# Twice-Yearly Lenacapavir, Teropavimab, and Zinlirvimab for HIV-1: Week 52 Resistance Analyses

Poster #567


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## Conclusions

- The twice-yearly combination of lenacapavir (LEN), teropavimab (TAB), and zinlirvimab (ZAB) maintained a high rate of virological suppression in people with HIV-1 highly susceptible to both broadly neutralizing antibodies (bNAb) at Weeks 26 and 52[1,2]
- After 52 weeks of treatment with LEN, TAB, and ZAB, emergent resistance to study drugs was infrequent
- One participant with low-level viremia and no detected resistance showed evidence of clonal expansion of HIV-1 infected T cells, which may have contributed to detectable viremia
- These findings support ongoing evaluation of LEN, TAB, and ZAB as the first potential twice-yearly HIV-1 combination treatment regimen

## Plain Language Summary

- Lenacapavir is an injection that doctors use to treat HIV in people whose previous HIV medicines no longer work; teropavimab and zinlirvimab are new medicines given as infusions (into a vein) that researchers are still testing to treat HIV
- People can receive lenacapavir, teropavimab, and zinlirvimab together once every 6 months, which is different from most HIV treatments that are taken as daily pills
- In this study, researchers tested these medicines in participants who were taking daily HIV pills and already had very low or undetectable levels of HIV in their blood (called virologic suppression)
- Researchers checked for any new cases of resistance (meaning that the medicines no longer work against the HIV) that had developed after people started treatment with lenacapavir, teropavimab, and zinlirvimab. Over 52 weeks, only 2 out of 53 participants had HIV that developed resistance


**Footnotes:** [1]Assay cut-off: 1000 copies/mL. [2]Assay cut-off: 500 copies/mL. [3]Assay cut-off: 765 copies/mL.



**References:** **1.** Ogbuagu O, et al. CROI 2025. Oral 151. **2.** Ogbuagu O, et al. EACS 2025. Oral PS09.2. **3.** Claborn KR, et al. *Psychol Health Med*. 2015;20:255–65. **4.** Cooper SE, et al. *Clin Infect Dis*. 2022;75:S541–8. **5.** SUNLENCA® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215973s006,215974s008lbl.pdf (Accessed Jan 2026). **6.** SUNLENCA® Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf (Accessed Jan 2026). **7.** YEZTUGO® Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/220020s000lbl.pdf (Accessed Jan 2026). **8.** Gautam R, et al. *Nat Med*. 2018;24:610–6. **9.** VanderVeen LA, et al. *AIDS*. 2024;38:607–10.



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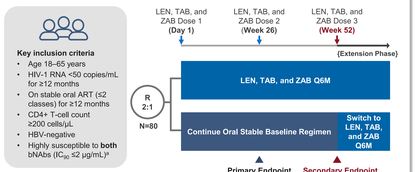
**Author Disclosures:** **Laurie A. VanderVeen, Lisa Selzer, Yu Hu, Jiani Li, Ross Martin, Nan Zhang, Kwad Mponponsuo, Sean E. Collins,** and **Christian Callebaut** are all employees and shareholders of Gilead Sciences, Inc. **Joseph Eron** reports advisory board participation for Gilead Sciences, Inc., ViiV, Merck, and Abbvie; and research contract funding from Gilead Sciences, Inc.

## Background

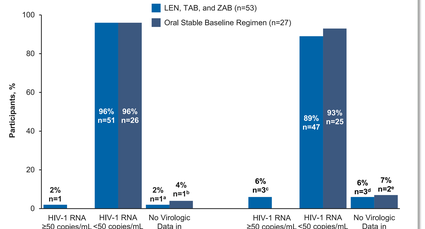
- Antiretroviral therapy (ART) with less frequent dosing intervals may offer advantages over daily oral ART for some people with HIV-1, such as improved adherence and reduced pill burden[3,4]
- LEN, the first-in-class HIV-1 capsid inhibitor, is approved for the treatment of multidrug-resistant HIV-1 and for HIV-1 prevention, and can be administered subcutaneously twice yearly[5–7]
- TAB (3BNC117-LS, GS-5423) and ZAB (10-1074-LS, GS-2872) are bNAbs that target the HIV envelope (ENV) and can also be dosed twice yearly[8]
  - TAB targets the CD4-binding site while ZAB targets the V3 glycan on the HIV-1 ENV[8]
- In a Phase 2, ongoing, open-label study (NCT05729568; **Figure 1**), LEN, TAB, and ZAB are being investigated in combination as a twice-yearly treatment for HIV-1
  - Twice-yearly LEN, TAB, and ZAB maintained virological suppression (HIV-1 RNA <50 copies/mL) in 96% and 89% of participants with HIV-1 highly susceptible to both bNAbs at Weeks 26 and 52, respectively (**Figure 2**)[1,2]

### Figure 1. Phase 2 Study Design




[a]By PhenoSense® HIV mAb Assay (Monogram Biosciences).
ART, antiretroviral therapy; bNAb, broadly neutralizing antibody; HBV, hepatitis B virus; $IC_{90}$, 90% inhibitory concentration; LEN, lenacapavir; mAb, monoclonal antibody; Q6M, every 6 months; R, randomized; TAB, teropavimab; ZAB, zinlirvimab.

### Figure 2. Virologic Outcomes by US FDA Snapshot Algorithm at Weeks 26 and 52




Data may not add up to 100% due to rounding.
[a]Discontinued due to investigator's discretion (relocation).
[b]Discontinued due to adverse event (metastatic pancreatic carcinoma).
[c]All three participants restarted standard first-line oral antiretroviral therapy (bictegravir/emtricitabine/tenofovir alafenamide) and resuppressed during follow-up.
[d]n=2 discontinued due to participant decision and n=1 discontinued due to relocation.
[e]n=1 discontinued due to participant decision and n=1 discontinued due to adverse event.
FDA, Food and Drug Administration; LEN, lenacapavir; TAB, teropavimab; ZAB, zinlirvimab.

## Objective

- To describe Week 52 resistance analyses for participants switching from daily oral ART to twice-yearly LEN, TAB, and ZAB in the ongoing Phase 2 study

## Methods

### Study Design

- Virologically suppressed participants with HIV-1 highly susceptible to TAB and ZAB (90% inhibitory concentration [$IC_{90}$] ≤2 µg/mL by PhenoSense® mAb Assay [Monogram Biosciences]) were enrolled
- Eligible participants were randomized 2:1 to receive twice-yearly subcutaneous LEN 927 mg (plus 600 mg of LEN oral loading on Days 1 and 2) and intravenous TAB 2550 mg and ZAB 2550 mg, or to stay on their oral stable baseline regimen (SBR)

### Pre-Treatment (Baseline) Analyses

- HIV-1 proviral ENV genotyping and phenotyping were performed at screening for all participants to assess for pre-existing resistance
- HIV-1 subtype was determined based on nucleotide identity of the consensus ENV gene against curated subtype reference sequences from GenBank® (www.ncbi.nlm.nih.gov/genbank/)[9]
- HIV-1 ENV sequences were analyzed for the presence of the potential N-linked glycosylation motif at position N332 (Asn-X-Ser/Thr, where X can be any amino acid except proline)
  - Mutations that disrupt this motif have been associated with resistance to ZAB

### On-Treatment (Post-Baseline) Analyses

- Post-baseline resistance testing was conducted for participants meeting virologic failure criteria (HIV-1 RNA ≥50 copies/mL, subsequently confirmed and ≥200 copies/mL, or ≥200 copies/mL at study drug discontinuation/last visit)
- Plasma HIV-1 RNA genotype and phenotype were assessed using GenoSure® HIV ENV*, PhenoSense® mAb RNA[†], GenoSure® Gag[†], PhenoSense® Gag, PhenoSense® GT[†], GeneSeq® IN[†], and PhenoSense® IN[†] (Monogram Biosciences)
  - Nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor and capsid inhibitor primary resistance-associated mutations are presented in **Table 1**
- An alternative next generation sequencing assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) was used in cases of assay failure or for exploratory purposes

### Table 1. Primary RAMs for CAI, INSTI, and NRTI Classes

| Class | |
|---|---|
| **CAI** | L56I, M66I, Q67H/K/N, K70H/N/R/S, N74D/S, A105S/T, T107A/C/N/S |
| **INSTI** | T66A/I/K, E92G/Q/V, G118R, F121C/Y, G140R, Y143C/H/R, S147G, Q148H/K/R, N155H/S, R263K |
| **NRTI** | M41L, K65E/N/R, D67N, T69 insertion, K70E/R, L74I/V, Y115F, Q151M, M184I/V, L210W, T215F/Y, K219E/N/Q/R |

CAI, capsid inhibitor; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RAM, resistance-associated mutation.

### Single-Genome Sequencing Analyses

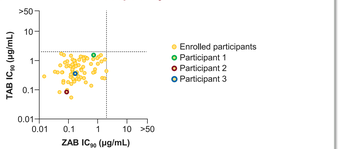
- Clonality of plasma HIV-1 RNA samples was evaluated by single-genome sequencing of the p6-RT (HXB2 nucleotides 1849–3410) and ENV (HXB2 nucleotides 5953–8882) regions
  - RNA was extracted, reverse transcribed and cDNA subjected to nested polymerase chain reaction following endpoint dilution
  - Amplicons were sequenced using next-generation deep sequencing (Novogene)
  - Phylogenetic analysis of the sequences was performed by constructing a maximum likelihood tree (FastTree)
  - Root-to-leaf distances representing path length from most recent common ancestor to the individual sample were analyzed using the DendroPy Python library (Version 4.0.0)

## Results

### Pre-Treatment (Baseline) Analyses

- Of 80 participants enrolled and dosed (LEN, TAB, and ZAB, n=53; SBR, n=27), most had subtype B HIV-1 (n=75/80, 94%)
- All enrolled participants demonstrated phenotypic susceptibility to TAB and ZAB at baseline
  - Baseline bNAb $IC_{90}$ values for LEN, TAB, and ZAB-treated participants ranged from 0.05–1.71 µg/mL for TAB and 0.01–1.99 µg/mL for ZAB (**Figure 3**)

### Figure 3. Baseline TAB and ZAB Susceptibility



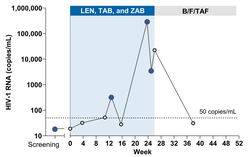

$IC_{90}$, 90% inhibitory concentration; TAB, teropavimab; ZAB, zinlirvimab

## Results (Cont.)

### On-Treatment (Post-Baseline Through Week 52) Analysis

- Three participants (5.7%) in the LEN, TAB, and ZAB group (Participants 1, 2, and 3, as shown in **Figure 3**) and no participants in the SBR group met resistance analysis criteria (**Figures 4–6**)

### Figure 4. Virologic Analysis of Participant 1

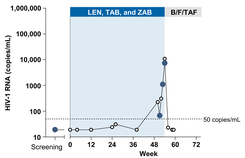



| | Visit | | | |
|---|---|---|---|---|
| | Screening | Week 12 | Week 24 | Week 26 |
| **HIV-1 RNA, copies/mL** | <20 | 333 | 287,000 | 3550 |
| **RAMs** | | | | |
| CA | None | None | – | Q67H |
| RT | – | – | – | None |
| IN | – | – | – | None |
| **ZAB susceptibility signature** | | | | |
| ENV | N332 glycan motif detected | AF | N332 glycan not detected | N332 glycan not detected |
| **Drug susceptibility** | | | | |
| LEN (FC from WT) | – | 0.8 | – | 5.2 |
| TAB ($IC_{90}$ µg/mL)) | 1.53 | AF | 1.58 | AF |
| ZAB ($IC_{90}$ µg/mL)) | 0.72 | AF | >50 | AF |

"–" = not tested. Blue circles indicate resistance testing visits.
AF, assay failure; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CA, capsid; ENV, envelope; FC, fold change; $IC_{90}$, 90% inhibitory concentration; IN, integrase; LEN, lenacapavir; RAM, resistance-associated mutation; RT, reverse transcriptase; TAB, teropavimab; WT, wild-type; ZAB, zinlirvimab.

- **Participant 1** developed LEN resistance (Q67H) and resistance to ZAB ($IC_{90}$ >50 µg/mL) at Week 24
  - This participant had rapid HIV-1 RNA suppression after switching to oral bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF)

### Figure 5. Virologic Analysis of Participant 2

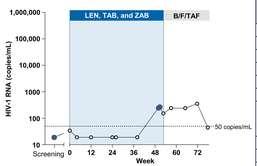



| | Visit | | | |
|---|---|---|---|---|
| | Screening | Week 52[a] | Week 52[a] | Week 52[a] |
| **HIV-1 RNA, copies/mL** | <20 | 68 | 1130 | 7460 |
| **RAMs** | | | | |
| CA | – | AF | None | – |
| RT | – | – | – | – |
| IN | – | – | – | – |
| **ZAB susceptibility signature** | | | | |
| ENV | N332 glycan motif detected | – | N332 glycan not detected | – |
| **Drug susceptibility** | | | | |
| LEN (FC from WT) | – | AF | 1.5 | – |
| TAB ($IC_{90}$ µg/mL)) | 0.08 | AF | AF | AF |
| ZAB ($IC_{90}$ µg/mL)) | 0.09 | AF | AF | AF |

"–" = not tested. *These were re-tests for virologic rebound confirmation as per protocol. Blue circles indicate resistance testing visits.
AF, assay failure; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CA, capsid; ENV, envelope; FC, fold change; $IC_{90}$, 90% inhibitory concentration; IN, integrase; LEN, lenacapavir; RAM, resistance-associated mutation; RT, reverse transcriptase; TAB, teropavimab; WT, wild-type; ZAB, zinlirvimab.

- **Participant 2** had predicted loss of ZAB susceptibility at Week 52 without LEN resistance
  - This participant had rapid HIV-1 RNA suppression after switching to oral B/F/TAF

### Figure 6. Virologic Analysis of Participant 3




| | Visit | | |
|---|---|---|---|
| | Screening | Week 50[a] | Week 50[a] |
| **HIV-1 RNA, copies/mL** | <20 | 248 | 262 |
| **RAMs** | | | |
| CA | – | AF | None |
| RT | – | – | None |
| IN | – | – | None |
| **ZAB susceptibility signature** | | | |
| ENV | N332 glycan motif detected | – | N332 glycan motif detected |
| **Drug susceptibility** | | | |
| LEN (FC from WT) | – | AF | AF |
| TAB ($IC_{90}$ µg/mL)) | 0.36 | AF | AF |
| ZAB ($IC_{90}$ µg/mL)) | 0.17 | AF | AF |

"–" = not tested. *These were re-tests for virologic rebound confirmation as per protocol. Blue circles indicate resistance testing visits.
AF, assay failure; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; CA, capsid; ENV, envelope; FC, fold change; $IC_{90}$, 90% inhibitory concentration; IN, integrase; LEN, lenacapavir; RAM, resistance-associated mutation; RT, reverse transcriptase; SGS, single-genome sequencing; TAB, teropavimab; WT, wild-type; ZAB, zinlirvimab.

- **Participant 3** had persistent low-level viremia after restarting oral B/F/TAF with no resistance detected
  - This participant resuppressed 180 days following initiation of oral B/F/TAF

- Single-genome sequencing of the p6-RT (**Figure 7A**) and ENV (**Figure 7B**) regions was conducted for Participant 3
  - Single-genome analysis of longitudinal plasma sequences identified 37% (13/35) and 7.7% (2/26) identical p6-RT and ENV sequences, respectively, suggesting clonal T-cell expansion may have contributed to low-level viremia

### Figure 7. Single-Genome Sequencing Analysis of the p6-RT (A) and ENV (B) Regions for Participant 3

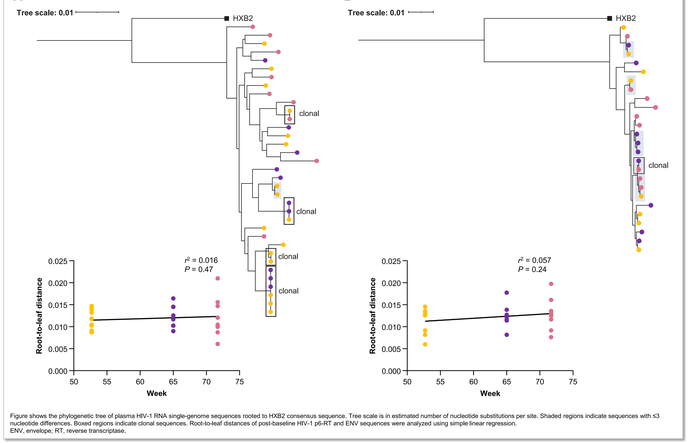
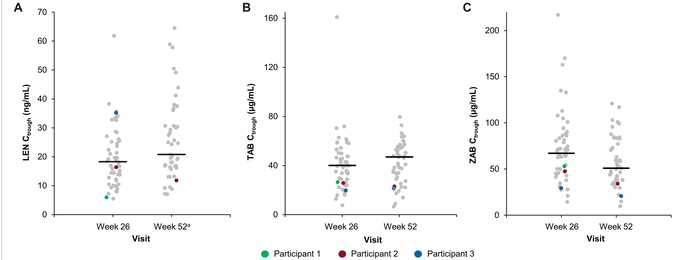



Figure shows the phylogenetic tree of plasma HIV-1 RNA single-genome sequences rooted to HXB2 consensus sequence. Tree scale is in estimated number of nucleotide substitutions per site. Shaded regions indicate sequences with ≤3 nucleotide differences. Boxed regions indicate clonal sequences. Root-to-leaf distances of post-baseline HIV-1 p6-RT and ENV sequences were analyzed using simple linear regression.
ENV, envelope; RT, reverse transcriptase.

### Relative Exposures to LEN, TAB, and ZAB Through Week 52

- Exposures of LEN (**Figure 8A**), TAB (**Figure 8B**), and ZAB (**Figure 8C**) in the three participants with virologic rebound were relatively lower than the study population median; however, they still fell within the range observed in participants who remained virologically suppressed

### Figure 8. Distribution of $C_{trough}$ at Weeks 26 and 52 for LEN (A), TAB (B), and ZAB (C)




Black lines indicate the median. [a]No Week 52 LEN pharmacokinetic result was available for Participant 3.
$C_{trough}$, trough concentration; LEN, lenacapavir; TAB, teropavimab; ZAB, zinlirvimab.