Lenacapavir for PrEP

PURPOSE Trials & Implementation

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Disclosures

I have no disclosures.

Agenda

1. Brief background
2. Review of PURPOSE 1 & PURPOSE 2 studies
3. Discuss implementation considerations

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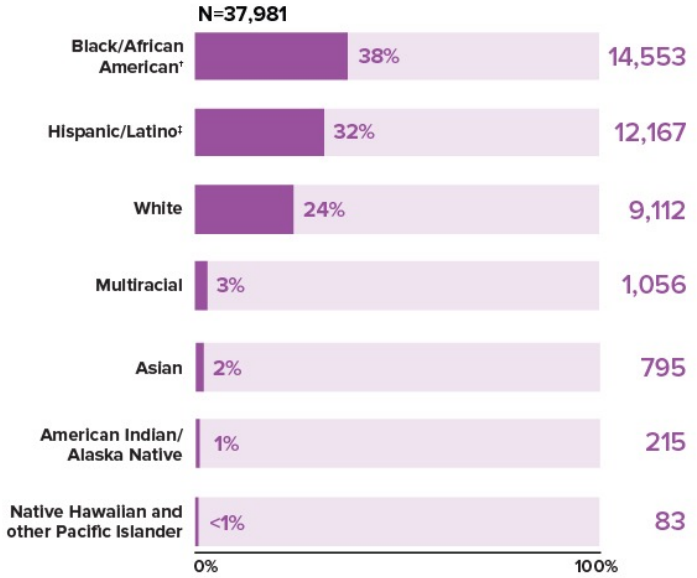
HIV diagnoses in the US and 6 territories and freely associated states by race and ethnicity, 2022*

Racism, HIV stigma, discrimination, homophobia, poverty, and other barriers to health care continue to drive disparities in HIV diagnoses.



* Among people aged 13 and older.

† *Black* refers to people having origins in any of the Black racial groups of Africa. *African American* is a term often used for people of African descent with ancestry in North America.

‡ Hispanic/Latino people can be of any race.

Source: CDC. Diagnoses, deaths, and prevalence of HIV in the United States and 6 territories and freely associated states, 2022. *HIV Surveillance Report*, 2022;35.

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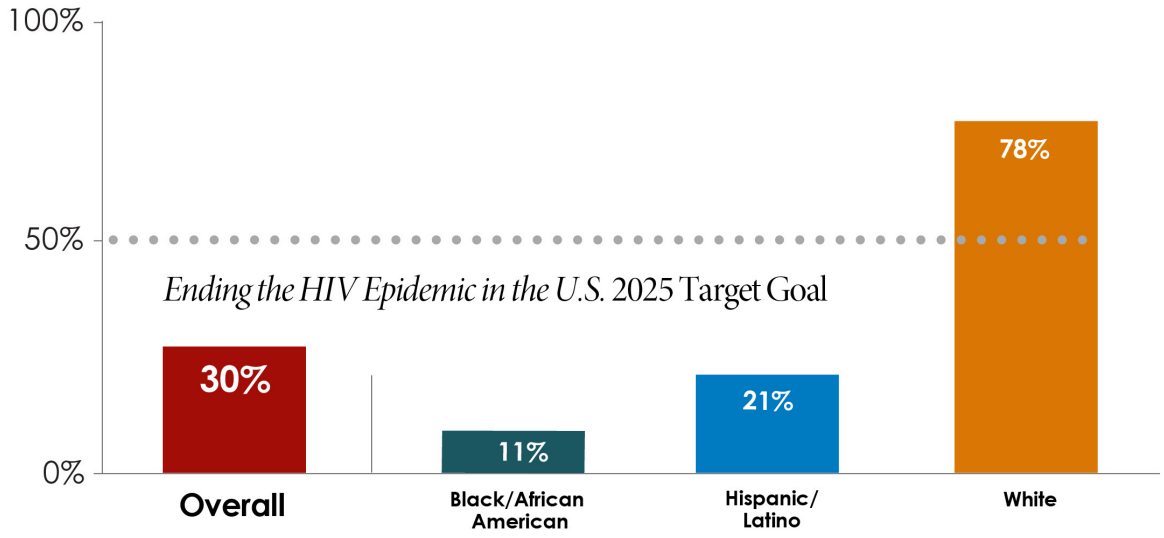
WHILE NEARLY ONE-THIRD OF PEOPLE ELIGIBLE FOR PREP WERE PRESCRIBED IT IN 2021, STARK DISPARITIES REMAIN

ESTIMATED PREP COVERAGE IN THE U.S., BY RACE/ETHNICITY, 2021*



*Data unavailable for other races/ethnicities.

CDC HIV Surveillance Data Tables, 2023. https://www.cdc.gov/hiv/library/reports/surveillance-data-tables

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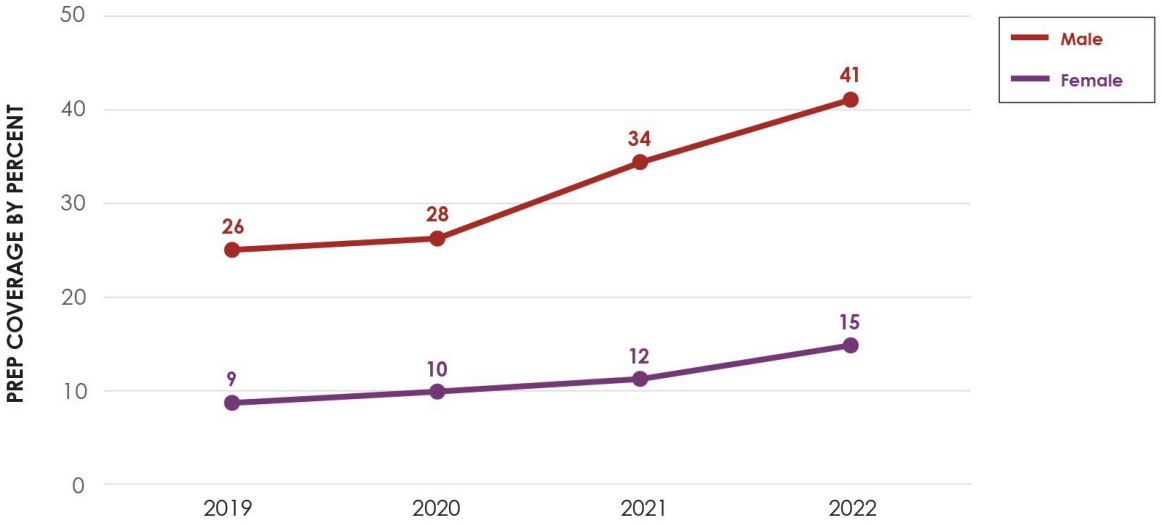
PrEP disparities are increasing

TRENDS IN PREP PRESCRIPTIONS AMONG PEOPLE WHO COULD BENEFIT, BY SEX AT BIRTH, 2019-2022*



*Data are preliminary.
Source: Centers for Disease Control and Prevention

32% of transgender women and 28% of transgender men who were HIV-negative used PrEP

https://www.cdc.gov/hiv/library/reports/surveillance-data-tables; https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-special-report-number-27.pdf; Reisner SL et al, LGBT Health, 2021.

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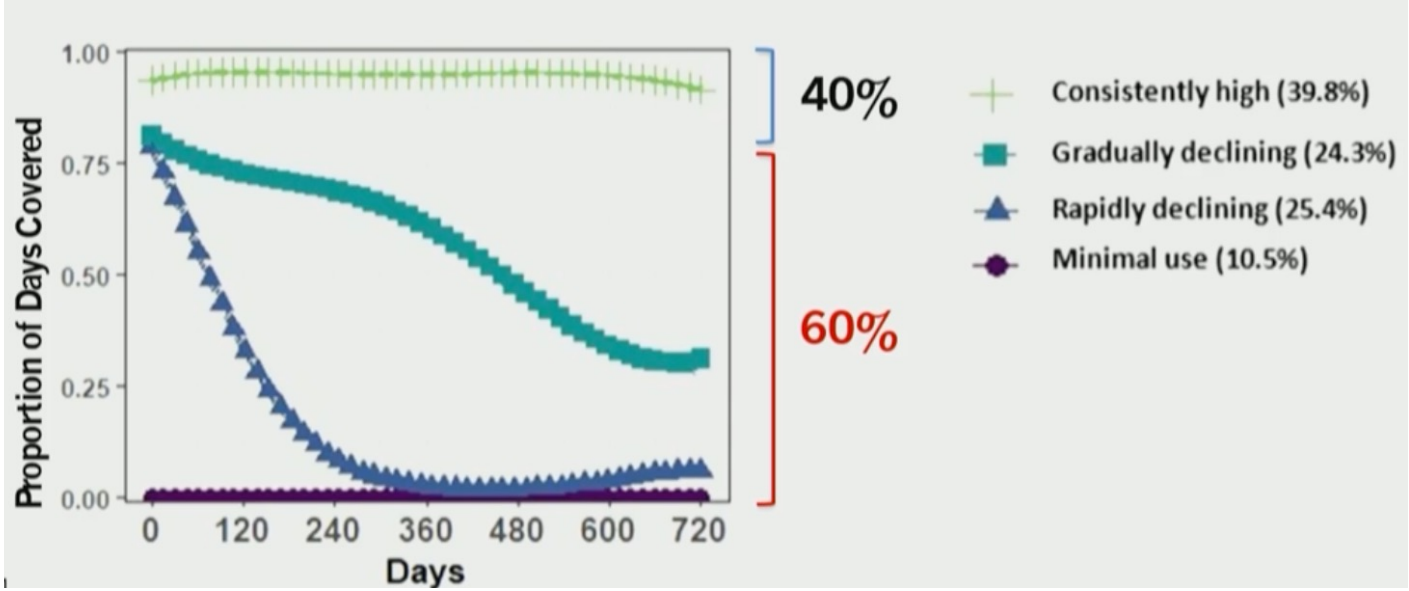
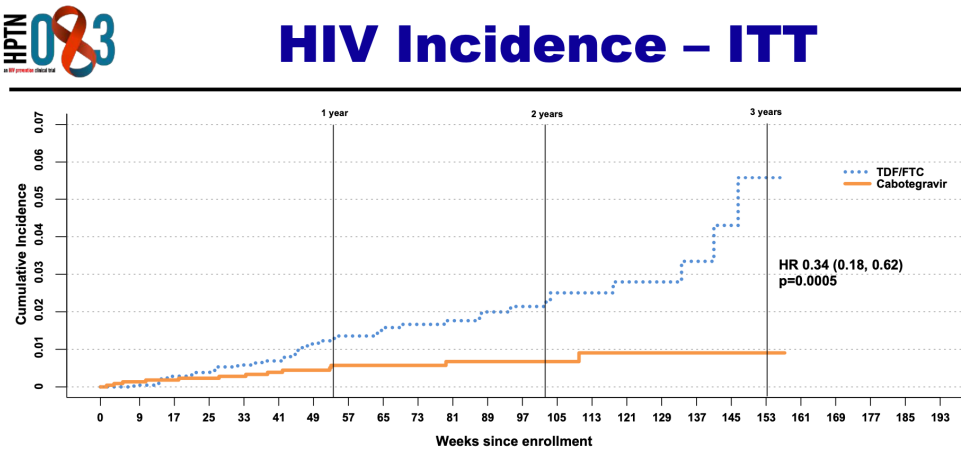
Decreasing adherence to oral PrEP in the real world



Unigew, OFID 2024

What about injectable options?

- CAB-LA injections every 8 weeks superior to oral TDF/FTC with 66-89% reduction in HIV incidence in two large randomized controlled trials: HPTN 083 & HPTN 084
- Difference appears to be driven by higher adherence to CAB-LA
- In an open-label extension among HPTN 084 study participants, 78% of participants chose CAB-LA for PrEP



Delany-Moretlwe S et al. HIV4P 2021, LB1479; Delany-Moretlwe S et al. CROI 2023, OALBX02

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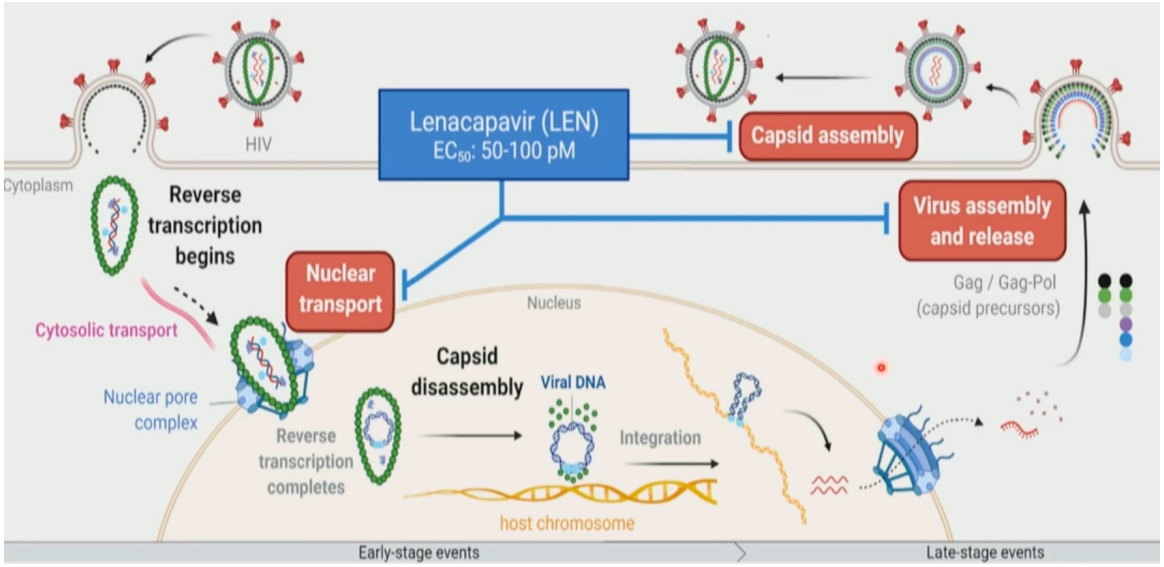
Lenacapavir: a first-in-class multistage HIV capsid inhibitor



LEN is a small molecule capsid inhibitor:

- High potency (EC_{50} = 100 pM)
- Multistage, selective inhibitor of HIV capsid mechanism
- No overlapping resistance with approved ARV agents
- Well-characterized PK including a long half-life
- Potential for a flexible dosing profile (oral or injectable)

- **Approved** in combination with an optimized background regimen for **HIV treatment** in persons with multidrug-resistant HIV-1 infection
- **LEN (twice yearly, subcutaneous, single agent) is being studied for HIV prevention (PrEP)**

Hitchcock, Int J Antimicrob Agents, 2023

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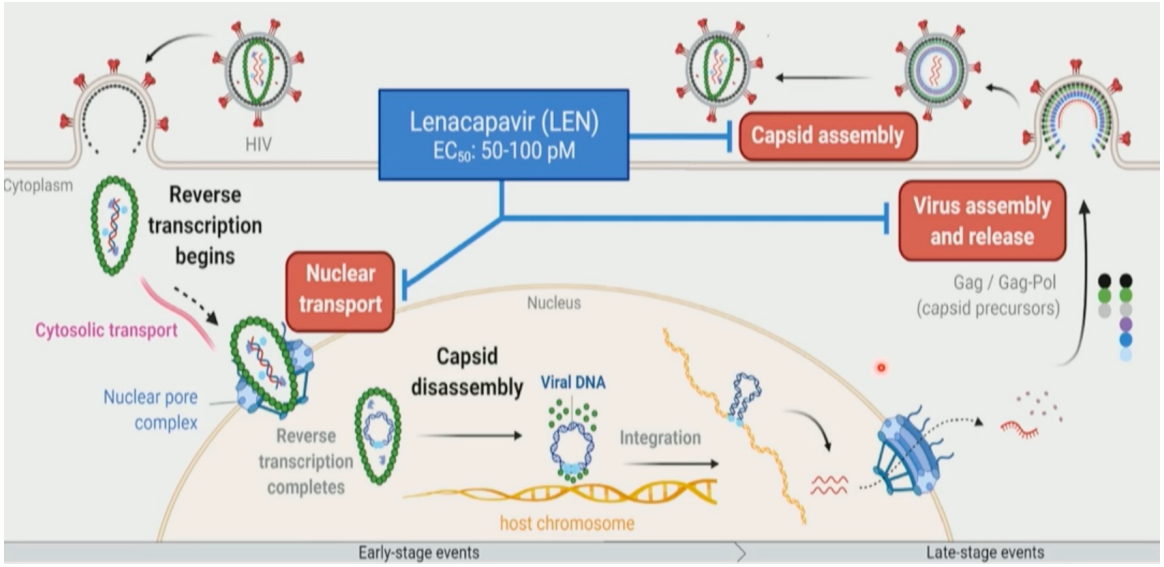
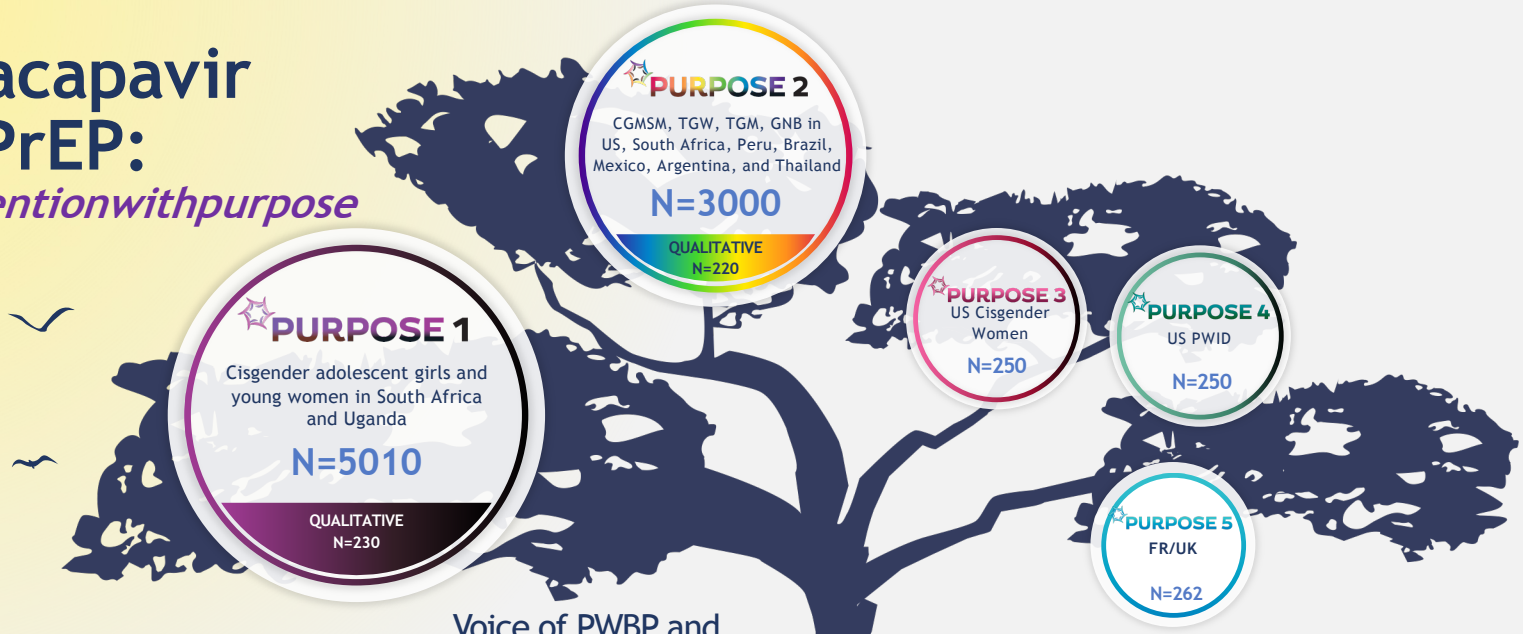
Lenacapavir: a first-in-class multistage HIV capsid inhibitor



Hitchcock, Int J Antimicrob Agents, 2023

Lenacapavir for PrEP:

#preventionwithpurpose



Partnerships

Voice of PWBP and community (G-CAGs)

Person-centric design

Diversity, equity, inclusion

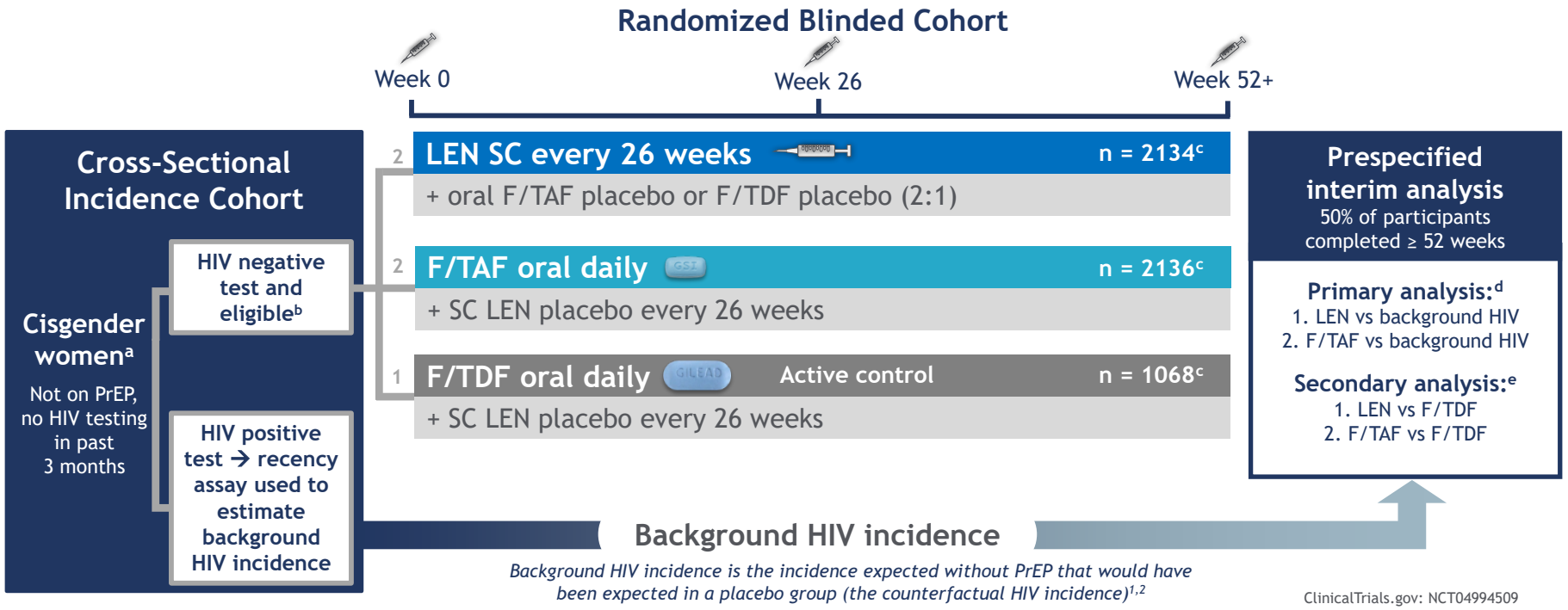
Proof of concept that capsid inhibitors prevent SHIV in non-human primates;
Robust pharmacokinetic and safety database in persons with and without HIV;

Capella **LEN for HIV Tx in MDR HIV**

- PURPOSE 1 NCT identifier: NCT04994509; PURPOSE 2 NCT identifier: NCT04925752
CGMSM, cisgender men who have sex with men; G-CAG, Global Community Advisory Groups; GNB, gender nonbinary individuals; LEN, lenacapavir; MDR, multi-drug resistant; PWBP, people who would benefit from PrEP; PWID, people who inject drugs; SHIV, simian-human immunodeficiency virus; TGM, transgender men; TGW, transgender women; Tx, treatment; US, United States.

Purpose Studies. Available at: https://www.purposestudies.com/. Accessed July 2023.

PURPOSE 1 Study Design

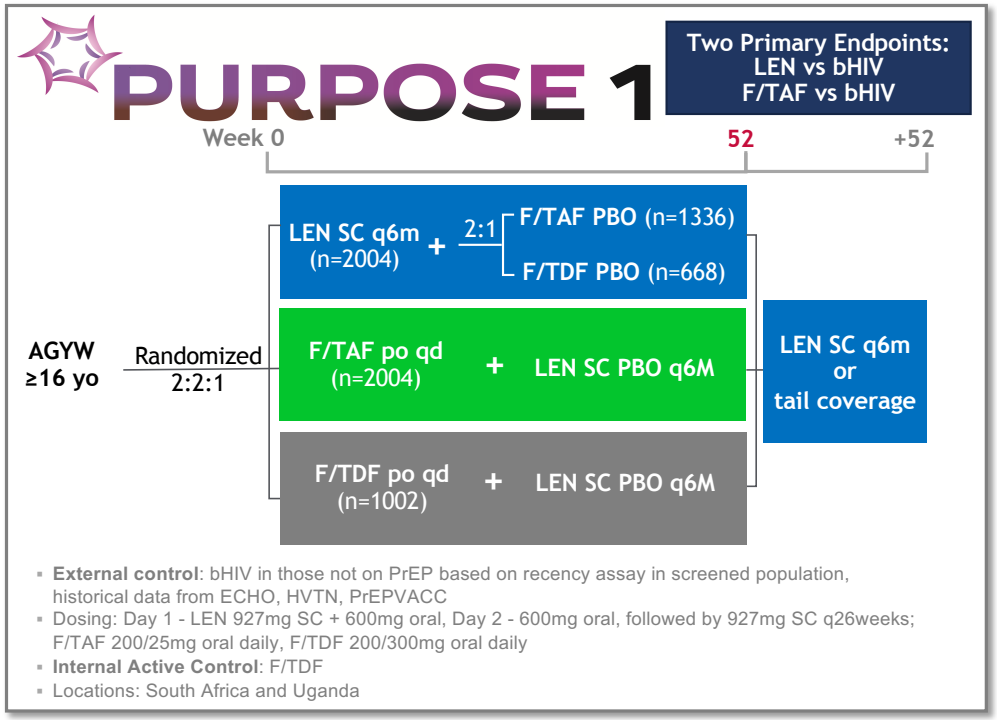


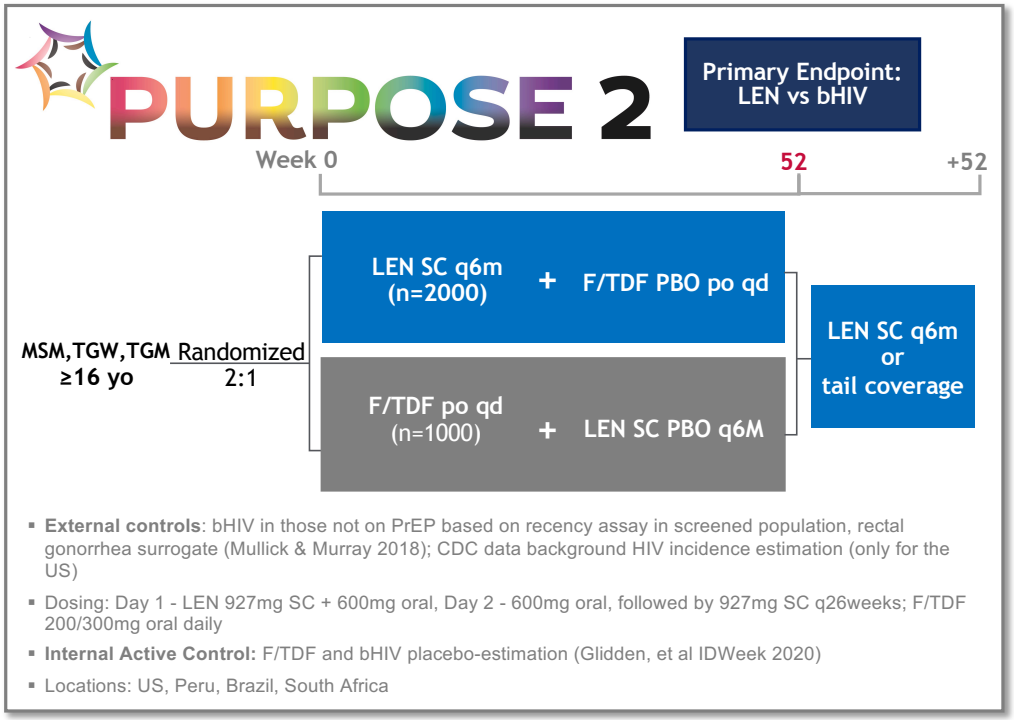
[a]The first participant was screened in August 2021, the 50th percentile participant was randomized in May 2023, and the last participant was randomized in September 2023. [b]Eligibility criteria included: weight ≥ 35 kg, eGFR ≥ 60 ml/min, not pregnant. [c]n numbers represent the full analysis set for efficacy analyses. [d]IRR was assessed using a Wald test or likelihood ratio test if there were zero infections.[1,2] [e]IRR was assessed using Poisson regression or an exact conditional Poisson regression model in case of zero infections. **eGFR**, estimated glomerular filtration rate; **F/TAF**, emtricitabine/tenofovir alafenamide; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **IRR**, incidence rate ratio.

1. Gao F, et al. *Stat Commun Infect Dis.* 2021;13(1):20200009. **2.** Shao Y, Gao F. *Stat Commun Infect Dis.* 2024;16(1):20230004.

‡

LEN for Pre-Exposure Prophylaxis (PrEP): The PURPOSE Studies





These studies used a counterfactual analysis to determine efficacy

AGYW, adolescent girls and young women; bHIV, background HIV incidence; LEN, lenacapavir; PBO, placebo; SC, subcutaneous
Data on file, Gilead Sciences

Baseline Characteristics

PURPOSE 1

Characteristic	LEN, n = 2138	F/TAF, n = 2137	F/TDF, n = 1070
Age, years, median (range)	21 (16-25)	21 (16-26)[a]	21 (16-25)
Age 16 to <18, years, n (%)	56 (2.6)	45 (2.1)	23 (2.1)
Black race,[b] n (%)	2135 (99.9)	2136 (100)	1068 (99.8)
Highest education level college/university,[c] n (%)	183 (8.6)	198 (9.3)	109 (10.2)
Marital status, n (%)			
Married	26 (1.2)	30 (1.4)	17 (1.6)
Living with primary partner	148 (6.9)	132 (6.2)	73 (6.8)
STIs, n (%)			
Chlamydia trachomatis	520 (24.3)	562 (26.3)	263 (24.6)
Neisseria gonorrhoeae	197 (9.2)	178 (8.3)	90 (8.4)
Trichomonas vaginalis	154 (7.2)	165 (7.7)	82 (7.7)
Syphilis	57 (2.7)	63 (2.9)	29 (2.7)
Any prior use of PrEP, n (%)	143 (6.7)	121 (5.7)	71 (6.6)
Any prior HIV testing, n (%)	1713 (80.1)	1731 (81.0)	860 (80.4)
Median time since last HIV test, months (Q1, Q3)	6.8 (4.7, 11.5)	6.6 (4.8, 11.0)	6.5 (4.6, 11.0)

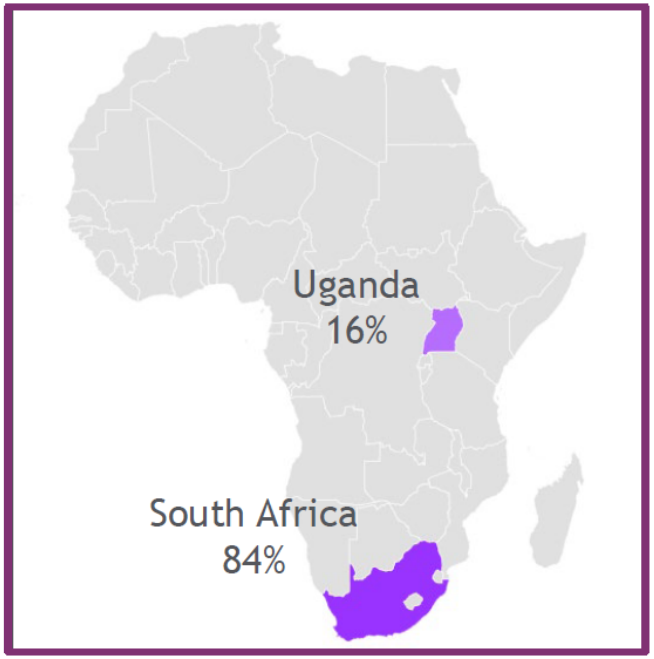
PURPOSE 2

Characteristic	LEN, n = 2183	F/TDF, n = 1088
Age, years, median (range)	28 (17-74)	29 (17-73)
Age 16 to ≤ 25, years, n (%)	752 (34.4)	344 (31.6)
Non-White race,[d] n (%)	1453 (66.8)	742 (68.3)
Hispanic/Latine ethnicity,[e] n (%)	1378 (63.2)	675 (62.0)
Gender identity, n (%)		
Cisgender man	1697 (77.7)	846 (77.8)
Gender-diverse	486 (22.3)	242 (22.2)
STIs, n (%)		
Chlamydia trachomatis, Neisseria gonorrhoeae or Trichomonas vaginalis[f,g]	382 (18.2)	207 (20.0)
Syphilis	84 (3.8)	43 (4.0)
No prior HIV test, n (%)	597 (27.3)	306 (28.1)
Any prior lifetime use of PrEP, n (%)	515 (23.6)	249 (22.9)
Self-reported use of stimulants with sex in last 12 weeks, n (%)	491 (22.5)	271 (24.9)

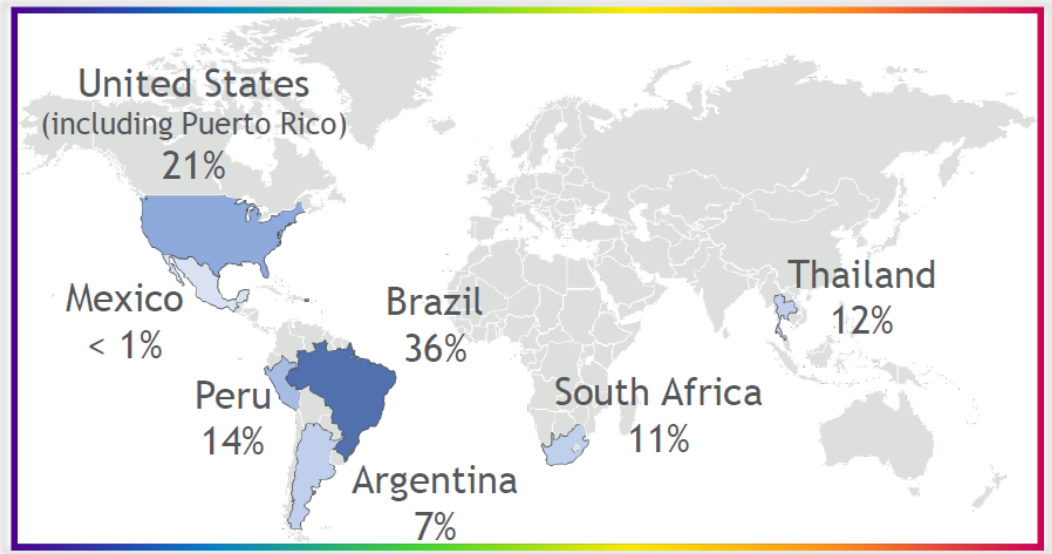
Baseline demographics and clinical characteristics were balanced across randomized groups

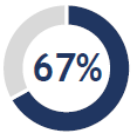
Global Distribution of Participants

PURPOSE 1

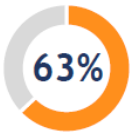


PURPOSE 2

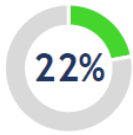




Non-White

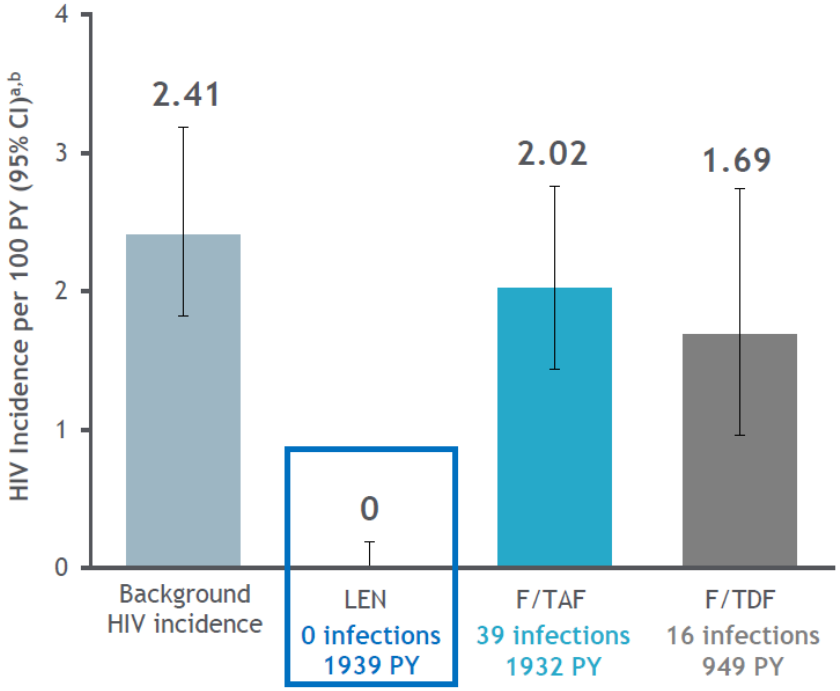


Hispanic/
Latine



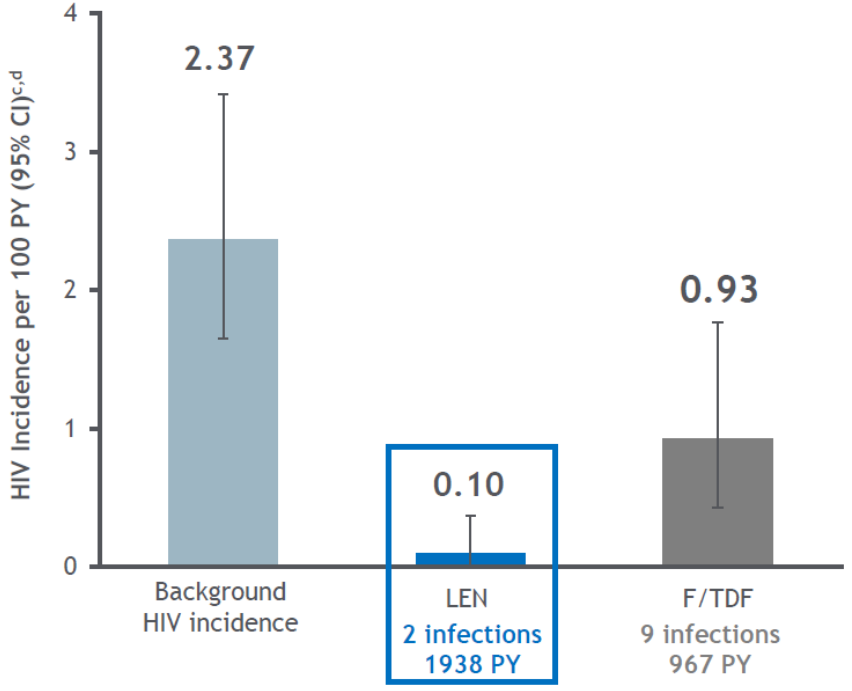
Gender-diverse

PURPOSE 1: Zero HIV Infections in Cisgender Women Receiving LEN



Median follow-up duration: 44.0 weeks

PURPOSE 2: Two HIV Infections in Participants Receiving LEN

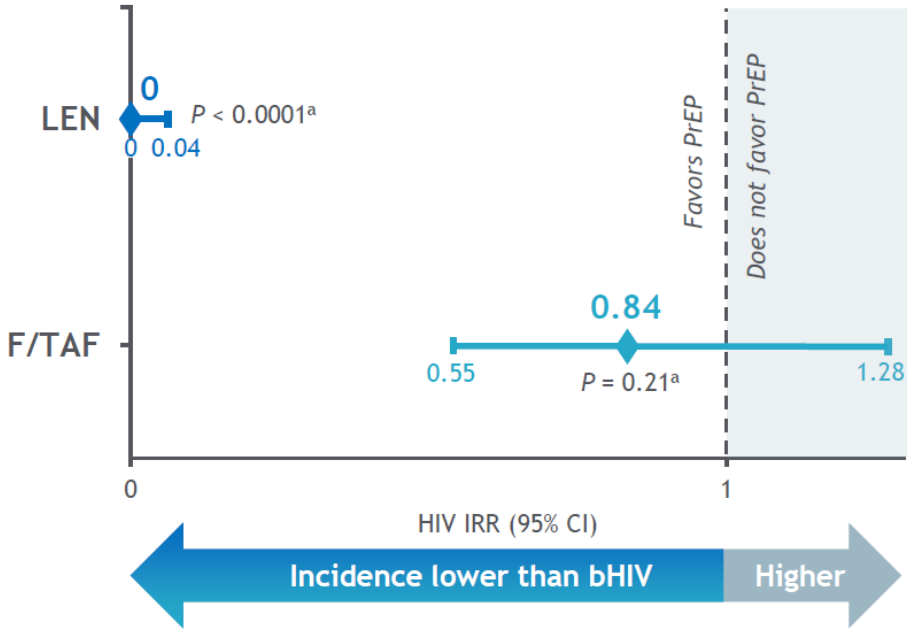


Median follow-up duration: 39.4 weeks

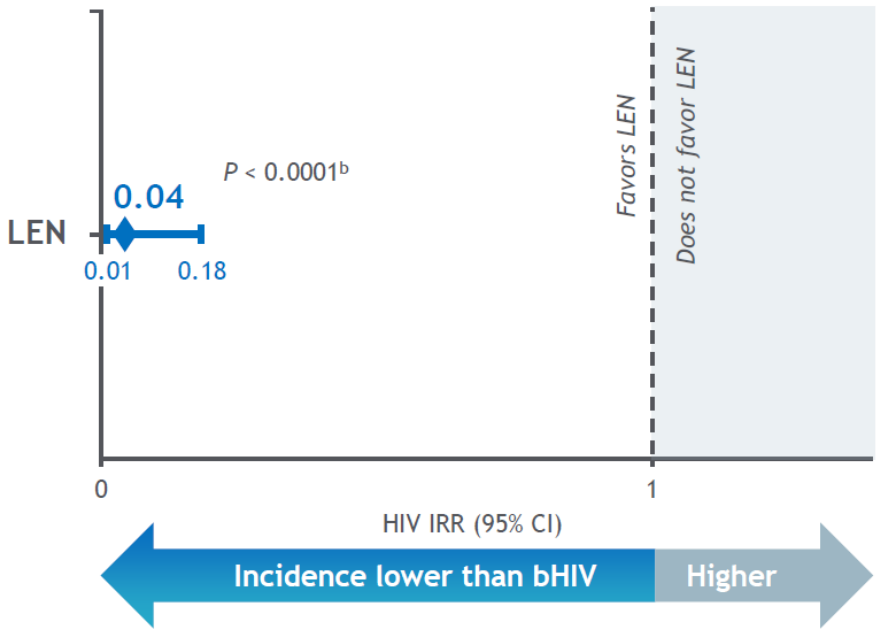
[a]Overall n: background HIV incidence group, 8094; LEN, 2134; F/TAF, 2136; F/TDF, 1068. [b]95% CIs: background HIV incidence group, 1.82-3.19; LEN, 0-0.19; F/TAF, 1.44-2.76; F/TDF, 0.96-2.74. [c]Overall n: background HIV incidence group, 4634; LEN, 2179; F/TDF, 1086.
[d]95% CIs: background HIV incidence group, 1.649-3.417; LEN, 0.012-0.373; F/TDF, 0.426-1.768.
PY, person-years.

Kelley, ID Week, 2024

PURPOSE 1 Primary Analysis: LEN Has 100% Efficacy for PrEP



PURPOSE 2 Primary Analysis: LEN Has 96% Efficacy for PrEP



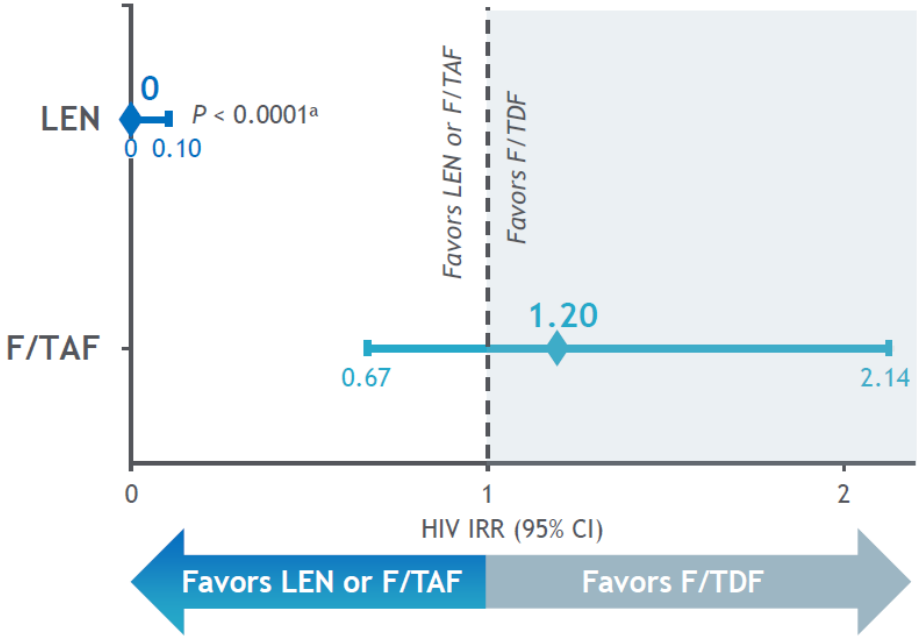
LEN reduced HIV infections by 100% in PURPOSE 1 and by 96% in PURPOSE 2 compared with background HIV incidence; in PURPOSE 1, F/TAF was not different from background HIV incidence

[a]HIV IRR vs background HIV was assessed using a likelihood ratio test (LEN, due to zero infections), and a Wald test (F/TAF).[1,2] [b]HIV IRR vs background HIV was assessed using a Wald test.[2]
bHIV, background HIV incidence.

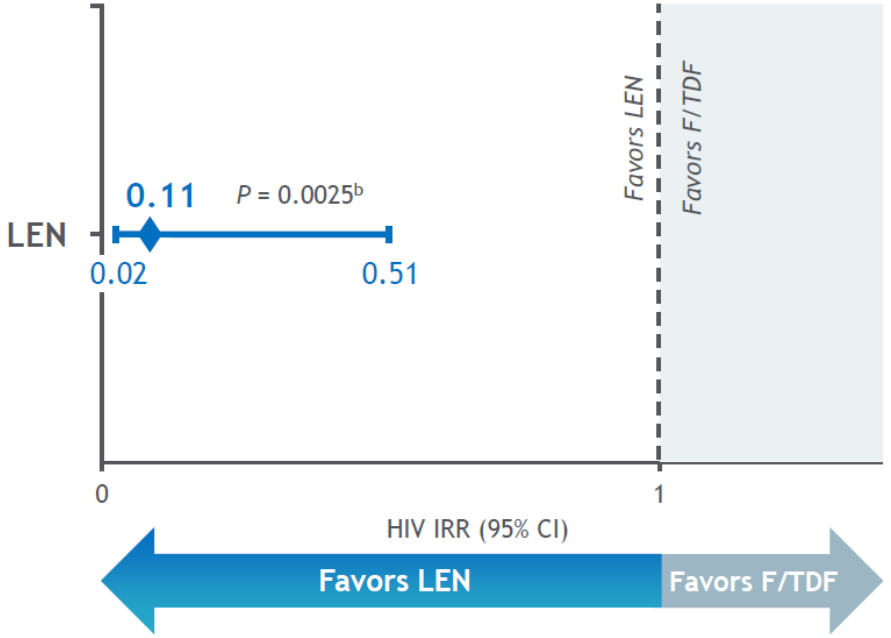
1. Shao Y, Gao F. *Stat Commun Infect Dis.* 2024;16(1):20230004. 2. Gao F, et al. *Stat Commun Infect Dis.* 2021;13(1):20200009.

Kelley, ID Week, 2024

PURPOSE 1 Secondary Analysis: LEN Superior to F/TDF



PURPOSE 2 Secondary Analysis: LEN Superior to F/TDF



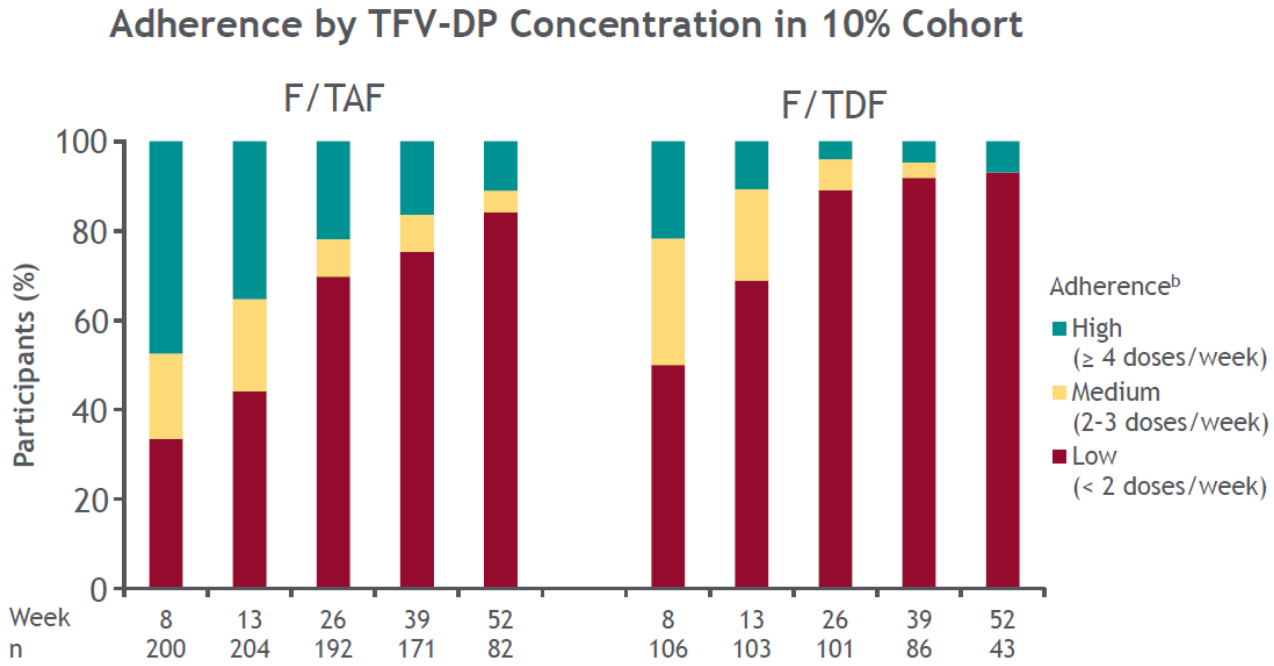
LEN reduced HIV infections by 100% in PURPOSE 1 and by 89% in PURPOSE 2 compared with daily oral F/TDF; in PURPOSE 1, F/TAF was not numerically different from F/TDF

[a]HIV IRR vs F/TDF was assessed using an exact conditional Poisson regression model (LEN, due to zero infections). [b]HIV IRR vs F/TDF was assessed using Poisson regression.

PURPOSE 1 Adherence to Injections Was Much Higher vs Oral F/TAF and F/TDF

Injections were on time[a] for:

- 91.5% (4545/4967) at Week 26
- 92.8% (2025/2181) at Week 52

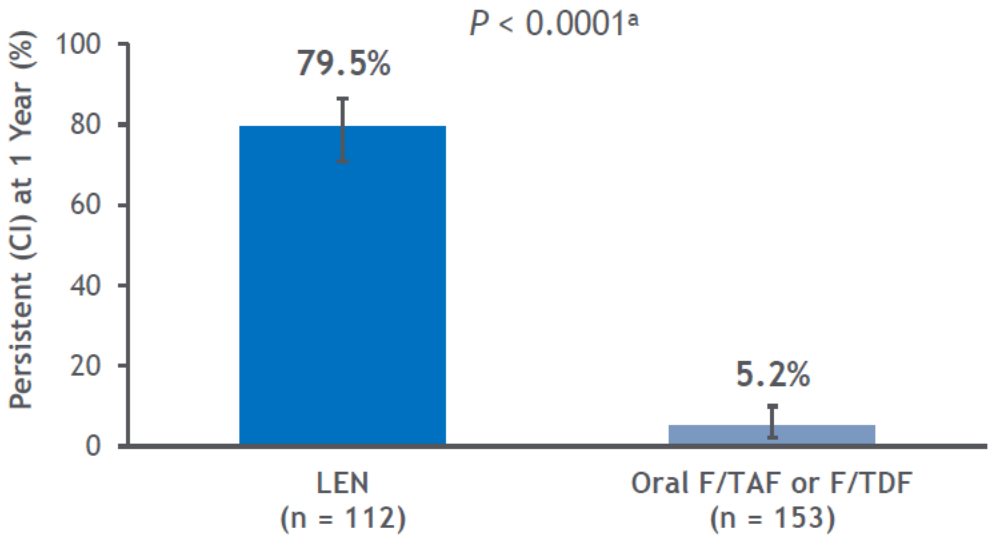


Kelley, ID Week, 2024

Notably in the F/TAF group, there was a significantly lower likelihood of HIV infection associated with medium or high adherence compared with low adherence (odds ratio 0.11; 95% CI 0.012-0.49; *P* = 0.0006)

Higher Annual Persistence on Twice-Yearly LEN Versus Daily Oral F/TAF or F/TDF

Annual persistence on LEN was assessed by on-time injections at Week 26 and Week 52 (within 28 weeks of the last injection).
Annual persistence on oral F/TAF or F/TDF was assessed by TFV-DP concentration in DBS



Annual persistence was significantly higher on twice-yearly LEN than on daily oral F/TAF or F/TDF, which helps elucidate the LEN efficacy findings in PURPOSE 1

Bekker, Glasgow 2024

Adherence to LEN Injections Was High and Consistent
Adherence to F/TDF Was High but Declined Over Time

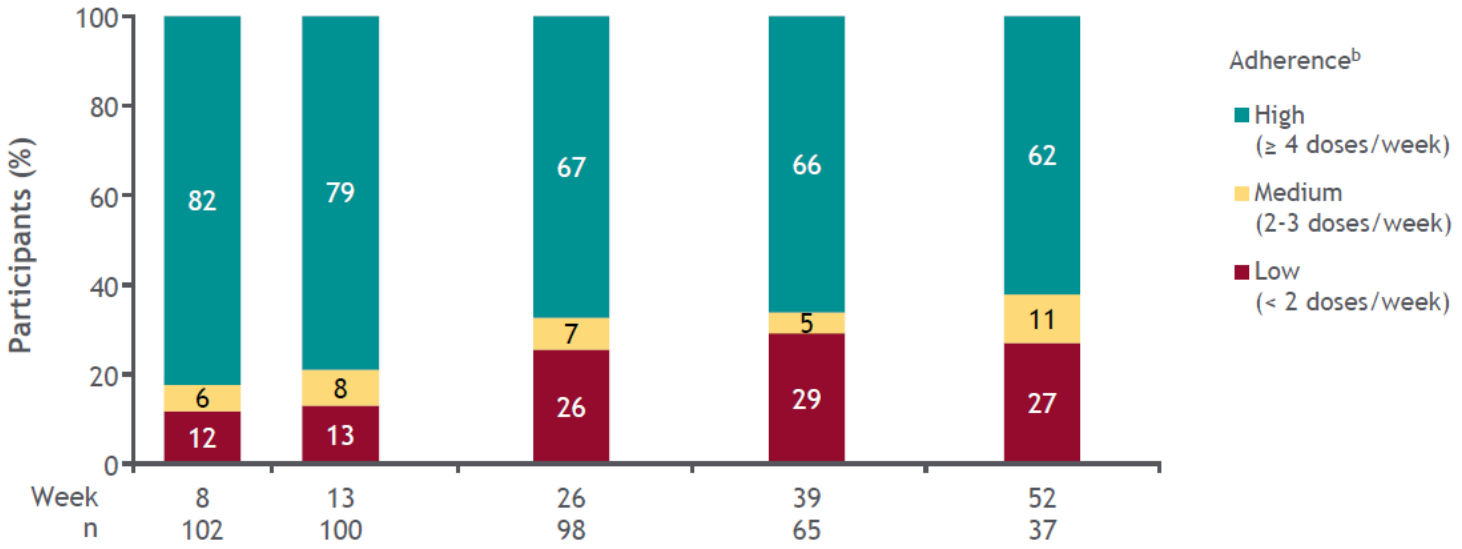
Injection Adherence

LEN injections were on time for:[a]

- 90% (1729/1912) at Week 26
- 93% (678/727) at Week 52

On-time injection rate was similar for LEN and placebo (F/TDF) injections

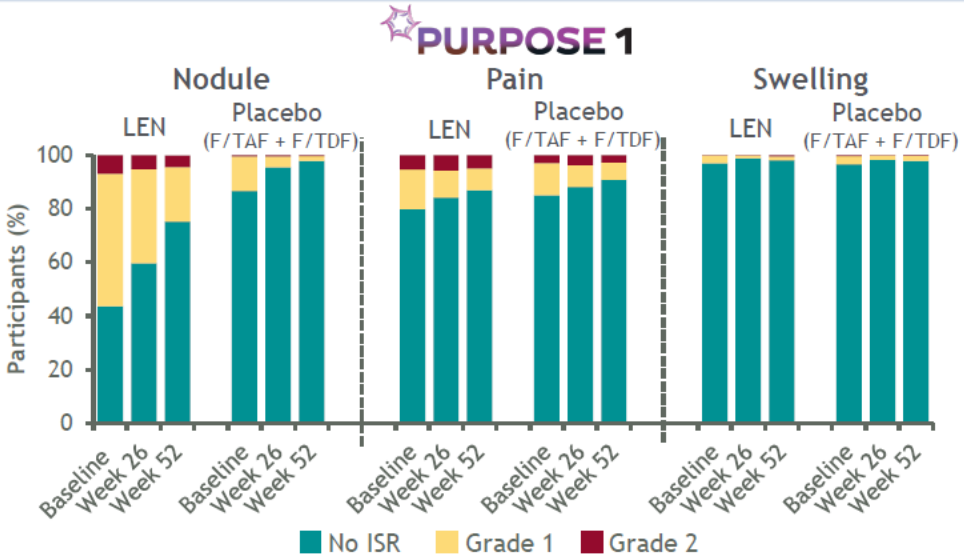
Adherence by TFV-DP Concentration in 10% Cohort

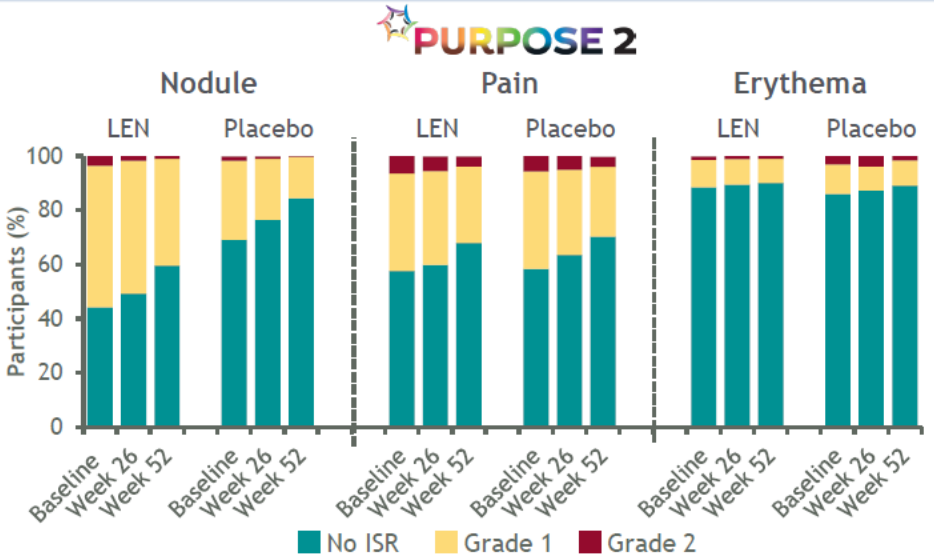


Ogbuagu, Glasgow 2024

Injection-Site Reaction Frequency and Grade Diminish With Subsequent Injections

LEN is injected into the SC space and forms a drug depot that may be palpable under the skin but is usually not visible. As the drug elutes over time, the depot gets smaller, and the nodules resolve or reduce in size substantially prior to the next injection. The frequency of ISRs, including nodules, decreased with subsequent doses (also observed with HIV treatment[1]).





In PURPOSE 1, among 25,329 LEN/placebo injections, only 4 ISRs led to discontinuation (all LEN)
In PURPOSE 2, among 15,239 LEN/placebo injections, only 29 ISRs led to discontinuation (LEN, 26; F/TDF, 3)

Injection-Site Reaction Frequency and Grade Diminish With Subsequent Injections

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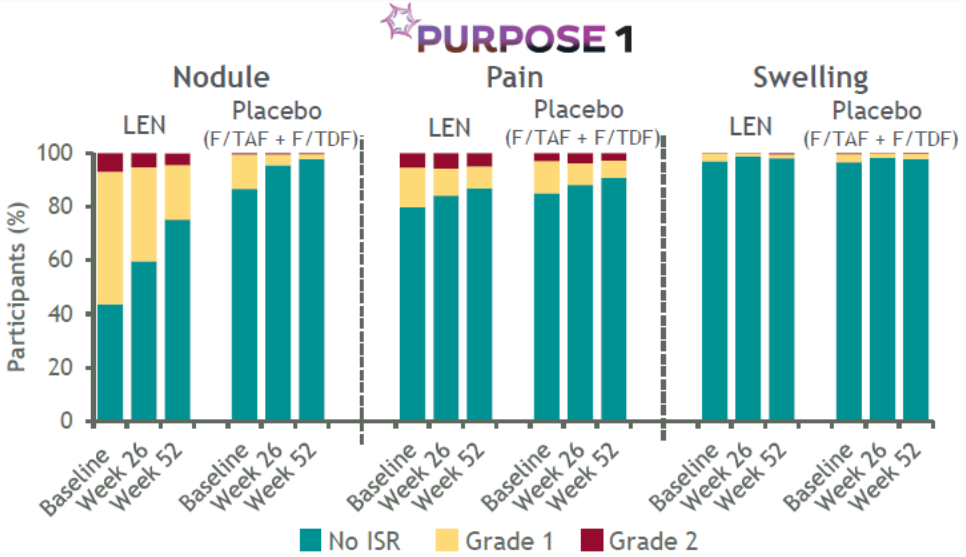

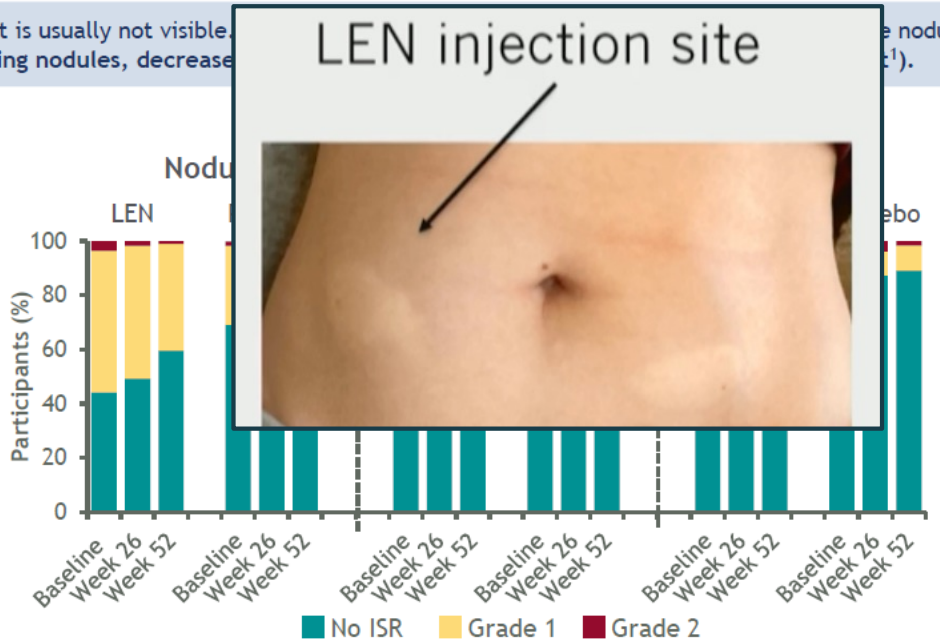

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In PURPOSE 2, among 15,239 LEN/placebo injections, only 29 ISRs led to discontinuation (LEN, 26; F/TDF, 3)

Photo courtesy of Jean-Michel Molina

PURPOSE 1 Pregnancies Were Common and Outcomes Similar to Expected Rates in the Population

Participants and Pregnancies, n (%)	LEN n = 2138	F/TAF n = 2137	F/TDF n = 1070
Participants with confirmed pregnancies	184	208	95
Confirmed pregnancies	193	219	98
Completed pregnancies	105 (54.4)	119 (54.3)	53 (54.1)
Ongoing pregnancies	88 (45.6)	100 (45.7)	45 (45.9)
Births[a]	55 (28.5)	45 (20.5)	21 (21.4)
Interrupted pregnancies	50 (25.9)	74 (33.8)	32 (32.7)
Induced abortion	30 (15.5)	40 (18.3)	20 (20.4)
Spontaneous miscarriage[b]	20 (10.4)	34 (15.5)	12 (12.2)

Expected spontaneous miscarriage rate:[1,2]

- ~10-20% of clinically recognized pregnancies
- ~30% of biochemically detected pregnancies

Available pregnancy outcomes were similar to those expected for the population[3]

PURPOSE 1 and 2 Data Summary

	PURPOSE 1	PURPOSE 2
Study population	Cisgender women	CGBMSM, TGW, TGM, and GNB people who have sex with partners assigned male sex at birth
Baseline demographics and clinical characteristics	Balanced across randomized groups	Balanced across randomized groups
Efficacy	LEN HIV prevention efficacy was **superior** to both background HIV incidence and daily oral F/TDF **Zero HIV infections** among 2134 participants receiving LEN LEN reduced HIV infections by **100%** compared with bHIV incidence and daily oral F/TDF	LEN HIV prevention efficacy was **superior** to both background HIV incidence and daily oral F/TDF **Two HIV infections** among 2179 participants receiving LEN LEN reduced HIV infections by **96%** compared with bHIV incidence and by 89% compared with daily oral F/TDF
Safety	LEN and F/TAF were **safe and well tolerated** Most common ISRs: SC nodules, injection-site pain, and **swelling** **ISR frequency and grade diminished** with subsequent injections (also observed in other studies[1-3]) **Adherence to F/TDF was too low to impact eGFR**	LEN and F/TDF were **safe and well tolerated** Most common ISRs: SC nodules, injection-site pain, and **erythema** **ISR frequency and grade diminished** with subsequent injections (also observed in other studies[1-4]) LEN increased eGFR while F/TDF decreased eGFR; this **difference was more pronounced** in PURPOSE 2 vs PURPOSE 1

Twice-yearly LEN offers an efficacious, safe, and well-tolerated choice for HIV prevention in the most globally racially, ethnically, and gender-diverse Phase 3 program conducted to date. All trial participants are being offered open-label LEN.

June 18, 2025

Yeztugo® (Lenacapavir) Is Now the First and Only FDA-Approved HIV Prevention Option Offering 6 Months of Protection

World Health Organization

FDA approval of injectable lenacapavir marks progress for HIV prevention

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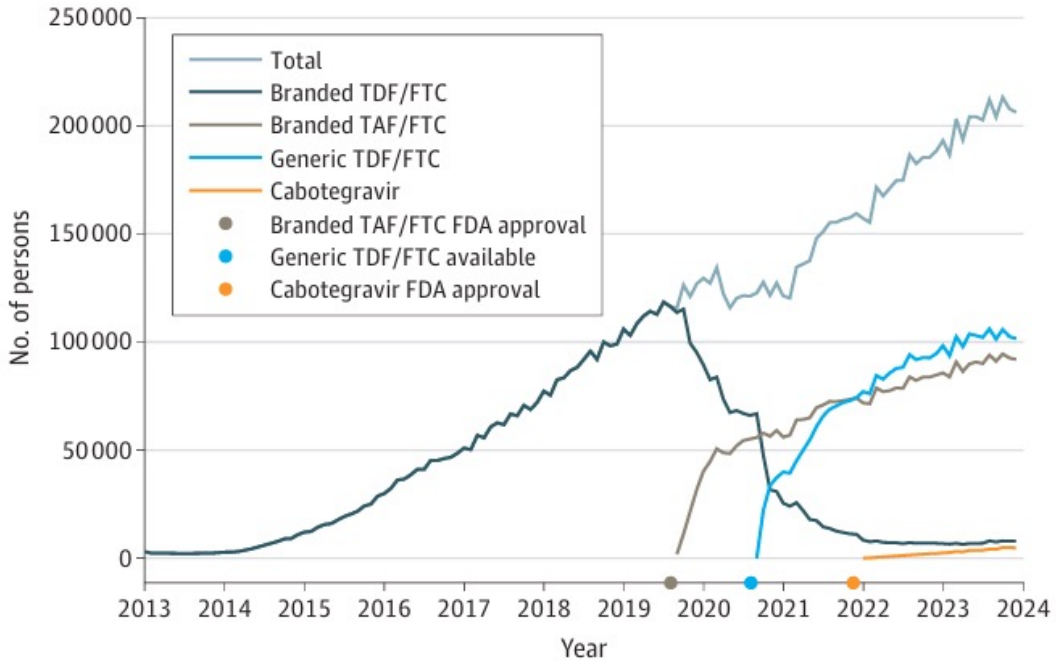
Comparing CAB-LA vs. LEN

Characteristic	CAB-LA	Lenacapavir
Drug class	Integrase Strand Transfer Inhibitor	Capsid inhibitor
Populations included in trials	- MSM and TGW - Cisgender women	- MSM, TG and NB populations - Cisgender women
Schedule of injections	Injections at baseline, 1 month, then every 2 months	- Injections at baseline and every 6 mo - 2 tablets on days 1 and 2
# injection visits/year	7	2
Location and type of injection	- Ventrogluteal or dorsogluteal, (thigh) - One 3 mL intramuscular injection	- Abdomen, alternative site thigh - Two 1.5 mL subcutaneous injections
Effectiveness	66-89% reduction compared with TDF/FTC	89-100% reduction compared with TDF/FTC
Side effects	- Injection site reactions common, improve with subsequent injections	- Injection site reactions common, improve with subsequent injections - Nodules
Cost	- $4K/injection - $28K/year	- $14K/injection - $28K/year

Trends in oral and injectable PrEP Prescriptions, 2013-2023

Figure. Persons Prescribed Preexposure Prophylaxis (PrEP) by Type of PrEP Medication—United States, January 2013 Through December 2023



Mann et al, JAMA Oct 2024

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Multi-level barriers to broad scale-up of injectable PrEP

Level	Barriers
Individual	• **Lack of awareness of injectable PrEP** • Fear of needles • Injection site reactions • Fear of long-term side effects
Organizational	• Provider comfort administering injections • Staffing to handle **complex insurance navigation** • Systems to track and remind patients of visits
Structural	• **High cost** • Insurance / access issues

Adapted from Albert Liu, MD

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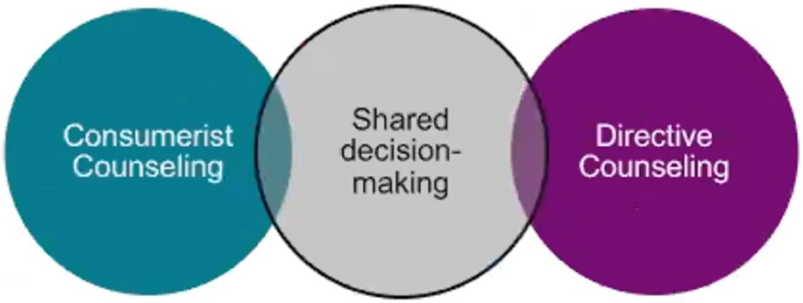
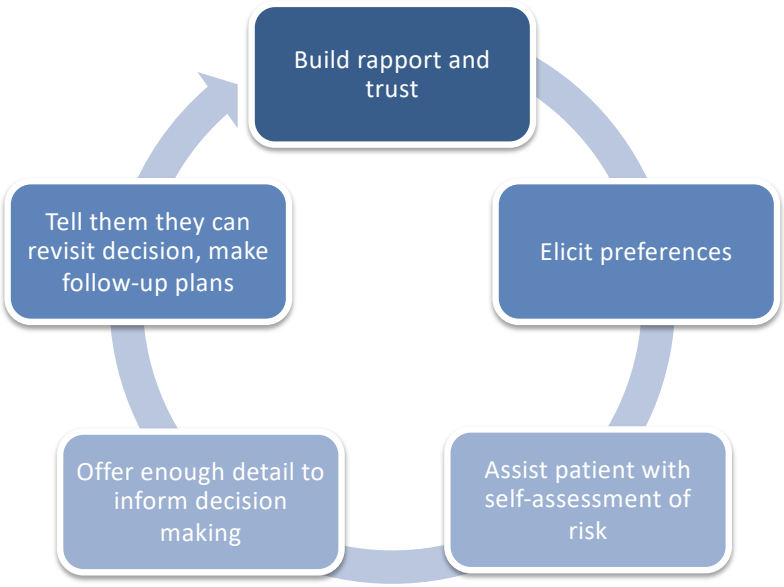
Lessons from Contraception





Adapted from Seidman D, Symposia CROI 2022; Dehlendorf, Contraception 2018; Sewell et al, Curr HIV/AIDS 2021.

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Successful Solutions and Strategies for CAB LA Integration

Key takeaways from clinics in the PILLAR implementation study

Practice Preparation

- **Tasking shifting**
- Injection training
- Flexible Scheduling
- **Staff enthusiasm & high motivation to offer CAB LA**
- Prior experience with injectables

Patient Selection

- **Patient awareness and education**
- Screen for stigma and pill fatigue
- Offer to individual who test positive for STIs or use injection drugs
- Patient-provider discussion guides

Benefits Verification

- Delegate staff to lead insurance processes
- **Coordinate and collaborate with pharmacies**
- Use ViiV insurance support systems

Inventory Management

- **Medication tracking** and delivery logs
- Stock needles for larger BMI individuals

Injection Visits

- **Flexible scheduling**
- Use telehealth to support clinic flow
- Integrate other care for convenience
- Injection training for different body types

Continuation

- **Patient scheduling & tracking systems**
- **Integrated care** – combine with other care
- Support services (e.g., telehealth, transportation)
- Patient reminders sent across multiple mediums (text, phone, email, etc.)

CAB, cabotegravir; LA, long-acting; STI, sexually transmitted infection.

Khan, HIVR4P 2024

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LEN for PrEP Key Takeaways

- Similarly to CAB-LA, lenacapavir found to be superior to oral PrEP for all genders
  - LEN administration every 26 weeks is promising for acceptability and implementation
  - Injection site reactions common, but did not result in significant discontinuation
- Injectable PrEP may be preferred among different populations
  - Increase privacy, reduce stigma
  - Reduce burden and adherence challenges with taking a daily pill
  - Increased choice can lead to increased PrEP uptake and persistence
- Expanding injectable PrEP use among communities highly impacted by HIV (and with lower uptake of oral PrEP) could help reduce disparities in HIV prevention
  - We need to expand our reach, not just switch current PrEP users to new formulations
  - Individual, organizational, and structural barriers to implementation need to be addressed to maximize impact
  - The future of LEN: once yearly IM formulation

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