



# Resistance Analyses of the PURPOSE Studies Through the End of the Randomized Blinded Phase

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# Disclosures

- All authors are employees of Gilead Sciences, Inc. (Foster City, CA, USA)
- All authors contributed to and approved the presentation
- Gilead Sciences funded and designed the studies with input from the PIs and G-CAG. The PIs and study staff gathered data; Gilead Sciences monitored the conduct of the trial, received the data, and performed analyses



# LEN for PrEP Demonstrates High Efficacy With Limited Resistance Emergence



LEN is a first-in-class, multistage HIV-1 **capsid inhibitor** and, therefore, has **no known cross-resistance** to any currently approved antiretroviral agents<sup>1,2</sup>



The **primary analyses** from **PURPOSE 1** and **PURPOSE 2** demonstrated high efficacy of **LEN** and **limited resistance emergence**<sup>3-5</sup>

**We describe resistance analyses for PURPOSE 1 and PURPOSE 2 through the end of the randomized blinded phase**

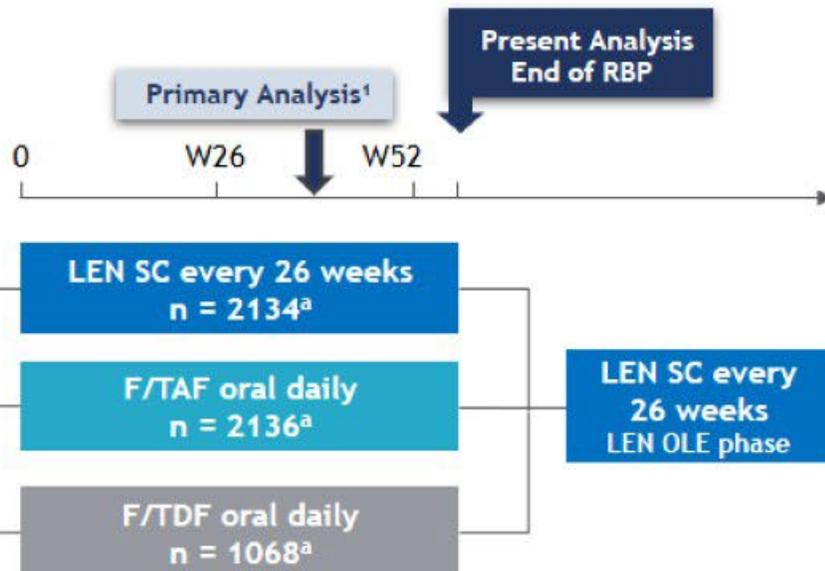
LEN, lenacapavir; PrEP, pre-exposure prophylaxis.

1. Margot N, et al. *Antimicrob Agents Chemother.* 2021;65:e02057-20. 2. Link JO, et al. *Nature.* 2020;584:614-8. 3. Bekker LG, et al. *N Engl J Med.* 2024;391:1179-92. 4. Kelley CF, et al. *N Engl J Med.* 2025;392:1261-76. 5. Cox S, et al. *J Infect Dis.* 2026;233:e203-11.

# PURPOSE 1 and PURPOSE 2 are Ongoing Phase 3, Double-Blind, Active-Controlled Randomized Trials<sup>1,2</sup>

## PURPOSE 1

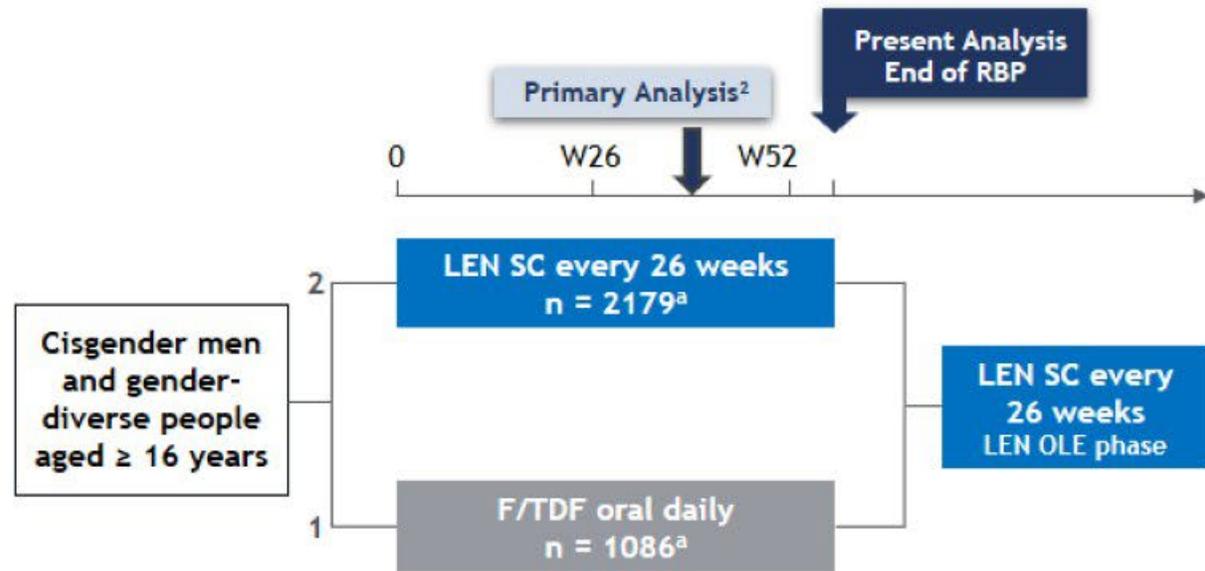
Randomized Blinded Phase



ClinicalTrials.gov: NCT04994509

## PURPOSE 2

Randomized Blinded Phase



ClinicalTrials.gov: NCT04925752

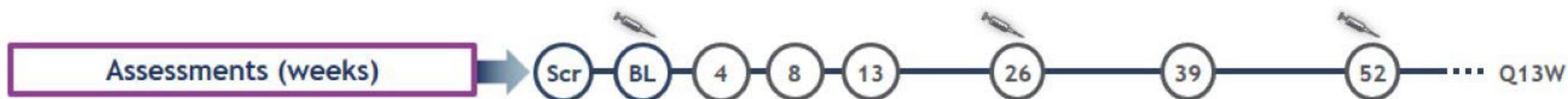
**We report a resistance analysis from study start through the end of the randomized blinded phase encompassing an additional 3297 PY of follow-up**

<sup>a</sup>Included in the full analysis set for primary efficacy analyses (additional participants are included in the safety analysis).<sup>1,2</sup>

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; OLE, open label extension; PY, person-years; RBP, randomized blinded phase; SC, subcutaneous;

W, week. 1. Bekker LG, et al. *N Engl J Med.* 2024;391:1179-92. 2. Kelley CF, et al. *N Engl J Med.* 2025;392:1261-76.

# HIV Testing During the Randomized Blinded Phase



## Screening/Baseline HIV Testing



- Rapid point-of-care + central laboratory 4th generation Ag/Ab test
- Quantitative HIV-1 RNA NAAT test

Retrospective HIV-1 RNA quantitative NAAT testing was done for all participants with incident HIV infection

## Follow-Up Visit HIV Testing (W4, 8, 13, Then Q13W)<sup>a</sup>



- Rapid point-of-care and central laboratory 4th generation Ag/Ab tests with same confirmation procedures

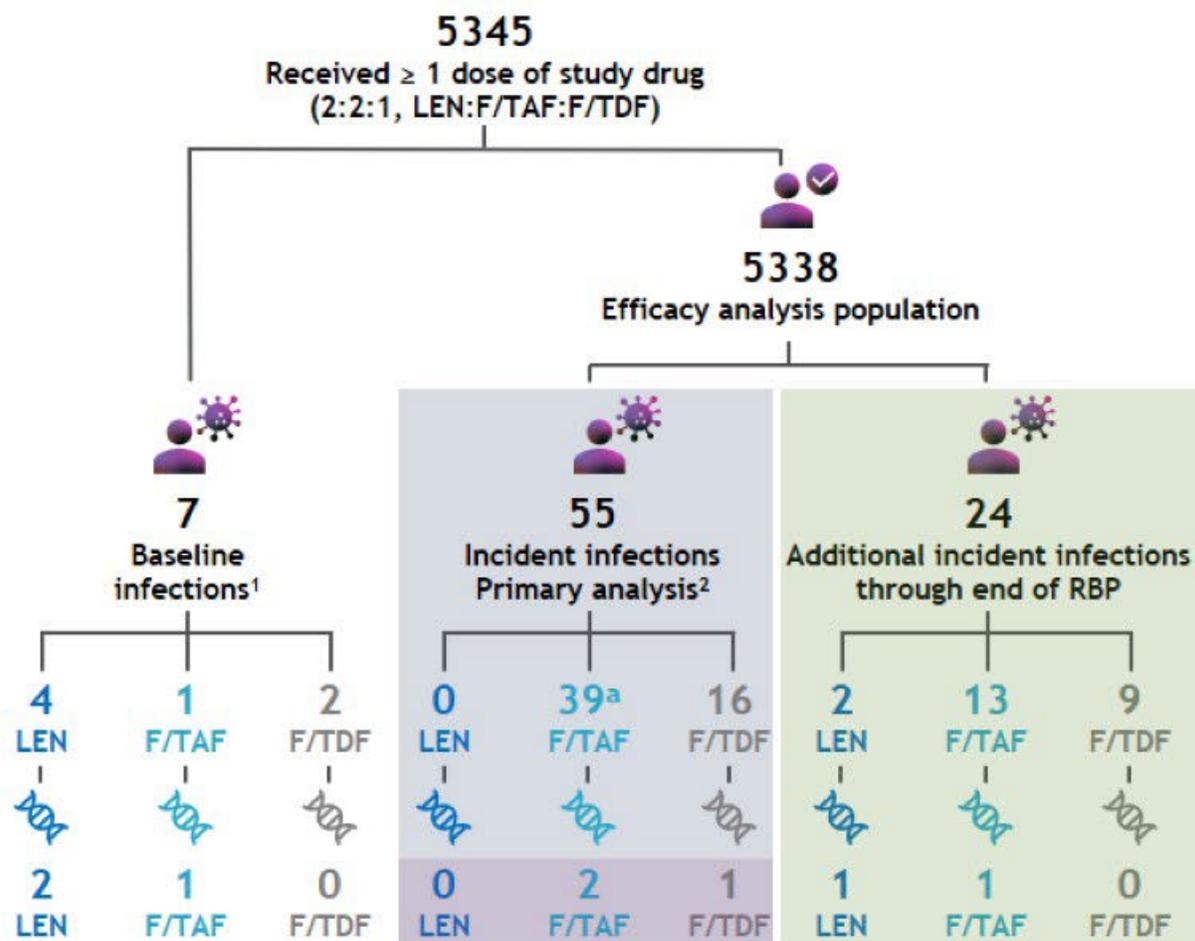
**Resistance Analysis Population:**  
Participants who acquired HIV and had a viral load of  $\geq 200$  copies/mL were evaluated for resistance by genotyping the HIV-1 capsid, protease, reverse transcriptase, and integrase genes

**The resistance analysis population included participants who acquired HIV through the end of the randomized blinded phase**

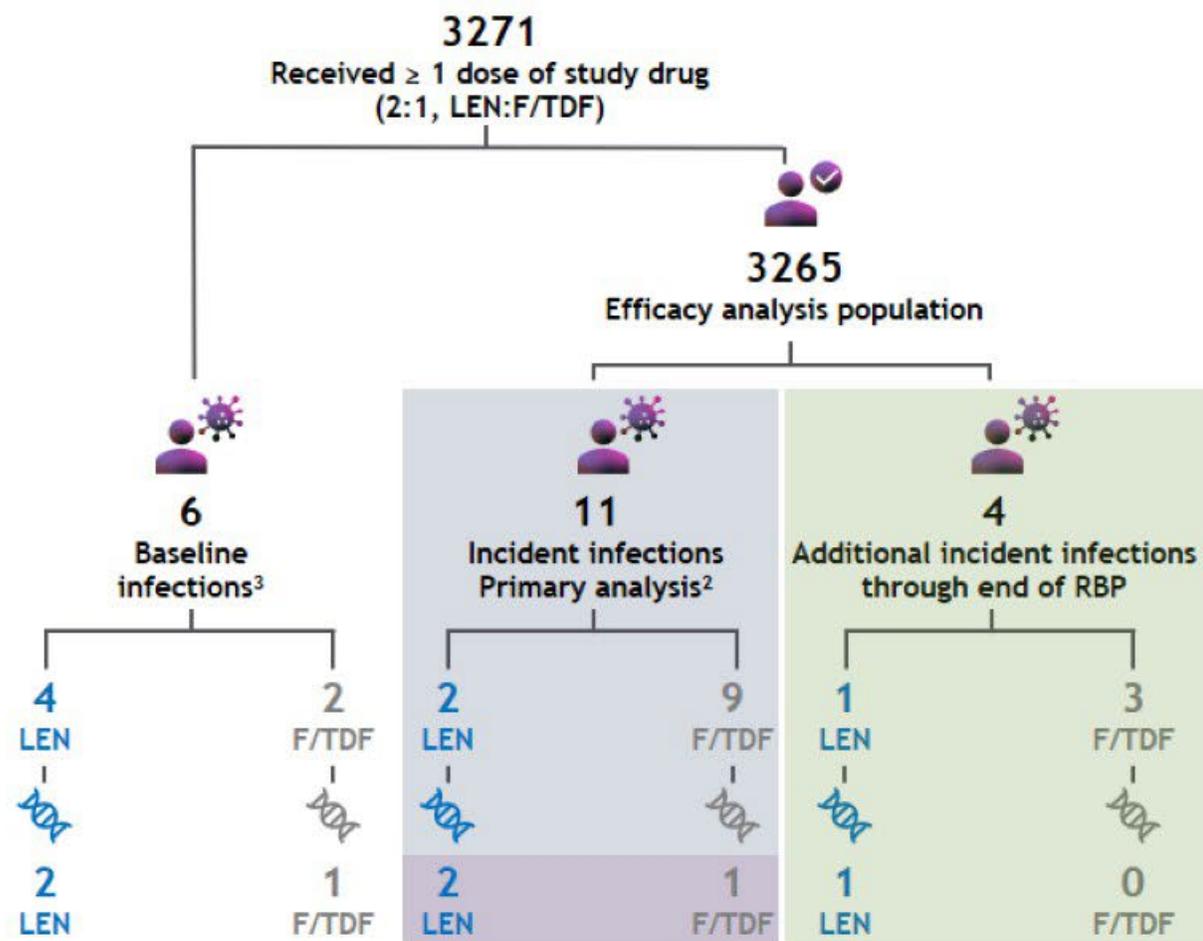
<sup>a</sup>Participants who presented later than 28 weeks after their previous injection or who had a > 7-day gap in daily oral PrEP (T/TDF or F/TAF) underwent quantitative HIV-1 RNA testing in addition to rapid point-of-care antigen-antibody and central laboratory antigen-antibody testing. Ab, antibody; Ag, antigen; BL, baseline; F/TAF, emtricitabine/tenofovir alafenamide; T/TDF, emtricitabine/tenofovir disoproxil fumarate; NAAT, nucleic acid amplification test; PrEP, pre-exposure prophylaxis; Q13W, every 13 weeks; Scr, screening; W, week.

# Participants Who Acquired HIV

## PURPOSE 1



## PURPOSE 2

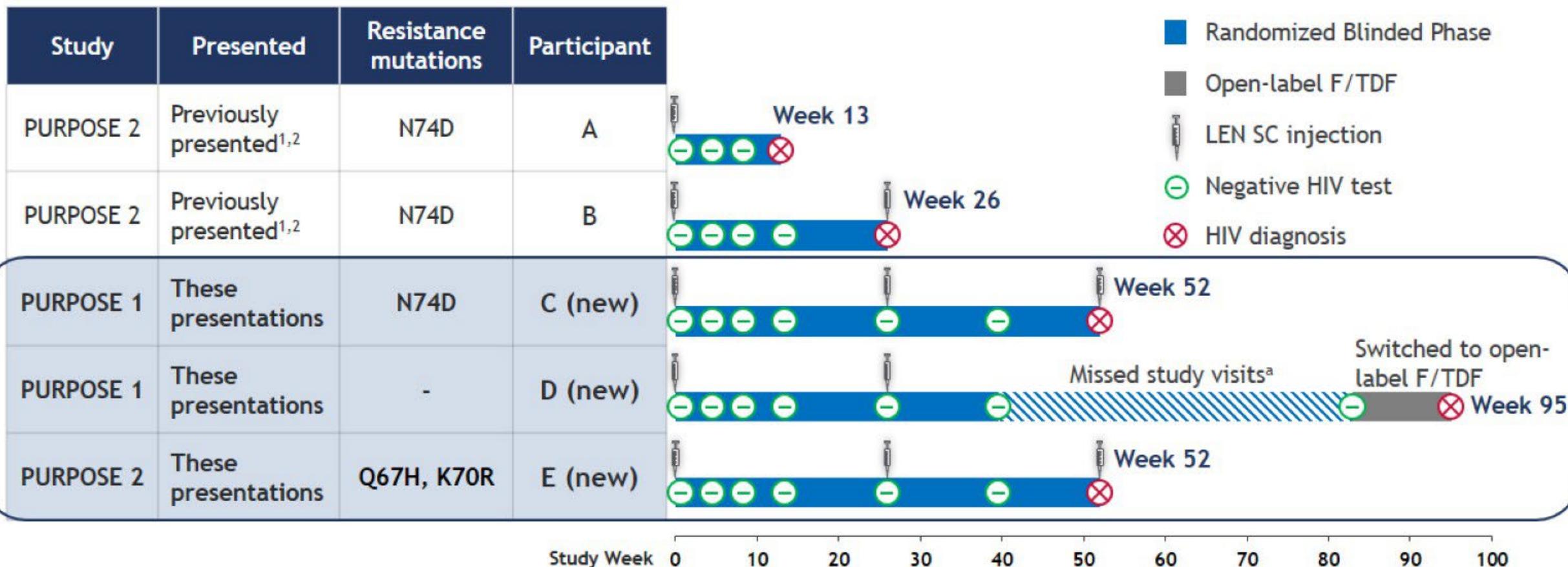


Participants with resistance

<sup>a</sup>Two participants in the F/TAF arm of PURPOSE 1 were not included in the resistance analysis population due to viral load of < 200 copies/mL or withdrawn consent.

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; RBP, randomized blinded phase.

# HIV Incidence and Resistance in LEN-Randomized Participants During PURPOSE 1 and PURPOSE 2



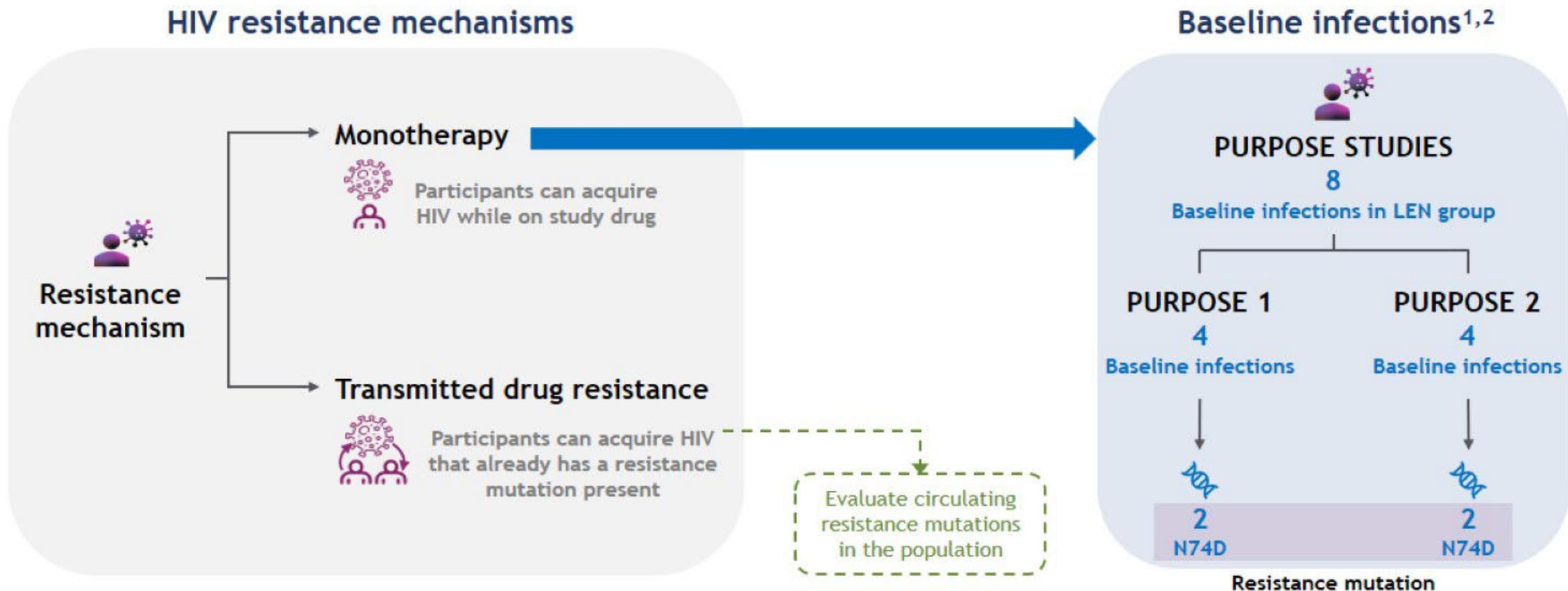
**Of the 5 HIV infections acquired on LEN in the PURPOSE studies, 3 had the N74D resistance mutation**

<sup>a</sup>Missed LEN injections.

- indicates no resistance mutation was detected. F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SC, subcutaneous.

1. Ogbuagu O, et al. Oral O49 presented at: HIV Glasgow; November 10-13, 2024; Glasgow, UK. 2. Kelley CF, et al. *N Engl J Med.* 2025;392:1261-76.

# LEN Resistance Likely Emerged Due to Monotherapy



**All baseline infections were wild type prior to receiving LEN injections  
N74D emerged in 4 of 8 cases**

# Prior Studies Demonstrated Circulating N74D is Low<sup>1,2</sup>

Los Alamos National Laboratory Database<sup>1</sup>

HIV subtype (N = 24,398)	Mutation <sup>a</sup>	Count	Prevalence (%)
A1 (n = 2964)	N74D	0	0.00
AD (n = 28)	N74D	0	0.00
AE (n = 2518)	N74D	0	0.00
B (n = 9609)	N74D	0	0.00
BF (n = 10)	N74D	0	0.00
C (n = 8170)	N74D	1	0.01
D (n = 931)	N74D	3	0.3
F1/F2 (n = 168)	N74D	0	0.00

ART Naïve and Experienced Clinical Participants<sup>2</sup>

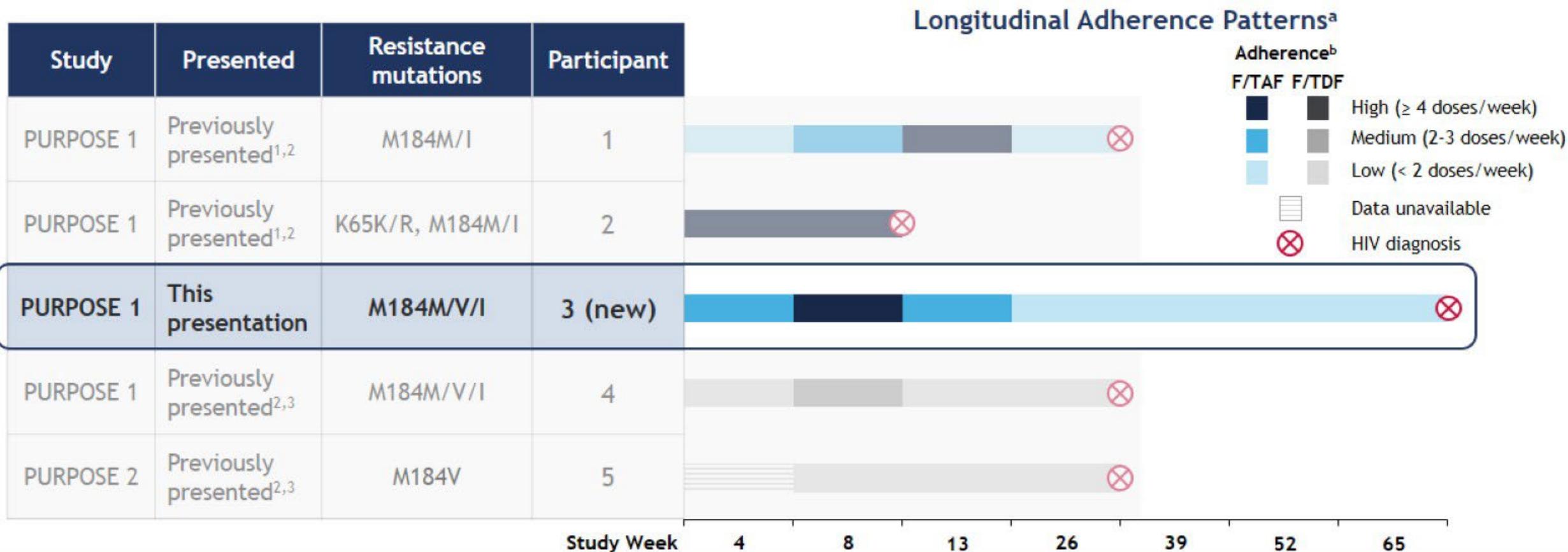
HIV subtype (N = 1495)	Mutation	Count	Prevalence (%)
A1 (n = 14)	N74D	0	0.00
AG (n = 655)	N74D	0	0.00
B (n = 675)	N74D	0	0.00
CRF06 (n = 58)	N74D	0	0.00
D (n = 30)	N74D	0	0.00
F1 (n = 35)	N74D	0	0.00
Other non-B (n = 28)	N74D	0	0.00

**N74 was found at very low levels, suggesting that transmitted N74D did not contribute to HIV acquisition while on LEN and was likely acquired during LEN monotherapy**

<sup>a</sup>N74 mutations in sequences from the Los Alamos National Laboratory database.<sup>1</sup> ART, antiretroviral treatment; LEN, lenacapavir.

1. Los Alamos National Laboratory. <http://www.hiv.lanl.gov>. Accessed Feb. 9, 2026. 2. Marcelin A, et al. *J Antimicrob Chemother.* 2020;75:1588-90.

# HIV Resistance in F/TAF- and F/TDF-Randomized Participants in PURPOSE 1 and PURPOSE 2



**Of the 89 HIV infections acquired on F/TAF or F/TDF in the PURPOSE studies, only 5 participants had resistance with the majority from suboptimal study drug adherence**

<sup>a</sup>Each box represents DBS-based adherence for the corresponding time period. <sup>b</sup>By TFV-DP DBS levels. For F/TAF, adherence was categorized as the following: low,  $< 450$  fmol/punch (dosing  $< 2$  days/week); medium,  $\geq 450$  to  $< 950$  fmol/punch (dosing 2-3 days/week); high,  $\geq 950$  fmol/punch (dosing  $\geq 4$  days/week). For F/TDF, adherence was categorized as the following: low,  $< 350$  fmol/punch (dosing  $< 2$  days/week); medium,  $\geq 350$  to  $< 700$  fmol/punch (dosing 2-3 days/week); high,  $\geq 700$  fmol/punch (dosing  $\geq 4$  days/week). DBS, dried blood spot; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate.

1. Bekker LG, et al. *N Engl J Med.* 2024;391:1179-92. 2. Cox S, et al. *J Infect Dis.* 2026;233:e203-11. 3. Kelley CF, et al. *N Engl J Med.* 2025;392:1261-76.

# Conclusions



Twice-yearly SC LEN was highly efficacious for HIV prevention throughout the randomized blinded phase of PURPOSE 1 and PURPOSE 2<sup>1,2</sup>



Acquisition of HIV while receiving LEN was rare and resistance emergence was likely due to LEN monotherapy, consistent with other PrEP agents



The PURPOSE studies demonstrated a very low level of resistance while receiving F/TAF or F/TDF, similar to previous clinical studies

**These findings from PURPOSE 1 and PURPOSE 2 reinforce LEN's potential as a durable and effective long-acting PrEP option**

F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; PrEP, pre-exposure prophylaxis; SC, subcutaneous.

1. Ndlovu N, et al. Oral 128 presented at: 33rd Conference on Retroviruses and Opportunistic Infections; February 22-25, 2026; Denver, CO, USA.

2. Cantos VD, et al. Oral 129 presented at: 33rd Conference on Retroviruses and Opportunistic Infections; February 22-25, 2026; Denver, CO, USA.

# Acknowledgments

- We extend our gratitude to the PURPOSE trial participants and their communities, our Global Community Advisory and Accountability Groups, the site staff and investigators, and all the members of the PURPOSE study teams
- This study was funded by Gilead Sciences, Inc.
- Medical writing support was provided by Simon Wigfield, PhD, of Aspire Scientific Ltd (Manchester, UK), and was funded by Gilead Sciences, Inc.
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