall acceptability (proportion of women reporting a favorable experience) across 46 studies and 19,080 was 87.4% (95% CI: 83.5% to 90.5%)**. This review also found that most women who used the ring liked it, whereas hypothetical acceptance was low among women who had no direct experience.[32] • An additional systematic review on vaginal rings focused in low- and middle-income countries that included 68 RCTs and observational studies also found high acceptability, and the **vast majority reported the ring was easy to insert and remove**. Most women disclosed ring use to partners, although some women feared violence or anger from partners if ring use was discovered. Ring acceptability increased over time, both as women got used to using the ring and as the ring became popularized in their community. **Women expressed preferences for devices that were easily accessible, long-acting, and partner-approved that could prevent both HIV infection and pregnancy and that could also be used without the partner's awareness, with minimal impact on sex, and with few side effects**.[33] • A systematic review specific to DVR including 21 studies, all with a geographic focus in sub-Saharan Africa, found similar high acceptability. **The review also noted that partner influence can affect ring use and that perceived community awareness and acceptance of the ring was important.** [34]	.

[32] Ridgeway K, Montgomery ET, Smith K, Torjesen K, van der Straten A, Achilles SL, Griffin JB. Vaginal ring acceptability: A systematic review and meta-analysis of vaginal ring experiences from around the world. Contraception. 2022 Feb;106:16-33. doi: 10.1016/j.contraception.2021.10.001.

[33] Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, Baggaley R, van der Straten A. Vaginal ring acceptability and related preferences among women in low- and middle-income countries: A systematic review and narrative synthesis. PLoS One. 2019 Nov 8;14(11):e0224898. doi: 10.1371/journal.pone.0224898.

[34] Schwartz K , Bhavaraju N , Ridgeway K , Gomez A. End-user perspectives on their ability, motivation and opportunity to use the dapivirine vaginal ring. AIDS 2020; 2020.

	• Thirty citations on acceptability were found through current search, the vast majority of which related to ASPIRE, the Ring Study, DREAM, or HOPE, in addition to acceptability outcomes reported in the included phase II safety study. As found in the other reviews, **DVR was highly acceptable among women with experience using the product.**	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o No o Probably no o Possibly/Probably yes o Yes o Varies o Don't know	As per WHO Guideline panel's rationale above.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
o No o Probably no o Probably yes o Yes o Varies o Don't know	• **Multiple studies of the dapivirine vaginal ring have been conducted, thus proving its feasibility across a variety of trial settings**. In addition to the safety study, two phase III RCTs, and two open-label extension projects included in this review of the evidence, additional safety studies have been successfully conducted among adolescent young women in the United States, post-menopausal women in the United States, and among healthy women in Europe. [35, 36, 37] • **DVR is relatively easy to transport and store**. It does not require refrigeration and can be stored at room temperature.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o No o Probably no o Probably yes o Yes o Varies o Don't know	As per WHO Guideline panel's rationale above. Dapivirine ring is SAHPRA registered and can be implemented using the existing NDoH Programmatic infrastructure.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	9 June 2022	RO, JN, HD, HS, LJ, TL	Dapivirine ring not be included in the EML. May be considered for sub-group, where standard of care (TE) cannot be used if the price per ring decreased to R52.00 per ring. Available evidence is restricted to placebo-controlled data.

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[36] Chen BA, Zhang J, Gundacker HM, Hendrix CW, Hoesley CJ, Salata RA, Dezzutti CS, van der Straten A, Hall WB, Jacobson CE, Johnson S, McGowan I, Nel AM, Soto-Torres L, Marzinke MA; MTN-024/IPM 031 Protocol Team for the Microbicide Trials Network. Phase 2a Safety, Pharmacokinetics, and Acceptability of Dapivirine Vaginal Rings in US Postmenopausal Women. Clin Infect Dis. 2019 Mar 19;68(7):1144-1151. doi: 10.1093/cid/ciy654.

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Short report: Cost-effectiveness of dapivirine ring compared to oral PrEP

Date: 23 May 2022
Author: Lise Jamieson
Declaration of Interest: LJ (Health Economics and Epidemiology Research Office (HE^{2}RO), University of Witwatersrand) has no interests pertaining to dapivirine vaginal ring.

SUMMARY

Summary Table. Cost-effectiveness comparison of dapivirine ring (DVR) vs standard of care (oral PrEP)

	Dapivirine ring analysis		
	Oral PrEP	Dapivirine ring	
		29% effectiveness	*62% effectiveness*
Incremental cost per HIV infection averted (2023-2042)			
USD	$13,445	$60,707	$26,549
ZAR	R196,393	R886,741	R387,800
Incremental cost per life year saved (2023-2042)			
USD	$4,741	$19,985	$9,337
ZAR	R69,250	R291,912	R136,378
Budget impact (2023-2027)			
Number on intervention per year	529,000-577,069	528,000-575,000	528,000-575,000
Cost per year, ZAR	R565-616 million	R999-1,088 million	R1,001-1,091 million
Threshold price for DVR to be as cost-effective as oral PrEP, ZAR			
	-	R52	R107

Modelling assumptions:
- Baseline: no PrEP
- Effectiveness: 65% (oral PrEP); 29%-62% (DVR)
- Average duration on PrEP: 5 months (oral PrEP); 5 months (DVR)
- Populations targeted: women aged 15-49, female sex workers
- Coverage: 5% across target population

Cost assumptions:
- Provision of dapivirine ring, total cost = R1,892 (incl cost of ring $14.59/R213.11 per ring)
- Provision of oral PrEP, total cost = R1,067 (incl cost of TDF/FTC R68.65/month)
- 3-monthly visits for both oral PrEP and dapivirine ring

Oral PrEP is a more cost-effective intervention in comparison to the dapivirine ring owing to the higher effectiveness and lower cost. Current price estimate for the dapivirine ring to enter the South African market is set at $14.59/ring, or R213.11/ring. For DVR to be as cost-effective as oral PrEP, it would need to cost substantially less at R52/ring (under a 29% effectiveness assumption) up to R107/ring (under a 62% effectiveness assumption).

FULL REPORT

Methods

- ***Modelling and assumptions***

The impact of PrEP (oral PrEP, dapivirine ring) on the HIV epidemic was estimated using the Thembisa model (version 4.4), a deterministic compartmental HIV transmission model of the South African HIV epidemic (Johnson and Dorrington 2021).

Oral PrEP effectiveness, accounting for both efficacy and adherence, was assumed to be 65% for women (Fonner et al. 2016). *Dapivirine ring effectiveness* was assumed to be 29% based on the pooled results from two phase III placebo-controlled randomized trials, ASPIRE and the ring study (Baeten et al. 2016; Nel et al. 2016). A second scenario was included to model an effectiveness estimate of 62%, the upper limit estimate from two open-label extension projects (OLEs), HOPE and DREAM (Baeten et al. 2021; Nel et al. 2021).

- ***Costs***

Costs were estimated from the provider perspective, the South African government. All costs are presented in both 2021 South African Rand (ZAR) and United States Dollar (USD), and uninflated. In addition, we present the numbers of women on dapivirine ring and the total cost for the next 5 years to inform the health budget.

An ingredients-based approach was used to estimate the average cost of oral PrEP (TDF/FTC) and dapivirine ring provision, using data from PrEP demonstration sites and subsequent implementation programmes, as well as following current PrEP guidelines. Full methodology for the estimation of oral PrEP cost has been described elsewhere (Jamieson et al. 2020). The cost of dapivirine ring provision was structured using similar methodology; however, we adjusted the ingredients to include the dapivirine ring, additional professional nurse time for the initial insertion of the ring at initiation, and removed laboratory monitoring tests which are not required (e.g. ALT, creatinine testing, which are included in the oral PrEP costs).

In line with standard of care PrEP, visits are scheduled 3-monthly under both the oral PrEP and dapivirine ring scenarios.

The cost of oral PrEP is set at $4.70/month (R68.65/month, based on a tender price; Master Procurement Circular January 2021; using the average 2021 exchange rate of 14.61 ZAR = 1 USD). *The cost of one dapivirine ring* (for a month) is set at $14.59/ring, or R213.11/ring (IPM price, as per NEMLC review).

- ***Scenarios***

We modelled the provision of PrEP to women aged 15-49 years, including to female sex workers, scaling up coverage to 5% across target populations for both interventions (oral PrEP, dapivirine ring). Based on data from the South African PrEP implementation programme, the average duration on oral PrEP is estimated to be 5 months (Johnson and Dorrington 2021). We assumed the same duration for women initiating on the dapivirine ring, as a best guess as no implementation data outside of a trial setting is available.

We estimated cost-effectiveness as cost per HIV infection averted and cost per life year saved over a 5- and 20-year time horizon (2023-2027 and 2023-2042), over a *baseline of no PrEP*, but including currently available HIV interventions in South Africa (e.g. high coverages for condom provision, HIV testing services, and medical male circumcision). This allows us to determine the impact of a reduction in HIV incidence due to oral PrEP and the dapivirine ring on the need for subsequent ART, in addition to existing prevention interventions. The estimation of the cost of the HIV programme followed the same methodology as the South African HIV Investment Case.

- ***Threshold* analysis**

Anticipating a lower cost-effectiveness of the dapivirine ring due to a higher cost of the ring, and lower effectiveness, compared to oral PrEP, we conduct a threshold analysis on the price to estimate the price level at which the dapivirine ring is similarly cost-effective compared to oral PrEP.

Results

Table 1. Estimated cost of dapivirine and ring oral PrEP provision, per person initiated

	Dapivirine ring			Oral PrEP		
	Cost (USD)	***Cost (ZAR)***	***%***	***Cost (USD)***	***Cost (ZAR)***	***%***
Drugs	88	1,279	68%	28	412	37%
Labs	7	98	5%	16	235	21%
Consumables	0.5	7	0.3%	1	21	3%
Staff	27	394	21%	19	280	29%
Overheads	8	114	6%	8	120	11%
Total Cost	**130**	**1,892**		**73**	**1,067**	

The cost of provision of dapivirine ring and oral PrEP was estimated at $130 and $73 per woman initiated, respectively, for the average duration of 5 months after initiation, that they are in the PrEP programme (Table 1).

Table 2a. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 USD)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (USD, billions)	10.04	10.40	10.39	10.24
Incremental cost (USD, billions)	-	352 (4%)	350 (3%)	195 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (USD)	**-**	***63,477***	***25,859***	***13,637***
Incremental cost per life year saved (USD)	**-**	***693,612***	***58,204***	***29,853***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (USD, billions)	41.40	43.05	43.00	42.25
Incremental cost (USD, billions)	-	1,650 (4%)	1,598 (4%)	850 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (USD)	**-**	***60,707***	***26,549***	***13,445***
Incremental cost per life year saved (USD)	**-**	***19,985***	***9,337***	***4,741***

Table 2b. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 ZAR)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (ZAR, billions)	146.71	151.85	151.83	149.56
Incremental cost (ZAR, billions)	-	5.1 (4%)	5.1 (3%)	2.8 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (ZAR)	**-**	***927,197***	***377,720***	***199,193***
Incremental cost per life year saved (ZAR)	**-**	***10,131,497***	***850,183***	***436,056***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (ZAR, billions)	604.68	628.79	628.03	617.10
Incremental cost (ZAR, billions)	-	24.1 (4%)	23.3 (4%)	12.4 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (ZAR)	**-**	***886,741***	***387,800***	***196,393***
Incremental cost per life year saved (ZAR)	**-**	***291,912***	***136,378***	***69,250***

Over a 20-year time horizon, oral PrEP is estimated to be more cost effective, at $13,445/HIV infection averted, compared to the dapivirine ring under both 29% effectiveness ($60,707/HIV infection averted) and 62% effectiveness ($26,549/HIV infection averted) (Table 2a). Similar conclusions are reached under the 5-year time horizon analysis, and for incremental cost per life year saved. Note, the incremental cost per life year saved is substantially higher in the 5-year time horizon analysis as the effects of AIDS deaths have not yet been realized in the short time frame.

Results in ZAR are shown in Table 2b.

Table 3. Cost estimates for budget, years 2022/23 to 2026/27

	2022/23	2023/24	2024/25	2025/26	2026/27
Number of dapivirine ring clients	528,259	535,369	547,638	561,056	575,189
Total cost of dapivirine ring (USD, millions)	68	69	71	73	75
Total cost of dapivirine ring (ZAR, millions)	999	1,013	1,036	1,061	1,088

Assuming a coverage rate of 5% for 15-49-year-old women, we can expect a total of 528,000 to 575,000 women to take up the dapivirine ring at a cost of R999-R,1088 million (or $68-75 million) per year, over the next 5 years and assuming the cost of the ring remains at $14.59 or R213.11 per ring and women remain on the dapivirine ring for an average of 5 months.

Table 4. Threshold analysis: estimated price at which the dapivirine ring remains as cost-effective as oral PrEP

Solving for		***29% effectiveness***	***62% effectiveness***
Incremental cost/HIV infection averted			
	USD	$3.33	$7.33
	ZAR	R49	R107
Incremental cost/life year saved			
	USD	$3.54	$7.35
	ZAR	R52	R107

The estimated price at which the dapivirine ring becomes similarly cost-effective compared to oral PrEP would be $3.54/ring (if assuming 29% effectiveness) and ~$7.35/ring (if assuming 62% effectiveness).

Conclusion

Assuming the same duration and coverage between the PrEP interventions and the same target population, oral PrEP is more cost-effective than the dapivirine ring. This is mostly due to both the higher effectiveness (65% for oral PrEP vs 29% for dapivirine ring) and the lower cost per month of provision ($73 or R1,067 per woman initiated for oral PrEP vs $130 or R1,892 per woman initiated for dapivirine ring).

If the dapivirine ring achieves a consistent 62% effectiveness, it will still be less cost-effective compared to oral PrEP, as long as the price remains higher than $7.35/ring. A lower effectiveness of the dapivirine ring will result in the lower price per ring required in order to meet the same level of cost-effectiveness compared to oral PrEP.

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Number on intervention per year	529,000-577,069	528,000-575,000	528,000-575,000
Cost per year, ZAR	R565-616 million	R999-1,088 million	R1,001-1,091 million
Threshold price for DVR to be as cost-effective as oral PrEP, ZAR			
	-	R52	R107

Modelling assumptions:
- Baseline: no PrEP
- Effectiveness: 65% (oral PrEP); 29%-62% (DVR)
- Average duration on PrEP: 5 months (oral PrEP); 5 months (DVR)
- Populations targeted: women aged 15-49, female sex workers
- Coverage: 5% across target population

Cost assumptions:
- Provision of dapivirine ring, total cost = R1,892 (incl cost of ring $14.59/R213.11 per ring)
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Methods

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- ***Scenarios***

We modelled the provision of PrEP to women aged 15-49 years, including to female sex workers, scaling up coverage to 5% across target populations for both interventions (oral PrEP, dapivirine ring). Based on data from the South African PrEP implementation programme, the average duration on oral PrEP is estimated to be 5 months (Johnson and Dorrington 2021). We assumed the same duration for women initiating on the dapivirine ring, as a best guess as no implementation data outside of a trial setting is available.

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Staff	27	394	21%	19	280	29%
Overheads	8	114	6%	8	120	11%
Total Cost	**130**	**1,892**		**73**	**1,067**	

The cost of provision of dapivirine ring and oral PrEP was estimated at $130 and $73 per woman initiated, respectively, for the average duration of 5 months after initiation, that they are in the PrEP programme (Table 1).

Table 2a. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 USD)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (USD, billions)	10.04	10.40	10.39	10.24
Incremental cost (USD, billions)	-	352 (4%)	350 (3%)	195 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (USD)	**-**	***63,477***	***25,859***	***13,637***
Incremental cost per life year saved (USD)	**-**	***693,612***	***58,204***	***29,853***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (USD, billions)	41.40	43.05	43.00	42.25
Incremental cost (USD, billions)	-	1,650 (4%)	1,598 (4%)	850 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (USD)	**-**	***60,707***	***26,549***	***13,445***
Incremental cost per life year saved (USD)	**-**	***19,985***	***9,337***	***4,741***

Table 2b. Impact and cost-effectiveness of dapivirine ring and oral PrEP over a 5- and 20-year time horizon (2021 ZAR)

		Dapivirine ring		
	Baseline	*29% effectiveness*	*62% effectiveness*	Oral PrEP
5-year time horizon (2023-2027)				
Total Cost of the HIV programme (ZAR, billions)	146.71	151.85	151.83	149.56
Incremental cost (ZAR, billions)	-	5.1 (4%)	5.1 (3%)	2.8 (2%)
Total new HIV infections (thousands)	0.91	0.91	0.90	0.90
HIV infections averted (thousands)	-	5.5 (1%)	13.6 (1%)	14.3 (2%)
Total life years lost to AIDS (millions)	11.39	11.39	11.39	11.39
Life years saved (thousands)	-	0.5 (0.004%)	6 (0.1%)	7 (0.1%)
Incremental cost per HIV infection averted (ZAR)	**-**	***927,197***	***377,720***	***199,193***
Incremental cost per life year saved (ZAR)	**-**	***10,131,497***	***850,183***	***436,056***
20-year time horizon (2023-2042)				
Total Cost of the HIV programme (ZAR, billions)	604.68	628.79	628.03	617.10
Incremental cost (ZAR, billions)	-	24.1 (4%)	23.3 (4%)	12.4 (2%)
Total new HIV infections (millions)	2.94	2.91	2.88	2.88
HIV infections averted (thousands)	-	27 (1%)	60 (2%)	63 (2%)
Total life years lost to AIDS (millions)	36.02	35.94	35.85	35.84
Life years saved (thousands)	-	83 (0.2%)	171 (0.5%)	179 (0.5%)
Incremental cost per HIV infection averted (ZAR)	**-**	***886,741***	***387,800***	***196,393***
Incremental cost per life year saved (ZAR)	**-**	***291,912***	***136,378***	***69,250***

Over a 20-year time horizon, oral PrEP is estimated to be more cost effective, at $13,445/HIV infection averted, compared to the dapivirine ring under both 29% effectiveness ($60,707/HIV infection averted) and 62% effectiveness ($26,549/HIV infection averted) (Table 2a). Similar conclusions are reached under the 5-year time horizon analysis, and for incremental cost per life year saved. Note, the incremental cost per life year saved is substantially higher in the 5-year time horizon analysis as the effects of AIDS deaths have not yet been realized in the short time frame.

Results in ZAR are shown in Table 2b.

Table 3. Cost estimates for budget, years 2022/23 to 2026/27

	2022/23	2023/24	2024/25	2025/26	2026/27
Number of dapivirine ring clients	528,259	535,369	547,638	561,056	575,189
Total cost of dapivirine ring (USD, millions)	68	69	71	73	75
Total cost of dapivirine ring (ZAR, millions)	999	1,013	1,036	1,061	1,088

Assuming a coverage rate of 5% for 15-49-year-old women, we can expect a total of 528,000 to 575,000 women to take up the dapivirine ring at a cost of R999-R,1088 million (or $68-75 million) per year, over the next 5 years and assuming the cost of the ring remains at $14.59 or R213.11 per ring and women remain on the dapivirine ring for an average of 5 months.

Table 4. Threshold analysis: estimated price at which the dapivirine ring remains as cost-effective as oral PrEP

Solving for		***29% effectiveness***	***62% effectiveness***
Incremental cost/HIV infection averted			
	USD	$3.33	$7.33
	ZAR	R49	R107
Incremental cost/life year saved			
	USD	$3.54	$7.35
	ZAR	R52	R107

The estimated price at which the dapivirine ring becomes similarly cost-effective compared to oral PrEP would be $3.54/ring (if assuming 29% effectiveness) and ~$7.35/ring (if assuming 62% effectiveness).

Conclusion

Assuming the same duration and coverage between the PrEP interventions and the same target population, oral PrEP is more cost-effective than the dapivirine ring. This is mostly due to both the higher effectiveness (65% for oral PrEP vs 29% for dapivirine ring) and the lower cost per month of provision ($73 or R1,067 per woman initiated for oral PrEP vs $130 or R1,892 per woman initiated for dapivirine ring).

If the dapivirine ring achieves a consistent 62% effectiveness, it will still be less cost-effective compared to oral PrEP, as long as the price remains higher than $7.35/ring. A lower effectiveness of the dapivirine ring will result in the lower price per ring required in order to meet the same level of cost-effectiveness compared to oral PrEP.

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EVIDENCE SUMMARY

Title: Evidence review of the use of cabotegravir as pre-exposure prophylaxis for HIV.

Date: 15 May 2022
Updated: 29 August 2024 (inclusion of NEMLC due diligence commentary on donated stock)

Reviewers: Jeremy Nel, Lise Jamieson
Affiliation and declaration of interests: JN (Division of Infectious Diseases, Department of Medicine, University of the Witwatersrand); LJ (Health Economics and Epidemiology Research Office (HE2RO), University of Witwatersrand). JN and LJ have no conflicts of interest relating to cabotegravir, but JN has received speaker's fees from Mylan, Cipla, J&J relating to HIV topics.

Background:
Pre-exposure prophylaxis (PrEP) is an effective prevention option for any sexually active person who might be exposed to HIV through contact with HIV in the genital tract or blood. In South Africa to date, the only available PrEP formulation has been an oral fixed-dose combination consisting of tenofovir and emtricitabine (TDF-FTC). Clinical trial data suggests that the efficacy of this regimen is critically dependent on adherence levels however.(1) Programmatic data suggests a high rate of early discontinuation of TDF-FTC-based PrEP in real-world settings, and roll out in South Africa has been poor.(2)

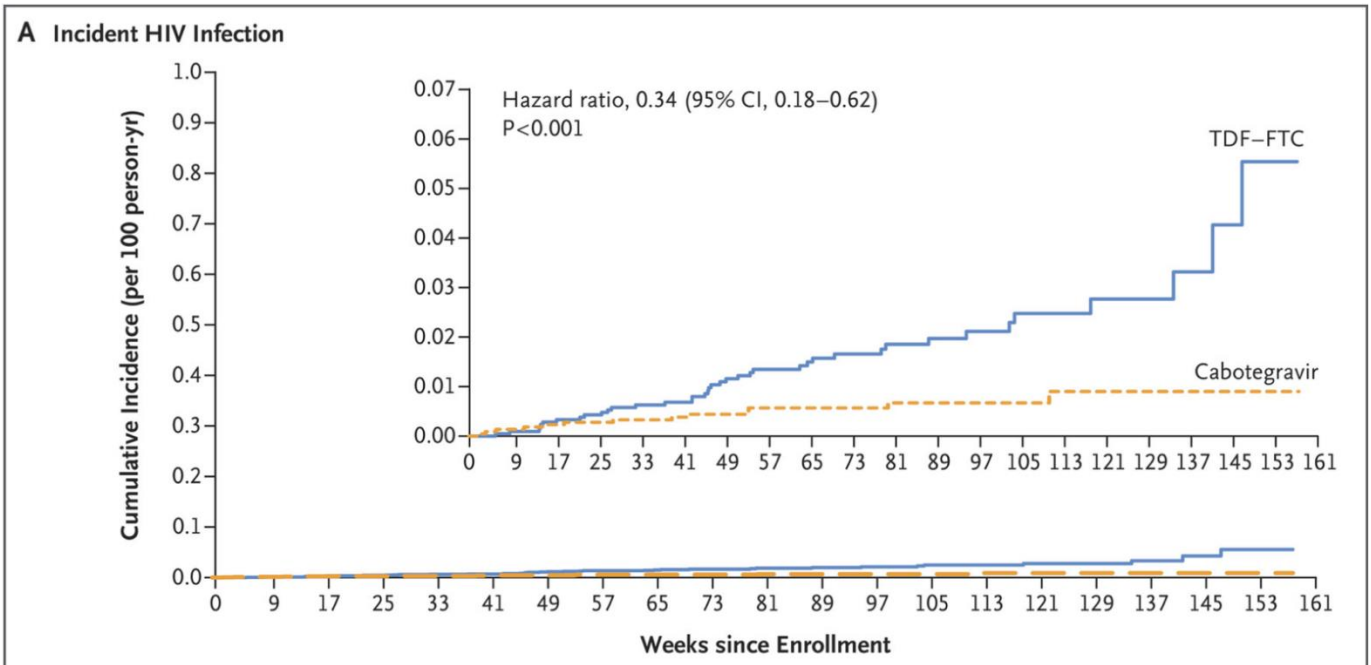
Cabotegravir (CAB) has been formulated as an injectable nanoparticle suspension with a long half-life that permits dosing every eight weeks. Its use as PrEP has recently been the subject of 2 published phase 3 randomised control trials. This evidence summary outlines the key findings of these 2 trials. Both compared long-acting injectable CAB to oral TDF-FTC, and the trials had almost identical designs. They differed primarily in the population under study - HPTN 083 evaluated the drugs in HIV-negative cisgender men and transgender women, whereas HPTN 084 assessed the drugs in HIV-negative women. In each case, there were three phases to the trial: (1) an oral-lead in phase where oral CAB or TDF-FTC was given (in addition to placebo), (2) an injection phase where participants received long-acting CAB injections 8-weekly (plus daily oral placebo) or daily TDF-FTC (plus 8-weekly placebo injection), and (3) a tail phase for those who stopped injections early for any reason (e.g. tolerability, or pregnancy). The role of the oral lead-in phase was to assess drug tolerability prior to potentially receiving a long-acting form of the drugs. Only patients who demonstrated at least 50% adherence to the oral lead in doses (as determined by pill count) were permitted to move to the injection phase. The overall goal of the trials was to assess incident HIV infection in each trial.

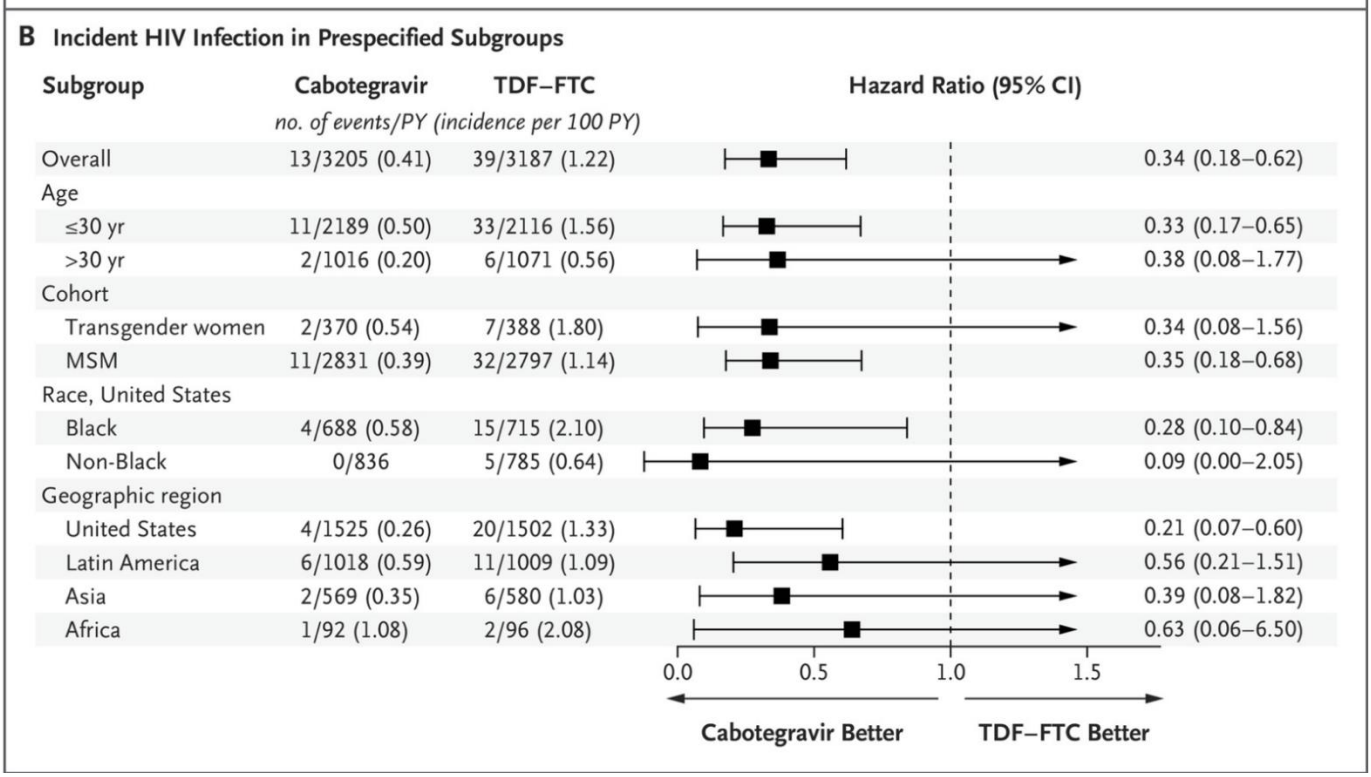
HPTN 083(3)
4570 patients underwent randomisation and baseline characteristics were similar between the two groups. Participant retention was 87% at one year, with a median follow-up of 1.4 years (IQR 0.8-1.9). The injection phase consisted of 8-weekly injections starting from week 5 and lasting until week 185.

Efficacy

HIV infection was acquired after enrolment by 52 participants – 13 in the CAB group (incidence 0.14 per 100 person-years) and 39 in the TDF-FTC group (incidence 1.22 per 100 years). The hazard ratio for infection in the CAB arm was 0.34 (95% CI 0.18-0.62). The effect was consistent across all prespecified subgroups. The trial was stopped early for efficacy at the first pre-planned interim analysis. Of the 13 infections in the CAB group, 4 were deemed to have occurred before enrolment, 5 occurred in patients who had not taken a recent dose of CAB, 3 occurred in the oral

lead-in phase, and 4 occurred in participants who had received the injectable form of CAB, and were adherent to the regimen. CAB drug levels were normal in these four patients.





CAB resistance mutations

Integrase gene resistance was detected in 5 patients in the CAB arm (1 with baseline infection and 4 with incident infection). Of note, none of these cases occurred in the "tail" phase after CAB administration.

Safety

With the exception of injection site reactions, the side-effect profile was very similar between the two arms. Grade 2 or higher adverse events (AEs) occurred in over 90% of both arms, driven primarily by decreased creatinine clearance (in ~71% of participants overall). Serious AEs occurred in 5.3% of each arm. There were 11 deaths in the study – 7 in the TDF-FTC arm (1 thought to be related to the drug) and 4 in the CAB arm (none thought to be related to the drug). Injection site reactions were reported in 81% of the CAB arm (vs 31% of the TDF-FTC arm), were mostly mild-moderate in severity, and occurred mostly with the initial doses. 2.4% of participants in the CAB arm permanently discontinued the injections due to an injection-related AE. A mean annualised increase in weight of 1.23 kg (95% CI 1.05-1.42) was seen in the CAB arm, compared to 0.37kg (0.18-0.55) in the TDF-FTC arm.

Refer to table 1 for the summary of findings for the HPTN 083(3) trial.

HPTN 084(4)

3224 participants were enrolled; baseline characteristics were again well-balanced between the two arms. Participant retention was 90% at one year, and 86% at two years, and the median follow-up period was 1.24 years (IQR 0.92-1.56). The injection phase consisted of 8-weekly infections from week 5 to week 153.

Efficacy

40 incident HIV infections occurred in the trial – 4 in the CAB group (incidence 0.2 per 100 person-years, 95% CI 0.06-0.52)) and 36 in the TDF-FTC group (incidence 1.85 per 100 person years, 95% CI 1.3-2.57). The hazard ratio was 0.12 (95% CI 0.05-0.31, p<0.0001). Of the 4 incident cases in the CAB arm, 3 occurred prior to receiving any CAB injections, and the 4th case occurred after a delayed visit of 16 weeks between injections. Outcomes were consistent across prespecified subgroups. As with HPTN 083, the trial was stopped early due to efficacy.

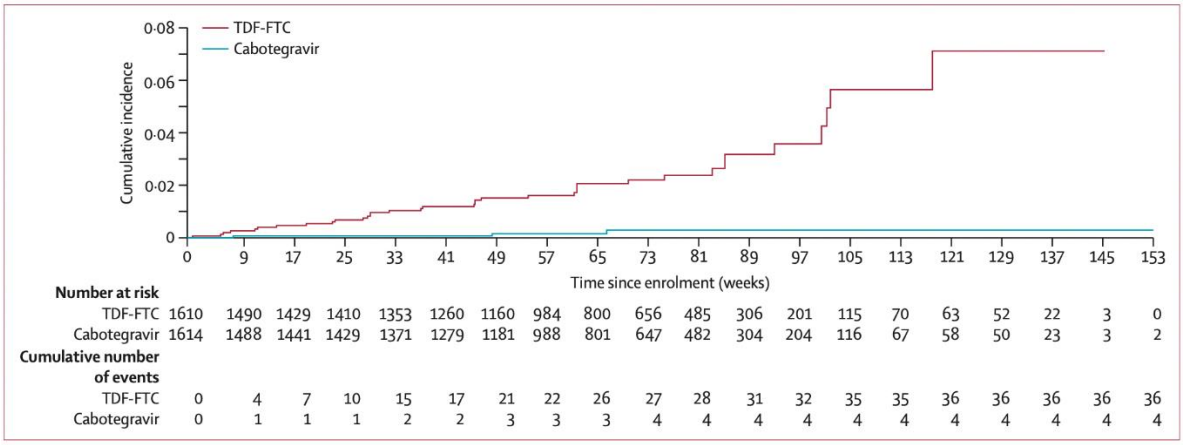


***Figure 3*: Cumulative HIV incidence by study group**
Kaplan-Meier estimates of HIV infection are shown. Four HIV infections were observed in the cabotegravir group (HIV incidence 0·20 per 100 person-years [95% CI 0·06–0·52]) and 36 in the TDF-FTC group (1·85 per 100 person-years [1·3–2·57]). Participants in the cabotegravir group had an 88% lower risk of HIV infection than those in the TDF-FTC group (hazard ratio 0·12 [0·05–0·31]; p<0·0001). TDF-FTC=tenofovir disoproxil fumarate plus emtricitabine.

CAB resistance mutations

No major *integrase* resistance mutations were detected in any of the four "breakthrough" infections in the CAB group.

Safety

Safety findings were very similar to those in HPTN 083, and with the exception of injection-site reactions (which were more common in the CAB group, 38% vs 10%), these were well-balanced between groups. Grade 2 or worse AEs occurred in 92% of participants (again driven by a change in creatinine clearance that was not clinically significant in the majority of cases), and grade 3 or worse AEs in 17%. Serious AEs occurred in 2.0% of each arm. No injection-site reactions led to discontinuation. There were 3 deaths in the CAB arm (vs 0 in the TDF-FTC arm) but none were thought by blinded assessors to be linked to the drug. Weight gain was again more prominent in the CAB arm, but the difference was relatively small (2.4 kg per year vs 2.1 kg per year).

Refer to table 2 for the summary of findings for the HPTN 083(4) trial.

Table 1: Summary of findings for the HPTN 083 trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LA-CAB	TDF-FTC	Hazard (95% CI)	Absolute (95% CI)		
Incident HIV (follow-up: mean 1.4 years; assessed with: per 100 person-years)												
1	RCT	serious[a]	not serious	not serious	not serious	strong association	0.41 per 100 person years	1.22 per 100 person years	**HR 0.34** (0.18 to 0.62)	**8 fewer per 1,000 person years** (from 10 fewer to 5 fewer)	⊕⊕⊕⊕ High	CRITICAL
Grade 2 or higher Adverse Events (follow-up: mean 1.4 years)												
1	RCT	serious[a]	not serious	not serious	not serious	none	2106/2280 (92.4%)	2116/2282 (92.7%)	**RR 1.00** (0.98 to 1.01)	**0 fewer per 1,000 person years** (from 19 fewer to 9 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **LA-CAB:** long-acting carbotegravir; **RCT**: randomised controlled trial; **RR:** risk ratio

Explanations

a. Trial stopped early for benefit

Table 2: Summary of findings for the HPTN 084 trial

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LA- CAB	TDF-FTC	Hazard (95% CI)	Absolute (95% CI)		
Incident HIV (follow-up: mean 1.24 years; assessed with: 100 patient years)												
1	RCT	serious[a]	not serious	not serious	not serious	very strong association	0.2 per 100 person years	1.85 per 100 person years	**HR 0.12** (0.05 to 0.31)	**16 fewer per 1,000 person years** (from 18 fewer to 13 fewer)	⊕⊕⊕⊕ High	CRITICAL
Grade 2 or higher Adverse Events (follow-up: mean 1.24 years)												
1	RCT	serious[b]	not serious	not serious	not serious	none	1487/1614 (92.1%)	1486/1610 (92.3%)	**HR 1.00** (0.95 to 1.05)	**0 fewer per 1,000** (from 11 fewer to 9 more)	⊕⊕⊕◯ Moderate	IMPORTANT

CI: confidence interval; **LA-CAB:** long-acting carbotegravir; **RCT**: randomised controlled trial; **RR:** risk ratio

a. Trial stopped early due to efficacy. Limited number of events.

b. Trial stopped early due to efficacy.

Conclusions

Two well-conducted RCTs both demonstrated the markedly superior efficacy of CAB relative to TDF-FTC; both trials were stopped early for efficacy. This efficacy advantage appears to be driven by a greater proportion of time with therapeutic drug levels (in turn driven by greater adherence). There were no significant differences in adverse events between CAB and TDF-FTC regimens, with the exception of injection site reactions. The latter were more common in the CAB arm, but were generally mild and occurred less frequently with subsequent injections. Given the long pharmacokinetic "tail" of CAB, there is a theoretical concern that non-adherence might drive the development of integrase-inhibitor drug resistance (due to there being a prolonged period of sub-therapeutic drug levels with non-adherence). This was not borne out by either trial however, although the absolute number of incident HIV cases is still very low.

Of note:

- CAB data for pregnant women is extremely limited, and so the safety and efficacy in this subgroup has not been established. This is being researched currently via an open-label extension to HPTN083.
- As the trials were stopped early, long-term safety data is not available yet; the median follow-up was 1.4 years in HPTN083 and 1.24 in HPTN084, instead of the planned 3 years. This longer-term data being collected via open-label extensions to both trials.
- Routine HIV diagnostics such as "rapid" HIV antibody testing and ELISA assays were found to be associated with delayed diagnosis of incident HIV infections in both studies, and so HIV viral load testing may need to be performed instead to ensure that incident infections are rapidly detected. This is in contrast to HIV PrEP with tenofovir/emtricitabine, where screening for HIV by rapid tests or ELISA is adequate. Delayed diagnosis of incident HIV likely contributed to the development of drug resistance in several cases.
- There are important drug-drug interactions, including with rifampicin, that might limit CAB's use in programmatic settings.
- The total budgetary cost of CAB remains to be fully assessed, as the price is not currently known.

As no safety concerns were identified during the oral lead-in phase in these prevention studies and also in treatment studies, it is possible that this can be omitted. However, clinical data for this is currently lacking. It is being researched in an open-label extension to HPTN083 and HPTN084.

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: Although the efficacy of CAB is high, and the safety profile acceptable, the PHC/Adult Hospital Level Committee suggests not to use CAB as PrEP for HIV, until such time as the price becomes known, and the evidence of efficacy for regimens that do not include an oral lead-in phase are available. *Rationale:* Two phase 3 RCTs both found that PrEP with long-acting injectable CAB had greater efficacy than oral tenofovir plus emtricitabine. A model to assess budgetary impact and cost-effectiveness analysis has been developed, however until a price is confirmed, a final recommendation cannot be made. **Level of Evidence: High certainty evidence** **Review indicator:** Evidence of efficacy in regimens that do not require oral lead-in doses, information on cost.					
NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): Accepted **UPDATED NEMLC RECOMMENDATION (e-ratified, 30 MARCH 2023):** Updated recommendation following completion of the budget impact analysis (March 2023) ratified by NEMLC, as above.					
Monitoring and evaluation considerations					
Research priorities					

NEMLC COMMENTS ON DONATED STOCK (29 AUGUST 2024)

The Committee noted that donated stock of CAB from USAID has been accepted by the NDoH, in accordance with the SAHPRA's medicine donations policy. The donation will be for a 2-year period. The NEMLC raised the following concerns regarding this donation of CAB for PrEP which were addressed by the programme as detailed below:

IMPLEMENTATION CONSIDERATIONS:

- The standard ART regimen in South Africa is dolutegravir based. Defaulting while on CAB therapy could result in HIV acquisition with potential integrase inhibitor resistance. Monitoring and support to minimize the risk of defaulting CAB therapy is recommended. Programme guidance and training on screening candidates who are most likely to benefit from therapy is advised. NEMLC notes the plan for screening, monitoring, and support, as outlined in the guidelines provided by the programme including the development of a comprehensive job aid. NEMLC notes that people who seroconvert will be identified, and transitioned to ARV therapy with adequate monitoring as appropriate.
- Clients on CAB therapy who have a breakthrough infection are at high risk of false negative HIV test results if standard HIV antibody- and/or antigen-based diagnostic tests are used. It is suggested that nucleic acid testing be considered instead (e.g. HIV viral load), possibly for a limited assessment period in view of the cost implications with expanded viral load testing. NEMLC notes the testing strategy outlined in the programme guidelines, as it stands. NEMLC also understands that alternative strategies are being implemented currently in pilot sites, and that the programme may amend their strategy, based on findings from these pilot sites.
- Adequate monitoring of both benefits and harms is strongly recommended to inform decision making once the donated stock is depleted. NEMLC notes that facilities identified as pilot sites will be required to record CAB uptake on a tracker register as part of three different PrEP products offered at these sites. Data on uptake, retention and switches will be recorded in a standardized format at each site and collated monthly.

SUSTAINABILITY OF SUPPLY CONSIDERATIONS:

- Concerns regarding continuity of care (once donated stock is depleted) were noted as CAB remains a non-EML medicine, until such time that more affordable generic alternatives become available. NEMLC notes the continuity of care recommendations put forward by the programme - should alternative access to injectable PrEP not be available at the end of the 2-year pilot program, clients will be transitioned to oral PrEP. NEMLC acknowledges though that moving clients at high risk of HIV acquisition to a less effective method of prevention, is not ideal.

Appendix 2: 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 [ ] *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	Two large well-designed RCTs showing substantially better efficacy of CAB over TDF-FTC – see grade tables above
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [x] None [ ]	Men/transgender women: 8 fewer infections per 1000 patient years (95% CI: 5-10) compared to oral TE. Women: 13 fewer infection per 1000 patient years (95% CI 14-18) compared to oral TE.
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	Two large well-designed RCTs showing that CAB regimen was generally well-tolerated, and as well tolerated as TDF-FTC - see grade tables above
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	CAB compared to TE: Serious AEs were uncommon (2-5%), as were drug discontinuations (0-4%). No deaths were attributable to CAB in either trial.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	Strong reduction in incident HIV at the cost of more injection site reactions, the vast majority of which were mild/moderate and settled with time.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Feasible, but would require more frequent patient visits to clinic (8-weekly). Would also likely require retraining for healthcare workers on good injection technique.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [x]	Not registered with SAHPRA and so SEP unknown. A recent cost-effectiveness analysis concluded: "*The cost per CAB-LA injection needed to be less than twice that of a 2-month supply of TDF/FTC to remain as cost-effective, with threshold prices ranging between $9.03/injection [high uptake; CAB taken for median 12 months vs 5 months on TDF/FTC] and $14.47/injection [medium uptake; CAB and TDF/FTV both taken for median 5 months].*"(6) - https://dx.doi.org/10.2139/ssrn.4047136

		See attached budget impact analysis in the appendix. Local price is needed to confirm budget impact and determine affordability.
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 [ ]	Survey data and clinical trial suggest a patient preference for long-acting injectable forms of PrEP.(5)
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	No survey data available pertaining to equity, but the Committee was of the opinion that there would be no impact on health inequity.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	15 May 2022	JN. LJ	Although the efficacy of CAB is high, and the safety profile acceptable, CAB is not recommended as PrEP for HIV, until the medicine is SAHPRA-registered, available at an affordable price and there is updated evidence of efficacy for regimens that do not include an oral lead-in phase are available.
V5.0	28 March 2023	ERC Update	The recommendation has been updated following registration by SAHPRA and completion of the BIA, although a final price is yet to be announced.
V5.1	29 August 2024	NEMLC update	NEMLC comments added in response to donated stock offered by USAID

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National Essential Medicines List Pharmacoeconomics and Budget impact analysis
Component: HIV infection

Date: 01 February 2023
Medication: Cabotegravir (injectable)
Indication: For the prevention of HIV infection in HIV negative individuals at risk of HIV acquisition

1 INTRODUCTION

This document is an annexure to the medicine review of injectable cabotegravir (CAB) for pre-exposure prophylaxis (PrEP) for the prevention of HIV infection. The review showed that CAB had superior efficacy to the standard-of-care oral PrEP formulation, tenofovir/emtricitabine (TDF/FTC). Efficacy of CAB was evaluated through two well-conducted randomized clinical trials (HPTN 083 and HPTN 084). These trials have shown CAB to be highly effective in preventing HIV infection, reducing the risk of HIV acquisition by 66% (95% confidence interval (CI) 38%-82%) in men who have sex with men (MSM) and transgender women, and by 89% (95%CI 68%-96%) in young women, compared to oral TDF/FTC, after 12 months of follow-up. Further follow-up for the latter (in young women) have confirmed similar results after 24 months of follow up.

This efficacy advantage appears to be driven by a greater proportion of time with therapeutic drug levels (in turn driven by greater adherence). There were no significant differences in adverse events between CAB and TDF/FTC regimens, with the exception of injection site reactions. The latter were more common in the CAB arm, but were generally mild and occurred less frequently with subsequent injections.

Currently there is no price for CAB as this product has not yet been negotiated for the South African market. This report describes a cost-effectiveness analysis that compares the scaling up of CAB compared to scaling up TDF/FTC, with different assumptions for coverage and duration on PrEP, with the base-case being the current low TDF/FTC roll-out. Our analysis also includes a threshold analysis with the aim of estimating the optimal price at which CAB remains as cost-effective as TDF/FTC.

This report is a summary of the modelling study by Jamieson et al [1], which aimed to evaluate the cost-effectiveness of scaling up CAB vs. scaling up TDF/FTC, compared to a baseline of the current TDF/FTC roll-out programme.

2 PHARMACOECONOMICS MODEL – METHODS AND SCENARIOS

The impact of CAB and TDF/FTC was estimated using Thembisa (version 4.4, C++), a **deterministic compartmental HIV transmission model of the South African HIV epidemic** [2]. The model population is stratified by age, sex, sexual experience, sexual behaviour, marital status, HIV testing history and male circumcision status. More detailed information about the model can be access at www.thembisa.org.

We modelled the **impact over a 20-year time horizon (2022-2041)** separately for TDF/FTC and CAB with target populations female sex workers (FSW), MSM, adolescent girls and young women (AGYW) (aged 15-24 years), and heterosexual adolescent boys and young men (ABYM) (aged 15-24 years). We **assumed two coverage levels for scaling up PrEP** (TDF/FTC and CAB) for each population (**high and medium coverage**), assuming a higher uptake by CAB users, based on studies showing a higher stated preference for injectable products compared to TDF/FTC [3–5].

PrEP coverage was assumed to increase linearly over a 3-year period. Based on South African PrEP implementation programme data [2], **TDF/FTC coverage is assumed to be low at baseline** (between 0.5% and 3% of the relevant target populations), and the average duration on TDF/FTC is assumed to be 5 months for AGYW and ABYM, and 11 months for

MSM, and there is no TDF/FTC uptake in CAB scenarios. We assume a 1-month supply of TDF/FTC at last visit will provide an additional month of protection.

For CAB the average duration in the programme was modelled under two sub-scenarios:

1) **minimum duration scenario**, in which users remain in the programme for a similar time as they would on TDF/FTC (i.e. 5 months for AGYW and ABYM, and 11 months for MSM);
2) **maximum duration scenario**, in which users remain on PrEP for longer than TDF/FTC, i.e. 12 months (AGYW, ABYM) or 24 months (MSM).

3 CLINICAL INPUTS AND COSTS

Effectiveness

TDF/FTC effectiveness, accounting for both efficacy and adherence, is assumed to be 85% for adolescent boys and young men (ABYM) and MSM, and 65% for adolescent girls and young women (AGYW) and female sex workers (FSW) [6,7].

CAB effectiveness, compared to TDF/FTC, was assumed to be 66% in men and 89% in women [8,9]. For modelling purposes we need to estimate their effectiveness compared to no PrEP; we modified the trial results to approximate a 95% effectiveness for CAB (i.e. 0.95 = 1-(1-0.85) x (1-0.66) for men; 0.96 = 1-(1-0.65) x (1-0.89) for women).

Costs

Costs were analysed from the perspective of the provider, the South African government, and reported in 2021 South African Rand (ZAR).

The **average cost of PrEP provision was estimated using an ingredients-based approach.** Briefly, PrEP is provided in primary healthcare clinics and includes rapid HIV testing, counselling, provision of condoms, syndromic screening for sexually transmitted infections with treatment referral, adherence counselling, training, outreach, mobilisation, monitoring and evaluation costs. The cost of TDF/FTC is R68.65 per month.

The cost of CAB provision was structured using similar methodology with adjustments (increasing professional nurse time for the injection administration, removing creatinine testing). Since the cost of drug is currently unknown, in our initial modelling we varied the price between 1-to-5-fold the 2-monthly price of TDF/FTC.

Table 1. Key assumptions on duration, coverage, effectiveness and cost of CAB and TDF/FTC

	TDF/FTC		**CAB**			
			Minimum duration		***Maximum duration***	
	Medium coverage	**High coverage**	**Medium coverage**	**High coverage**	**Medium coverage**	**High coverage**
Duration	5mo (AGYW, FSW, ABYM); 11mo (MSM)		*Same as for TDF/FTC*		12mo (AGYW, FSW, ABYM); 24mo (MSM)	
Coverage	5% (AGYW, ABYM); 15% (FSW, MSM)	10% (AGYW, ABYM); 30% (FSW, MSM)	25% (FSW, MSM); 20% (AGYW); 10% (ABYM)	50% (FSW, MSM); 40% (AGYW); 20% (ABYM)	40% (FSW, MSM); 35% (AGYW); 20% (ABYM)	67% (FSW, MSM); 60% (AGYW); 35% (ABYM)
Effectiveness	65% (AGYW, FSW); 85% (ABYM, MSM)		95% (all populations)			
Cost per person initiated*	R1,113-R1,145 (AGYW, FSW, ABYM); R1,692 (MSM)		R1,146-1,190 (AGYW, FSW, ABYM); R1,777 (MSM)		R1,911-2,006 (AGYW, FSW, ABYM, MSM 1st year); R1,528 (MSM 2nd year)	

*For comparison reasons we assume the cost of CAB is the same as for TDF/FTC (2-month supply)

Cost-effectiveness

We analysed cost-effectiveness over a 20-year time horizon (2022-2041), over a baseline of currently available HIV interventions in South Africa. Outcomes of interest were cost per life year saved and cost per HIV infection averted. Further, using the modelling output- the total cost of the HIV programme, the cost of provision of PrEP and the impact of each of the PrEP technologies, **we solve for the optimal price at which CAB is as cost-effective as TDF/FTC.**

Sensitivity analysis

Several sensitivity analyses are conducted in Jamieson et al [1]; however, of note there are two key analyses which may be of importance to this review: (1) assuming CAB **coverage would be the same as that of TDF/FTC scenarios**, and (2) the **inclusion of annual PCR testing** in the HIV diagnostic algorithm for CAB provision. We consider the impact of these on the threshold price and the budget impact analysis (BIA).

4 RESULTS

Epidemiological impact

Over the 20-year period, CAB averted up to 52,000 infections averted/year in the high coverage, maximum duration scenario, 42,800 infections averted/year (high coverage, minimum duration), 35,600 infections averted (medium coverage, maximum duration), 26,400 infections averted/year (medium coverage, minimum duration).

TDF/FTC averted at most 16,300-9,000 infections annually in high and medium coverage scenarios.

Overall CAB scenarios averted 15%-28% of new HIV infections over baseline (current TDF/FTC roll-out) compared to 4%-8% with the scaling up of TDF/FTC, over the 20-year period (Table 2).

Costs and cost-effectiveness

Under the assumption that CAB drug costs were equal to that of TDF/FTC for the same 2-month period (i.e. cost of 1 injection = cost of 2 months of TDF/FTC):

- the incremental cost of CAB to the HIV programme was higher than TDF/FTC (5%-14% vs 2%-4%) over the 20-year period, due to higher assumed uptake of CAB.
- The cost per infection averted was R88,414-R96,558 (TDF/FTC) and R65,306-R84,419 (CAB) over the 20-year period.

For CAB to remain as cost-effective as TDF/FTC, the cost of the drug would need to be between 1- and 2-fold that of TDF/FTC (2 months' supply).

Table 2: Impact and cost-effectiveness of CAB-LA compared to baseline* and oral TDF/FTC compared to baseline, over a 20-year time horizon (2022-41)

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to TDF/FTC drug†	Total cost of the HIV programme (2021 ZAR)		Incremental cost effectiveness (2021 ZAR)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			603			
Medium PrEP coverage									
TDF/FTC	2.89	4%	37.00	1%	N/A	615	2%	88,414	33,725
CAB-LA minimum duration	2.58	15%	36.19	3%	1x	632	5%	65,306	24,912
					2x	649	8%	105,335	40,182
					3x	667	11%	145,364	55,451
					4x	685	13%	185,393	70,721
					5x	702	16%	225,423	85,991
CAB-LA maximum duration	2.44	19%	35.81	4%	1x	647	7%	75,330	28,889
					2x	675	12%	123,385	47,319
					3x	704	17%	171,441	65,749
					4x	732	21%	219,497	84,178
					5x	760	26%	267,552	102,608
High PrEP coverage									
TDF/FTC	2.78	8%	36.68	2%	N/A	627	4%	96,558	36,483
CAB-LA minimum duration	2.31	24%	35.41	5%	1x	663	10%	84,419	31,327
					2x	699	16%	133,611	49,582
					3x	734	22%	182,802	67,836
					4x	769	27%	231,993	86,090
					5x	804	33%	281,185	104,345
CAB-LA maximum duration	2.17	28%	35.03	6%	1x	688	14%	99,108	36,665
					2x	740	23%	159,432	58,982
					3x	791	31%	219,757	81,300
					4x	843	40%	280,081	103,617
					5x	894	48%	340,406	125,934

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead). Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, ZAR = South African Rand, BL = Baseline, PrEP = pre-exposure prophylaxis

We estimated the **threshold price for CAB per injection** to be between R132 (high coverage, maximum duration) to R211 (medium coverage, minimum duration) if it was to remain as cost-effective as TDF/FTC (Table 3).

Table 3: Estimated cost threshold per CAB injection to ensure CAB remains as cost-effective as oral TDF/FTC (2021 ZAR)

	Minimum duration scenario		Maximum duration scenario	
Cost per CAB injection solving for	***Medium coverage***	***High coverage***	***Medium coverage***	***High coverage***
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R211	R169	R172	R132
CAB cost/life year saved = TDF/FTC cost/life year saved	R211	R174	R171	R136

Sensitivity analyses and the impact on the threshold price

When assuming CAB coverage would be the same as that of TDF/FTC scenarios (refer to Table 1), the threshold price increases to R219 to R282 per injection (Table 4).

If we include an annual PCR testing in the HIV diagnostic algorithm for CAB provision, the threshold price decreases to between R7 to R90 per injection (Table 4). As the cost of providing CAB services increases (inclusion of PCR), the need to decrease the cost of the injection becomes greater in order to reduce the ICER of CAB to align with the ICER of TDF/FTC.

Table 4: Estimated cost threshold per CAB injection to ensure CAB remains as cost-effective as oral TDF/FTC (2021 ZAR) – under sensitivity analyses

	Minimum duration scenario		Maximum duration scenario	
Cost per CAB injection solving for	***Medium coverage***	***High coverage***	***Medium coverage***	***High coverage***
CAB coverage the same as that of TDF/FTC				
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R282	R272	R245	R222
CAB cost/life year saved = TDF/FTC cost/life year saved	R281	R270	R239	R219
Annual PCR testing				
CAB cost/HIV infection averted = TDF/FTC cost/HIV infection averted	R90	R48	R47	R7
CAB cost/life year saved = TDF/FTC cost/life year saved	R90	R53	R46	R12

5 PUBLISHED HEALTH ECONOMICS

There are a limited number of published cost-effectiveness studies on CAB, particularly for South Africa. Glaubius et al [10] found a risk-prioritized strategy cost-effective (<$1600 per life-year gained) over 10 years under a threshold of 3x gross domestic product, compared to no PrEP. Van Vliet et al [11] found CAB cost-effective at a price of <$16/year over 40 years under an arbitrary threshold of <$519/disability-adjusted life year averted.

A modelling study done in the United States found that the CAB injection would need to be between 1- and 2-fold the price of TDF/FTC for it to remain as cost-effective [12] .

6 BUDGET IMPACT ANALYSIS

The cost of CAB for the South African market is currently unknown. The expected volume/uptake is also uncertain. We therefore present two scenarios, both of which aim to get to the lowest range of the cost: 1) medium coverage with minimum duration on CAB (i.e. the same duration users would have been on TDF/FTC (see Table 1), 2) assuming the same coverage and duration for CAB as for TDF/FTC (as per our sensitivity analysis). Assumptions for coverage, duration and cost are noted in the table below for each scenario.

Under a conservative scenario where we expect the lowest scale-up of CAB modelled, we can expect between 383,000 and 611,000 initiates per year at a cost of R700 million to R1.1 billion per year (Table 5). If we expect a higher uptake of CAB compared to TDF/FTC, an estimated 1.1 million to 1.7 million users will initiate CAB annually at a cost of R1.6 billion to R2.5 billion per year.

Table 5. Cost of CAB provision (2021 ZAR) from 2023/24 to 2027/28

Medium coverage; minimum duration on CAB ***Coverage**: 25% (FSW, MSM); 20% (AGYW);10% (ABYM)* ***Duration**: 5mo (AGYW, FSW, ABYM); 11mo (MSM)* ***Cost**: R211/injection; **Total cost of provision (incl drugs)**: R1,445-R1,488 (AGYW, FSW, ABYM); R2,313 (MSM)*					
	2023/24	**2024/25**	**2025/26**	**2026/27**	**2027/28**
Number of users initiated	1,085,900	1,555,955	1,574,404	1,620,995	1,671,383
Cost of providing CAB (billions)	1.627	2.328	2.352	2.421	2.496
Incremental cost to programme* (billions)	1.240	1.774	1.759	1.773	1.782
Same coverage and duration on CAB as TDF/FTC ***Coverage**: 5% (AGYW, ABYM); 15% (FSW, MSM)* ***Duration**: 5mo (AGYW, FSW, ABYM); 11mo (MSM)* ***Cost**: R282/injection; **Total cost of provision (incl drugs)**: R1,734-R1,754 (AGYW, FSW, ABYM); R2,829 (MSM)*					
	2023/24	**2024/25**	**2025/26**	**2026/27**	**2027/28**
Number of users initiated	383,893	562,880	576,831	593,806	611,248
Cost of providing CAB (billions)	0.701	1.026	1.049	1.080	1.111
Incremental cost to programme* (billions)	0.421	0.628	0.631	0.636	0.638

*compared to baseline scenario with continued low TDF/FTC coverage; incremental cost accounts for down-the-line impacts of averted HIV infections, including the reduction in the need for HIV treatment.

7 CONCLUSION

CAB will be as cost-effective compared to scaling up TDF/FTC in the same population if the price can range between R132-R211 per injection, dependent on the underlying coverage and duration assumptions. Lowering the CAB coverage to equal that of TDF/FTC scale-up, we estimate a slight increase in this threshold price (up to R282/injection). Changing the HIV diagnostic algorithm to include PCR testing annually, will cause the threshold price to decrease significantly (R7-R90/injection).

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Version	Date	Reviewer(s)	Conclusion
First	01 Feb 2023	Lise Jamieson	CAB will be as cost-effective compared to scaling up TDF/FTC in the same population if the price can range between R132-R211 per injection, dependent on the underlying coverage and duration assumptions.