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.

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[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.

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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.

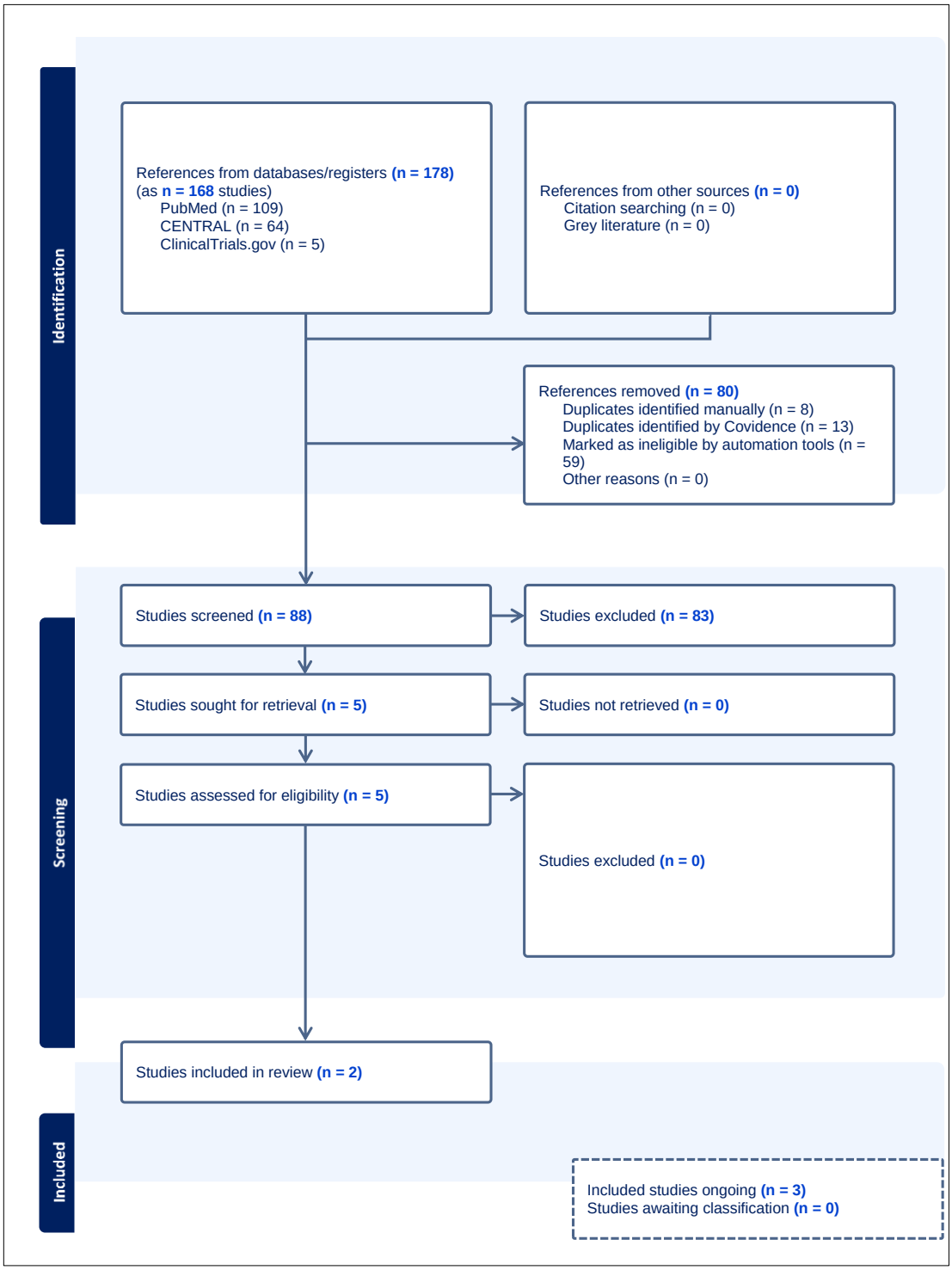

Figure 1: PRISMA flow diagram for review

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).

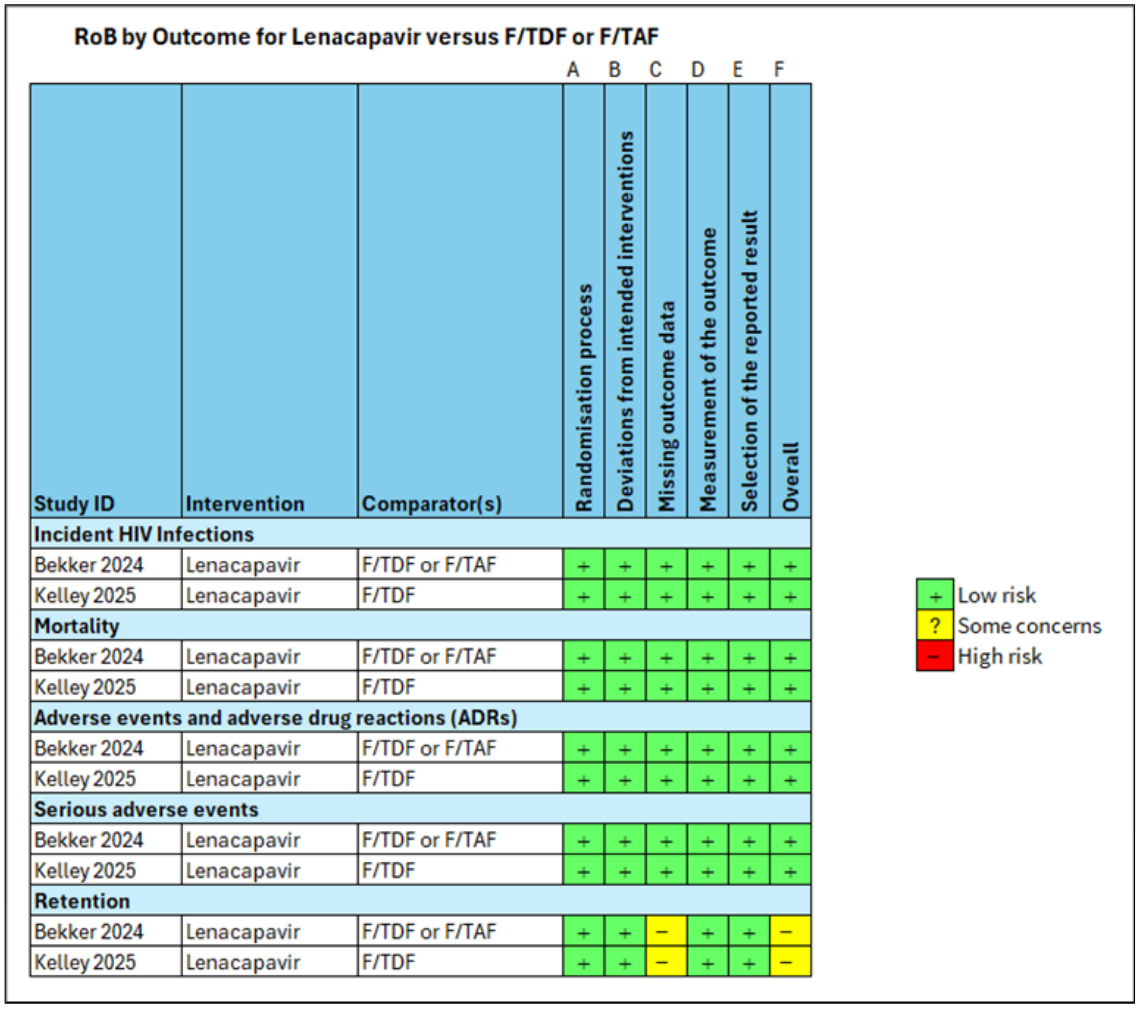

Figure 2: Consolidated Risk of Bias 2.0 by outcome for LEN *vs* F/TDF or F/TAF

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.

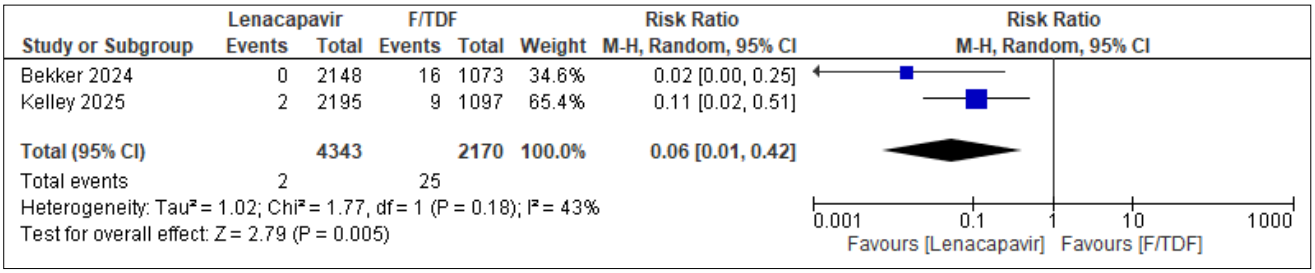

Figure 3: Forest plot of LEN injectable vs. F/TDF; New HIV infections

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.

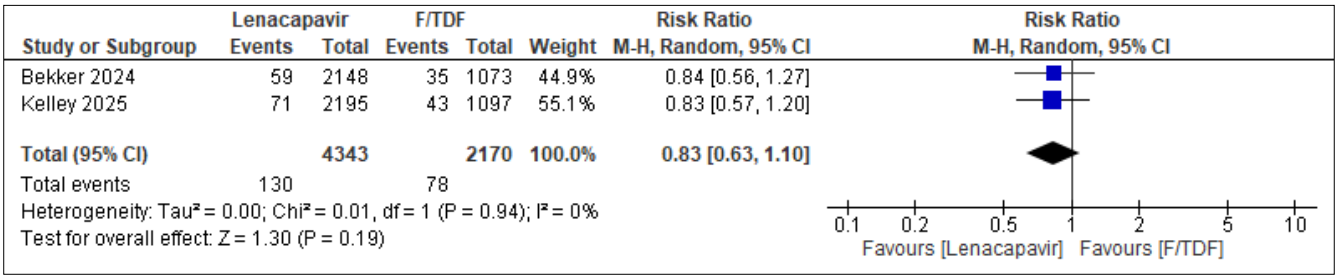

Figure 4: Forest plot of LEN injectable vs. F/TDF; SAEs

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.

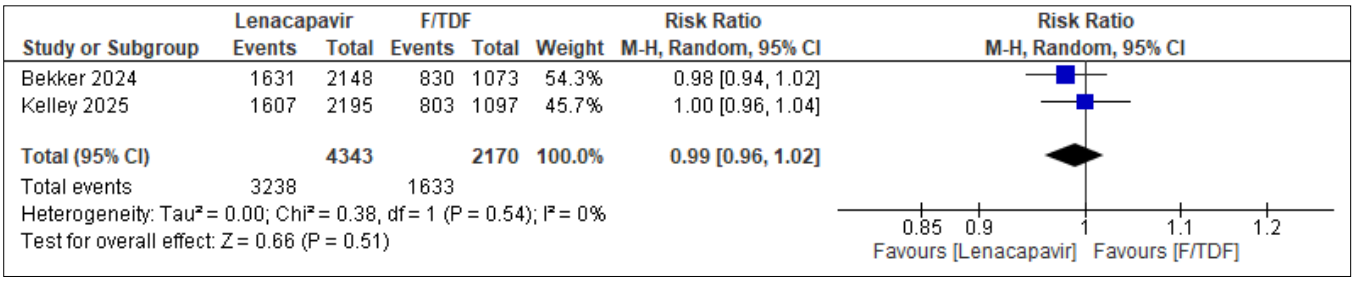

Figure 5: Forest plot of LEN injectable vs. F/TDF; AEs

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.

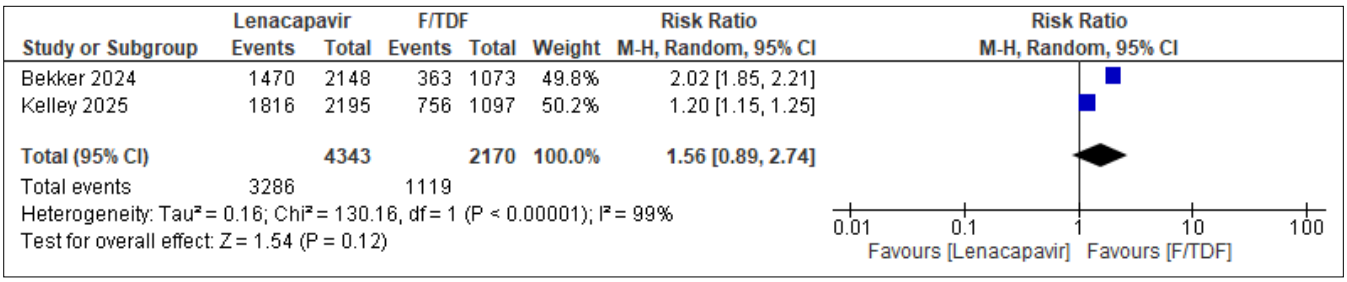

Figure 6: Forest plot of LEN injectable vs. F/TDF; ADRs

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.

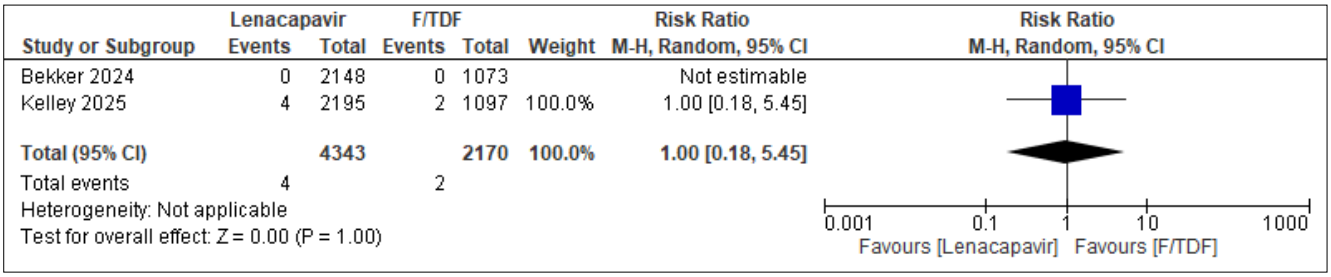

Figure 7: Forest plot of LEN injectable vs. F/TDF; Mortality

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.

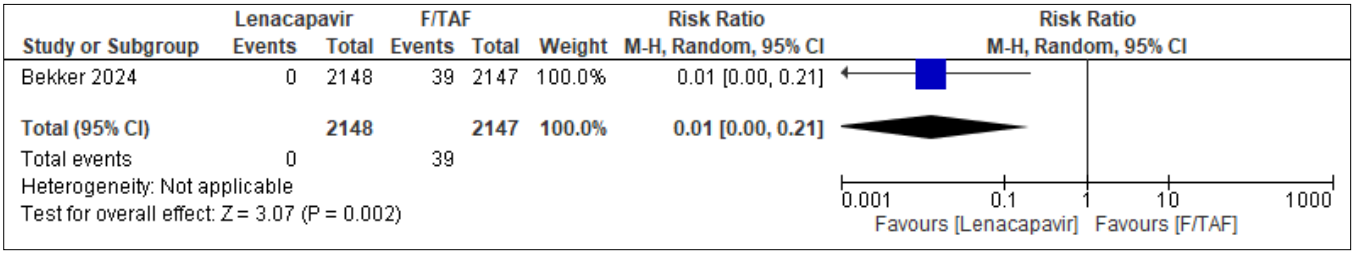

Figure 8: Forest plot of LEN injectable vs. F/TAF; New HIV infections

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.

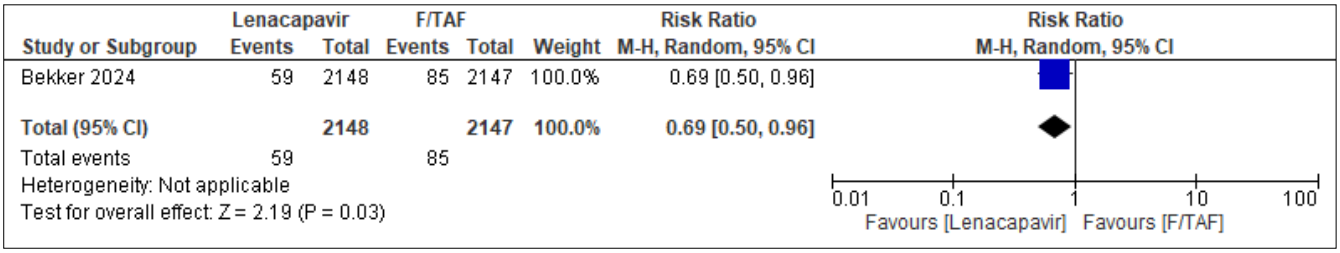

Figure 9: Forest plot of LEN injectable vs. F/TAF; SAEs

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.

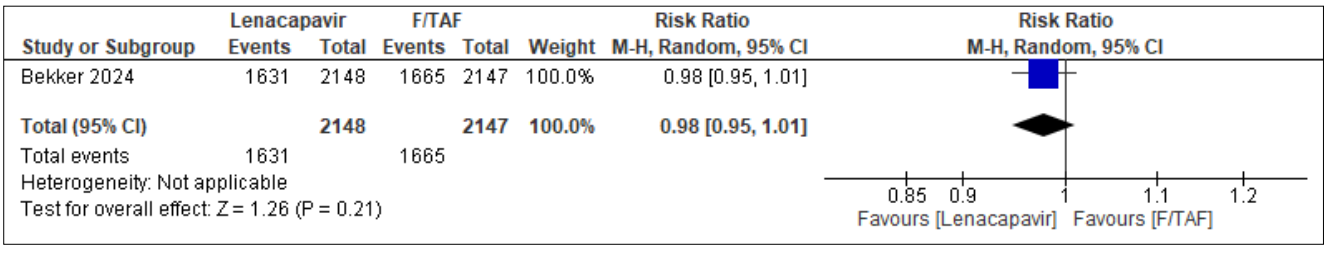

Figure 10: Forest plot of LEN injectable vs. F/TAF; AEs

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.

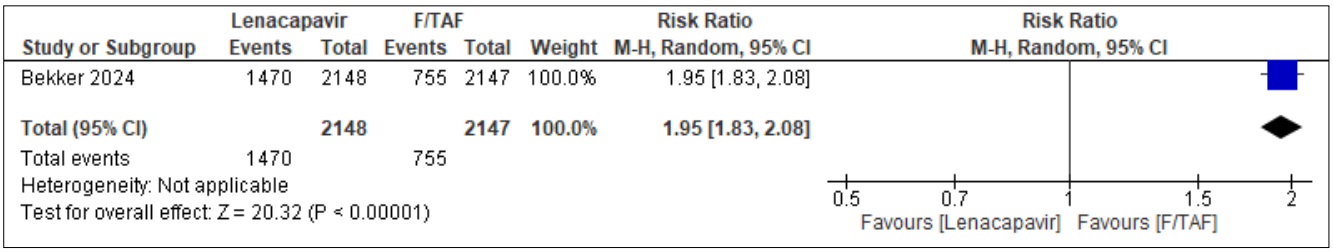

Figure 11: Forest plot of LEN injectable vs. F/TAF; ADRs

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.

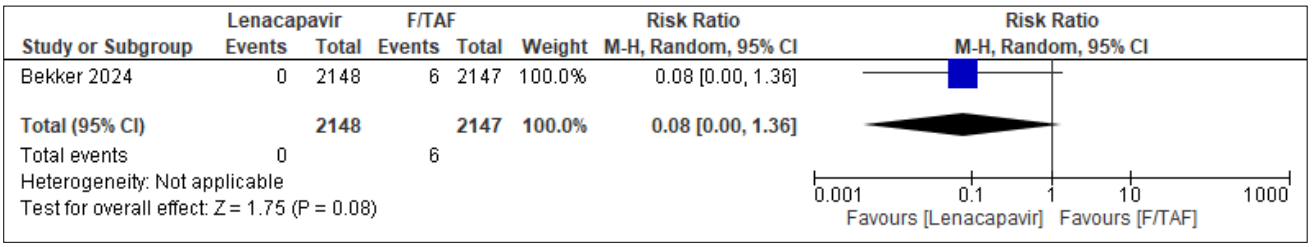

Figure 12: Forest plot of LEN injectable vs. F/TAF; Mortality

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	

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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.

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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

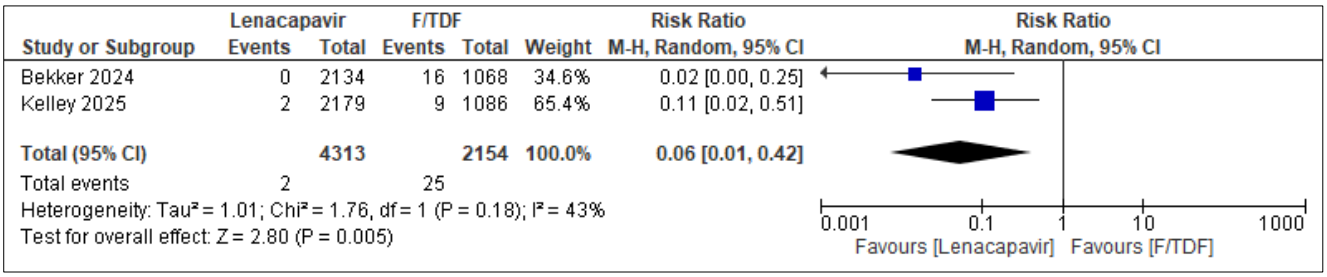
We conducted a sensitivity analysis, where those with baseline HIV infection per arm were excluded from the denominators in each of the study groups. The analysis did not substantially affect the overall relative effect sizes and their 95% CIs. Hence, we report the original forest plots, associated effect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

Effects of the intervention

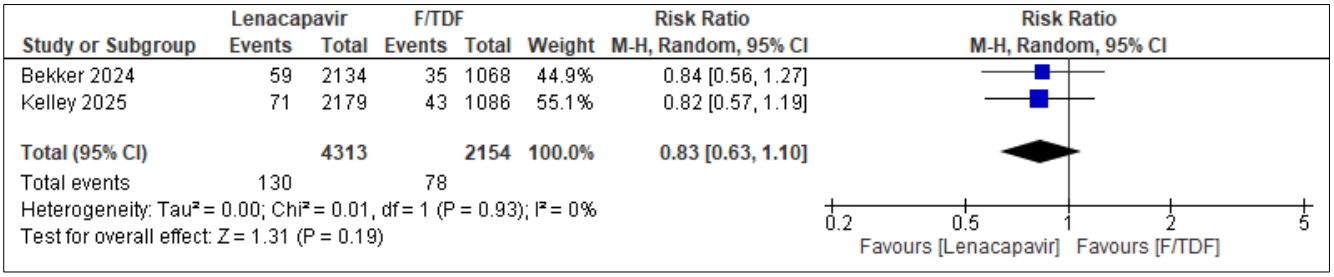
Modified ITT analyses

Lenacapavir injectable versus F/TDF

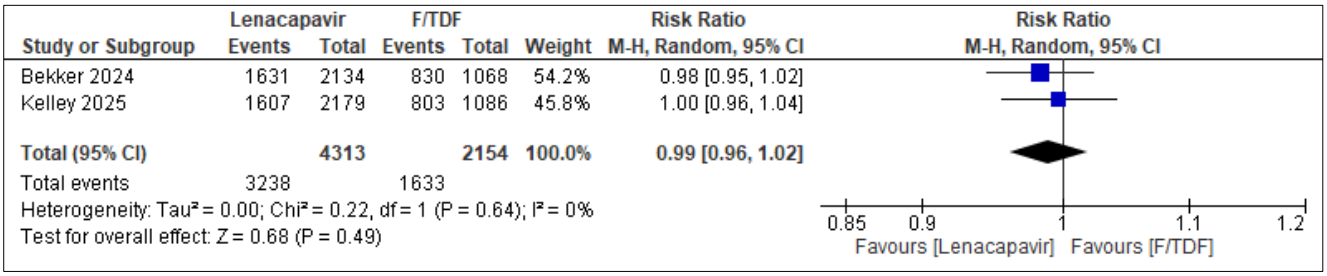
1. New HIV infections



2. SAEs



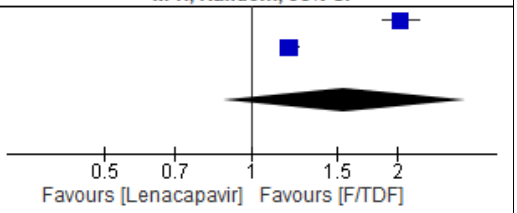
3. AEs



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)

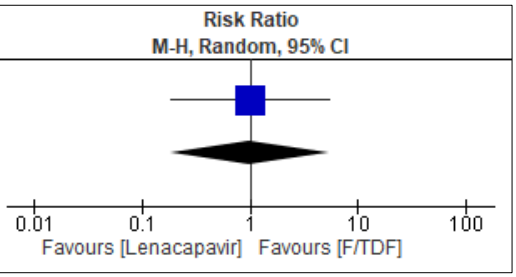


Footnotes
(1) Denominators: No. of participants who received at least one injection
(2) Denominators: No. of participants who received at least one injection

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			

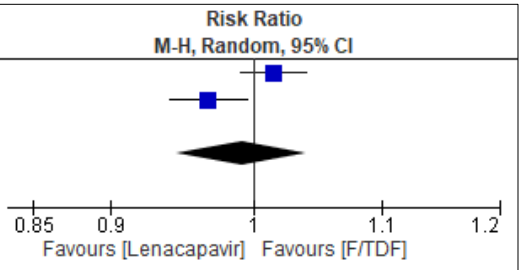
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



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)

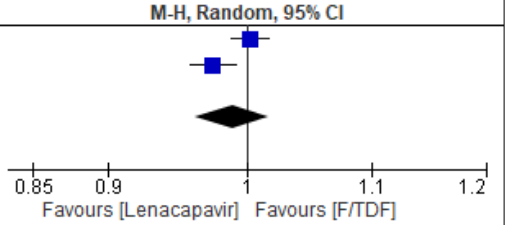


Footnotes
(1) Denominator: No. of participants with at least one post-baseline blood result
(2) Denominator: No. of participants with at least one postbaseline blood result

7. Retention at Week 26

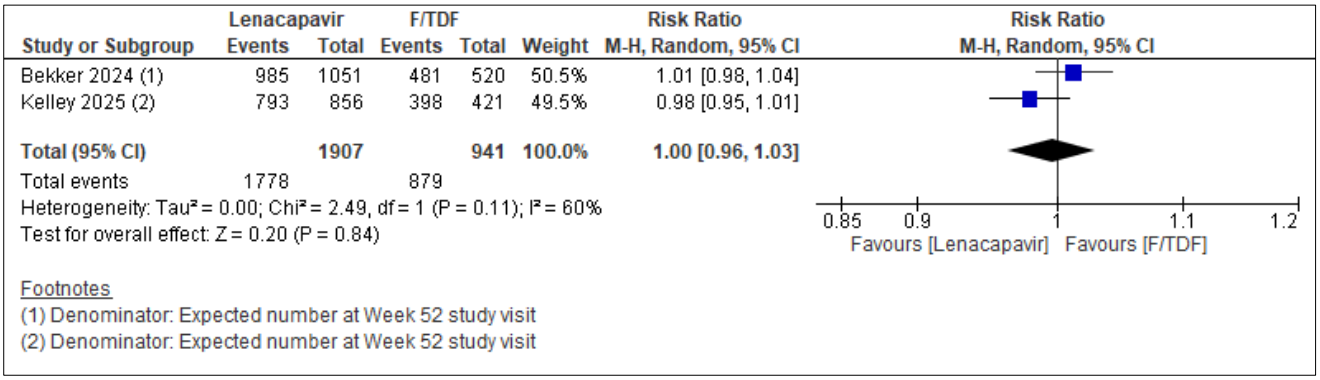
Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	1940	2007	963	999	51.2%	1.00 [0.99, 1.02]
Kelley 2025 (2)	1882	2010	952	991	48.8%	0.97 [0.96, 0.99]
Total (95% CI)		**4017**		**1990**	**100.0%**	**0.99 [0.96, 1.02]**
Total events	3822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



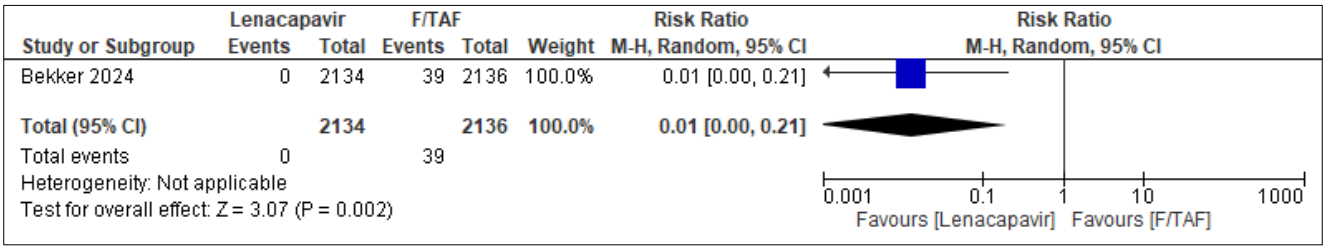
Study or Subgroup	Lenacapavir Events	Total	F/TDF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024 (1)	985	1051	481	520	50.5%	1.01 [0.98, 1.04]
Kelley 2025 (2)	793	856	398	421	49.5%	0.98 [0.95, 1.01]
Total (95% CI)		**1907**		**941**	**100.0%**	**1.00 [0.96, 1.03]**
Total events	1778		879			

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

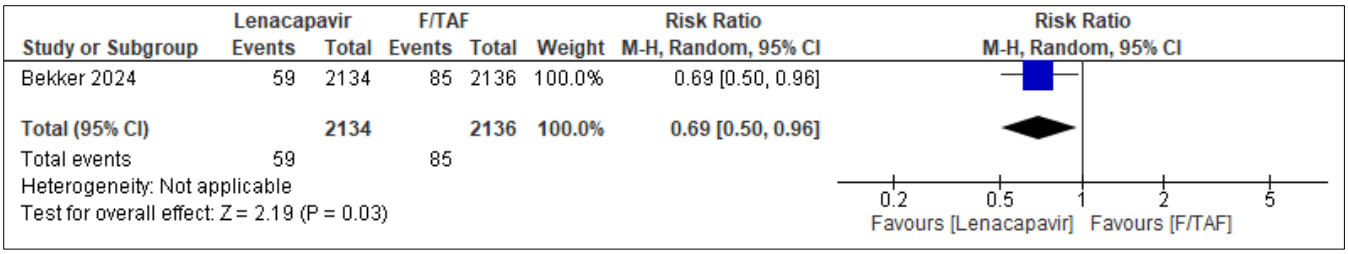
1. New HIV infections



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)

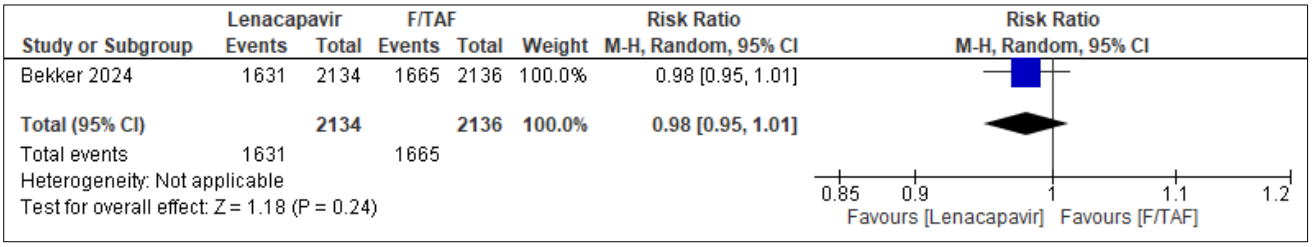
2. SAEs



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



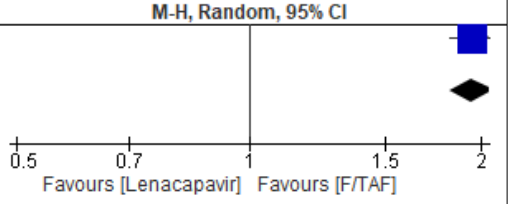
Study or Subgroup	Lenacapavir Events	Total	F/TAF Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bekker 2024	1631	2134	1665	2136	100.0%	0.98 [0.95, 1.01]
Total (95% CI)		**2134**		**2136**	**100.0%**	**0.98 [0.95, 1.01]**
Total events	1631		1665			

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)

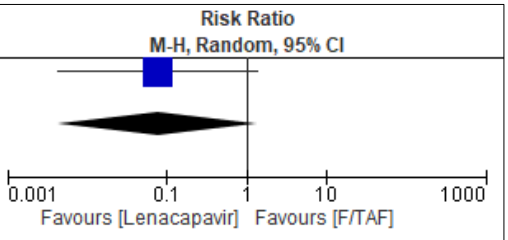


Footnotes
(1) Denominators: No. of participants who received at least one injection

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			

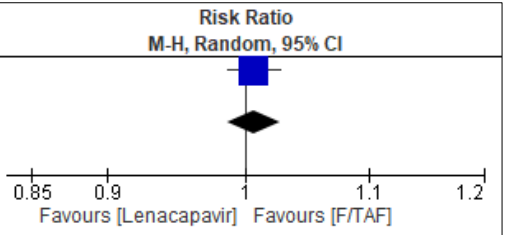
Heterogeneity: Not applicable
Test for overall effect: Z = 1.75 (P = 0.08)



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)

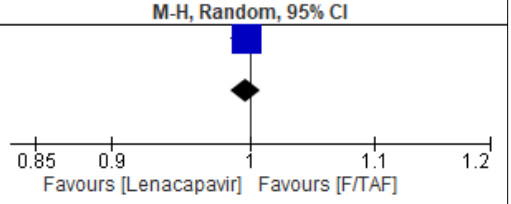


Footnotes
(1) Denominator: No. of participants with at least one post-baseline blood result

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)



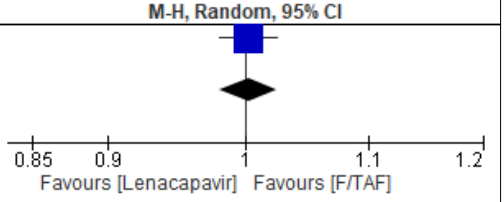
Footnotes
(1) Denominator: Expected number at Week 26 study visit

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