New science and guidelines on long-acting prevention technologies

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On behalf of the WHO PrEP and PEP team: Michelle Rodolph, Mateo Prochazka, Heather Ingold and Heather-Marie Schmidt

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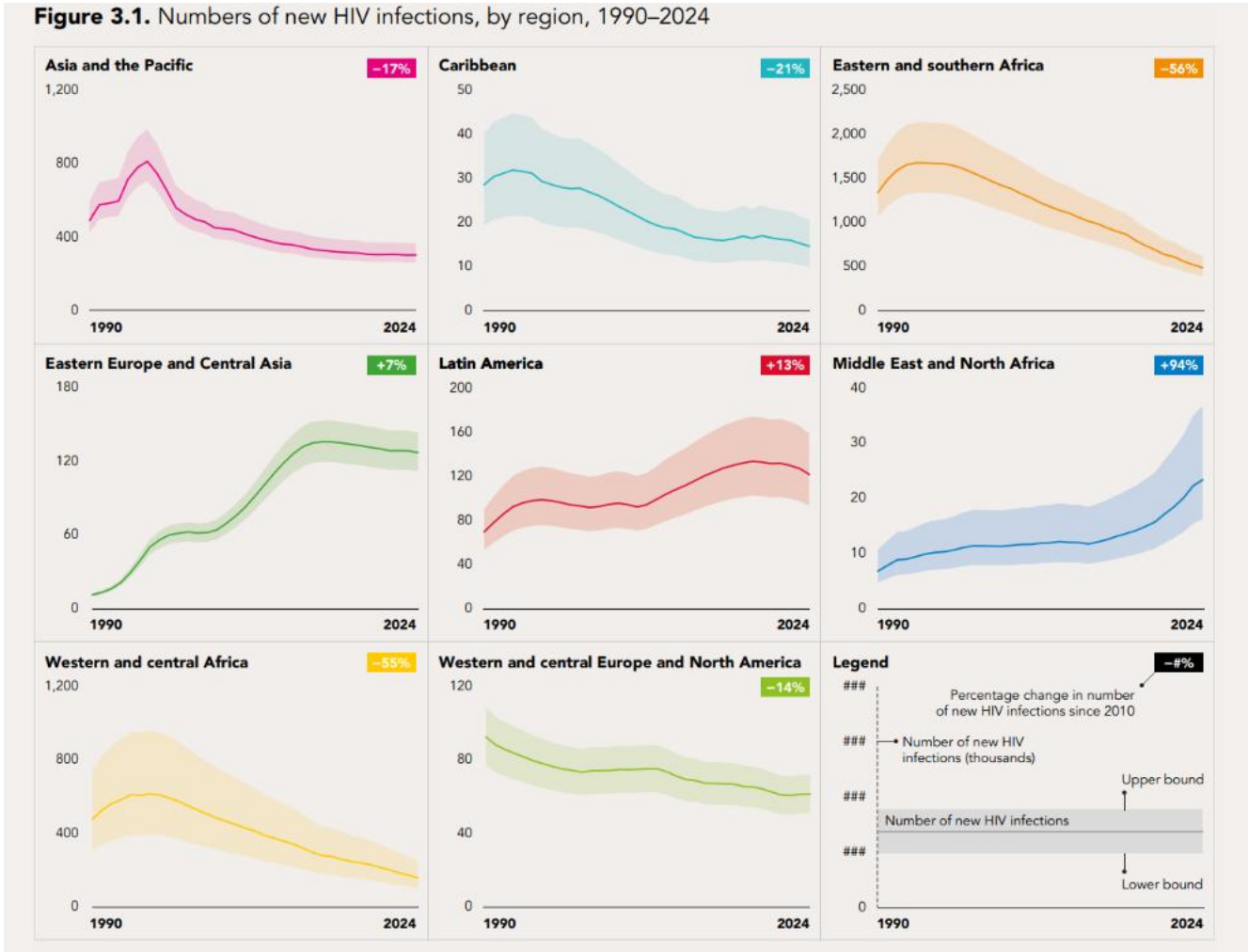
PrEP is not being used to it's full potential

3.9M people used PrEP at least once in 2024; the majority used oral PrEP



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Source: Global AIDS Monitoring, 2025 (https://aidsinfo.unaids.org/).

The HIV Prevention Pipeline

In development: Preclinical and clinical

- Long-acting implants
- Preventive vaccines
- Multipurpose vaginal ring
- Long-acting vaginal ring
- Patches
- Douche
- Vaginal Film
- Vaginal Gel
- Monthly oral PrEP
- Vaginal/ Mucosal Inserts
- Broadly neutralizing antibodies
- Injectable

In development: Efficacy trials under way

- Daily oral PrEP [1]
- Combo oral PrEP/OC

Possible dual pill to market by 2025 [2]

Newly Approved and Recommended

- Dapivirine vaginal ring
- Injectable cabotegravir
- Injectable lenacapavir

And in implementation science projects:

www.prepwatch.org/resources/implementation-study-tracker/

Currently available

- HIV treatment for people living with HIV/U=U
- Male & female condoms
- Voluntary medical male circumcision
- Syringe exchange programs
- Daily oral PrEP

Event-driven for some populations

- PEP

[1] In Oct 2019, US FDA approved F/TAF for adults and adolescents who have no HIV risk from receptive vaginal sex; still in development for cisgender women.

[2] Efficacy trials not required; bioequivalency of the two approved products when dosed together may be all that is required.

AVAC Advocacy. Access. Equity. avac.org June 2025

WHO recommendations on HIV pre-exposure prophylaxis (PrEP)

- 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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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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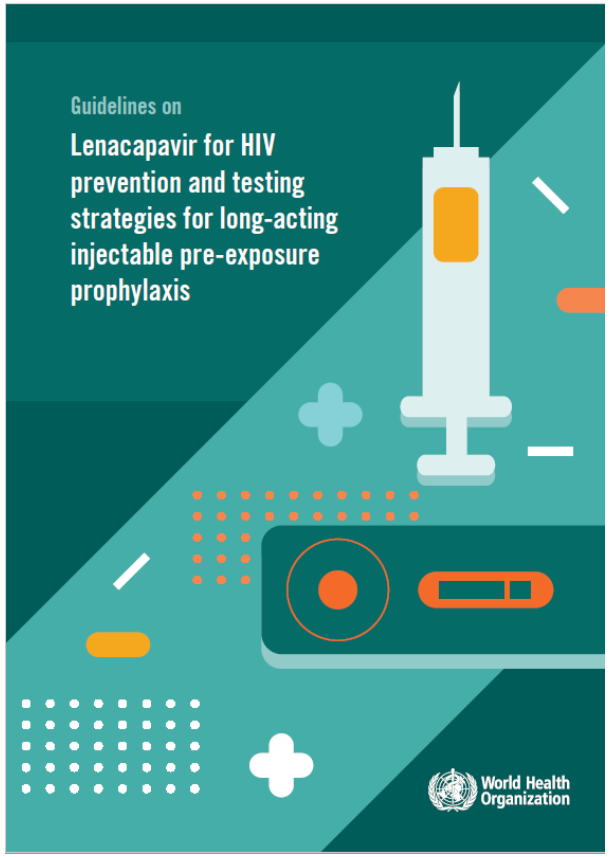
Lenacapavir (LEN) for HIV prevention

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
  - LEN for PrEP has US-FDA approval for prevention, EU market authorization (and EMA positive opinion for EU-M4all), under consideration in additional regulatory agencies, WHO pre-qualification and for collaborative regulatory approval
  - 9 early adopter countries are expected to begin programmatic LEN implementation by early 2026 through GF; PEPFAR is also supporting LEN

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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)
  - *NOTE: for presentations >28 weeks, LEN must be restarted if no oral LEN bridging*

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

- **Oral loading doses are needed to reach target PK levels <3-24 hours of taking first 2 pills**

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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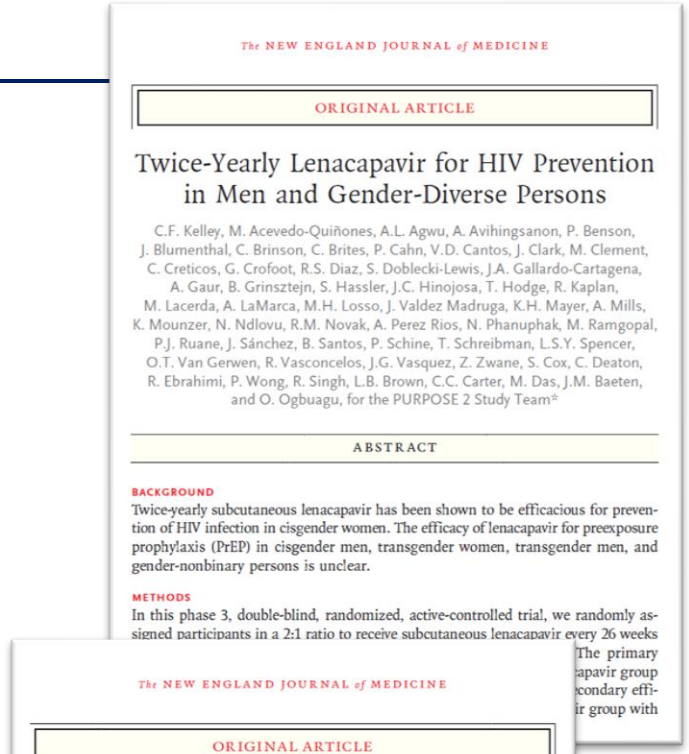
Efficacy and safety for LEN for prevention

- 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)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

C.F. Kelley, M. Acevedo-Quiñones, A.L. Agwu, A. Avihingsanon, P. Benson, J. Blumenthal, C. Brinson, C. Brites, P. Cahn, V.D. Cantos, J. Clark, M. Clement, C. Creticos, G. Crofoot, R.S. Diaz, S. Doblecki-Lewis, J.A. Gallardo-Cartagena, A. Gaur, B. Grinsztejn, S. Hassler, J.C. Hinojosa, T. Hodge, R. Kaplan, M. Lacerda, A. LaMarca, M.H. Losso, J. Valdez Madruga, K.H. Mayer, A. Mills, K. Mounzer, N. Ndlovu, R.M. Novak, A. Perez Rios, N. Phanuphak, M. Ramgopal, P.J. Ruane, J. Sánchez, B. Santos, P. Schine, T. Schreibman, L.S.Y. Spencer, O.T. Van Gerwen, R. Vasconcelos, J.G. Vasquez, Z. Zwane, S. Cox, C. Deaton, R. Ebrahimi, P. Wong, R. Singh, L.B. Brown, C.C. Carter, M. Das, J.M. Baeten, and O. Ogbuagu, for the PURPOSE 2 Study Team*

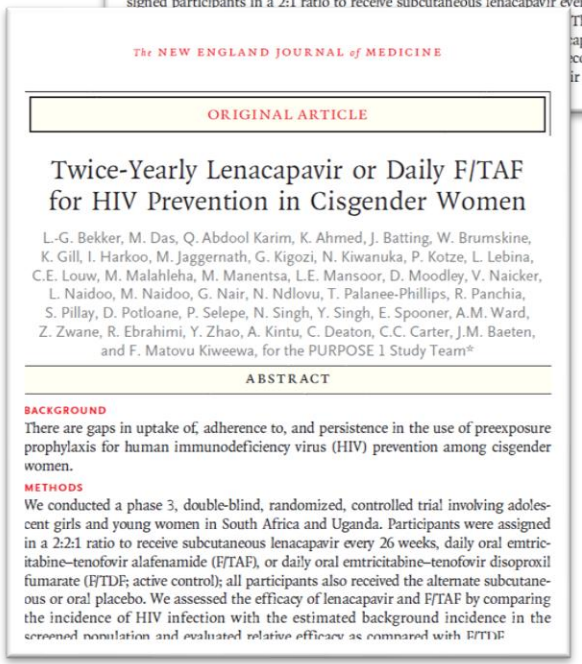
ABSTRACT

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

L.-G. Bekker, M. Das, Q. Abdool Karim, K. Ahmed, J. Batting, W. Brumskine, K. Gill, I. Harkoo, M. Jaggernath, G. Kigozi, N. Kiwanuka, P. Kotze, L. Lebina, C.E. Louw, M. Malahleha, M. Manentsa, L.E. Mansoor, D. Moodley, V. Naicker, L. Naidoo, M. Naidoo, G. Nair, N. Ndlovu, T. Palanee-Phillips, R. Panchia, S. Pillay, D. Potloane, P. Selepe, N. Singh, Y. Singh, E. Spooner, A.M. Ward, Z. Zwane, R. Ebrahimi, Y. Zhao, A. Kintu, C. Deaton, C.C. Carter, J.M. Baeten, and F. Matovu Kiweewa, for the PURPOSE 1 Study Team*

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 control); 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 screened population and evaluated relative efficacy as compared with F/TDF

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Pregnancy and breastfeeding

- **WHO-recommended PrEP products, including LEN, do not need to be discontinued** during pregnancy and breastfeeding.
    - **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.
- 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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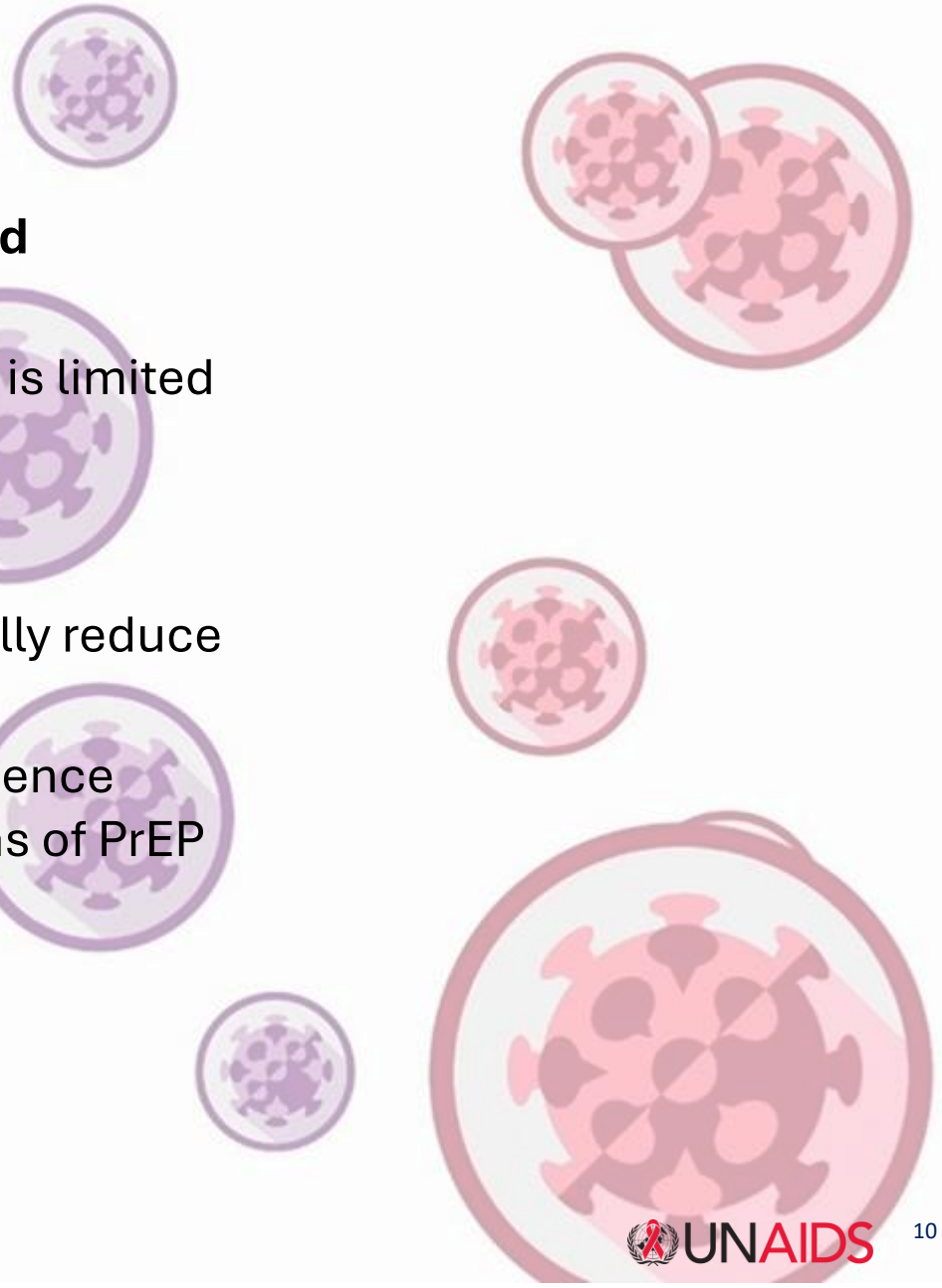
Impact of LEN on HIV prevention

- **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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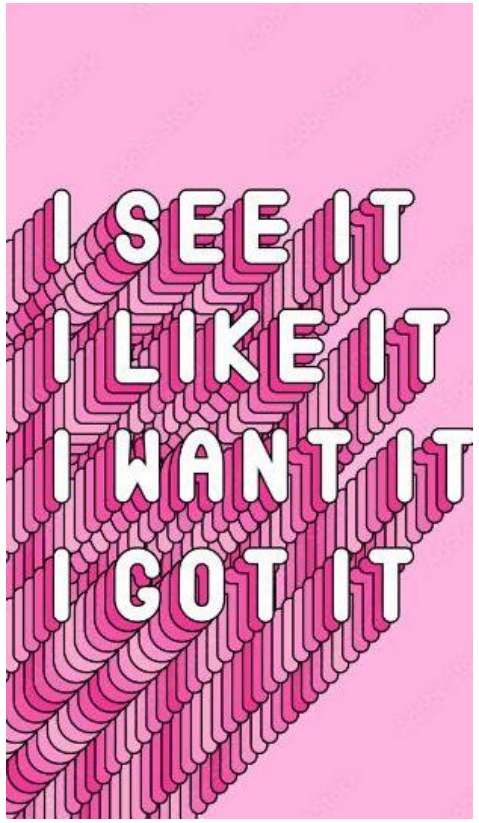
Values, preferences and feasibility for LEN

- **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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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
  - **community engagement** throughout introduction
  - **differentiated service delivery** models
  - **integration** of services to maximize acceptability and access
  - **awareness raising** and **demand generation** activities
  - **provider training**
  - **supporting persistence / effective use / client recall**
  - **monitoring and surveillance systems** incorporating LEN and:
    - adverse event monitoring during **pregnancy and breastfeeding**
    - **seroconversions** and **drug resistance (LEN specific)**

The WHO and Jhpiego Provider Training Toolkit on Use of Oral and Long-Acting HIV Pre-Exposure Prophylaxis (PrEP)

This toolkit is designed to help clinicians develop knowledge and skills to provide multiple HIV PrEP methods. The toolkit includes resources for oral PrEP, long-acting cabotegravir (CAB-LA), dapivirine vaginal ring (DVR), and long-acting lenacapavir (LEN).

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

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Research Gaps

- Implementation science can provide answers to outstanding questions on:
  - Product choice, switching and persistence 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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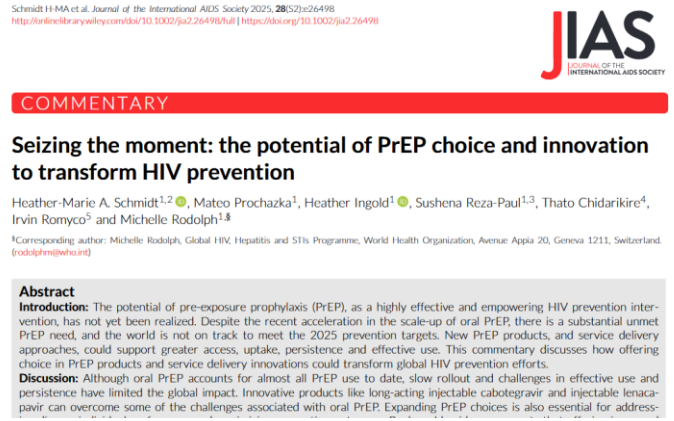
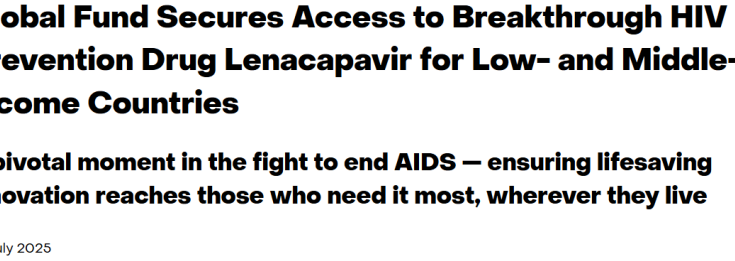
Key takeaways

- LEN offers enormous potential to increase HIV prevention coverage: it's acceptable, efficacious, safe and long-lasting (and likely to be fairly affordable for LMICs)
- LEN can be a great option for people who struggle with oral pill taking/effective use, for whom oral PrEP isn't suitable or desired, for those wanting increased convenience and for those wanting increased discretion; it won't fix access issues (and could exacerbate them) and it is not a "silver bullet"
- LEN implementation should leverage successes and lessons from oral PrEP (and CAB-LA rollout) e.g. build (and fund) demand, support DSD, integrate into prevention programs, enable rapid and broad access, facilitate choice, prompt new opportunities for innovation
- Implementation science should be leveraged to support quality rollout, not delay it
- There is momentum and donor support for LEN





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jhpiego

A WHO Global PrEP Network & Jhpiego Webinar

From Oral PrEP to LEN: Leveling Up Prevention with the WHO–Jhpiego PrEP Provider Training Toolkit

1pm CET 8 October 2025