The Lens on LEN: The basics on injectable lenacapavir as PrEP

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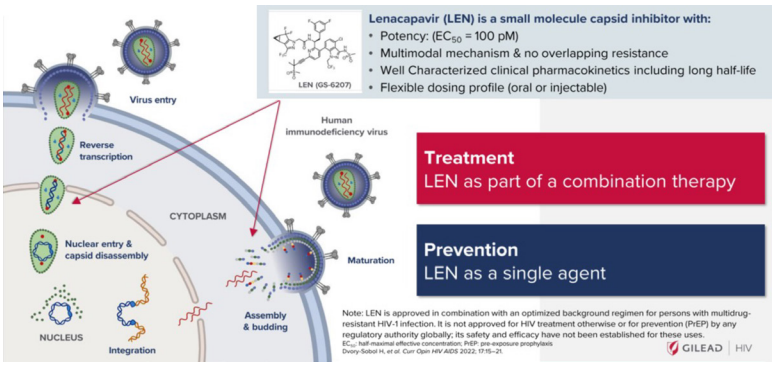
In late June 2024, Gilead Sciences announced an early review of the data of the PURPOSE 1 trial by an independent monitoring board, which found that injectable lenacapavir (LEN) provided as prevention was safe and highly effective against HIV. The product is being tested among 5,300 HIV-negative cisgender women ages 16-25 in Uganda and South Africa. No infections were seen among those receiving LEN. A companion efficacy trial, PURPOSE 2, is underway in other populations, with results also underway. A snapshot of these trials is available here.

This advocates' primer provides background on the product and trials; a summary of the early findings of PURPOSE 1; key questions and next steps.

What is LEN?

Lenacapavir (LEN) is an investigational antiretroviral drug that is being studied as a potential PrEP product. Injectable LEN is an HIV capsid inhibitor. Capsid inhibitors damage the protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can degrade the HIV capsid during multiple stages of the viral life cycle. This prevents HIV from multiplying and can reduce the amount of HIV in the body.

Lenacapavir Foundation of our long-acting portfolio



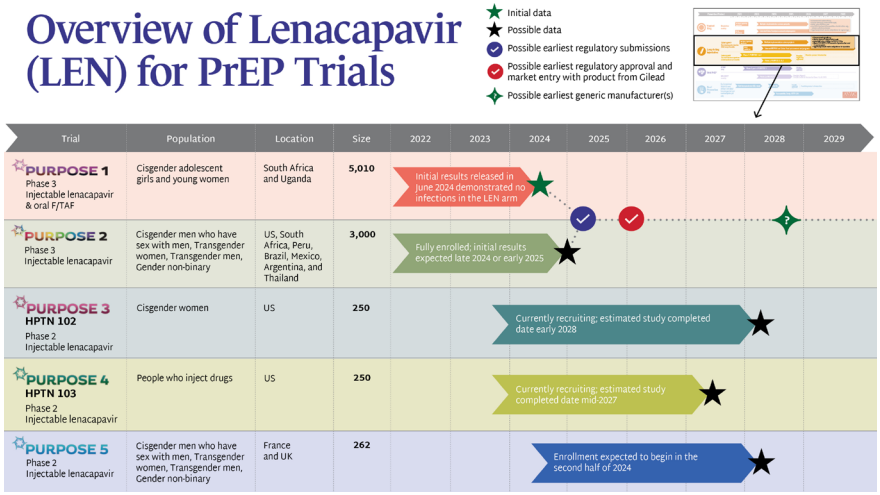
LEN for PrEP is delivered in two subcutaneous injections in the abdomen once every six months. There is also an oral loading dose—two at the time of first injection and two more a day later. It was developed by Gilead Sciences, which is currently the sole manufacturer.

Lenacapavir has been approved for HIV treatment since 2022. Gilead developed lenacapavir for use against multi-drug resistant HIV. Lenacapavir for treatment is used in combination with other antiretrovirals and is administered every six months.

How is LEN different from CAB?

	Cabotegravir (CAB)	Lenacapavir (LEN)
ARV drug class	Integrase Strand Transfer Inhibitor	Capsid Inhibitor
Injection type	Intramuscular	Subcutaneous
Injection site	Gluteal muscle (buttocks)	Abdomen
Injection volume	One 3 ml injections	Two 1.5 ml injections
Frequency/interval	First injection followed by a second one month later, then every 2 months	First injection along with two oral tablets, followed by two more tablets on day 2 and then injections every 6 months
Efficacy	Very high efficacy in all populations	Very high efficacy among cisgender women; data in other populations pending
Regulatory approvals and guidelines	19 regulatory approvals as of June 2024; WHO recommendation as additional prevention option in July 2022	Regulatory submissions and potential normative guidance anticipated in 2025
Price in LMICs	±$180/year	TBD
Developer/Manufacturer	ViiV Healthcare	Gilead Sciences
Generic Manufacturers	Three licenses through MPP to Aurobindo, Cipla and Viatris – all Indian-based manufacturers, with expected earliest market access in 2027	Gilead announced its intention to sign direct voluntary licenses with generic drug makers in several regions

What trials are being done?



The PURPOSE efficacy trials are testing LEN in various populations. Efficacy trials must be able to prove that new tools work *and* meet ethical standards by providing participants with the best available prevention package, requiring innovative trial designs as the prevention landscape improves. In PURPOSE 1, LEN was compared for efficacy to oral F/TDF as well as an estimated background incidence rate of HIV. Background incidence is an estimate of a baseline incident rate in the population being studied. It is one of several "external controls" the US FDA has begun to consider in these innovative designs to estimate incidence if the trial had included a placebo arm.

PURPOSE 1 enrolled more than 5,300 cisgender adolescent girls and young women ages 16-25 to evaluate injectable lenacapavir for PrEP and a daily pill of emtricitabine/tenofovir alafenamide (F/TAF, brand name DESCOVY) for PrEP. The studies were conducted across 25 sites in South Africa and three in Uganda. In June 2024, Gilead reported early results of efficacy in the lenacapavir arm, with zero infections compared to background incidence, (bHIV) and compared to daily pills of F/TDF (brand name, Truvada). In PURPOSE 1, bHIV was 2.4%. This table references HIV incidence in placebo-controlled prevention trials between 2003-2023.

Based on the data, the independent monitoring board recommended an early stop to the blinded phase of the trial and recommended the trial offer open-label lenacapavir to all participants. If approved by regulators, LEN will be the second long-acting injectable PrEP option to enter the market.

An additional arm of the study tested daily oral F/TAF among the same population, compared to daily oral F/TDF and background incidence. Interim results show that F/TAF was numerically similar in its levels of protection to F/TDF, but the data is limited to date, and more analysis on the relative efficacy of F/TAF among this population of cisgender women is anticipated and should be closely evaluated. PURPOSE 1 is generating needed data that was not provided in earlier studies of F/TAF, which showed efficacy but only enrolled cisgender men and transgender women who have sex with men.

PURPOSE 1 includes pregnant and lactating people, and the trial is conducting lenacapavir-exposure assessments during pregnancy, postpartum, in infants, and in breastmilk to support the potential use of this investigational product among pregnant and lactating people. This data is expected later in 2024 and 2025.

PURPOSE 2 is underway in Argentina, Brazil, Mexico, Peru, South Africa, Thailand and the US, testing twice-yearly lenacapavir for PrEP among cisgender men who have sex with men, transgender women, transgender men, and gender non-binary people. Results from PURPOSE 2 are expected by early 2025. The trial set global goals for the inclusion of historically excluded and disproportionately affected populations. These include: 50% Black and 20% Hispanic/LatinX cisgender men who have sex with men among US-based enrollees; 20% transgender women globally. Transgender men and gender nonbinary individuals were intentionally enrolled for the first time in any Phase 3 PrEP trial.

Both **PURPOSE 1 and 2** include adolescents (16-17 years old) for the first time in PrEP trials. Safety and efficacy findings of LEN for this specific group are expected in the full data analysis.

PURPOSE 3 is a Phase 2, randomized, open-label study of safety and acceptability of injectable LEN for PrEP compared to oral TDF/FTC (brand name, Truvada) among cisgender women in the US who are disproportionately affected by HIV, with a focus on Black women and other women of color.

PURPOSE 4 is a Phase 2, randomized, open-label study to evaluate the safety and acceptability of injectable LEN for PrEP in people who inject drugs in the US.

PURPOSE 5 will be a Phase 2 study conducted in France and United Kingdom assessing consistent and continuous use of injectable LEN for PrEP compared with F/TDF in people who may benefit from PrEP but who are not currently taking it.

It will be imperative to understand how the early efficacy results of PURPOSE 1 will influence PURPOSE 2-5. Understanding the data and taking action to accelerate the introduction of proven products and expanding access to those products is key to ending the epidemic.

How was civil society engaged in the process?

The PURPOSE program represents an important advance in Gilead's research and development by incorporating civil society engagement and Good Participatory Practice (GPP). Across the PURPOSE program, GPP is helping to advance ethical and effective conduct of clinical trials, through consultations on study design and the establishment of Global Community Accountability Groups (GCAGs) for each PURPOSE efficacy study. These GCAGs grew out of multiple consultations during the protocol review process, including those led by AVAC and various partners.

Comprised of diverse stakeholders from historically underrepresented and disproportionately affected populations, GCAG members provide ongoing guidance, oversight and recommendations resulting in critical supports and more inclusive data-gathering, with broad implications for future access. These processes resulted in:

- The inclusion of adolescents.
- Participants offered free contraceptives without requiring their use.
- Allowing pregnant or breastfeeding participants to continue with the study.
- Monitoring for intimate partner violence and providing appropriate support.

These robust GPP practices are ensuring transparency and trust with trial communities and laying a foundation for product acceptability and use in the future.

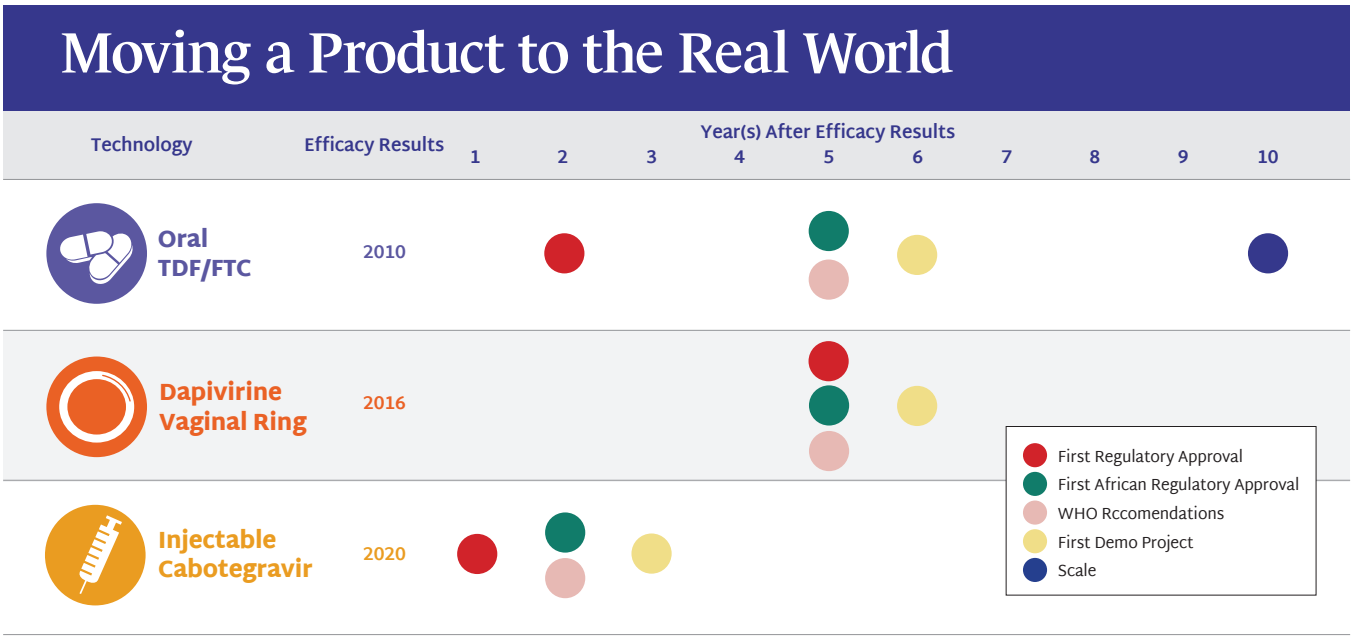
What happens next?

There is no time to waste if the world is to translate these exciting clinical trial results into actual public health impact and expand the toolbox of HIV prevention choices. Lessons learned from rollout of daily oral PrEP, and more recently the dapivirine vaginal ring and injectable cabotegravir, can help speed regulatory approval, guideline development in key countries, the design of effective programs, and community understanding and acceptance of lenacapavir for PrEP. There are a number of concurrent actions that are needed now. Gilead, policy makers, normative agencies, donors, program implementers, researchers, generic manufacturers, civil society, advocates and communities each have critical roles to play in the coming months and years. AVAC is working with a wide range of partners to develop a comprehensive map of all the moving parts and identify specific priority actions and actors responsible for ensuring time is not wasted and opportunity not squandered. Here is an initial set of priorities.

- Gilead announced an early stop to the blinded phase of the PURPOSE 1 trial and a transition to an open-label phase. Gilead issued a statement on their access planning, and has committed to offering lenacapavir to all trial participants until the product is available through public health programs.
- Gilead now must expedite plans for submission to regulatory agencies, including the US Food and Drug Administration (FDA) and a robust number of additional regulatory agencies, especially in countries with high HIV burden. Regulatory agencies should prepare to fast-track regulatory review.
- WHO should initiate the process for developing guidelines, plan for a Guideline Development Group by early 2025, and ensure WHO Guidelines are in place by the time regulatory approvals might be granted.
- PEPFAR and the Global Fund should work urgently with other donors and Ministries of Health to negotiate price and volume guarantees with Gilead to ensure there is a sustainable supply for the initial introduction period until generics are registered and readily available, likely at least three years.

- Funders, Ministries of Health, implementers and civil society partners need to collaboratively design a comprehensive introduction strategy that breaks the sequential nature of traditional approaches to scale and speed up introduction, moving toward a parallel approach where research, implementation science, and scale programs are designed, funded and implemented in parallel. All stakeholders, working through the Coalition to Accelerate Access to Long-Acting PrEP, should commit to developing a robust introduction strategy ahead of regulatory approvals and WHO guidelines to ensure time is not lost.
- Following Gilead's announcement last month that they are developing a direct voluntary licensing program for lenacapavir, it is imperative that Gilead grant non-exclusive licenses to multiple generic manufacturers in multiple geographies before the end of the year; that license agreements are made publicly available; and that the licenses include access to finished product based on public health imperatives, and not on World Bank country classifications or geographical location.

If approved, LEN for PrEP will add a potent new option to the prevention toolkit— alongside oral PrEP, injectable CAB and the dapivirine vaginal ring. But realizing the potential of highly protective interventions depends on accelerating and expanding access to the full suite of HIV prevention choices, and rolling out LEN better and faster than the options that came before. It has taken more than ten years to reach scale following the trial results that showed the life-saving benefits of F/TDF. The time from efficacy results to approval improved marginally with CAB for PrEP, while DVR moves slowly forward in expanding access. The field must not again squander months and years.



What can advocates do now?

- **Talk to your community**. What might the results mean for them? Understanding specific questions and concerns will help frame advocacy priorities. Help communities understand the PURPOSE trials, the potential significance of LEN as an every six-month injection, the regulatory process and timelines, and the importance of scaling up existing PrEP programs in the meantime, with a range of choices.
- **Demand equitable PrEP access and programming for choice**. This entails funding commitments, setting targets and embracing innovation. The global health community must

move with speed, scale and urgency in designing, funding and implementing comprehensive and integrated PrEP programs that offer a choice of product and service delivery models.

- **Advocate for affordable pricing**. Gilead has not yet set a price for LEN for PrEP. Various cost-effectiveness analyses have shown that injectable PrEP must be priced in the range of generic daily oral TDF/FTC to be considered cost-effective. While this may not be possible at product launch, the field needs to collaborate to reach this price point as quickly as possible; it is essential to build volume in the market with supplies from Gilead at a price no higher than CAB for PrEP and to support multiple generic manufacturers to enable production at scale. Advocates must demand pricing transparency and a clear, accelerated pathway to cost-effective PrEP programs.

- **Hold decision-makers on LEN accountable**. Is there clarity about next steps? Are there targets and milestones in place? Is there adequate funding and available product to support rollout? How might decisions be made about who would get the product first, if it's licensed and introduced through phased rollout?

- **Work locally with research sites and PrEP progams**. Bring your advocacy know-how to sites for planned and ongoing research to ensure communication, access and continued work meet your needs.

Resources

- Country-planning matrix to track introduction of next-generation PrEP: https://www.prepwatch.org/resources/product-introduction-country-planning-matrix/
- The pipeline of products getting towards to the market: https://avac.org/resource/infographic/years-ahead-in-hiv-prevention-research-time-to-market/
- Lessons from Oral PrEP Programs and their Implications for Next Generation Prevention, https://www.prepwatch.org/resources/getting-rollout-right/
- Coalition to Accelerate Access to Long-Acting PrEP, https://www.prepwatch.org/coalition-long-acting-prep/, including TOR, Fact Sheet, and quarterly reports
- BioPIC Adaptable Product Introduction Framework, https://avac.org/resource/report/biopic-adaptable-product-introduction-framework/

About AVAC

AVAC is an international non-profit organization that leverages its independent voice and global partnerships to accelerate ethical development and equitable delivery of effective HIV prevention options, as part of a comprehensive and integrated pathway to global health equity. Follow AVAC on Twitter @HIVpxresearch and find more at www.avac.org.