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, adults and adolescents
  - 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 10.2.4.2: 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	<u>Individuals ≥30kg and ≥10 years</u> TDF + 3TC + DTG ("TLD") *LoE:IIa*[9] **Note***:* DTG-based regimens are now recommended as first line ART in all women of child-bearing potential. <u>Patients on rifampicin-based TB treatment:</u>

	TDF + FTC + EFV *LoE:IIa[10]* **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	Start protease inhibitor-based regimen: 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.	If chronic hepatitis B coinfection and eGFR 30-50 ml/min: TAF + FTC + DTG. Other scenarios: *LoE:IIb[13]* 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	If plasma VL >50 copies/mL:

	» 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://knowledgehub.health.gov.za/elibrary/third-line-antiretrovirals)
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.

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.

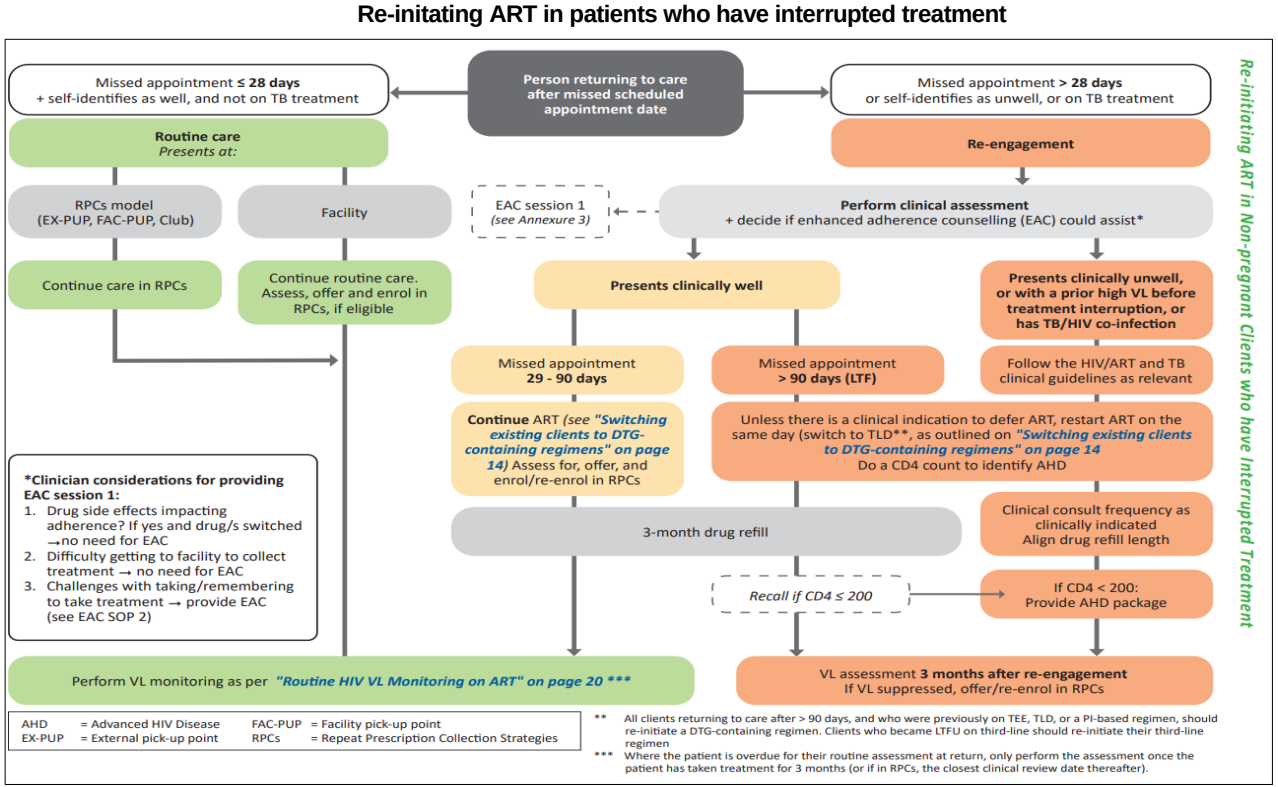


Figure 11.2: Management algorithm of a patient who returns to care after interrupting treatment. Incorporated from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates.

MONITORING ON ART	

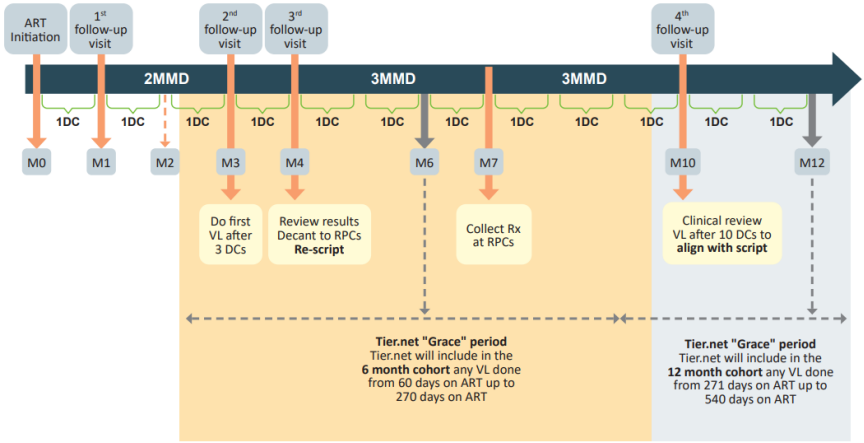
Baseline evaluation	» WHO staging (See table above).
	» Check CD4 count.
	» <u>If CD4 <200 cells/mm^3:</u>
	  » Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). CrAg testing is done reflexly on the CD4 sample if CD4 <100 cells/mm^3. If patient's 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.
- Professional Information Leaflets.

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. See PHC Section 15.7.2 Epilepsy in Adolescents and Adults for further guidance.
Metformin	May increase metformin concentration.	*Metformin initiation:* Initiate metformin at a low dose (500 mg to 1000 mg total daily dose), titrating up as needed. Do not exceed 2 g daily. *DTG initiation:* If patient stabilised on metformin dose ≤ 2g daily, retain metformin dose and monitor for side effects. If patient stabilised on >2 g daily, reduce dose of metformin to ≤2 g daily and monitor. *Patients with renal impairment:* Close monitoring of renal function required. Do not co-prescribe if eGFR <30 mL/min.
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. See PHC Section 15.7.2 Epilepsy in Adolescents and Adults for further guidance.
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 Adult Hospital Level 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 (900 mg if weight >30 kg) plus rifapentine (900 mg 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.

LoE:IIb[32]

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.

Note:

For pregnant women living with HIV:

- If CD4 count > 200 cells/mm^3 and initiating ART, defer TPT until after delivery.
- If CD4 count ≤ 200 cells/mm^3 and initiating ART, offer 12 months of isoniazid as TPT, after excluding active tuberculosis disease.
- Ensure that routine screening against TB is conducted at each antenatal visit.

LoE:IIb[33]

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.
- Children: 12 mg/kg to a maximum dose of 800 mg immediately

LoE:IVb[36]

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, adults and adolescents.
  - 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, 500 mg to 1 g, 4 to 6 hourly as required (maximum of 4 g 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.: *LoE:IIa*[43]
- Aciclovir, oral, 800 mg five times daily for 7 days (4 hourly missing the middle of the night dose).

If secondary infection is present:

ADD

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

Pain:

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

If inadequate pain relief:

ADD

- Tramadol, oral, 50 to 100 mg, 6 hourly as a starting dose. (Doctor prescribed.)
  - May be increased to a maximum daily dose of 400 mg.

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.
- In patients receiving tenofovir, monitor creatinine/eGFR at month 3, month 10, and every 12 months thereafter. Align with VL monitoring schedule.

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 to 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 (<10 years old))

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 to 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

Maternal VL	Risk profile	Prophylaxis	Comment
			to 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

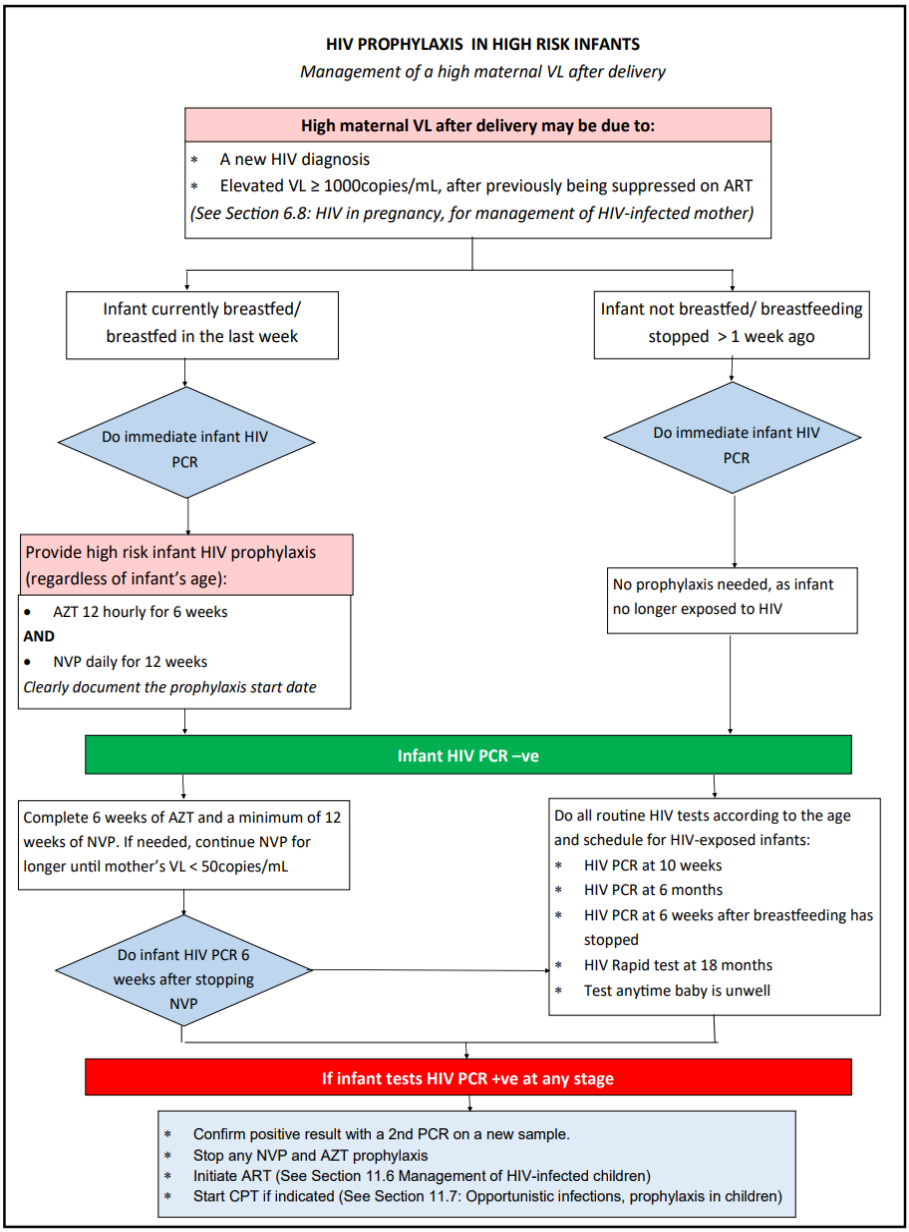


Figure 11.4: HIV prophylaxis in HIV-exposed infant at high risk after delivery

LoE:IIIb[46]

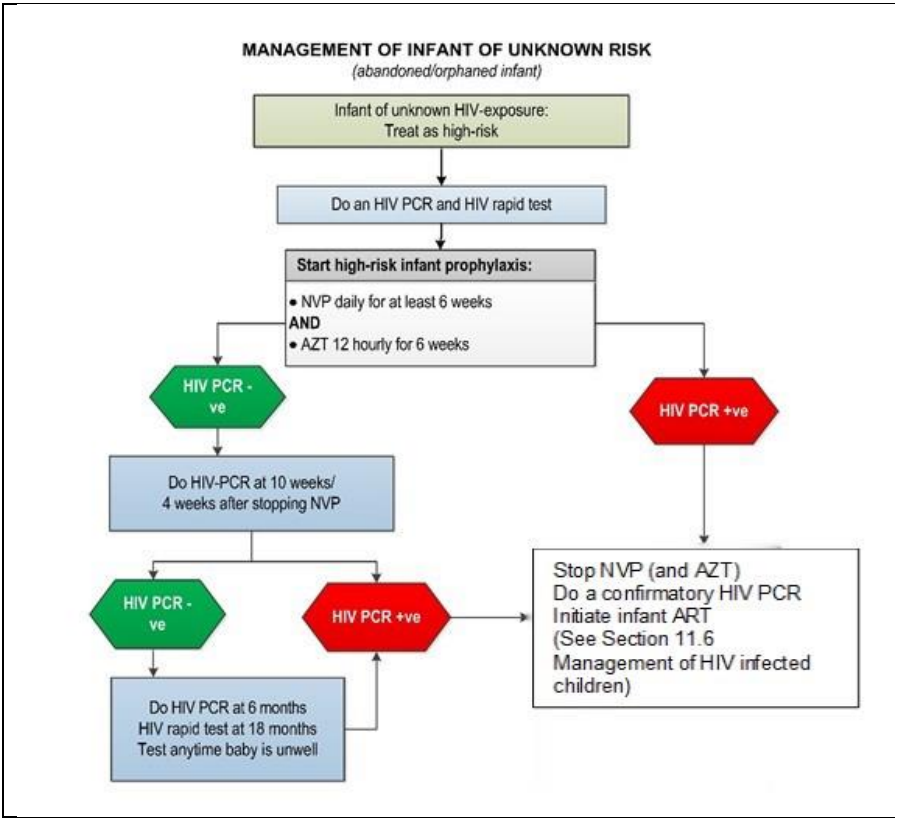


Figure 11.5: Management of HIV-exposed infant of unknown risk

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 to 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 to 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: Vaccines for routine administration).

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.

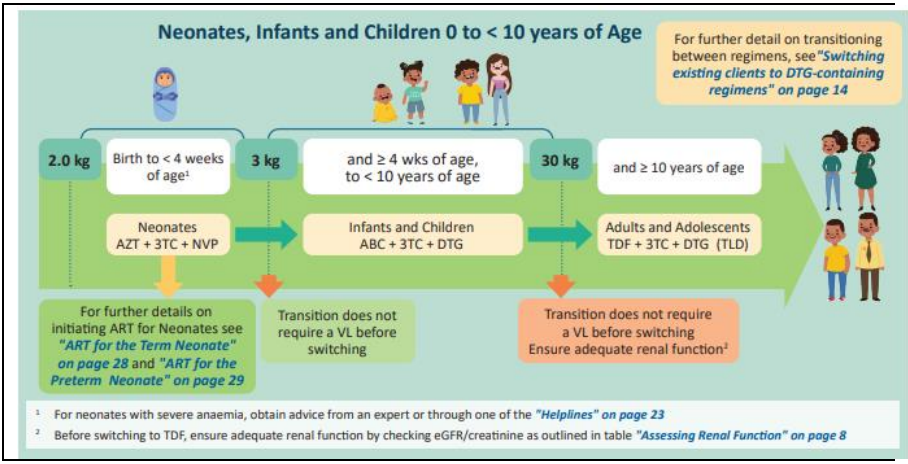


Figure 11.6: First-line paediatric ART-switching algorithm for neonates/infants/children (adopted from the NDoH 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates).

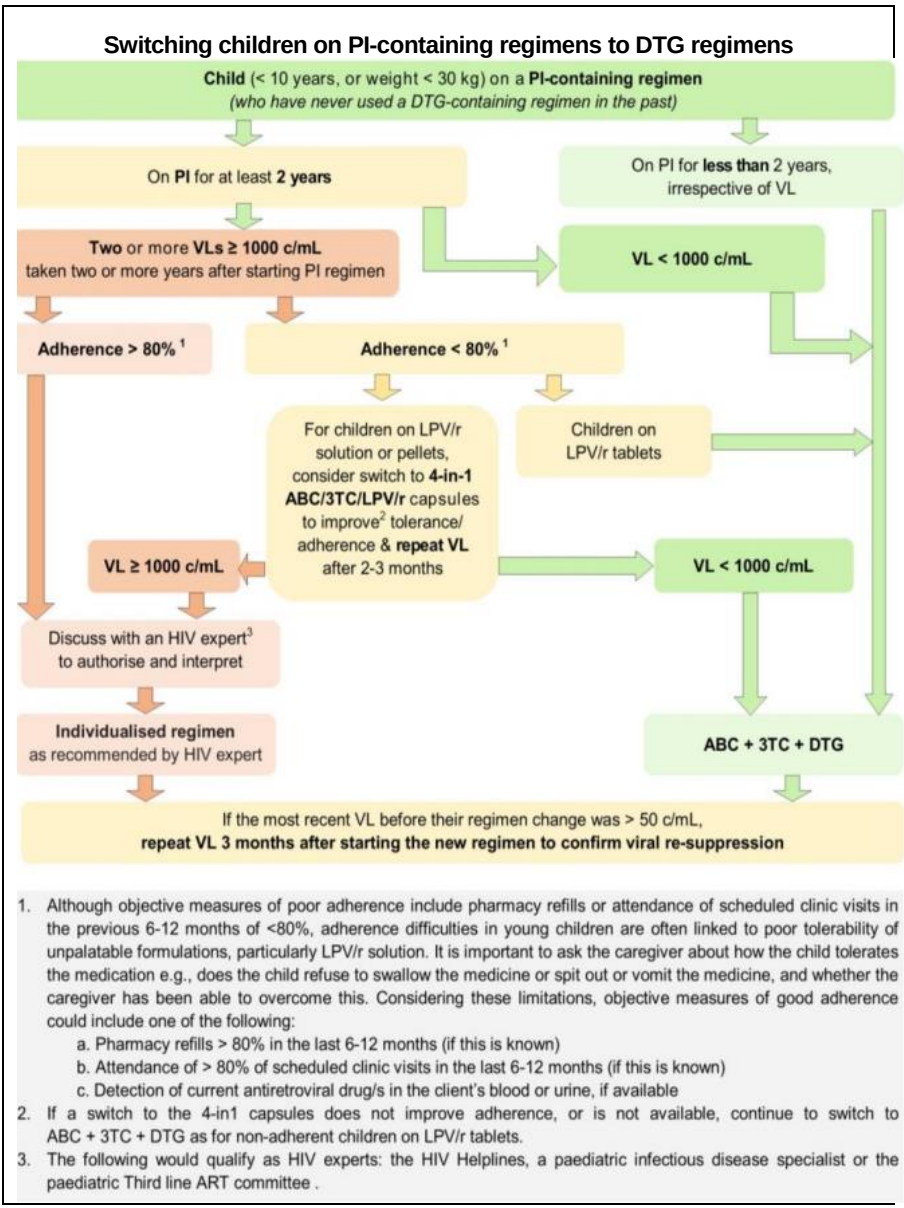
LoE:IIIb[51]

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

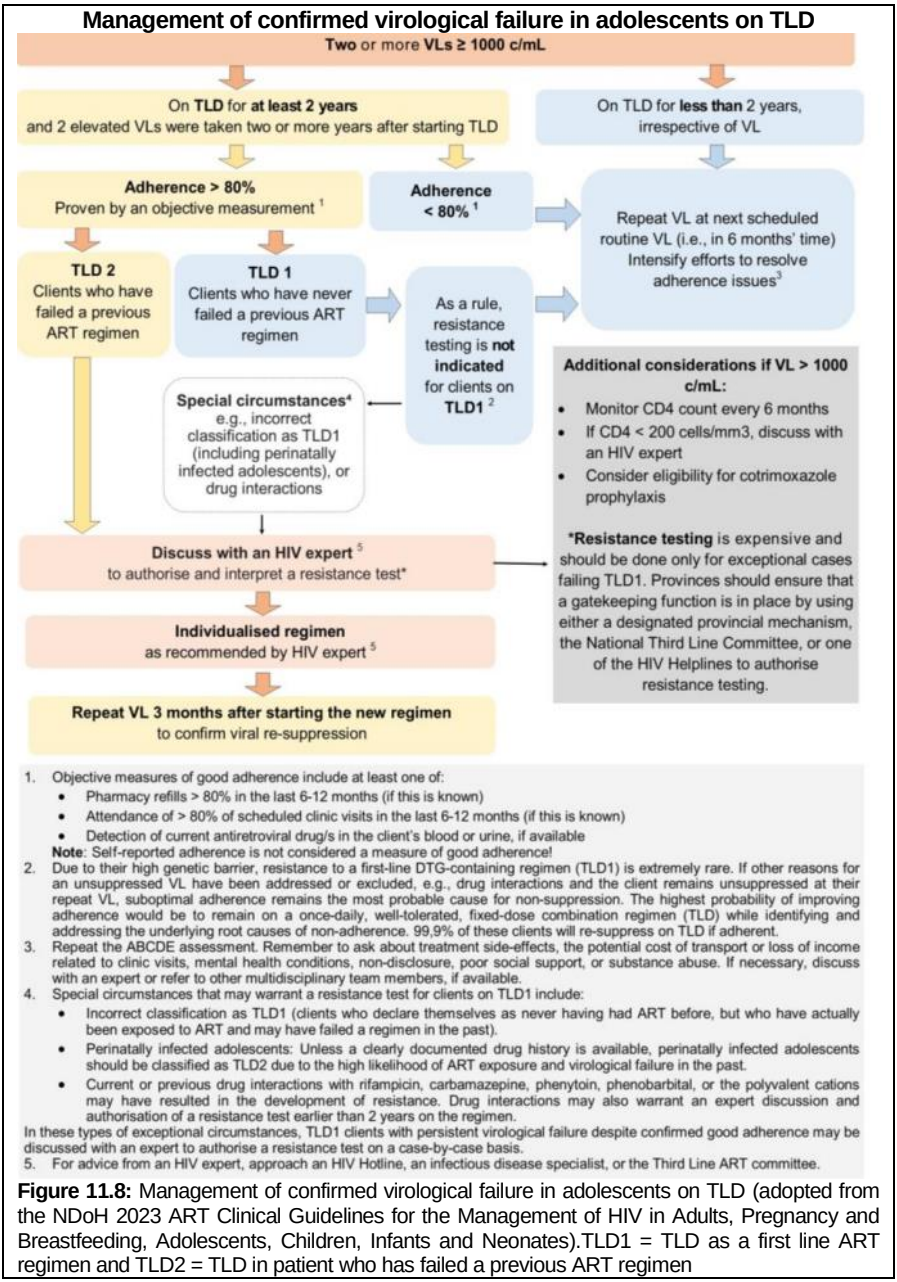
Third-line (patients failing ALD2)

Discuss with expert

» Application forms for third-line antiretroviral therapy (patients failing ALD2) can be accessed at the following link: https://knowledgehub.health.gov.za/elibrary/third-line-antiretrovirals.

» Important information to assist in applying for third-line antiretrovirals can be found at https://knowledgehub.health.gov.za/elibrary/third-line-antiretrovirals.

Applications can be emailed to TLART@health.gov.za. *LoE:IIIb*[52]



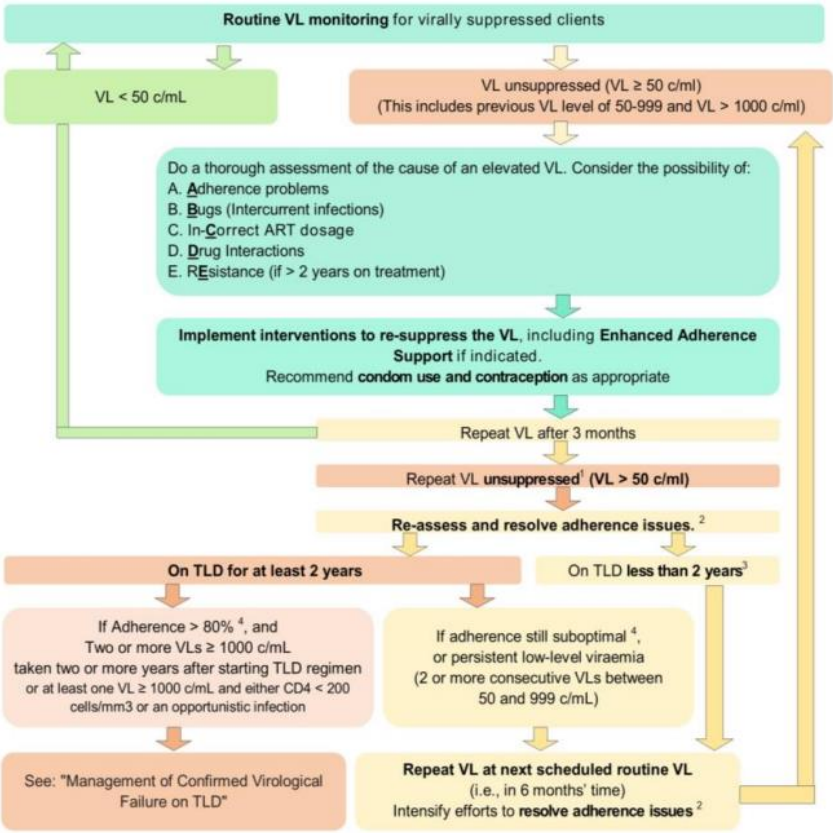
1. Objective measures of good adherence include at least one of:
   - Pharmacy refills > 80% in the last 6-12 months (if this is known)
   - Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known)
   - Detection of current antiretroviral drug/s in the client's blood or urine, if available

   Note: Self-reported adherence is not considered a measure of good adherence!
2. Due to their high genetic barrier, resistance to a first-line DTG-containing regimen (TLD1) 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.
3. Repeat the ABCDE assessment. Remember to ask about treatment side-effects, the potential cost of transport or loss of income related to clinic visits, mental health conditions, non-disclosure, poor social support, or substance abuse. If necessary, discuss with an expert or refer to other multidisciplinary team members, if available.
4. Special circumstances that may warrant a resistance test for clients on TLD1 include:
   - Incorrect classification as TLD1 (clients who declare themselves as never having had ART before, but who have actually been exposed to ART and may have failed a regimen in the past).
   - Perinatally infected adolescents: Unless a clearly documented drug history is available, perinatally infected adolescents should be classified as TLD2 due to the high likelihood of ART exposure and virological failure in the past.
   - Current or previous drug interactions with rifampicin, carbamazepine, phenytoin, phenobarbital, or the polyvalent cations may have resulted in the development of resistance. Drug interactions may also warrant an expert discussion and authorisation of a resistance test earlier than 2 years on the regimen.

   In these types of exceptional circumstances, TLD1 clients with persistent virological failure despite confirmed good adherence may be discussed with an expert to authorise a resistance test on a case-by-case basis.
5. For advice from an HIV expert, approach an HIV Hotline, an infectious disease specialist, or the Third Line ART committee.

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).

	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)
20–24.9	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	6 capsules 12 hourly					2 x 100 mg tabs 12 hourly **OR** 20 mL 12 hourly
25–29.9	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	Not recommended	LPV/RTV std dose **PLUS** oral RTV powder 300 mg (3 packets) 12 hourly	6 x 100/25 mg paed tabs 12 hourly **OR** 3 x 200/50 mg adult tabs 12 hourly	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	2 x 200 mg caps/tabs at night	1 x 300 mg tab 12 hourly **OR** 1 x AZT/3TC 300/150 mg tab 12 hourly
30–39.9	5 mL 12 hourly **OR** 10 capsules 12 hourly **OR** 4 x 100/25 mg paed tabs 12 hourly			8 x 100/25 mg paed tabs 12 hourly **OR**			
≥ 40						2 x 200 mg caps/tabs at night **OR**	

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

LoE:IIIb[54]

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

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: Vaccines for routine administration).

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: Chapter 23.

11.8.3 DIARRHOEA, HIV-ASSOCIATED

See Section 2.9: Diarrhoea.

11.8.4 PNEUMONIA

See Section 17.3.4: Pneumonia

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

DESCRIPTION

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medicines by HIV-uninfected 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 counselling and testing, HIV management, ART, and PEP.

All individuals requesting PrEP should be assessed and initiated on PrEP if eligible.

Individuals initiated on PrEP must meet the following criteria:

- HIV-uninfected.
- Willing and able to adhere to PrEP.
- Prepared to come for repeat HIV testing every 3 months if on oral PrEP or every 6 months if on injectable PrEP.
- No contra-indications to, or drug interactions with, available PrEP options.
- Meet the legal definition for independent self-consent i.e. > 18 years or for adolescents aged 12-18 years, assessed as having the mental capacity to understand the risks, benefits, social and other implications of PrEP.
  - » Adolescents aged 12-18 years who do not meet the mental capacity requirements for independent consent, will require consent from a parent, guardian or caregiver before PrEP can be initiated.
- No suspicion of acute HIV-infection (see clinical features, below).
  Note:
  - » Acute HIV infection may not always be symptomatic and clinical features are often non-specific. If there is a history of potential HIV exposure within the preceding 48-72 hours, consider providing PEP see Section 21.3.6: Post exposure Prophylaxis (PEP)).
  - » 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. Consider providing PEP– see Section 21.1.6.3.

Clinical features of acute HIV infection *LoE:IVb*[55]

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 or unknown HIV status.
- Weight < 35kg.
- Hypersensitivity to active substance or excipients for the respective PrEP options.

Contraindications specific to PrEP options

Oral PrEP (tenofovir/emtricitabine (TDF+FTC))	Injectable PrEP (lenacapavir (LEN))
• Estimated creatinine clearance or eGFR <60 mL/min. • Use of nephrotoxic medicines e.g. aminoglycosides. • Unwilling or unable to adhere to daily oral PrEP.	• Estimated creatinine clearance or eGFR <15 mL/min or on renal replacement therapy. • Severe hepatic impairment (Child-Pugh Class C). • Unwilling or unable to adhere to 6-monthly injectable PrEP.

SCREENING INVESTIGATIONS BEFORE STARTING PrEP

Investigation	Screen applicable		Purpose	Action
	Oral PrEP	Injectable PrEP		
HIV test (using algorithm in the HTS guidelines*)	Yes	Yes	Assessment of HIV status.	If HIV-negative: consider PrEP If HIV-positive: Link to treatment and care services.
Estimated creatinine clearance (eGFR)	Yes	No	To identify pre-existing renal disease.	Do not initiate oral PrEP if eGFR <60 mL/min. Repeat eGFR two weeks after baseline screen if baseline eGFR < 60mL/min. If renal function returns to normal and other PrEP criteria are met, oral PrEP may be initiated. Refer for further investigation if renal function remains abnormal - injectable PrEP may be considered if eGFR ≥ 15mL/min.
Hepatitis B surface antigen (HBsAg)	Yes	No but may screen for hepatitis B once injectable PrEP commenced**	To caution those with hepatitis B infection of risk of hepatitis flare upon discontinuation of oral PrEP. Hepatitis flare not identified as	If hepatitis B surface antigen is negative, test for hepatitis B surface antibodies to assess for hepatitis B vaccine eligibility if there is no history of previous hepatitis B vaccination (see table 11.14 below). If HBsAg-positive, refer in accordance with Adult Hospital Section 1.2.4.2 Hepatitis B, chronic (Non-HIV co-infection).

			a risk with lenacapavir.	
Urine pregnancy test	Yes	Yes	To identify if pregnant.	Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP. Offer contraception, where appropriate, to avoid unintended pregnancy (see Section 7 Family planning)
RPR	Yes	Yes	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	Yes	Yes	To diagnose and treat STI.	Manage according to STI guidelines.
*Refer to HIV Testing Services guidelines **Refer to the National Guidelines for the Management of Viral Hepatitis for detailed guidance on screening for Hepatitis B. Link: https://knowledgehub.health.gov.za/elibrary/national-guidelines-management-viral-hepatitis				

Table 11.14: Screening investigations before starting PrEP

Note:

» TDF + FTC is active against hepatitis B (HBV) infection. HBV infection is not a contra-indication to PrEP, but will require LFT monitoring in patients on oral PrEP. 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)	Interpretation of results	Action
Negative (-)	Negative (-)	No Hepatitis B infection and no immunity present	Start PrEP: TDF+FTC *or* LEN may be offered. Vaccinate with Hep B vaccine concurrently if available, (do not delay PrEP initiation).
Negative (-)	Positive (+)	No Hepatitis B infection present but immunity present	Start PrEP: TDF+FTC *or* LEN may be offered. No Hep B vaccine needed.
Positive (+)	N/A	Hepatitis B infection present	Start PrEP: TDF+FTC *or* LEN may be offered. Refer for HBV evaluation and monitoring of liver function.

Table 11.15: PrEP eligibility determined by hepatitis B immune status

PrEP follow up and monitoring

<table>
<tr><th>Activity</th><th>Frequency</th></tr>
<tr><td>Confirmation of HIV-negative status</td><td>Oral PrEP: At 1 month, then every 3 months.
Injectable PrEP: At 1 month then every 6 months</td></tr>
<tr><td>Address side effects</td><td>Every visit.</td></tr>
<tr><td>Adherence counselling</td><td>Every visit.</td></tr>
<tr><td>Estimated creatinine clearance
(For pregnant women use serum creatinine to determine renal function)</td><td>Frequency dependant on pregnancy status, age and co-morbidity:
<table>
<tr><th rowspan="2">Age/ pregnant</th><th rowspan="2">Co-morbidity</th><th colspan="2">Creatinine</th></tr>
<tr><th>Oral PrEP</th><th>Injectable PrEP</th></tr>
<tr><td><30 years</td><td>None</td><td>Baseline</td><td>n/a</td></tr>
<tr><td>30–49 years</td><td>None</td><td>Baseline</td><td>n/a</td></tr>
<tr><td><50 years</td><td>Diabetes/ hypertension</td><td colspan="2">Baseline, annually</td></tr>
<tr><td>≥ 50 years</td><td>None</td><td colspan="2">Baseline</td></tr>
<tr><td>≥ 50 years</td><td>Diabetes/ hypertension</td><td colspan="2">Baseline, annually</td></tr>
<tr><td>Pregnant</td><td>n/a</td><td colspan="2">Baseline, 3 & 6 months</td></tr>
</table></td></tr>
<tr><td>STI syndromic screening and treatment</td><td>Every visit.</td></tr>
<tr><td>PrEP supply</td><td>TDF+FTC: 1 month supply, then 3 monthly supply.
LEN:.Loading dose tablets: Day 1 tablets to be administered during clinic visit with supply for Day 2. Injections to be administered by healthcare staff every 6 months.</td></tr>
<tr><td>Behavioural sexual risk reduction counselling</td><td>Every visit.</td></tr>
</table>

Table 11.16: Monitoring of person(s) on PrEP

PREP REGIMENS AND SAFETY

ORAL PrEP (TDF-FTC) REGIMEN

A fixed dose combination formulation of: *LoE:Ia*[56]

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

AND

- Emtricitabine, oral, 200 mg daily.
  - **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 are achieved. *LoE:IIIb*[57]

SAFETY

Relevant medicine interaction information with TDF + FTC combination

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

Table 11.17: Oral PrEP drug interactions

Safety in pregnancy and lactation

- Oral PrEP may be offered to pregnant and breastfeeding women.
- The choice to start, continue or discontinue oral PrEP when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. All pregnant women must receive the routine information and counselling provided to all HIV-uninfected at-risk individuals. Refer to the National guidelines for the provision of Pre-Exposure prophylaxis (PrEP) for further detail.

LoE:Ib[58]

Side effects of TDF + FTC combination

Major	Renal toxicity, decreased bone mineral density. .
Minor	Gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss.

Table 11.18: Side effects of oral PrEP

Note:

» Minor side effects are relatively common (approximately 1 in 10 individuals in the first 1 to 2 months). Usually mild and self-limiting; do not require discontinuation.

» Renal toxicity and decreased bone mineral density usually reversible upon stopping TDF + FTC.

INJECTABLE PrEP (LENACAPAVIR) REGIMEN

LoE:IVa[59]

Initiation Day 1	• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) **AND** • LEN, oral, 600 mg (2 X 300 mg tablets) during clinic visit.
Initiation Day 2	• LEN, oral, 600 mg (2 X 300 mg tablets) o Do not take the Day 1 and Day 2 oral doses on the same day. o Supply 2 X 300mg tablets for self-administration at home.
Continuation	• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) every six months, (26 weeks +/- 2 weeks) from the date of the last injection. o Confirm HIV status is still negative before each injection is administered at the clinic.

Table 11.19: Dose regimen for initiating LEN as PrEP

Management of missed doses of LEN

a) Initiation phase - missed oral dose on Day 2

- LEN, oral, 600 mg (2 X 300 mg tablets), take as soon as possible.

LoE:IVa[60]

b) Continuation phase –missed injection

Time since last injection	Dosage recommendation
› 28 weeks	• Reinitiate LEN as per table 11.19 above o Reassess if injectable PrEP still suitable for the client. o Confirm HIV status is still negative.

Table 11.20: Management of injection delays during continuation phase

SAFETY

Some common drug interactions with lenacapavir are listed below. For more comprehensive information on drug interactions, see the online HIV Drug Interaction Checker https://www.hiv-druginteractions.org/checker.

Medicine groups	Interaction information	Recommendation
TB medicines: • Rifapentine	Potential interaction	Use oral PrEP instead for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication).
TB medicines • Rifampicin • Rifabutin	Potential interaction	**Individuals on rifampicin/rifabutin treatment requesting PrEP:** Use oral PrEP for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication). **Individuals established on LEN who develop TB require additional doses of LEN as detailed below:** <u>a) RIFAMPICIN-based TB regimen:</u> Initiate rifampicin starting at least 2 days after LEN is first initiated. Day 1 of Rifampicin: treatment: • LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) **AND** • LEN, oral, 600 mg (2 X 300 mg tablets) during clinic visit. Day 2 of Rifampicin treatment: • LEN, oral, 600 mg (2 X 300 mg tablets) o Do not take the Day 1 and Day 2 oral doses on the same day. o Supply 2 X 300mg tablets for self-administration at home. o If rifampicin is co-administered for longer than 6 months, continue to administer usual LEN doses as scheduled, plus administer additional doses of LEN (as above) every 6 months after rifampicin initiation for the duration of TB treatment. <u>b) RIFABUTIN-based TB regimen:</u> Day 1 of Rifabutin treatment: • LEN, subcutaneous injection, 463,5 mg (1 X 1.5 mL injections) o If rifabutin is co-administered for longer than 6 months, continue to administer usual LEN doses as scheduled, plus administer additional doses of LEN (as above) every 6 months after rifabutin initiation for the duration of TB treatment. Revert to the LEN continuation dosing schedule as per table 11.19 above once TB treatment has been discontinued. *LoE:IVa*[61]
Hormonal contraception	No interaction	No dose adjustments required

Anticonvulsants: • Carbamazepine • Phenobarbital • Phenytoin	Potential interaction	Refer to doctor for switching to lamotrigine, levetiracetam, or valprorate (valproate not for girls and young women of child-bearing potential) see PHC Section 15.7.2 Epilepsy in Adolescents and Adults).
Illicit/recreational drug use • Ketamine	Potential interaction	LEN may increase ketamine-related effects such as respiratory depression and hallucinations. Avoid use of ketamine
Erectile dysfunction • Sildenafil • Tadalafil • Vardenafil	Potential interaction	LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines, (*Clients opting to self-fund erectile dysfunction treatment, should be advised to start on a lower dose and titrate to effects or side effects*.)

Table 11.20: LEN drug interactions

Note:

» Due to the long half-life of injectable lenacapavir, drug interactions may be significant for up to 9 months following subcutaneous injection.

Safety in pregnancy and lactation

- LEN may be offered to pregnant and breastfeeding women.
- There is currently no evidence that LEN is associated with any adverse pregnancy outcomes. While data on LEN use during pregnancy is still emerging (from trials like PURPOSE 1 and ongoing pregnancy registries), no evidence of teratogenicity or increased risk of adverse outcomes has been identified from animal studies, pharmacokinetic data, or monitored pregnancies to date. Outcomes like miscarriage, stillbirth, and birth defects align with or below background rates. By contrast, the pregnancy risks of acquiring HIV in pregnancy are well established and substantial.
- The choice to start, continue or discontinue LEN when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. All pregnant women must receive the routine information and counselling provided to all HIV-uninfected at-risk individuals. Refer to the National guidelines for Pre-Exposure prophylaxis (PrEP): Lenacapavir implementation guidelines for further information and guidance on monitoring of pregnancy outcomes.

LoE:Ib[62]

Side effects of LEN

Very common	Injection site reactions, including necrosis and ulcer (often linked to improper administration)
Common	Dizziness, vomiting, diarrhoea, headache, nausea

Table 11.21: Side effects of LEN

LoE:IVa[63]

Note:

» Very common side effects defined as more than 1 in 10 individuals and common as more than 1 in 100 but less than 1 in 10 individuals.

» For individuals who may need to switch from LEN to oral PrEP, initiate oral PrEP within 28 weeks of the last LEN injection.

STOPPING PrEP

PrEP should be stopped if the individual:

- Tests HIV-positive.
- Develops renal disease (for oral PrEP: eGFR < 60mL/min and injectable PrEP eGFR < 15mL/min).
- Is non-adherent to available PrEP options
- Does not need or want PrEP any longer.
- No longer meets eligibility criteria as detailed above.
- Presents with safety concerns where the risks of PrEP use outweigh potential benefit.

Note:

» Continue oral PrEP for 7 days after the last potential HIV exposure.
» Patients with chronic HBV may experience a hepatitis flare on discontinuation of oral PrEP.
» Injectable lenacapavir has an extended washout period and drug levels decline slowly during the tail period (residual concentrations may remain up to 12 months or longer after injection). During the tail period, protection against HIV diminishes although the potential for drug interactions remains. This period should be covered with oral PrEP (TDF+FTC) if there is still risk of HIV exposure and condoms are not feasible i.e. initiate oral PrEP within 28 weeks of the last LEN injection.

REFERRAL

» HBsAg-positive.
» Discontinuation of TDF + FTC in patients with HBV.

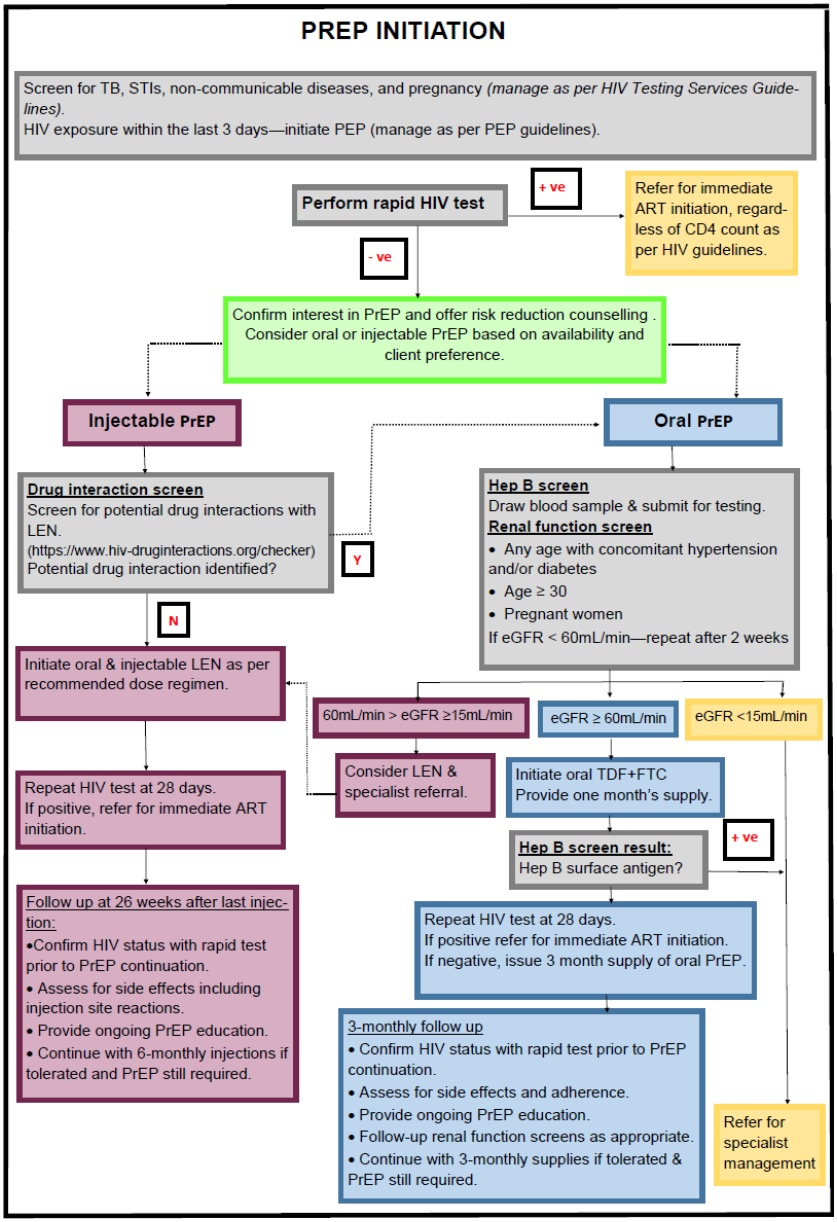


Figure 11.10: PrEP initiation algorithm
(Note: For patients diagnosed with TB while on LEN, refer to Table 11.20 above for guidance on supplemental doses of LEN).

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.

References:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[9]Dolutegravir, oral (first-line ART): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).

https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART): Rutherford GW, Horvath H. Dolutegravir Plus Two Nucleoside Reverse Transcriptase Inhibitors versus Efavirenz Plus Two Nucleoside Reverse Transcriptase Inhibitors As Initial Antiretroviral Therapy for People with HIV: A Systematic Review. PLoS One. 2016 Oct 13;11(10):e0162775. https://www.ncbi.nlm.nih.gov/pubmed/27736859

Dolutegravir, oral (first-line ART): South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

[10] Dolutegravir, oral (first-line ART in pregnancy/ WOCP): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in pregnant women and women of child-bearing potential (WOCP), 17 June 2021.

https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

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

[11] Dolutegravir, oral (first-line ART with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).

https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Dolutegravir, oral (first-line ART with concomitant rifampicin): Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin:

results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013; 62(1):21-27. https://pubmed.ncbi.nlm.nih.gov/23075918/

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

[12] National Department of Health: Affordable Medicines, EDP-PHC/Adult Hospital level. Medicine Review: Atazanavir/ritonavir vs lopinavir/ritonavir in HIV, 27July2021.

https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[13] TAF: NDoH review: Tenofovir alafenamide for HIV_14 March 2024_v4_final

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

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

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

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

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

[18]Dolutegravir, oral (double-dose with concomitant rifampicin): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Dolutegravir in HIV-infected patients commencing first-line antiretroviral therapy, updated 27 July 2021 (including addendum of use of dolutegravir with rifampicin).

https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

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

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

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

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

[21] LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA,

et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

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

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

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

[24] Dosing of ART and ADRs: Dosing of ART and ADRs: Dosing of ART and ADRs: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

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

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

Dosing of ART (renal impairment): Lucas GM, Ross MJ, Stock PG, Shlipak MG, Wyatt CM, Gupta SK, et al.; HIV Medicine Association of the Infectious Diseases Society of America. Clinical practice guideline for the management of chronic kidney disease in patients infected

with HIV: 2014 update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 Nov 1;59(9):e96-138. http://www.ncbi.nlm.nih.gov/pubmed/25234519

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

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

ART-rifampicin drug interaction: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

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

Drug interactions with dolutegravir: South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023.

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

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

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

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

Cotrimoxazole, oral (primary prophylaxis in pregnancy): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Evidence summary: Is co-trimoxazole safe to use in pregnancy, March 2011. http://www.health.gov.za/

[29] Cotrimoxazole, oral: National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine review: CD4 cut-off for cotrimoxazole for OI prophylaxis in PLHIV, May 2017. http://www.health.gov.za/

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

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

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

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

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

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

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

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

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

[33] IPT in pregnancy: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Evidence review: IPT in pregnancy_v2.0_27 Novl 2025_final approved. https://www.health.gov.za/wp-content/uploads/2025/12/Isoniazid-Preventative-Therapy-IPT-in-Pregnancy_V2.0-27-November-2025.pdf t

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

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

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

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

[36] Fluconazole, oral (pre-referral dose for cryptococcosis): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

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

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

Fluconazole, oral (cryptococcosis): NICD data on file

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

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

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

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

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

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

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

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

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

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

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

[42] Antivirals to treat herpes simplex (therapeutic class): Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815

[43] Antivirals to treat herpes zoster (therapeutic class): McDonald EM, De Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. Antiviral Therapy 2012; 17(2): 255-264. https://www.ncbi.nlm.nih.gov/pubmed/22300753

[44] Management HIV-infected children and adolescents: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

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.

[45] PMTCT(risk-stratified): Beste S, Essajee S, Siberry G, Hannaford A, Dara J, Sugandhi N, Penazzato M. Optimal Antiretroviral Prophylaxis in Infants at High Risk of Acquiring HIV: A Systematic Review. Pediatr Infect Dis J. 2018 Feb;37(2):169-175. https://www.ncbi.nlm.nih.gov/pubmed/29319636

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

[46]PMTCT (HIV prophylaxis in high risk infants – management of high maternal VL after delivery): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

PMTCT (HIV prophylaxis in high risk infants – management of high maternal VL after delivery): 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.

[47]PMTCT (Infant of unknown HIV-exposure): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

PMTCT (Infant of unknown HIV-exposure): 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.

[48]PMTCT Nielsen-Saines K, et. al. Three Postpartum Antiretroviral Regimens to prevent Intrapartum HIV infection. NEJM. 2012;366:2368-2379.

[49]Monitoring in HIV-infected children: WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Monitoring in HIV-infected children: 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.

[50]Eligibility criteria for ART (children): World Health Organisation. WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Eligibility criteria for ART (children): 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.

[51] ART regimen algorithm (children): 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.

[52]Adjustment of previous 1st line regimens/switching algorithm (children): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Adjustment of previous 1st line regimens/switching algorithm (children): 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.

[53]Lopinavir/ritonavir weight-band dosing (children): WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021. https://www.who.int/publications/i/item/9789240031593

Lopinavir/ritonavir weight-band dosing (children): 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.

[54]NDoH Paeditraic EML. 2023.Ed July 2023.

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)

[55] Legal definition for consent (adolescents): Strode A, Slack CM, Essack Z, Toohey JD, Bekker LG. Be legally wise: When is parental consent required for adolescents' access to pre-exposure prophylaxis (PrEP)? South Afr J HIV Med. 2020 Nov 10;21(1):1129. doi: 10.4102/sajhivmed.v21i1.1129. PMID: 33240536; PMCID: PMC7669975.

[56] PrEP regimen (Tenofovir + emtricitabine): Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'reilly KR, Koechlin FM, Rodolph M, Hodges-Mameletzis I, Grant RM. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. AIDS. AIDS. 2016 Jul 31;30(12):1973-83. http://www.ncbi.nlm.nih.gov/pubmed/27149090

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

[57] PrEP regimen (Tenofovir + emtricitabine: adequate dosing): Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, Cohen MS, Kashuba AD. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011 Dec 7;3(112):112re4. https://www.ncbi.nlm.nih.gov/pubmed/22158861

PrEP regimen (Tenofovir + emtricitabine: adequate dosing): National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection. https://www.knowledgehub.org.za/

[58] Oral PrEP – safety in pregnancy and lactation

NDoH 2021 Updated guidelines for the provision of oral pe-exposure prophylaxis (PrEP) to persons at substantital risk of HIV infection. 18 Oct 2021. https://knowledgehub.health.gov.za/system/files/elibdownloads/2022-08/PrEP%20Guidelines%20Update%2012%20%20Nov%20%202021%20Final.pdf

Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO. Pg 9.

[59] PrEP regimen (LEN): SAHPRA approved Professional Information Leaflet (PIL): Lenacapavir 464 mg solution for injection Gilead. Gilead Sciences South Africa (Pty) Ltd. Date of first authorisation 21 Oct 2025.

[60] PrEP regimen (LEN): SAHPRA approved Professional Information Leaflet (PIL): Lenacapavir 464 mg solution for injection Gilead. Gilead Sciences South Africa (Pty) Ltd. Date of first authorisation 21 Oct 2025.

[61] Interaction with TB meds: SAHPRA approved Professional Information Leaflet (PIL): Lenacapavir 464 mg solution for injection Gilead. Gilead Sciences South Africa (Pty) Ltd. Date of first authorisation 21 Oct 2025.

[62] PrEP regimen (LEN) – safety in pregnancy and lactation:

National Department of Health Evidence Review. Lenacapavir for PrEP Medicine Review-4C-4 Sep 2025

Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO. Web Annex G Abstract: outcomes for lenacapvir administration during pregnancy.

National Depatrment of Health. National guidelines for Pre-Exposure prophyalxis (PrEP): Lenacapvir implementation guidelines (Dec 2025).

[63] PrEP regimen (LEN): SAHPRA approved Professional Information Leaflet (PIL): Lenacapavir 464 mg solution for injection Gilead. Gilead Sciences South Africa (Pty) Ltd. Date of first authorisation 21 Oct 2025.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH
NEMLC SUMMARY REPORT ON UPDATES MADE TO THE
THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS
PHC Chp 11 HIV and AIDS

Document Version Control

Report Version	Date	Detail
V1.0	*16/10/2025*	*Update – provisional draft STG for PrEP*
V1.0	*27/11/2025*	*Update – guidance on IPT in pregnancy*
V1.0	*26/02/2026*	*Update – approved STG for PrEP*
V1.1	*04/06/2026*	Update – management of interaction between LEN and TB medicines

Specific guidance products

No	Guidance Product	Tick	Number
1.	Primary Health Care Level STGs – *HIV*	√	*11*
2.	Adult Hospital Level STGs		
3.	Paediatric Hospital Level STGs		
4.	Tertiary and Quaternary EML		

Summary Tables

Medicine Amendments

Medicine amendment recommendations, with supporting evidence and rationale are listed below. If appropriate can include non-medicine amendments if appropriate (for example if item has a large impact on how medicine is accessed). Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG). Include updates post initial publication first or mark/highlight appropriately.

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / DELETED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Version v1.0:							
Section 11.11 HIV Pre-exposure prophylaxis (PrEP)	√				Lenacapavir	ADDED subject to SAHPRA	n/a

						registration and reference price being met.	
Report Version 1.0 :							
Section 11.1 ART, adults & adolescents (10-19yrs old)	√	√			ART and anticonvulsants	Editorial amendment	n/a
Section 11.2.2 TPT in pregnancy	√	√			Isoniazid	Amended	n/a
Section 11.11 HIV Pre-exposure prophylaxis (PrEP)	√				Lenacapavir	AMENDED Subject to reference price being met.	n/a
Report Version 1.1 :							
Section 11.11 HIV Pre-exposure prophylaxis (PrEP)	√				Lenacapavir	AMENDED Revised guidance on management of LEN-TB medication DDI	n/a

*Therapeutic Interchange

Report V1.1

PHC HIV Chapter 11

NOTE

The PHC and AH HIV chapters are in the process of being updated to align with the recently updated National Consolidated Guidelines for the Prevention and Management of HIV in Adults, Adolescents, Children, Infants and Pregnant and Breastfeeding Women (Jan 2025).

Section 11.11 HIV Pre-exposure prophylaxis (PrEP)

Management of individuals who are diagnosed with TB while receiving LEN for HIV PrEP: Amended

The NEMLC, in consultation with the HIV programme, notes the gap in the current evidence to guide the management of the drug-drug interaction between LEN and rifampicin/rifabutin. After careful consideration of the local incidence of TB and ongoing efforts towards improved access to LEN, the consensus national recommendation is that individuals on LEN, who are diagnosed with TB, receive top-up doses of LEN when initiating treatment with a rifampicin- or rifabutin-based TB regimen as per the updated STG guidance detailed below,

Individuals receiving LEN and presenting to a health facility for TB treatment, should be referred to their LEN PHC facility for top-up dosing of LEN upon initiation of a rifampicin- or rifabutin-based TB regimen (refer to PHC HIV Chp 11.11 HIV PrEP for details). A pharmacokinetic study is being planned locally, to address some of the gaps identified in the available evidence.

Individuals on LEN who require initiation of a rifapentine-based TB treatment regimen should be switched to oral PrEP due to the lack of data on the management of this drug-drug interaction.

AMENDED FROM:

SAFETY

Some common drug interactions with lenacapavir are listed below. For more comprehensive information on drug interactions, see the online HIV Drug Interaction Checker: https://www.hiv-druginteractions.org/checker.

Medicine groups	Interaction information	Recommendation
Standard TB medicines: • Rifabutin • Rifampicin • Rifapentine	Potential interaction	Use oral PrEP instead for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication).
Hormonal contraception	No interaction	No dose adjustments required
Anticonvulsants: • Carbamazepine • Phenobarbital • Phenytoin	Potential interaction	Refer to doctor for switching to lamotrigine, valproate or levetiracetam (see PHC Section 15.7.2 Epilepsy in Adolescents and Adults).
Illicit/recreational drug use • Ketamine	Potential interaction	LEN may increase ketamine-related effects such as respiratory depression and hallucinations. Avoid use of ketamine
Erectile dysfunction • Sildenafil • Tadalafil • Vardenafil	Potential interaction	LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines, (*Clients opting to self-fund erectile dysfunction treatment, should be advised to start on a lower dose and titrate to effects or side effects*.)

Table 11.20: LEN drug interactions

AMENDED TO:

SAFETY

Some common drug interactions with lenacapavir are listed below. For more comprehensive information on drug interactions, see the online HIV Drug Interaction Checker https://www.hiv-druginteractions.org/checker.

Medicine groups	Interaction information	Recommendation
TB medicines: • Rifapentine	Potential interaction	Use oral PrEP instead for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication).
TB medicines • Rifampicin • Rifabutin	Potential interaction	**Individuals on rifampicin/rifabutin treatment requesting PrEP:** Use oral PrEP for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication). **Individuals established on LEN who develop TB require additional doses of LEN as detailed below.** <u>a) RIFAMPICIN-based TB regimen:</u> Initiate rifampicin starting at least 2 days after LEN is first initiated. Day 1 of Rifampicin: treatment: • LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) **AND** • LEN, oral, 600 mg (2 X 300 mg tablets) during clinic visit. Day 2 of Rifampicin treatment: • LEN, oral, 600 mg (2 X 300 mg tablets) ○ Do not take the Day 1 and Day 2 oral doses on the same day. ○ Supply 2 X 300mg tablets for self-administration at home ○ If rifampicin is co-administered for longer than 6 months, continue to administer usual LEN doses as scheduled, plus administer additional doses of LEN (as above) every 6 months after rifampicin initiation for the duration of TB treatment. <u>b) RIFABUTIN-based TB regimen:</u> Day 1 of Rifabutin treatment:

		• LEN, subcutaneous injection, 463,5 mg (1 X 1.5 mL injections) ○ If rifabutin is co-administered for longer than 6 months, continue to administer usual LEN doses as scheduled, plus administer additional doses of LEN (as above) every 6 months after rifabutin initiation for the duration of TB treatment. Revert to the LEN continuation dosing schedule as per table 11.19 above once TB treatment has been discontinued.
Hormonal contraception	No interaction	No dose adjustments required
Anticonvulsants: • Carbamazepine • Phenobarbital • Phenytoin	Potential interaction	Refer to doctor for switching to lamotrigine, levetiracetam, or valprorate (valproate not for girls and young women of child-bearing potential) see PHC Section 15.7.2 Epilepsy in Adolescents and Adults).
Illicit/recreational drug use • Ketamine	Potential interaction	LEN may increase ketamine-related effects such as respiratory depression and hallucinations. Avoid use of ketamine
Erectile dysfunction • Sildenafil • Tadalafil • Vardenafil	Potential interaction	LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines, (*Clients opting to self-fund erectile dysfunction treatment, should be advised to start on a lower dose and titrate to effects or side effects*.)

Table 11.20: LEN drug interactions

Report V1.0
PHC HIV Chapter 11

Section 11.1 Antiretroviral therapy, adults and adolescents (10-19 years old)

Drug interactions with dolutegravir - anticonvulsants: Editorial amendment
A cross reference has been added to the updated guidance on epilepsy management PHC Section 15.7.2 Epilepsy in Adolescents and Adults.

Drug interactions with boosted PIs - anticonvulsants: Editorial amendment
A cross reference has been added to the updated guidance on epilepsy management PHC Section 15.7.2 Epilepsy in Adolescents and Adults.

Section 11.2.2 Tuberculosis preventative therapy (TPT)

TPT in pregnant women living with HIV: Amended
Isoniazid: Guidance amended
On 25 January 2025, the NDoH released a circular jointly issued by the NEMLC and NDoH TB program recommending that TPT be avoided in all pregnant women. This consensus recommendation was informed by concerns with the complexity of implementing guidance for the use of TPT in pregnant women that was stratified based on HIV status and CD4 count. Concerns with the approach of avoiding TPT in all pregnant women, were subsequently raised by clinicians at the SA HIV Clinicians Society Conference (Aug 2025), and a poll taken after debate, indicated strong support from clinicians for a CD4 count stratified approach to IPT initiation in pregnant women living with HIV. This prompted further collaboration between the NDoH TB and HIV programs with the resultant alignment of a package of care for people with Advanced HIV Disease[1], defined as any client (including pregnant women) with a CD4 count < 200 cells/mm^3, or WHO Stage 3 or 4 clinical conditions. This package contains several elements, including:

- systematic TB screening and investigation, and IPT if TB is excluded,
- screening for cryptococcal antigenaemia,
- screening and management of serious bacterial infections,
- CPT prophylaxis,
- ART,
- Adherence support, and
- Intensified follow-up.

Pregnant women with CD4<200 cells/mm^3 are eligible for this package of care for advanced HIV disease. This package therefore, provides opportunity to reconsider CD4 count stratification in deciding on administration of IPT in pregnancy, and alignment with the Advanced HIV Disease definition (i.e., CD4 < 200), will facilitate implementation as part of a comprehensive care package. The NEMLC supports a CD4 count-stratified approach as informed by the evidence review undertaken and programmatic support with implementation.

NEMLC Recommendation:

[1] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

See the NEMLC recommendation below. A copy of the complete evidence review[2] may be found at the end of this report or on the NHI website.

NEMLC recommendation 27 NOV 2025

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 13 November 2025: We recommend that pregnant women living with HIV, with: • CD_4 counts ≤ 200 cells/mm³ and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease. • CD_4 counts > 200 cells/mm³ 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/m³(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). However, a CD4 cut off of 350 was not deemed programmatically feasible. The current programmatic "package of care" for patients with advanced HIV (CD4< 200), for which pregnant women are eligible, includes IPT. The ERC therefore suggests administering 12 months of IPT for all pregnant women with newly diagnosed HIV with a CD4< 200, co-initiated with ART, after screening for active TB, as part of the AHD package of care* **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/mm³ (low certainty evidence from an observational study) **Review indicator**: New high quality evidence of benefit or harm.					
NEMLC RECOMMENDATION (MEETING 27 November 2025): NEMLC supports the ERC recommendation as detailed above (dated 13 Nov 2025).					
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.					

[2] NEMLC Evidence review. TPT in pregnancy. V2.0_27 Nov 2025

STG Update: PHC Chp 11 Section 11.2.2 Tuberculosis preventative therapy

AMENDED FROM:

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

AMENDED TO:

NOTE: For pregnant women living with HIV:
- If CD4 count > 200 cells/mm^3 and initiating ART, defer TPT until after delivery
- If CD4 count ≤ 200 cells/mm^3 and initiating ART, offer 12 months of isoniazid as TPT, after excluding active tuberculosis disease
- Ensure that routine screening against TB is conducted at each antenatal visit.

Section 11.11 HIV Pre-exposure prophylaxis (PrEP)

Medicine Treatment:
Lenacapavir: Added (subject to reference price being met)

NEMLC Recommendation:
The NEMLC strongly recommends the use of Lenacapavir (LEN) for HIV PrEP based on the evidence reviewed. Inclusion on the EML is contingent upon the reference price (as modelled in the economic analysis) being met.
The NEMLC supports acceptance of the Global Fund's grant towards the procurement of lenacapavir. While the Committee notes potential equity concerns with this limited grant, it does present opportunity to further our understanding of pharmacovigilance concerns, as well as facilitate the development of a strategy for a scaled roll out of lenacapavir once procured at the stated reference price.

KEY RECOMMENDATIONS

Type of ERC recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not using the option or using the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
	☐	☐	☐	☑
High-level summary of conclusions from the Evidence to Decision Framework – See link	For HIV prevention in susceptible individuals, the ERC recommends the use of long-acting injectable LEN for use as pre-exposure prophylaxis (PrEP) (strong recommendation, moderate certainty of the evidence).			
NEMLC Ratification	**Date**	**Comments**		
	04 September 2025	**Global Fund (GC7) grant:** The Committee supported the acceptance of the grant allocation from the Global Fund, as it presents an opportunity to enhance our understanding of potential pharmacovigilance concerns and will support programmatic development of a strategy for large-scale rollout. **Addition to the EML:** For HIV prevention in susceptible individuals, the NEMLC recommends the use of long-acting injectable LEN for use as pre-exposure prophylaxis (PrEP), contingent on the reference price (as included in the accompanying economic analysis) being met*, and confirmation of SAHPRA registration. **Reference price conversion to ZAR for tablet and injection formulations to be reviewed at the time of tender negotiations.*		

Therapeutic Interchange Considerations (if applicable)	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick the box
						☑
Trigger for review	Update with evidence from ongoing trials. A change in the price of medicines. Other SAHPRA-approved HIV PrEP options.					

STG Update: PHC Chapter 11 Section 11.11 HIV PrEP

STG updates: updates to the STG are included below in response to external comments received. A comprehensive list of external comments received with responses from NEMLC is tabulated in Addendum 1 below.

Eligibility for HIV PrEP – risk of HIV infection: *'Individuals at substantial risk of HIV infection'* has been removed as a criterion for HIV PrEP eligibility in line with the NDoH PrEP guideline (2021)[3] which recommends that *'Any person requesting PrEP, should be considered for PrEP, even if he/she may not be perceived to be at risk by the provider*.'

Eligibility for HIV PrEP – consent: Guidance has been added advising on the legal definition for independent consent, which has been aligned to guidance included for other preventative therapies such as family planning. Individuals requesting PrEP, must meet the legal definition for independent self-consent i.e. > 18 years or for adolescents aged 12-18 years, assessed as having the mental capacity to understand the risks, benefits, social

[3] National Department of Health. 2021 updated guidelines for the provision of oral pre-exposure prophylaxis (PrEP) to persons at substantial risk of HIV infection https://knowledgehub.health.gov.za/elibrary/updated-guidelines-provision-oral-pre-exposure-prophylaxis-prep-persons-substantial-risk

and other implications of PrEP. Adolescents aged 12-18 years who do not meet the mental capacity requirements for independent consent, will require consent from a parent, guardian or caregiver before PrEP can be initiated[4].

Contraindications to PrEP – weight threshold: A minimum weight threshold of 35kg has been applied for individuals seeking access to either oral PrEP or LEN to facilitate ease of implementation. The professional information leaflets (PIL) for LEN[5] and oral PrEP[6] recommend a minimum weight of 35kg. The recently updated National Consolidated guidelines for the prevention and management of HIV in adults, adolescents, children, infants and pregnant and breastfeeding women (Nov 2025)[7] includes the following amendment for ART : *"Tenofovir disoproxil fumarate (TDF) weight-related eligibility criteria decreased from 35 kg to 30kg"*, (feedback from the HIV program is that this amendment was informed by the WHO recommendation[8] in support of improved access for adolescents, accessing a one-pill-once-a-day regimen) for the treatment of HIV.

The NEMLC acknowledged that the risk calculus for the prevention of HIV and treatment of HIV is different and that a lower minimum weight (i.e. 30kg) for PLWH would be reasonable approach. The Committee recommended that for HIV PrEP, a consistent weight cut-off of 35kg be applied for both oral PrEP and LEN which will align with the national HIV PrEP guidelines[9,10] as well as the WHO recommendations for PrEP[11]. For the treatment of HIV, a weight cut-off of 30kg will be applied to the STGs to ensure alignment with the national ART guidelines.[12]

Contraindications to PrEP – age threshold and Tanner staging: The historic basis for the inclusion of Tanner staging in the HIV PrEP STG was informed by the potential risks of oral PrEP on bone mineral density. Feedback from the HIV program is that Tanner staging is not being done well in clinical practice and the program has advocated for the removal of Tanner staging as a criteria for access to PrEP, which was also supported by local paediatric experts consulted. Furthermore, the bone mineral density concerns with TDF presents less of a risk when used as PrEP which is generally used for a shorter duration, relative to ART. The Committee supported the removal of Tanner staging along with reference to the age threshold of 15 years.

Contraindications to oral PrEP – renal function: The threshold of eGFR <60mL/min has been retained as a contraindication to the use of TDF-FTC as oral PrEP, in accordance with the South African Health Products (SAHPRA)-approved professional information leaflet[13].

Screening investigations – baseline screening for hepatitis B: Baseline screening for hepatitis B is recommended for oral PrEP users as an alert to monitoring for a hepatitis flare up upon discontinuation of oral PrEP. Hepatitis flare up has not been identified as a risk with the use of lenacapavir, which is not contra-indicated in patients diagnosed with hepatitis B.

---

[4] Strode A, Slack CM, Essack Z, Toohey JD, Bekker LG. Be legally wise: When is parental consent required for adolescents' access to pre-exposure prophylaxis (PrEP)? South Afr J HIV Med. 2020 Nov 10;21(1):1129. doi: 10.4102/sajhivmed.v21i1.1129. PMID: 33240536; PMCID: PMC7669975.

[5] Professional Information (PI) Leaflet. Lenacapavir 464 mg solution for injection Gilead. Gilead Sciences South Africa (Pty) Ltd. Date of first authorisation 21 Oct 2025

[6] Professional Information (PI) Leaflet. TRUVADA (film-coated tablet). PHARMACARE LIMITED. Date of most recent amendment 27 November 2015.

[7] National Department of Health. National Consolidated guidelines for the prevention and management of HIV in adults, adolescents, children, infants and pregnant and breastfeeding women (draft Nov 2025)

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

[9] National Department of Health. Pre-Exposure Prophylaxis (PrEP): Lenacapavir Implementation Guidelines. December 2025.

[10] National Department of Health. 2021 Updated Guidelines for the provision of oral pre-exposure prophylaxis (PrEP) to persons at substantial risk of HIV infection.

[11] Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP). Geneva: World Health Organization; 2025. Licence: CC BY-NC-SA 3.0 IGO.

[12] National Department of Health. National Consolidated guidelines for the prevention and management of HIV in adults, adolescents, children, infants and pregnant and breastfeeding women (draft Nov 2025)

[13] Professional Information Leaflet. Truvada®. Pharmacare Limited. Most recent amendment: 27 Nov 2015. Accessed online chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.sahpra.org.za/wp-content/uploads/2020/02/Truvada_PI_Aspen_MCC-format-27-November-2015.pdf

Screening investigations – liver function testing for oral PrEP: Liver function screening (i.e. alanine transferase (ALT)) in individuals identified as hepatitis B surface antigen positive (HBsAg +ve) has been removed from the STG. Individuals identified as HBsAg +ve and who are initiated on oral PrEP should be referred for specialist monitoring and care as TDF-FTC may potentiate the risk of hepatic adverse effects. Furthermore, there is a risk of hepatitis flare upon discontinuation of TDF-FTC.

Lenacapavir - delayed injections and use of oral bridging: Available evidence supports extended use of oral bridging for up to six months after the last lenacapavir injection (in the event of extended delays to injection administration). However, the limited access of lenacapavir via the Global Fund GC7 allocation, requires a considered approach towards ensuring optimal use of a limited resource. NEMLC therefore does not recommend extended bridging with oral lenacapavir beyond a single dose. Individuals who present more than 28 weeks after their last lenacapavir injection will require that lenacapavir be re-initiated as per the recommended initiation regimen.

PrEP – safety in pregnancy: The Committee acknowledged that data on pregnancy outcomes following exposure to oral PrEP is more extensive than for LEN, as oral PrEP has been on the market for a longer duration and the data would be cumulative for use as both ART as well as PrEP. The risk:benefit considerations for both oral PrEP and LEN, supports the use of either PrEP option during pregnancy for young women deemed at risk of acquiring HIV. The Committee also noted that there is a lag with updates to the SAHPRA approved product information (PI)[14] which still lists pregnancy and lactation as a contraindication to oral PrEP.

Management of potential drug-drug interactions: The NEMLC has noted discordant international guidance on the management of potential drug interactions with lenacapavir. More specifically, the Federal Drug Administration (FDA) in the United States provides dose guidance for lenacapavir in individuals requiring subsequent treatment with interacting medicines such as TB and antiepileptic medicines[15], while the European Medicines Agency (EMA) advises against concomitant use of medicines that could potentially interaction with lenacapavir[16]. The NEMLC recommends that lenacapavir be avoided where possible, in individuals receiving treatment with medicines that have a potential to interact with lenacapavir. This conservative approach is recommended as evidence on the use of lenacapavir is still evolving. Guidance on potential drug interactions with lenacapavir can be sourced online: https://www.hiv-druginteractions.org/checker.

AMENDED FROM

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 counselling and testing, HIV management, ART, and PEP.
All individuals requesting PrEP should be assessed and initiated if eligible.

Individuals initiated on PrEP must meet the following criteria:

- HIV-negative.
- Willing and able to adhere to PrEP.
- Prepared to come for repeat HIV testing every 3 months if on oral PrEP or every 6 months if on injectable PrEP.

[14] Professional Information (PI) Leaflet. TRUVADA (film-coated tablet). PHARMACARE LIMITED. Date of most recent amendment 27 November 2015.
[15] Federal Drug Administration approved prescribing information for Yeztugo. Last reviewed 6/2025 accessed online https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf
[16] European Medicines Agency. Summary of product characteristics: Yeytuo. Accessed online https://www.ema.europa.eu/en/documents/product-information/yeytuo-epar-product-information_en.pdf

- No contra-indications to or drug interactions with available PrEP options.
- 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

General contraindications to PrEP

- Pre-existing HIV infection or unknown HIV status.
- Young women/men <35 kg or <15 years of age who are not Tanner stage 3 (sexual maturity) or greater.

Contraindications specific to PrEP options

Oral PrEP (tenofovir/emtricitabine (TDF+FTC))	**Injectable PrEP (lenacapavir (LEN))**
• Estimated creatinine clearance or eGFR <60 mL/min. • Use of nephrotoxic medicines e.g. aminoglycosides. • Unwilling or unable to adhere to daily oral PrEP.	• Estimated creatinine clearance or eGFR <15 mL/min or on renal replacement therapy. • Severe hepatic impairment (Child-Pugh Class C). • Unwilling or unable to adhere to 6 monthly injectable PrEP.

SREENING INVESTIGATIONS BEFORE STARTING PrEP

Investigation	Screen applicable		Purpose	Action
	Oral PrEP	Injectable PrEP		
HIV test (using algorithm in the HTS guidelines*)	Yes	Yes	Assessment of HIV status.	If HIV-negative, consider PrEP If HIV-positive: Link to treatment and care services.
Estimated creatinine clearance (eGFR)	Yes	No	To identify pre-existing renal disease.	Do not initiate oral PrEP if creatinine clearance/eGFR <60 mL/min. Repeat creatinine clearance two weeks after baseline screen if baseline eGFR < 60mL/min. If renal function returns to normal and other PrEP criteria are met, oral PrEP may be initiated. Refer for further investigation if renal function remains abnormal - injectable PrEP may be considered if eGFR > 15mL/min.
Hepatitis B surface antigen (HBsAg)	Yes	No but may screen for hepatitis B once injectable PrEP commenced	To caution those with hepatitis B infection of risk of hepatitis flare upon discontinuation of oral PrEP. Hepatitis flare not identified as a risk with lenacapavir.	Assess eligibility for vaccination if available (see table below). If HBsAg-positive, refer to specialist.
Urine pregnancy test	Yes	Yes	To identify if pregnant.	Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP.

RPR	Yes	Yes	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	Yes	Yes	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 in patients on oral PrEP. 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 oral PrEP eligibility

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP: TDF+FTC or lenacapavir may be offered Vaccinate with Hep B vaccine concurrently if available.
Negative (-)	Positive (+)	Start PrEP: TDF+FTC or lenacapavir may be offered No Hep B vaccine needed
Positive (+)	N/A	Start PrEP: TDF+FTC or lenacapavir may be offered. Refer for HBV evaluation and monitoring of liver function.

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	Oral Prep: At 1 month, then every 3 months. Injectable PrEP: At 1 month then every 6 months
Address side effects	Every visit.
Adherence counseling	Every visit.
Estimated creatinine clearance	Frequency dependant on pregnancy status, age and co-morbidity:
STI screening and treatment	Every visit.
PrEP supply	Oral PrEP (TDF+FTC): 1 month supply, then 3 monthly supply. Lenacapavir. Loading dose tablets: Day 1 tablets to be administered during clinic visit with supply for Day 2.

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

	Injections to be administered by healthcare staff every six months.
Behavioural sexual risk reduction counseling	Every visit.

Table 11.15: Monitoring of person(s) on PrEP

PREP REGIMENS AND SAFETY

ORAL PrEP (TDF-FTC) REGIMEN

A fixed dose combination formulation of:

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

AND

- Emtricitabine, oral, 200 mg daily.

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.

SAFETY

Relevant medicine interaction information with TDF + FTC combination

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 daily oral PrEP regimen. Advise other prevention methods or consider injectable PrEP regimen.

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 to 2 months).
- Mild and self-limiting; do not require discontinuation.
- Renal toxicity and decreased bone mineral density usually reversible upon stopping TDF + FTC.

INJECTABLE PREP (LENACAPAVIR) REGIMEN

Initiation Day 1	• LEN, subcutaneous injection, 927 mg (2X1.5mL injections) **AND** • LEN, oral, 600 mg (2 X 300 mg tablets)
Initiation Day 2	• LEN, oral, 600 mg (2 X 300 mg tablets) ○ Do not take the Day 1 and Day 2 oral doses on the same day.
Continuation	• LEN, subcutaneous injection, 927 mg (2X1.5mL injections) every six months or 26 weeks from the last injection.

Table 11.18: Dose regimen for initiating lenacapavir as PrEP

MANAGEMENT OF MISSED DOSES OF LEN

A) INITIATION PHASE - MISSED ORAL DOSE ON DAY 2

- LEN, oral, 600 mg (2 X 300 mg tablets), take as soon as possible.

B) CONTINUATION PHASE – DELAYED INJECTION

Time since last injection	Dosage recommendation
26-28 weeks	• LEN, oral, 300 mg (1 X 300 mg tablets) as a single dose **AND** • LEN, subcutaneous injection, 927 mg (2 X 1.5mL injections). o Administer injection on same day as single oral dose. o Continue with LEN injection every six months or 26 weeks from the last injection.
› 28 weeks	Reinitiate LEN as per table 11.18 above o Reassess if injectable PrEP still suitable for the client. o Confirm HIV status is still negative.

Table 11.19: Management of injection delays during continuation phase

SAFETY

Some common drug interactions with lenacapavir listed below. For more comprehensive information on drug interactions, see https://www.hiv-druginteractions.org/checker.

Medicine groups	Interaction information	Recommendation
Standard TB medicines: • Rifabutin • Rifampicin • Rifapentine	Potential interaction	Use oral PrEP instead until TB treatment completed.
Hormonal contraception	No interaction.	No dose adjustments required
Anticonvulsants: • Carbamazepine • Phenobarbital • Phenytoin	Potential interaction	Refer to doctor for switching to alternative anticonvulsant treatment.
Illicit/recreational drug use • Ketamine	Potential interaction	LEN may increase ketamine-related effects such as respiration depression and hallucinations. Avoid use of ketamine
Erectile dysfunction • Sildenafil • Tadalafil • Vardenafil	Potential interaction	LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines.

Table 11.20: LEN drug interactions

Note:

- Due to the long half-life of injectable lenacapavir, drug interactions may be significant for up to 9 months following subcutaneous injection.

Side effects of lenacapvir

Major	Injection site reactions, including necrosis and ulcer (often linked to improper administration) , headache, nausea
Minor	Dizziness, vomiting, diarrhoea

Table 11.21: Side effects of LEN

Note:

- Major side effects reported in at least 5% (approximately 5 in 100 individuals in the PURPOSE 1 and/or 2 studies).
- For individuals who may need to switch from LEN to oral PrEP, initiate oral PrEP within 28 weeks of the last LEN injection.

STOPPING PREP

PrEP should be stopped if individual:

- Tests HIV-positive.
- Develops renal disease (for oral PrEP: eGFR <60mL/min and injectable PrEP eGFR < 15mL/min)
- Is non-adherent to PrEP.
- Does not need or want PrEP.
- No longer meets eligibility criteria.
- Presents with safety concerns where the risks of PrEP use outweigh potential benefit.

Note:

- Continue oral PrEP for 7 days after the last potential HIV exposure.
- Patients with chronic HBV may experience a hepatitis flare on discontinuation of oral PrEP.
- Injectable lenacapvir has an extended washout period and drug levels decline slowly during the tail period. During the tail period, protection against HIV diminishes although the potential for drug interactions remains.

REFERRAL

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

AMENDED TO:

- **Pre-exposure prophylaxis (PrEP)**

Z20.6 + Z29.2

DESCRIPTION

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medicines by HIV-uninfected 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 counselling and testing, HIV management, ART, and PEP.
All individuals requesting PrEP should be assessed and initiated on PrEP if eligible.

Individuals initiated on PrEP must meet the following criteria:

- HIV-uninfected.
- Willing and able to adhere to PrEP.
- Prepared to come for repeat HIV testing every 3 months if on oral PrEP or every 6 months if on injectable PrEP.
- No contra-indications to, or drug interactions with available PrEP options.
- Meet the legal definition for independent self-consent i.e. > 18 years or for adolescents aged 12-18 years, assessed as having the mental capacity to understand the risks, benefits, social and other implications of PrEP.
  - » Adolescents aged 12-18 years who do not meet the mental capacity requirements for independent consent, will require consent from a parent, guardian or caregiver before PrEP can be initiated.
-
- No suspicion of acute HIV-infection (see clinical features, below).

  Note:

» Acute HIV infection may not always be symptomatic and clinical features are often non-specific. If there is a history of potential HIV exposure within the preceding 48-72 hours, consider providing PEP see Section 21.3.6: Post exposure Prophylaxis (PEP)).
» 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. Consider providing PEP– see Section 21.1.6.3.

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 or unknown HIV status.
- Weight < 35kg.
- Hypersensitivity to active substance or excipients for the respective PrEP options.

Contraindications specific to PrEP options

Oral PrEP (tenofovir/emtricitabine (TDF+FTC))	Injectable PrEP (lenacapavir (LEN))
• Estimated creatinine clearance or eGFR <60 mL/min. • Use of nephrotoxic medicines e.g. aminoglycosides. • Unwilling or unable to adhere to daily oral PrEP.	• Estimated creatinine clearance or eGFR <15 mL/min or on renal replacement therapy. • Severe hepatic impairment (Child-Pugh Class C). • Unwilling or unable to adhere to 6-monthly injectable PrEP.

SCREENING INVESTIGATIONS BEFORE STARTING PrEP

Investigation	Screen applicable		Purpose	Action
	Oral PrEP	Injectable PrEP		
HIV test (using algorithm in the HTS guidelines*)	Yes	Yes	Assessment of HIV status.	If HIV-negative: consider PrEP If HIV-positive: Link to treatment and care services.
Estimated creatinine clearance (eGFR)	Yes	No	To identify pre-existing renal disease.	Do not initiate oral PrEP if creatinine clearance/eGFR <60 mL/min. Repeat two weeks after baseline screen if baseline eGFR < 60mL/min. If renal function returns to normal and other PrEP criteria are met, oral PrEP may be initiated. Refer for further investigation if renal function remains abnormal - injectable PrEP may be considered if eGFR ≥ 15mL/min.
Hepatitis B surface antigen (HBsAg)	Yes	No but may screen for hepatitis B once injectable PrEP commenced**	To caution those with hepatitis B infection of risk of hepatitis flare upon discontinuation of oral PrEP. Hepatitis flare not identified as a risk with lenacapavir.	If hepatitis B surface antigen is negative, test for hepatitis B surface antibodies to assess for hepatitis B vaccine eligibility if there is no history of previous hepatitis B vaccination (see table 11.14 below). If HBsAg-positive, refer in accordance with AH Section 1.2.4.2 Hepatitis B, chronic (Non-HIV co-infection).
Urine pregnancy test	Yes	Yes	To identify if pregnant.	Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP. Offer contraception, where appropriate, to avoid unintended pregnancy (see Section 7 Family planning)

RPR	Yes	Yes	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	Yes	Yes	To diagnose and treat STI.	Manage according to STI guidelines.
*Refer to HIV Testing Services guidelines **Refer to the National Guidelines for the Management of Viral Hepatitis for detailed guidance on screening for Hepatitis B. Link: https://knowledgehub.health.gov.za/elibrary/national-guidelines-management-viral-hepatitis				

Table 11.14: Screening investigations before starting PrEP

Note:

- TDF + FTC is active against hepatitis B (HBV) infection. HBV infection is not a contra-indication to PrEP, but will require LFT monitoring in patients on oral PrEP. 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)	Interpretation of results	Action
Negative (-)	Negative (-)	No Hepatitis B infection and no immunity present	Start PrEP: TDF+FTC *or* LEN may be offered. Vaccinate with Hep B vaccine concurrently if available, (do not delay PrEP initiation).
Negative (-)	Positive (+)	No Hepatitis B infection present but immunity present	Start PrEP: TDF+FTC *or* LEN may be offered. No Hep B vaccine needed.
Positive (+)	N/A	Hepatitis B infection present	Start PrEP: TDF+FTC *or* LEN may be offered. Refer for HBV evaluation and monitoring of liver function.

Table 11.15: PrEP eligibility determined by hepatitis B immune status

PrEP follow up and monitoring

<table>
<tr><th>Activity</th><th>Frequency</th></tr>
<tr><td>Confirmation of HIV-negative status</td><td>Oral PrEP: At 1 month, then every 3 months.
Injectable PrEP: At 1 month then every 6 months</td></tr>
<tr><td>Address side effects</td><td>Every visit.</td></tr>
<tr><td>Adherence counselling</td><td>Every visit.</td></tr>
<tr><td>Estimated creatinine clearance
(For pregnant women use serum creatinine to determine renal function)</td><td>Frequency dependant on pregnancy status, age and co-morbidity:
<table>
<tr><th rowspan="2">Age/ pregnant</th><th rowspan="2">Co-morbidity</th><th colspan="2">Creatinine</th></tr>
<tr><th>Oral PrEP</th><th>Injectable PrEP</th></tr>
<tr><td><30 years</td><td>None</td><td>Baseline</td><td>n/a</td></tr>
<tr><td>30–49 years</td><td>None</td><td>Baseline</td><td>n/a</td></tr>
<tr><td><50 years</td><td>Diabetes/ hypertension</td><td colspan="2">Baseline, annually</td></tr>
<tr><td>≥ 50 years</td><td>None</td><td colspan="2">Baseline</td></tr>
<tr><td>≥ 50 years</td><td>Diabetes/ hypertension</td><td colspan="2">Baseline, annually</td></tr>
<tr><td>Pregnant</td><td>n/a</td><td colspan="2">Baseline, 3 & 6 months</td></tr>
</table></td></tr>
<tr><td>STI syndromic screening and treatment</td><td>Every visit.</td></tr>
<tr><td>PrEP supply</td><td>TDF+FTC: 1 month supply, then 3 monthly supply.
LEN:.Loading dose tablets: Day 1 tablets to be administered during clinic visit with supply for Day 2. Injections to be administered by healthcare staff every 6 months.</td></tr>
<tr><td>Behavioural sexual risk reduction counselling</td><td>Every visit.</td></tr>
</table>

Table 11.16: Monitoring of person(s) on PrEP

PREP REGIMENS AND SAFETY

ORAL PrEP (TDF-FTC) REGIMEN

A fixed dose combination formulation of:

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

AND

- Emtricitabine, oral, 200 mg daily.
- **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 are achieved.

SAFETY

Relevant medicine interaction information with TDF + FTC combination

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

Table 11.17: Oral PrEP drug interactions

Safety in pregnancy and lactation

- Oral PrEP may be offered to pregnant and breastfeeding women.
- The choice to start, continue or discontinue oral PrEP when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. All pregnant women must receive the routine information and counselling provided to all HIV-uninfected at-risk individuals. Refer to the National guidelines for the provision of Pre-Exposure prophylaxis (PrEP), for further detail.

Side effects of TDF + FTC combination

Major	Renal toxicity, decreased bone mineral density. .
Minor	Gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss.

Table 11.18: Side effects of oral PrEP

Note:

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

INJECTABLE PREP (LENACAPAVIR) REGIMEN

Initiation **Day 1**	• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) **AND** • LEN, oral, 600 mg (2 X 300 mg tablets) during clinic visit.
Initiation **Day 2**	• LEN, oral, 600 mg (2 X 300 mg tablets) o Do not take the Day 1 and Day 2 oral doses on the same day. o Supply 2 X 300mg tablets for self-administration at home.
Continuation	• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) every six months (26 weeks +/- 2 weeks) from the date of the last injection. o Confirm HIV status is still negative before each injection is administered at the clinic.

Table 11.19: Dose regimen for initiating LEN as PrEP

MANAGEMENT OF MISSED DOSES OF LEN

- **INITIATION PHASE - MISSED ORAL DOSE ON DAY 2**
- LEN, oral, 600 mg (2 X 300 mg tablets), take as soon as possible.

- **CONTINUATION PHASE –MISSED INJECTION**

Time since last injection	Dosage recommendation
› 28 weeks	• Reinitiate LEN as per table 11.19 above o Reassess if injectable PrEP still suitable for the client. o Confirm HIV status is still negative.

Table 11.20: Management of injection delays during continuation phase

SAFETY

Some common drug interactions with lenacapavir are listed below. For more comprehensive information on drug interactions, see the online HIV Drug Interaction Checker: https://www.hiv-druginteractions.org/checker.

Medicine groups	Interaction information	Recommendation
Standard TB medicines: • Rifabutin • Rifampicin • Rifapentine	Potential interaction	Use oral PrEP instead for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication).
Hormonal contraception	No interaction	No dose adjustments required
Anticonvulsants: • Carbamazepine • Phenobarbital • Phenytoin	Potential interaction	Refer to doctor for switching to lamotrigine, valproate or levetiracetam (see PHC Section 15.7.2 Epilepsy in Adolescents and Adults).
Illicit/recreational drug use • Ketamine	Potential interaction	LEN may increase ketamine-related effects such as respiratory depression and hallucinations. Avoid use of ketamine
Erectile dysfunction • Sildenafil • Tadalafil • Vardenafil	Potential interaction	LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines, (*Clients opting to self-fund erectile dysfunction treatment, should be advised to start on a lower dose and titrate to effects or side effects*.)

Table 11.20: LEN drug interactions

Note:

- Due to the long half-life of injectable lenacapavir, drug interactions may be significant for up to 9 months following subcutaneous injection.

Safety in pregnancy and lactation

- LEN may be offered to pregnant and breastfeeding women.
- There is currently no evidence that LEN is associated with any adverse pregnancy outcomes. While data on LEN use during pregnancy is still emerging (from trials like PURPOSE 1 and ongoing pregnancy registries), no evidence of teratogenicity or increased risk of adverse outcomes has been identified from animal studies, pharmacokinetic data, or monitored pregnancies to date. Outcomes like miscarriage, stillbirth, and birth defects align with or below background rates. By contrast, the pregnancy risks of acquiring HIV in pregnancy are well established and substantial.
- The choice to start, continue or discontinue LEN when a woman becomes pregnant should be made by the woman, following discussion of the risks and benefits with her health-care provider. All pregnant women must receive the routine information and counselling provided to all HIV-uninfected at-risk individuals. Refer to the National guidelines for Pre-Exposure prophylaxis (PrEP): Lenacapavir implementation guidelines for further information and guidance on monitoring of pregnancy outcomes.

Side effects of LEN

Very common	Injection site reactions, including necrosis and ulcer (often linked to improper administration)
Common	Dizziness, vomiting, diarrhoea, headache, nausea

Table 11.21: Side effects of LEN

Note:

- Very common side effects defined as more than 1 in 10 individuals and common as more than 1 in 100 but less than 1 in 10 individuals.
- For individuals who may need to switch from LEN to oral PrEP, initiate oral PrEP within 28 weeks of the last LEN injection.

STOPPING PREP

PrEP should be stopped if individual:

- Tests HIV-positive.
- Develops renal disease (for oral PrEP: eGFR < 60mL/min and injectable PrEP eGFR < 15mL/min)
- Is non-adherent to available PrEP options.
- Does not need or want PrEP any longer.
- No longer meets eligibility criteria as detailed above.
- Presents with safety concerns where the risks of PrEP use outweigh potential benefit.

Note:

- Continue oral PrEP for 7 days after the last potential HIV exposure.
- Patients with chronic HBV may experience a hepatitis flare on discontinuation of oral PrEP.
- Injectable lenacapavir has an extended washout period and drug levels decline slowly during the tail period (residual concentrations may remain up to 12 months or longer after injection). During the tail period, protection against HIV diminishes although the potential for drug interactions remains. This period should be covered with oral PrEP (TDF+FTC) if there is still risk of HIV exposure and condoms are not feasible i.e. initiate oral PrEP within 28 weeks of the last LEN injection.

REFERRAL

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

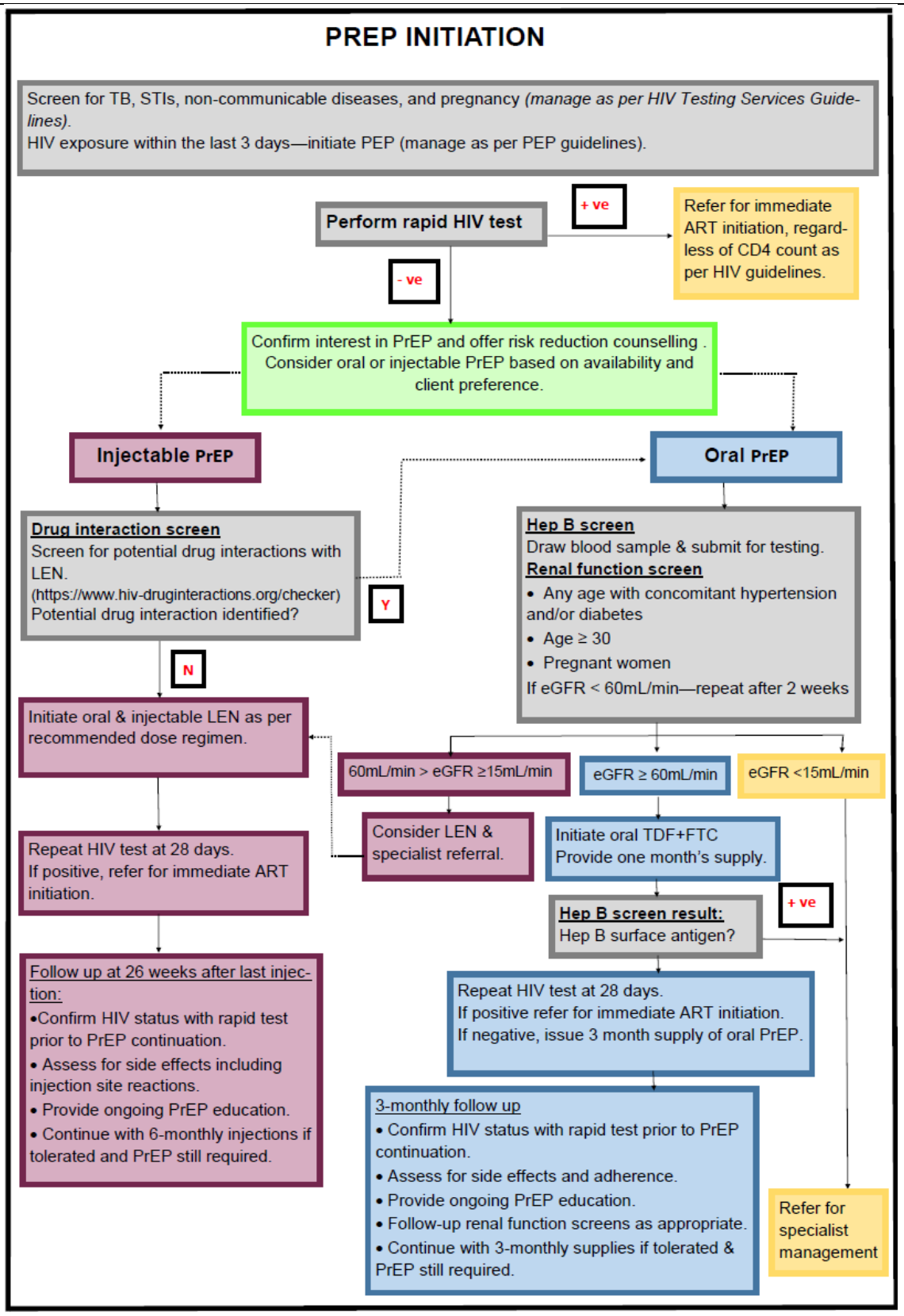


Figure 11.10: PrEP initiation algorithm

Addendum 1: Summary of external comments received in response to the draft HIV PrEP STG with NEMLC responses

Comments received with thanks from the following individuals/organisations

No.	Individual/s	Title	Organisation
1.	Ms M Upfold,	Senior Research & Responsible Pharmacist:	CAPRISA Vulindlela Pharmacy, Vulindlela Clinical Research Site Centre for the AIDS Programme of Research in South Africa
2.	Prof LG Bekker	Director of the Desmond Tutu HIV Centre	The Desmond Tutu HIV Centre, UCT.
3.	Dr K Sweatman & Dr V Mudalay	Clinical editor Lead: Clinical Content Team	Knowledge Translation Unit
4.	Ms A Uys	Pharmacist	Medicines Information Centre, UCT
5.	Mr D Rasebotsoa		Department of Correctional Services
6.	Dr M Necibi		ZF Mgcawu District. Northern Cape Department of Health
7.	Ms M Wolmarans	Chief Director: Health Systems Digital Information	NHI Digital Health Systems
8.	Dr J Wessels & Dr D Davey	Honorary Senior Lecturer in the Department of Biostatistics and Epidemiology at the University of Cape Town	Centre for Maternal, foetal, newborn and child health care strategies
9.	Dr YG Kanno	LMIC Coordinator, Government Engagement and Policy	Access to Medicines Foundation, The Netherlands
10.	Dr M Reid & A Smith	Senior Director Medical Affairs, Gilead Patient Solutions Senior Director International Medical Affairs at Gilead Sciences ·	Gilead, Sub-Saharan Africa

List of comments received with responses as tabulated below.

No	DETAILS	COMMITTEE RESPONSES
	ICD-10 codes	
1.	Because the EMR for PHC uses ICD-11, both ICD-10 and ICD-11 codes should be included in the Guideline Coding Table: Exposure to HIV: - ICD-10: Z20.6 - ICD-11: QC20.0 HIV prophylactic treatment / PrEP: - ICD-10: Z29.2 - ICD-11: XM7V4 Record PrEP type, start date, follow-up dates, HIV test results, injection dates, and bridging doses in the EMR using ICD-11 codes.	ICD-11 codes not added The STGs currently only include ICD-10 codes, which are not actively being applied at a system level at present. Any change to include ICD-11 would need to be applicable to all STGs as part of a comprehensive coding and informatics project. Implementation guidance to be covered by HIV program guidelines.
	Description	
2.	*STG: All individuals requesting PrEP should be assessed and initiated if eligible* Spelling - eligible	Amended
	Individuals initiated on PrEP must meet the following criteria	

3.	STG: HIV-negative. HIV-Negative with no history of possible risk exposure to HIV infection in the past 4 weeks.	See amendment under Response 4 below.
4.	*"No suspicion of acute HIV-infection (see clinical features, below"* In practice we have included a history of potential HIV exposure within the last 48-72 hours. In these cases we recommend PEP to PrEP approach	Amended as follows: "No suspicion of acute HIV-infection (see clinical features, below. Note: Clinical features of acute HIV infection may not always be symptomatic and are often non-specific. If there is a history of potential HIV exposure within the preceding 48-72 hours, consider a switch to PEP see Section 21.3.6: Post exposure Prophylaxis (PEP))."
5.	Prepared to come for repeat HIV testing every 3 months if on oral PrEP or every 6 months if on injectable PrEP. Prepared to adhere to self-testing protocols (for Oral PrEP modalities) and to come for repeat HIV testing every 3 months if on oral PrEP or every 6 months if on injectable PrEP.	Not amended See Response 33 below regarding guidance on self-testing.
6.	Add emphasis on ruling out acute HIV infection before each LEN injection.	Added under the LEN continuation regimen: ○ "Confirm HIV status is still negative before each injection." See Response 48 below.
7.	Area of Concern: need for explicit guidance on adolescents, pregnancy/ breastfeeding and other special populations. Substantive comment: The guideline should provide clear evidence-based eligibility criteria and safety considerations for all population eligible under which SAHPRA approval with particular attention to adolescent and pregnant/ breastfeeding women. The Access to Medicine Index 2024, [8] found that the including of pregnant and lactating women in clinical trials remain extremely limited. The report emphasises that companies should ensure inclusion of special populations, such as pregnant and breastfeeding individuals in clinical research. **Motivation:** [We] welcome the commitment to ensure accelerated access to generic LEN and reduce its cost recognising the transparency on pricing, and the overall speed at which access is being ensured.[6] South Africa's guideline should embody these same principles: • Transparency: public reporting on pricing, procurement and distribution • Speed: rapid implementation leveraging existing PrEP infrastructure • Equity: prioritize access for populations bearing highest HIV burden • Accountability: monitoring and evaluation with public reporting on real world impact	**Adolescents:** STG amended to include adolescents aged 12-18 years provided that individuals meet the legal definition for independent self-consent i.e. > 18 years or for adolescents aged 12-18 years, assessed as having the mental capacity to understand the risks, benefits, social and other implications of PrEP **Pregnancy:** Guidance on safety in pregnancy included in the STG. **Transparency on pricing:** The LEN economic evaluation is published on the NHI website and includes a NEMLC recommended reference price. Once generic LEN is available and awarded on tender, details will be published on the MHPL as for all other EML medicines. **Implementation and monitoring is outside of NEMLC's scope.** Feedback from the HIV program as follows:**:** *A PrEP module on the current SyNCH system will provide a robust cohort tracking and monitoring system across all populations including side effects, adverse event and pregnancy outcome monitoring. In addition the pregnancy outcomes will be linked to existing pregnancy registries.*

8.	*STG: Clinical features of acute HIV infection* *"No suspicion of acute HIV-infection (see clinical features, below"* Clinical features of acute HIV infection (HIV seroconversion is not always symptomatic and signs/symptoms of acute HIV infection are non-specific)	Amended as follows: "No suspicion of acute HIV-infection (see clinical features, below). Note: Clinical features of acute HIV infection may not always be symptomatic and are often non-specific. If there is a history of potential HIV exposure within the preceding 48-72 hours, consider a switch to PEP see Section 21.3.6: Post exposure Prophylaxis (PEP))."
	Contraindications to PrEP	
9.	*STG: CONTRAINDICATIONS TO PrEP* ADD: - Allergy to PrEP products.	STG amended to include: "Hypersensitivity to active substance or excipients for the respective PrEP options."
10.	*STG: Young women/men <35 kg or <15 years of age who are not Tanner stage 3 (sexual maturity) or greater.* Young women/men <30 kg for Oral TDF-based PrEP, <35 kg for LA Injectable PrEP	Not amended – uniform weight threshold of 35kg applied for both oral PrEP and LEN to facilitate ease of implementation.
11.	*STG: Young women/men <35 kg or <15 years of age who are not Tanner stage 3 (sexual maturity) or greater.* Do we need to include the tanner staging- in our hands this causes confusion and generally isn't done well at primary health care level and doesn't add much help	Reference to age threshold and Tanner staging removed.
12.	*STG: Young women/men <35 kg or <15 years of age who are not Tanner stage 3 (sexual maturity) or greater.* Could we consider using PrEP at a younger age? Think this recommendation came from previous CI to TDF? Maybe consider LEN for adolescents and adults >35kg (as per Yeztugo PI)	
13.	Reference paediatric STGs for clients <15 years or <35 kg.	Cross-reference not added. Paed STGs do not currently include HIV PrEP guidance. Refer to responses in 10, 11 and 12 above.
14.	*STG- Injectable PrEP: Unwilling or unable to adhere to* 6-monthly *injectable PrEP.* Just for clarity, keep '6-monthly' on the same line with hyphen between '6' and 'monthly'. It was originally unhyphenated, with 6 on line above and monthly below. I initially missed the 6 and registered "….monthly injectable PrEP' as that part of the phrase was all on the same line!	Editorial - amended
	Contraindications specific to PrEP options	
15.	STG: Estimated creatinine clearance (eGFR). Do not initiate oral PrEP if creatinine clearance/eGFR <60 mL/min eGFR <50 mL/min if > 16 years; eGFR <80 mL/min if 10-16 years; Serum Creatinine > 85 umole/l in pregnant women.	Not amended Current STG guidance is in accordance with SAHPRA approved PI. Refer to NDoH prg guidelines for guidance on managing specific cohorts.
16.	*STG: Oral PrEP* Unwilling or unable to adhere to daily oral PrEP. Relative contraindication, the client can be offered the "Intermittent/On-Demand "2-1-1" Oral PrEP"	Not amended Intermittent/On-Demand "2-1-1" Oral PrEP is not a NEMLC approved EML indication. Indication to be considered for review during the next review cycle.

	Screening investigations before starting PrEP	
17.	STG: Investigations HIV Acquisition Risk: 1. Possible HIV-Exposure within the past 72 Hours: - Oral PrEP: No - Injectable PrEP: No - Purpose: Assessment of HIV-Exposure. - Action: Provide PEP instead and repeat HIV test after 4 weeks. 2. Possible HIV-Exposure within the past 4 weeks: - Oral PrEP: No - Injectable PrEP: No - Purpose: Assessment of HIV-Exposure. - Action: Repeat HIV test after 4 weeks from the date of possible exposure.	The focus of the EML is on medicines management. Detailed clinical guidance to support implementation is included in the HIV program guidelines and Job Aids. The publications are intended to complement each other.
18.	Standardise HIV testing intervals: 3-monthly (oral), 6-monthly (injectable).	Noted.
19.	*STG: Estimated creatinine clearance (eGFR) – No need to screen before initiating PrEP* Should this be yes? Or do we assume that an eGFR < 15 will be "known" CKD?	Not amended. LEN may be administered in patients with CrCl ≥ 15 mL/min so the value of a baseline screen prior to initiating LEN is questionable as it could lead to potential delays with initiating PrEP and the additional costs to the healthcare system may not be justified. It is anticipated that patients with end stage renal disease or requiring renal replacement therapy will already be under the care of a nephrologist.
20.	STG: Repeat creatinine clearance two weeks after baseline screen if baseline eGFR < 60mL/min. eGFR <50 mL/min if > 16 years; eGFR <80 mL/min if 10-16 years; Serum Creatinine > 85 umol/l in pregnant women.	Not amended. See Response 15 above.
21.	STG: Hep B surface antigen (HBsAg) - No but may screen for hepatitis B once injectable PrEP commenced Under what circumstances would you screen for HepB once PrEP started?	Routine screening for Hep B not required for clients on injectable PrEP. Note added to refer to the National Guidelines for the Management of Viral Hepatitis for detailed guidance on eligibility for screening.
22.	*STG: Hep B surface antigen (HBsAg) - Assess eligibility for vaccination if available (see table below).* *If HBsAg-positive, refer to specialist.* The client on oral PrEP may be offered vaccination if HepB neg but the client on LEN will not have this benefit- is that fair/ethical? One would assume the risks of HepB infection & vaccinated status would be the same in both groups so they should have equal access to vaccine. Is Hep B vaccine supply sufficient for this or will it be prioritised for pregnant women on oral PrEP?	Given the risk of a hepatitis flare following the discontinuation of oral PrEP, baseline screening against Hep B is clinically important. In the case of LEN, it was not deemed pragmatic or cost effective to screen <u>*all*</u> potential recipients of LEN against Hep B especially if it could delay initiation of PrEP – screening to be done where deemed clinically appropriate – see response to 21 above. The emphasis with the PrEP guidance has been to avoid any potential delays with initiating LEN. STG amended as follows: "If hepatitis B surface antigen is negative, test for hepatitis B surface antibodies to assess for hepatitis B vaccine eligibility if there is no history of previous hepatitis B vaccination (see table 11.14 below). If HBsAg-positive, refer to specialist. **Hep B vaccine supply:** Eligibility for Hep B vaccine currently under review by NAGI.
23.	*STG – RPR: To diagnose syphilis infection for treatment.* Consider adding comment that this is a lab test not a rapid test- in WC we have had reports of people using rapid test for groups other than pregnant women, and so we included a testing page in PACK to clarify.	The focus of the EML is on medicines management. Detailed clinical guidance to support implementation is included in the program guidelines – this comment will

<table>
<tr><td></td><td></td><td>be referred to the STI program guideline review team for consideration, as review is currently underway.</td></tr>
<tr><td>24.</td><td>STG: 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.

in practice we also use a PEP to PrEP approach especially if high risk and condom use tricky</td><td>Amended with cross reference to PEP STG as follows:
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. Alternatively, PEP may be considered for inadvertent high risk exposures – see Section 21.1.6.3.</td></tr>
<tr><td>25.</td><td>STG - Hepatitis B immune status and oral PrEP eligibility
Does this imply that HBsAb must be done on all clients initiating PrEP?
Will only be done if HBsAg neg- so almost all. Does this require return visit for HbsAb result, or will Ag and Ab test be done on same day?</td><td>See Responses 21 and 22 above.</td></tr>
<tr><td>26.</td><td>Hepatitis B immune status and PrEP eligibility
You could consider adding in a column to label/interpret the immune status, e.g.,

1. No HBV infection and no immunity
2. No HBV infection. HBV immunity present
3. HBV infection

Or something similar….</td><td>Amended to include suggestions for interpretation of results

<table><tr><th>Hepatitis B surface antigen (HBsAg)</th><th>Hepatitis B surface antibody (HBsAb)</th><th>Interpretation of results</th></tr><tr><td>Negative (-)</td><td>Negative (-)</td><td>No Hepatitis B infection and no immunity present</td></tr><tr><td>Negative (-)</td><td>Positive (+)</td><td>No Hepatitis B infection present but immunity present</td></tr><tr><td>Positive (+)</td><td>N/A</td><td>Hepatitis B infection present</td></tr></table></td></tr>
<tr><td>27.</td><td>STG - Hepatitis B immune status and oral PrEP eligibility
Start PrEP: TDF+FTC or lenacapavir may be offered
Vaccinate with Hep B vaccine concurrently if available.

Does “concurrently” mean you should wait for HBsAg and HBsAb results before you start PrEP?</td><td>Amended as follows:
Vaccinate with Hep B vaccine concurrently if available, (do not delay PrEP initiation).</td></tr>
<tr><td>28.</td><td>STG: Hepatitis B surface antibody (HBsAb)
Positive (+)
Positive with HBsAb Titre ≥ 10 IU/ml</td><td>Not amended.
Refer to AH Section 1.2.4 Viral hepatitis for detailed guidance.</td></tr>
<tr><td>29.</td><td>STG: Action No Hep B vaccine needed
No Hep B Vaccine needed if HBsAb Titre ≥ 10 IU/ml.

If HBsAb < 10 IU/ml, vaccinate with Hep B Vaccine (1 dose) and repeat HBsAb Titre after 3 months.</td><td>Not amended.
NEMLC recommends a full course of vaccination (0, 1, and 6 months), and no routine rechecking of titres thereafter.
Refer to AH Section 1.2.4 Viral hepatitis for detailed guidance.</td></tr>
<tr><td>30.</td><td>STG: PrEP users with chronic hepatitis B infection who develop abnormal liver function tests should be referred for assessment.

Is it not all chronic Hep B infection that needs to be referred?
Unclear how abnormal LFT will be detected since ALT monitoring is not indicated. Perhaps they will be followed up at secondary level after the initial referral when they test HepB pos.</td><td>Amended as follows:
PrEP users with chronic hepatitis B infection should be referred for assessment.
PHC STG for chronic Hep B to be developed.</td></tr>
</table>

<table>
<tr><td>31.</td><td>Clarify follow-up responsibilities for chronic HBV: refer for specialist care and LFT monitoring.</td><td>Amended
See Response 30 above.</td></tr>
<tr><td></td><td colspan="2">PrEP follow up and monitoring</td></tr>
<tr><td>32.</td><td>STG – Activity

ADD: Family planning (If applicable)</td><td>Added to table 11.13 screening investigations before starting PrEP:
<u>Urine pregnancy test :</u> Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP. Offer contraception, where appropriate, to avoid unintended pregnancy (see Section 7 Family planning).</td></tr>
<tr><td>33.</td><td>STG: Confirmation of HIV-negative status

Can people use a HIV self test to confirm their status? Or oraquick? We have used oraquick HIVST in our studies on PrEP and never had a seroconversion that was undetected by the HIVST and aligns with WHO guidance.

According to the 2025 HTS guideline (and summarised in the Consolidated ART GL):

2025 HTS Guideline expands the use of HIV self-testing for PEP follow-up, for PrEP continuation from the second follow-up visit, for PrEP re-engagement

(provided testing is conducted at a health facility), within facility-based HTS for triage when insufficient HTS providers are available, and within index and social-network testing.</td><td>Not amended
Refer to the HIV program guidelines for detailed guidance on HIV testing.
Feedback from the HIV program on self-testing: The HIV program guideline limits the use of HIV self-testing for oral PrEP continuation after 4 months of regular use. Wide scale use of HIV self-testing is currently not supported by the HIV program as there is sufficient local experience at this time.</td></tr>
<tr><td>34.</td><td>STG: estimated CrCl: <30 yrs: n/a

Shouldn’t baseline be included here as well? It is listed in the table SCREENING INVESTIGATIONS BEFORE STARTING PrEP</td><td>Table amended to include guidance on renal function monitoring for both oral and injectable PrEP as relevant.</td></tr>
<tr><td>35.</td><td>STG: estimated CrCl: <50 yrs – Baseline and annual monitoring of Cr levels

in the setting of oral PrEP use otherwise low risk in Len</td><td>Baseline and annual screening of patients <50yrs with co-morbidities such as diabetes/hypertension is recommended as part of chronic disease management, irrespective of PrEP use (see PHC STG section 4.7.1 Hypertension in adults and 9.2.2 Type 2 diabetes mellitus, adults.</td></tr>
<tr><td>36.</td><td>STG: estimated CrCl –

<table>
<tr><td><50 years</td><td>Diabetes/ hypertension</td><td>Baseline, annually</td></tr>
<tr><td colspan="3">? Baseline, 3 Months then annually</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>≥ 50 years</td><td>Diabetes/ hypertension</td><td>Baseline, annually</td></tr>
<tr><td colspan="3">? Baseline, 3 Months then annually</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Pregnant</td><td>n/a</td><td>Baseline, 3 & 6 months</td></tr>
<tr><td colspan="3">Consider Serum Creatinine (Not eGFR)</td></tr>
<tr><td colspan="3"></td></tr>
</table>
</td><td>For patients with chronic diseases such as hypertension and diabetes, see response to 35 above.
Pregnant women - STG amended to include: “For pregnant women use serum creatinine to determine renal function.”</td></tr>
</table>

37.	*STG: estimated CrCl (table for guidance on monitoring)* Is this just for oral PrEP? Should be clarified in table that this only applies to oral PrEP.	Table amended to include guidance on renal function monitoring for both oral and injectable PrEP as relevant.
38.	Rephrase eGFR thresholds for clarity.	Table amended to include guidance on renal function monitoring for both oral and injectable PrEP as relevant.
39.	*STG:* STI screening and treatment STI syndromic screening and treatment. RPR	Editorial - amended
40.	*STG: PrEP supply: Lenacapavir. Loading dose tablets: Day 1 tablets to be administered during clinic visit with supply for Day 2. Injections to be administered by healthcare staff every 6 months.* ADD - By 28 weeks	Editorial – amended in table 11.18: Dose regimen for initiating LEN
41.	*STG: PrEP supply: Day 1 tablets to be administered during clinic visit with supply for Day 2. Injections to be administered by healthcare staff every 6 months.* Day 1, two 300 mg tablets to be administered during clinic visit with supply of two 300 mg tablets for Day 2. Injections to be administered by healthcare staff on Day 1 and then every 6 months.	Editorial – amended in table 11.18: Dose regimen for initiating LEN
42.	*STG: PrEP supply: Lenacapavir. Loading dose tablets: Day 1 tablets to be administered during clinic visit with supply for Day 2. Injections to be administered by healthcare staff every six months.* Specify that tablets and injection for Day 1 is given at clinic. Then day 2 - self administered tablets at home; then 6 monthly return for inj.	Editorial – amended in table 11.18: Dose regimen for initiating LEN
	Oral PrEP (TDF-FTC) Regimen	

<table>
<tr><td>43.</td><td>STG: ORAL PrEP (TDF-FTC) REGIMEN
DAILY ORAL PREP</td><td>Editorial
Not amended - dosing guidance relates to section on ORAL PrEP.</td></tr>
<tr><td>44.</td><td>STG: Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required. Continue oral PrEP for 7 days after the last potential HIV exposure.

Individuals should be counselled that additional barrier protection should be used until therapeutic levels achieved.

ADD as above</td><td></td></tr>
<tr><td>45.</td><td>STG – Notes:
ADD: Oral PrEP is safe to use during pregnancy and breastfeeding.</td><td>Guidance added on use of PrEP during pregnancy and lactation.</td></tr>
<tr><td></td><td colspan="2">Side effects of TDF + FTC combination</td></tr>
<tr><td>46.</td><td>STG:
Major:
Hematologic toxicity (FTC/3TC induced Pure Red Cell Aplasia)
Minor
TDF-Induced Tubular Wasting Syndrome</td><td>Not amended.
These are not listed in the SAHPRA PI specifically.
Tubular wasting syndrome already covered under renal toxicity.
Pure red cell aplasia and tubular wasting syndrome extremely rare side effects.</td></tr>
<tr><td>47.</td><td>STG: Renal toxicity and decreased bone mineral density usually reversible upon stopping TDF + FTC.

Renal toxicity, Hematologic toxicity and decreased bone mineral density usually reversible upon stopping the causing drug (TDF and/or FTC(3TC)</td><td>Not amended.
STGs advocate for fixed dose combinations for PrEP.</td></tr>
<tr><td></td><td colspan="2">Injectable PrEP (Lenacapavir) regimen</td></tr>
<tr><td>48</td><td>In the interest of visit alignment and integrated care, could we mention that there is a 2-week “grace” range before or after the 26-week doing interval? This is especially relevant for the pregnancy and breastfeeding context where we need to coordinate maternal and child visits for many reasons but also to promote retention in care and on PrEP
…Please make that note in the Fig 11.10 below as well (within 24-28 weeks since initiating Lenacapavir)</td><td rowspan="2">Amended as follows:

INJECTABLE PREP (LENACAPAVIR) REGIMEN
<table><tr><td>Initiation

Day 1</td><td>• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections)
AND
• LEN, oral, 600 mg (2 X 300 mg tablets) during clinic visit.</td></tr><tr><td>Initiation

Day 2</td><td>• LEN, oral, 600 mg (2 X 300 mg tablets)
○ Do not take the Day 1 and Day 2 oral doses on the same day.
○ Supply 2 X 300mg tablets for self-administration at home.</td></tr><tr><td>Continuation</td><td>• LEN, subcutaneous injection, 927 mg (2 X 1.5 mL injections) every six months (26 weeks +/- 2 weeks) from the date of the last injection.
○ Confirm HIV status is still negative before each injection is administered at the clinic.</td></tr></table>Table 11.18: Dose regimen for initiating LEN as PrEP</td></tr>
<tr><td>49.</td><td>STG: LEN Continuation
LEN, subcutaneous injection, 927 mg (2X1.5mL injections) every six months or 26 weeks from the last injection.
Maybe they should add +/- 2weeks, as it is written in the label. May help with the confusion above on bridging.</td></tr>
<tr><td></td><td colspan="2">Management of missed doses of LEN– Continuation Phase – delayed injection</td></tr>
</table>

<table>
<tr>
<td>50.</td>
<td>Recommendation for an oral LEN 300mg dose to be given together with the SC LEN 927mg for injections delayed between 26-28 weeks since last injection.

I think this wording may require some clarity, otherwise it may be misinterpreted. If you review the YEZTUGO PI, the recommendation for an oral LEN 300mg dose to be given weekly is only in the event of an anticipated delay in SC LEN injection – if client is between 26-28 weeks since last SC LEN injection, and for some reason client is not able to receive another SC LEN injection at that time, you can give oral LEN 300mg weekly until injections can be resumed, and the SC LEN on resumption, must be given within 7 days of the last oral dose.

There is no need to load with oral LEN if the SC LEN is given between 26-28 weeks since the last injection - there is a 2-week window on the dose every 26 weeks. i.e. can be given as early as 24-weeks since last SC injection and up to 28-weeks since last SC injection without the need for loading with an oral dose of LEN 300mg.</td>
<td rowspan="5">STG guidance amended as follows:

<table>
<tr><th>Time since last injection</th><th>Dosage recommendation</th></tr>
<tr><td>› 28 weeks</td><td>Reinitiate LEN as per table 11.18 above

○ Reassess if injectable PrEP still suitable for the client.
○ Confirm HIV status is still negative.</td></tr>
</table>
</td>
</tr>
<tr>
<td>51.</td>
<td>STG: 26-28 weeks

So is this for 26 weeks + 1 day ? I would suggest specificity around how many days late would need an additional oral dose of LEN</td>
</tr>
<tr>
<td>52.</td>
<td>STG: > 28 weeks

Is this 28 weeks + 1 day or more?</td>
</tr>
<tr>
<td>53.</td>
<td>NEMLC report:

<u>“Lenacapavir - delayed injections and use of oral bridging:</u> For individuals in the continuation phase, who present at weeks 26-28 after their last lenacapavir injection for a repeat injection, a single oral dose of lenacapvir 300mg should be administered in addition to the six monthly subcutaneous injection.”

We do not have any clinical or modeling evidence to support this strategy. I am not sure where or why it has arisen? my understanding is that if the maintenance injection is given before 28 weeks there is no need for oral loading. if given after 28 weeks then the client needs to be re-initiated as per first dose (len + full 2 day loading dose)</td>
</tr>
<tr>
<td>54.</td>
<td>Flagging the recommendation for an additional oral dose between week 26 and week 28 of Len injection schedule. This is not reflected in the SAHPRA-approved label and is not supported by clinical trial evidence underpinning registration. All pivotal trials demonstrated full efficacy and operational feasibility without the need for an interim oral bridging between weeks 26-28. Introducing it here may inadvertently create confusion and misalign national guidance with the regulatory standard. As long as it is within the 28 weeks, there is no need for an additional</td>
</tr>
</table>

	oral bridging during continuation injections with Len. Happy to support with further scientific clarification if helpful. Not consistent with label and no oral dose recommended	
55.	*STG: 26-28 weeks* • *LEN, oral, 300 mg (1 X 300 mg tablet) as a single dose* 26 +/- 2 weeks Oral reloading not needed	
56.	*NEMLC report* Explain restricted bridging based on limited LEN supply via the Global Fund GC7 allocation.	As the initial roll out of LEN will be undertaken with a limited supply based on the Global Fund GC7 allocation, the use of oral bridging with LEN is not supported by NEMLC. This is to conserve the limited supply of LEN. These individuals should be offered daily oral PrEP using TDF+FTC.
57.	*STG: > 28 weeks: Reinitiate LEN as per table 11.18 above* Consider including --- (Initiation Day 1&2) –	Editorial - amended See response 49 above.
	Safety	
58.	Add explicit reference to the HIV drug-interaction checker.	Editorial - added
59.	*STG: Standard TB meds - Use oral PrEP instead until TB treatment completed.* i think fair approach until we are beyond the "donation" constrained supply phase	No change to STG guidance i.e. use oral PrEP for individuals requiring concomitant TB medicines. Increased doses of LEN is not supported at this time due to the dose optimisation strategy employed during this time of limited supply from the Global Fund. Guidance has been updated in v1.1 of this report.
60.	*STG: Standard TB meds - Potential interaction* Potential interaction: Substantially decreases LEN concentrations.	Not amended (see also response 59 above).
61.	*STG: Standard TB meds - Use oral PrEP instead until TB treatment completed.* TB or TPT (3HP)..	Editorial – amended to encompass treatment and prophylaxis. STG amended to: Use oral PrEP instead for the duration of the TB medicine regimen and for two weeks after completion of TB regimen (to accommodate for the wash-out period of TB medication). completed
62.	*STG: Standard TB meds - Use oral PrEP instead until TB treatment completed.* If they are already on LEN, should we just add TDF/FTC until TB tx completed?	No evidence of efficacy or safety to support the addition of TDF/FTC to LEN. Patients established on LEN who are subsequently initiated on TB medication should be transitioned to oral PrEP until completion of the TB regimen. Amended for clarity – see Response 61 above. Guidance has been updated in v1.1 of this report.
63.	*STG: Anticonvulsants - Refer to doctor for switching to alternative anticonvulsant treatment.* Would TDF/FTC be an option for these patients as switching anticonvulsants is sometimes quite difficult. OR in the interim while switching - as it may take months.	Editorial amendment with addition of cross reference as follows: Refer to doctor for switching to lamotrigine, valproate or levetiracetam (see PHC Section 15.7.2 Epilepsy in Adolescents and Adults). Cross reference to PHC Section 15.7.2 Epilepsy in Adolescents and Adults also added to Tables 11.5 and Tables 11.6.

64.	*STG:* Potential interaction Potential interaction: Substantially decreases LEN concentrations. *STG: Refer to doctor for switching to alternative anticonvulsant treatment.* Refer to doctor for switching to altenative anticonvulsant treatment, or use oral PrEP instead (daily or intermittent (on demand 2-1-1 oral PrEP.	Not amended. See Responses 63 and Response 16 above.
65.	STG – illicit drug use Potential interaction Potential interaction, which may persist after discontinuation of LEN: LEN substantially increases Ketamine concentrations.	Not amended
66.	*STG: LEN may increase ketamine-related effects such as respiration depression and hallucinations.* *Avoid use of ketamine* Correct "respiration depression" to "respiratory depression."	Editorial - amended
67.	*STG: Erectile dysfunction Potential interaction* Potential interaction, which may persist after discontinuation of LEN: LEN may increase Erectile Dysfunction drugs concentrations. *Avoid concomitant use of erectile dysfunction medicines*. Avoid concomitant use of LEN and Erectile Dysfunction drugs or use alternative Erectile Dysfunction drugs. Refer to prescribing information of Erectile Dysfunction drugs for dose adjustments.	PDE5-nhibitors are non-EML for the management of erectile dysfunction. This guidance is included in the STG as a prompt for clinical staff when taking a medication history, as individuals may be self-administering these medicines. Amended to accommodate for clients opting to privately fund treatment with erectile dysfunction treatment: LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines, *(Clients opting to self-fund erectile dysfunction treatment, should be advised to start on a lower dose and titrate to effects or side effects.)*
68.	*STG: Erectile dysfunction - LEN may potentiate the effects of erectile dysfunction medicines. Avoid concomitant use of erectile dysfunction medicines* ADD: (or start with low dose?)	
69.	*STG Notes (side effects)* Important to add in the ISR counseling and ice prior to injections as well » Important to counsel clients that nodules may form with LEN injections: e.g., "the drug sits there and slowly dissolves and that is what is providing the protection" » For pain and injection site reaction, providers can use ice (*prior* to injection), paracetamol (following injection), and injection site selection (stomach vs. thigh or buttock, depending on preferred site)	The focus of the EML is on medicines management. Detailed clinical guidance to support injection technique is included in the HIV program guidelines and Job Aids. The publications are intended to complement each other.
70.	*STG Notes (side effects)* ADD: Lenacapavir is safe to use during pregnancy and breastfeeding.	Guidance added on use of PrEP during pregnancy and lactation. **Pregnancy:** There is currently no evidence that LEN is associated with any adverse pregnancy outcomes. While it's fair to acknowledge that human data on LEN is still emerging (primarily from trials like PURPOSE 1, with ongoing registries needed for rare events), no evidence of teratogenicity or increased adverse outcomes has surfaced from animal studies, pharmacokinetic data, or monitored pregnancies to date. Outcomes like miscarriage, stillbirth, and birth defects align with or below background rates. By

		contrast, the pregnancy risks of acquiring HIV in pregnancy are well established and substantial.
71.	*[New STG content – recommended addition]* PrEP during pregnancy and breastfeeding » Both oral and injectable PrEP regimens are suitable, safe and effective (in preventing HIV) to use during pregnancy and breastfeeding. » The choice of an oral versus injectable PrEP regimen should be based on the woman's context and preferences and whatever method she is likely to continue taking over time » Every effort should be made *to* ensure that women who initiate PrEP during antenatal care continue PrEP during postpartum period and whilst breastfeeding. To this end, PrEP follow-up visits should align with the baby's EPI schedule to minimise additional **visits** (see also the VISIT SCHEDULE FOR INTEGRATED CARE: MOTHER TAKING PREP on page 125 of the 2025 Consolidate ART Guideline) . **Do you want to refer to the calendar in the VTP guidelines here?** » To support visit alignment, the optimal timing for Lenacapavir postnataly is: > At delivery (or within week of delivery) > At the 6-month well mother-baby visit, > At the 12- and 18-month well mother-baby visits, and 6-monthly thereafter, depending on the mother's preferences and risk profile. » Considering that Lenacapavir has a 26-week dosing interval (within a 24-28 week range), the choice of oral PrEP versus 6-monthly Lenacapavir during pregnancy should consider the gestational age at the first antenatal booking relative to the expected date of delivery: > Lenacapavir provided at or before 14 weeks gestation is likely to align well with Lenacapavir at delivery, and 6-monthly during breastfeeding. > If able to take oral tablets daily, oral PrEP may allow for greater flexibility in the context of booking visits later than 14 weeks, frequent antenatal follow-up contacts, and uncertain delivery dates. > Choice in PrEP product should be given to the woman, regardless of her pregnancy or postpartum stage	See response 7 and 70 above.
72.	**Clinical eligibility criteria and special population** Area of Concern: need for explicit guidance on adolescents, pregnancy/ breastfeeding and other special populations. Substantive comment: The guideline should provide clear evidence-based eligibility criteria and safety considerations for all population eligible under which SAHPRA approval with particular attention to adolescent and pregnant/ breastfeeding women. The Access to Medicine Index 2024, [8] found that the including of pregnant and lactating	See responses 7, 12 and 70 above.

<table>
<tr><td></td><td>women in clinical trials remain extremely limited. The report emphasises that companies should ensure inclusion of special populations, such as pregnant and breastfeeding individuals in clinical research.</td><td></td></tr>
<tr><td></td><td colspan="2">Side Effects</td></tr>
<tr><td>73.</td><td>Side effects of lenacapvir
<table><tr><td>Major</td><td>Injection site reactions, including necrosis and ulcer (often linked to improper administration) , headache, nausea</td></tr><tr><td>Minor</td><td>Dizziness, vomiting, diarrhoea</td></tr></table>
Major – should be ‘common’

Minor – should be ‘less common’</td><td>“Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).”

“Very common – injection site reactions (Includes injection site nodule, pain, induration, erythema, swelling, pruritus, bruising, warmth, discolouration, oedema, ulcer, haematoma, haemorrhage, and discomfort.) “

FDA PI: frequency of drug reactions reported in PURPOSE 1 or 2
dizziness, vomiting, diarrhoea = 4%; headache = 7%, nausea = 5%

Editorial – amended to align with SAHPRA PI
<table><tr><td>Very common</td><td>Injection site reactions, including necrosis and ulcer (often linked to improper administration)</td></tr><tr><td>Common</td><td>Dizziness, vomiting, diarrhoea, headache, nausea</td></tr></table></td></tr>
<tr><td>74.</td><td>STG: Side effects of LEN
For individuals who may need to switch from LEN to oral PrEP, initiate oral PrEP within 28 weeks of the last LEN injection.

For individuals who may need to switch from LEN to Daily/Event-Based Oral PrEP (as per patient eligibility and preferences), initiate oral PrEP within 28 weeks of the last LEN injection.</td><td>Not added
See Response 16 above</td></tr>
<tr><td></td><td colspan="2">Stopping PrEP</td></tr>
<tr><td>75.</td><td>STG: Develops renal disease (for oral PrEP: eGFR < 60mL/min and injectable PrEP eGFR < 15mL/min)

eGFR <50 mL/min if > 16 years; eGFR <80 mL/min if 10-16 years, Serum Creatinine > 85 umole/l in pregnant women.</td><td>See Response 15 and 20 above</td></tr>
<tr><td>76.</td><td>STG: Injectable lenacapvir has an extended washout period and drug levels decline slowly during the tail period. During the tail period, protection against HIV diminishes although the potential for drug interactions remains.

ADD: This period should be covered with oral PrEP if there is still risk of HIV exposure and condoms not feasible.</td><td rowspan="2">Added the following:
This period should be covered with oral PrEP (TDF+FTC) if there is still risk of HIV exposure and condoms are not feasible, i.e. initiate oral PrEP within 28 weeks of the last LEN injection</td></tr>
<tr><td>77.</td><td>Strengthen tail-phase guidance, including urgent testing for seroconversion symptoms.</td></tr>
</table>

	Ensure tail-phase risk management is highlighted.	
78.	I think that these STGs should make the following clear, If Lenacapavir Gilead is discontinued and it is clinically appropriate to continue PrEP, alternative forms of PrEP should be considered and initiated within 28 weeks of the last Lenacapavir Gilead injection.	
79.	*STG: Is non-adherent to PrEP.* Switch to new method of PrEP if have problems with adherence?	Non-adherence may be relevant to either PrEP option. STG amended to: Is non-adherent to available PrEP options
80.	*STG: Does not need or want PrEP* consider adding ---- anymore.	Editorial STG amended to: Does not need or want PrEP any longer
81.	*STG:* No longer meets eligibility criteria. Example here? Drug interactions with TB or < 35 kgs ?	Cross reference to eligibility criteria added.
82.	*STG Notes - Patients with chronic HBV may experience a hepatitis flare on discontinuation of oral PrEP.* This is very rare, can be de-emphasized here (as a rare case)?	This is a rare event but has been retained to justify the difference with Hep B management between oral PrEP and LEN.
83.	*STG: Note - Injectable lenacapvir has an extended washout period and drug levels decline slowly during the tail period. During the tail period, protection against HIV diminishes although the potential for drug interactions remains.* Is it possible to provide guidance on the length of this tail period?	Amended as follows: Injectable lenacapavir has an extended washout period and drug levels decline slowly during the tail period (residual concentrations may remain up to 12 months or longer after injection).
84.	Add instructions to report breakthrough infections via drug resistance surveillance.	The focus of the EML is on medicines management. Detailed clinical guidance to support implementation and monitoring is included in the HIV program guidelines and Job Aids. The publications are intended to complement each other. Breakthrough infections should form part of routine adverse event reporting.
85.	Record PrEP type, start date, follow-up dates, HIV test results, injection dates, and bridging doses in the EMR using ICD-11 codes.	The focus of the EML is on medicines management. Detailed clinical guidance to support implementation and monitoring is included in the HIV program guidelines and Job Aids. The publications are intended to complement each other.
	Referral	
86.	*STG: Discontinuation of TDF + FTC in patients with HBV.* Discontinuation of LEN should be referred to take oral PrEP (TDF/FTC) esp during tail period	See Responses 76, 77 and above. Clients who discontinue LEN as PrEP do not require referral for specialist management.
87.	*STG* ADD: - Renal, Hematologic or Bone toxicity. - Breakthrough infection.	Not amended These are rare side effects and referral will be self-evident. See also Response 84 above.

	Algorithm	
88.	Add in window periods for 24-26 weeks with LEN and referral to oral PrEP if discontinued LEN in Figure too	The algorithm focuses on PrEP initiation – STG text covers detailed dose regimen as well as discontinuation.
	General comments in support of NEMLC recommendations	
89.	The updated STG correctly: - Removes "substantial risk" and supports PrEP for any requesting individual. - Adds lenacapavir (LEN) as a PrEP option, aligned with NEMLC's conditional recommendation. - Ensures injectable PrEP complements—rather than replaces—oral PrEP, in line with WHO 2025.	Noted
90.	The updated PrEP STG is well-aligned with clinical evidence, WHO 2025, economic analysis and national programme realities. The recommended refinements will strengthen clarity, digital system alignment, patient safety, and surveillance integration.	Noted
91.	*[We]* commend the Department of Health, National Essential Medicine Committee undertaking this critical update to South Africa's HIV prevention guidelines to incorporate lenacapavir, (LEN) a groundbreaking twice yearly injectable HIV PrEP option that represent a paradigm shift in biomedical HIV prevention.	Noted
	Programme, Equity, Access, M&E Considerations	
92.	Note limited early-phase LEN supply and clarify that LEN rollout may initially be restricted to selected sites.	Implementation issue to be covered by HIV program and implementation guidance.
93.	**Population prioritisation and targeting strategy** **Area of concern:** The draft Guideline may lack explicit population prioritisation criteria and transparent cost effectiveness comparisons between PrEP modalities. 1) The guideline must clearly articulate evidence-based population prioritisation for LEN distribution during the 2026-2028 donor funded period to maximise epidemiological impact and ensure equitable access to those at highest risk. **Motivation:** According to modeling estimates by the Health Economics and Epidemiology Research Office (HE2RO), for the Global Fund donated doses of LEN to have the biggest impact 55% would need to go to pregnant and breastfeeding women, 26% to men who have sex with men, and 18% to female sex workers with this scenario averting 20,500 new infections over the next five years. [1] **Recommendation:**	Implementation issue to be covered by HIV program and implementation guidance.

	• Include a dedicated section on phased implementation and population prioritisation with reference to the Access To Medicine Foundation's principle of pricing transparency.[5] Medicines must reach those who need them most. Equitable access requires explicit targeting strategies. • Define substantial risk with clear clinical and epidemiological criteria. Ref 1: Macdonald P, Nair G, Wattrus C, et al. Southern African HIV Clinicians Society guideline on pre-exposure prophylaxis to prevent HIV. S Afr J HIV Med. 2025;26(1), a1713. **https://doi.org/10.4102/sajhivmed.v26i1.1713** Ref: 5: Access To Medicine Foundation. "Commentary: Edging Closer to Lenacapavir Access in Low- and Middle-income Countries | Access to Medicine," n.d. https://accesstomedicinefoundation.org/access-insights/commentary-edging-closer-to-lenacapavir-access-in-low-and-middle-income-countries.	
94.	Motivation: The Access To Medicine Foundation emphasizes that clinical trials and access plans often prioritize a small number of countries or regions leaving populations in lower-income regions underserved. Only 3.5% clinical trials take place in low-income countries and more specifically only 43% of all clinical trials (297/685) analysed in the 2024 Index are conducted in low-and-middle –income countries (LMICs), despite being home to nearly 80% the global population. When certain areas are excluded from access plans, people living in these areas face significant delays or may never access new therapies.[6] This principle applies equally to intra country geographic equity. **Recommendations** • Define minimum geographic distribution standards for LEN • Address infrastructure barriers for LEN treatment access • Monitoring and accountability **of** access to the treatment **Ref 6:** Access To Medicine Foundation, "Patients in Low- and Middle-income Countries Largely Left Out of Clinical Trials, Limiting Access to New Treatments | Access to Medicine," n.d., https://accesstomedicinefoundation.org/resource/patients-in-low-and-middle-income-countries-largely-left-out-of-clinical-trails-limiting-access-to-new-treatments.	Implementation issue to be covered by HIV program and implementation guidance. *Response from HIV program: Detailed PrEP targets disaggregated by age, gender, geographical areas, populations (Pregnant and key populations) for both oral and lenacapavir are informed by epidemiological data.*
95.	**Transition from donor funding to sustainable domestic procurement** **Area of Concern**: Inadequate detail on the transition strategy from Global Fund donation to South African	Funding and procurement responsibilities are outside of NEMLC's remit to address. Feedback from the Affordable Medicines Directroate, NDoH as follows: The NDoH has been in discussions with relevant stakeholders (including generic manufacturers and

	government procurement when donor funding ends in 2028. **Substantive comment:** The guideline must include an explicit sustainability road map to prevent program disruption when transitioning from donated LEN to domestically procured generic versions. Motivation: The health minister emphasised that for sustainable implementation South Africa must move beyond donation and take ownership of the program with plans to include LEN in the model of Essential Medicines List and allocate resources in the medium-term expenditure framework to ensure that once generic version become available or price drop scale up can continue without interruption.[2] Generic availability timeline is critical: Generic LEN is anticipated as early as 2027 pending regulatory approval with partnerships securing agreements with Dr. Reddy's laboratories and Hetero labs to provide LEN at USD 40 per person per year.[7] Recommendation: • Establish clear milestones for essential medicines lists inclusion process with target dates • Develop Provincial procurement readiness protocols for generic tendering • Equitable pricing strategies play a significant part in increasing access to medicine as shown by the Access to Medicine Foundation's research findings on inclusive business models.[8] Ref 7: "Expanding Access to HIV Prevention Tool for Millions," September 24, 2025, https://www.gatesfoundation.org/ideas/media-center/press-releases/2025/09/hiv-prevention-lenacapavir. Ref 8: Access to Medicine, *Access to Medicine Index 2024*, n.d. https://accesstomedicinefoundation.org/medialibrary/2024-access-to-medicine-index-1762503416.pdf)	regulatory authorities) to facilitate expedited access to generic LEN. Discussions include affordability considerations in line with the NEMLC's recommended reference price as well as implementation strategies and volume forecasting as informed by the HIV program.
96.	**Clinical eligibility criteria and special population** Area of Concern: need for explicit guidance on adolescents, pregnancy/ breastfeeding and other special populations. Substantive comment: The guideline should provide clear evidence-based eligibility criteria and safety considerations for all population eligible under which SAHPRA approval with particular attention to adolescent and pregnant/ breastfeeding women. The Access to Medicine Index	As above.

	2024, [8] found that the including of pregnant and lactating women in clinical trials remain extremely limited. The report emphasises that companies should ensure inclusion of special populations, such as pregnant and breastfeeding individuals in clinical research. **Motivation:** The Access to Medicine Foundation welcomes the commitment to ensure accelerated access to generic LEN and reduce its cost recognising the transparency on pricing, and the overall speed at which access is being ensured.[6] South Africa's guideline should embody these same principles: • Transparency: public reporting on pricing, procurement and distribution • Speed: rapid implementation leveraging existing PrEP infrastructure • Equity: prioritize access for populations bearing highest HIV burden • Accountability: monitoring and evaluation with public reporting on real world impact	
97.	Area of concern: need for robust M&E system and explicit equity provisions to ensure LEN reaches rural and under-resourced settings. **Substantive comment:** The guidelines should establish a comprehensive M&E framework with standardised indicators while including explicit equity provisions to prevent inequitable access across provinces and between urban / rural settings. **Motivation** As a novel intervention with phased implementation and donor funded initial. Robust M&E is essential for demonstrating impact, identifying implication challenges early, ensuring accountability, and detecting safety signals. The Access to Medicine Foundation emphasises the importance of monitoring how commitments translate into real world impact[5] with exceptions for public reporting on progress. South Africa's HIV epidemic varies significantly by geography with rural provinces often bearing high burden but facing health care access barriers. LEN twice-yearly dosing offers unique advantages for rural populations, but benefits will only materialise with intentional geographic distribution strategies. **Recommendations** M&E Framework: Establish standardised indicators including coverage indicator, retention and adherence (6 months and 12 months continuation rates); safety monitoring, (injection sites reactions), effectiveness etc.	M&E is outside of NEMLC's remit to address. *Feedback from the HIV program is however as follows: PrEP module on SyNCH be part be part of roll-out strategy ensuring uptake, continuation switching across PrEP products by age, gender, identified populations and geographic reach will be closely monitored by the HIV program.*

	Equity provision: define minimum geographic distribution standards; prioritize sites serving high burden rural population, mechanism to address geographic inequities. South Africa has opportunity to demonstrate global leadership in implementing LEN for PrEP. A strong evidence-based guideline that addresses the concerns raised in this submission will position the country to maximize the extraordinary potential of this innovation to prevent HIV infections and move decisively toward epidemic control. *[We]* recognizes that planning for LEN access in LMICs is moving at a notable pace, promoting broader questions about whether the same urgency and scale should be expected for other diseases.	
	Editorial and Formatting Adjustments	
98.	- Correct the heading "SCREENING INVESTIGATIONS BEFORE STARTING PrEP." - Standardise spelling of lenacapavir. - Clean spacing and punctuation issues. - Confirm table numbering consistency.	Editorial
	Economic analysis	
99.	Area of concern: insufficient transparency on cost effectiveness comparisons between LEN and existing PrEP modalities [oral TDF/FTC, CAB_LA, Dapivirine ring). **Substantive Comment:** The guideline should present comprehensive cost effectiveness analysis comparing all available PrEP modalities including programmatic costs beyond drug acquisition to inform both clinical decision making and budgetary planning. Motivation: HE2RO estimates that scaling up LEN will be more cost effective than daily oral prep. Generic LEN is priced at USD 40 per person per year comparable to currently available daily oral PrEP regimens inconsistent with independent estimates.[5] However true cost effectiveness must account for: • Reduced clinic visit frequency [twice yearly versus quarterly versus daily adherence] • Adherence related costs and failure rates • Healthcare worker time and training requirements • Cold chain and storage requirements • Patient retention and satisfaction Both PURPOSE studies found superiority of LEN was mainly due to decreased adherence to oral PrEP regiments[3] , suggesting significant real world effectiveness advantages beyond equivalent drug costs. Recommendation:	Reviews and/or economic analysis with NEMLC recommendations are published on the Knowledge Hub for the following PrEP options: **Cabotegravir (CAB):** https://www.health.gov.za/wp-content/uploads/2024/09/Cabotegravir-as-PrEP-for-adults-_EvidenceSummary_v5.1_13-Sep-2024_FINAL.pdf **Dapivirine ring (DAP):** https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-09/DapivirineRingForPrEP_PHC-Review_9June2022_v5.pdf For the LEN review, the PICO question compares LEN as the intervention to oral PrEP as the current standard of care. CAB and DAP are currently not on the EML. **Feedback from Health economist (He2RO)** : *The cost-effectiveness analysis did account for several of these elements, including reduced clinic visit frequency, adherence in the oral TDF/FTC arm, healthcare worker time and training, and patient retention (in terms of duration on PrEP). Cold chain and storage requirements were not accounted for as both TDF/FTC and LEN do not require cold chain storage and can be kept at room temperature. Any other supply chain costs are not considered as their cost per patient are assumed similar between the arms. Patient satisfaction was not directly considered in this analysis.*

<table>
<tr><td></td><td>Reference the access to medicine foundations principle of pricing transparency in procurement processes.[5]

Ref 3: New York State Department of Health AIDS Institute. Interim Guidelines on the use of Twice e-yearly Lenacapavir for HIV prevention. July 2025. Available at: https://www.hivguidelines.org/guideline/hiv-prp-len/

Ref 5: Access To Medicine Foundation. “Commentary: Edging Closer to Lenacapavir Access in Low- and Middle-income Countries | Access to Medicine,” n.d. https://accesstomedicinefoundation.org/access-insights/commentary-edging-closer-to-lenacapavir-access-in-low-and-middle-income-countries.</td><td></td></tr>
<tr><td></td><td colspan="2">SAHPRA query – injection site administration</td></tr>
<tr><td>100.</td><td>The HIV program held a PrEP technical working group meeting yesterday in preparation for the roll out of LEN, which is expected early in the New Year.

Concerns were raised by several attendees regarding the recommended injection sites for subcutaneous (SC) administration as included on the SAHPRA approved PI i.e.

Method of administration

"Lenacapavir Gilead injections must only be administered subcutaneously into the abdomen or upper buttocks"

The pharmacokinetic parameters:

Similar exposures are achieved when "Lenacapavir Gilead is administered subcutaneously in the abdomen, upper buttocks, thigh, or back of upper arm".

As per the attached summary, local guidance differs from both the EU and USA which recommend the abdomen and thigh, both aligned to declarations under the pharmacokinetic parameters in the respective PIs.

Kindly requesting SAHPRA's inputs on the following:

1. The pharmacokinetic parameters in the local PI is more extensive than the US and EU - is SAHPRA able to share the supporting data for the additional injection sites included under kinetic parameters, notably upper buttocks and back of upper arm.

2. The evidence/safety concerns supporting SAHPRAs recommendation to limit injection sites to the abdomen or upper buttocks only, (i.e. rationale for mis-alignment with declared pharmacokinetic evidence).</td><td>SAHPRA Feedback (email correspondence dated 8 Dec 2025):

“SAHPRA had made its recommendation for abdominal and gluteal region administration sites based on the PK data from Study GS-US-200-4540 which appeared to suggest that C6months (plasma concentration) for the thigh and upper arm may fall below the minimum IQ4 of >15.5ng/ml based on the lower bounds of the 95% confidence intervals around the mean C6months plasma concentrations. The thigh and upper arm routes of administration suggested suboptimal exposure compared to the abdomen in Study GS-US-200-4540.

<table><tr><th>Site</th><th>Mean C6mo (ng/ml)</th><th>95% CI (ng/ml)</th></tr><tr><td>Abdomen</td><td>28.6</td><td>17.9 – 45.6</td></tr><tr><td>Thigh</td><td>22.6</td><td>13.9 – 36.7</td></tr><tr><td>Upper arm</td><td>18.7</td><td>12.6 – 27.8</td></tr><tr><td>Gluteal region (buttock)</td><td>25.2</td><td>15.7 – 40.4</td></tr></table>
The applicant was requested to provide clarity on the implications of lower bounds of the 95% CI for the mean C6mo for the thigh and upper arm administration sites. Unfortunately, no new data was submitted by the applicant.

We note that the pharmacokinetic parameters included other sites of administration that were not approved (thigh and upper arm). EMEA and FDA has brought this section in line with approved administration sites (abdomen and thigh).
We will urgently engage the applicant to amend the pharmacokinetic parameters to reflect information on the approved administration sites.

We will keep you updated. If the applicant provides the required information, the PI will be updated.”</td></tr>
</table>

	Injection sites targeted by clinical staff outside of SAHPRA's approval would be off-label. Sharing some concerns raised by clinical staff for context, as follows: • *Pregnant women - the abdomen and upper buttock are not deemed appropriate/conducive sites for this patient cohort.* • *Buttocks usually recommended for IM injections - (ref to 'upper' buttock is noted) - training will be required to emphasise this distinction.* • *Given the local incidence of obesity, is the 'upper buttock' an appropriate injection site in this cohort?*	

PHC/Adult Hospital Expert Review Committee: Evidence Summary Isoniazid Preventive Therapy in Pregnancy

Date: 9 November 2023
Updated: 13 November 2025 (Version 2.0)
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.

Oversight Group Support: Zahiera Adam

Research Question: What is the efficacy and safety of isoniazid preventive therapy in pregnant women?

1. Background and timeline of NEMLC 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 Appendix 1 Textbox 1). (8)

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) A CD4 count-based risk stratified approach was assessed by the NDoH TB program as not feasible to implement. Therefore NEMLC and the NDoH TB program jointly decided in March 2024 to defer TPT in all pregnant women with HIV (See Appendix 1 Textbox 2).

Local clinicians raised concerns about deferring TPT in pregnant women living with HIV (PWLHIV), particularly women with advanced HIV and a higher risk of incident TB. In August 2025, a debate on use of IPT in pregnancy was held at the SA HIV Clinicians Society Conference. A poll taken after the debate indicated strong support from clinicians for a CD4 count-guided approach to IPT initiation in pregnancy. The 2023 update of the Consolidated ART Guideline[1] clearly outlines a specific package of care for people with Advanced HIV Disease, defined as any client (including pregnant women) with a CD4 count < 200 cells/mm^3, or WHO Stage 3 or 4 clinical conditions. This comprehensive package of care now provides opportunity to reconsider a CD4 count risk stratification approach to IPT in PWLHIV, in line with the latest available evidence for benefit and harms. After collaborative engagement between the NDoH TB program, the HIV program and NEMLC, joint recommendation was made, as follows:

- PWLHIV with CD4 counts ≤ 200 cells/mm^3 and starting ART should receive 12 months of TPT after exclusion of active tuberculosis disease.
- In PWH with CD4 counts > 200 cells/mm3 and starting ART, TPT should be deferred to the post-partum period.

This document aims summarizes evidence for safety and efficacy of IPT to date, as well as programmatic implementation feasibility concerns to inform 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])

[1] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

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[2]. 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[3] 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,

[2] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[3] 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[4], 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[5] 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[6] (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[7] (n = 89) or exposed to IPT (possibly or definitely)(n = 39)[8]. 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.

[4] HAART refers to treatment regimens consisting of three or more antiretroviral drugs.

[5] In 103 women

[6] High tuberculosis prevalence defined as ≥ 60 cases per 100 000 population.

[7] Pregnancies were classified as IPT unexposed if pregnancy outcome occurred > 45 weeks after the final isoniazid dose.

[8] 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.[9]

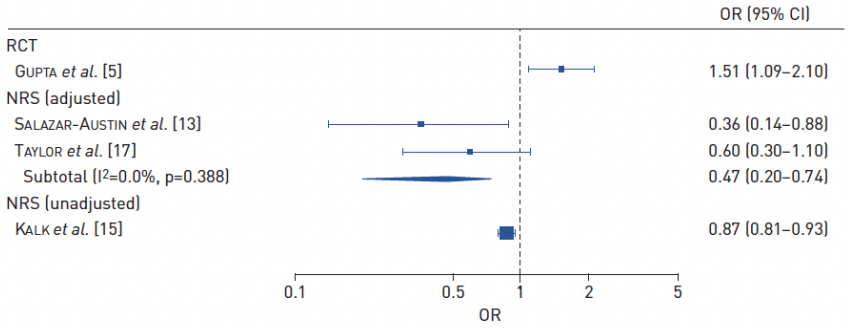
[9] The table contains a correction of an error detected in the review process and confirmed with the primary author of the systematic review.

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

5.1 Deliberations with the NDoH TB program in March 2024

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.

This recommendation was adopted by NEMLC in November 2024.

5.2 Deliberations with the NDoH TB program in October 2025

In 2023 the NDoH HIV Programme updated the Consolidated ART Guideline10 to clearly outline a specific package of care for people with Advanced HIV Disease (AHD), defined as any client (including pregnant women) with a CD4 count < 200 cells/mm3, or WHO Stage 3 or 4 clinical conditions. This package contains several elements, including:

- systematic TB screening and investigation, and IPT if TB is excluded,

[10] NDoH. 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. Accessible online https://knowledgehub.health.gov.za/elibrary/2023-art-clinical-guidelines-management-hiv-adults-pregnancy-and-breastfeeding-adolescents

- screening for cryptococcal antigenaemia,
- screening and management of serious bacterial infections,
- CPT prophylaxis,
- ART,
- Adherence support, and
- Intensified follow-up.

Pregnant women with CD4<200 cells/mm^3 are also eligible for this package of care for advanced HIV disease. As this package includes IPT, this provides an opportunity to reconsider CD4 count-based stratification to inform the administration of IPT in pregnancy, aligned with the AHD definition (i.e., CD4 < 200). This would allow the benefit of IPT for PWH at higher risk of TB, while minimising the programmatic complexity as the intervention will be nested within the newly established AHD programme, rather than a stand-alone intervention.

The TB programme have therefore suggested revisiting inclusion of a CD4 cut off, but used the AHD definition i.e. CD4<200 to guide initiation of IPT, so that IPT is administered to PWLWHA as part of the AHD package of care.

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 13 November 2025: We recommend that pregnant women living with HIV, with:

- CD_4 counts ≤ 200 cells/mm^3 and starting ART, receive 12 months of IPT after exclusion of active tuberculosis disease.
- CD_4 counts > 200 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). However, a CD4 cut off of 350 was not deemed programmatically feasible. The current programmatic "package of care" for patients with advanced HIV (CD4< 200), for which pregnant women are eligible, includes IPT. The ERC therefore suggests administering 12 months of IPT for all pregnant women with newly diagnosed HIV with a CD4< 200, co-initiated with ART, after screening for active TB, as part of the AHD package of care

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.

NEMLC RECOMMENDATION (MEETING 27 November 2025): NEMLC supports the ERC recommendation as detailed above (dated 13 Nov 2025).

Monitoring and evaluation considerations, and research priorities:

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

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

References

1. Gupta A, Montepiedra G, Aaron L, Theron G, McCarthy K, Bradford S, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. N Engl J Med. 2019;381(14):1333-46. 10.1056/NEJMoa1813060.
2. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database of Systematic Reviews. 2010(1). 10.1002/14651858.CD000171.pub3. https://doi.org//10.1002/14651858.CD000171.pub3.
3. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682-90. 10.1016/s0140-6736(14)60162-8.
4. Black A, Dawood H. NEMLC. Adult Hospital level Medication Review Process. Isoniazid Preventive Therapy. . 2018.
5. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Health. 2017;5(11):e1080-e9. 10.1016/s2214-109x(17)30372-8.
6. South African National Department Of Health. Standard Treatment Guidelines and Essential Medicines List for South Africa. Primary Health Care Level 2014.
7. Hakim J, Musiime V, Szubert AJ, Mallewa J, Siika A, Agutu C, et al. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. New England Journal of Medicine. 2017;377(3):233-45. 10.1056/NEJMoa1615822. https://www.nejm.org/doi/full/10.1056/NEJMoa1615822.
8. Kalk E, Heekes A, Mehta U, de Waal R, Jacob N, Cohen K, et al. Safety and Effectiveness of Isoniazid Preventive Therapy in Pregnant Women Living with Human Immunodeficiency Virus on Antiretroviral Therapy: An Observational Study Using Linked Population Data. Clin Infect Dis. 2020;71(8):e351-e8. 10.1093/cid/ciz1224.
9. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. WHO Guidelines Approved by the Guidelines Review Committee. Geneva2020.
10. South African National Department of Health. National Guidelines on the Treatment of Tuberculosis Infection. 2023. https://knowledgehub.health.gov.za/elibrary/national-guidelines-treatment-tuberculosis-infection.
11. Moro RN, Scott NA, Vernon A, Tepper NK, Goldberg SV, Schwartzman K, et al. Exposure to Latent Tuberculosis Treatment during Pregnancy. The PREVENT TB and the iAdhere Trials. Ann Am Thorac Soc. 2018;15(5):570-80. 10.1513/AnnalsATS.201704-326OC. https://www.ncbi.nlm.nih.gov/pubmed/29393655.
12. Franks AL, Binkin NJ, Snider DE , Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep. 1989;104(2):151-5.
13. Hamada Y., Figueroa C., Martín-Sánchez M., Falzon D., Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. Eur Respir J. 2020;55(3). 10.1183/13993003.01967-2019.
14. Theron G., Montepiedra G., Aaron L., McCarthy K., Chakhtoura N., Jean-Philippe P., et al. Individual and Composite Adverse Pregnancy Outcomes in a Randomized Trial on Isoniazid Preventative Therapy Among Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021;72(11):e784-e90. 10.1093/cid/ciaa1482.
15. Cherkos A. S., LaCourse S. M., Enquobahrie D. A., Richardson B. A., Bradford S., Montepiedra G., et al. Effect of pregnancy versus postpartum maternal isoniazid preventive therapy on infant growth in HIV-exposed uninfected infants: a post-hoc analysis of the TB APPRISE trial. EClinicalMedicine. 2023;58:101912. 10.1016/j.eclinm.2023.101912. https://www.ncbi.nlm.nih.gov/pubmed/36969345.
16. Taylor AW, Mosimaneotsile B, Mathebula U, Mathoma A, Moathlodi R, Theebetsile I, et al. Pregnancy Outcomes in HIV-Infected Women Receiving Long-Term Isoniazid Prophylaxis for Tuberculosis and Antiretroviral Therapy. Infectious Diseases in Obstetrics and Gynecology. 2013;2013:195637. 10.1155/2013/195637. https://doi.org/10.1155/2013/195637.
17. Gupta A., Hughes M. D., Cruz J. L., Avihingsanon A., Mwelase N., Severe P., et al. Adverse Pregnancy Outcomes among HIV-infected Women Taking Isoniazid Preventive Therapy During the First Trimester. Clin Infect Dis. 2023. 10.1093/cid/ciad583. https://www.ncbi.nlm.nih.gov/pubmed/37768207.
18. Salazar-Austin N, Cohn S, Lala S, Waja Z, Dooley KE, Hoffmann CJ, et al. Isoniazid Preventive Therapy and Pregnancy Outcomes in Women Living With Human Immunodeficiency Virus in the Tshepiso Cohort. Clin Infect Dis. 2020;71(6):1419-26. 10.1093/cid/ciz1024.
19. Tong S, Kaur A, Walker SP, Bryant V, Onwude JL, Permezel M. Miscarriage risk for asymptomatic women after a normal first-trimester prenatal visit. Obstet Gynecol. 2008;111(3):710-4. 10.1097/AOG.0b013e318163747c.
20. Singh P, Moulton LH, Barnes GL, Gupta A, Msandiwa R, Chaisson RE, et al. Pregnancy in Women With HIV in a Tuberculosis Preventive Therapy Trial. J Acquir Immune Defic Syndr. 2022;91(4):397-402. 10.1097/QAI.0000000000003078. https://www.ncbi.nlm.nih.gov/pubmed/36000934.
21. Tiam A, Machekano R, Gounder CR, Maama-Maime LB, Ntene-Sealiete K, Sahu M, et al. Preventing tuberculosis among HIV-infected pregnant women in Lesotho: the case for rolling out active case finding and isoniazid preventive therapy. J Acquir Immune Defic Syndr. 2014;67(1):e5-e11. 10.1097/qai.0000000000000209.
22. Kalk EK, Heekes A, Mehta U. Programmatic review of safety and effectiveness of isoniazid preventive therapy in HIV infected pregnant women on ART in routine care. Reproductive Toxicology. 2018; 80: 155.

23. Chang AH, Polesky A, Bhatia G. House calls by community health workers and public health nurses to improve adherence to isoniazid monotherapy for latent tuberculosis infection: a retrospective study. BMC Public Health. 2013;13(1):894. 10.1186/1471-2458-13-894. https://doi.org/10.1186/1471-2458-13-894.

24. Law I, Floyd K, The African TB Prevalence Survey Group. National tuberculosis prevalence surveys in Africa, 2008–2016: an overview of results and lessons learned. Tropical Medicine & International Health. 2020;25(11):1308-27. https://doi.org/10.1111/tmi.13485. https://onlinelibrary.wiley.com/doi/abs/10.1111/tmi.13485.
25. Tembo BP, Malangu NG. Prevalence and factors associated with multidrug/rifampicin resistant tuberculosis among suspected drug resistant tuberculosis patients in Botswana. BMC Infectious Diseases. 2019;19(1):779. 10.1186/s12879-019-4375-7. https://doi.org/10.1186/s12879-019-4375-7.
26. Delva GJ, Francois I, Claassen CW, Dorestan D, Bastien B, Medina-Moreno S, et al. Active Tuberculosis Case Finding in Port-au-Prince, Haiti: Experiences, Results, and Implications for Tuberculosis Control Programs. Tuberc Res Treat. 2016;2016:8020745. 10.1155/2016/8020745.

APPENDIX 1: HISTORIC ERC/NEMLC RECOMMENDATIONS

Textbox 1: ERC/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

Textbox 2: ERC/NEMLC Recommendation (2020-2024 review cycle)

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.

ERC Recommendation: Mar 2024

The ERC recommends that pregnant women living with HIV, with:

- CD_4 counts ≤ 350/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.

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

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

South African National Department of Health, National Essential Medicines List Committee

LENACAPAVIR AS PRE-EXPOSURE PROPHYLAXIS (PrEP) AGAINST HIV INFECTION

DATE: JUNE 2025

Medicine Class	[Yes] First-in-class, multi-stage HIV-1 capsid inhibitor	*If applicable* *Please consider the therapeutic interchange policy*
Medicine/s name **INN:** **South African name (if it differs from INN)**	Lenacapavir	*http://www.whocc.no/atc_ddd_index/*
Medicine/s (ATC5):	J05AX31	*http://www.whocc.no/atc_ddd_index/*
Indication (ICD-10 code):	Z29.81	*https://www.health.gov.za/icd-10-master-industry-table/*
SAHPRA Approved	No	SAHPRA registered health products database *https://medapps.sahpra.org.za:6006/*
Dosage form/s	Injection, with tablets for the loading dose	
Route of administration/s	Oral loading dose followed by subcutaneous injection	
Patient population	Any HIV-negative person who is at risk of HIV acquisition through sexual contact or exposure to blood, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs.	
Prevalence and/or incidence of condition	In South Africa, in 2024, the estimated overall HIV prevalence rate was 12.7% with the total number of people living with HIV (PLHIV) being approximately 8.0 million (Stats SA, 2024). Reported low adherence rates with PrEP have a significant impact on the success of HIV prevention (Van Damme, L. *et al.*, 2012; Young, A. *et al.*, 2023).	
Level of Care	PHC	
Prescriber level	Nurse-initiated, NIMART-trained providers	

EXECUTIVE SUMMARY

- Globally, an estimated 1.3 million new HIV infections occur annually, with cisgender women accounting for approximately 47% (610,000 of 1,300,000) of these cases. In Sub-Saharan Africa, cisgender women and girls represent a disproportionate burden, comprising 63% of new annual HIV infections (418,000 of 660,000) (UNAIDS, 2019). In contrast, data from the United States in 2022 indicate that 67% of new HIV diagnoses occurred among cisgender gay men, with over 70% of these diagnoses reported among individuals identifying as Black, Hispanic, or Latinx (Centers for Disease Control and Prevention [CDC], 2024a; CDC, 2024b).
- Despite the recognised efficacy of pre-exposure prophylaxis (PrEP), global uptake remains limited, reaching only 16.5% of the Joint United Nations Programme on HIV/AIDS (UNAIDS) target of 21.2 million users by 2025 (UNAIDS, 2024). Among populations disproportionately affected by HIV, both the uptake of and adherence to existing PrEP modalities remain suboptimal. These gaps highlight the urgent need to develop and implement alternative PrEP strategies—particularly long-acting formulations that minimise reliance on daily oral dosing or frequent injection visits (UNAIDS, 2024).
- The current standard of care for PrEP in South Africa, per the National Standard Treatment Guidelines (STGs), is daily oral F/TDF.
- We conducted a rapid systematic review of available evidence that assessed the effect of long-acting injectable Lenacapavir (LEN) for use as pre-exposure prophylaxis (PrEP) compared to standard of care tenofovir disoproxil fumarate plus emtricitabine (F/TDF) or other oral PrEP, tenofovir alafenamide plus emtricitabine (F/TAF) or other long-acting injectable PrEP such as long-acting injectable cabotegravir (CAB-LA) or placebo/no prophylaxis in any HIV-negative person who is at risk of HIV acquisition through sexual contact or exposure to blood, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs (restrictions: RCTs only).
- On 28 May 2025, we searched PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) databases for randomised controlled trials. We searched for ongoing studies in trial registries like clinicaltrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP). We identified two RCTs for inclusion (Bekker *et al*., 2024; Kelley *et al*., 2025):
    - Both were multicentre trials conducted in South Africa and Uganda (Bekker *et al*, 2024) and in the United States of America (USA), Brazil, Thailand, South Africa, Peru and Argentina (Kelley *et al*., 2025).
    - The PURPOSE 1 trial investigated the safety and efficacy of twice-yearly injectable LEN compared to daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The population sampled in the trial were adolescent girls and young women (16 to 25 years of age) (Bekker *et al*., 2024).
    - The second trial, PURPOSE 2, investigated the safety and efficacy of twice-yearly injectable LEN compared to daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The population included men and gender diverse persons aged at least 16 years and older (Kelley *et al*., 2025).
- Effectiveness results:
    - *Comparison 1: LEN compared to F/TDF*
        - Results in a large reduction in new HIV infections (52 weeks), Risk Ratio (RR) 0.06 (95% confidence interval (CI) 0.01 to 0.42), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 11 fewer cases per 1,000 (ranging from 11 fewer to 7 fewer), NNT 91
        - Results in little to no difference in serious adverse events (SAEs) (52 weeks), RR 0.83 (95% CI 0.63 to 1.10), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 6 fewer cases per 1,000 (ranging from 13 fewer to 4 more), NNT 167
        - Results in little to no difference in adverse events (AEs) (52 weeks), RR 0.99 (95% CI 0.96 to 1.02), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 8 fewer cases per 1,000 (ranging from 30 fewer to 15 more), NNT 125
        - Likely increases injection-site reactions (52 weeks), RR 1.56 (95% CI 0.89 to 2.74), two studies, n = 6,513, moderate certainty evidence. That is an absolute effect of 289 more cases per 1,000 (ranging from 57 fewer to 897 more), NNH 4
        - Results in little to no difference in all-cause mortality (52 weeks), RR 1.00 (95% CI 0.18 to 5.45), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 0 fewer cases per 1,000 (ranging from 1 fewer to 4 more), NNT 0
        - At week 52, retention was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group. Thus, LEN compared to F/TDF results in little to no difference in retention at weeks 26 and 52, high certainty evidence.

- *Comparison 2: LEN compared to F/TAF*
  - Results in a large reduction in new HIV infections (52 weeks), Risk Ratio (RR) 0.01 (95% CI 0.00 to 0.21), one study, n = 4,295, high certainty evidence. That is an absolute effect of 18 fewer cases per 1,000 (ranging from 18 fewer to 14 fewer), NNT 56
  - Results in little to no difference in SAEs at 52 weeks, RR 0.69 (95% CI 0.50 to 0.96), one study, n = 4,295, high certainty evidence. That is an absolute effect of 12 fewer cases per 1,000 (ranging from 20 fewer to 2 fewer), NNT 84
  - Results in little to no difference in AEs (52 weeks), RR 0.98 (95% CI 0.95 to 1.01), one study, n = 4,295, high certainty evidence. That is an absolute effect of 16 fewer cases per 1,000 (ranging from 39 fewer to 8 more), NNT 63
  - Increases injection-site reactions (52 weeks), RR 1.95 (95% CI 1.83 to 2.08), one study, n = 4,295, high certainty evidence. That is an absolute effect of 334 more cases per 1,000 (ranging from 292 more to 380 more), NNH 3
  - Results in little to no difference in mortality (52 weeks), RR 0.08 (95% CI 0.00 to 1.36), one study, n = 4,295, high certainty evidence. That is an absolute effect of 3 fewer cases per 1,000 (ranging from 3 fewer to 1 more), NNT 334
  - At week 52, retention was similar across the trial groups: in the LEN group, 45.9% (985/2,148) and 45.3% (973/2,147) in the F/TAF group. Thus, LEN compared to F/TAF results in little to no difference in retention at weeks 26 and 52, high certainty evidence.

➡ LEN has received approval by the US Federal Drug Administration (FDA) and European Medicines Agency (EMA) for use as PrEP (World Health Organization (WHO), 2025a). While local regulatory approval by the South African Health Products Regulatory Authority (SAHPRA) is still in progress, any opportunity that has the potential to positively alter the trajectory of the HIV epidemic in SA warrants consideration. Other contextual factors, including the cost-effectiveness, feasibility, acceptability, and equity, have been considered in the Evidence to Decision Framework (EtD) tables below.

➡ Evidence from the trials included in this review shows that the use of LEN, compared to either F/TDF or F/TAF, results in a large reduction of new HIV infections, with relatively few safety risks, apart from injection site reactions. This is further supported by the recently published WHO guidelines (WHO, 2025b) that recommend that long-acting injectable LEN be offered as an additional prevention choice for people at risk of contracting HIV (*strong recommendation, moderate to high certainty of evidence*).

➡ The ongoing trials identified will be monitored, and once results are published, this review will be updated.

KEY RECOMMENDATIONS

<table>
<tr><td>Type of ERC recommendation</td><td>We recommend against the option and for the alternative (strong)</td><td>We suggest not using the option or using the alternative (conditional)</td><td>We suggest using the option (conditional)</td><td>We recommend the option (strong)</td></tr>
<tr><td></td><td>☐</td><td>☐</td><td>☐</td><td>☑</td></tr>
<tr><td>High-level summary of conclusions from the Evidence to Decision Framework – See link</td><td colspan="4">For HIV prevention in susceptible individuals, the ERC recommends the use of long-acting injectable LEN for use as pre-exposure prophylaxis (PrEP) (strong recommendation, moderate certainty of the evidence).</td></tr>
<tr><td rowspan="2">NEMLC Ratification</td><td>Date</td><td colspan="3">Comments</td></tr>
<tr><td>04 September 2025</td><td colspan="3">Global Fund (GC7) grant:
The Committee supported the acceptance of the grant allocation from the Global Fund, as it presents an opportunity to enhance our understanding of potential pharmacovigilance concerns and will support programmatic development of a strategy for large-scale rollout.

Addition to the EML:
For HIV prevention in susceptible individuals, the NEMLC recommends the use of long-acting injectable LEN for use as pre-exposure prophylaxis (PrEP), contingent on the reference price (as included in the accompanying economic analysis) being met*, and confirmation of SAHPRA registration.
*Reference price conversion to ZAR for tablet and injection formulations to be reviewed at the time of tender negotiations.</td></tr>
<tr><td rowspan="2">Therapeutic Interchange Considerations (if applicable)</td><td rowspan="2">If YES:</td><td>Alternative medicine/s name (INN)</td><td>Alternative/s SAHPRA registered?</td><td>Formulation/s</td><td>Equipotent dose/ Dose range and dosing interval</td><td>If NO, tick the box</td></tr>
<tr><td></td><td></td><td></td><td></td><td>☑</td></tr>
<tr><td>Trigger for review</td><td colspan="5">Update with evidence from ongoing trials. A change in the price of medicines. Other SAHPRA-approved HIV PrEP options.</td></tr>
</table>

EVIDENCE TO DECISION FRAMEWORK

Question	
Should injectable LEN versus oral PrEP be used for HIV prevention in susceptible individuals?	
Population:	Any HIV-negative person who is at risk of HIV acquisition through sexual contact or exposure to blood, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs.
Intervention:	Long-acting injectable LEN (dosed as LEN SC injection either 6 or 12-monthly with a recognised PrEP (oral or other) lead-in.
Comparison:	a) Standard of care in SA STGs: Oral tenofovir disoproxil fumarate plus emtricitabine (F/TDF) b) Non-EML: Oral tenofovir alafenamide plus emtricitabine (F/TAF) c) Non-EML: Injectable CAB-LA (first injection followed by another a month later, then every 2 months) d) Placebo/no prophylaxis **We did not find any studies that compared injectable CAB-LA or placebo/no prophylaxis*
Setting:	Public Sector in South Africa
Perspective:	Public Health/Population

ASSESSMENT

Problem Priority
Why is this medicine being evaluated?

In South Africa, HIV incidence remains high, especially among adolescent girls and young women (AGYW), sex workers, men who have sex with men (MSM), transgender women, people who inject drugs (PWID), and serodiscordant couples. Although daily oral PrEP is available, many in these populations face barriers to adherence, including stigma, lack of privacy, pill fatigue, and challenges with daily pill-taking routines. Poor adherence to oral PrEP results in low effectiveness. Injectable PrEP offers a more discreet and convenient alternative that supports consistent use and may be better suited to individuals with low adherence to oral regimens. Additionally, the administration of injectable PrEP could potentially be integrated with other sexual and reproductive health services, including contraceptive injections, to streamline implementation and reduce clinic visits. This alignment supports health system efficiency and may improve uptake and continuity of HIV prevention among key populations.

Desirable Effects
How substantial are the desirable anticipated effects (i.e., benefits)?

Judgement	Research evidence	Additional considerations (by committee)
○ Trivial ○ Small ○ Moderate ○ **Large** ○ Varies (if so, why?) ○ Don't know	***Comparison 1: LEN vs. F/TDF***	*Background HIV incidence:* • In the PURPOSE-1 trial, the background HIV incidence in the screened population was 2.41 per 100 person-years (95% confidence interval [CI], 1.82 to 3.19), N=8,094. ***LEN reduced HIV incidence by 100% as compared with background HIV incidence*** (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; p<0.001) ***and by 100% as compared with F/TDF*** (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; p<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; p=0.21), and there was no evidence of a meaningful difference in HIV incidence between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14) (Bekker *et al.*, 2024). • PURPOSE-2: The background HIV incidence in the screened population was 2.37 per 100 person-years (95% CI, 1.65 to 3.42), N=4,634. ***The incidence of HIV infection with LEN was 96% lower than the background incidence*** (incidence

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with F/TDF	Risk difference with LEN injectable
New HIV infection	6,513 (2 RCTs)	⊕⊕⊕⊕ High[a]	**RR 0.06** (0.01 to 0.42)	12 per 1,000	**11 fewer per 1,000** (11 fewer to 7 fewer): NNT 91

Comparison 2: LEN vs. F/TAF

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with F/TAF	Risk difference with LEN injectable
New HIV infection	4,295 (1 RCT)	⨁⨁⨁⨁ High	**RR 0.01** (0.00 to 0.21)	18 per 1,000	**18 fewer per 1,000** (18 fewer to 14 fewer): NNT56

rate ratio, 0.04; 95% CI, 0.01 to 0.18; p<0.001), and ***the incidence with LEN was 89% lower than that with F/TDF*** (incidence rate ratio, 0.11; 95% CI, 0.02 to 0.51; p=0.002) (Kelley, *et al*., 2025).

Consideration 1: HIV is incurable and requires lifelong management. Not preventing HIV potentially leads to a massive downstream burden of long-term care. PrEP can also lead to the prevention of HIV transmission and secondary infections, which leads to a potentially large public health benefit.

Consideration 2: What is the utility of spending on a less effective intervention (oral PrEP)? Alternative randomised designs had substantial limitations: noninferiority to F/TDF was infeasible and violated the constancy assumption (given the inconsistent efficacy of F/TDF in previous trials involving women and variable adherence and effectiveness of F/TDF since the initial placebo-controlled trials), and superiority to placebo was unethical (given the international guidelines recommending F/TDF PrEP across populations). PrEP use remains suboptimal among women, particularly in populations with disproportionate HIV incidence, including young women, women in Africa, women of colour in the United States, and migrant women in multiple geographic areas (Bekker *et al*., 2024; Murray & Birnkrant, 2019)

Consideration 3: These results are seroconversions over one year; thus, the numbers may change over a more extended period (5 years), but retention in care remains an issue.

Undesirable Effects
How substantial are the undesirable anticipated effects (i.e., harms and toxicity)?

Judgement	Research evidence	Additional considerations (by committee)
○ Large ○ **Moderate** ○ Small ○ Trivial ○ Varies (if so, why?) ○ Don't know	***Comparison 1: LEN vs. F/TDF***	*Consideration 1:* In the PURPOSE-1 trial (population: adolescent and adult women), injection site reactions led to 0.2% discontinuation in the LEN group (Bekker *et al*., 2024). The population in the PURPOSE-2 trial (cisgender gay, bisexual, and other men, transgender women, transgender men, and gender-non-binary persons), injection site reactions led to 1.2% discontinuation in the LEN group and 0.3% in the F/TDF group (Kelley *et al*., 2025). The frequency and severity of these reactions improved with subsequent injections. Participants were more likely to discontinue due to ADRs (Kelley *et al*., 2025) – this may have implementation considerations and require targeted health promotion requirements. *Consideration 2:* There is concern around the development of resistance due to poor adherence to PrEP. In the PURPOSE-2 trial, ***two participants acquired HIV infection in the LEN group*** (Kelley *et al*., 2025). The LEN concentrations in both participants were within the range of the overall LEN concentrations in the pharmacokinetics cohort. ***Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit***. All nine participants in the F/TDF group who received a diagnosis of HIV infection had evidence of low or no adherence or had discontinued F/TDF more than 10 days before diagnosis. Eight of the nine participants had available dried-blood-spot samples to analyse tenofovir diphosphate concentrations. Of those eight participants, two had low concentrations and six were below the quantification limit. The one participant who was missing a dried-

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with F/TDF	Risk difference with LEN injectable
Serious adverse events	6513 (2 RCTs)	⊕⊕⊕⊕ High[b]	**RR 0.83** (0.63 to 1.10)	36 per 1,000	**6 fewer per 1,000** (13 fewer to 4 more): NNT 167
Adverse events	6513 (2 RCTs)	⊕⊕⊕⊕ High[b]	**RR 0.99** (0.96 to 1.02)	753 per 1,000	**8 fewer per 1,000** (30 fewer to 15 more): NNT 125
Adverse drug reactions	6513 (2 RCTs)	⊕⊕⊕◯ Moderate[c,d]	**RR 1.56** (0.89 to 2.74)	516 per 1,000	**289 more per 1,000** (57 fewer to 897 more): NNH 4
All-cause mortality	6513 (2 RCTs)	⊕⊕⊕⊕ High[e]	**RR 1.00** (0.18 to 5.45)	1 per 1,000	**0 fewer per 1,000** (1 fewer to 4 more): NNT 0
Retention at weeks 26 and 52	6513 (2 RCTs)	⊕⊕⊕⊕ High[f]	*Week 26*: Retention was similar across the trial groups: in the LEN group, 88.0% (3,822/4,343) and 88.2% (1,915/2,170) in the F/TDF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group.		

Comparison 2: LEN vs. F/TAF

Outcomes	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with F/TAF	Risk difference with LEN injectable
Serious adverse events	4295 (1 RCT)	⊕⊕⊕⊕ High	**RR 0.69** (0.50 to 0.96)	40 per 1,000	**12 fewer per 1,000** (20 fewer to 2 fewer): NNT 84
Adverse events	4295 (1 RCT)	⊕⊕⊕⊕ High[a]	**RR 0.98** (0.95 to 1.01)	776 per 1,000	**16 fewer per 1,000** (39 fewer to 8 more): NNT 63
Adverse drug reactions	4295 (1 RCT)	⊕⊕⊕⊕ High	**RR 1.95** (1.83 to 2.08)	352 per 1,000	**334 more per 1,000** (292 more to 380 more): NNH 3
Mortality	4295 (1 RCT)	⊕⊕⊕⊕ High[b]	**RR 0.08** (0.00 to 1.36)	3 per 1,000	**3 fewer per 1,000** (3 fewer to 1 more): NNT 334
Retention at weeks 26 and 52	4295 (1 RCT)	⊕⊕⊕⊕ High[c]	*Week 26*: Retention was similar across the trial groups: in the LEN group, 90.3% (1,940/2,148) and 90.9% (1,952/2,147) in the F/TAF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 45.9% (985/2,148) and 45.3% (973/2,147) in the F/TAF group.		

blood-spot sample had discontinued F/TDF. ***One participant was found to have an emtricitabine resistance mutation (M184V)***. LEN is only approved for use in persons with multidrug-resistant HIV who are highly treatment-experienced, which is a limited population. There is no evidence of circulating N74D in any population, and the N74 amino acid is highly conserved in all subtypes evaluated. Early emergence of the N74D mutation has been reported in vitro and in persons receiving LEN for HIV treatment, which suggests, along with the HIV testing described, that the two cases of HIV infection in the LEN group in this trial were infections that occurred during the trial period, with emergence of capsid resistance resulting from LEN monotherapy.

According to the recent WHO guideline, the likelihood of primary infection with a LEN-resistant HIV-1 strain remains very low, as resistance-associated mutations linked to LEN are rare among individuals without prior exposure to the agent (Van Zyl *et al*., 2025). Although resistance may develop if LEN is initiated during undiagnosed acute HIV-1 infection or if seroconversion occurs during the pharmacokinetic tail phase of the drug, such resistance does not compromise the efficacy of antiretroviral regimens currently endorsed by the WHO for first-, second-, or third-line therapy, due to the absence of cross-resistance between LEN and other antiretroviral classes. Furthermore, most LEN-associated resistance mutations are associated with reduced viral replication capacity, limiting their potential for transmission. Given the rarity of breakthrough infections, LEN PrEP is not expected to substantially contribute to developing LEN resistance at a population level. Nevertheless, existing HIV-1 drug resistance surveillance systems should be adapted and expanded to detect and monitor LEN-associated resistance

		mutations within populations where LEN PrEP is deployed (Van Zyl *et al*., 2025). *Consideration 3*: Retention in care over 52 weeks was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group. *Consideration 4:* In both the PURPOSE-1 and PURPOSE-2 trials, at the end of the one-year follow-up period, participants began to be made aware of the trial-group assignments and were offered the option to receive LEN in an open-label fashion. Further follow-up, including in the open-label extension phase of these trials, is needed to monitor the incidence of breakthrough HIV infection, delayed seroconversion and the development of resistance. *Consideration 5*: Special populations • Preliminary results from PURPOSE-1 trials showed that twice-yearly LEN was efficacious, safe, and well-tolerated in pregnant and lactating people. However, safety in pregnancy needs to be evaluated from a pharmacovigilance perspective. Monitoring adverse outcomes of the impact of LEN on pregnancy outcomes using a pregnancy registry. • Consider potential drug interactions

Certainty of evidence[1] **What is the overall certainty of the evidence of effects (across all critical outcomes)?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Very low ○ Low ○ **Moderate** ○ High ○ No included studies	The complete evidence profile and GRADE certainty of evidence (CoE) per outcome have been included in the tables above.	
Values **Is there important uncertainty about how people with conditions, caregivers, healthcare providers, or decision-makers value the main outcomes?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Important uncertainty ○ Possibly important uncertainty ○ **Probably no important uncertainty** ○ No important uncertainty	Do we expect that patients, healthcare providers, or people making decisions would place different value on the importance of the main outcomes? e.g. Clinicians may value an outcome differently from patients. Both users and providers perceived the efficacy of the intervention (Fonner *et al*., 2025a). Programme inputs: Lessons from Pilot Sites Offering Injectable Pre-Exposure Prophylaxis Overview - patients took up both CAB-LA and oral PrEP, and there was poor uptake of the dapivirine ring.	The ERC judged that there was no reason to suspect varying values among the affected population/healthcare providers/or others from those identified in the evidence.

[18] **CERTAINTY OF EVIDENCE**
High certainty: confident in the evidence / We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: mostly confident, but further research may change the effect / 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: some confidence, further research likely to change the effect / Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: findings indicate uncertain effect / We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect

Balance of effects **Does the balance of effects favour the medicine being considered an essential medicine? Do the desirable effects outweigh the undesirable effects?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ **Yes** ○ Probably Yes ○ Probably No ○ No ○ Varies (if so, why?) ○ Don't know	*Desirable effects judgment:* Large effect *Undesirable effects judgment:* Varies from trivial, small, unimportant or no effect for the following outcomes: SAEs, AEs, all-cause mortality, to a moderate effect for injection-site reactions	The ERC judged that the balance of health effects favours/probably favours the intervention (LEN injectable) because of large benefits, small to moderate harms, and moderate certainty of the evidence.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations (by committee)
○ **Large costs** ○ Moderate costs ○ Negligible costs or savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Research from an economic evaluation and budget impact analysis conducted by Health Economics and Epidemiology Research Office (HE²RO) showed that under a conservative scenario, compared to oral PrEP scale up, we can expect between 590,000 and 1.35 million initiates per year, requiring between 0.61-1.44 million doses per year. At a threshold price of R496 per 1.5ml injection (R992 per 6-monthly dose) and R321 per 300mg loading dose tablet, this would cost between R1.74 billion and R4.02 billion annually, including the cost of the drugs and service provision. This would result in a 5-11% increase in the annual HIV programme budget over the next 5 years, after accounting for the effect of reduced HIV infections and ART needs. Under an optimistic scenario with higher uptake and longer duration on the product, we can expect between 910,000 and 2.07 million initiates per year, requiring between 1.90 and 4.37 million doses per year. At a threshold price of R342 per 1.5ml injection (R684 per 6-monthly dose) and R221 per 300mg loading dose tablet, this would cost between R1.98 billion and R4.52 billion annually, including the cost of the drugs and service provision. This would result in a 6-13% increase in the annual HIV programme budget over the next 5 years, after accounting for the effect of reduced HIV infections and ART needs (*see the LEN economic analysis report attached*). **Price of medicines/treatment course** **Medicine** | **Tender price (ZAR)*** | **SEP (ZAR)*** Lenacapavir injection | *Not yet available* | *Not yet available* Lenacapavir tablets **Price of comparator/standard of care course (PHC Chp 11 HIV & AIDs 2020-4 Edition)** **Medicine** | **Tender price (ZAR)*** | **SEP (ZAR)*** TDF/FTC Fixed dose combination of tenofovir disoproxil fumarate 300mg and emtricitabine 200 mg:	*Consideration 1:* It is important to look at both LEN *vs. the* standard of care AND LEN *vs*. those not on PrEP at all. *Consideration 2:* Training, health system-related implementation costs, and adherence counselling that form part of the costing. *Consideration 3*: The difference in uptake between men and women. *Consideration 4*: Oral PrEP use affects future ART drug regimen options. The ERC judged that the costs (budget impact) for LEN among the target population groups are higher due to a possible large number of users. However, LEN will have a significant impact in reducing HIV infections by between 20%-32% over baseline, compared to oral TDF/FTC, which, even at scaled-up levels, will only reduce HIV infections by 5%. This is a higher impact than any other HIV prevention intervention. For the purpose of decision-making, the ERC judged that while cost remains an important consideration for the budget, it was emphasised that cost should not be the primary barrier to rollout, given LEN's substantial impact. The threshold price provides a useful benchmark, but it should not be a deterrent to acquiring LEN if it cannot be obtained at this price. They judged the cost of oral PrEP in the same population to be less expensive; however, it is a less effective intervention, with existing rollout demonstrating that most users do not maintain

Tenemine® (28 tabs)	R56.53	
Duotemtric® (28 tabs)	R73.18	
Hetemcit® (28 tabs)	R59.37	
Prepetam® (30 tabs)		R250.47
Didivir® (30 tabs)		R263.65
Emtevir® (30 tabs)		R194.99
Tenobine® (30 tabs)		R604.52

* *MHPL 1 August 2025 and SEP database 24 June 2025*

Price of therapeutic alternative medicines/ treatment course, if applicable:
No therapeutic equivalent alternatives are available at the time of review.

persistent, effective use over time and often discontinue before their next scheduled visit.

Equity **What would be the impact on health equity?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ Reduced ○ Probably reduced ○ Probably no impact ○ **Probably increased** ○ Increased ○ Varies ○ Don't know	The population targeted for PrEP included those at high risk of contracting HIV, specifically including vulnerable populations such as sex workers, people who inject drugs, MSM and gender-diverse individuals, and adolescent girls and young women (AGYW). A **PROGRESS-Plus** assessment was not conducted, i.e. **P**lace of residence, **R**ace/ethnicity/culture/language, **O**ccupation, **G**ender/sex, **R**eligion, **E**ducation, **S**ocioeconomic status, **S**ocial capital, personal characteristics associated with discrimination (age, disability), features of relationships, and time-dependent relationships (instances where a person may be temporarily disadvantaged). However, in a recent WHO guideline, the guideline development group (GDG) concluded that introducing LEN “alongside existing HIV prevention options would likely increase equity”. Six-monthly injections may expand prevention options for individuals who struggle with daily pill adherence, potentially improving equity in HIV services; it may help reduce cost and time barriers that often arise from requiring more frequent clinic visits; this reduced schedule could particularly benefit individuals with caregiving and/or employment responsibilities. The long dosing interval can also ease integration of LEN for PrEP into other preventive services, such as contraception, antenatal care and postnatal care, as LEN injections will be required only every six months. Centralised delivery could inadvertently limit access if not paired with community-based or decentralised services; this highlights the need for inclusive implementation strategies (WHO, 2025b). Programme inputs: In the absence of a single exit price, concerns for beneficiaries of medical schemes and private sector pricing differences.	The ERC considered the following aspects that affect equity [adherence, dosing interval, structural barriers]. The ERC judged that there was no reason to suspect differences in the impact on health equity from that presented in the evidence.

Acceptability **Is the option acceptable to recommend as an essential medicine to key stakeholders?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies (if so, why?) ○ Don't know	A systematic review of values and preferences (Fonner *et al*., 2025a) found that, although there is some variation among individuals and populations, injectable PrEP is highly acceptable. The review showed a "clear preference for injectable PrEP options requiring infrequent dosing (for example, six months or more), such as LEN, due to the reduced burden on users." Among providers of injectable PrEP, implementation was perceived as appropriate, feasible and acceptable, although some identified internal and external barriers to implementation. The review also recommended that future studies further explore the end-user preferences of LEN and other PrEP options. Indirect evidence from other injectable PrEP (CAB-LA) studies done locally showed that: • *Demand and uptake*: The introduction of CAB-LA was well received across implementation projects. When offered alongside other prevention options, CAB-LA emerged as the preferred choice for most clients. The availability of injectable options also successfully attracted more men to PrEP services, with one project reporting 65% male enrolment for CAB-LA compared to 39% for oral PrEP programmes. PrEP uptake was notably higher at sites where all three PrEP options (oral PrEP, Ring, and CAB-LA) were available compared to sites with only one or two options. • *Client preferences and experience:* Clients favoured CAB-LA primarily due to convenience and ease of use compared to oral medication, reduced pill burden, and simplified adherence requirements. However, oral PrEP and the dapivirine ring remain important options for specific populations, including individuals with diverse needs and people comfortable with daily pill-taking routines. CAB-LA uptake was high, especially amongst age groups 20-34 and females.	The ERC considered the following aspects to affect acceptability: low burden, fit with lifestyle, perceived efficacy, six-monthly dosing, reduced stigma, and implementation considerations (see below). LEN was efficacious, safe, and well-tolerated in pregnant and lactating people (Bekker *et al*., 2025). The ERC considered the following key stakeholders: users and providers. The ERC judged that there was no reason to suspect differences in acceptability from that presented in the evidence.

Feasibility **Is the option feasible to implement?**		
Judgement	**Research evidence**	**Additional considerations (by committee)**
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies (if so, why?) ○ Don't know	In a recent WHO guideline, the guideline development group (GDG) concluded that introducing LEN as an additional prevention option in HIV programmes would likely be feasible. The rationale for this judgment was based on the fact that clinical trial sites across many countries successfully delivered LEN, suggesting that, with adequate planning, integrating this injectable PrEP into existing services may be achievable. Indirect evidence from CAB-LA implementation supports the feasibility of implementing long-acting injectable PrEP, though real-world data specific to LEN are still needed (WHO, 2025b). No therapeutic equivalents are available currently. Programme inputs: injectables such as CAB-LA are being implemented currently, and LEN can be integrated into existing services, including sexual and reproductive health services. *Healthcare provider training* • Continuous training and mentorship support are essential due to high staff turnover • Specific attention is needed for injection technique and scheduling • Administration of ice or a cold compress before and after the injection • Regular reinforcement of protocols for missed or off-schedule injections • Awareness about the availability of new PrEP methods among healthcare providers • Training of health care providers should cover all available PrEP and HIV prevention products *Clinical considerations* • Injectable PrEP is well-tolerated - injection site reactions are the primary complaint • Most injection site reactions resolve within approximately 4 days • A few cases of missed HIV infections at initiation when using rapid testing • Return rates for second injections exceed 70% *Feasibility for healthcare system*: Implementation of CAB-LA services was reported to be feasible across the different project settings and service delivery models. These included	Positive feasibility considerations: • Only two visits/year needed • Could interface with other services, e.g., family planning or collection of chronic medication • With training, it could be nurse-initiated • Likely to be easier to implement than oral PrEP • Already endorsed by the NDoH[1] Negative feasibility considerations: • High cost • Not yet registered with SAHPRA • Need surveillance for resistance • Pharmacovigilance monitoring The ERC considered the following aspects to affect feasibility [integration into existing services, need for real-world data]. The ERC judged that there was no reason to suspect differences in feasibility from that presented in the evidence. [1]Debate on the Health Budget vote – 18; Dr Aaron Motsoaledi, Minister of Health; National Assembly; 9 July 2025; Available from: *https://www.health.gov.za/wp-content/uploads/2025/07/Ministers-Health-Budget-Speech-9-July-2025.pdf*

	rural, peri-urban and urban settings, nurse-led models in fixed and mobile clinics, public health oral PrEP delivery sites, and community pharmacies. CAB-LA injections are practical in pubic PHC clinics and mobiles, with no major logistical challenges related to transportation or storage. *Overall, a high acceptability and confidence among healthcare providers, but all partners highlighted the need for HCPs to be well trained on the choice and the complexities of providing CAB-LA:* • Understanding the clinical aspects of injections can be challenging • Training and retraining of health care providers are important – turnover is high, critical to have skills and buy-in • Multiple injections – CAB-LA, contraception, STI treatment • Re-initiations and how to handle missed visits require more HCP support and training • Job aids were beneficial *Monitoring PrEP use, effectiveness, and adherence across all methods requires more time to draw reliable conclusions.* *Additional support and guidance required for:* • Injection pain and injection site reactions are needed • Returning on time for follow-up visits • Simplified choice counselling • Transitioning to other PrEP and HIV prevention methods • Bridging doses and injection scheduling for mobile populations • Stopping CAB-LA and monitoring HIV status during the tail *Strengthen guidance on HIV testing* • Review testing requirements and frequency of testing, especially for long-acting injectables • More evidence is required for the use of self-screening tests	
**Where time allows, we encourage reviewers to look for evidence from systematic reviews of qualitative studies (QES) when considering the equity, acceptability and feasibility domains*		

SUMMARY OF JUDGEMENTS

	Judgement						
Desirable effects	Trivial	Small	Moderate	**LARGE**		Varies	Don't know
Undesirable effects	Large	**MODERATE**	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	**MODERATE**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**PROBABLY NO IMPORTANT UNCERTAINTY OR VARIABILITY**	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**FAVOURS THE INTERVENTION**	Varies	Don't know
Resources required	**LARGE COSTS**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Equity	Reduced	Probably reduced	Probably no impact	**PROBABLY INCREASED**	Increased	Varies	Don't know
Acceptability	No	Probably no	**PROBABLY YES**	Yes		Varies	Don't know
Feasibility	No	Probably no	**PROBABLY YES**	Yes		Varies	Don't know

Steps of developing a recommendation:

1. Committee agrees on direction of recommendation (for/against)
2. Committee agrees on strength of recommendation (strong/conditional)

Signalling questions for the chair/methodologists (above) are done via committee consensus.

TYPE OF RECOMMENDATION[2]

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	○	✓

CONCLUSIONS

Recommendation

For HIV prevention in susceptible individuals, the ERC recommends the use of long-acting injectable LEN for use as pre-exposure prophylaxis (PrEP) (*strong recommendation, moderate certainty of the evidence*).

Good practice recommendations: Ongoing pharmacovigilance monitoring, including pregnancy outcomes. Ongoing use of barrier protection, such as condoms, to prevent other STIs.

Justification

The ERC judged that the balance of desirable and undesirable consequences favours the use of long-acting injectable LEN over oral F/TDF and oral F/TAF in any HIV-negative person who is at risk of HIV acquisition through sexual contact or exposure to blood, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals, AGYW and people who inject drugs. Specifically, the ERC felt that the benefits outweighed the risks and that the intervention was considered feasible and acceptable.

Restrictions

N/A

Implementation considerations

These were considered based on indirect evidence from other injectable PrEP (CAB-LA) local studies. Injectables such as CAB-LA are being implemented currently, and LEN can be integrated into existing HIV prevention and care services, including sexual and reproductive health services. Positive feasibility considerations include reduced clinic visits due to the six-monthly dosing interval and reduced stigma. However, it requires healthcare provider training on injection technique, and could be nurse-initiated. Negative feasibility considerations include the high cost, the fact that LEN is not yet registered with SAHPRA, the need for surveillance for the emergence of resistance, and pharmacovigilance monitoring.

Monitoring and evaluation

Based on guidance in the current literature and/or collective experience, the NEMLC judged that monitoring PrEP use, effectiveness, safety and adherence across all methods requires more time to draw reliable conclusions.

Research priorities

The NEMLC proposes that further research is needed on the long-term efficacy and safety of long-acting injectable LEN, including monitoring of adherence, especially as clients' HIV risk perceptions may change over time. There is a need for an expansion of current HIV-1 drug-resistance surveillance programmes to monitor the emergence of LEN-associated resistance mutations occurring in populations in which LEN PrEP is administered. Alternative loading dose regimens and the optimal transition approaches between the different PrEP options need to be explored.

---

[2] STRENGTH OF THE RECOMMENDATION:

Strong recommendation

Strong recommendations are those recommendations for which the guideline development group is confident that the desirable consequences of implementing the recommendation outweigh the undesirable consequences. Strong recommendations can be adopted as practice (most patients should receive the recommended medicine) or policy (adapted as policy) in most situations. For patients, most people would want the recommended medicine and only a small proportion would not.

Conditional recommendation

The guideline development group is less certain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are very small. Therefore, discussion (or substantial debate) may be required before a conditional recommendation can be adopted as practice or policy. For patients, the majority if people would want the recommended medicine, but many would not.

TABLE OF CONTENTS

REPORT

BACKGROUND

Through the implementation of its National Strategic Plan for HIV, TB, and STIs, South Africa (SA) has taken positive strides in managing its HIV disease burden. As of November 2022, the SA HIV program supports over 5.7 million people on treatment, with 92% of those tested reported to be virally suppressed (National Department of Health, 2023a). Furthermore, the number of people living with HIV decreased from 14.0% in 2017 to 12.7% in 2022 (Human Sciences Research Council, 2023). The healthcare and economic burden associated with maintaining such a program remains a challenge, especially since the recent United States Agency for International Development (USAID) funding cuts, where the repercussions towards the 95-95-95 targets are yet to be realised. Strategies aimed at disrupting viral transmission, such as pre-exposure prophylaxis (PrEP), remain an important pillar in managing the HIV epidemic.

Routine access to HIV PrEP in the public sector is currently limited to an oral fixed-dose combination consisting of tenofovir and emtricitabine (F/TDF). Sub-optimal adherence and poor programmatic rollout of oral PrEP have been reported as significant barriers to benefit realisation (Pike, Rousseau and Bekker, 2023). A dapivirine-eluting vaginal ring was reviewed by the National Essential Medicines List Committee (NEMLC) in June 2022 but was not supported for inclusion on the essential medicines list (EML) due to both cost and lack of comparative evidence to the oral standard of care (National Department of Health, 2022).

Cabotegravir (CAB), an injectable long-acting formulation dosed every eight weeks, was registered by the South African Health Products and Regulatory Authority (SAHPRA) for PrEP in 2022 (South African Health Products Regulatory Authority, 2022) and is anticipated to be a breakthrough with regard to improved patient adherence. However, at the time of writing, CAB is not yet commercially available in South Africa. CAB was reviewed by NEMLC in May 2022 (National Department of Health, 2024), but in the absence of a confirmed price, the Committee has been unable to finalise its recommendation for use in the public sector. Furthermore, NEMLC raised several implementation and sustainability concerns during its deliberations on a CAB stock donation program (NEMLC, 2024). Several local qualitative studies are underway, which may provide further insights into the feasibility and acceptability of injectable PrEP in our healthcare setting.

Lenacapavir (LEN), another injectable formulation with a longer duration of action than CAB, is currently being investigated for HIV PrEP. LEN is described as a first-in-class capsid inhibitor that disrupts viral replication through protein binding in the capsid, resulting in multiple inhibitory effects. LEN's slow release from the injection site allows for a six-monthly subcutaneous dosing regimen (Di Perri, 2023), which is initiated with an oral loading dose of two 300mg LEN tablets on days one and two. Interim findings from ongoing studies are being lauded as a significant breakthrough in the fight against HIV transmission (Sax, 2024). LEN has received approval from the U.S. Federal Drug Administration (FDA) for use as PrEP (WHO, 2025a). While local regulatory approval by SAHPRA is still in progress, any opportunity that has the potential to positively alter the trajectory of the HIV epidemic in SA warrants consideration.

Interim results from the two RCTs (PURPOSE 1 and 2 trials) (Bekker *et al*., 2024; Kelley *et al*., 2025) that have been published, compare the efficacy of LEN and oral PrEP alternatives against the 'background HIV incidence rate' *(which involved baseline screening against HIV with a recency test being performed on positive samples to determine recent HIV infection*) - the demonstrated efficacy of oral PrEP would deem placebo comparators unethical. Both trials were stopped early; an external independent data monitoring committee reviewed the interim efficacy analysis and concluded that the prespecified efficacy criteria for stopping the randomised, blinded phase of the trial had been met (Bekker *et al*., 2024; Kelley *et al*., 2025). This review aims to summarise the evidence on the efficacy and safety of long-acting injectable LEN compared to F/TDF (standard of care), as well as to other PrEP, including oral tenofovir alafenamide plus emtricitabine (F/TAF), injectable CAB and placebo/no prophylaxis for HIV PrEP.

PURPOSE/OBJECTIVE, i.e., PICO question:

Population Subgroups	Any HIV-negative person who is at risk of HIV acquisition through sexual contact or exposure to blood, including men who have sex with men, serodiscordant heterosexual couples, heterosexuals and people who inject drugs.
Intervention(s)	Long-acting injectable LEN (dosed as LEN SC injection either 6 or 12 monthly) with a recognised PrEP (oral or other) lead-in.
Comparator(s)*	1. Standard of care in SA STGs: Oral tenofovir disoproxil fumarate plus emtricitabine 2. Non-EML: Oral tenofovir alafenamide plus emtricitabine (F/TAF) 3. Non-EML: Injectable CAB-LA (long-acting injectable cabotegravir) (first injection followed by another a month later, then every 2 months) 4. Placebo/no prophylaxis
Outcome(s)	Efficacy: Incidence of HIV infection (or relative risk of HIV infection) Safety: Serious adverse events (SAEs), adverse events (AEs), adverse drug reactions, mortality Other possible secondary outcomes: Retention Adherence to PrEP Incidence of other sexually transmitted infections (STIs) and behaviour change associated with PrEP use Viral mutations among those who contract HIV
Study types	RCTs

**The current standard of care in SA is oral PrEP. The dapivirine ring was considered in the last review cycle. It may have a role in certain settings where females may need a discreet form of PrEP. It was considered, but not included in the PICO (https://www.health.gov.za/wp-content/uploads/2024/03/DapivirineRingForPrEP_PHC-Review_9June2022_v5.pdf). We also did not find any trials that looked at this comparator.*

METHODS

We used a prespecified protocol (PROSPERO registration: 1080791) that follows the Cochrane methodology (Garritty *et al*., 2021) and the National Department of Health Technology Assessment Methods Guide for rapid systematic reviews (National Department of Health, 2023b).

Study design

We used a tiered approach, first considering high-quality, relevant, and up-to-date clinical practice guidelines, followed by systematic reviews (SRs) of randomised controlled trials (RCTs), and then RCTs. Should none of these be available, observational study designs were sought as needed (Cochrane Collaboration, 2020). We conducted a systematic review of RCTs.

1. **Data Sources**
   We searched the PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases for randomised controlled trials on 28 May 2025. We searched for ongoing studies in trial registries like clinicaltrials.gov and the WHO's International Clinical Trials Registry Platform (ICTRP).

2. **Search Strategy**
   NG developed and conducted the search strategy without language or publication restrictions. An experienced information specialist (JO) was consulted for guidance on refinement of the PubMed search strategy. Search terms used are found in Appendix 1: Search Strategies.

3. **Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis**
   The eligibility criteria for the review were developed *a priori* and comprised the components as indicated above in the PICO elements. Screening of titles and abstracts, full-text screening, and selection of studies were done independently and in duplicate by two reviewers (SE, NG). We used the Covidence software (Covidence, 2025) for screening. We summarised the selection process graphically in a PRISMA flow diagram (Figure 1). Data extraction and appraisal were conducted independently and in

duplicate (SE, NG), and disagreements were resolved through discussion. The main characteristics of the included studies and study outcomes are shown in Appendix 2.
We used RevMan (Review Manager, 2020) to perform data analysis. A meta-analysis was conducted using a random-effects model. We reported risk ratios for dichotomous data with 95% confidence intervals (CI). A narrative synthesis was presented for any outcomes where insufficient data were found for a meta-analysis.

We reviewed and extracted the underlying evidence from the relevant trials for the effectiveness Grading of Recommendations Assessment, Development and Evaluation (GRADE) Evidence to Decision (EtD) criteria (benefit, harms, and balance of effects) (SE, NG). Economic evaluations were conducted (by the Health Economics and Epidemiology Research Office [HE²RO]): 1) rapid review of economic evaluations, 2) pricing analysis, and 3) budget impact analysis, and are reported in supplementary reports. We did not plan a qualitative or equity assessment for this review. However, we extracted variables for qualitative criteria (values, equity, feasibility, and acceptability) from the eligible studies and similar studies identified during the search process.

4. Assessment of methodological quality

We appraised the RCTs using the Cochrane risk of bias tool (RoB 2.0) (Higgins, 2023; Sterne, 2019), assessing the risk of bias in duplicate for primary outcomes in the included studies and resolving disagreements through discussion (SE, NG) or by adjudication. The standard Cochrane risk of bias assessment tool 2.0 (RoB 2), considers the following domains: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias. For each domain and overall risk of bias judgment, we summarised the risk of bias levels as 'low risk of bias', 'some concerns of bias', or 'high risk of bias' (Figure 2).

5. GRADE assessment

The GRADE framework was used to assess the overall confidence of the evidence, considering various factors that may decrease our confidence in the trial findings, including risk of bias, inconsistency, imprecision, publication bias, and indirectness (Guyatt *et al*., 2011). GRADE assessments were conducted using GRADEPro software by SE, NG, TK and MM. Pooled effects across outcomes and certainty of evidence are reported in the GRADE Evidence Profile and SoF tables.

RESULTS

1. Search results

An electronic search of the databases, with no language or publication date restrictions, retrieved 178 records, of which 168 were RCTs. Following deduplication and identification of ineligible records by automation tools, 88 records were screened, of which five were identified for full-text screening. See Figure 1 for the PRISMA flow diagram. None of the studies assessed for eligibility were excluded. Appendix 3 presents the results of the search for planned/ongoing trials.

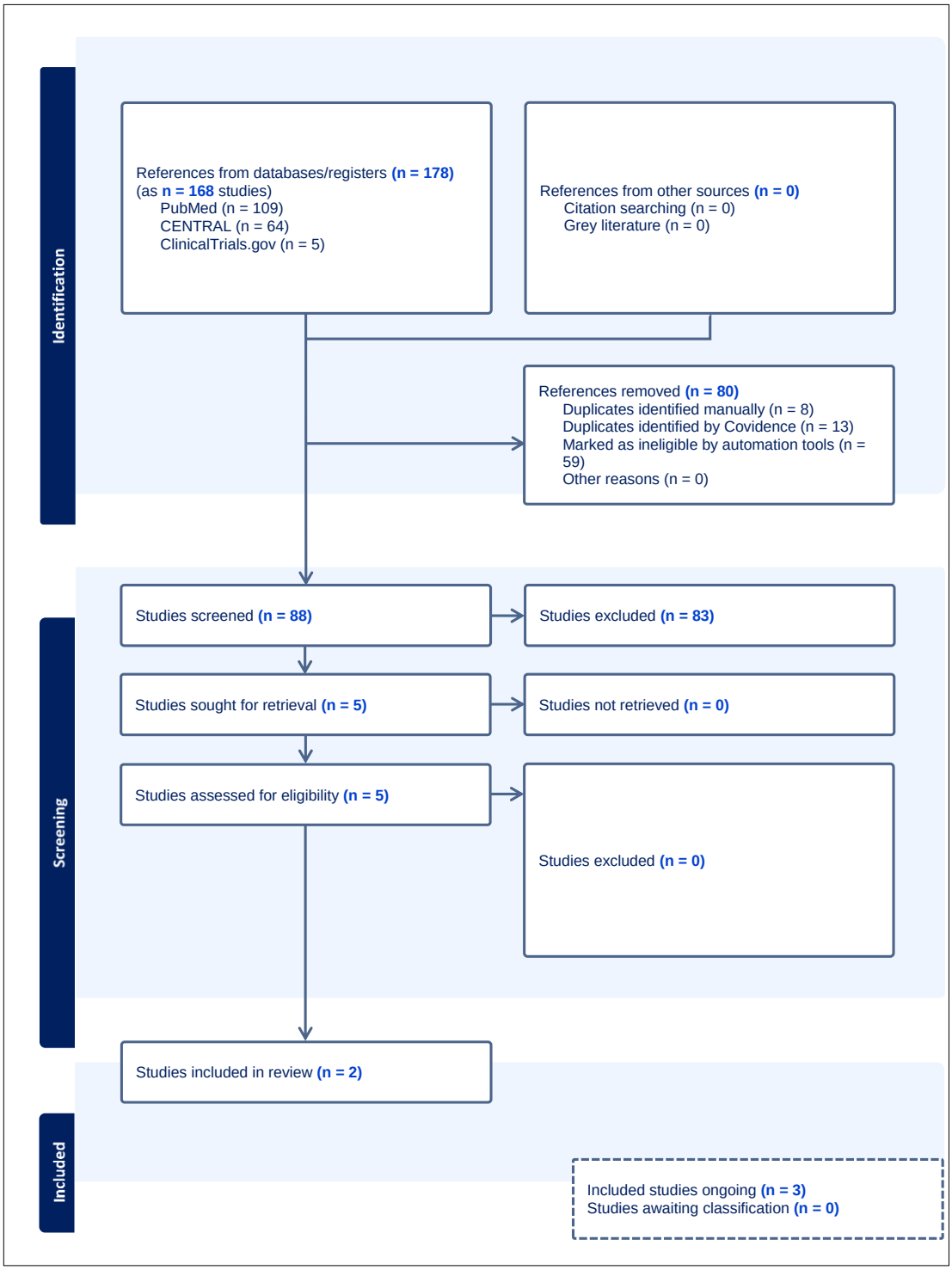


Figure 1: PRISMA flow diagram for review

2. Description of included studies (clinical practice guidelines, systematic reviews and RCTs)

We included two RCTs: both were multicentre trials (Bekker *et al*., 2024; Kelley *et al*., 2025) conducted in South Africa and Uganda (Bekker *et al*., 2024) and in the United States of America (USA), Brazil, Thailand, South Africa, Peru and Argentina (Kelley *et al*., 2025). One trial investigated the safety and efficacy of twice-yearly injectable LEN compared to daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF) (Bekker *et al*., 2024), PURPOSE 1. The second trial, PURPOSE 2 (Kelley *et al*., 2025), investigated the safety and efficacy of twice-yearly injectable LEN compared to daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The population sampled in the trials were adolescent girls and young women (16 to 25 years

of age) (Bekker *et al*., 2024) and men and gender diverse persons aged at least 16 years and older (Kelley *et al*., 2025). The follow-up duration was 52 weeks in both trials. The analytic sample sizes ranged from n = 1,073 to 2,148. The ages ranged from 16 to 26 years (Bekker *et al*., 2024) and 17 to 74 years (Kelley *et al*., 2025).

Outcomes assessed in both included studies were: i) incident HIV infection, ii) serious adverse events (SAEs), iii) adverse events (AEs), iv) adverse drug reactions (ADRs), v) mortality, vi) clinical laboratory abnormalities, vii) retention (at 26 and 52 weeks), and viii) adherence. Appendix 2 provides a detailed description of these studies. A summary of available qualitative literature is summarised in Appendix 4.

3. Methodological quality of included studies

Risk of Bias Assessment of RCTs

For the outcomes of incident HIV infection, SAEs, AEs, ADRs, mortality and clinical laboratory abnormalities, both trials (Bekker *et al*., 2024; Kelley *et al*., 2025) were judged as having a low risk of bias. For the retention outcomes, both trials (Bekker, 2024; Kelley, 2025) were assessed as having 'some concerns' in Domain 3 (Missing outcomes) due to insufficient information on how the expected numbers at follow-up were calculated (Figure 2).

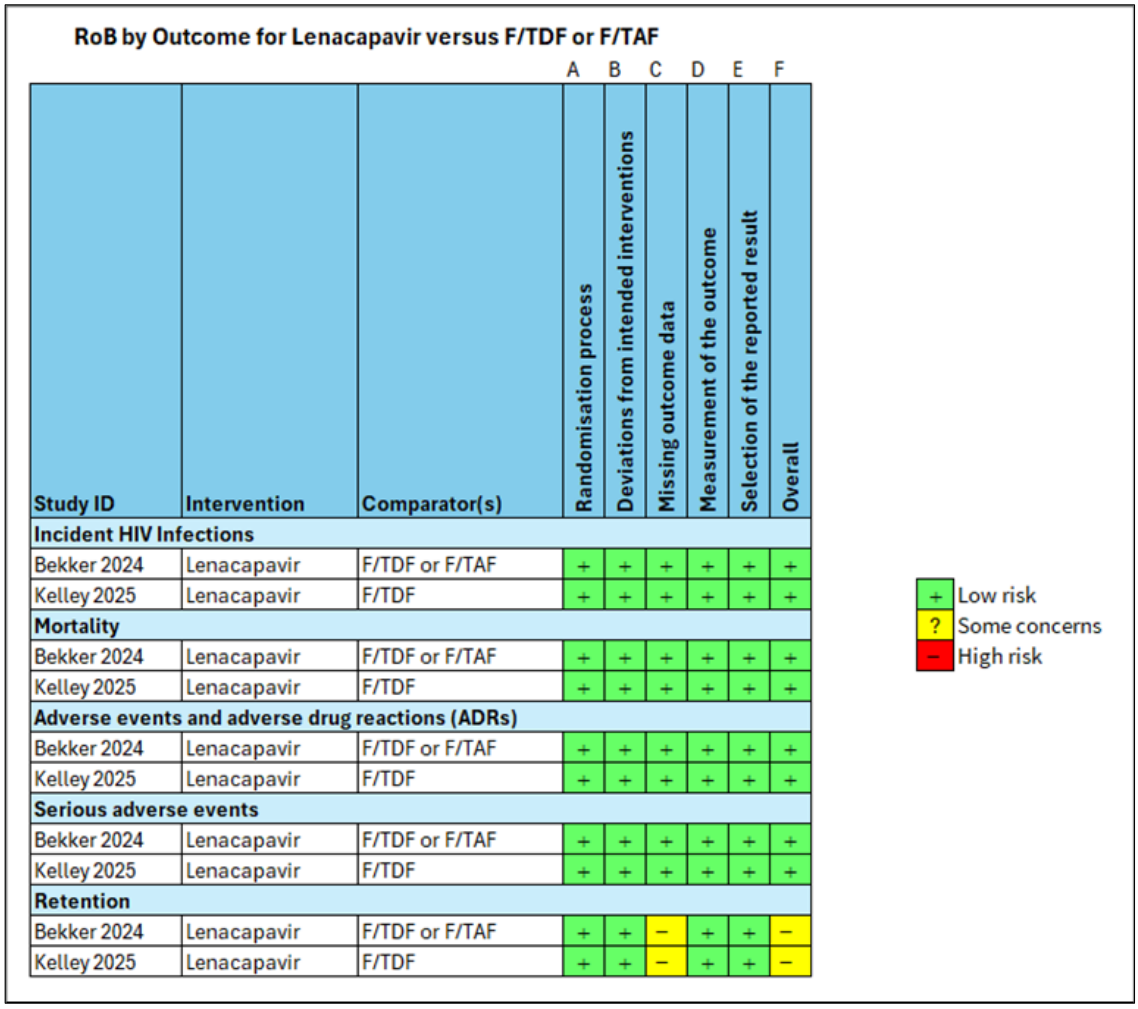


Figure 2: Consolidated Risk of Bias 2.0 by outcome for LEN *vs* F/TDF or F/TAF

EFFECTS OF THE INTERVENTION

The GRADE Evidence Profile in Tables 1 and 3 and the Summary of Findings in Tables 2 and 4 summarise the effects of the intervention for each of the following outcomes. Appendix 5 summarises the SAEs, AEs, and ADRs as reported by the studies. In both trials, adverse events (including injection-site reactions and laboratory abnormalities) were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (US National Institute of Allergy and Infectious Diseases, Division of AIDS, 2017); AEs were coded according to the Medical Dictionary for Regulatory Activities, version 27.0 (Medical Dictionary for Regulatory Activities, 2024).

Comparison	Number of included studies
Comparison 1: LEN *vs* F/TDF	Two trials
Comparison 2: LEN *vs* F/TAF	One trial
Comparison 3: LEN *vs* Cabotegravir	No included studies (none available)
Comparison 3: LEN *vs* Placebo/no prophylaxis	No included studies (none available)

Comparison 1	Number of included studies
LEN injectable versus F/TDF	Two

1. New HIV infections

LEN compared to F/TDF results in a large reduction in new HIV infections (52 weeks), Risk Ratio (RR) 0.06 (95% confidence interval (CI) 0.01 to 0.42), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 11 fewer cases per 1,000 (ranging from 11 fewer to 7 fewer). Two studies (Bekker, 2024 and Kelley, 2025) had available event/total group data to evaluate this outcome. Figure 3 shows the forest plot for this comparison.

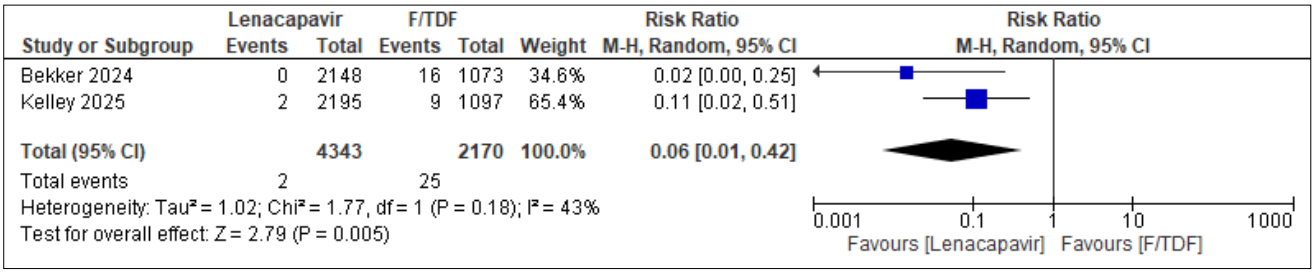


Figure 3: Forest plot of LEN injectable vs. F/TDF; New HIV infections

2. Serious adverse events (SAEs)

LEN compared to F/TDF results in little to no difference in SAEs (52 weeks), RR 0.83 (95% CI 0.63 to 1.10), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 6 fewer cases per 1,000 (ranging from 13 fewer to 4 more). Two studies (Bekker *et al*., 2024 and Kelley *et al*., 2025) had available event/total group data to evaluate this outcome. Figure 4 shows the forest plot for this comparison.

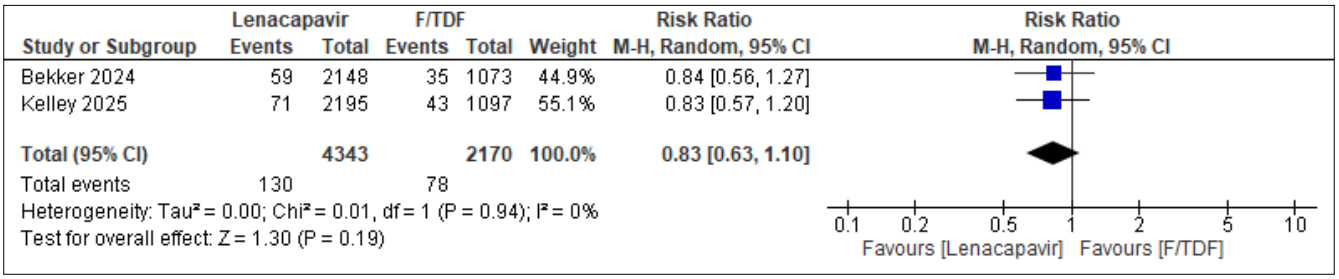


Figure 4: Forest plot of LEN injectable vs. F/TDF; SAEs

3. Adverse events (AEs)

LEN compared to F/TDF results in little to no difference in AEs (52 weeks), RR 0.99 (95% CI 0.96 to 1.02), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 8 fewer cases per 1,000 (ranging from 30 fewer to 15 more). Two studies (Bekker *et al*., 2024 and Kelley *et al*., 2025) had available event/total group data to evaluate this outcome. Figure 5 shows the forest plot for this comparison.

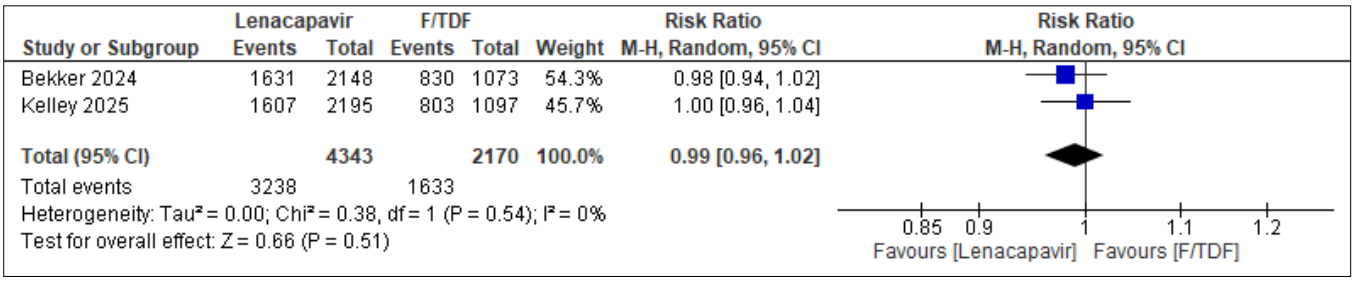


Figure 5: Forest plot of LEN injectable vs. F/TDF; AEs

4. Adverse drug reactions (ADRs): injection-site reactions

These were injection-site reactions as reported in the studies. LEN compared to F/TDF likely increases injection-site reactions (52 weeks), RR 1.56 (95% CI 0.89 to 2.74), two studies, n = 6,513, moderate certainty evidence. That is an absolute effect of 289 more cases per 1,000 (ranging from 57 fewer to 897 more). Two studies (Bekker *et al*., 2024 and Kelley *et al*., 2025) had available event/total group data to evaluate this outcome. Figure 6 shows the forest plot for this comparison.

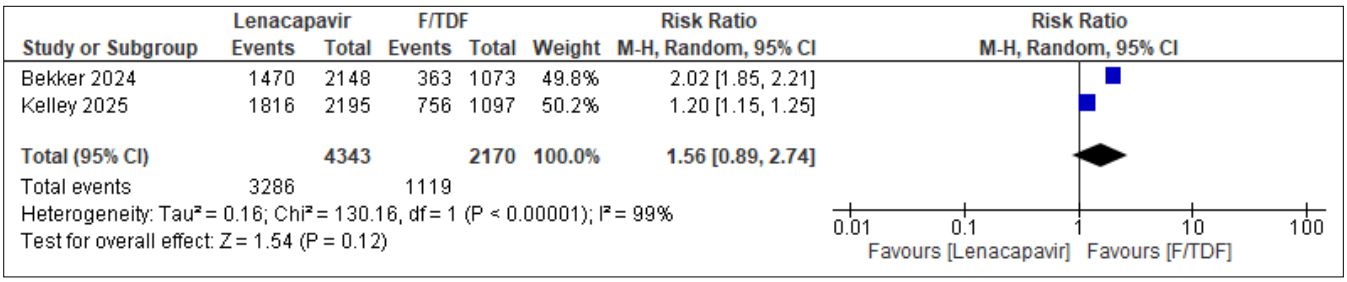


Figure 6: Forest plot of LEN injectable vs. F/TDF; ADRs

5. All-cause mortality

LEN compared to F/TDF results in little to no difference in all-cause mortality (52 weeks), RR 1.00 (95% CI 0.18 to 5.45), two studies, n = 6,513, high certainty evidence. That is an absolute effect of 0 fewer cases per 1,000 (ranging from 1 fewer to 4 more). None of the deaths were considered by the investigator to be related to a trial drug or comparator. Two studies (Bekker *et al*., 2024 and Kelley *et al*., 2025) had available event/total group data to evaluate this outcome. Figure 7 shows the forest plot for this comparison.

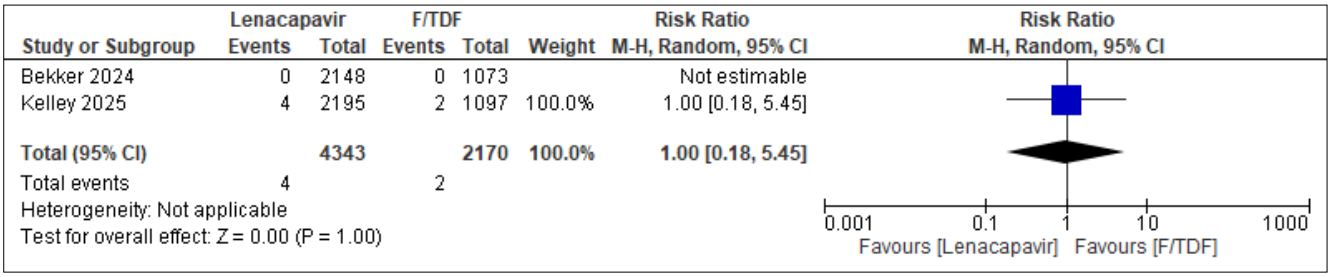


Figure 7: Forest plot of LEN injectable vs. F/TDF; Mortality

6. Retention at weeks 26 and 52

Week 26: Retention was similar across the trial groups: in the LEN group, 88.0% (3,822/4,343) and 88.2% (1,915/2,170) in the F/TDF group.

Week 52: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group. Thus, LEN compared to F/TDF results in little to no difference in retention at weeks 26 and 52, high certainty evidence.

Table 1: Comparison 1 GRADE evidence profile

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEN injectable	F/TDF	Relative (95% CI)	Absolute (95% CI)	
New HIV infection											
2	randomised trials	not serious	not serious	not serious[a]	not serious	none	2/4343 (0.0%)	25/2170 (1.2%)	**RR 0.06** (0.01 to 0.42)	**11 fewer per 1,000** (from 11 fewer to 7 fewer)	⊕⊕⊕⊕ High[a]
Serious adverse events											
2	randomised trials	not serious	not serious	not serious	not serious[b]	none	130/4343 (3.0%)	78/2170 (3.6%)	**RR 0.83** (0.63 to 1.10)	**6 fewer per 1,000** (from 13 fewer to 4 more)	⊕⊕⊕⊕ High[b]
Adverse events											
2	randomised trials	not serious	not serious	not serious	not serious[b]	none	3238/4343 (74.6%)	1633/2170 (75.3%)	**RR 0.99** (0.96 to 1.02)	**8 fewer per 1,000** (from 30 fewer to 15 more)	⊕⊕⊕⊕ High[b]
Adverse drug reactions: injection-site reactions											
2	randomised trials	not serious	not serious[c]	not serious	serious[d]	none	3286/4343 (75.7%)	1119/2170 (51.6%)	**RR 1.56** (0.89 to 2.74)	**289 more per 1,000** (from 57 fewer to 897 more)	⊕⊕⊕◯ Moderate[c,d]
All-cause mortality											
2	randomised trials	not serious	not serious	not serious	not serious[e]	none	4/4343 (0.1%)	2/2170 (0.1%)	**RR 1.00** (0.18 to 5.45)	**0 fewer per 1,000** (from 1 fewer to 4 more)	⊕⊕⊕⊕ High[e]
Retention at weeks 26 and 52											
2	randomised trials	not serious[f]	not serious	not serious	not serious	none	*Week 26*: Retention was similar across the trial groups: in the LEN group, 88.0% (3,822/4,343) and 88.2% (1,915/2,170) in the F/TDF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group.				⊕⊕⊕⊕ High[f]

CI: confidence interval; **RR:** risk ratio

Explanations

a. Not downgraded for indirectness: Bekker, 2024; population was cisgender women and Kelley, 2025; population was men and gender-diverse persons
b. Not downgraded for imprecision: the absolute 95% CI ranges from a trivial reduction to a trivial increase
c. Not downgraded despite considerable heterogeneity, I^2=99% which may be explained by the different trial populations
d. Downgraded by one level for imprecision: wide absolute 95% confidence interval ranging from a trivial reduction to an important increase
e. Not downgraded for imprecision: Despite the low event rate, this is a rare event with a narrow absolute 95% CI, and we are confident that there is no effect between the intervention and the comparator
f. Not downgraded for risk of bias, even though we assessed Domain 3 as having some concerns of bias, due to the expected numbers per visit used as the denominator (no information was provided on how the expected LTFU rate was calculated)

Table 2: Comparison 1 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with F/TDF	Risk with LEN injectable			
New HIV infection	12 per 1,000	**1 per 1,000** (0 to 5)	**RR 0.06** (0.01 to 0.42)	6513 (2 RCTs)	⊕⊕⊕⊕ High[a]
Serious adverse events	36 per 1,000	**30 per 1,000** (23 to 40)	**RR 0.83** (0.63 to 1.10)	6513 (2 RCTs)	⊕⊕⊕⊕ High[b]
Adverse events	753 per 1,000	**745 per 1,000** (722 to 768)	**RR 0.99** (0.96 to 1.02)	6513 (2 RCTs)	⊕⊕⊕⊕ High[b]
Adverse drug reactions: injection-site reactions	516 per 1,000	**804 per 1,000** (459 to 1,000)	**RR 1.56** (0.89 to 2.74)	6513 (2 RCTs)	⊕⊕⊕◯ Moderate[c,d]
All-cause mortality	1 per 1,000	**1 per 1,000** (0 to 5)	**RR 1.00** (0.18 to 5.45)	6513 (2 RCTs)	⊕⊕⊕⊕ High[e]
Retention at weeks 26 and 52	*Week 26*: Retention was similar across the trial groups: in the LEN group, 88.0% (3,822/4,343) and 88.2% (1,915/2,170) in the F/TDF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 40.9% (1,778/4,343) and 40.5% (879/2,170) in the F/TDF group.			6513 (2 RCTs)	⊕⊕⊕⊕ High[f]

*__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.

Comparison 2	Number of included studies
LEN injectable versus F/TAF	One

1. New HIV infections

LEN compared to F/TAF results in a large reduction in new HIV infections (52 weeks), Risk Ratio (RR) 0.01 (95% CI 0.00 to 0.21), one study, n = 4,295, high certainty evidence. That is an absolute effect of 18 fewer cases per 1,000 (ranging from 18 fewer to 14 fewer). One study (Bekker *et al.*, 2024) had available event/total group data to evaluate this outcome. Figure 8 shows the forest plot for this comparison.

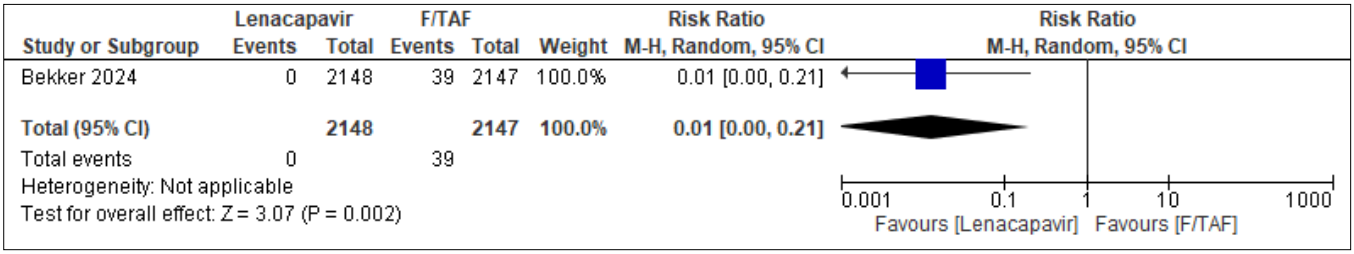


Figure 8: Forest plot of LEN injectable vs. F/TAF; New HIV infections

2. Serious adverse events (SAEs)

LEN compared to F/TAF results in little to no difference in SAEs at 52 weeks, RR 0.69 (95% CI 0.50 to 0.96), one study, n = 4,295, high certainty evidence. That is an absolute effect of 12 fewer cases per 1,000 (ranging from 20 fewer to 2 fewer). One study (Bekker *et al.*, 2024) had available event/total group data to evaluate this outcome. Figure 9 shows the forest plot for this comparison.

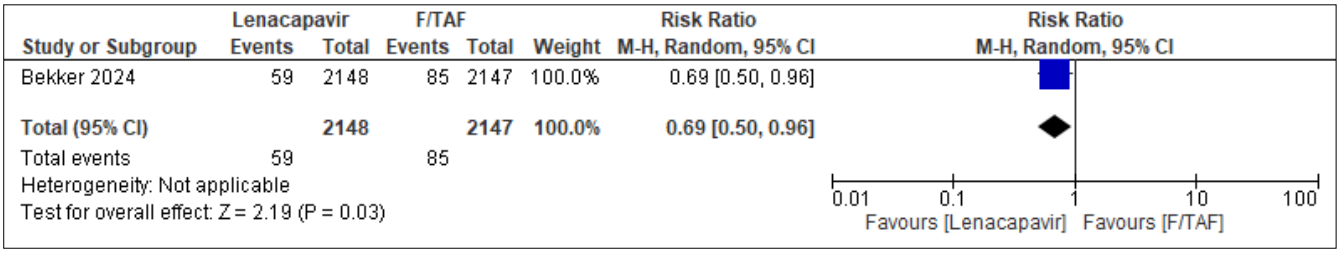


Figure 9: Forest plot of LEN injectable vs. F/TAF; SAEs

3. Adverse events (AEs)

LEN compared to F/TAF results in little to no difference in AEs (52 weeks), RR 0.98 (95% CI 0.95 to 1.01), one study, n = 4,295, high certainty evidence. That is an absolute effect of 16 fewer cases per 1,000 (ranging from 39 fewer to 8 more). One study (Bekker *et al.*, 2024) had available event/total group data to evaluate this outcome. Figure 10 shows the forest plot for this comparison.

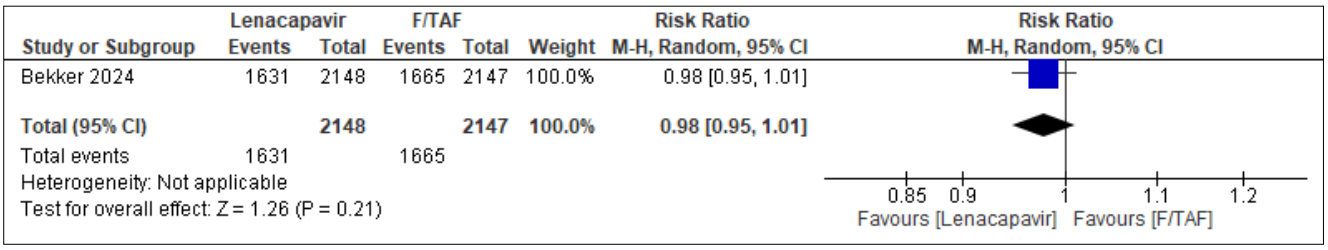


Figure 10: Forest plot of LEN injectable vs. F/TAF; AEs

4. Adverse drug reactions (ADRs): injection-site reactions

LEN compared to F/TAF increases injection-site reactions (52 weeks), RR 1.95 (95% CI 1.83 to 2.08), one study, n = 4,295, high certainty evidence. That is an absolute effect of 334 more cases per 1,000 (ranging from 292 more to 380 more). One study (Bekker *et al.*, 2024) had available event/total group data to evaluate this outcome. Figure 11 shows the forest plot for this comparison.

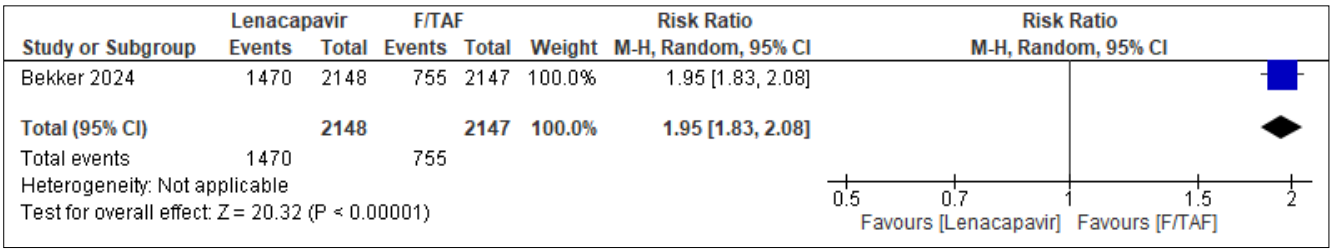


Figure 11: Forest plot of LEN injectable vs. F/TAF; ADRs

5. All-cause mortality

LEN compared to F/TAF results in little to no difference in mortality (52 weeks), RR 0.08 (95% CI 0.00 to 1.36), one study, n = 4,295, high certainty evidence. That is an absolute effect of 3 fewer cases per 1,000 (ranging from 3 fewer to 1 more). None of the deaths were considered by the investigator to be related to a trial drug or comparator. One study (Bekker *et al.*, 2024) had available event/total group data to evaluate this outcome. Figure 12 shows the forest plot for this comparison.

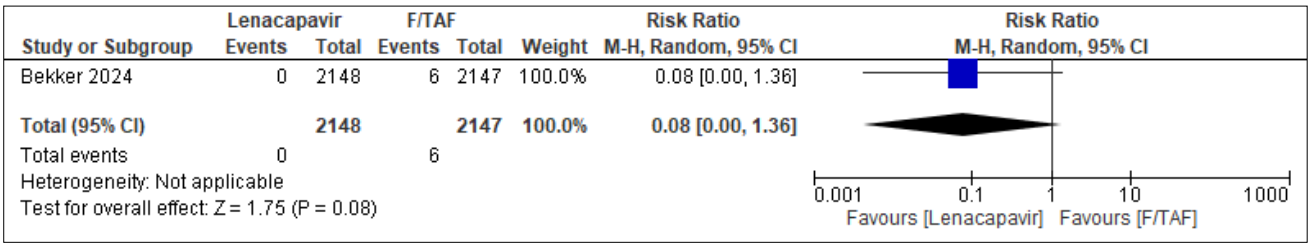


Figure 12: Forest plot of LEN injectable vs. F/TAF; Mortality

6. Retention at weeks 26 and 52

Week 26: Retention was similar across the trial groups: in the LEN group, 90.3% (1,940/2,148) and 90.9% (1,952/2,147) in the F/TAF group.

Week 52: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 45.9% (985/2,148) and 45.3% (973/2,147) in the F/TAF group. Thus, LEN compared to F/TAF results in little to no difference in retention at weeks 26 and 52, high certainty evidence.

Adherence

PURPOSE 1 (Bekker et al., 2024)
Injections were administered timeously in 91.5% of the participants (4,545/4,967) at week 26, and in 92.8% of the participants (2,025/2,181) at week 52; and the percentages were similar across the LEN, F/TAF, and F/TDF groups. Adherence was assessed based on tenofovir diphosphate levels in red cells in dried-blood-spot samples from all trial visits from a randomly preselected 10% of participants in the F/TAF and F/TDF groups. “Among the preselected 10% sample of participants assessed for tenofovir diphosphate levels, most participants in both the F/TAF and F/TDF groups had low adherence (<2 doses/week)”; in 34% at week 8, in 70% at week 26, and 84% at week 52 in the F/TAF group and 50% at week 8, and in 89% at week 26, and 93% at week 52 in the F/TDF group (Fig. 3A: Bekker, 2024).

PURPOSE 2 (Kelley et al., 2025)
“Overall adherence to LEN or placebo injection was similar in the two groups (administered on time in 2,606 of 2,864 participants [91.0%] at week 26 and in 1,016 of 1,095 [92.8%] at week 52) (Fig. 3A and Table S8: Kelley, 2025). Tenofovir diphosphate concentrations consistent with high adherence (≥four tablets per week) were seen in 82% of the participants at week 8, in 67% at week 26, and in 62% at week 52 (Fig. 3B: Kelley, 2025).”

Incidence of other sexually transmitted infections (STIs)

PURPOSE 1 (Bekker et al., 2024)
“The incidence of laboratory-diagnosed *C. trachomatis*, *N. gonorrhoeae*, or *T. vaginalis* infection at asymptomatic screening every 26 weeks was high and similar in the three groups: in the LEN group, 48.7 per 100 person-years (930 events during 1,908.8 person-years); in the F/TAF group, 50.8 per 100 person-years (965 events during 1,899.4 person-years); and in the F/TDF group, 48.4 per 100 person-years (452 events during 933.4 person-years). More details are provided in Table S9”.

PURPOSE 2 (Kelley et al., 2025)
There were more incident STIs identified in the LEN group than in the F/TDF group: (71.8% [1,504 of 2,096 participants] in the LEN group and 64.5% [668 of 1,036 participants] in the F/TDF group. The incidence of laboratory-diagnosed *C. trachomatis* and N. gonorrhoeae reported was 77.9 per 100 person-years (1,504 events during 1,931.0 person-years) in the LEN group and 69.4 per 100 person-years (668 events during 962.1 person-years) in the F/TDF group (Table S10).

Viral mutations among those who contracted HIV

PURPOSE 1 (Bekker et al., 2024)
It was not reported, and there were no HIV acquisitions in the LEN arm.

PURPOSE-2 (Kelley et al., 2025)
Two participants acquired HIV infection in the LEN group. The LEN concentrations in both participants were within the range of the overall LEN concentrations in the pharmacokinetics cohort. Both participants had the N74D capsid resistance mutation found at their HIV diagnosis visit. All nine participants in the F/TDF group who received a diagnosis of HIV infection had evidence of low or no adherence or had discontinued F/TDF more than 10 days before diagnosis. Eight of the nine participants had available dried-blood-spot samples to analyse tenofovir diphosphate concentrations. Of those eight participants, two had low concentrations and six were below the quantification limit. The one participant who was missing a dried-blood-spot sample had discontinued F/TDF. One participant was found to have an emtricitabine resistance mutation (M184V).

Table 3: Comparison 2 GRADE evidence profile

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEN injectable	F/TAF	Relative (95% CI)	Absolute (95% CI)	
New HIV infection											
1	randomised trials	not serious	not serious	not serious	not serious	none	0/2148 (0.0%)	39/2147 (1.8%)	**RR 0.01** (0.00 to 0.21)	**18 fewer per 1,000**	⊕⊕⊕⊕ High
Serious adverse events											
1	randomised trials	not serious	not serious	not serious	not serious	none	59/2148 (2.7%)	85/2147 (4.0%)	**RR 0.69** (0.50 to 0.96)	**12 fewer per 1,000** (from 20 fewer to 2 fewer)	⊕⊕⊕⊕ High
Adverse events											
1	randomised trials	not serious	not serious	not serious	not serious[a]	none	1631/2148 (75.9%)	1665/2147 (77.6%)	**RR 0.98** (0.95 to 1.01)	**16 fewer per 1,000** (from 39 fewer to 8 more)	⊕⊕⊕⊕ High[a]
Adverse drug reactions: injection site reactions											
1	randomised trials	not serious	not serious	not serious	not serious	none	1470/2148 (68.4%)	755/2147 (35.2%)	**RR 1.95** (1.83 to 2.08)	**334 more per 1,000** (from 292 more to 380 more)	⊕⊕⊕⊕ High
All-cause mortality											
1	randomised trials	not serious	not serious	not serious	not serious[b]	none	0/2148 (0.0%)	6/2147 (0.3%)	**RR 0.08** (0.00 to 1.36)	**3 fewer per 1,000**	⊕⊕⊕⊕ High[b]
Retention at weeks 26 and 52											
1	randomised trials	not serious[c]	not serious	not serious	not serious	none	*Week 26*: Retention was similar across the trial groups: in the LEN group, 90.3% (1,940/2,148) and 90.9% (1,952/2,147) in the F/TAF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 45.9% (985/2,148) and 45.3% (973/2,147) in the F/TAF group.					⊕⊕⊕⊕ High[c]

CI: confidence interval; **RR:** risk ratio

Explanations
a. Not downgraded for imprecision: the absolute 95% CI ranges from a small reduction to a trivial increase
b. Not downgraded for imprecision: Despite the low event rate, this is a rare event with a narrow absolute 95% CI, and we are confident that there is no effect between the intervention and the comparator
c. Not downgraded for risk of bias, even though we assessed Domain 3 as having some concerns of bias, due to the expected numbers per visit used as the denominator (no information was provided on how the expected LTFU rate was calculated)

Table 4: Comparison 2 Summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with F/TAF	Risk with LEN injectable			
New HIV infection	18 per 1,000	**0 per 1,000** (0 to 4)	**RR 0.01** (0.00 to 0.21)	4295 (1 RCT)	⊕⊕⊕⊕ High
Serious adverse events	40 per 1,000	**27 per 1,000** (20 to 38)	**RR 0.69** (0.50 to 0.96)	4295 (1 RCT)	⊕⊕⊕⊕ High
Adverse events	776 per 1,000	**760 per 1,000** (737 to 783)	**RR 0.98** (0.95 to 1.01)	4295 (1 RCT)	⊕⊕⊕⊕ High[a]
Adverse drug reactions	352 per 1,000	**686 per 1,000** (644 to 731)	**RR 1.95** (1.83 to 2.08)	4295 (1 RCT)	⊕⊕⊕⊕ High
Mortality	3 per 1,000	**0 per 1,000** (0 to 4)	**RR 0.08** (0.00 to 1.36)	4295 (1 RCT)	⊕⊕⊕⊕ High[b]
Retention at weeks 26 and 52	*Week 26*: Retention was similar across the trial groups: in the LEN group, 90.3% (1,940/2,148) and 90.9% (1,952/2,147) in the F/TAF group. *Week 52*: Similarly, at week 52, retention was similar across the trial groups: in the LEN group, 45.9% (985/2,148) and 45.3% (973/2,147) in the F/TAF group.			4295 (1 RCT)	⊕⊕⊕⊕ High[c]

*__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.

DISCUSSION

LEN compared to F/TDF showed a large reduction in new HIV infections over 52 weeks (one year): RR 0.06, 95% CI 0.01 to 0.42, two trials, n=6,513, high certainty evidence. In absolute terms, this is 11 fewer cases per 1,000 (ranging from 11 fewer to 7 fewer). Similarly, LEN compared to F/TAF showed a large reduction in new HIV infections: RR 0.01, 95% CI 0.00 to 0.21, one trial, n=4,295, high certainty evidence. That is an absolute effect of 18 fewer cases per 1,000 (ranging from 18 fewer to 14 fewer).

There was little to no difference in SAEs, AEs and all-cause mortality when LEN was compared to either F/TDF and F/TAF. However, LEN compared to F/TDF likely increases injection-site reactions (52 weeks), RR 1.56 (95% CI 0.89 to 2.74), two studies, n = 6,513, moderate certainty evidence. That is an absolute effect of 289 more cases per 1,000 (ranging from 57 fewer to 897 more). Also, LEN compared to F/TAF increases injection-site reactions (52 weeks), RR 1.95 (95% CI 1.83 to 2.08), one study, n = 4,295, high certainty evidence. That is an absolute effect of 334 more cases per 1,000 (ranging from 292 more to 380 more). LEN is administered into the subcutaneous tissue, where it establishes a drug depot that may be palpable as a nodule but is typically not visible beneath the skin surface (Bekker *et al.*, 2024). Histopathological analyses of biopsy specimens from both animal and human subjects have demonstrated the potential for a granulomatous or foreign body-type reaction at the depot's site (Castagna *et al.*, 2023; Kumar *et al.*, 2022). As the drug is gradually released, the depot diminishes, and any resulting nodules either resolve completely or reduce in size before subsequent dosing. While injection-site reactions to LEN were relatively frequent and anticipated, discontinuation due to such events was uncommon across clinical trials. Moreover, the incidence of these reactions—including the formation of nodules—was observed to decline with repeated dosing, a pattern also reported in studies investigating LEN for HIV treatment (Kumar *et al.*, 2022).

Retention in care was similar in both groups when LEN was compared to F/TDF or F/TAF. Retention in care at 52 weeks was 40.9% in the LEN group compared to 40.5% in the F/TDF group and 45.9% in the LEN group compared to 45.3% in the F/TAF group. Thus, LEN compared to F/TAF results in little to no difference in retention at weeks 26 and 52, high certainty evidence. Injections were administered timeously in 91.5% of the participants (4,545/4,967) at week 26, and in 92.8% of the participants (2,025/2,181) at week 52; and the percentages were similar across the LEN, F/TAF, and F/TDF groups (Bekker *et al.*, 2024). Similarly, adherence to LEN or placebo injection was similar in the two groups (administered on time in 2,606 of 2,864 participants [91.0%] at week 26 and in 1,016 of 1,095 [92.8%] at week 52) (Kelley *et al.*, 2025). Adherence was assessed based on tenofovir diphosphate levels in red cells in dried-blood-spot samples from all trial visits from a randomly preselected 10% of participants in the F/TAF and F/TDF groups; most participants in both the F/TAF and F/TDF groups had low adherence (<2 doses/week) (Bekker *et al.*, 2024). In contrast, tenofovir diphosphate concentrations consistent with high adherence (≥four tablets per week) were seen in 82% of the participants at week 8, in 67% at week 26, and in 62% at week 52 (Kelley *et al.*, 2025). Adherence to daily oral F/TAF and F/TDF regimens was suboptimal, aligning with previous findings of low adherence to daily oral F/TDF and, consequently, reduced effectiveness among cohorts of women—particularly younger women—across diverse geographic regions (Bekker *et al.*, 2024). Several factors may contribute to the limited adherence and persistence with F/TAF and F/TDF, including HIV-related stigma, aversion to or inexperience with daily oral medication routines, and misperceptions regarding personal risk of HIV acquisition (Bekker *et al.*, 2024). Further follow-up, including in the open-label extension phase of these trials, is needed to monitor the incidence of breakthrough HIV infection and delayed seroconversion and the development of resistance. There was a high incidence of other STIs as noted in both trials, which may reflect the sexual behavioural characteristics of the trial participants, including high levels of sexual exposure and the use of drugs in conjunction with sex (Kelley *et al.*, 2025).

On 14 July 2025, the WHO released guidelines on LEN for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (WHO, 2025b). The systematic review underpinning this guidance also identified the PURPOSE 1 and 2 trials (Fonner *et al.*, 2025b). The authors chose not to pool results from the two trials as the trials were conducted among different populations, which is a different approach from the one we took, where we considered the different populations but chose to pool as we assumed that the mechanism of action of LEN is consistent across populations. The relative treatment effect is expected to be similar due to underlying biological plausibility. Where there was heterogeneity due to the different populations (e.g. ADRs in comparison one), we addressed this in the GRADE table comments. The recent WHO systematic review (Fonner *et al.*, 2025b) concluded that LEN is “an effective means of HIV prevention and appears to have few safety risks beyond injection site reactions”. However, reviewers noted that there

may be an increased risk of resistance to capsid inhibitors among people who experience a breakthrough infection.

There are only two included trials, with three ongoing. The data is thus limited, but given the large sample size, we are confident that the data is representative of the populations included in the trials. No trials compared LEN to CAB-LA, limiting our ability to make inferences about one injectable PrEP compared to another.

CONCLUSION

Evidence from the trials confirms that the use of LEN, compared to either F/TDF or F/TAF, results in a large reduction of new HIV infections, with relatively few safety risks, apart from injection site reactions, which supports the broader implementation of injectable PrEP in public health HIV prevention programmes. This is further supported by the recently published WHO guidelines (WHO, 2025b) that recommend that long-acting injectable LEN be offered as an additional prevention choice for people at risk of contracting HIV (strong recommendation, moderate to high certainty of evidence). Long-term follow-up is needed to monitor the durability of the preventative effects of LEN, together with pharmacovigilance monitoring and expansion of current HIV-1 drug-resistance surveillance programmes to monitor the emergence of LEN-associated resistance mutations occurring in populations in which LEN PrEP is administered (WHO, 2025b).

REVIEW TEAM

NAME	DECLARATION OF INTERESTS	PICO	PROTOCOL	TITLE, ABSTRACT & FULL TEXT SCREEN	WRITE UP, REF, APPENDICES	RoB ASSESSMENT	GRADE ASSESSMENT	META-ANALYSIS/EtD	EtD FRAMEWORK	CLINICAL EXPERTISE	QUALITY ASSURANCE
Lead reviewer: Dr S Ebrahim	No specific interests to declare		X	X	X	X	X	X	X		
Other Reviewers-alphabetical											
Ms Z Adam	No specific interests to declare	X		X	X				X		X
Prof K Cohen	No specific interests to declare	X							X	X	X
Dr H Dawood	No specific interests to declare									X	X
Mrs S Durao	No specific interests to declare	X									
Dr N Gloeck	No specific interests to declare	X	X	X	X	X	X	X	X		
Dr J Nel	No specific interests to declare								X	X	
Prof P Sinxadi	No specific interests to declare								X	X	
Dr G Tatz	No specific interests to declare								X	X	

ACKNOWLEDGEMENTS

- Ms Joy Oliver for advising on the search strategy
- Prof Tamara Kredo for advice on the meta-analysis and Prof Michael McCaul for advice on the GRADE assessments
- Ms Hasina Subedar and members of the HIV programme for local qualitative data and programme insights
- Expert Review Committee (ERC) for finalising the recommendations
- National Essential Medicines List Committee (NEMLC) for ratifying recommendations

REFERENCES

Bekker, L.-G, Das, M., Abdool Karim, Q., Ahmed, K., Batting, J., Brumskine, W., et al. (2024). 'Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women'. *New England Journal of Medicine*, *391*(13), pp. 1179–1192. doi: https://doi.org/10.1056/nejmoa2407001

Castagna A., Arevalo J.L.B., Molina J., et al. (2023). 'Follow-up of injection site reactions in clinical studies of people using lenacapavir every 6 months for HIV treatment'. In: *Proceedings and Abstracts of the 19th European AIDS Conference*, October 18–21, 2023. Warsaw, Poland: European AIDS Clinical Society. Abstract.

Centers for Disease Control and Prevention (2024a). *HIV Surveillance Report: Diagnoses, Deaths, and Prevalence of HIV in the United States and 6 Territories and Freely Associated States*, 2022. [online] Available at: https://stacks.cdc.gov/view/cdc/156509 (Accessed: 22 July 2025).

Centers for Disease Control and Prevention (2024b). *HIV Surveillance Supplemental Report: Estimated HIV Incidence and Prevalence in the United States, 2018–2022*. [online] Available at: https://stacks.cdc.gov/view/cdc/156513 (Accessed: 22 July 2025).

Cochrane Collaboration (2020). 'Collaborating in response to COVID-19: Editorial and methods initiatives across Cochrane'. *The Cochrane Database of Systematic Reviews*, *12*(Suppl 1), p.CD202002. doi: 10.1002/14651858.CD202002

Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. 2025. Available at www.covidence.org

Di Perri, G. (2023). 'Pharmacological outlook of Lenacapavir: a novel first-in-class-acting HIV-1 capsid inhibitor'. *Infezioni in Medicina*, *31*(4), pp. 495–499. doi: https://doi.org/10.53854/liim-3104-8

Fonner V., Louis Charles K., Lee M.T., Prochazka Nunez M., Schmidt H.M., Rodolph M. (2025a). 'Web Annex C. Systematic review of values and preferences for LEN as pre-exposure prophylaxis and other forms of long-acting injectable PrEP'. In: *Guidelines on LEN for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP)*. Geneva: World Health Organization. doi: https://doi.org/10.2471/B09477

Fonner V, Louis Charles K, Lee MT, Prochazka Nunez M, Schmidt HM, Rodolph M. (2025b). 'Web Annex B. Safety and efficacy of long-acting injectable lenacapavir as pre-exposure prophylaxis to reduce the risk of HIV acquisition: a systematic review'. In: *Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP)*. Geneva: World Health Organization. doi: https://doi.org/10.2471/B09478

Garritty, C., Gartlehner, G., Nussbaumer-Streit, B., King, V. J., Hamel, C., Kamel, C., et al. (2021). 'Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews'. *Journal of Clinical Epidemiology*, *130*, pp.13-22. doi: https://doi.org/10.1016/j.jclinepi.2020.10.007

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., et al. (2011). 'GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables'. *Journal of Clinical Epidemiology*, *64*(4), pp. 383-394. doi: https://doi.org/10.1016/j.jclinepi.2010.04.026

Higgins, J. P. T., Savović, J., Page, M. J., Elbers, R. G., & Sterne, J. A. C. (2023) 'Chapter 8: Assessing risk of bias in a randomized trial'. In Higgins J.P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M.J., & Welch V.A. (Eds.) *Cochrane Handbook for Systematic Reviews of Interventions*, pp.205-228. doi: https://doi.org/10.1002/9781119536604.ch8

Human Sciences Research Council (2023). *New HIV survey highlights progress and ongoing disparities in South Africa's HIV epidemic*. [online] Available at: https://hsrc.ac.za/press-releases/sabssm/new-hiv-survey-highlights-progress-and-ongoing-disparities-in-south-africas-hiv-epidemic/ (Accessed: 29 May 2025)

Joint United Nations Programme on HIV/AIDS (UNAIDS) (2024). *The urgency of now: AIDS at a crossroads*. [online] Available at: https://www.unaids.org/sites/default/files/media_asset/2024-unaids-global-aids-update_en.pdf (Accessed: 22 July 2025).

Kelley, C.F., Acevedo-Quiñones, M., Agwu, A.L., Avihingsanon, A., Benson, P., et al. (2025). 'Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons'. *New England Journal of Medicine*, *392*(13), pp. 1261–1276. doi: https://doi.org/10.1056/nejmoa2411858

Kumar P, Gupta S, Segal-Maurer S, et al. (2022) 'Injection-site reaction experience in clinical studies of people using lenacapavir for HIV treatment'. In: *Proceedings and Abstracts of the 24th International AIDS Conference*, July 29–August 2, 2022. Montreal: International AIDS Society. Abstract.

Medical Dictionary for Regulatory Activities (2024). What's New MedDRA Version 27.0. Available at: https://admin.meddra.org/sites/default/files/guidance/file/whatsnew_27_0_English.pdf (Accessed: 01 July 2025).

Murray, J. and Birnkrant, D., 2019. 'Gender parity in clinical PrEP trials'. *New England Journal of Medicine*, *381*(26), pp.2584-2585. doi: https://doi.org/10.1056/nejmc1915473

National Department of Health (2022). *Dapivirine Ring for PrEP: PHC Review*, *9 June 2022, v5*. *Evidence Review*. [online] Available at: https://www.health.gov.za/wp-content/uploads/2024/03/DapivirineRingForPrEP_PHC-Review_9June2022_v5.pdf (Accessed: 29 May 2025).

National Department of Health (2023a). *The National Strategic Plan for HIV, TB and STIs, 2023–2028*. [online] Available at: https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/NSP-HIV-TB-STIs-2023-2028-MARCH20_23-PRINT2.pdf (Accessed: 29 May 2025).

National Department of Health (2023b). H*ealth Technology Assessment Methods Guide 2022-2027*. [online] Available at: https://www.health.gov.za/wp-content/uploads/2024/04/HTA-Methods-Guide_FINAL_Sep-2023.pdf (Accessed: 29 May 2025).

National Department of Health (2024). *Cabotegravir as PrEP for Adults: Evidence Summary, 13 September 2024, v5.1 FINAL. Evidence Review*. [online] Available at: https://www.health.gov.za/wp-content/uploads/2024/09/Cabotegravir-as-PrEP-for-adults-_EvidenceSummary_v5.1_13-Sep-2024_FINAL.pdf (Accessed: 29 May 2025).

National Essential Medicines List Committee (NEMLC) (2024). *Confidential NEMLC minutes, 29 August 2024*. Unpublished internal document.

Pike, C., Rousseau, E. and Bekker, L.-G. (2023) 'Promises and potential pitfalls of long-acting injectable pre-exposure prophylaxis', *Southern African Journal of HIV Medicine, 24*(1), a1497. doi: https://doi.org/10.4102/sajhivmed.v24i1.1497

Review Manager (RevMan). Version 5.4.1. The Cochrane Collaboration, 2020. Available at revman.cochrane.org

Sax, P.E. (2024). 'Lenacapavir PrEP trial brings down the house at the International AIDS Conference. HIV and ID Observations', *NEJM Journal Watch*. Available at: https://blogs.jwatch.org/hiv-id-observations/index.php/Lenacapavir-prep-trial-brings-down-the-house-at-the-international-aids-conference/2024/07/25/ (Accessed: 29 May 2025).

South African Health Products Regulatory Authority (2022). *SAHPRA registers new long-acting HIV pre-exposure prophylaxis*. Available at: https://www.sahpra.org.za/press-releases/sahpra-registers-new-long-acting-hiv-pre-exposure-prophylaxis/ (Accessed: 29 May 2025).

Stats SA (2024). *2024 Mid-year Population Estimates*. Statssa.gov.za. [online] Available at: https://www.statssa.gov.za/?p=17440 (Accessed: 29 May 2025).

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). 'RoB 2: a revised tool for assessing risk of bias in randomised trials'. B*MJ, 366*(l4898). doi: https://doi.org/10.1136/bmj.l4898

UNAIDS (2019). *AIDSinfo | UNAIDS*. Unaids.org. [online] Available at: https://aidsinfo.unaids.org (Accessed: 22 July 2025).

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS (2017). *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1*. [online] Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf (Accessed: 11 July 2025).

Van Damme, L., Corneli, A., Ahmed, K., Agot, K., Lombaard, J., Kapiga, S., et al. (2012). 'Preexposure Prophylaxis for HIV Infection among African Women'. *New England Journal of Medicine, 367*(5), pp.411–422. doi: https://doi.org/10.1056/nejmoa1202614

Van Zyl G., Prochazka M., Schmidt H.M., Rodolph M., Jordan M.R., Shafer R.W. (2025). 'Web Annex F. Lenacapavir-associated drug resistance: implications for scaling up long-acting PrEP'. In: *Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP)*. Geneva: World Health Organization. doi: https://doi.org/10.2471/B09481

World Health Organization (WHO) (2025a). *FDA approval of injectable lenacapavir marks progress for HIV prevention*. [online] Available at: https://www.who.int/news/item/19-06-2025-fda-approval-of-injectable-Lenacapavir-marks-progress-for-hiv-prevention (Accessed: 02 July 2025).

World Health Organization (WHO) (2025b). *Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis (PrEP)*. Geneva: World Health Organization. Available at: https://www.who.int/publications/i/item/9789240111608 (Accessed 15 July 2025)

Young, A., Mancuso, N., Atujuna, M., Tenza, S., Chitukuta, M., Kemigisha, D., et al. (2023). 'Adolescent Girls and Young Women's Experiences with Disclosing Oral PrEP or Dapivirine Vaginal Ring Use: A Multi-Country Qualitative Analysis'. *AIDS and Behavior, 27*(12), pp.3941–3951. doi: https://doi.org/10.1007/s10461-023-04109-w

Appendix 1: Search strategy

PubMed

Comment: We did not include a specific search string for PrEP, as this made the search too narrow

Search	Query	Results
#7	Search: #5 AND #6	26
#6	Search: pre-exposure prophylaxis[mh] OR pre-exposure prophylaxis[tiab] OR pre-exposure prophylaxi[tiab] OR PREP[tiab] OR chemoprophylaxis[tiab] OR chemoprevention[tiab] OR chemo prevention[tiab]	33,272
#5	Search: #3 AND #4	109
#4	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]) NOT (animals [mh] NOT humans [mh])	5,605,527
#3	Search: #1 AND #2	189
#2	Search: Lenacapavir [Supplementary Concept] OR Lenacapavir[tiab] OR sunlenca[tiab]	198
#1	Search: HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw]))	482,759

Cochrane library

Search ID#	Query	Results
#1	Lenacapavir or sunlenca	64
#2	MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees	539
#3	prep or "pre-exposure prophylaxis"	3085
#4	#2 or #3	3085
#5	MeSH descriptor: [HIV] explode all trees	4127
#6	hiv or "human immunodeficiency virus"	34978
#7	#5 or #6	34978
#8	#1 and (#4 or #7)	64

Appendix 2: Characteristics of included studies

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Cisgender Women				

Bekker LG, Das M, Abdool Karim Q, Ahmed K, Batting J, Brumskine W, Gill K, Harkoo I, Jaggernath M, Kigozi G, Kiwanuka N. Twice-yearly Lenacapavir or daily F/TAF for HIV prevention in cisgender women. New England Journal of Medicine. 2024;391(13):1179-92. DOI: 10.1056/NEJMoa2407001	<u>Design</u>
	Phase 3, multicentre, double-blind, randomised, active-controlled trial (PURPOSE 1)
	
	<u>Setting</u>
	South Africa (25 trial sites) and Uganda (3 trial sites)
	
	<u>Follow-up duration (weeks)</u>
	52
	
	<u>Funding</u>
	Funded by Gilead Sciences; PURPOSE 1 (ClinicalTrials.gov number, NCT04994509.)
	
	<u>Declarations</u>
	Listed in the paper and supplementary file
	
	<u>Informed Consent</u>
	“All participants or guardians provided written informed consent; adolescents 16 or 17 years of age provided assent with guardian consent unless local ethics guidelines allowed them to consent for themselves”.
		Adolescent girls and young
		women (16 to 25 years of age) who were sexually
		active with male partners, were not using PrEP, and had an unknown HIV status and no HIV testing within the previous 3 months, were eligible.
		
		<u>Sample size</u>
		N=5,368 participants were randomly assigned (2,148 to Lenacapavir, 2,147 to emtricitabine-tenofovir
		alafenamide (F/TAF) and 1,073 to tenofovir disoproxil fumarate (F/TDF)
		
		N=5,338 participants were included in the modified intention-to-treat (ITT) analysis (2,134 in the Lenacapavir group, 2,136 in the emtricitabine-tenofovir alafenamide (F/TAF) group, and 1,068 in the tenofovir disoproxil fumarate (F/TDF) group
			<u>Intervention</u>
			Subcutaneous Lenacapavir
			(927 mg, in two 1.5-ml injections) every 26 weeks (within a window of ±7 days) with loading doses of two 300-mg tablets of Lenacapavir on each of days 1 and 2
			
			<u>Comparator/s</u>
			• Daily oral F/TAF (200 mg of emtricitabine and 25 mg of TAF)
			• Daily oral F/TDF (200 mg of emtricitabine and 300 mg of TDF)
				<u>Primary Outcomes</u>
				Incident HIV infection
				
				<u>Secondary Outcomes</u>
				Safety endpoints
				• Adverse events
				• Clinical laboratory abnormalities
				
				Results
				• Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed:
				  ○ 0 infections among 2134 participants in the Lenacapavir group (0 per 100 person-years; 95% confidence interval [CI], 0.00 to 0.19)
				  ○ 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and
				  ○ 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74)
				• Safety:
				  ○ AEs, any grade: 1,631 (76.4%) Lenacapavir group, 1,665 (77.9%) F/TAF group, and 830 (77.7%) F/TDF group
				  ○ SAE: 59 (2.8%) Lenacapavir group, 85 (4.0%) F/TAF group, and 35 (3.3%) F/TDF group
				  ○ There were six deaths, all in the F/TAF group. None of the deaths was considered by the investigator to be related to a trial drug or placebo
				  ○ Clinical laboratory abnormalities, any grade*: 90.7% (1,929/2,126) Lenacapavir group, 90.1% (1,904/2,113) F/TAF group, and 91.0% (959/1,054) F/TDF group
				  ○ Injection-site reactions**: There were no serious injection-site reactions reported in any of the three groups. Regarding any grade injection-site reactions: 68.8% (1,470/2,138) Lenacapavir group, 35.3%

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				(755/2,136) F/TAF group, and 33.9% (363/1,070) F/TDF group *Denominator: No. of participants with at least one post-baseline laboratory result **Denominator: No. of participants who received at least one Injection

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Men and Gender-Diverse Persons				

Kelley CF, Acevedo-Quiñones M, Agwu AL, Avihingsanon A, Benson P, Blumenthal J, Brinson C, Brites C, Cahn P, Cantos VD, Clark J. Twice-yearly Lenacapavir for HIV prevention in men and gender-diverse persons. New England Journal of Medicine. 2025 Apr 3;392(13):1261-76. DOI: 10.1056/NEJMoa2411858	Design
	Phase 3, multicentre, double-blind, randomised controlled trial (PURPOSE 2)
	
	Setting
	United States (61 trial sites), Brazil (9 sites), Thailand (7 sites),
	South Africa (6 sites), Peru (5 sites), Argentina (3 sites), and
	Mexico (one site)
	
	Follow-up duration (weeks)
	52
	
	Funding
	Funded by Gilead Sciences; PURPOSE 2 (ClinicalTrials.gov number, NCT04925752)
	
	Declarations
	Listed in the paper and supplementary file
	
	Informed Consent
	"All the participants provided written informed consent; participants who were younger than 18 years of age provided assent along with parental or guardian consent".
		Eligible participants were cisgender gay, bisexual, and other men, transgender women, transgender men, and gender-nonbinary persons who have condomless receptive anal sex with partners assigned male at birth were at
		least 16 years of age; had unknown HIV status;
		and reported no HIV testing or PrEP use in the
		3 months before screening
		
		Sample size*
		N=3,292 participants were randomly assigned (2,195 to Lenacapavir, and 1,097 to tenofovir disoproxil fumarate (F/TDF)
		
		N=3,265 participants were included in the modified ITT (2,179 in the Lenacapavir group, and 1,086 in the tenofovir disoproxil fumarate (F/TDF) group
			Intervention
			Subcutaneous Lenacapavir
			(927 mg, in two 1.5-ml injections) every 26 weeks (within a window of ±7 days) with oral loading doses of two 300-mg tablets of Lenacapavir each on days 1 and 2
			
			Comparator/s
			Daily oral F/TDF (200 mg of emtricitabine and 300 mg of TDF)
				Primary Outcomes
				Incident HIV infection
				
				Secondary Outcomes
				Safety end points
				• Adverse events
				• Clinical laboratory abnormalities
				
				Results
				• A total of 11 new HIV infections were observed:
				  ○ Two participants in the Lenacapavir group (0.10 per 100 person-years; 95% CI, 0.01 to 0.37)
				  ○ Nine participants in the F/TDF group (0.93 per 100 person-years; 95% CI, 0.43 to 1.77)
				• Safety:
				  ○ AEs, any grade: 1,607 (73.7%) Lenacapavir group, and 803 (73.9%) F/TDF group
				  ○ SAE: 71 (3.3%) Lenacapavir group, and 43 (4.0%) F/TDF group
				  ○ There were six deaths, four in the Lenacapavir group and two in the F/TDF group. None of the deaths were considered by the investigator to be related to a trial drug or placebo
				  ○ Clinical laboratory abnormalities, any grade*: 84.6% (1,822/2,153) Lenacapavir group, and 87.5% (937/1,071) F/TDF group
				  ○ Injection-site reactions: There were no serious injection-site reactions reported in either group. Regarding any grade injection-site reactions: 83.3% (1,816/2,179) Lenacapavir group, and 69.6% (756/1,086) F/TDF group
				
				*The denominators are based on participants with post-baseline values

Appendix 3: Characteristics of planned and ongoing studies

TREATMENT (PER ARM)	SAMPLE SIZE	STUDY POPULATION	SPONSOR	REGISTRATION NUMBER	FULL-TEXT LINK	SOURCE
Intervention: Participants will receive subcutaneous (SC) Lenacapavir (LEN) 927 mg on Day 1 and Week 26 and oral LEN 600 mg on Days 1 and 2. *Comparator*: Participants will receive oral Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) (200/300 mg) daily for 52 weeks	250, recruiting	Cisgender females, aged 18 years and older	Gilead Sciences	Study Identifiers: PURPOSE 3; HPTN-102; GS-US-528-6020; NCT06101329	https://clinicaltrials.gov/study/NCT06101329	CENTRAL (28 May 2025)
Intervention: Participants will receive subcutaneous (SC) Lenacapavir (LEN) 927 mg on Day 1 and Week 26 and oral LEN 600 mg on Days 1 and 2. *Comparator*: Participants will receive oral Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) (200/300 mg) daily for 52 weeks	180, recruiting	People who inject drugs (PWID), all sexes, aged 18 years and older	Gilead Sciences	Study Identifiers: PURPOSE 4; HPTN-103; GS-US-528-6363; NCT06101342	https://clinicaltrials.gov/study/NCT06101342	CENTRAL (28 May 2025)
Intervention: Participants will receive subcutaneous (SC) Lenacapavir (LEN) 927 mg on Day 1 and Week 26 and oral LEN 600 mg on Days 1 and 2. *Comparator*: Participants will receive oral Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) (200/300 mg) daily for 52 weeks	262, recruiting	Cisgender male, Cisgender female, Transgender male, Transgender female, and Gender non-binary persons, aged 18 years and older	Gilead Sciences	Study Identifiers: PURPOSE 5; GS-US-528-6727; NCT06513312; CTIS 2023-507891-31	https://clinicaltrials.gov/study/NCT06513312	CENTRAL (28 May 2025)

Appendix 4: Qualitative criteria

We did not identify any published literature on the acceptability and feasibility of Lenacapavir (LEN) when used as pre-exposure prophylaxis (PrEP) of HIV infection. Qualitative studies on injectable cabotegravir (CAB) have been initiated in South Africa and are due to conclude in the fourth quarter of 2025. These studies include:

- The LAPIS (Let's Adolescents and Young People Initiate and Stay) study, led by the Africa Health Research Institute (AHRI)
- Fast PrEP, led by the Desmond Tutu Health Foundation,
- Project PrEP, led by Wits Reproductive Health and HIV Institute (Wits RHI),
- AXIS, led by Ezintsha

To note, the CATALYST study, a trial evaluating the efficacy, safety and acceptability of LEN as antiretroviral therapy for people living with HIV (PLHIV), has been terminated early due to the USAID funding cuts.

A narrative summary of qualitative studies undertaken in PLHIV who received treatment with LEN is included below. This indirect evidence provides insights into user and healthcare worker (HCW) acceptability of injectable LEN.

Alford et al (Alford *et. al*, 2025) published the results of a qualitative study involving interviews with 34 cisgender males and females living with HIV, as well as focus groups involving 14 HCWs in the UK. Responses were recorded as the perceived benefits of a long-acting injectable formulation over oral therapies and not in response to actual exposure to LEN. Participants' responses were categorised into four main themes:

- LEN as a treatment option: 88% of patient participants expressed an interest in being switched to LEN, with convenience and improved lifestyle expressed as perceived benefits. Efficacy, side effects and aversion to needles were some of the patient concerns. Concerns expressed by HCWs included risks from side effects, potential for drug resistance and delayed response times to addressing resistance (i.e., six-monthly appointments with patients impacting response times), equity and access to LEN.
- LEN *vs*. oral ART: PLHIV considered injectable ART superior to oral ART primarily due to perceived improved adherence, with HCWs echoing many patients' sentiments. The benefits of an injectable formulation were perceived as far less beneficial, if paired concomitantly with oral ARVs.
- Switching consideration: With evolving evidence, the efficacy and safety of switching from established oral ARVs to the new injectable formulation were a concern for patients. The strictness of the dosing window for repeat injections and the risks of missed appointments were also noted as concerns. HCW felt that switching to an injectable formulation should be reserved for patients who can maintain the discipline of strict appointment schedules and have a history of well-controlled disease, i.e., history of undetectable viral loads.
- Administration of LEN: Approximately three-quarters of patient participants preferred HCW administration of the injection. Participants with a history of self-administration of injectable therapies (e.g. insulin, interferon) were more likely to consider self-administration. HCWs felt that subcutaneous administration would allow patient self-administration training, but concerns about overwhelming healthcare services with training and implementation requirements were noted.

Ramgopal *et al*. (Ramgopal *et. al*, 2025) published results from their health-related quality of life (HRQoL) outcomes study as part of the CAPELLA study (n=72) (Segal-Mauer *et. al*, 2022) in heavily treatment-experienced PLHIV. Results from the three qualitative assessment tools are summarised below:

- EQ-5D-5L: mean scores remained stable over the 52-week assessment period with scores comparable to United States (US) norms.
- Short Form 36 (SF-36): Both physical and mental component scores were comparable to US norms at baseline and remained stable over the assessment period.

- Numeric Pain Rating Scale (NPRS): Minimal changes were observed in NPRS scores, consistent with mild injection-site reactions.

We acknowledge that factors relating to non-adherence when LEN is used as treatment versus prevention may differ. Therefore, local studies assessing adherence when used as PrEP will be a more accurate indicator of anticipated adherence in our setting. Furthermore, HRQoL findings from the CAPELLA study involving heavily pre-treated PLHIV have limited applicability as these results would have been influenced by multiple co-morbidities and treatments that may not necessarily be relevant in a HIV preventative care setting.

References

Alford, K., Sidat, S., Bristowe, K., Cicconi, P., Vera, J.H. & Cresswell, F. (2025). 'Lenacapavir: Patient and healthcare provider perceptions and the potential role for a twice-yearly injectable HIV treatment'. *HIV Medicine, 26*(3), pp.441–450. doi: https://doi.org/10.1111/hiv.13748

Ramgopal, M., Mezzio, D.J., Dunn, K., Liu, S.Y., Paul, D., Rhee, M.S. & Castagna, A. (2025). 'Participant-reported outcomes from the CAPELLA clinical trial of Lenacapavir-based regimens in heavily treatment-experienced adults with HIV'. *AIDS and Behavior, 29*(5), pp.1553–1561. doi: https://doi.org/10.1007/s10461-025-04625-x

Segal-Maurer, S., DeJesus, E., Stellbrink, H.J., Castagna, A., Richmond, G.J., Sinclair, G.I., et al. (2022). 'Capsid inhibition with Lenacapavir in multidrug-resistant HIV-1 infection'. *New England Journal of Medicine, 386*(19), pp.1793–1803. doi: https://doi.org/10.1056/NEJMoa2115542

Appendix 5: Summary of serious adverse events, adverse events, adverse drug reactions, and laboratory abnormalities

Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions (Injection-site reactions	Laboratory abnormalities
Bekker 2024	• The incidence of serious adverse events was 2.8% (59/2,138 participants) in the Lenacapavir group, 4.0% (85/2,137) in the F/TAF group, and 3.3% (35/1,070) in the F/TDF group (Table S11). • There were six deaths, all in the F/TAF group (from asphyxia resulting from strangulation, non-accidental burns, a knife stab to the chest, haemorrhage due to a traffic accident, autopsy-confirmed ischaemic cardiomyopathy, and ovarian cancer). None of the deaths were considered by the investigator to be related to a trial drug or placebo.	• The most common adverse events, aside from injection-site reactions, were headache in 13.3% (285/2,138 participants in the Lenacapavir group, 16.5% (352/2,137 in the F/TAF group, and 14.5% (155/1,070) in the F/TDF group). • The percentage of participants with AEs was generally similar across the trial groups, except for a lower percentage with nausea and vomiting in the Lenacapavir group (6.7% and 5.8%, respectively) than in the F/TAF group (10.9% and 11.0%) and the F/TDF group (13.3% and 10.0%). • The incidence of grade 3 or higher AEs was similar across the trial groups, in 4.1% (88/2,138 participants) in the Lenacapavir group, 4.4% (95/2,137) in the F/TAF group, and 4.7% (50/1,070) in the F/TDF group (Table S10). • AEs leading to discontinuation of the trial regimen occurred in 0.2% (5/2,138 participants) in the Lenacapavir group, 0.1% (2/2,137) in the F/TAF group and in none of the 1,070 participants in the F/TDF group (Table S12). • There were 510 pregnancies among 487 participants: 193 pregnancies in the Lenacapavir group, 219 in the F/TAF group, and 98 in the F/TDF group. At the time of the interim analysis, o 277 pregnancies (54.3%) were completed, and 233 (45.7%) were ongoing. o There were 121 births (23.7%), 66 spontaneous abortions (12.9%), and 90	• A total of 25,329 injections were administered (10,154 in 2,138 participants in the Lenacapavir group and 15,175 in 3,206 participants receiving placebo injections in the F/TAF and F/TDF groups. • Injection-site reactions reported as being related to Lenacapavir or placebo or trial procedures occurred in 68.8% (1,470 of 2,138 participants) in the Lenacapavir group, 35.3% (755/2,136) in the F/TAF group, and 33.9% (363/1,070) participants in the F/TDF group; the latter two groups were given placebo injections (Table 2). • Subcutaneous nodules were observed in 63.8% of those in the Lenacapavir group and 16.6% receiving placebo injections (Fig. S6). • Nearly all injection-site reactions were grade 1 or 2 in severity; higher-grade reactions were rare and occurred in similar percentages of participants with Lenacapavir and placebo, and no reactions were serious. The frequency of injection site reactions diminished with subsequent injections (Fig. S6). • Keloid formation was not reported. • Four participants (0.2%) in the Lenacapavir group discontinued the trial regimen owing to injection site reactions, compared to no placebo injection participants.	• Laboratory abnormalities occurred in 90.5% of the participants (4,792/5,293). • Most laboratory abnormalities were grade 1 or 2. • In the Lenacapavir group, grade 1 events occurred in 20.7% (441/2,126 participants), and grade 2 events occurred in 64.7% (1,376/2,126; the respective values in the F/TAF group were 20.4% (430/2,113) and 64.9% (1,371/2,113), and in the F/TDF group were 18.7% (197/1,054) and 66.5% (701/1,054). • Grade 3 and 4 laboratory abnormalities were less common (<5% in all groups) (Table S13).

Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions (Injection-site reactions	Laboratory abnormalities
		induced abortions (17.6%) (Table S14). ○ A congenital abnormality of polydactyly was observed in an infant born to a participant in the Lenacapavir group who had a strong family history of this condition; the investigator considered this abnormality to be unrelated to the drug. ○ Among pregnant participants, HIV infection occurred in no participants in the Lenacapavir group, in 4 participants in the F/TAF group, and in 1 participant in the F/TDF group.		

Study ID	Serious Adverse Events	Adverse Events	Adverse Drug Reactions (Injection-site reactions	Laboratory abnormalities
Kelley 2025	SAEs occurred in 3.3% (71/2,183) in the Lenacapavir group and 4.0% (43/1,088) in the F/TDF group.	• Excluding injection-site reactions, the three most common AEs were rectal chlamydia infection (in 289 participants [13.2%] in the Lenacapavir group and 128 [11.8%] in the F/TDF group), oropharyngeal gonococcal infection (in 283 [13.0%] in the Lenacapavir group and 119 [10.9%] in the F/TDF group), and rectal gonococcal infection (in 233 [10.7%] in the Lenacapavir group and 99 [9.1%] in the F/TDF group) (Table 2). • Overall, the incidence of AEs was similar in the two groups with respect to grade 2 or higher adverse events (in 1173 [53.7%] in the lenacapavir group and 594 [54.6%] in the F/TDF group). • Grade 3 or higher AEs occurred in 91 [4.2%] in the Lenacapavir group and 65 [6.0%] in the F/TDF group (Table S13). • There were 0.3% (7/2,183) discontinuations due to AEs in the Lenacapavir group and 0.6% (7/1,088) in the F/TDF group (Table S14). • There were six deaths (four in the lenacapavir group and two in the F/TDF group); none were assessed by the investigator as being related to a trial drug. • No participant became pregnant.	• A total of 10,094 lenacapavir injections were administered in the lenacapavir group, and 5145 placebo injections were administered in the F/TDF group. • Injection-site reactions were reported in 1,816 participants (83.2%) in the Lenacapavir group and 756 (69.5%) in the F/TDF group. • Most injection-site reactions were mild (grade 1) or moderate (grade 2) in severity (Fig. S4). • Subcutaneous nodules, pain, and erythema were the most commonly reported injection-site reactions in the Lenacapavir and F/TDF groups. ○ Subcutaneous nodules occurred more frequently in the Lenacapavir group than in the F/TDF group (63.4% *vs*. 39.2%). • The incidence of pain in the Lenacapavir group was similar to that in the F/TDF group (56.4% *vs*. 53.4%). • Keloid formation in response to injection was not reported. • The frequency and severity of injection-site reactions diminished with subsequent injections. • A total of 26 participants (1.2%) in the Lenacapavir group and 3 (0.3%) in the F/TDF group discontinued the trial regimen because of injection-site reactions.	• Laboratory abnormalities occurred in 84.6% (1,822/2,153) of the participants in the Lenacapavir group and 87.5% (937/1,071) in the F/TDF group; most were grade 1 or 2 in severity and occurred in similar frequencies in the two trial groups, except for more frequent occurrence of decreased creatinine clearance in the F/TDF group. • A notable difference between the groups in laboratory measures was the median change from baseline in estimated glomerular filtration rate according to the Cockcroft–Gault formula: at week 26, there was a slight increase in the Lenacapavir group (+1.2 ml per minute [interquartile range, −8.0 to 10.9]) and a decline in the F/TDF group (−3.0 ml per minute [interquartile range, −12.4 to 6.5]) (p<0.001); at week 52, there was an increase in the Lenacapavir group (+0.6 ml per minute [interquartile range, −10.3 to 10.8]) and a decline in the F/TDF group (−2.9 ml per minute [interquartile range, −13.8 to 7.4]) (p = 0.002). • Grade 3 and 4 laboratory abnormalities occurred in 11.3% (243/2,153) participants in the Lenacapavir group and 13.7% (147/1,071) participants in the F/TDF group (Table S15).

Appendix 6: Sensitivity analyses

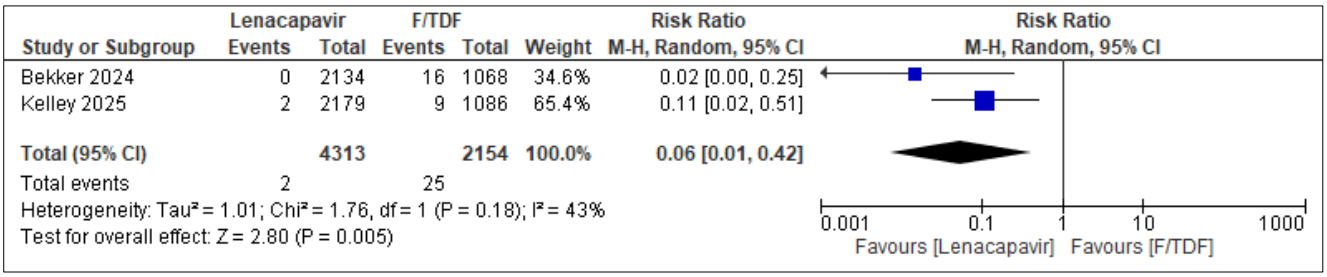
We conducted a sensitivity analysis, where those with baseline HIV infection per arm were excluded from the denominators in each of the study groups. The analysis did not substantially affect the overall relative effect sizes and their 95% CIs. Hence, we report the original forest plots, associated effect sizes, and 95% CIs.

Effects of the intervention

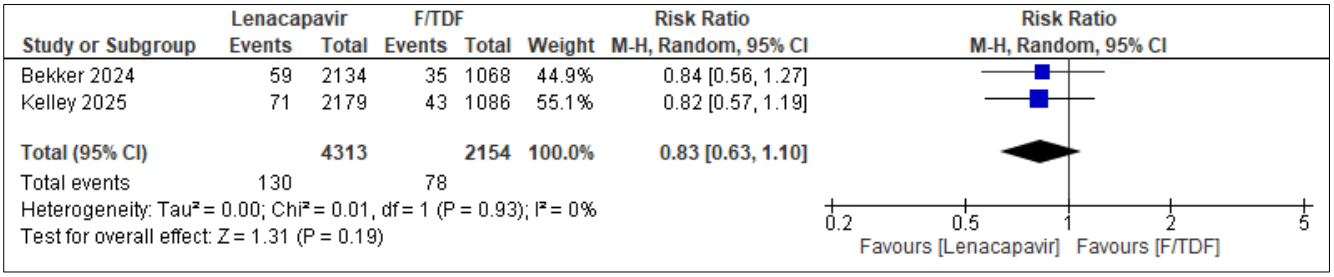
Modified ITT analyses

Lenacapavir injectable versus F/TDF

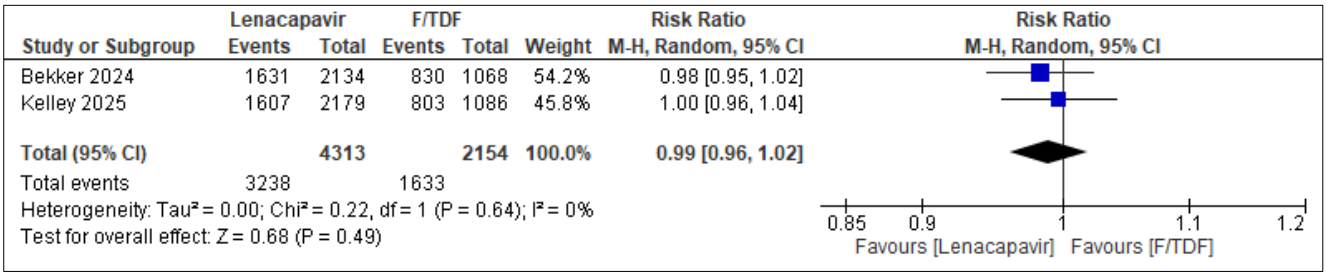
1. New HIV infections



2. SAEs



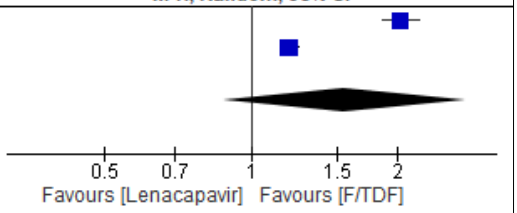
3. AEs



4. ADRs

Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1470	2138	363	1070	49.8%	2.03 [1.86, 2.21]
Kelley 2025 (2)	1816	2183	756	1088	50.2%	1.20 [1.15, 1.25]
Total (95% CI)		**4321**		**2158**	**100.0%**	**1.56 [0.88, 2.75]**
Total events	3286		1119			

Heterogeneity: Tau² = 0.17; Chi² = 134.29, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.52 (P = 0.13)

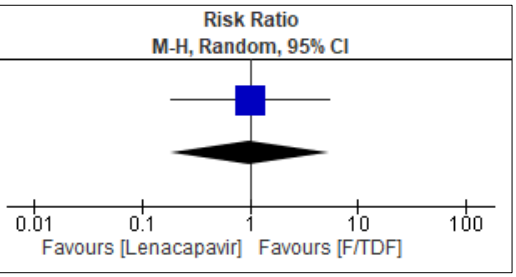


Footnotes
(1) Denominators: No. of participants who received at least one injection
(2) Denominators: No. of participants who received at least one injection

5. Mortality

Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	0	2134	0	1068		Not estimable
Kelley 2025	4	2179	2	1086	100.0%	1.00 [0.18, 5.43]
Total (95% CI)		**4313**		**2154**	**100.0%**	**1.00 [0.18, 5.43]**
Total events	4		2			

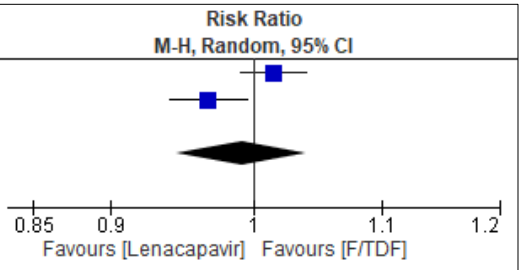
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



6. Laboratory abnormalities

Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1929	2126	959	1073	51.2%	1.02 [0.99, 1.04]
Kelley 2025 (2)	1822	2153	937	1071	48.8%	0.97 [0.94, 1.00]
Total (95% CI)		**4279**		**2144**	**100.0%**	**0.99 [0.95, 1.04]**
Total events	3751		1896			

Heterogeneity: Tau² = 0.00; Chi² = 6.32, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 0.35 (P = 0.73)

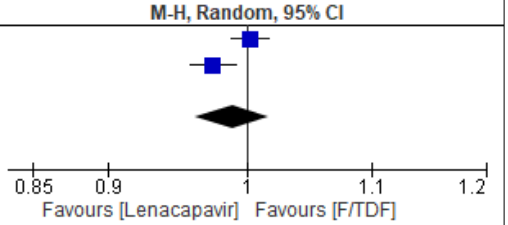


Footnotes
(1) Denominator: No. of participants with at least one post-baseline blood result
(2) Denominator: No. of participants with at least one postbaseline blood result

7. Retention at Week 26

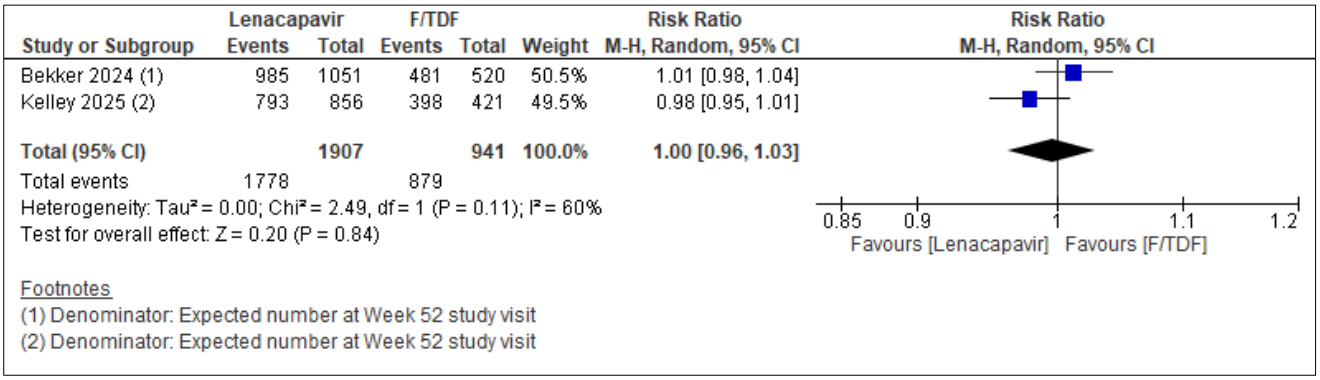
Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1940	2007	963	999	51.2%	1.00 [0.99, 1.02]
Kelley 2025 (2)	1882	2010	952	991	48.8%	0.97 [0.96, 0.99]
Total (95% CI)		**4017**		**1990**	**100.0%**	**0.99 [0.96, 1.02]**
Total events	3822		1915			

Heterogeneity: Tau² = 0.00; Chi² = 6.35, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 0.77 (P = 0.44)



Footnotes
(1) Denominator: Expected number at Week 26 study visit
(2) Denominator: Expected number at Week 26 study visit

8. Retention at Week 52



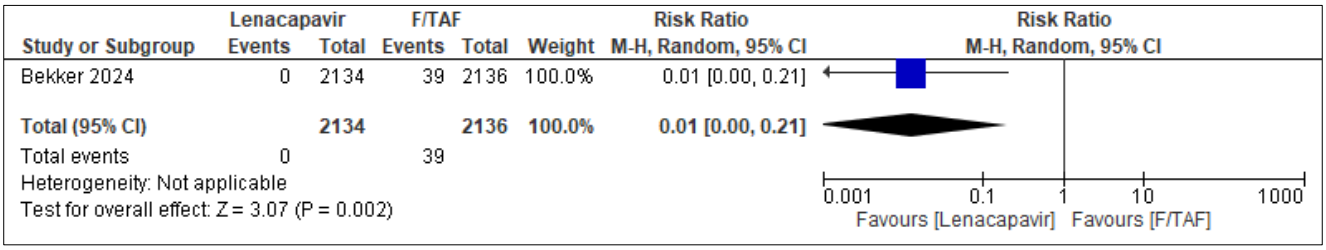
Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	985	1051	481	520	50.5%	1.01 [0.98, 1.04]
Kelley 2025 (2)	793	856	398	421	49.5%	0.98 [0.95, 1.01]
Total (95% CI)		**1907**		**941**	**100.0%**	**1.00 [0.96, 1.03]**
Total events	1778		879			

Heterogeneity: Tau² = 0.00; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 0.20 (P = 0.84)

Footnotes
(1) Denominator: Expected number at Week 52 study visit
(2) Denominator: Expected number at Week 52 study visit

Lenacapavir injectable versus F/TAF

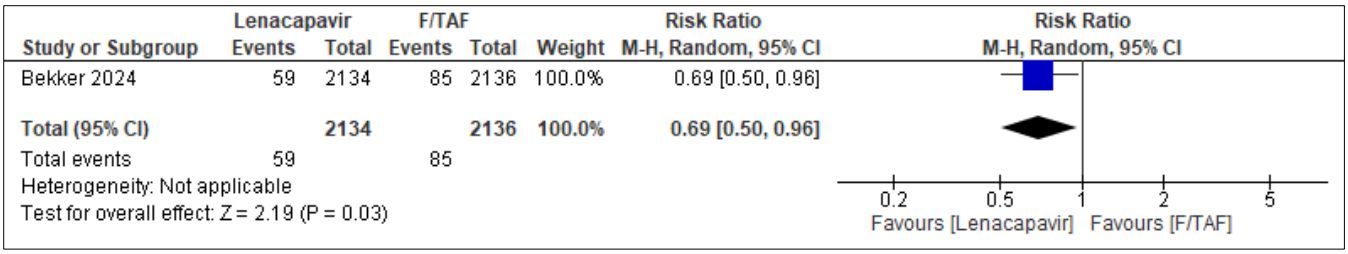
1. New HIV infections



Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	0	2134	39	2136	100.0%	0.01 [0.00, 0.21]
Total (95% CI)		**2134**		**2136**	**100.0%**	**0.01 [0.00, 0.21]**
Total events	0		39			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.07 (P = 0.002)

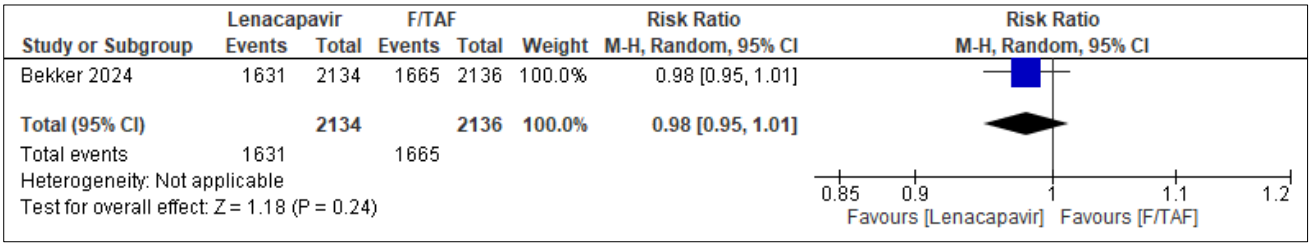
2. SAEs



Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	59	2134	85	2136	100.0%	0.69 [0.50, 0.96]
Total (95% CI)		**2134**		**2136**	**100.0%**	**0.69 [0.50, 0.96]**
Total events	59		85			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.19 (P = 0.03)

3. AEs



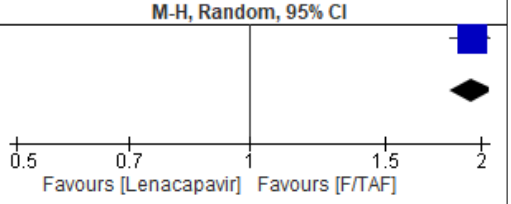
Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	1631	2134	1665	2136	100.0%	0.98 [0.95, 1.01]
Total (95% CI)		**2134**		**2136**	**100.0%**	**0.98 [0.95, 1.01]**
Total events	1631		1665			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)

4. ADRs

Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1470	2138	755	2136	100.0%	1.95 [1.82, 2.07]
Total (95% CI)		**2138**		**2136**	**100.0%**	**1.95 [1.82, 2.07]**
Total events	1470		755			

Heterogeneity: Not applicable
Test for overall effect: Z = 20.35 (P < 0.00001)

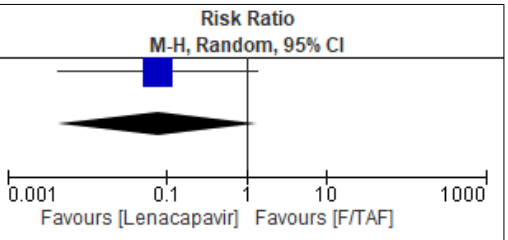


Footnotes
(1) Denominators: No. of participants who received at least one injection

5. Mortality

Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	0	2134	6	2136	100.0%	0.08 [0.00, 1.37]
Total (95% CI)		**2134**		**2136**	**100.0%**	**0.08 [0.00, 1.37]**
Total events	0		6			

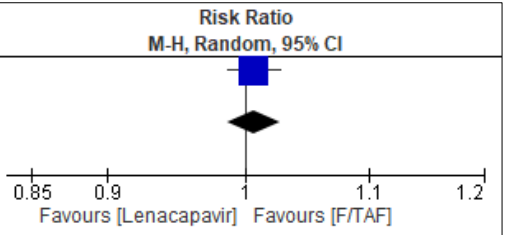
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)



6. Laboratory abnormalities

Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1929	2126	1904	2113	100.0%	1.01 [0.99, 1.03]
Total (95% CI)		**2126**		**2113**	**100.0%**	**1.01 [0.99, 1.03]**
Total events	1929		1904			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

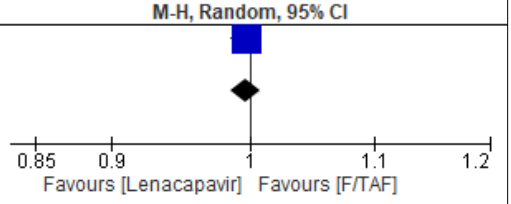


Footnotes
(1) Denominator: No. of participants with at least one post-baseline blood result

7. Retention at Week 26

Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1940	2007	1952	2014	100.0%	1.00 [0.99, 1.01]
Total (95% CI)		**2007**		**2014**	**100.0%**	**1.00 [0.99, 1.01]**
Total events	1940		1952			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)



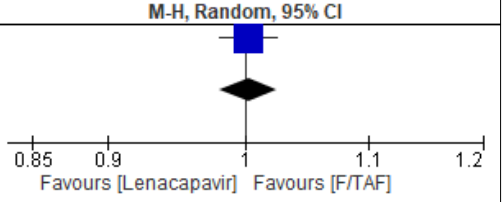
Footnotes
(1) Denominator: Expected number at Week 26 study visit

8. Retention at Week 52

Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	985	1051	973	1041	100.0%	1.00 [0.98, 1.03]
Total (95% CI)		**1051**		**1041**	**100.0%**	**1.00 [0.98, 1.03]**
Total events	985		973			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.24 (P = 0.81)



Footnotes

(1) Denominator: Expected number at Week 52 study visit

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

Date: 24 July 2025
Medication: Lenacapavir (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 lenacapavir for HIV prevention in South Africa, comparing it to daily oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), the current standard-of-care PrEP formulation. South Africa, with the world's largest HIV treatment and oral PrEP programs, still faces high HIV incidence among adolescent girls and young women (AGYW) and men who have sex with men (MSM), populations for whom lenacapavir for HIV prevention trials were conducted.

Lenacapavir demonstrated superior efficacy to TDF/FTC through two well-conducted randomized clinical trials, PURPOSE-1 and PURPOSE-2 [1,2]. PURPOSE-1, conducted at 28 sites in South Africa and Uganda, studied cisgender adolescent girls and young women (aged 16-26 years) over 4,821 person-years of follow-up [2]. There were zero HIV infections among 2,134 participants in the lenacapavir group, achieving 100% efficacy. PURPOSE-2, conducted across 88 sites in various countries including South Africa, evaluated lenacapavir in cisgender men and transgender and gender non-binary individuals who have sex with partners assigned male at birth (aged 16+ years) [1]. An interim analysis revealed a 96% reduction in HIV acquisition risk for lenacapavir users, with only two new HIV cases among 2,180 lenacapavir recipients compared to nine among 1,087 TDF/FTC recipients. Both trials were unblinded early due to lenacapavir meeting its efficacy endpoints.

While the originator company has issued voluntary licenses to six generic manufacturers, including in low- and middle-income countries (LMIC), there is currently no public price information for lenacapavir for any LMIC. Cheaper generic production will likely take several years to start, time that a country like South Africa will pay for in tens of thousands of avoidable infections. This report describes a cost-effectiveness analysis that compares the scaling up of lenacapavir compared to TDF/FTC, with varying assumptions for cost, coverage and duration. Our analysis also includes a threshold analysis with the aim of estimating the optimal price at which lenacapavir remains as cost-effective as TDF/FTC.

2 PHARMACOECONOMICS MODEL – METHODS AND SCENARIOS

This analysis uses Thembisa (version 4.8), a deterministic compartmental HIV transmission model of the South African HIV epidemic, to estimate the impact of the scale up of lenacapavir and TDF/FTC [3]. The model population is stratified by age, sex, sexual experience, sexual behavior, marital status, HIV testing

history, and male circumcision status. More detailed information about the model can be access at www.thembisa.org.

Lenacapavir and TDF/FTC scale-up were modeled over a 20-year horizon, starting from 2026, targeting all women (including AGYW, pregnant women, FSW), heterosexual men, and MSM. The baseline scenario was the current HIV programme, including the current TDF/FTC roll-out trajectory in South Africa, which has the following coverage levels for FSW (11%), MSM (10%), other women (1%, including 7% AGYW),and heterosexual men (0.2%) (Table 1). The scale-up scenarios modelled were:

- **TDF/FTC scale-up**: We assumed higher oral TDF/FTC initiation rates than at baseline, resulting in higher coverage levels for FSW (22%), MSM (21%), other women (3%, including 16% for AGYW, 41% for pregnant women), and heterosexual men (0.5%). Average duration on TDF/FTC was assumed to be 3 months (women, heterosexual men) and 6 months (MSM).
- **Conservative lenacapavir scale-up**: We assumed the same initiation rates as TDF/FTC scale-up, but an average duration of 6 months (women, heterosexual men) and 12 months (MSM). This resulted in coverages of 40% of FSW, 28% of MSM, 7% of other women (31% of AGYW, 41% of pregnant women), and 1% of heterosexual men.
- **Optimistic lenacapavir scale-up**: We doubled initiation rates compared to TDF/FTC scale-up and assumed longer use durations: 12 months (women, heterosexual men) and 24 months (MSM). These resulted in coverages of 65% FSW, 49% MSM, 14% other women (51% AGYW, 54% pregnant women), and 3% heterosexual men.

Under lenacapavir scenarios, for TDF/FTC we assume no further scale-up, using the same initiation rates as the baseline scenario. Tail protection for lenacapavir, referring to the period during which drug levels remain high enough to offer some continued protection against HIV after the primary dosing effect has waned, was considered to be an average of 6 months after the initial 6 months' protection, based on early pharmacokinetic data [2]. All scenarios and key assumptions are detailed in Table 1 below.

3 CLINICAL INPUTS AND COSTS

Effectiveness

TDF/FTC effectiveness, accounting for both efficacy and adherence, is assumed to be 85% for MSM, and 65% for heterosexual men and women [4–6]. **Lenacapavir effectiveness** was assumed to be 99% in all populations [1,2].

Costs

Costs were analysed from the perspective of the provider, the South African government, and reported in 2025 South African Rand (ZAR). The exchange rate used was ZAR 18.60 = 1 USD, based on reported exchange rates from the Reserve Bank from Jan-May 2025 [7].

The **average cost of PrEP provision was estimated using an ingredients-based approach,** with the cost dependent on the duration assumed**.** Briefly, PrEP is provided in primary healthcare clinics and includes repeat rapid HIV testing, counselling, provision of condoms, syndromic screening for sexual lytransmitted infections with treatment referral, adherence counselling, training, outreach, mobilisation, and monitoring and evaluation costs. The cost of TDF/FTC (drug only) is R64.85 per month [8].

Lenacapavir provision costs were structured similarly to the current oral TDF/FTC programme, but included more professional nurse time for injection administration, and excluded lab monitoring (creatinine and alanine transaminase testing) as these are not required with lenacapavir. In terms of dosing, a client requires two 1.5ml (927mg total) lenacapavir injections at initiation and 6-monthly thereafter, plus two 300mg lenacapavir tablets at initiation and day 2 each (1200mg total) as a loading dose. Since a local price for lenacapavir in South Africa is unknown, our initial analysis assumed it be $100 per person per year (PPPY), or R1,860, for 4 injections and including the cost of the initial loading dose, based on a recent cost-of-goods analysis [9]. To note, Hill et al (2024) estimated that this price could decrease to $40 (or R744) PPPY once a global volume of 10 million treatment-years has been reached, and an updated estimate from the same group, still under peer-review, suggests that even lower pricing is possible: $35-$46 PPPY, and $25 PPPY once a committed demand of 5-10 million people globally has been reached [10]. Important to note is that the models do not account for drug interaction-related dose adjustments, or for additional loading doses which may be required if clients come late for their next injection visit.

Table 1. Key assumptions on duration, coverage, effectiveness and cost of lenacapavir and TDF/FTC

	Baseline *(current TDF/FTC trajectory)*	**TDF/FTC scale-up**	**Lenacapavir conservative scale-up** *Same initiation rates as TDF/FTC scale-up, 6-12m duration*	**Lenacapavir optimistic scale-up** *Higher initiation rates than TDF/FTC scale-up, 12-24m duration*	**Source**
Coverage scenarios *(% coverage in population)*					
Coverage of TDF/FTC	11% FSW 10% MSM 7% AGYW 0% pregnant women 0.2% heterosexual men	22% FSW 21% MSM 16% AGYW 41% pregnant women 0.5% heterosexual men	6% FSW 7% MSM 5% AGYW 0% pregnant women 0.2% heterosexual men	3% FSW 4% MSM 3% AGYW 0% pregnant women 0.2% heterosexual men	[3] for baseline initiation rates, relative uptake between populations; other initiation rates assumed
Coverage of injectable lenacapavir	0% all populations		40% FSW 28% MSM 31% AGYW 41% pregnant women 1% heterosexual men	65% FSW 49% MSM 51% AGYW 54% pregnant women 3% heterosexual men	Assumed same or double initiation rates as TDF/FTC scale-up

	Baseline *(current TDF/FTC trajectory)*	TDF/FTC scale-up	Lenacapavir conservative scale-up *Same initiation rates as TDF/FTC scale-up, 6-12m duration*	Lenacapavir optimistic scale-up *Higher initiation rates than TDF/FTC scale-up, 12-24m duration*	Source
Duration of protection, including tail protection (months)	3m (women, heterosexual men) 6m (MSM)		6m (+6m tail) (women, heterosexual men) 12m (+6m tail) (MSM)	12m (+6m tail protection) (women, heterosexual men) 24m (+6m tail) (MSM)	[2,11]
Effectiveness in preventing HIV infection	65% (women, heterosexual men) 85% (MSM)		99% (all populations)		[1,2,4–6,12,13]
Cost of provision of PrEP (per person initiated in ZAR) **					
TDF/FTC	R1,050 (women, heterosexual men), R1,319 (MSM)				HE²RO HIV unit cost model
Injectable lenacapavir	N/A		R1,463-R1,459 (women, heterosexual men), R2,518 (MSM)	R2,550-R2,541 (women, heterosexual men), R4,682 (MSM)	

***Full service cost presented includes costs for staff, HIV and laboratory testing, drugs, consumables and overheads. TDF/FTC price for drug only = R64.85 per month; assumed price for lenacapavir (drug only, includes cost of loading dose) = $100 or R1,860 PPPY.*

Cost effectiveness

Cost effectiveness was estimated over a 20-year time horizon (2026-2045) as incremental cost per HIV infection averted and incremental cost per life year saved. Threshold prices for lenacapavir were estimated to determine the price point at which it would be as cost-effective as further scaling up TDF/FTC. Prices for injections and loading dose tablets were calculated separately, proportionally allocated based on the ratio of active pharmaceutical ingredient (API) in each formulation: 927mg lenacapavir per injection vs 1200mg loading dose.

Sensitivity analysis

A probabilistic sensitivity analysis was conducted to assess the uncertainty of 58 parameters in the model, including PrEP-specific parameters such as effectiveness of TDF/FTC and lenacapavir, tail protection of lenacapavir and reduced condom use while on either PrEP type, and consisted of 1,000 Monte Carlo simulations sampled data from predetermined distributions for all parameters. Median estimates of the threshold price with 2.5th and 97.5th percentiles.

4 RESULTS

Epidemiological impact

Our optimistic lenacapavir scenario averted up to 52,200 HIV infections per year over the modelled period, while our conservative lenacapavir scenario averted up to 33,000 infections per year. In comparison, TDF/FTC scale-up averted a maximum of 8,600 infections per year. Over 20 years combined, lenacapavir scenarios averted 20%-32% of new HIV infections over baseline compared to 5% with TDF/FTC scale-up.

Costs, cost-effectiveness and price threshold estimates

Assuming a price for lenacapavir of $100/R1,860 PPPY, total HIV programme costs would increase by 5%-17% over 2026-2045, depending on uptake and duration. In comparison, TDF/FTC scale-up at current prices will increase the cost of the HIV programme by 3% over the same period (Table 2). The incremental cost-effectiveness ratios (ICERs) of oral TDF/FTC scale-up were R177,691/HIV infection averted and R139,303/life year saved over baseline. At an assumed price of $100 PPPY, lenacapavir would be more cost-effective than oral TDF/FTC scale-up, even at higher uptake and duration, with R74,392-R147,232/HIV infection averted across scenarios and R60,388-R118,229/life year saved. In terms of averting disability-adjusted life years (DALYs), cost-effectiveness for scaling up the different PrEP modalities were R29,729/DALY averted (oral TDF/FTC), R27,567/DALY averted (conservative lenacapavir scale-up), and R64,087/DALY averted (optimistic lenacapavir scale-up).

Under the conservative scenario, the price of lenacapavir would need to be R1,985 PPPY for four injections (or R496 per one 1.5ml injection) and R1,285 for the 1200mg loading dose (R321 per 300mg tablet) to be as cost-effective as TDF/FTC scale-up in terms of incremental cost per life year saved. Under the optimistic scenario, the threshold price decreases to R1,366 PPPY (R342 per one 1.5ml injection) and R884 for the 1200mg loading dose (R221 per 300mg tablet). Results comparing cost-effectiveness per HIV infection averted produced similar price thresholds.

Table 2. Effect and cost-effectiveness of oral TDF/FTC and long-acting injectable lenacapavir scale-up compared with baseline, over a 20-year period (2026–45)

	Total cost of the HIV programme		Incremental cost effectiveness			New HIV infections		Life years lost due to AIDS		Disability-adjusted life year (DALY)	
Scenario	**Cost (billions, ZAR)**	**Incremental cost over baseline, %**	**Cost per infection averted (ZAR)**	**Cost per life year saved (ZAR)**	**Cost per DALY averted (ZAR)**	**Number (millions)**	**% averted over baseline**	**Number (millions)**	**% saved over baseline**	**Number (millions)**	**% averted over baseline**
Baseline	R729	-	-	-		2.63	-	18.75	-	23.75	-
Oral TDF/FTC scale up	R752	3%	R177,691	R139,303	R29,729	2.50	5%	18.59	1%	23.01	3%
Lenacapavir (assumed drug price $100/PPPY)											
Conservative: same initiation rates as TDF/FTC; 6-12m duration	R768	5%	R74,392	R60,388	R27,567	2.11	20%	18.11	3%	22.35	6%
Optimistic: higher initiation rates than TDF/FTC, 12-24m duration	R854	17%	R147,232	R118,229	R64,087	1.78	32%	17.69	6%	21.81	8%

Abbreviations: DALY = disability-adjusted life year; TDF/FTC = tenofovir/emtricitabine, ZAR = South African Rand, PPPY=per person per year

Sensitivity analyses and their impact on the threshold price

Accounting for model uncertainty, lenacapavir still showed a substantial impact on the percentage of new HIV infections averted over baseline (95% UB: 17.1%-19.8% for conservative 6-12-month duration; 28.6%-33.8% for optimistic 12-24-month duration), exceeding TDF/FTC (UB 4.6%-4.9%) (Table 3).

Table 3: Uncertainty ranges around the impact of TDF/FTC and lenacapavir over a 20-year time horizon (2026-2045); based on a probabilistic sensitivity analysis

Estimates represented are the median estimate with 2.5th and 97.5th percentiles in brackets.

	New HIV infections		Life years lost due to AIDS	
Scenario	**Number (millions)**	**% averted over baseline**	**Number (millions)**	**% saved over baseline**
Baseline	2.56 (1.83-3.64)	-	18.52 (16.61-20.94)	-
Oral *TDF/FTC* scale up	2.44 (1.74-3.46)	4.8% (4.6%-4.9%)	18.37 (16.49-20.74)	0.8% (0.7%-1.0%)
Lenacapavir				
Conservative: same initiation rates as TDF/FTC, 6-12m duration	2.07 (1.51-2.92)	19.4% (17.1%-19.8%)	17.90 (16.23-20.05)	3.3% (2.3%-4.2%)
Optimistic: higher initiation rates than TDF/FTC, 12-24m duration	1.75 (1.30-2.41)	31.7% (28.6%-33.8%)	17.49 (15.95-19.45)	5.6% (4.0%-7.1%)

Price thresholds varied substantially once the uncertainty in model parameters was accounted for. For a conservative uptake of lenacapavir, with 6-12-month duration and same initiation rates as TDF/FTC, the injection price ranged between R1,217 and R3,313 PPPY (R304-R828/injection), and loading dose R788-R2,144 per person initiated for 4x300mg tablets (Table 4). For an optimistic uptake of lenacapavir, with higher initiation rates and 12-24-month duration, these thresholds ranged between R963 and R2,114 PPPY for injections (R241-R528/injection) and R623-R1,368 per loading dose per initiation (4x300mg tablets).

Table 4: Uncertainty lower and upper bound price thresholds, compared to TDF/FTC scale up cost-effectiveness, over the 20-year period, based on a probabilistic sensitivity analysis

Lenacapavir scenario	**Cost of injections per person per year (ZAR)** (4x 1.5ml 463mg injections per year)	**Cost per loading dose per initiation (ZAR)** (4x 300mg tablets per initiation)
Conservative: same initiation rates as TDF/FTC, 6-12m duration	R1,217 - R3,313	R788 - R2,144
Optimistic: higher initiation rates than TDF/FTC, 12-24m duration	R963 - R2,114	R623 - R1,368

5 Published Health Economics

There are a limited number of published cost-effectiveness studies on lenacapavir for HIV prevention. Existing cost-effectiveness analyses of lenacapavir for HIV prevention highlight its potential to significantly reduce HIV incidence, while mentioning critical challenges related to affordability and access. A modeling analysis for Eastern and Southern Africa, including South Africa, Zimbabwe, and western Kenya, projected that lenacapavir could avert 12.3%-18.0% of infections over 10 years at a coverage of 1.6%-4.0% of the population, with maximum per-dose prices ranging from $16.58 in western Kenya to $106.28 in South Africa when compared to a cost-effectiveness threshold of <US$500 per disability-adjusted life-year averted in 2021 USD [14]. If adjusting these estimates for inflation using South African consumer price index figures and above-mentioned exchange rates for 2025, these would be equivalent to R4,888 PPPY in 2025. In a higher coverage scenario, prices would need to be lower still to maintain cost-effectiveness, emphasizing that widespread impact is contingent on reduced costs [14]. Another modeling study evaluating lenacapavir impact and cost-effectiveness for South Africa found that it would significantly reduce HIV acquisitions, by 22% with 5% coverage of populations groups prioritized by HIV risk, and up to 35% with 20% risk-prioritized coverage [15]. To be cost-effective under a threshold of US$500 per disability-adjusted life-year averted, the price per person per year for 5% risk-prioritized coverage is $105.98 PPPY (95% confidence interval $97.64-$114.42) (the equivalent price in 2025 ZAR would be R2,437 PPPY). This maximum annual cost decreases with higher coverage, reaching $45.91 PPPY (95% confidence interval $43.58-$48.29) for 20% risk-prioritized coverage (the equivalent price in 2025 ZAR would be R1,056 PPPY).

While lenacapavir is sold at a very high price in high income countries (currently ~$28,000 annually for treatment in the United States), cost-of-goods analyses suggest generic versions could be manufactured for as little as $25-$100 per person per year, particularly with large-scale uptake [9,10].

6 Budget Impact Analysis

The cost of lenacapavir for the South African market is currently unknown, and the expected volume/uptake is also uncertain. Consequently, we present budget impacts based on our optimistic and conservative lenacapavir scenarios, using their threshold prices based on cost-effectiveness relative to TDF/FTC scale-up. Under the conservative scenario, the price threshold was R496 per one 1.5ml injection (2 are required per visit) and R321 per 300mg loading dose tablet (4 tablets are required per initiation). Under the optimistic scenario, the price threshold was R342 per one 1.5ml 463mg injection (2 required per visit, R1,366 PPPY) and R221 per 300mg tablet (i.e. R884 for 4 tablets per person initiated).

Under a conservative scenario, we can expect between 590,000 and 1.35 million initiates per year, requiring between 1.23-2.88 million doses per year (Table 5). At a threshold price of R496 per injection and R321 per 300mg loading dose tablet, this would cost between R1.74 billion and R4.02 billion annually, including the cost of the drugs and service provision. This would result in a 5-11% increase in the annual HIV programme budget over the next 5 years, after accounting for the effect of reduced HIV infections and ART need.

Under an optimistic scenario, we can expect between 910,000 and 2.07 million initiates per year, requiring between 3.80-8.75 million doses per year (Table 5). At a threshold price of R342 per injection and R221

per 300mg loading dose tablet, this would cost between R1.98 billion and R4.52 billion annually, including the cost of the drugs and service provision. This would result in a 6-13% increase in the annual HIV programme budget over the next 5 years, after accounting for the effect of reduced HIV infections and ART need.

Table 5. Cost of lenacapavir provision from 2025/2026-2029/30, for conservative and optimistic scale-up scenarios

Conservative lenacapavir scale-up, same initiation rates as TDF/FTC, 6-12-month duration					
	2025/26	**2026/27**	**2027/28**	**2028/29**	**2029/30**
Number people initiated (millions)	0.59	0.78	0.97	1.15	1.35
Number doses required (millions)	0.61	0.82	1.03	1.23	1.44
Total cost (2025 ZAR, billions)	**1.74**	**2.32**	**2.88**	**3.43**	**4.02**
Scenario description and assumptions: *Coverage: 40% FSW, 28% MSM, 7% women (31% AGYW, 41% pregnant women), 1% heterosexual men* *Duration: 6mo (women, non-MSM); 12mo (MSM)* *Cost of drugs: R496/1.5ml 463mg injection (dose: 2 injections/visit); R321 per 300mg loading dose tablet (4 required/initiation)* *Total cost of provision (including drugs) per person initiated: R2,896-R2,900 (women, heterosexual men); R4,022 (MSM)*					
Optimistic lenacapavir scale-up, higher initiation rates than TDF/FTC, 12-24-month duration					
	2025/26	**2026/27**	**2027/28**	**2028/29**	**2029/30**
Number people initiated (millions)	0.91	1.23	1.52	1.78	2.07
Number doses required (millions)	1.90	2.59	3.20	3.76	4.37
Total cost (2025 ZAR, billions)	**1.98**	**2.69**	**3.31**	**3.89**	**4.52**
Scenario description and assumptions: *Coverage: 65% FSW, 49% MSM, 14% women (51% AGYW, 54% pregnant women), 3% heterosexual men* *Duration: 12mo (women, non-MSM); 24mo (MSM)* *Cost of drugs: R342/1.5ml 463mg injection (dose: 2 injections/visit); R221 per 300mg loading dose tablet (4 required/initiation)* *Total cost of provision (including drugs) per person initiated: R2,953-R2,963 (women, heterosexual men); R4,566 (MSM)*					

7 CONCLUSION

Lenacapavir will have a significant impact in reducing HIV infections, by between 20%-32% over baseline, compared to oral TDF/FTC, which even at scaled up levels will only reduce HIV infections by 5%. This is a higher impact than any other HIV prevention intervention studied in consecutive HIV Investment Case analyses since 2015. It is second only to the preventative impact of 95% ART uptake [16]. Lenacapavir can be as cost-effective as further scaling up oral PrEP with TDF/FTC if its price ranges between R342-R496 per injection and R221-R321 per 300mg loading dose tablet, depending on the uptake and duration assumptions. Accounting for uncertainty in the model, these prices ranged from R241 to R828 per 1.5ml injection and from R623 to R2,144 for the loading dose (4x300mg tablets). As the cost-of-goods analyses cited under Hill (2024) and Fortunak (2025) have shown, the price of lenacapavir will depend on the volume of the global market [9,10], most of which will be in South Africa as home to the largest population at risk of HIV acquisition [17].

8 REFERENCES

1 Kelley CF, Acevedo-Quiñones M, Agwu AL, Avihingsanon A, Benson P, Blumenthal J, *et al.* **Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons**. *N Engl J Med* 2025; **392**:1261–1276.

2 Bekker L-G, Das M, Abdool Karim Q, Ahmed K, Batting J, Brumskine W, *et al.* **Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women**. *N Engl J Med* Published Online First: 24 July 2024. doi:10.1056/NEJMoa2407001

3 Johnson L, Dorrington R. Thembisa version 4.8: a model for evaluating the impact of HIV/AIDS in South Africa. ; 2025. https://thembisa.org/content/downloadPage/Thembisa4_7report (accessed 14 Apr2025).

4 Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, *et al.* **On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection**. *N Engl J Med* 2015; **373**:2237–2246.

5 McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, *et al.* **Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial**. *The Lancet* 2016; **387**:53–60.

6 Bekker L-G, Roux S, Sebastien E, Yola N, Amico KR, Hughes JP, *et al.* **Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial**. *Lancet HIV* 2018; **5**:e68–e78.

7 Selected Historical Rates. The South African Reserve Bank. 2025.https://www.resbank.co.za/en/home/what-we-do/statistics/key-statistics/selected-historical-rates (accessed 14 Apr2025).

8 National Department of Health. Master Health Product List. May 2025. https://www.health.gov.za/tenders/ (accessed 21 May2025).

9 Hill A, Levi J, Fairhead C, Pilkington V, Wang J, Johnson M, *et al.* **Lenacapavir to prevent HIV infection: current prices versus estimated costs of production**. *J Antimicrob Chemother* 2024; **79**:2906–2915.

10 Fortunak JM, Layne J, Johnson M, Smalley S, Lutterodt A, Roberts D, *et al.* Lenacapavir to Prevent HIV Infection: Updated Estimated Costs of Production for Generic Treatments. 2025. doi:10.2139/ssrn.5293409

11 Landovitz RJ, Li S, Eron JJ, Grinsztejn B, Dawood H, Liu AY, *et al.* **Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial**. *Lancet HIV* 2020; **7**:e472–e481.

12 Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, *et al.* **Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial**. *The Lancet* 2022; **399**:1779–1789.

13 Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, *et al.* **Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women**. *N Engl J Med* 2021; **385**:595–608.

14 Wu L, Kaftan D, Wittenauer R, Arrouzet C, Patel N, Saravis AL, *et al.* **Health impact, budget impact, and price threshold for cost-effectiveness of lenacapavir for HIV pre-exposure prophylaxis in eastern and southern Africa: a modelling analysis**. *Lancet HIV* 2024; **11**:e765–e773.

15 Kaftan D, Sharma M, Resar D, Milali M, Mudimu E, Wu L, *et al.* **Cost thresholds for anticipated long-acting HIV pre-exposure prophylaxis products in Eastern and Southern Africa: a mathematical modelling study**. *J Int AIDS Soc* 2025; **28**. doi:10.1002/jia2.26427

16 South African HIV Investment Case: 2023 Full report. Health Economics and Epidemiology Research Office (HE2RO); 2023. https://www.heroza.org/publications/south-african-hiv-investment-case/ (accessed 16 Jul2025).

17 Carter A, Zhang M, Tram KH, Walters MK, Jahagirdar D, Brewer ED, *et al.* **Global, regional, and national burden of HIV/AIDS, 1990–2021, and forecasts to 2050, for 204 countries and territories: the Global Burden of Disease Study 2021**. *Lancet HIV* 2024; **11**:e807–e822.

Model developed by: L Jamieson (Thembisa model developed by Dr. LF Johnson at UCT, modified by L Jamieson)
Affiliation: Health Economics and Epidemiology Research Office (HE²RO), University of Witwatersrand

Report updated by: L Jamieson
Affiliation: Health Economics and Epidemiology Research Office (HE²RO), University of Witwatersrand

Conflicts of interest: LJ has no conflicts of interests related to lenacapavir.

Version	Date	Reviewer(s)	Conclusion
First	14 July 2025	Lise Jamieson	Lenacapavir is projected to significantly reduce HIV infections by 20-32% over baseline, outperforming oral TDF/FTC's 5% reduction, even at scaled-up levels. To achieve comparable cost-effectiveness to TDF/FTC in the same population, lenacapavir's price would need to be between R342-R496 per injection and R221-R321 per 300mg loading dose tablet, depending on uptake and duration.