



# PURPOSE

Prevention with PURPOSE



**IAS** 2025

## Lenacapavir Dosing in Special Situations: Tuberculosis and Beyond

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# Acknowledgments and Presenter Disclosures

## Acknowledgments

I want to begin my talk by extending my deepest gratitude to the PURPOSE trial participants who have shared their time, experiences, and bodies for the purposes of this research, and their families and communities, the global community advisory and accountability groups, the site staff and investigators, and the members of the PURPOSE study teams. Much of the fight against HIV and AIDS relies upon people living with HIV and people who want or need PrEP continuing to put themselves forward and this research and our fight against HIV and AIDS is indebted to those past and present.

## Disclosures

- Honoraria for advisories from Gilead Sciences, Merck (Pty) Ltd, ViiV Healthcare; Research grants to the Desmond Tutu Health Foundation to conduct implementation science obtained from Johnson & Johnson, ViiV Healthcare; Served on the Data Safety Monitoring Board for the PrEPVACC HIV Vaccine trial
- Gilead Sciences funded the study and designed the study with input from the PIs and G-CAGs. The PIs and study staff gathered data; Gilead Sciences, Inc. monitored conduct of the trial, received the data, and performed analyses
- Medical writing support was provided by Samantha Santangelo, PhD (Aspire Scientific Ltd, UK), and was funded by Gilead Sciences, Inc.





# Summary

## What are your main questions?

- Is oral LEN suitable for PWBP if twice-yearly LEN injection will be delayed?
- Can LEN be administered with rifamycins for TB?
- Can LEN for PrEP be coadministered with erectile dysfunction drugs and statins?

## What did you find?

- Weekly oral LEN is used if a LEN SC injection is delayed, and a supplemental LEN regimen is used whenever rifamycins are initiated for TB

## Why is it important?

- Oral bridging with weekly LEN is feasible and effective if PWBP miss a scheduled LEN SC injection
- PWBP can receive TB treatment along with additional LEN supplementation to maintain LEN at efficacious levels
- PWBP can safely take PDE5 inhibitors and statins during LEN for PrEP



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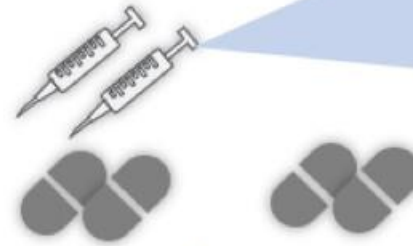
# Initiation of LEN for PrEP Requires Oral LEN Loading Tablets and Injections<sup>1,2</sup>

## Initiation regimen

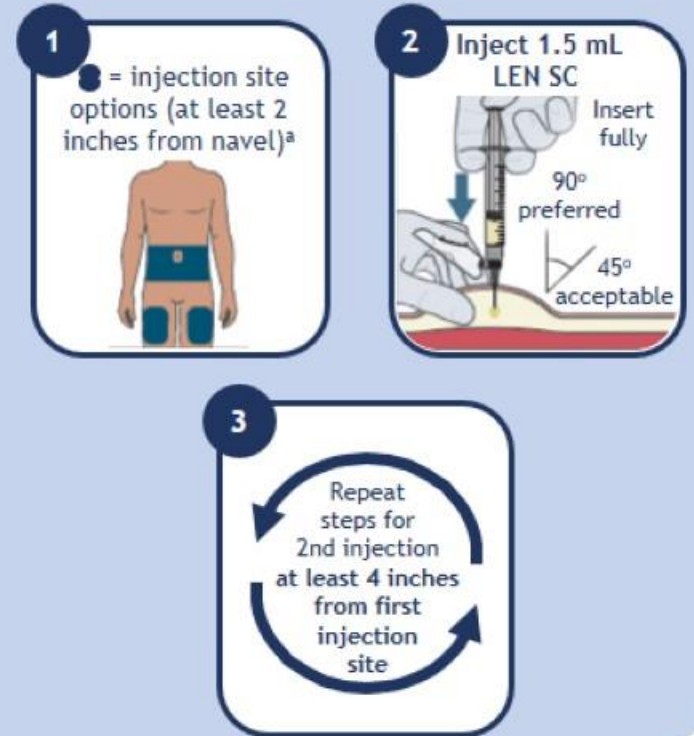
LEN SC 927 mg Day 1

LEN PO 600 mg Days 1 and 2

LEN for PrEP Day 1 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



<sup>a</sup>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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf) (accessed June 26, 2025).

4 2. Jogiraju V, et al. Poster #PESUB22 presented at the 24th International AIDS Conference; July 29-August 2, 2022; Montreal, Canada, and virtually.



# LEN Initiation Dosing with Oral Loading Achieves LEN Target Concentrations by Day 2 through Week 26<sup>1</sup>

LEN for PrEP  
initiation regimen<sup>a,1</sup>

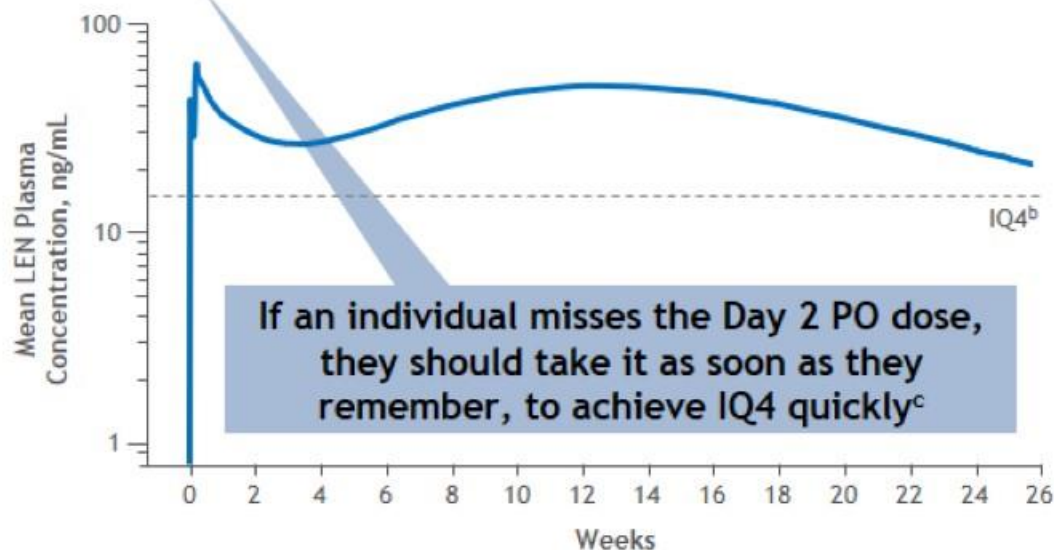


LEN SC

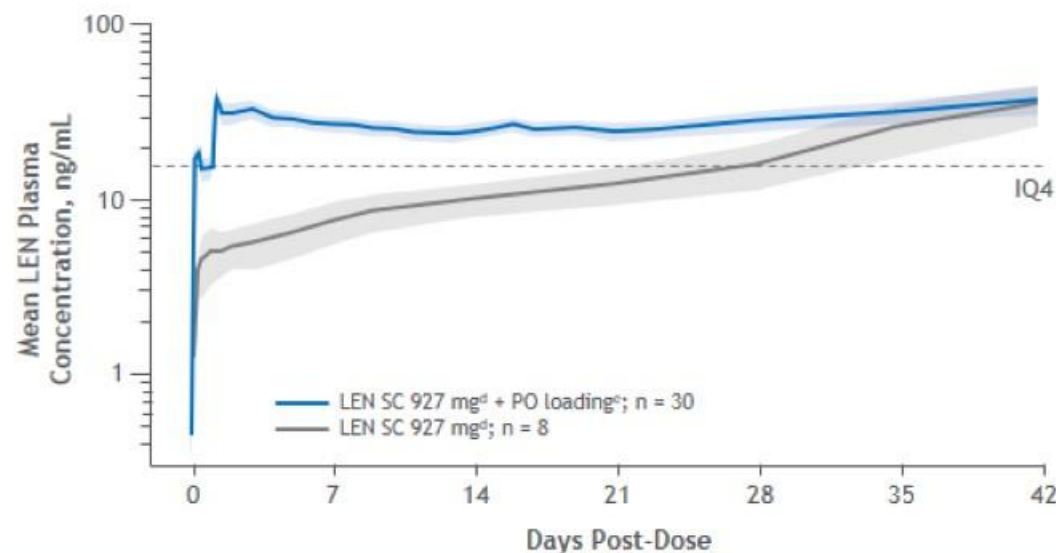


Day 1 2

Week 26



Time to reach IQ4 with and without  
LEN oral loading<sup>2,c</sup>



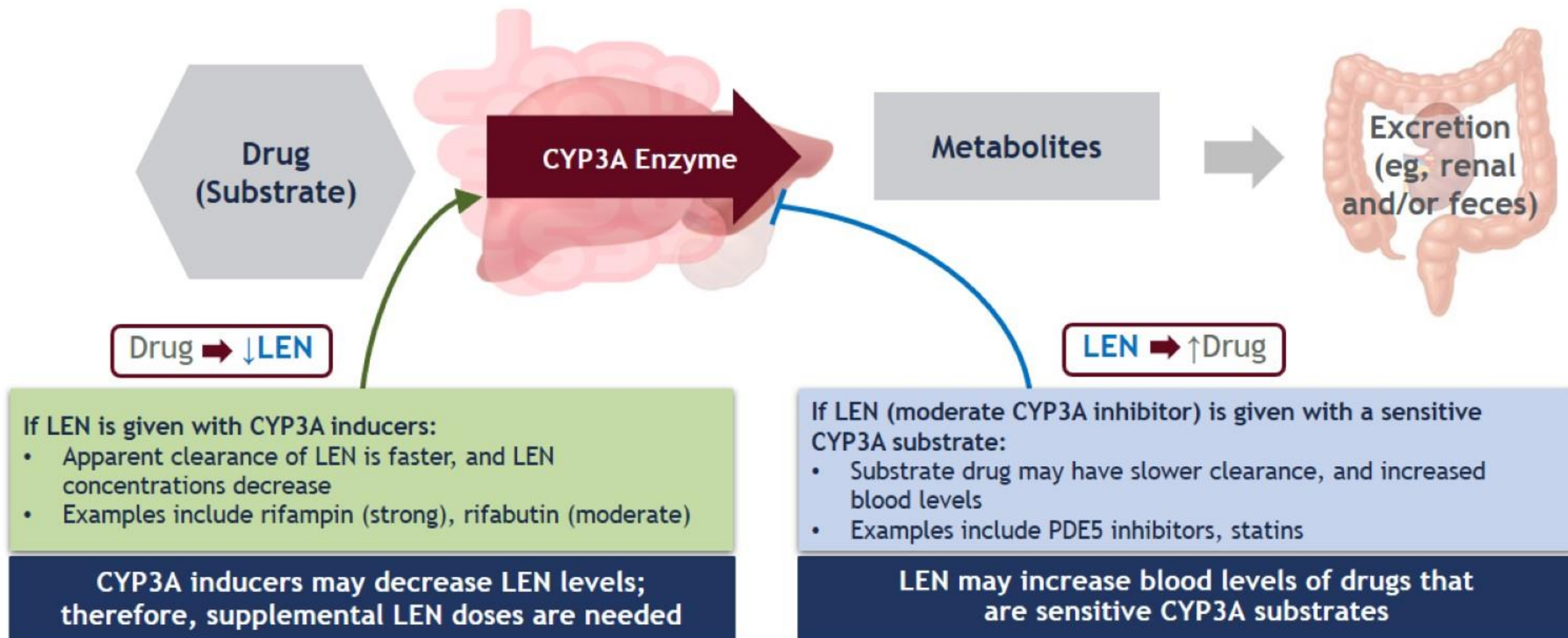
**Omission of LEN oral loading significantly delays achievement of target concentrations**

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

# LEN is a Substrate of CYP3A<sup>a</sup> and Moderately Inhibits CYP3A<sup>1,2</sup>



<sup>a</sup>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](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),



# 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?<sup>1</sup>



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<sup>1</sup>



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

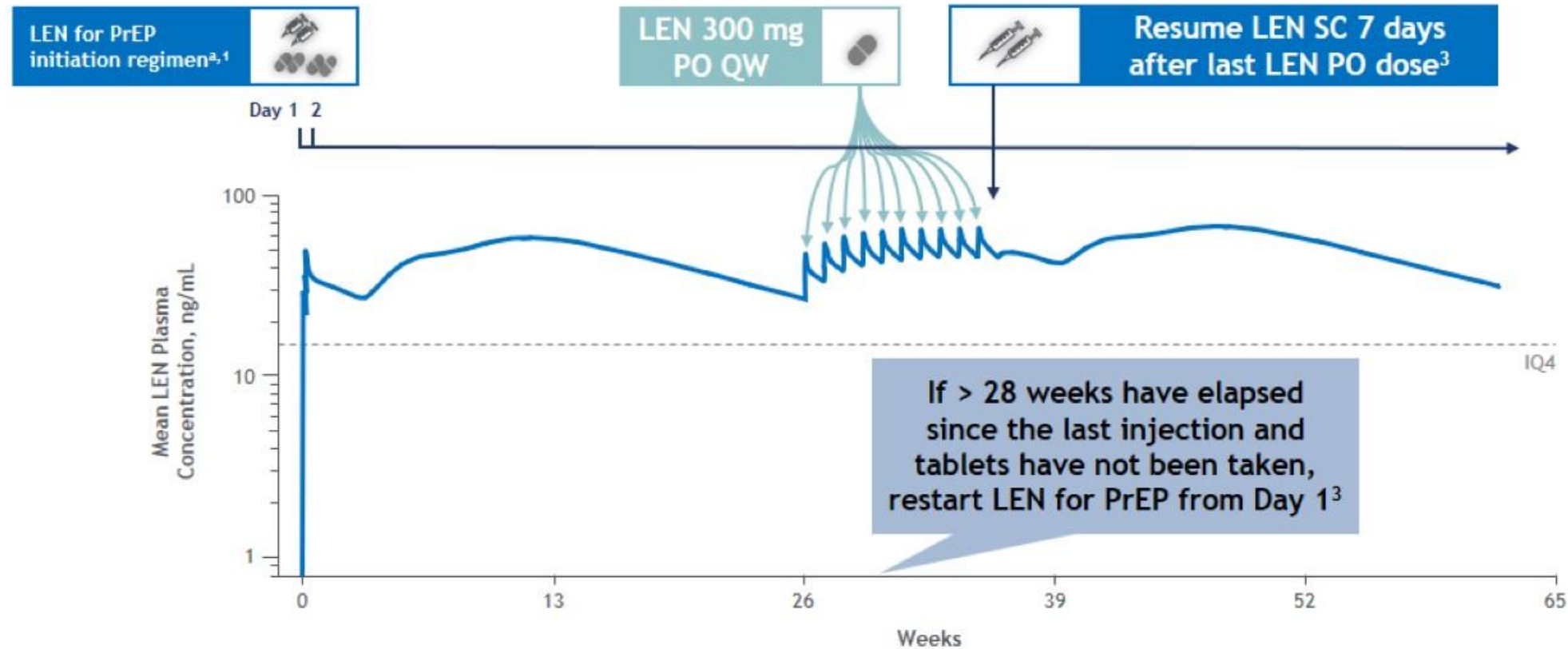
CYP, cytochrome P450; LEN, lenacapavir; PDE5, phosphodiesterase type 5; PrEP, pre-exposure prophylaxis; TB, tuberculosis.

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

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



# Weekly LEN PO Maintains LEN at Target Concentration Until LEN SC Can Be Resumed<sup>1,2</sup>



**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<sup>3</sup>**

<sup>1</sup>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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf) (accessed June 26, 2025).

# 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?



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

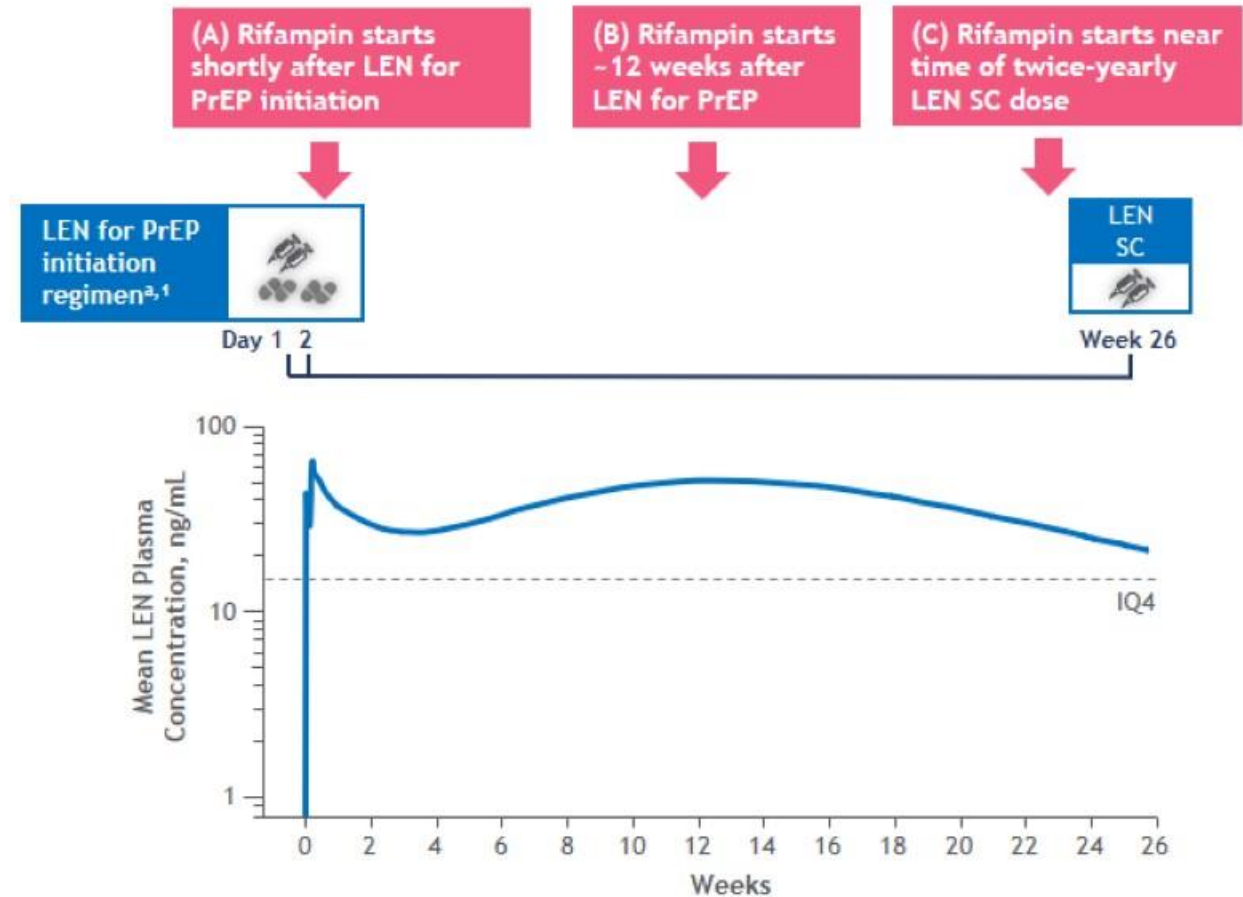


**Supplemental LEN dosing for rifampin coadministration consists of repeating the LEN initiation dosing when rifampin is started**

# Supplemental LEN Initiation Regimen Can Be Used Regardless of When Rifampin (Strong CYP3A Inducer) is Initiated for TB<sup>1</sup>

- PK simulations supported the supplemental LEN dosing recommendation for rifampin initiated at any time during the LEN dosing interval, including scenarios where rifampin starts:

- Shortly after LEN initiation
- Near LEN  $C_{max}$
- Near LEN  $C_{trough}$



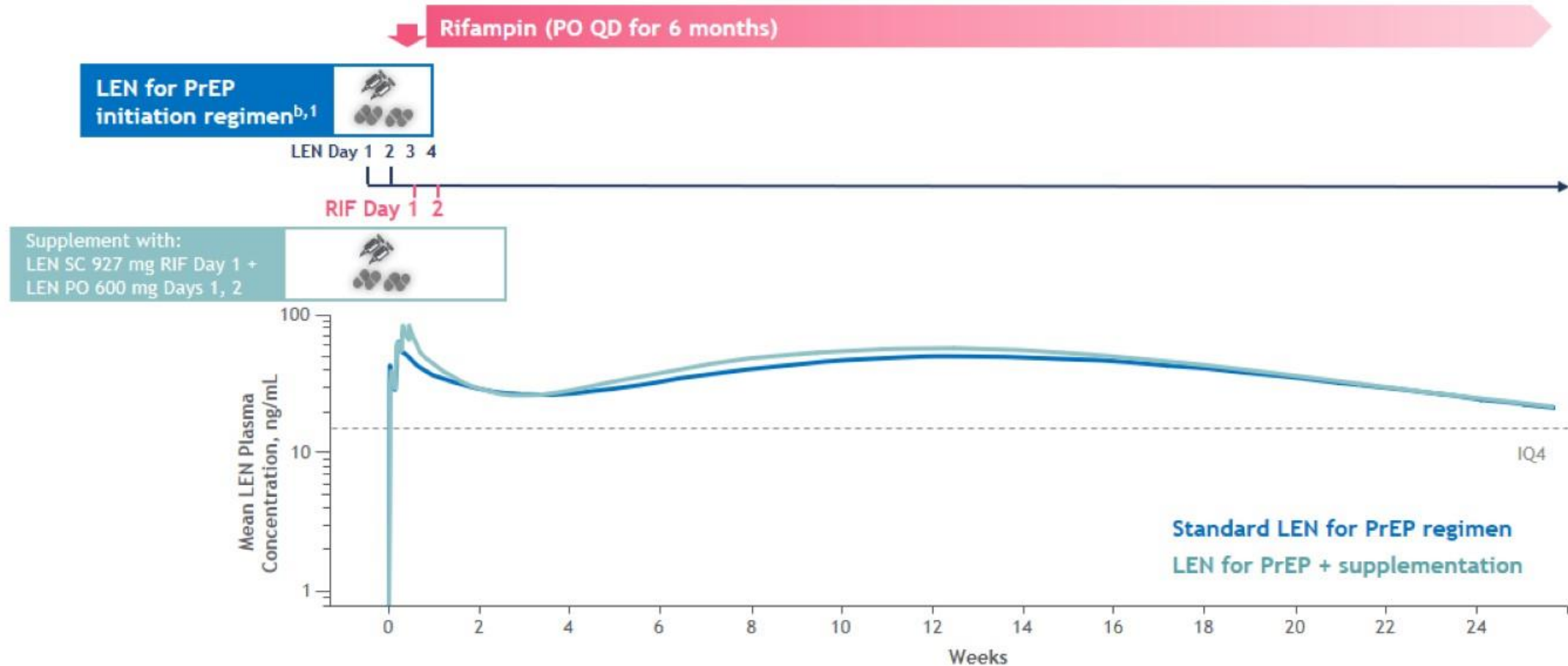
<sup>3</sup>LEN PO 600 mg on Days 1 and 2 + LEN SC 927 mg (2 × 1.5 mL) on Day 1, then twice yearly.

$C_{max}$ , 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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf) (accessed June 26, 2025).



# Rifampin<sup>a</sup> Can Be Initiated with Supplemental LEN Initiation Regimen Beginning Day 3 of LEN for PrEP<sup>1</sup>

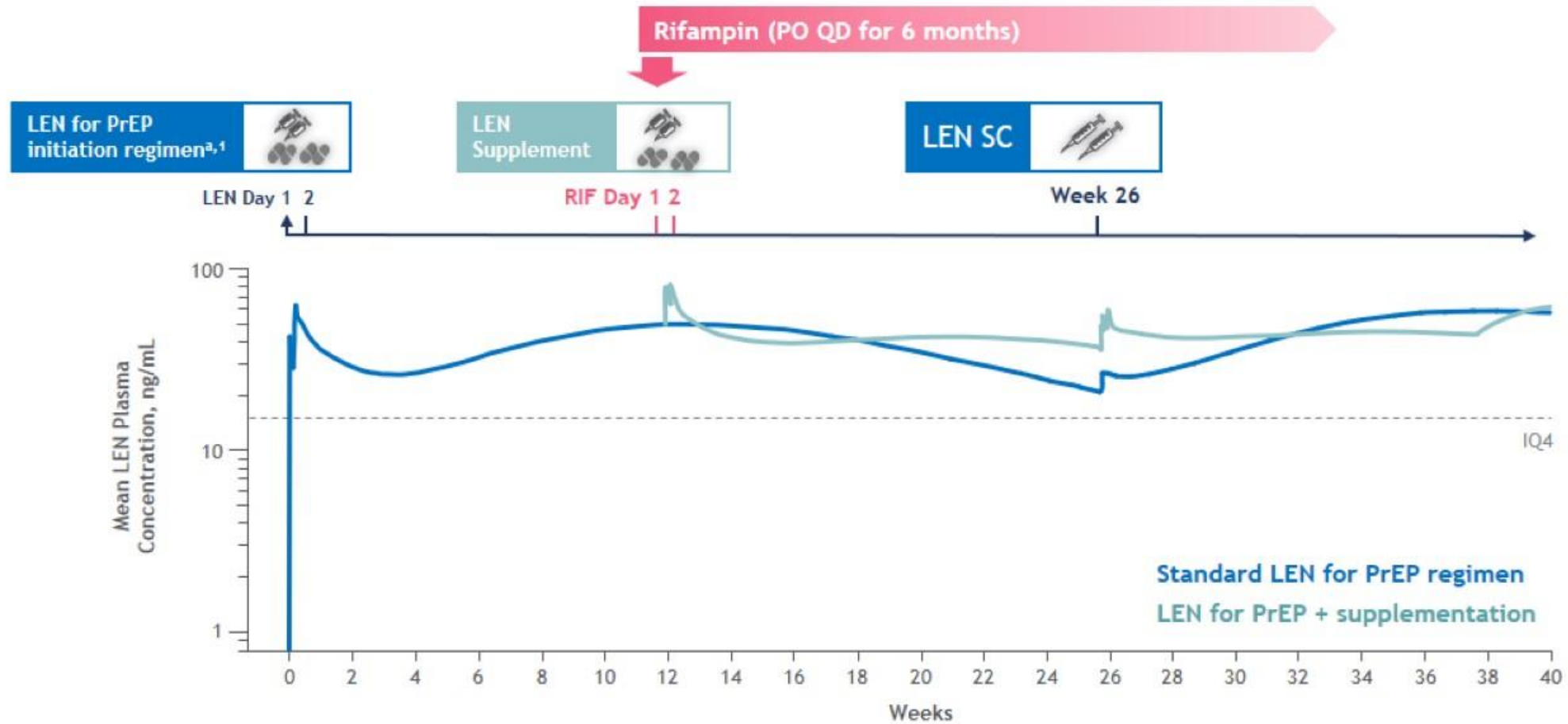


**Repeating LEN initiation dosing (SC and PO) beginning Day 3 of LEN for PrEP maintains target LEN concentrations when rifampin is started no sooner than 2 days after starting LEN for PrEP**

PK simulation; <sup>a</sup>A strong CYP3A inducer like rifampin should only be initiated > 2 days after LEN for PrEP is initiated. <sup>b</sup>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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf) (accessed June 26, 2025).

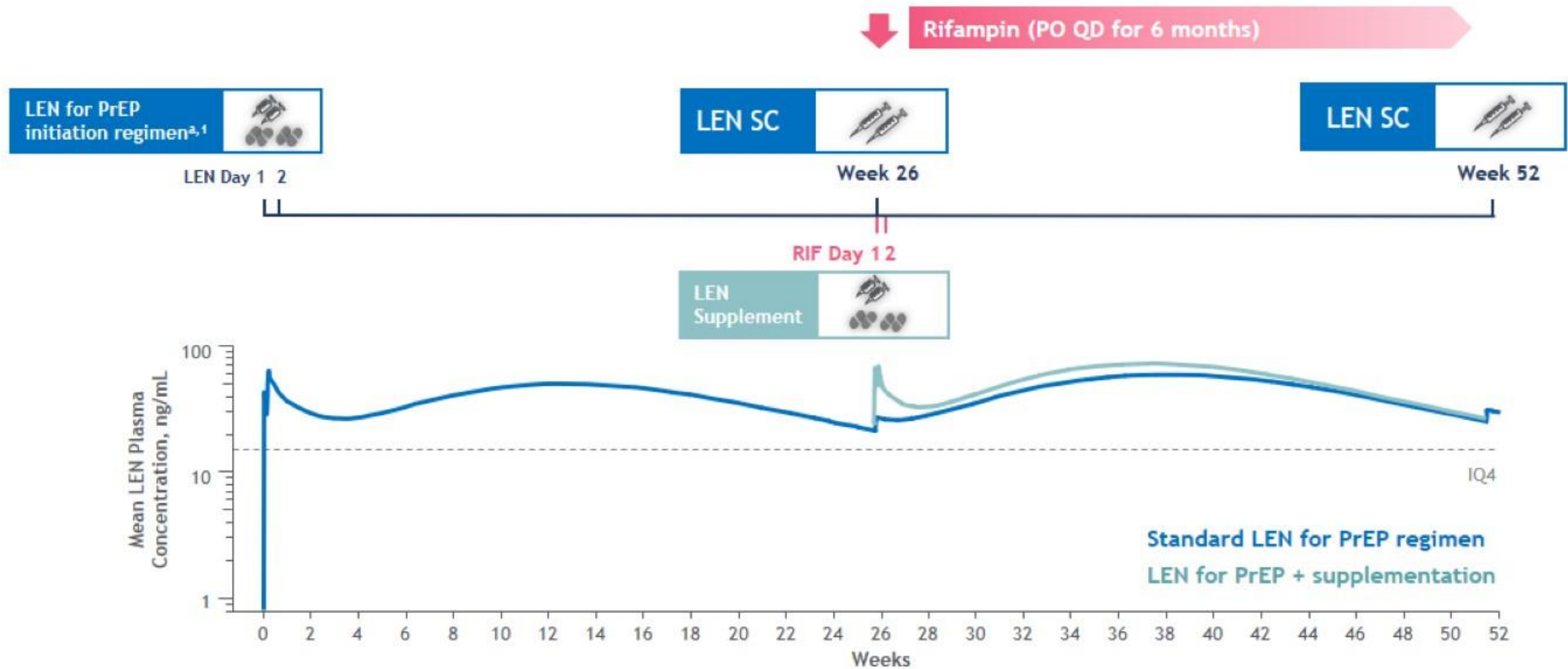
# Rifampin Can Be Initiated with Supplemental LEN Initiation Regimen Near LEN Peak Concentration



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



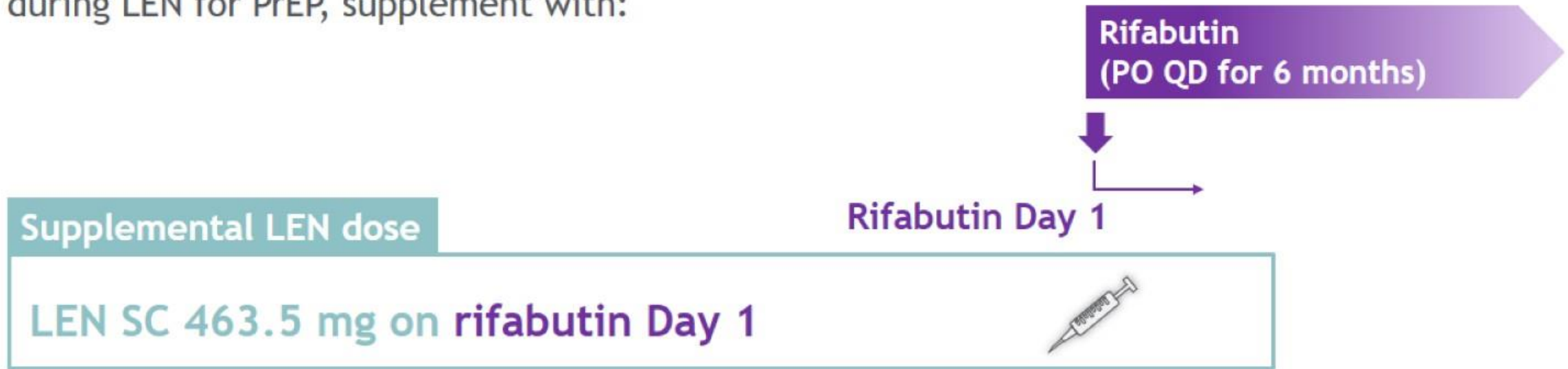
# Rifampin Can Be Initiated with Supplemental LEN Initiation Regimen Near LEN Trough Concentration



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

# 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:

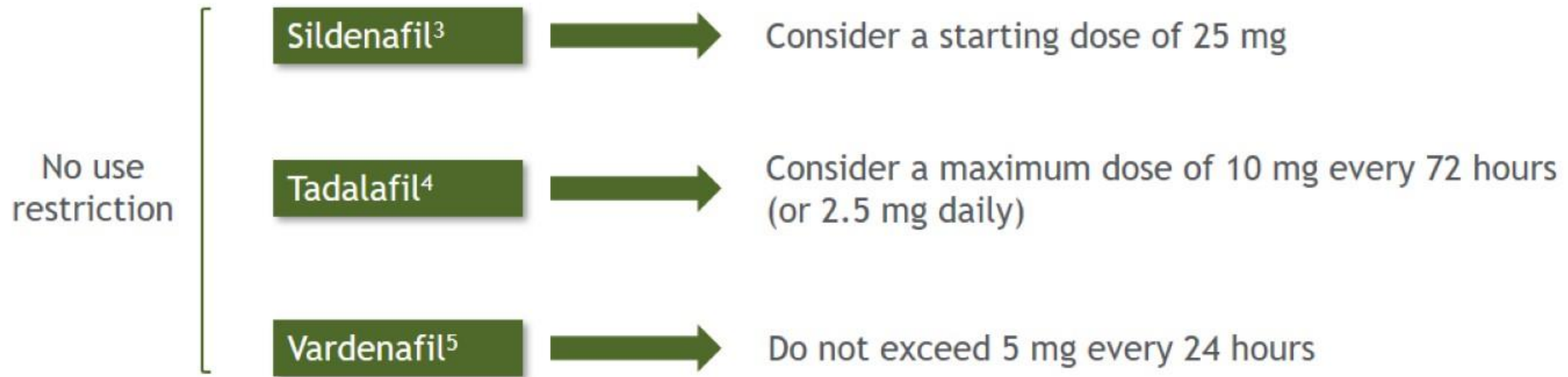


**Rifabutin is a moderate inducer; hence, just 1 of the usual 2 LEN SC injections is sufficient to maintain target LEN concentrations**



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

# LEN Can Be Coadministered with PDE5 Inhibitors Used for Erectile Dysfunction<sup>1,2</sup>



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

LEN, lenacapavir; PDE5, phosphodiesterase type 5.

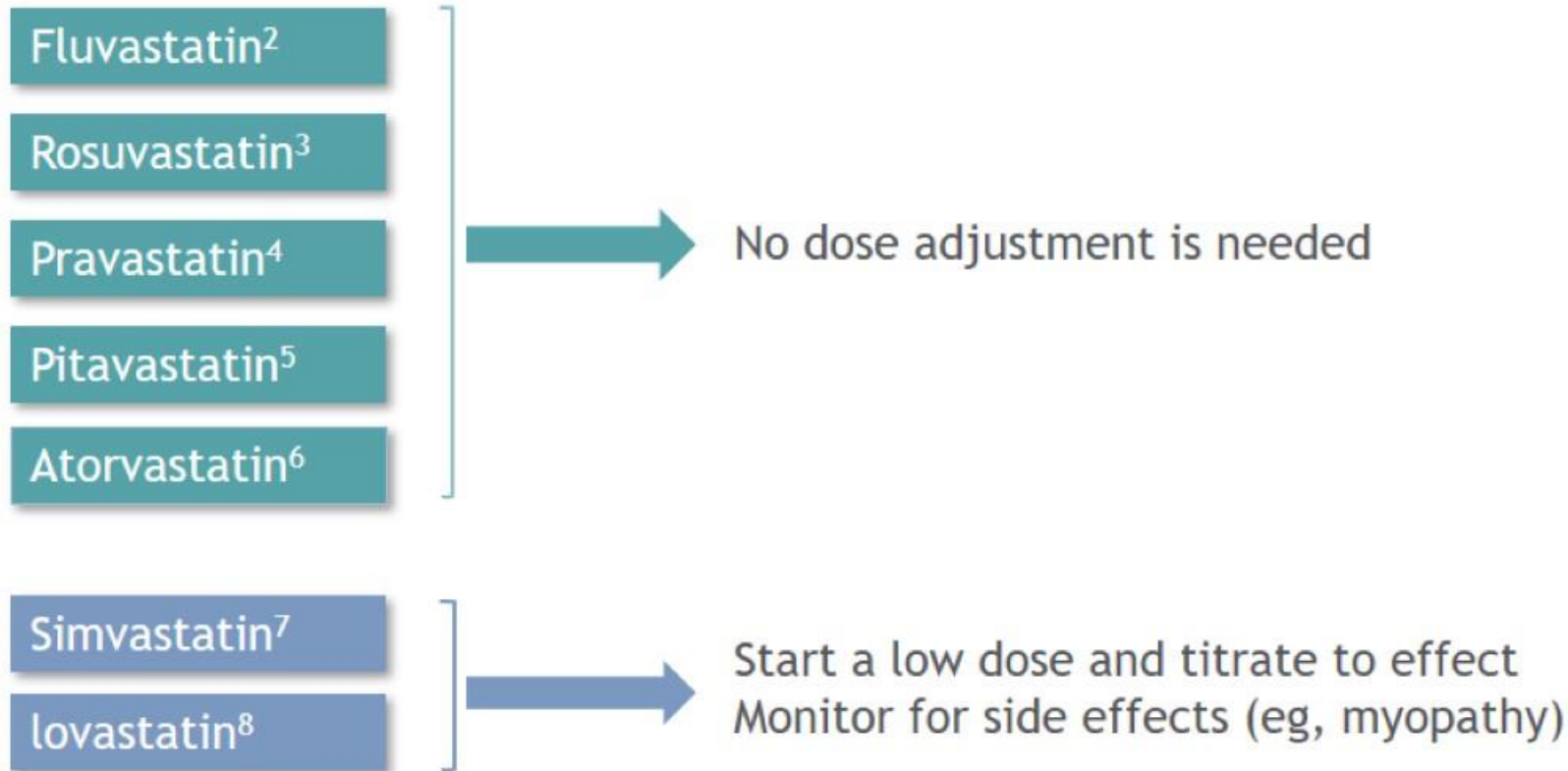
1. Gilead Sciences. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2022/215973s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf). 2. University of Liverpool. <https://www.hiv-druginteractions.org/checker>.

3. Pfizer. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/20895s039s042lbl.pdf](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](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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021400s017lbl.pdf). All accessed June 26, 2025.



# LEN Can Be Coadministered with Statins<sup>1</sup>



**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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf). 2. Novartis. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/021192s019lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021192s019lbl.pdf). 3. AstraZeneca. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/021366s016lbl.pdf](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](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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022363s015lbl.pdf). 6. Pfizer. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020702s073lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020702s073lbl.pdf). 7. Synthon. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/021961lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021961lbl.pdf). 8. MSD. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/019643s086087lbl.pdf](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<sup>a</sup> 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**

<sup>a</sup>Used for erectile dysfunction.



# Accelerating Access for Global HIV Prevention

## Expansive licensing

Earliest and geographically broadest (120 countries) voluntary licensing strategy ever for an antiretroviral

## Rapid technology transfer

Agreements with 6 generics & full technology transfer within 3 months; Global Fund 2 million people for 3 years

## Simultaneous submissions

US Approval June 2025  
EU, EUM4All, South Africa, Brazil, Canada, Australia, Switzerland & more coming

## Expediting Regulatory Review

EU-M4all application enables faster reviews in low- and middle-income countries

## WHO endorsement

Guidelines released July 14, 2025 & prequalification later this year will facilitate global adoption

## Manufacturing readiness

Gilead-supplied no-profit product & partnership agreements, bridging to sustainable generic supply

Collaborative implementation science studies to inform sustainable access, eg South Africa (Project PrEP, UNITAID/Wits RHI; ALIGN, Gates Foundation/Desmond Tutu Health Foundation) and Brazil (ImPrEP, IUNITAID/Fiocruz)

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