PURPOSE

Prevention with PURPOSE

IAS 2025

Some Special Populations in Purpose 1

Linda-Gail Bekker (on behalf of whole protocol team)

13th International AIDS Society (IAS) Conference on HIV Science; July 13-17, 2025; Kigali, Rwanda

PURPOSE 1 Study Design

Randomized Blinded Cohort

Participants randomized to LEN received loading doses of two 300-mg tablets of LEN on each of Days 1 and 2; participants randomized to F/TAF or F/TDF received matched placebos

Cross-Sectional Incidence Cohort

Cisgender women[a]

Not on PrEP, no HIV testing in the past 3 months, negative pregnancy test

- **HIV-negative test and eligible**[b]
- **HIV-positive test → recency assay used to estimate background HIV incidence**

2 **LEN SC every 26 weeks** — n = 2134[c]
+ oral F/TAF placebo or F/TDF placebo (2:1)

2 **F/TAF oral daily** — n = 2136[c]
+ SC LEN placebo every 26 weeks

1 **F/TDF oral daily** — Active control — n = 1068[c]
+ SC LEN placebo every 26 weeks

Background HIV incidence[d] **(n = 8094)**

Prespecified Interim Analysis[e]

50% of participants completed ≥ 52 weeks

Primary analysis[f]**:**
1. LEN vs background HIV
2. F/TAF vs background HIV

Secondary analysis[g]**:**
1. LEN vs F/TDF
2. F/TAF vs F/TDF

ClinicalTrials.gov: NCT04994509

[a]First participant screened August 2021; 50th-percentile participant randomized May 2023; last participant randomized September 2023. [b]Eligibility criteria included: body weight ≥ 35 kg, eGFR ≥ 60 mL/min, not pregnant. [c]n numbers represent the full analysis set for efficacy analyses. [d]Background HIV incidence is the incidence expected without PrEP that would have been expected in a placebo group (the counterfactual HIV incidence). [e]Because the randomized blinded phase was stopped early due to an efficacy outcome, the interim analysis served as the primary analysis. [f]IRR was assessed using a Wald test or likelihood ratio test if there were zero infections. [g]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; **LEN**, lenacapavir; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous.

Bekker LG, et al. *N Engl J Med*. 2024;391:1179-92.

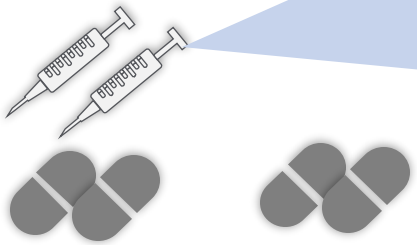
Initiation of LEN for PrEP Requires Oral LEN Loading Tablets and Injections[1,2]

LEN for PrEP Day 1 — 2

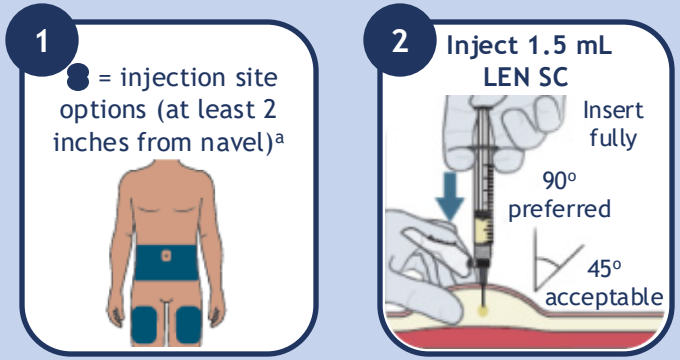
Initiation regimen

LEN SC 927 mg Day 1

LEN PO 600 mg Days 1 and 2



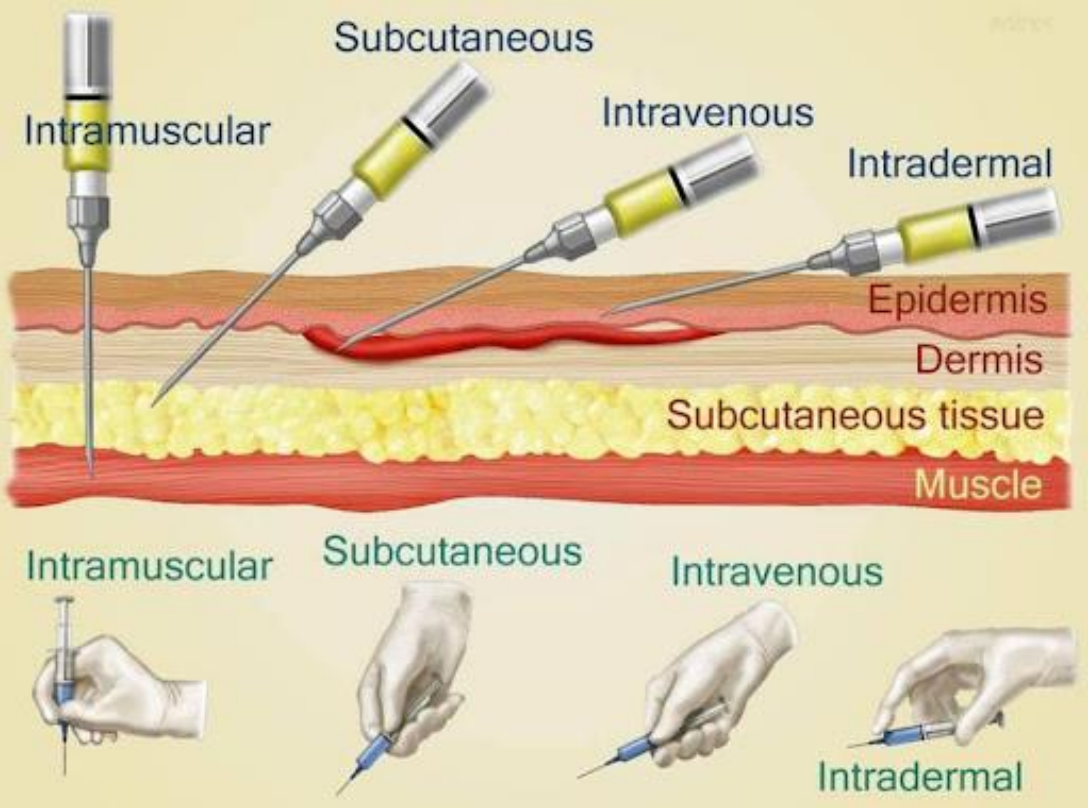
All 4 pills cannot be taken on 1 day because they will not be absorbed by the GI tract; they need to be taken 24 hours apart

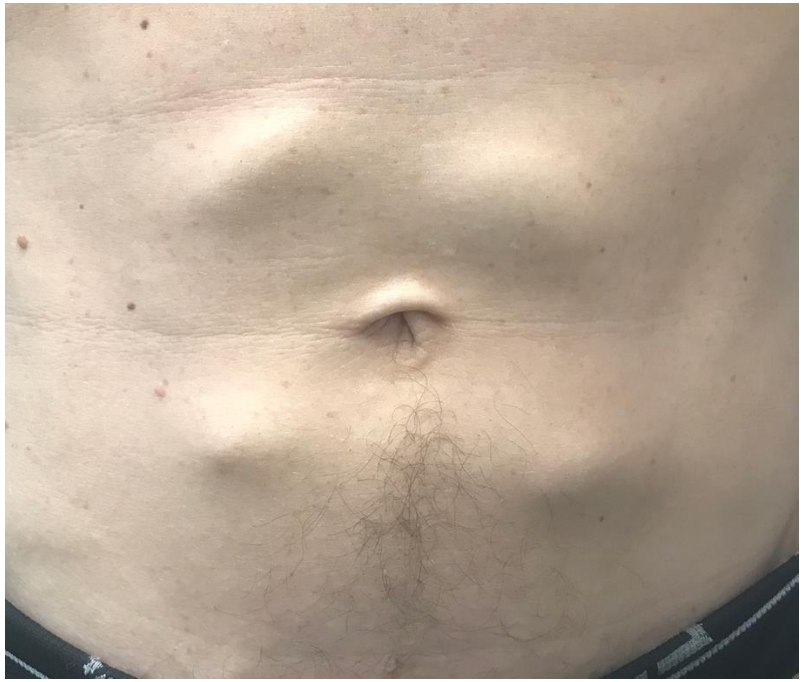


[a]Injection sites are depicted as per the United States Prescribing Information. **GI**, gastrointestinal; **LEN**, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous(ly).

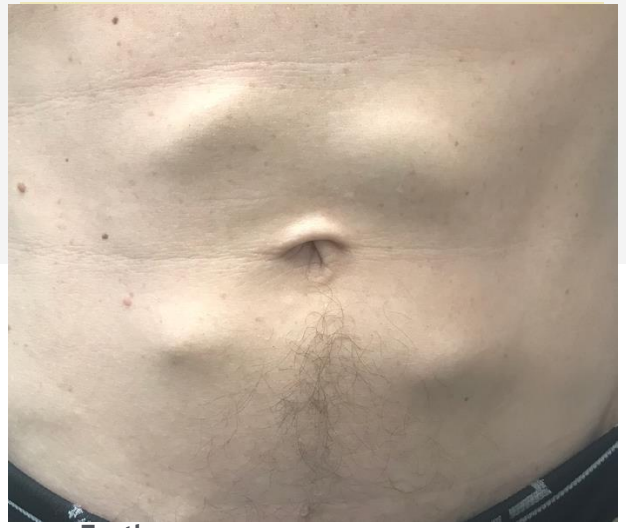
1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).
2. Jogiraju V, et al. Poster #PESUB22 presented at the 24th International AIDS Conference; July 29–August 2, 2022; Montreal, Canada, and virtually.

Subcutaneous nodules

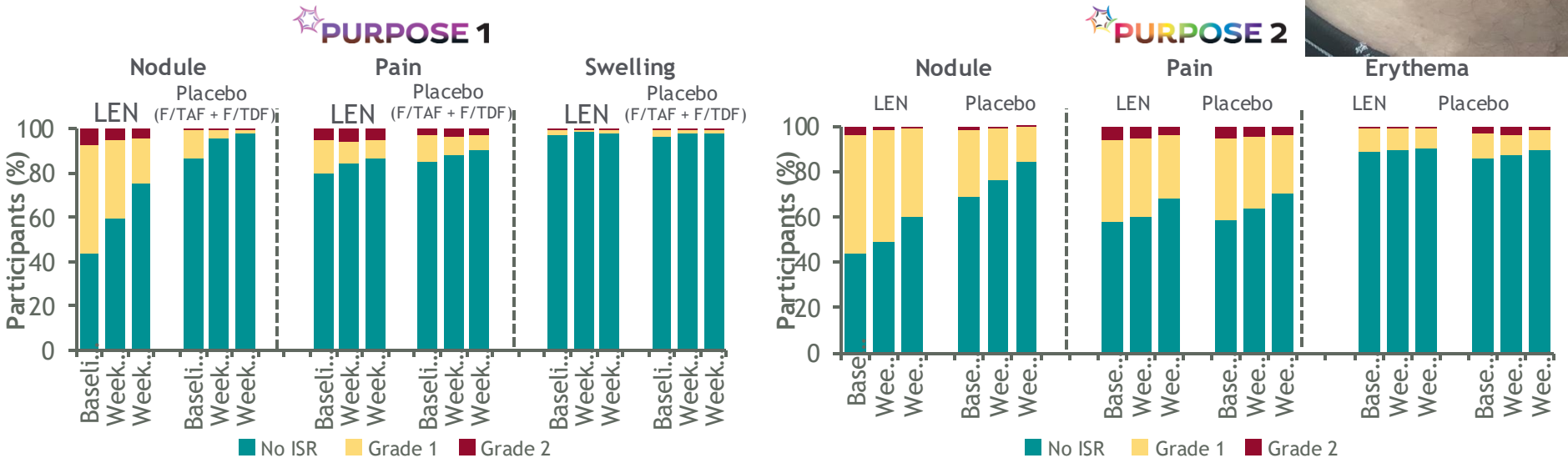




Injection-Site Reaction: Frequency and Grade



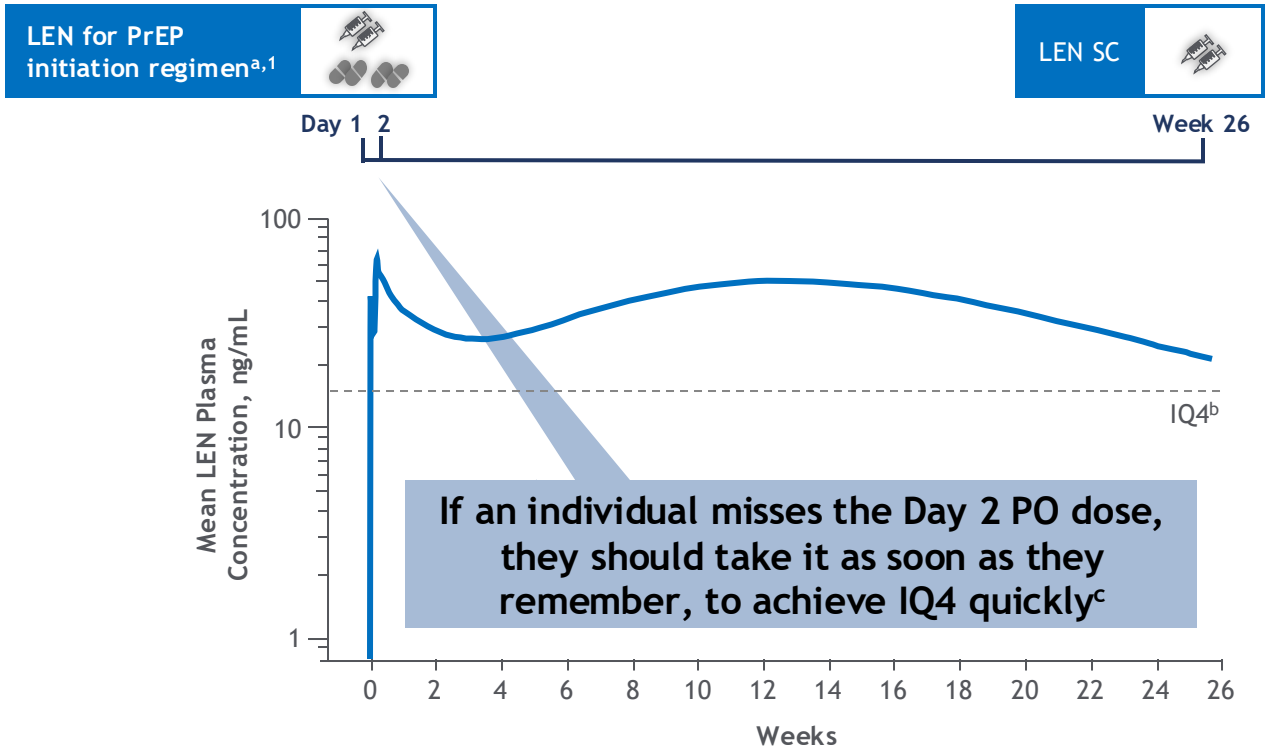
LEN is injected into the SC space and forms a drug depot that may be palpable under the skin but may not be visible. As the drug elutes over time, the depot gets smaller, and the nodules resolve or reduce in size prior to the next injection.
The frequency of ISRs, including nodules, decreased with subsequent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

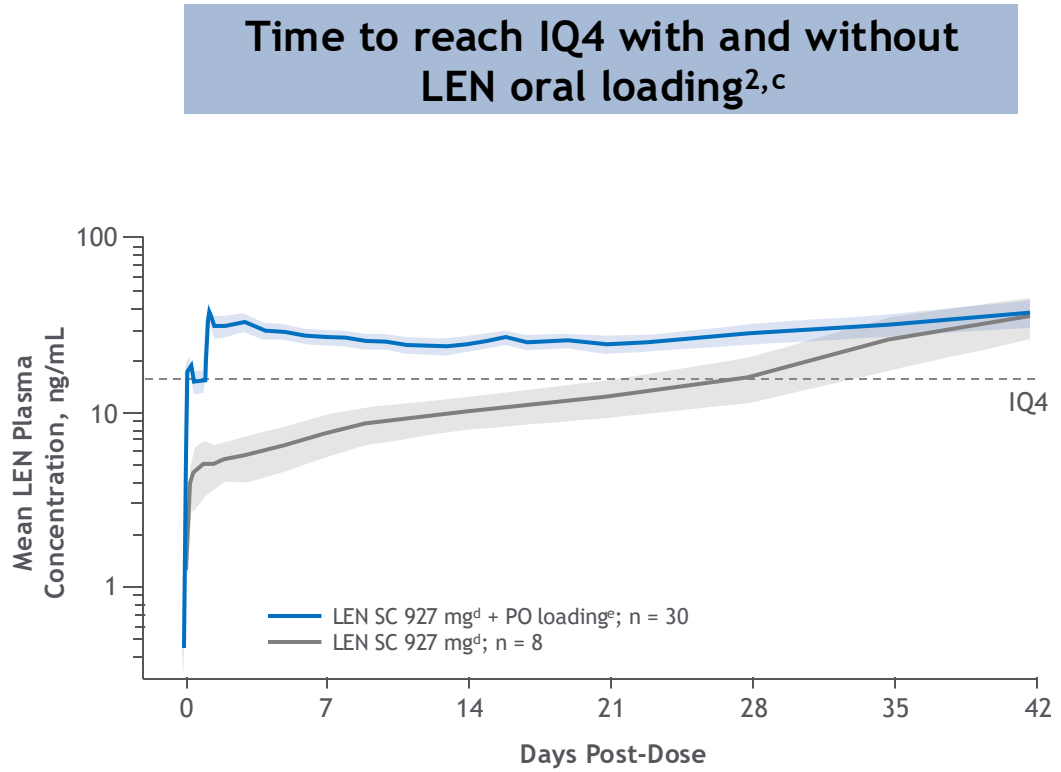


In PURPOSE 1, among 25,329 LEN/placebo injections, only 4 ISRs led to discontinuation (all LEN)
In PURPOSE 2, among 15,239 LEN/placebo injections, only 29 ISRs led to discontinuation (LEN, 26; F/TDF, 3)

AEs coded according to Medical Dictionary for Regulatory Activities, Version 27.0. Grade 1 and 2 ISRs are shown. In PURPOSE 1: LEN n: baseline, 2138; Week 26, 1930; Week 52, 862. Placebo (F/TAF + F/TDF) n: baseline, 3206; Week 26, 2883; Week 52, 1274; SC nodules, injection-site pain, and swelling were the most commonly reported ISRs, occurring in 63.8%, 31.2%, and 4.4% of participants in the LEN group, respectively, vs 16.6%, 23.7%, and 5.4% of participants given placebo injections; Grade 3 ISRs in the LEN group: n = 1 nodule; F/TDF group: n = 1 pain. In PURPOSE 2, LEN n: baseline, 2183;
Week 26, 1859; Week 52, 744; Placebo n: baseline, 1088; Week 26, 946; Week 52, 379; SC nodules, injection-site pain, and erythema were the most commonly reported ISRs; over the period of study, they occurred in 63.4%, 56.4 %, and 17.3% of participants in the LEN group, respectively, vs 39.2%, 53.4%, and 19.4% of participants given placebo injections; Grade 3 ISRs in the LEN group: n = 4 pain, n = 3 erythema; F/TDF group: n = 1 pain. **1.** Kumar P, et al. Abstract EPB184 presented at the 24th International AIDS Conference, July 29 to August 2, 2022; Montreal, Canada.

LEN Initiation Dosing with Oral Loading Achieves LEN Target Concentrations by Day 2 through Week 26[1]





Omission of LEN oral loading significantly delays achievement of target concentrations

[a]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly. [b]IQ4 = 4-fold above $paEC_{95}$ 15.5 ng/mL; [c]If an individual misses the Day 2 dose, they will not be able to achieve IQ4 on Day 2. [d]LEN sodium 309 mg/mL; 2 × 1.5 mL; [e]LEN PO 600 mg on Days 1 and 2.

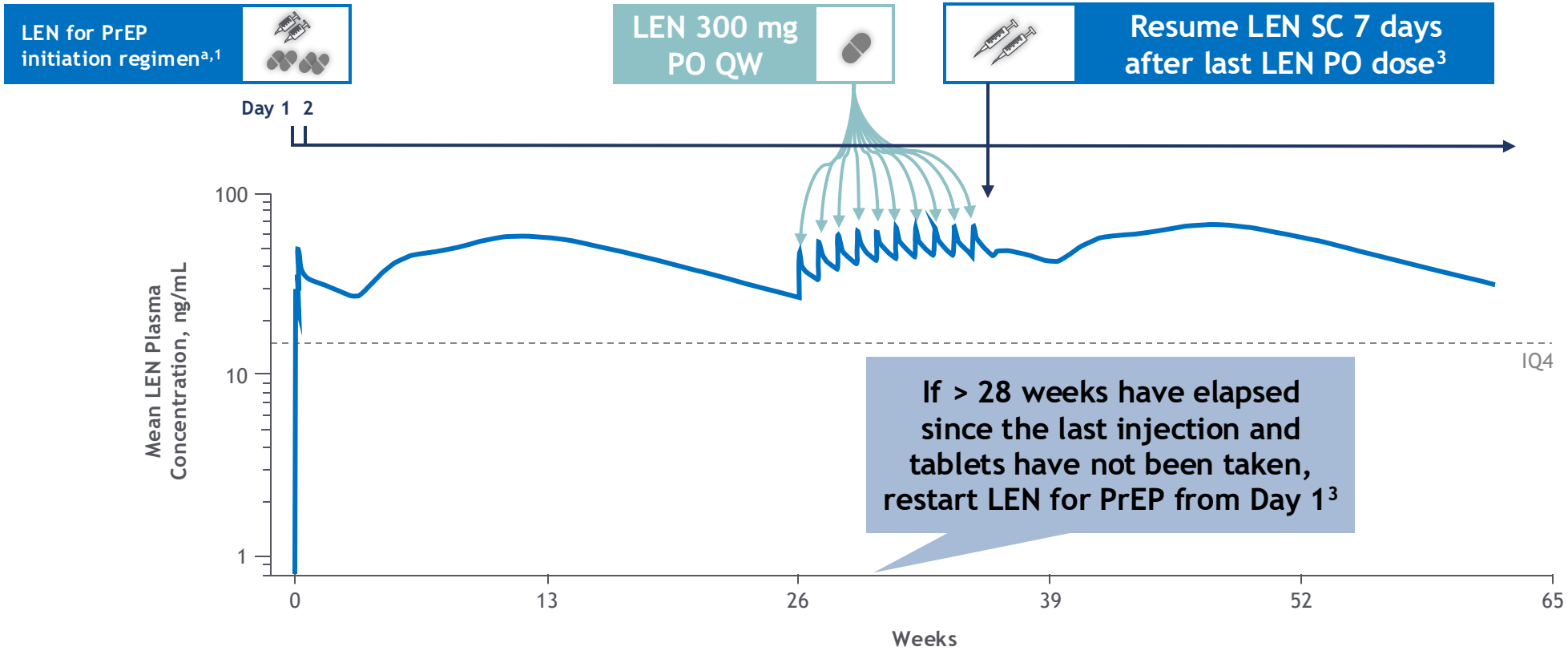
IQ4, inhibitory quotient 4; **LEN,** lenacapavir; **$paEC_{95}$,** protein-adjusted effective concentration to achieve 95% effective inhibition; **PO,** oral(ly); **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneously.

1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025). 2. Jogiraju V, et al. Poster PESUB22 presented at AIDS 2022; June 29-Aug 2, 2022; Montreal, Canada.

Special Situation: What If Someone Taking LEN-for-PrEP is Unable to Get Their Twice-Yearly Injection on Time?

LEN, lenacapavir; **PrEP**, pre-exposure prophylaxis.

Weekly LEN PO Maintains LEN at Target Concentration Until LEN SC Can Be Resumed[1,2]



Individuals who anticipate a missing/delayed LEN SC injection should take LEN PO 300 mg once every 7 days starting 26-28 weeks after the last LEN SC injection, for up to 6 months if needed, before resuming LEN SC[3]

[a]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly.

IQ4, inhibitory quotient 4; **LEN,** lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QW**, once weekly; **SC**, subcutaneous.

1. Ogbuagu OE, et al. *AIDS*. 2025;39:639-48. 2. Jogiraju V, et al. Poster TUPEB07 presented at IAS 2023; July 23-26, 2023; Brisbane, Australia. 3. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

Gill K, et al. IAS 2025, OAC0503

Efficacy, Safety, and Pharmacokinetics of Twice-Yearly Subcutaneous Lenacapavir for PrEP Among Adolescents and Young People in the Phase 3 Trials PURPOSE 1 and PURPOSE 2

PURPOSE 1

PURPOSE 2

PURPOSE 1

N=2183

Cisgender women aged 16–25 years

- LEN SC every 26 weeks
- F/TAF oral daily
- F/TDF oral daily

Study duration: ≥52 weeks

PURPOSE 2

N=3271

CGBMSM, TGW, TGM and GNB aged ≥16 years

- LEN SC every 26 weeks
- F/TDF oral daily

Study duration: ≥52 weeks

Objective: Evaluate the efficacy, safety, and PK of twice-yearly SC LEN in youth (aged 16-25) compared with adults in PURPOSE 1 and PURPOSE 2

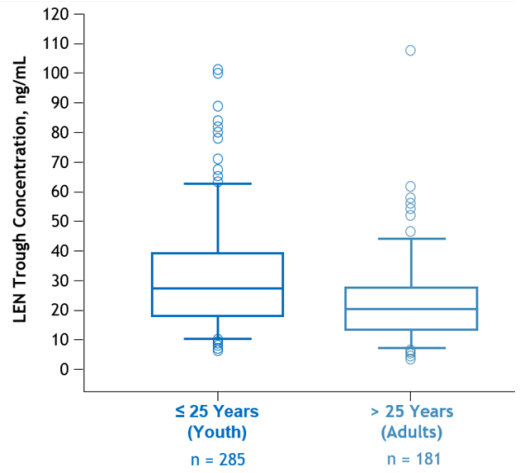
Characteristic	PURPOSE 1 (16-25 years)		PURPOSE 2 (≥ 16 years)	
	< 18 years LEN, n = 56	≥ 18 years LEN, n = 2084	≤ 25 years LEN, n = 752	> 25 years LEN, n = 1431
Median age, years (range)	17 (16-17)	21 (18-25)	22 (17-25)	32 (26-74)
16 to < 18 years, n (%)	56 (100)	0	3 (0.4)	0
≥ 18 years, n (%)	0	2084 (100)	749 (99.6)	1431 (100)

Only 2 HIV acquisitions occurred in youth, both in PURPOSE 2

LEN was safe and well tolerated in youth

- **AEs and lab abnormalities were generally similar** in youth receiving LEN in PURPOSE 1 and 2 compared with adults
- **ISR in youth were mostly low grade and consistent** with those reported in PURPOSE 1 and 2

Observed LEN plasma concentrations were comparable between youth and adults



Similar to adults, twice-yearly SC LEN had high efficacy, favorable safety, and no clinically relevant PK differences in youth, supporting the potential of LEN to address challenges with daily oral PrEP in youth

PURPOSE

Prevention with PURPOSE

IAS 2025

Inclusion of Pregnant and Lactating People in the PURPOSE 1 Study: Efficacy, Safety, and Pharmacokinetics

Linda-Gail Bekker[1], Dhayendre Moodley[2], Ishana Harkoo[2], Godfrey Kigozi[3], Cheryl Emily Louw[4], Moelo Malahleha[5], Thesla Palanee-Phillips[6], Ravindre Panchia[7], Nishanta Singh[8], Dazon Dixon Diallo[9], Lillian Mworeko[10], Sarah Puryear[11], Pamela Wong[11], Priyanka Arora[11], Marjorie Imperial[11], Chris Deaton[12], Alexander Kintu[11], Moupali Das[11], Flavia Matovu Kiweewa[13]

[1]The Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; [2]Centre for the AIDS Programme of Research in South Africa, University of KwaZulu-Natal, Durban, South Africa; [3]Africa Medical and Behavioral Sciences Organization, Kalisizo, Uganda; [4]Madibeng Centre for Research, Brits, South Africa; [5]Synergy Biomed Research Institute, East London, South Africa; [6]Wits RHI, University of the Witwatersrand, School of Public Health, Johannesburg, South Africa; [7]Perinatal HIV Research Unit, University of the Witwatersrand, Soweto, South Africa; [8]HIV and Other Infectious Diseases Research Unit, South African Medical Research Council, Durban, South Africa; [9]SisterLove, Inc., Atlanta, GA, USA; [10]International Community of Women Living with HIV Eastern Africa, Kampala, Uganda; [11]Gilead Sciences, Inc., Foster City, CA, USA; [12]Gilead Sciences, Inc., Cambridge, UK; [13]Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda

13th International AIDS Society (IAS) Conference on HIV Science; July 13-17, 2025; Kigali, Rwanda

PURPOSE: First to Include Pregnant and Lactating People in Phase 3 HIV PrEP Trials

Pregnant and lactating people are disproportionately vulnerable to HIV-1 acquisition but **historically excluded** from Phase 3 HIV trials,[1,2] despite an **urgent unmet need** for HIV prevention options

LEN is a **first-in-class**, multistage HIV-1 capsid inhibitor with **high potency** and a **long half-life**, supporting **twice-yearly SC injection**[3,4]

Preclinical studies **do not indicate harmful effects of LEN** on fertility, pregnancy, fetal development, or postnatal development[4]

We evaluated the efficacy, safety, and PK of twice-yearly SC LEN for HIV prevention in pregnant and lactating people in PURPOSE 1

Middle image from: https://www.impaactnetwork.org/who-and-impaact-call-action-webinar-world-aids-day, reproduced with permission; © WHO, IMPAACT, CIPHER (2021). Right image from: https://www.hivpregnancyethics.org/, reproduced under a CC BY-NC 4.0 license. **LEN**, lenacapavir; **PK**, pharmacokinetics; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous. 1. Drake AL, et al. *PLoS Med*. 2014;11:e1001608. 2.Davey DLJ, et al. *Lancet HIV*. 2022;9(3):e214-e222. 3. Link JO, et al. *Nature*. 2020;584:614-18. 4. Sunlenca USPI. Gilead Sciences, Inc. December 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf (accessed May 13, 2025).

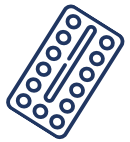
PURPOSE 1: Developing a New Model for Ethical and Inclusive Study Design for Pregnant and Lactating People

KEY STAKEHOLDERS

- We engaged investigators and site staff, community stakeholders, regulatory agencies, ethics committees, and maternal/pediatric health experts to responsibly include pregnant and lactating people in PURPOSE 1

CONTRACEPTION

- To respect autonomy and reproductive choice, free contraception was offered during the study but not required



INCLUSION

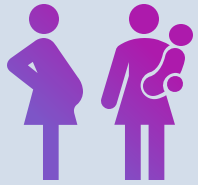
- Participants who became pregnant could remain in the study after reconsent (fathers were also given the option to consent for their unborn infants)
- PURPOSE 1 implemented all WHO and IMPAACT toolkit recommendations for the inclusion of pregnant and lactating people[1]

IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; **WHO**, World Health Organization.

1. WHO and IMPAACT Network. https://iris.who.int/bitstream/handle/10665/349842/9789240040182-eng.pdf?sequence=1 (accessed June 4, 2025).

Nested PK Sub-Study: Designed to Limit Burden on Pregnant and Lactating Participants and their Infants

Pregnancy, Breast Milk, and Infant PK Sub-Study

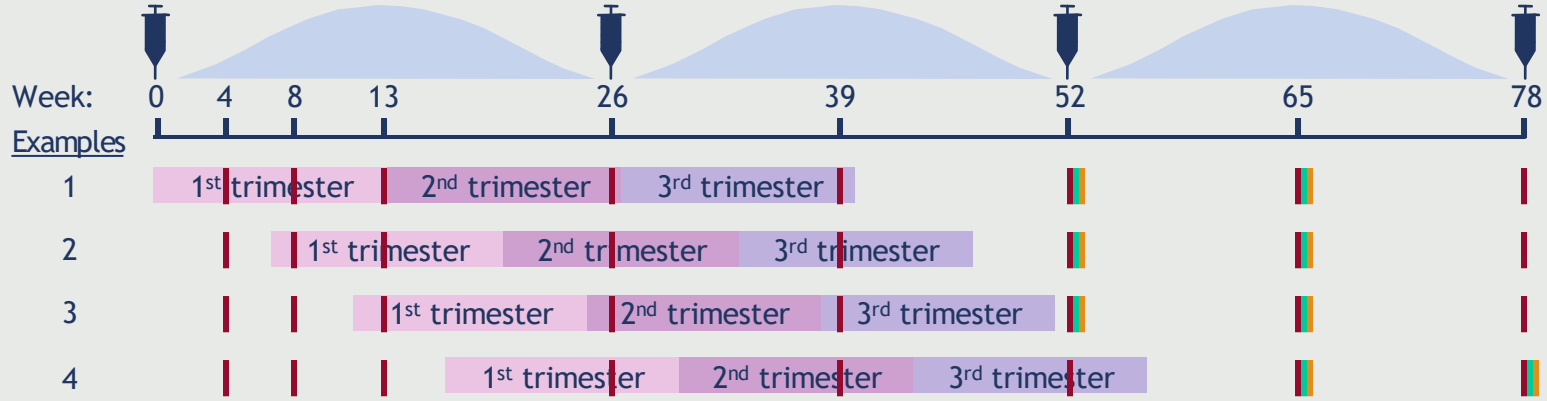


Includes people who became pregnant while receiving LEN, and their infants

PK samples taken at each visit

- Maternal plasma
- Infant plasma
- Breast milk

Schedule of PK sampling in pregnant and postpartum participants



- **Objectives:** To describe maternal systemic drug concentrations during pregnancy and postpartum and assess drug concentrations in breast milk and infants, while limiting visit burden for participants

EGA, estimated gestational age; **LEN**, lenacapavir; **PK**, pharmacokinetics.

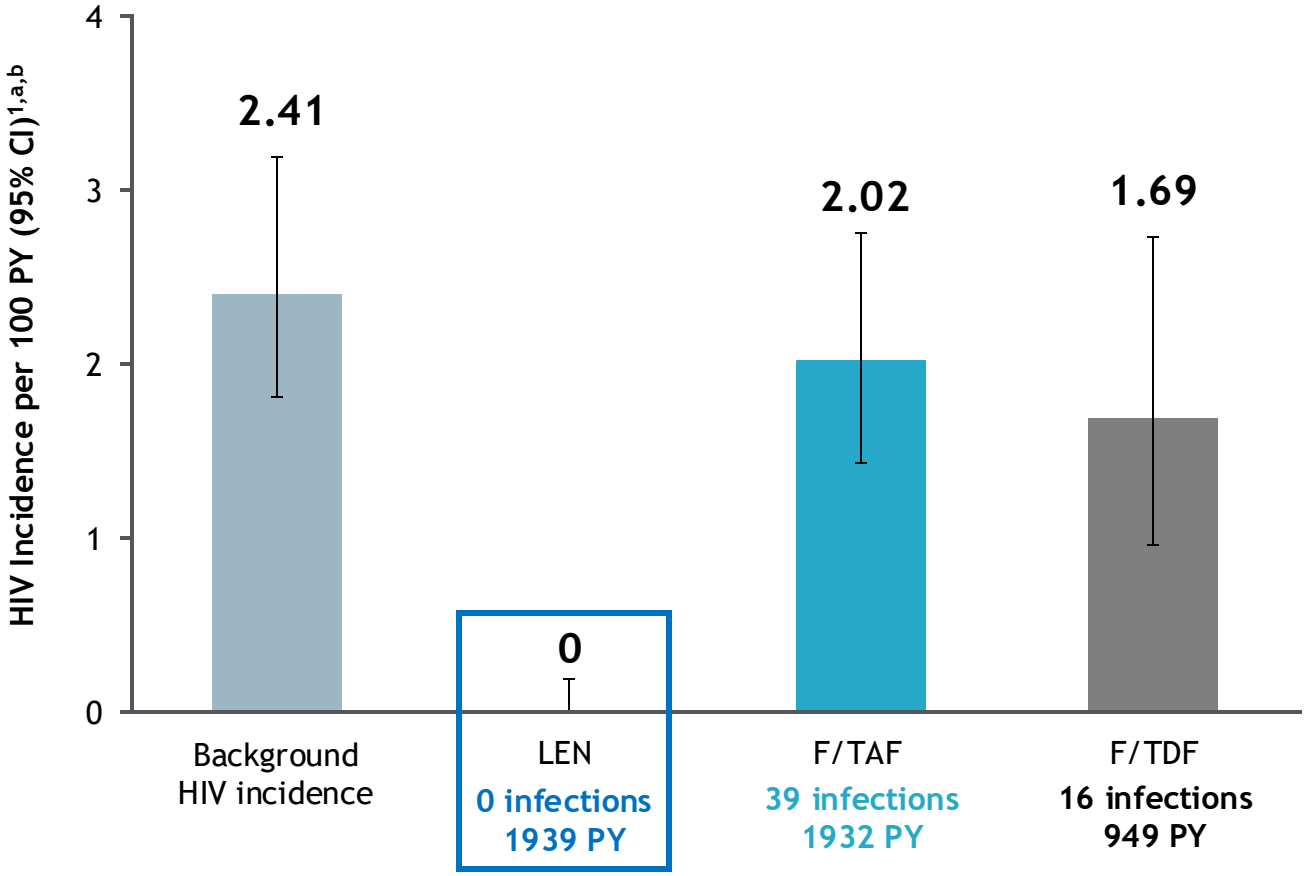
Baseline Demographics and Characteristics

Characteristic	LEN, n = 2140		F/TAF, n = 2135		F/TDF, n = 1070	
	Pregnancy, n = 184	No Pregnancy, n = 1956	Pregnancy, n = 208	No Pregnancy, n = 1927	Pregnancy, n = 95	No Pregnancy, n = 975
Age, years, median (range)[b]	21 (17-25)	21 (16-25)	22 (16-25)	21 (16-26)	21 (17-25)	21 (16-25)
Age 16 to < 18 years, n (%)	3 (1.6)	53 (2.7)	2 (1.0)	43 (2.2)	1 (1.1)	22 (2.3)
Black race,[c] n (%)	184 (100)	1953 (99.8)	207 (99.5)	1927 (100)	95 (100)	973 (99.8)
Some or no primary school, n (%)	46 (25.0)	140 (7.2)	41 (19.7)	133 (6.9)	20 (21.1)	56 (5.7)
Marital status, n (%)						
Married	6 (3.3)	20 (1.0)	7 (3.4)	23 (1.2)	2 (2.1)	15 (1.5)
Living with primary partner, n (%)	21 (11.4)	127 (6.5)	13 (6.3)	119 (6.2)	5 (5.3)	68 (7.0)
Any *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, or Syphilis, n (%)	63 (34.2)	664 (33.9)	72 (34.6)	702 (36.4)	40 (42.1)	333 (34.2)
Any prior use of PrEP, n (%)	10 (5.4)	133 (6.8)	10 (4.8)	114 (5.9)	5 (5.3)	66 (6.8)
Any prior HIV testing, n (%)	145 (78.8)	1570 (80.3)	169 (81.3)	1562 (81.1)	77 (81.1)	783 (80.3)
Modified VOICE risk score, median (Q1, Q3)	6.0 (5.0, 7.0)	7.0 (5.0, 7.0)	7.0 (6.0, 7.0)	7.0 (5.0, 7.0)	7.0 (6.0, 7.0)	7.0 (5.0, 7.0)
Intercourse for financial or material support in past 3 months, n (%)	76 (41.8)	417 (21.6)	79 (38.5)	424 (22.3)	44 (47.3)	207 (21.5)

487 participants with 509 pregnancies included[1]
Baseline demographics and characteristics were similar regardless of pregnancy or study arm

Participants with ≥ 1 confirmed pregnancy during the RBP primary analysis versus those with no reported pregnancies. Missing data and participants who preferred not to answer are excluded.
[a]Age on first study drug dose date. [c]All non-Black participants were multiracial. **F/TAF,** emtricitabine/tenofovir alafenamide; **F/TDF,** emtricitabine/tenofovir disoproxil fumarate; **LEN,** lenacapavir; **PrEP,** pre-exposure prophylaxis; **Q,** quartile; **RBP**, randomized blinded phase. 1. Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92.

Zero HIV Infections in Women Receiving LEN in PURPOSE 1



Five incident HIV infections in participants with pregnancies:

- 0/184 on LEN
- 4/208 on F/TAF
- 1/95 on F/TDF

No cases of vertical transmission

[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.
F/TAF, emtricitabine/tenofovir alafenamide; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LEN**, lenacapavir; **PY**, person-years.

Bekker L-G, et al. *N Engl J Med*. 2024;391:1179-92.

Pregnancy Outcomes Were Similar to Expected Rates in the Population

Participants and Pregnancies[1]	LEN n = 193	F/TAF n = 218	F/TDF n = 98
Confirmed pregnancies	193	218	98
Participants with confirmed pregnancy(ies)[a]	184	208	95
Pregnancy status, n (%)			
Completed	186 (96.4)	207 (95.0)	97 (99.0)
Unknown	7 (3.6)	11 (5.0)	1 (1.0)
Live births, n (%)[b]	128 (66.3)	119 (54.6)	56 (57.1)
Pregnancy losses, n (%)	60 (31.1)	89 (40.8)	41 (41.8)
Stillbirth[c]	5 (2.6)	6 (2.8)	3 (3.1)
Induced abortion	35 (18.1)	50 (22.9)	23 (23.5)
Spontaneous miscarriage[d]	20 (10.4)	33 (15.1)	15 (15.3)

- In total, 10 congenital abnormalities were reported (six in LEN arm; four in F/TAF arm)[e]

Expected spontaneous miscarriage rate[2,3]:

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

The incidence of congenital anomalies was within the expected background rate[4,5]

Pregnancy outcomes were similar to those expected for the population[5] and balanced across study arms

Analyses limited to pregnancies diagnosed while on RBP-assigned study drug and diagnosed prior to May 8, 2024 (data cutoff for RBP primary analysis). Denominator = number of confirmed pregnancies. Pregnancy outcomes included for all pregnancies, including outcomes that occurred after switch to open-label phases. [a]Some participants had >1 pregnancy. [b]Live birth data include three pregnancies that have two outcomes due to twins. [c]Fetal death occurring at ≥ 20 weeks' gestation. [d]Spontaneous miscarriage occurring at < 20 weeks' gestation. [e]Congenital abnormalities reported in LEN arm: congenital hemangioma (n = 1), umbilical hernia (n = 1), left hand polydactyly (n = 1), perimembranous ventricular septal defect (n = 1), congenital ventricular septal defect (n = 1), congenital reducible umbilical hernia (n = 1); in F/TAF arm: infant bilateral hydrocele (n = 1), right inguinal hernia and umbilical hernia, neonatal jaundice (n = 1), Down syndrome (n = 1), clubfoot (n = 1).
F/TAF, emtricitabine/tenofovir alafenamide; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **LEN**, lenacapavir; **RBP**, randomized blinded phase.
1. Bekker L-G, et al. *N Engl J Med.* 2024;391:1179-92. 2. ACOG Committee on Practice Bulletins—Gynecology. *Obstet Gynecol.* 2018;132:e197-207. 3. Wilcox AJ, et al. *N Engl J Med.* 1988;319:189-94. 4. Mugo NR, et al. *JAMA.* 2014;312:362-71. 5. Makanani B, et al. *J Acquir Immune Defic Syndr.* 2018;79:566-72.

LEN is Safe and Well Tolerated During Pregnancy and Postpartum

Participants,[a,b] n (%)	LEN n = 184	F/TAF n = 208	F/TDF n = 95
Any adverse events during pregnancy and postpartum	135 (73.4)	142 (68.3)	68 (71.6)
Grade ≥ 2	112 (60.9)	112 (53.8)	55 (57.9)
Grade ≥ 3	36 (19.6)	39 (18.8)	22 (23.2)
Serious adverse events	41 (22.3)	50 (24.0)	22 (23.2)
Adverse events leading to discontinuation of study drug	1 (0.5)[c]	0	0
Adverse events during pregnancy and postpartum occurring in ≥ 10% of participants in any group[d]			
Urinary tract infection	39 (21.2)	34 (16.3)	27 (28.4)
Vulvovaginal candidiasis	17 (9.2)	22 (10.6)	8 (8.4)
Upper respiratory tract infection	20 (10.9)	16 (7.7)	6 (6.3)

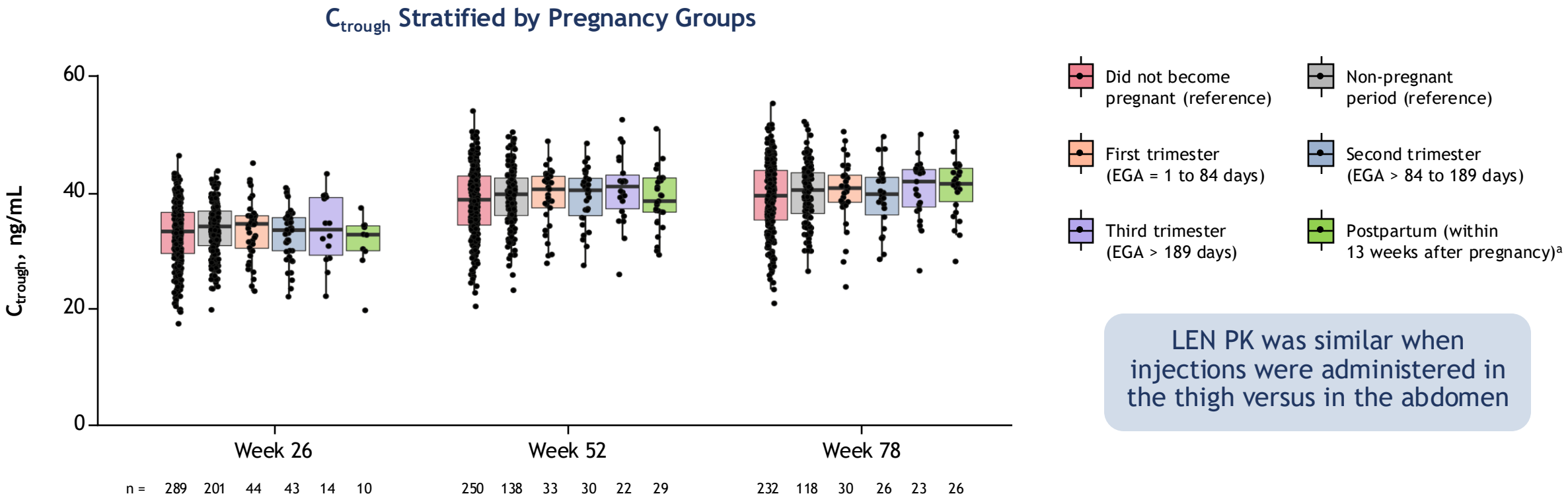
- Of participants who received at least one LEN injection during pregnancy/postpartum, 33.3% (44/132) reported ISRs to study SC injection (all Grade 1 or 2 in severity); the most common ISRs were nodules (26.5%; n = 35) and injection-site pain (12.9%; n = 17)

Adverse events were generally consistent with prior LEN, F/TAF, and F/TDF trials[1-3]

These analyses are limited to confirmed pregnancies included in the RBP primary analysis (data cutoff: May 8, 2024). Adverse events coded according to Medical Dictionary for Regulatory Activities Version 27.1 and graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [a]Limited to adverse events occurring during the RBP with onset from last menstrual period date to pregnancy outcome date + 6 weeks.[b]ISRs to non-study medications are included but ISRs to study SC injection are excluded. [c]Discontinuation due to spontaneous miscarriage. [d]Spontaneous miscarriages have been excluded. **F/TAF**, emtricitabine/tenofovir alafenamide; **F/TDF**, emtricitabine/tenofovir disoproxil fumarate; **ISR**, injection site reaction; **LEN**, lenacapavir; **RBP**, randomized blinded phase; **SC**, subcutaneous. 1. Ogbuagu O, et al. *Lancet HIV*. 2023;10:e497-505. 2. Mayer KH, et al. *Lancet*. 2020;396:239-54. 3. Baeten JM, et al. *N Engl J Med*. 2012;367:399-410.

LEN Exposures Were Similar in Pregnant People Versus Non-Pregnant People

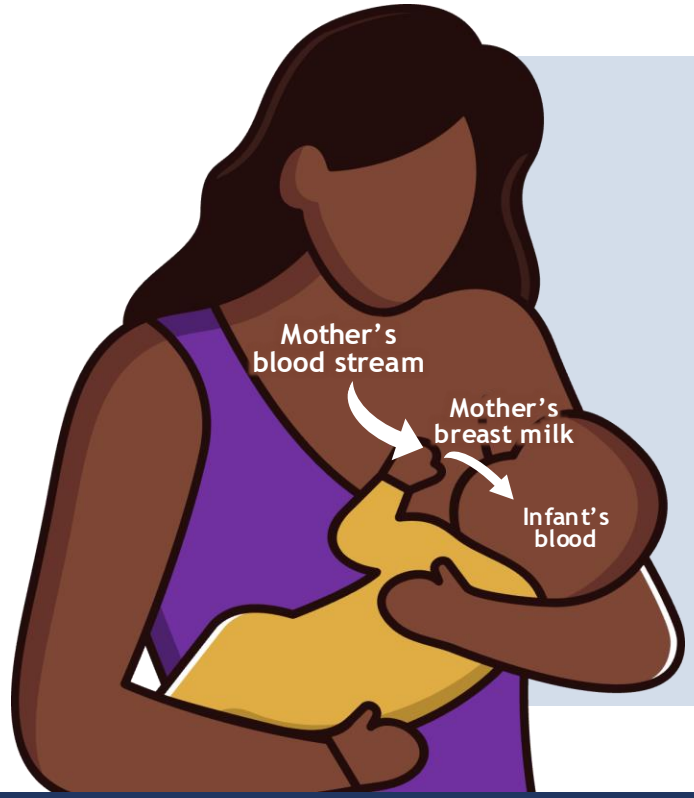
Across Week 26, Week 52, and Week 78 combined, a total of 107 first trimester, 99 second trimester, 59 third trimester, and 65 postpartum model-derived C_{trough} data were available



LEN PK was similar when injections were administered in the thigh versus in the abdomen

Box plots present model-derived C_{trough}. C_{max} showed a similar trend. Bottom and top of boxes represent Q1 and Q3, respectively; horizontal lines within boxes represent medians; whiskers represent ± 1.5 IQR. The population includes participants with available PK samples up to March 27, 2025. Pregnant people received thigh and/or abdomen injections. Model-derived LEN C_{trough} values following on-time complete injections were included. On-time complete injection was defined as both injections administered in full dose within ± 2 weeks of the target day relative to previous injection. Model-derived C_{trough} values were based on simulated concentration-time profiles for each participant. Concentration-time profiles were only simulated up to 26 weeks following the last on-time complete injection or the start of oral bridging or oral reloading, whichever came first. [a]Following childbirth or early pregnancy termination. **C_{max}**, maximum concentration; **C_{trough}**, trough concentration; **EGA**, estimated gestational age; **IQR**, interquartile range; **LEN**, lenacapavir; **PK**, pharmacokinetics; **Q**, quartile.

Minimal Exposure to LEN Observed in Breastfed Infants



- Median (Q1, Q3) **breastmilk-to-mother plasma ratio was 0.52** (0.38, 0.77) in 102 matched breast milk–mother pairs[a]
- Median (Q1, Q3) **breastfed-infant-to-mother plasma ratio was 0.02** (0.01, 0.05) in 98 matched mother-infant pairs[b]

LEN was present in breastmilk, but LEN concentrations were very low in breastfed infants

[a]Population limited to participants in the LEN PK breast-milk analysis set who received SC LEN in the RBP and became pregnant in RBP; ratio was calculated if the breast milk and plasma from the mother were collected at the same visit. [b]Population limited to participants in the LEN PK infant analysis set where the mother received SC LEN in RBP and became pregnant in RBP; ratio was calculated if plasma from the infant and mother was collected at the same visit. **LEN**, lenacapavir; **PK**, pharmacokinetics; **Q**, quartile; **RBP**, randomized blinded phase.

Conclusions

- PURPOSE 1 sets a new paradigm for ethical and inclusive trial design to accelerate data availability to support new PrEP options for pregnant and lactating people
- Twice-yearly LEN was efficacious, safe, and well tolerated in pregnant and lactating people
- No dose adjustment is required in pregnancy or post-partum
- 95% of eligible participants chose to continue or initiate LEN in the open-label extension, including participants who became pregnant during the RBP
- LEN for PrEP use in pregnancy supported in the US FDA label[1] and 2025 WHO Guidelines[2]

Proactive inclusion of pregnant and lactating women in PURPOSE 1 supports early adoption of LEN for PrEP in pregnant and lactating people

FDA, Food and Drug Administration, **LEN**, lenacapavir; **PK**, pharmacokinetics; **PrEP**, pre-exposure prophylaxis; **RBP**, randomized blinded phase; **WHO**, World Health Organization.

1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed July 15, 2025). 2. Word Health Organization. Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis. July 14, 2025 (https://www.who.int/publications/i/item/9789240111608)

PURPOSE

Prevention with PURPOSE

IAS 2025

Lenacapavir Dosing in Special Situations: Tuberculosis and Beyond

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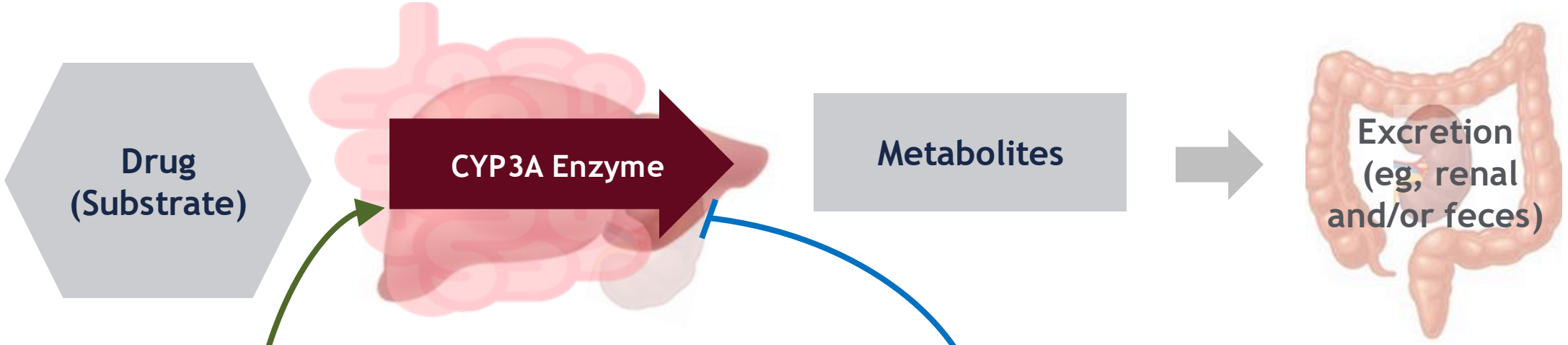
13th International AIDS Society (IAS) Conference on HIV Science 2025; July 13-17, 2025; Kigali, Rwanda

LEN is a Substrate of CYP3A[a] and Moderately Inhibits CYP3A[1,2]



Drug ➡ ↓LEN

If LEN is given with CYP3A inducers:
- Apparent clearance of LEN is faster, and LEN concentrations decrease
- Examples include rifampin (strong), rifabutin (moderate)

CYP3A inducers may decrease LEN levels; therefore, supplemental LEN doses are needed

LEN ➡ ↑Drug

If LEN (moderate CYP3A inhibitor) is given with a sensitive CYP3A substrate:
- Substrate drug may have slower clearance, and increased blood levels
- Examples include PDE5 inhibitors, statins

LEN may increase blood levels of drugs that are sensitive CYP3A substrates

[a]UGT and P-gp are also involved in LEN metabolism.

CYP, cytochrome P450; **LEN**, lenacapavir; **PDE5**, phosphodiesterase type 5; **P-gp**, P-glycoprotein; **UGT**, uridine diphosphate-glucuronosyltransferase.

1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025). 2. Begley R, et al. Oral #89 presented at CROI (Virtual), March 6-10, 2021.

People Using LEN for PrEP May Need to Use Alternative Dosing in Special Situations

What if someone taking LEN-for-PrEP is unable to receive a twice-yearly injection on time?

What if someone taking LEN-for-PrEP requires treatment with rifamycin antibiotics for TB, which are strong or moderate inducers of CYP3A and can lower LEN concentrations?[1]

What if someone taking LEN-for-PrEP also takes a PDE5 inhibitor for erectile dysfunction or a statin for hypercholesterolemia, which are metabolized by CYP3A? LEN is a moderate inhibitor of CYP3A and may increase concentrations of some drugs[1]

Dosing recommendations are provided for individuals who must delay a LEN injection, are starting TB treatment, or are taking LEN with other drugs

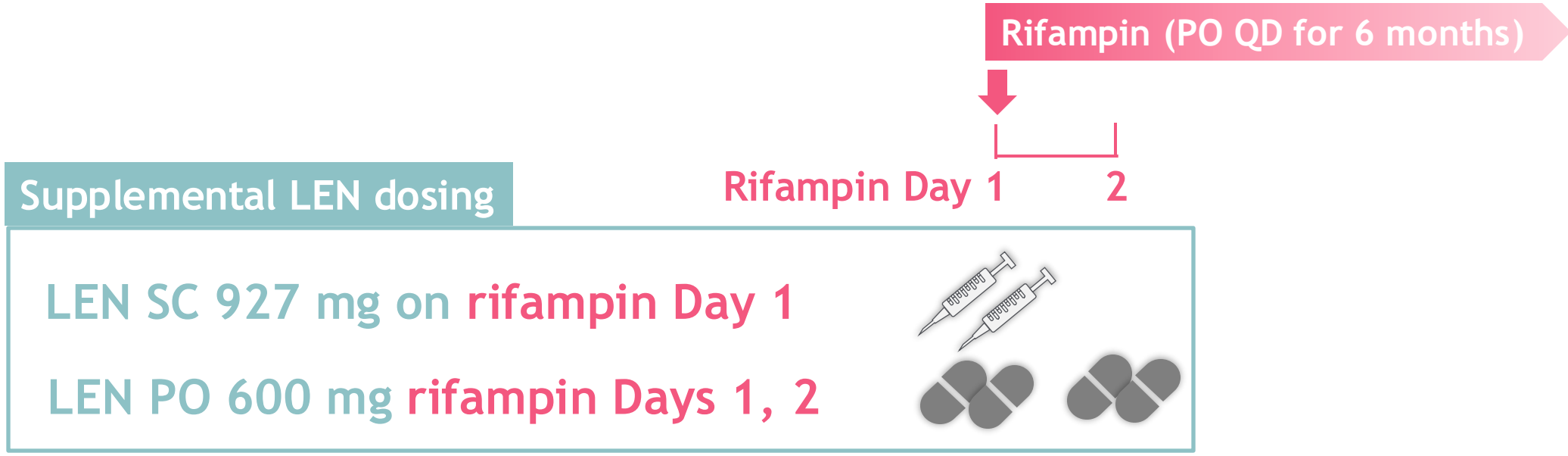
CYP, cytochrome P450; **LEN**, lenacapavir; **PDE5**, phosphodiesterase type 5; **PrEP**, pre-exposure prophylaxis; **TB**, tuberculosis.

1. Begley R, et al. Oral #89 presented at CROI (Virtual), March 6-10, 2021.

Special Situation: What If Someone Taking LEN-for-PrEP Needs to Take Rifampin (Strong CYP3A Inducer) or Rifabutin (Moderate CYP3A Inducer) to Treat or Prevent TB?

CYP, cytochrome P450; **LEN,** lenacapavir; **PrEP**, pre-exposure prophylaxis; **TB**, tuberculosis.

Giving Supplemental LEN (Initiation Regimen) Allows Coadministration of LEN for PrEP with Rifampin



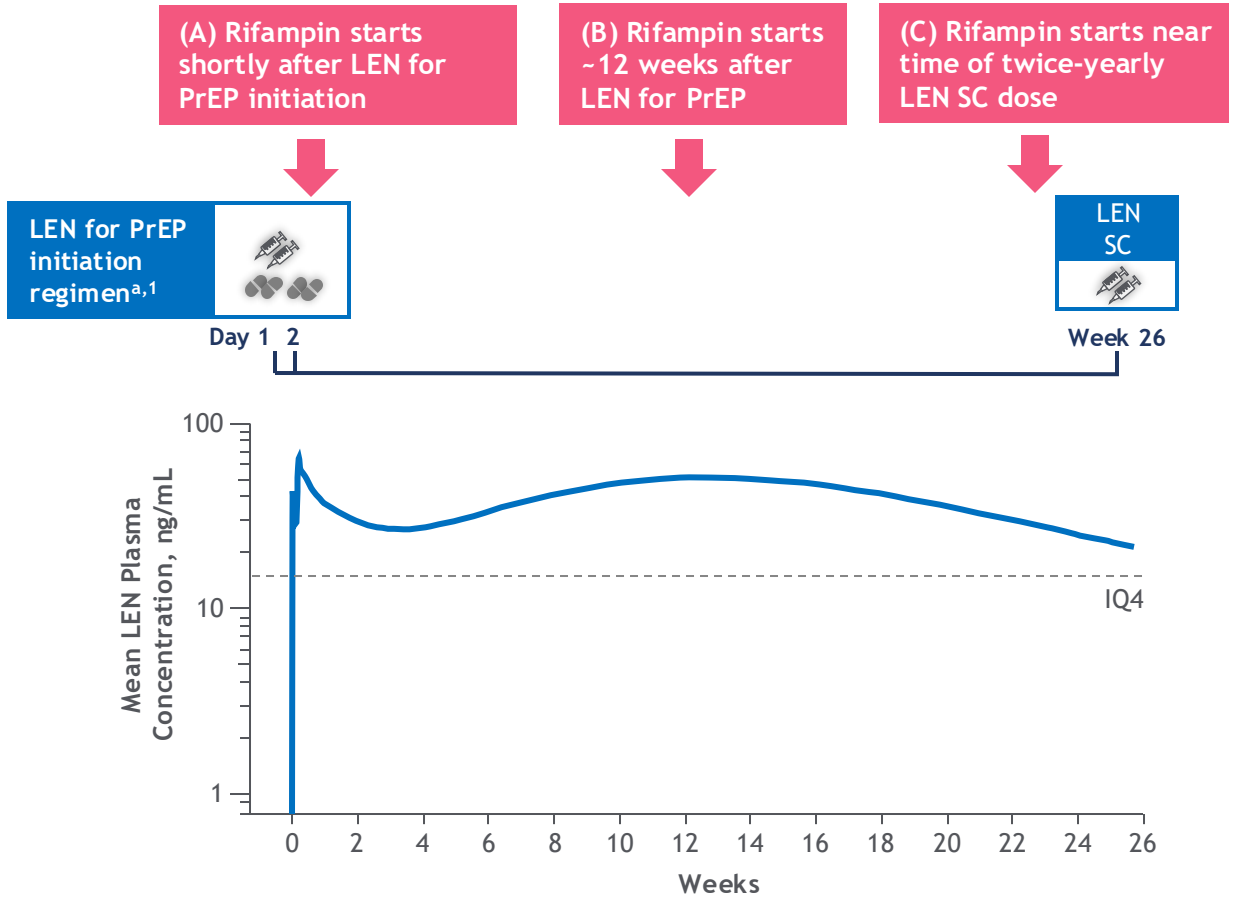
Supplemental LEN dosing for rifampin coadministration consists of repeating the LEN initiation dosing when rifampin is started

LEN, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QD**, once daily; **SC**, subcutaneously.

Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

Supplemental LEN Initiation Regimen Can Be Used Regardless of When Rifampin (Strong CYP3A Inducer) is Initiated for TB[1]

- PK simulations supported the supplemental LEN dosing recommendation for rifampin initiated at any time during the LEN dosing interval, including scenarios where rifampin starts:
  A. Shortly after LEN initiation
  B. Near LEN C_{max}
  C. Near LEN C_{trough}

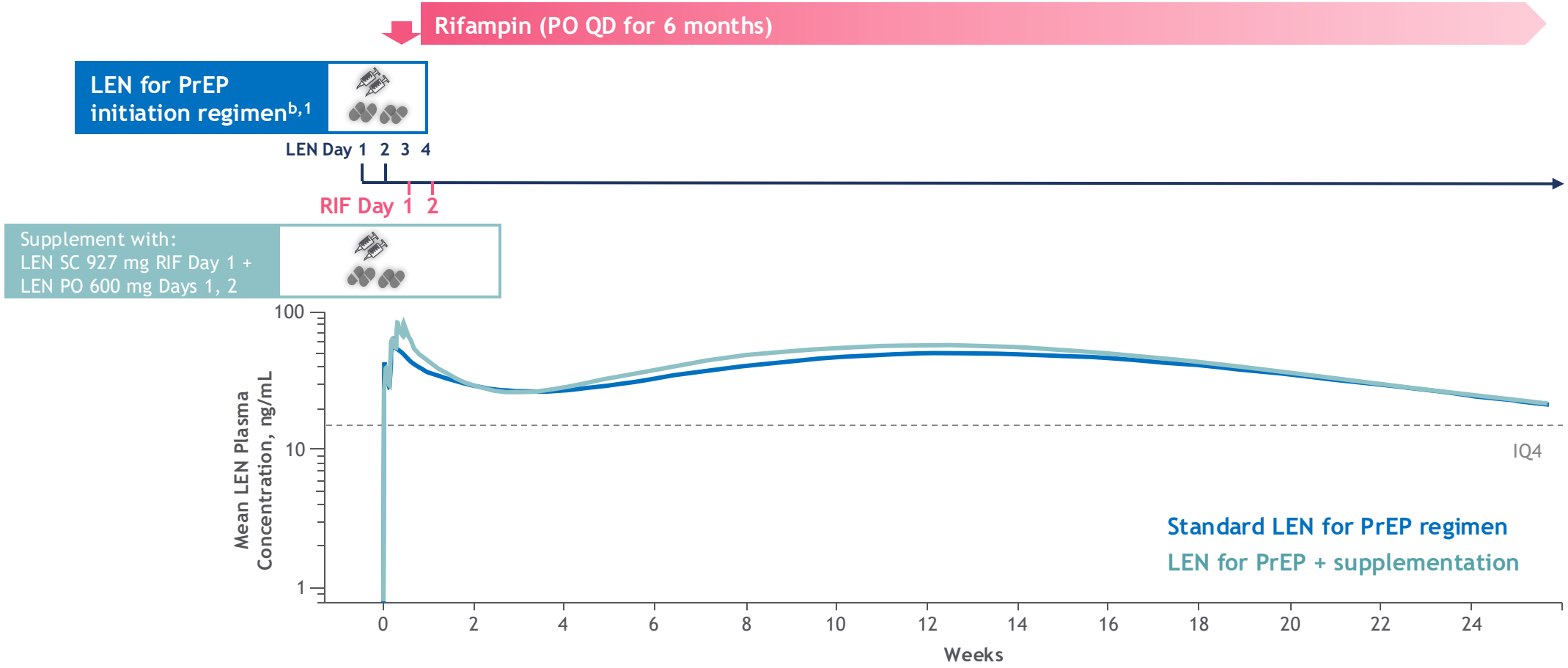


[a]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly.

C_{max}, peak concentration; **C_{trough}**, trough concentration; **CYP**, cytochrome P450; **IQ4,** inhibitory quotient 4; **LEN,** lenacapavir; **PK**, pharmacokinetics; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous; **TB**, tuberculosis.

1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

Rifampin[a] Can Be Initiated with Supplemental LEN Initiation Regimen Dosing Beginning Day 3 of LEN for PrEP[1]

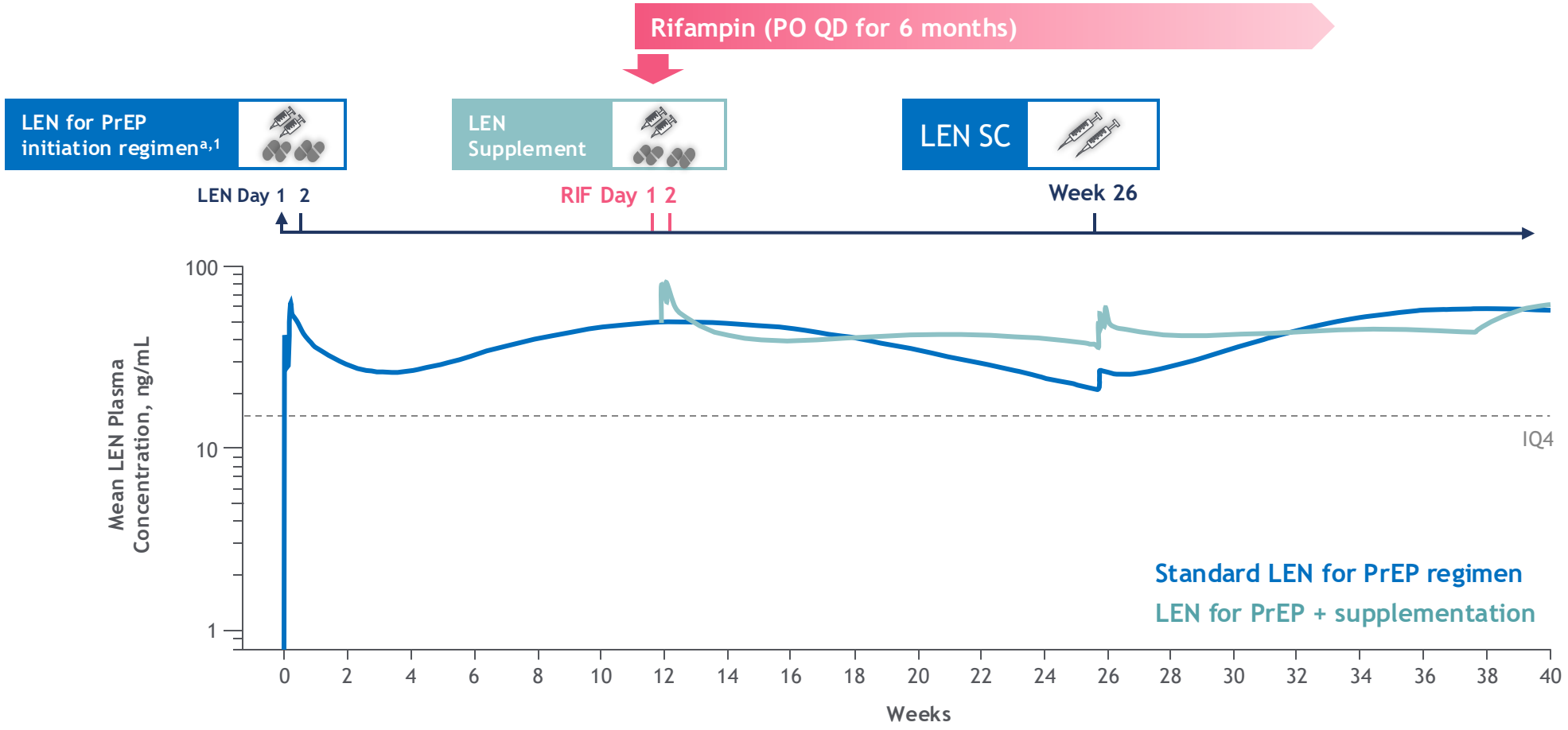


Repeating LEN initiation dosing (SC and PO) beginning Day 3 of LEN for PrEP maintains target LEN concentrations when rifampin is started no sooner than 2 days after starting LEN for PrEP

PK simulation; [a]A strong CYP3A inducer like rifampin should only be initiated > 2 days after LEN for PrEP is initiated. [b]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly. **CYP**, cytochrome P450; **IQ4**, inhibitory quotient 4

LEN, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QD**, once daily; **RIF**, rifampin; **SC**, subcutaneous(ly). 1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

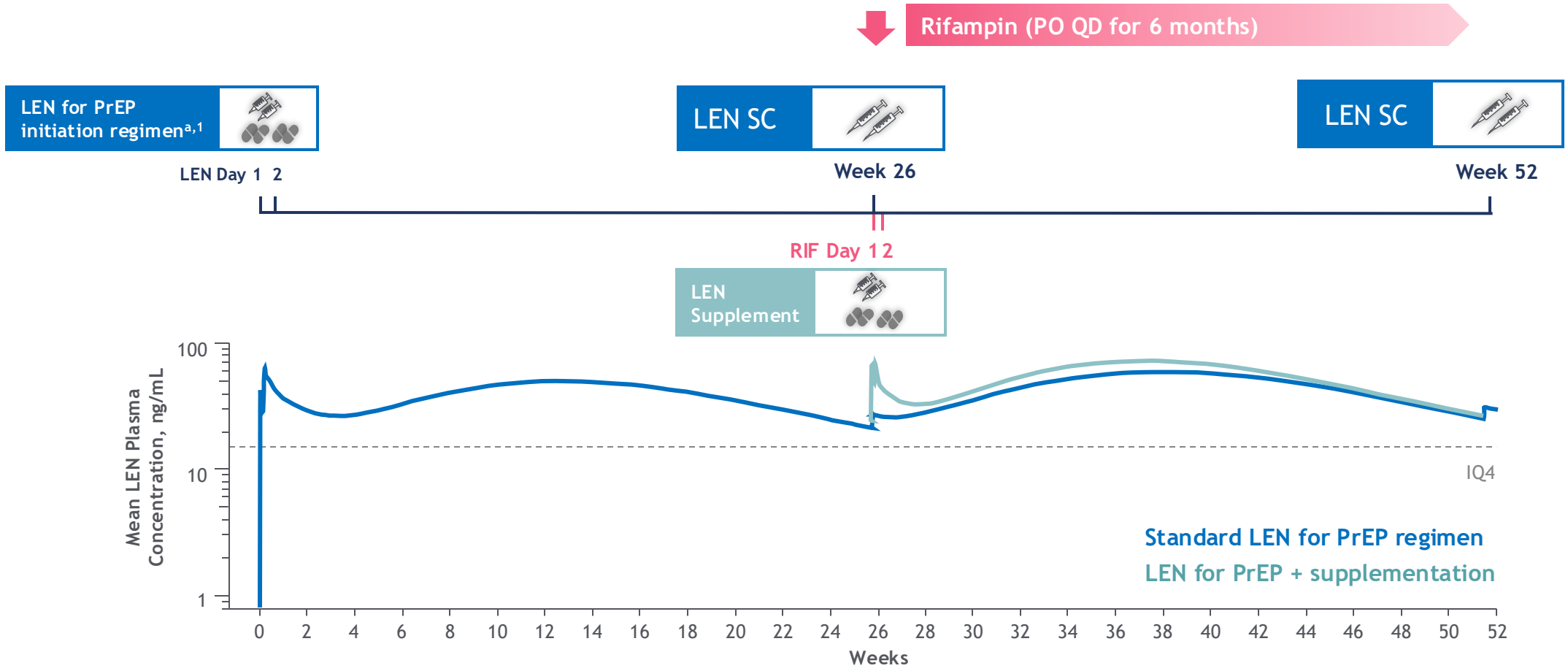
Rifampin Can Be Initiated with Supplemental Initiation Regimen Dosing Near LEN Peak Concentration



Repeating LEN initiation dosing (SC and PO) on the day that rifampin is started maintains target LEN concentrations when rifampin is started near LEN C_{max}

PK simulation; [a]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly. **C_{max}**, peak concentration; **IQ4**, inhibitory quotient 4; **LEN**, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QD**, once daily; **RIF**, rifampin; **SC**, subcutaneous. 1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

Rifampin Can Be Initiated with Supplemental LEN Dosing Near LEN Trough Concentration



Repeating LEN initiation dosing (SC and PO) the day that rifampin is started maintains target LEN concentrations when rifampin is started near LEN C_{trough}

PK simulation; [a]LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 x 1.5 mL) on Day 1, then twice yearly. **C_{trough}**, trough concentration; **IQ4**, inhibitory quotient 4; **LEN**, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QD**, once daily; **RIF**, rifampin; **SC**, subcutaneous. 1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (accessed June 26, 2025).

Rifabutin (Moderate CYP3A Inducer) Requires a Lower Supplemental LEN Dose (1 SC Injection)

- Regardless of when rifabutin is initiated during LEN for PrEP, supplement with:

Rifabutin
(PO QD for 6 months)

Rifabutin Day 1

Supplemental LEN dose

LEN SC 463.5 mg on **rifabutin Day 1**

Rifabutin is a moderate inducer; hence, just 1 of the usual 2 LEN SC injections is sufficient to maintain target LEN concentrations

CYP, cytochrome P450; **LEN**, lenacapavir; **PO**, orally; **PrEP**, pre-exposure prophylaxis; **QD**, once daily; **SC**, subcutaneous(ly).

LEN ➡ ↑Drug

What If Someone Taking LEN-for-PrEP Also Takes a PDE5 Inhibitor for Erectile Dysfunction or a Statin for Hypercholesterolemia?

LEN, lenacapavir; **PDE5**, phosphodiesterase type 5; **PrEP**, pre-exposure prophylaxis.

LEN Can Be Coadministered with PDE5 Inhibitors Used for Erectile Dysfunction[1,2]

No use restriction

- Sildenafil[3] → Consider a starting dose of 25 mg
- Tadalafil[4] → Consider a maximum dose of 10 mg every 72 hours (or 2.5 mg daily)
- Vardenafil[5] → Do not exceed 5 mg every 24 hours

Start with a low dose of PDE5 inhibitors, and titrate to desired effect

LEN, lenacapavir; **PDE5**, phosphodiesterase type 5.

1. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf. 2. University of Liverpool. https://www.hiv-druginteractions.org/checker.
3. Pfizer. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/20895s039s042lbl.pdf. 4. Eli Lilly. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021368s20s21lbl.pdf.
5. Bayer Healthcare. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021400s017lbl.pdf. All accessed June 26, 2025.

LEN Can Be Coadministered with Statins[1]

- Fluvastatin[2]
- Rosuvastatin[3]
- Pravastatin[4]
- Pitavastatin[5]
- Atorvastatin[6]

→ No dose adjustment is needed

- Simvastatin[7]
- lovastatin[8]

→ Start a low dose and titrate to effect
Monitor for side effects (eg, myopathy)

Among the statins, only simvastatin and lovastatin require a lower dose and monitoring when coadministered with LEN

LEN, lenacapavir. Gilead Sciences. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf. 2. Novartis. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021192s019lbl.pdf. 3. AstraZeneca. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021366s016lbl.pdf. 4. Bristol Myers Squibb. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/019898s060lbl.pdf. 5. Kowa Pharmaceuticals. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022363s015lbl.pdf. 6. Pfizer. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s073lbl.pdf. 7. Synthon. https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021961lbl.pdf. 8. MSD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019643s086087lbl.pdf. All accessed June 26, 2025

Simple Dosing Strategies Allow LEN to Be Used in a Variety of Special Situations

- Oral bridging with weekly LEN PO is feasible and effective if an individual cannot receive scheduled LEN SC injections
- People taking LEN for PrEP can start rifampin (or other strong CYP3A inducers) and rifabutin (or other moderate CYP3A inducers including rifapentine) at any time using simple supplemental LEN dosing

  Drug ➡ ↓LEN
- PDE5 inhibitors[a] and statins and can be taken during LEN for PrEP, with few requiring minimal dose reductions

  LEN ➡ ↑Drug

LEN provides high protection across diverse settings, including these special dosing situations

[a]Used for erectile dysfunction.

CYP, cytochrome P450; **LEN**, lenacapavir; **PDE5**, phosphodiesterase type 5; **PO**, oral; **PrEP**, pre-exposure prophylaxis; **SC**, subcutaneous.

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PURPOSE 1 Study Team

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