Genotypic Data From Participants Screened for the PURPOSE 1 and PURPOSE 2 Studies Demonstrate Low Levels of Overall Circulating Resistance and No Phenotypic Resistance to Lenacapavir

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TUPEC178

PURPOSE 1
PURPOSE 2

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Conclusions

- This analysis informs on circulating drug resistance substitutions across the multiple PURPOSE study locations evaluating lenacapavir (LEN) for HIV prevention
- Overall, among participants found to have pre-existing HIV infection during PURPOSE 1 and PURPOSE 2 screening, there were low levels of circulating resistance, including in the integrase strand-transfer inhibitor (INSTI) class
- No substitutions associated with LEN resistance were found in the populations where the PURPOSE 1 and PURPOSE 2 studies were conducted

Plain Language Summary

- Human immunodeficiency virus (HIV) prevention medication, also known as pre-exposure prophylaxis (or PrEP), helps to lower the chances of getting HIV
- Like most viruses, HIV can change over time. When this happens, the virus may stop responding to a medicine. This is called “resistance”
- Resistance can happen in two ways. Some people may already have a type of HIV that does not respond to certain medicines. In others, resistance may develop after they start treatment if there is not enough medicine in the body to fully stop the virus from multiplying
- It is important to study resistance for all medicines used to prevent HIV
- Lenacapavir (or LEN) is a type of PrEP that is given as an injection twice a year (every 6 months)
- In two clinical studies, called PURPOSE 1 and PURPOSE 2, LEN worked very well to protect people from getting HIV. Earlier presentations looked at what kinds of changes in the virus (mutations) were present in those people who got HIV during the study
- In the PURPOSE 1 and PURPOSE 2 studies, some people were found to have HIV before they started PrEP. We call this group the “background incidence population”, and it includes people from several different countries
- This study looked at the changes in the HIV virus in the background incidence population
- We found that the HIV virus that is already resistant to LEN is very rare in the places where the PURPOSE studies took place

Introduction

- LEN is a first-in-class, multistage HIV-1 capsid inhibitor and, therefore, has no known cross-resistance to any currently approved antiretroviral agents[1,2]
- Twice-yearly subcutaneous LEN was highly efficacious for HIV prevention throughout the randomized blinded phase of the PURPOSE 1 and PURPOSE 2 studies,[3,4] and has been approved for HIV prevention in multiple countries worldwide[5,6]
  - The primary endpoint in both trials was incidence of HIV infection compared with background incidence in the screened population (PURPOSE 1, 8094 participants, 2.41 per 100 person-years [95% CI, 1.82 to 3.19]; PURPOSE 2, 4634 participants, 2.37 per 100 person-years [95% CI, 1.65 to 3.42])[3,4]
- Previously presented resistance mutations in these studies are shown in **Table 1**
- During the primary analyses of the PURPOSE studies, limited resistance emergence was observed[7]
  - Through the end of the randomized blinded phase, two participants in PURPOSE 1 and three participants in PURPOSE 2 in the LEN group acquired HIV[8-10]
    - Three participants (one in PURPOSE 1; two in PURPOSE 2) had the LEN-associated N74D resistance mutation, and one (in PURPOSE 2) had the Q67H and K70R resistance mutations[10]
- Some participants had unrecognized HIV-1 infection at baseline and were dosed with study drug
  - In this population, eight participants in the LEN group of PURPOSE 1 (n = 4) and PURPOSE 2 (n = 4) had acquired HIV and no resistance was present at Day 1[8-10]
  - The N74D resistance mutation emerged in two participants with baseline infections in each study[10]

Table 1. Emergent Capsid Resistance in Participants Who Acquired HIV While Receiving LEN

Study	Phase	Participants in LEN Group, n	Resistance Mutations in LEN Group	Previous Presentation
PURPOSE 1	On study	1	N74D	Cox et al. CROI 2026[10]
PURPOSE 1	Baseline[a]	2	N74D	Cox et al. *J Infect Dis* 2026[7]
PURPOSE 2	On study	2	N74D	Cox et al. *J Infect Dis* 2026[7]
PURPOSE 2	On study	1	Q67H + K70R	Cox et al. CROI 2026[10]
PURPOSE 2	Baseline[a]	2	N74D	Cox et al. *J Infect Dis* 2026[7]

[a]Participants who had unrecognized HIV-1 infection at baseline and were dosed with study drug. LEN, lenacapavir.

Objective

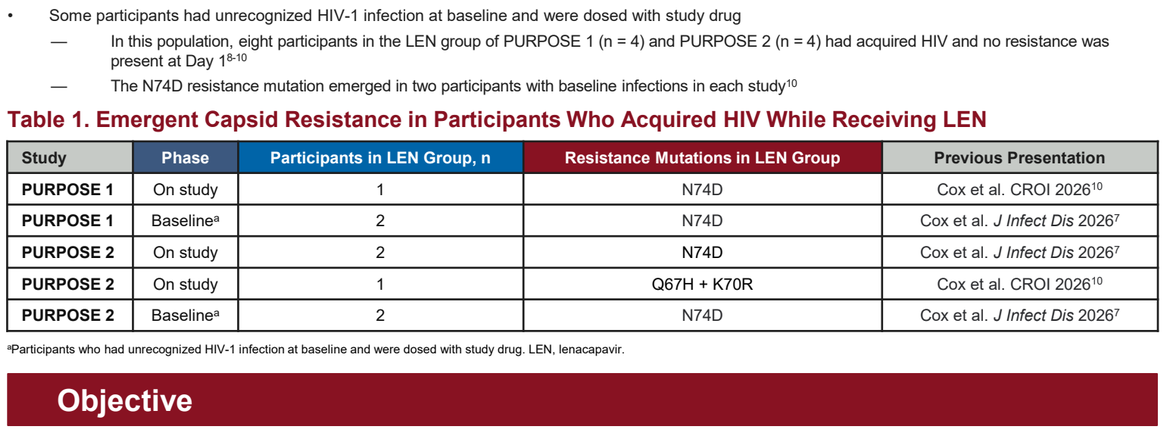
- To report circulating resistance substitutions found in the same locations where the PURPOSE 1 and PURPOSE 2 studies were conducted

Methods

Study Designs and Procedures

- PURPOSE 1 (NCT04994509)[3] is a Phase 3, double-blind, active-controlled randomized trial conducted in cisgender adolescent girls and young women aged 16 to 25 in South Africa and Uganda
- PURPOSE 2 (NCT04925752)[4] is a Phase 3, double-blind, active-controlled randomized trial conducted in cisgender men and gender-diverse individuals aged ≥ 16 years in the USA, Brazil, Thailand, South Africa, Peru, Argentina, and Mexico (**Figure 1**)
- All participants underwent HIV testing at screening:
  - Participants who were HIV negative and met screening criteria were randomized to LEN
  - Participants who were diagnosed with HIV and met screening criteria made up the background incidence population, used in the primary efficacy analysis

Figure 1. PURPOSE 1[3] and PURPOSE 2[4] Study Designs



[a]Included in the full analysis set for primary efficacy analyses (additional participants are included in the safety analysis). [b]Recency assay data were used to estimate background HIV incidence (persons testing HIV positive were referred to HIV care).[3,4] [c]Samples for present analysis collected between September 2021 and July 2024. [d]Samples for present analysis collected between September 2021 and November 2024.
F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; LEN, lenacapavir; SC, subcutaneous.

Resistance Analysis Population

- The resistance analysis population included two groups of participants:
  - Those with a positive HIV-1 test result at screening
  - Those with a positive HIV-1 test result post-randomization
- Screened participants were assessed using the same HIV risk eligibility criteria and study locations as randomized participants. Details of these populations and the genotypic testing performed within each are shown in **Table 2**
- Resistance-associated mutations (RAMs) by drug class are shown in **Table 3**

Table 2. Participants in the Resistance Analysis Population

Study Phase	Population	Participants With Data, n		Genotypic Testing Performed[a]
		PURPOSE 1	PURPOSE 2	
Background incidence population diagnosed with HIV	Screened with positive HIV-1 test result, viral load > 75 copies/mL	170	263	CA, RT, PR, and IN
Randomized	Randomized to receive LEN, F/TAF, or F/TDF who acquired HIV before or during PrEP, viral load > 200 copies/mL	66	21	**Received LEN:** PR, RT, and IN **Received F/TAF or F/TDF:** PR, IN, and CA
Total		236	284	

[a]Nonstudy drug-related genes were tested because the goal of the analysis, due to the study being blinded, was to assess transmitted/circulating drug resistance, rather than acquired drug resistance.
CA, HIV capsid; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; IN, integrase; LEN, lenacapavir; PR, protease; PrEP, pre-exposure prophylaxis; RT, reverse transcriptase.

Table 3. Resistance-Associated Mutations By Drug Class

Drug Class	Resistance-Associated Substitutions
Primary CAI	L56I, M66I, Q67H/K/N, K70H/N/S/R, N74D/H/K/S, A105S/T, T107A/C/N/S
Primary PI	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
Primary INSTI	T66I/A/K, E92Q/G/V, G118R, F121C/Y, G140R, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
Secondary INSTI	M50I, L68V/I, L74M/I, T97A, S119P/R/T, E138K/A/T, G140A/C/S, P145S, Q146R/I/K/L/P, V151A/I/L, S153F/Y, E157K/Q, S230R
Primary NNRTI	L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C/L, M230L/I, Y318
Primary NRTI	M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
Thymidine analog	M41L, D67N, K70R, L210W, T215Y/F, K219E/Q/N/R

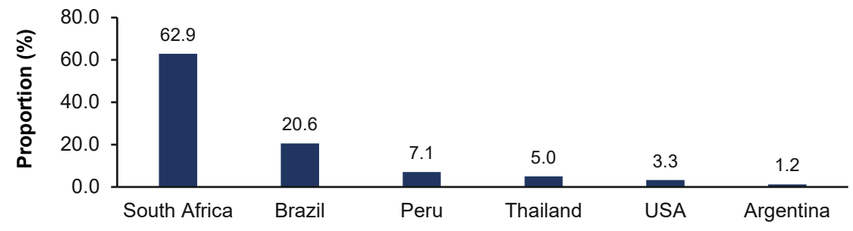
CAI, capsid inhibitor; INSTI, integrase strand-transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; R, resistance.

Results

Participants

- Countries represented in the resistance analysis population are shown in **Figure 2**, and selected participant baseline characteristics are shown in **Table 4** (PURPOSE 1) and **Table 5** (PURPOSE 2); HIV subtype for participants with data is shown in **Table 6**

Figure 2. Proportion of Incidence Samples by Country Across Both PURPOSE 1[a] and PURPOSE 2



[a]Note that 100% of PURPOSE 1 samples were from South Africa; data were unable to be used from Uganda for this analysis.

Table 4. PURPOSE 1 Baseline Characteristics

Characteristic	Randomized (n = 5368)	Background Incidence Population Diagnosed With HIV (n = 504)
Median age, years (range)	21 (16-26)	22 (17-25)
Black race, n (%)	5362 (99.9)	503 (99.8)
Marital status: married, n (%)	52 (1.0)	10 (1.4)
Any prior use of PrEP, n (%)	335 (6.2)	19 (3.8)
Any prior HIV testing, n (%)	4322 (80.5)	391 (77.6)
Median time since last HIV test, months (Q1, Q3)	6.7 (4.7, 11.2)	8.0 (5.1, 13.6)

PrEP, pre-exposure prophylaxis; Q, quartile.

Participants
84.3% South Africa
15.7% Uganda

Table 5. PURPOSE 2 Baseline Characteristics

Characteristic		Randomized (n = 3292)	Background Incidence Population Diagnosed With HIV (n = 378)
Median age, years (range)		29 (17-74)	28 (18-80)
Age 16 to ≤ 25, years, n (%)		1101 (33.4)	131 (34.7)
Non-White race, n (%)		2219 (67.4)	338 (89.4)
Hispanic/Latine ethnicity, n (%)		2062 (62.7)	169 (44.7)
Gender identity, n (%)	Cisgender man	2558 (77.7)	283 (74.9)
	Gender diverse	734 (22.3)	95 (25.1)
History of STI diagnosis in past 24 weeks, n (%)		404 (12.3)	41 (10.8)
No prior HIV test, n (%)		908 (27.6)	123 (32.5)
Use of stimulants[a] with sex in last 12 weeks, n (%)		768 (23.3)	74 (19.6)

[a]Self-reported. STI, sexually transmitted infection.

Participants
Brazil 35.6%
USA 20.6%
Peru 13.7%
Thailand 11.9%
South Africa 10.9%
Argentina 6.9%
Mexico 0.4%

Table 6. HIV Subtype Prevalence

HIV Subtype, n (%)	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
B	0	115 (40.5)	115 (22.1)
Non-B	236 (100)	169 (59.5)	405 (77.9)
A	0	1 (0.4)	1 (0.2)
AC	1 (0.4)	0	1 (0.2)
AD	1 (0.4)	0	1 (0.2)
CRF02_AG	0	5 (1.8)	5 (1.0)
CRF01_AE	0	22 (7.7)	22 (4.2)
BC	0	2 (0.7)	2 (0.4)
BF	0	18 (6.3)	18 (3.5)
C	233 (98.7)	107 (37.7)	340 (65.4)
D	1 (0.4)	1 (0.4)	2 (0.4)
F1	0	11 (3.9)	11 (2.1)
G	0	2 (0.7)	2 (0.4)

Resistance Analysis

- HIV capsid substitutions at amino acid positions associated with LEN resistance were observed in 3.0% of participants, consisting of T107A/S/V (2.6% altogether), and K70R or N74T (0.2% each; **Table 7**)[11,12]
  - None of these substitutions are associated with reduced susceptibility to LEN and are likely naturally occurring polymorphisms
  - **Table 8** compares the susceptibilities of the CA substitutions observed here with LEN RAMs that emerged when HIV was acquired during LEN exposure (N74D and Q67H + K70R)
- Pre-existing phenotypic resistance to LEN was not observed in any participant analyzed. The following mutations were observed:
  - Primary INSTI RAMs in 0.4% of participants (**Table 9**)
  - Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) RAMs in 2.3% of participants (**Table 10**)
  - Non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs in 20.5% of participants (**Table 11**)
  - Protease inhibitor (PI) RAMs in 2.3% of participants (**Table 12**)

Table 7. CA Substitutions at Positions Associated With LEN Resistance

Detected Substitution at CA Position Associated With Resistance, n (%)	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
Number of participants with data	228	277	505
K70R	1 (0.4)	0	1 (0.2)
N74T	1 (0.4)	0	1 (0.2)
T107A	1 (0.4)	1 (0.4)	2 (0.4)
T107S	5 (2.1)	4 (1.4)	9 (1.8)
T107V	0	2 (0.7)	2 (0.4)
RAMs observed previously in the primary analysis and RBP			
N74D	0	0	0
Q67H + K70R	0	0	0

CA, HIV capsid; LEN, lenacapavir; RAM, resistance-associated mutation; RBP, randomized blinded phase.

Table 8. Summary of LEN EC_{50} Fold Changes of CA Substitutions at Positions Associated With LEN Resistance

CA Substitutions	Mean LEN EC_{50} Fold Change From WT
K70R[a]	0.8
N74T[b]	1.2
T107A[a]	1
T107S[a]	0.9
T107V[c]	1
N74D[a]	10.2
Q67H + K70R[a]	72.5

[a]Average from 40 HIV-1 clinical isolates and 44 SDMs were tested using three complementary phenotypic assays: the 2-day single-cycle PhenoSense Gag-Pro reporter assay, the 5-day multicycle MT-2 cytopathic assay, and the 5-day multicycle RevLun antiviral reporter assay.[11] [b]Single-cycle PhenoSense Gag-Pro assay.[13] [c]Three-day single-cycle antiviral assay conducted in MT-4 cells.[12]
CA, HIV capsid; EC_{50}, 50% effective inhibitory concentration; LEN, lenacapavir; SDM, site-directed mutation; WT, wild type.

Table 9. INSTI RAMs

Detected INSTI RAMS, n (%)[a]	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
Participants with data, n	227	279	506
Primary INSTI-associated[b]	1 (0.4)	1 (0.4)	2 (0.4)
G140R	1 (0.4)	0	1 (0.2)
Y143C	0	1 (0.4)	1 (0.2)
Secondary INSTI-associated[c]			
M50I	70 (30.8)	63 (22.6)	133 (26.3)
L68V	3 (1.3)	1 (0.4)	4 (0.8)
L74M	2 (0.9)	4 (1.4)	6 (1.2)
T97A	3 (1.3)	5 (1.8)	8 (1.5)
S119P/R/T	40 (17.6)	69 (24.7)	109 (21.5)
V151I	0	4 (1.4)	4 (0.8)
E157K/Q	3 (1.3)	6 (2.2)	9 (1.8)

[a]Denominators are participants with data. [b]Primary INSTI-R mutations: T66A/I/K, E92G/Q/V, G118R, F121C/Y, G140R, Y143C/H/R, S147G, Q148H/K/R, N155H/S, and R263K in IN. [c]Secondary INSTI-R mutations: M50I, L68I/V, L74M, T97A, S119P/R/T, E138A/K/T, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/I/L, S153F/Y, E157K/Q, and S230R in IN.
IN, integrase; INSTI, integrase strand-transfer inhibitor; R, resistance; RAM, resistance-associated mutation.

Table 10. NRTI RAMs

Detected NRTI RAMs, n (%)[a]	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
Participants with data, n	174	270	444
NRTI-associated[b]	4 (1.3)	6 (2.2)	10 (2.3)
TAMs	4 (1.3)	2 (0.7)	6 (1.4)
M41L	1 (0.3)	1 (0.4)	2 (0.5)
K65R	0	1 (0.4)	1 (0.2)
K65E	0	1 (0.4)	1 (0.2)
D67N	1 (0.3)	0	1 (0.2)
K70E	0	1 (0.4)	1 (0.2)
K70R	1 (0.3)	1 (0.4)	2 (0.5)
L74I	1 (0.3)	0	1 (0.2)
F77L	0	1 (0.4)	1 (0.2)
M184V	2 (0.7)	3 (1.1)	5 (1.1)
K219R	1 (0.3)	0	1 (0.2)

[a]Denominators are participants with data. [b]NRTI-R mutations: M41L, K65R/E/N, D67N, T69 deletion/insertion, K70E/R, L74I/V, V75I, F77L, Y115F, F116Y, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT.
NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; R, resistance; RAM, resistance-associated mutation; RT, reverse transcriptase; TAM, thymidine analog mutation.

Table 11. NNRTI RAMs

Detected NNRTI RAMs, n (%)[a]	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
Participants with data, n	234	282	516
NNRTI-associated[b]	62 (26.5)	44 (15.6)	106 (20.5)
L100I	0	1 (0.4)	1 (0.2)
K101E/H/P	4 (1.7)	4 (1.4)	8 (1.6)
K103N/S	39 (16.7)	23 (8.2)	62 (12.0)
V106M	3 (1.3)	2 (0.7)	5 (1.0)
V108I	1 (0.4)	1 (0.4)	2 (0.4)
E138A/G/K/Q	16 (6.8)	19 (6.7)	35 (6.8)
Y181C	2 (0.9)	0	2 (0.4)
Y188L	2 (0.9)	1 (0.4)	3 (0.6)
G190A/S	5 (2.1)	2 (0.7)	7 (1.4)
P225H	5 (2.1)	1 (0.4)	6 (1.2)
M230I	0	1 (0.4)	1 (0.2)

[a]Denominators are participants with data. [b]NNRTI-R mutations: L100I, K101E/H/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/Q/S, H221Y, P225H, F227C, and M230I/L in RT.
NNRTI, non-nucleoside reverse transcriptase inhibitor; R, resistance; RAM, resistance-associated mutation; RT, reverse transcriptase.

Table 12. Primary PI RAMs

Detected PI RAMs, n (%)[a]	PURPOSE 1 (n = 236)	PURPOSE 2 (n = 284)	All (N = 520)
Participants with data, n	203	281	484
Primary PI-associated[b]	3 (1.5)	8 (2.8)	11 (2.3)
M46I/L	3 (1.5)	4 (1.4)	7 (1.4)
I50L/V	0	2 (0.7)	2 (0.4)
Q58E	0	3 (1.1)	3 (0.6)
V82A/F/L/S/T	0	1 (0.4)	1 (0.2)
L90M	0	1 (0.4)	1 (0.2)

[a]Denominators are participants with data. [b]PI-R mutations: D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54L/M/V, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M in PR.
PI, protease inhibitor; PR, protease; R, resistance; RAM, resistance-associated mutation.

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