Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable PrEP

WHO Guidelines on LEN for PrEP
https://iris.who.int/bitstream/handle/10665/381892/9789240111608-eng.pdf?sequence=1

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WHO recommendations on HIV pre-exposure prophylaxis (PrEP)

- In 2024, 3.9M people used PrEP at least once (<20% of the 21.2M person target for 2025)
- WHO has recommended four products for use as PrEP:
  - **Oral PrEP containing tenofovir** *(2015)*
  - **Dapivirine vaginal ring** *(2021)*
  - **Long-acting injectable cabotegravir** *(2022)*
  - **Long acting injectable lenacapavir** *(2025)*

As part of comprehensive HIV prevention approaches, based on evidence for effectiveness, safety, community values and preferences, likely cost effectiveness etc.

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Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable PrEP

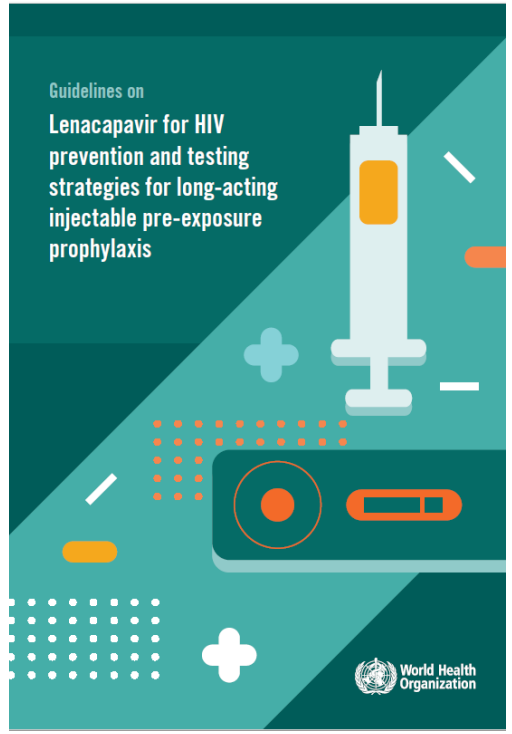
New recommendations

Recommendation [NEW]

Long-acting injectable lenacapavir should be offered as an additional prevention choice for people at risk of HIV, as part of combination prevention approaches. *(strong recommendation, moderate to high certainty of evidence)*

Recommendation [NEW]

Rapid diagnostic tests may be used for HIV testing for initiation, continuation and discontinuation of long-acting PrEP. *(strong recommendation, very low certainty of evidence)*.



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Lenacapavir (LEN) for HIV prevention

WHO Recommendation 2025

Recommendation [NEW]

Long-acting injectable lenacapavir should be offered as an additional prevention choice for people at risk of HIV, as part of combination prevention approaches. *(strong recommendation, moderate to high certainty of evidence)*

- **Lenacapavir (LEN)** is a first in class HIV-1 capsid inhibitor
  - Sub-cutaneous injectable formulation administered every 6 months, accompanied by an oral loading dose
  - Approved by US FDA in 2022 for treatment of multidrug resistant HIV in highly treatment experienced PLHIV, and in June 2025 for HIV prevention

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Dosing for lenacapavir

- **Subcutaneous injections every six month**
  - Day 1: 2 subcutaneous injections of 1.5mL each
  - Every 26 weeks (+/- 2 weeks)

- **Oral loading dose**
  - Day 1: 2 tablets of 300mg each
  - Day 2: 2 tablets of 300mg each

- **Oral loading dose is needed to reach target PK levels within first 3-24 hours of taking first 2 pills**
  - Without the oral loading dose, protection levels from the injection are reached after weeks 3-4
  - No oral loading needed for follow-up injections if they are on time (28 weeks maximum)

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Dosing for Lenacapavir

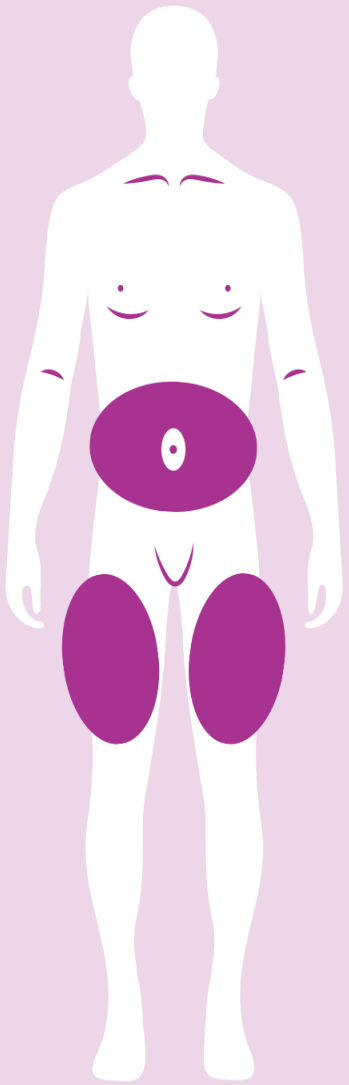
- **Day 1: Initiation injections 1 &2, Loading dose of 2 pills**

- **Day 2: Loading Dose of 2 pills**

- **Follow-up Injections** every 6 months (26 weeks) +/- 14 days. No pills required

LEN Injection site, technique (Video)

https://rise.articulate.com/share/2_N6M1Gu2tg5VxcA_Xl_us9FsH9EzFSd#/lessons/hxi2TN5Xe2s2BsFF_tLl4-qwqRxr-9Fd



- LEN should be injected **subcutaneously** in either the **abdominal** or **thigh** area
  - If the abdominal area is chosen, the injection should be within **5 cm (2 in) of the navel**
  - The second injection should be at least 10 cm (4 in) from the first
- Providers should choose the location per client's preferences: area with more body fat and skin

Step 1: Gently pinch a broad portion of skin at the injection site
Step 2: At the apex of pinched skin, insert the needle fully, perpendicular (at a 90° angle) to the skin
Step 3: Slowly push the plunger to carefully perform the injection. Pause for several seconds after injecting. Remove the needle from the skin at the same angle it was inserted
Step 4: Apply dry gauze at the injection site, and then replace it with a bandage
Step 5: Dispose of needle and syringe in sharps container.
REPEAT STEPS 1-5 FOR SECOND INJECTION

Efficacy and safety for LEN for prevention

- PURPOSE 1 and 2 trials demonstrated **high efficacy**, showing a significant reduction in HIV acquisition compared with background incidence and daily oral PrEP (TDF/FTC)
  - **PURPOSE 1: 100% efficacy** (0 HIV infections) compared to background HIV incidence
  - **PURPOSE 2: 96% efficacy** (2 HIV infections among 2180 participants) compared background HIV incidence rates
- Rates of most **adverse events were similar between LEN and oral PrEP** (TDF/FTC), and most were mild or moderate
  - Injection site reactions (ISRs) to LEN were common, but typically mild, decreased over time and did not lead to high rates of discontinuation
- No difference in safety or efficacy for adolescents aged 16-17 years
- Data remain limited for some key populations, such as PWID (explored in PURPOSE 4)


ORIGINAL ARTICLE

Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons

ABSTRACT

BACKGROUND

Twice-yearly subcutaneous lenacapavir has been shown to be efficacious for prevention of HIV infection in cisgender women. The efficacy of lenacapavir for preexposure prophylaxis (PrEP) in cisgender men, transgender women, transgender men, and gender-nonbinary persons is unclear.

METHODS

In this phase 3, double-blind, randomized, active-controlled trial, we randomly assigned participants in a 2:1 ratio to receive subcutaneous lenacapavir every 26 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

ABSTRACT

BACKGROUND

There are gaps in uptake of, adherence to, and persistence in the use of preexposure prophylaxis for human immunodeficiency virus (HIV) prevention among cisgender women.

METHODS

We conducted a phase 3, double-blind, randomized, controlled trial involving adolescent girls and young women in South Africa and Uganda. Participants were assigned in a 2:2:1 ratio to receive subcutaneous lenacapavir every 26 weeks, daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active controls; all participants also received the alternate subcutaneous or oral placebo. We assessed the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection with the estimated background incidence in the

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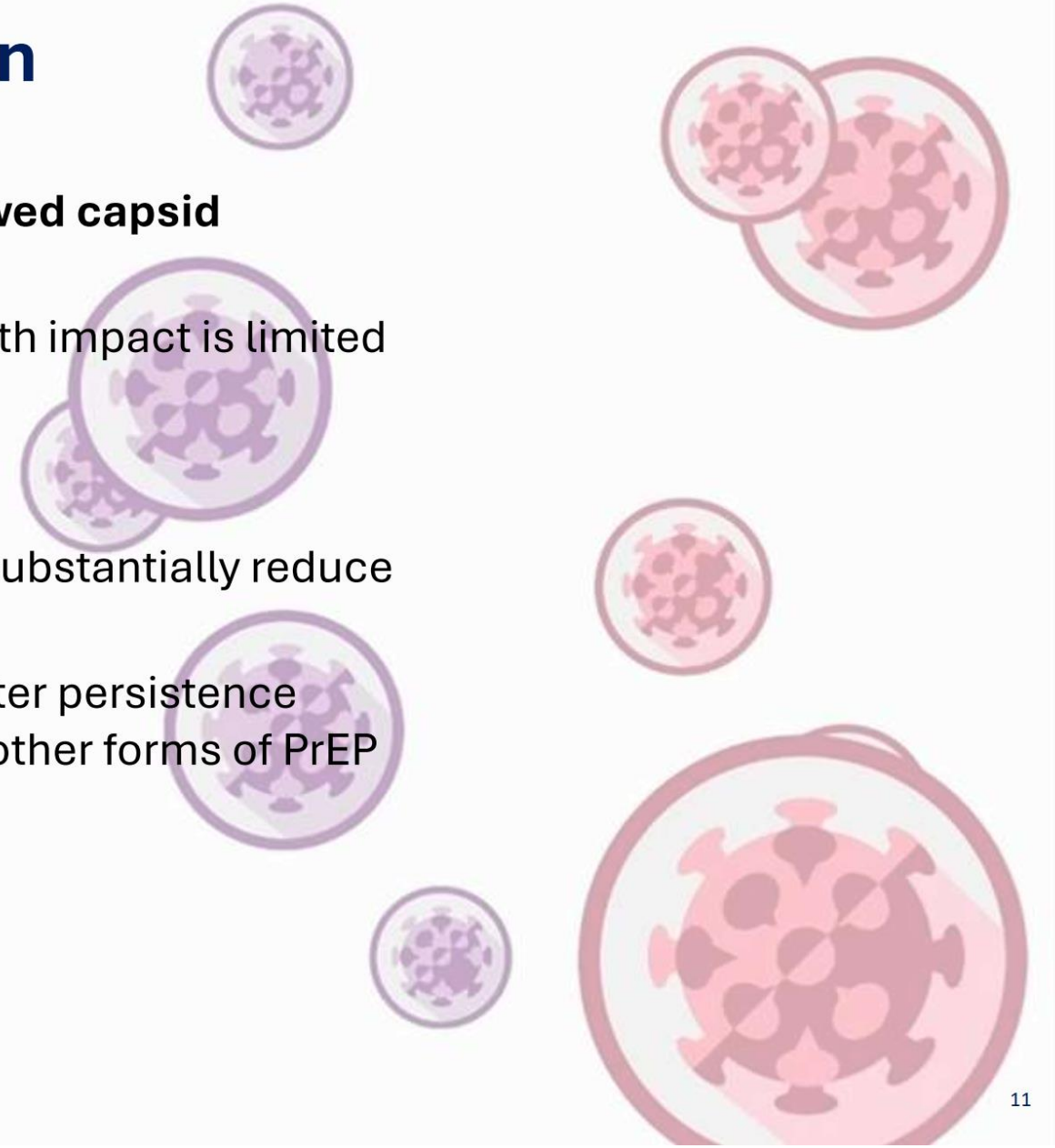
Impact of LEN on HIV prevention

- **Two breakthrough infections in PURPOSE 2 showed capsid inhibitor resistance (N74D)**
  - As LEN is first in class ARV, current public health impact is limited
  - Ongoing surveillance is needed

- Mathematical modelling suggests that LEN could substantially reduce new HIV infections
  - Increased coverage, higher efficacy and/or better persistence contributed to higher impacts compared with other forms of PrEP in some models



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Lenacapavir use in pregnancy

- **LEN showed no increase in adverse pregnancy or birth outcomes** in pregnancies with outcome data available in PURPOSE 1. There were a total of 193 pregnancies in PURPOSE 1 among 184 women.
- **No dose adjustment is likely to be required during pregnancy**, with pharmacokinetic data indicating standard dosing remains effective.
- **WHO-recommended PrEP products, including LEN, can be continued** during pregnancy and breastfeeding.
- When someone becomes pregnant, the choice to start, continue, stop, or switch PrEP, should be made by the individual, following discussion of the risks and benefits with a health care provider.

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Values, preferences and feasibility for LEN

- **Injectable PrEP was highly acceptable to individuals**, with users citing convenience, potential for discreet use and effectiveness
  - Interim analysis of PURPOSE 1, suggested 2/3 of participants preferred LEN
  - Clear preference for less frequent dosing (e.g. ≥6 months), due to reduced user burden
  - **Concerns varied by setting**, including injection-related pain, potential side effects, scheduling challenges for follow-up doses and costs
- Evidence suggests **providers find injectable PrEP acceptable and feasible**, although concerns remain about costs and logistics
- **LEN is likely to be feasible for implementation in national PrEP programs**
  - Clinical trial sites across multiple countries successfully delivered LEN, suggesting integration into existing services is achievable
  - Indirect evidence from CAB-LA implementation into broader programmes supports the feasibility of implementing LEN

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Toxicity and drug-to-drug interactions

Drug class	Interaction and management
Antibiotics for treatment of TB: Rifabutin, Rifampicin, Rifapentine	**Potential interaction which requires a dose adjustment** Induction of CYP3A4 can substantially reduce LEN concentrations which may result in loss of its prevention efficacy.
Anticonvulsants: Carbamazepine, Phenobarbital, Phenytoin	
Illicit/recreational drugs: Ketamin	**Potential interaction, which may persist after discontinuation of lenacapavir:** These drugs concentrations may increase due to inhibition of CYP3A4 by LEN.
Drugs used for erectile dysfunction: Avanafil, Sildenafil, Tadalafil, Vardenafil	
Gender-affirming hormones	**No dose adjustment required:** LEN is a moderate inhibitor of CYP3A4 and could potentially increase exposure of these hormones, although to an extent that does not require dose adjustment
Hormonal contraceptives	

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Note: LEN is **not contraindicated for individuals with HBV or HCV**.

Offering **choice** in prevention and PrEP products can increase uptake, effective use, satisfaction and protection

- WHO does not support one PrEP product over any other
- Providers should explain the advantages, disadvantages and features of different options
- Different attributes may be more or less important for different people
- Choice is dynamic

The best PrEP product is the one someone wants to use and will use well

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Implications for implementation

- **LEN** should be delivered as an **additional prevention choice** alongside other HIV PrEP and prevention options.
- Considerations for introduction should include:
  - population-specific needs e.g. adolescents, KPs, PBF
  - **differentiated service delivery** models
  - **integration** of services to maximize acceptability and access
  - **awareness raising** and **demand generation** activities
  - **provider training**
- Monitoring and surveillance systems should include:
  - routine PrEP data collection AND
  - adverse event monitoring during **pregnancy and breastfeeding**
  - **seroconversions** and **drug resistance (LEN specific)**

- Successful introduction of LEN depends on the full participation of **communities** in designing, implementing and monitoring programmes.

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Lenacapavir: Implementation considerations (2)

- **Differentiated service delivery**
  - Task sharing with nurses, pharmacists, community health workers and peers;
  - Delivery in community settings, such as pharmacies, mobile sites, community-based organizations and other types of community centres;
  - Leveraging virtual interventions and telehealth, including digital tools and delivery channels;
  - integration with other services, including antenatal and postnatal services.

- LEN should be offered as part of a comprehensive person-centred service package tailored to the local context and the needs and preferences of individuals. Clients should be offered a choice of PrEP products, as this can increase **PrEP uptake, coverage and persistence**.

Provision of other PrEP Options (Oral PrEP, DVR, CAB-LA	Sexual and reproductive health services (including contraceptive services)
Condoms and lubricants	Gender-based violence services
PEP	Harm reduction services for PWIDs
Screening and treatment of STIs and viral hepatitis	Mental health support

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PROVIDER TRAINING TOOLKIT ON USE OF ORAL AND LONG-ACTING HIV PRE-EXPOSURE PROPHYLAXIS (PREP)

- Suite of training materials to train providers on delivery of all 4 WHO recommended PrEP products: oral, DVR, CAB-LA, LEN
- Four self-paced digital lessons
- Downloadable job aids
- Adaptable resources for classroom-based training
- Complementary mobile application for access to WHO guidance and interactive clinical tools

Learn more at:

jhpiego.org/HIVPrEPToolkit

Simplified testing for long-acting PrEP

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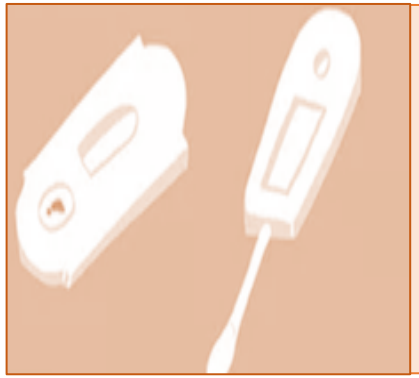
New WHO recommendation

Rapid diagnostic tests may be used for HIV testing for initiation, continuation and discontinuation of long-acting PrEP

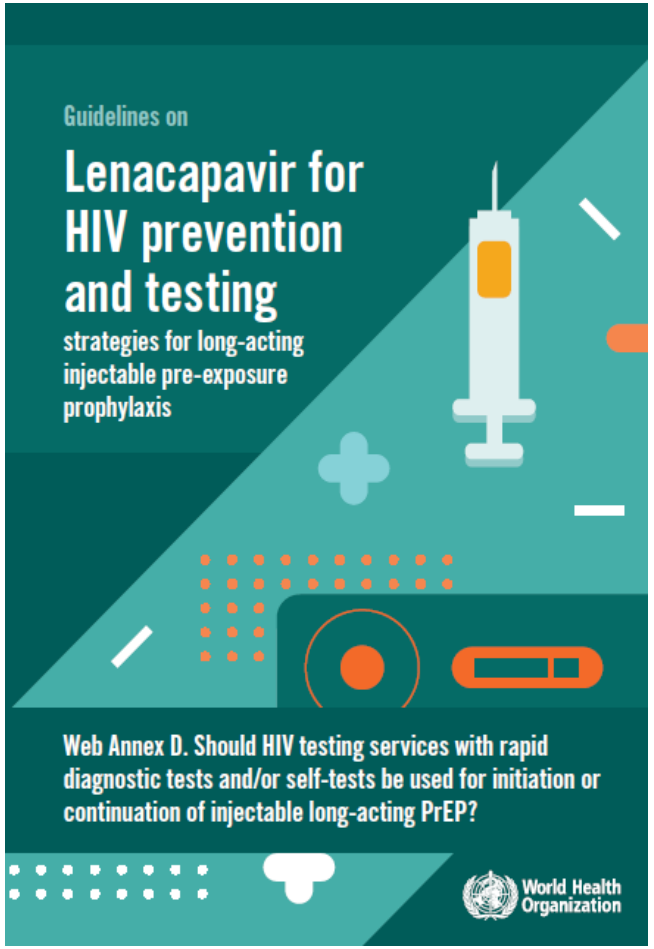
(strong recommendation, very low certainty of evidence)



- HIVST may be an important implementation consideration in some contexts, increasing programme flexibility and testing frequency
- Implementation research remains important in this area
- WHO will review emerging evidence as soon as it is available and update guidance

HIV RDTs for injectable LA-PrEP

WHO Recommendation 2025



- WHO recommends using **HIV RDTs** for individuals initiating or continuing **long-acting injectable PrEP**, such as CAB-LA and LEN
- **HIVST** remains a recommended option **for oral PrEP, the DVR and post-exposure prophylaxis (PEP),** as it may offer additional flexibility across PrEP programmes
  - **Providers generally welcomed simplified testing strategies**, emphasizing the importance of rapid, same-day results to avoid delays in initiating or continuing injectable LA-PrEP).
  - **End users favoured test methods that reduce clinic visits**, suggesting potential future roles for HIVST in injectable LA-PrEP delivery.
- **Further implementation research is needed** to fully determine the **role of HIVST** in delivering injectable LA-PrEP

Research Gaps

- Implementation science can provide answers to outstanding questions on:
  - Product choice and switching in the real world
  - Optimal service delivery approaches, including differentiated service delivery models, for access, uptake and persistence (on-time injections)
  - Adolescents, key populations (including PWID) and other vulnerable populations
  - Costs and impact country-specific modelling
  - Drug resistance
- **Further research should not delay programmatic implementation in countries**

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Next steps

- LEN has received US-FDA approval for prevention, EU market authorization (and EMA positive opinion for EU-M4all), under consideration in additional regulatory agencies
- LEN is being considered for WHO pre-qualification
- Collaborative registration procedure (CRP) through WHO: Gilead submission expected October 2025
- 9 early adopter countries are expected to begin programmatic LEN implementation by early 2026
- Countries are getting ready for LEN e.g. updating their guidelines, creating implementation plans, undertaking modelling/estimating demand

JIAS

COMMENTARY

Seizing the moment: the potential of PrEP choice and innovation to transform HIV prevention

Heather-Marie A. Schmidt[1,2], Mateo Prochazka[1], Heather Ingold[1], Sushena Reza-Paul[1,3], Thato Chidarikire[4], Irvin Romyo[5] and Michelle Rudolph[1,6]

Abstract

Introduction: The potential of pre-exposure prophylaxis (PrEP), as a highly effective and empowering HIV prevention intervention, has not yet been realized. Despite the recent acceleration in the scale-up of oral PrEP, there is a substantial unmet PrEP need, and the world is not on track to meet the 2025 prevention targets. New PrEP products, and service delivery approaches, could support greater access, uptake, persistence and effective use. This commentary discusses how offering choice in PrEP products and service delivery innovations could transform global HIV prevention efforts.

Discussion: Although oral PrEP accounts for almost all PrEP use to date, slow rollout and challenges in effective use and persistence have limited the global impact. Innovative products like long-acting injectable cabotegravir and injectable lenacapavir can overcome some of the challenges associated with oral PrEP. Expanding PrEP choices is also essential for addressing diverse individual preferences and maximizing prevention outcomes. Real-world evidence suggests that offering increased options can drive demand and increase coverage of prevention.

Equally critical is tailoring service delivery through differentiated service delivery (DSD) models that prioritize accessibility

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