HIV-Specific T Cell Responses in Virologically Suppressed PWH Receiving Lenacapavir, Teropavimab, and Zinlirvimab

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Disclosures

Yanhui Cai, Anne-Maud Ferreira, Jeffrey J. Wallin were employees and shareholders of Gilead Sciences, Inc. at the time of analysis

Liao Zhang and **Sean E. Collins** are employees and shareholders of Gilead Sciences, Inc.

Hiroshi Takata, Julian Pacheco Mendez, Sam Nathanson, and Lydie Trautmann report no conflict of interest

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Background

- HIV infection can induce T cell responses, which are reduced upon successful treatment with antiretroviral therapy (ART), but may still be detectable over time in virologically suppressed (VS) people with HIV-1 (PWH) on ART[1,2]
  - Greater HIV-1 specific T cell responses may play a role in long-term viral control as well as HIV-1 cure or remission strategies
- Small increases in HIV-specific T cell responses were initially observed when the broadly neutralizing antibodies (bNAb), 3BNC117 and 10-1074, were dosed during analytical treatment interruption or at ART initiation[3,4]
- A similar observation was recently reported with the long-acting bNAbs teropavimab (**TAB**, also 3BNC117-LS) and zinlirvimab (**ZAB**, also 10-1074-LS)[5]
  - This bNAb-induced anti-HIV-1 T cell response could be a potential component of a strategy for HIV cure
  - Whether similar responses will occur in VS PWH who receive bNAbs is unknown
- In a Phase 1b study (NCT04811040), VS PWH switched to the long-acting regimen of lenacapavir (LEN; an HIV-1 capsid inhibitor), TAB, and ZAB, and maintained viral suppression for 6 months[6,7]

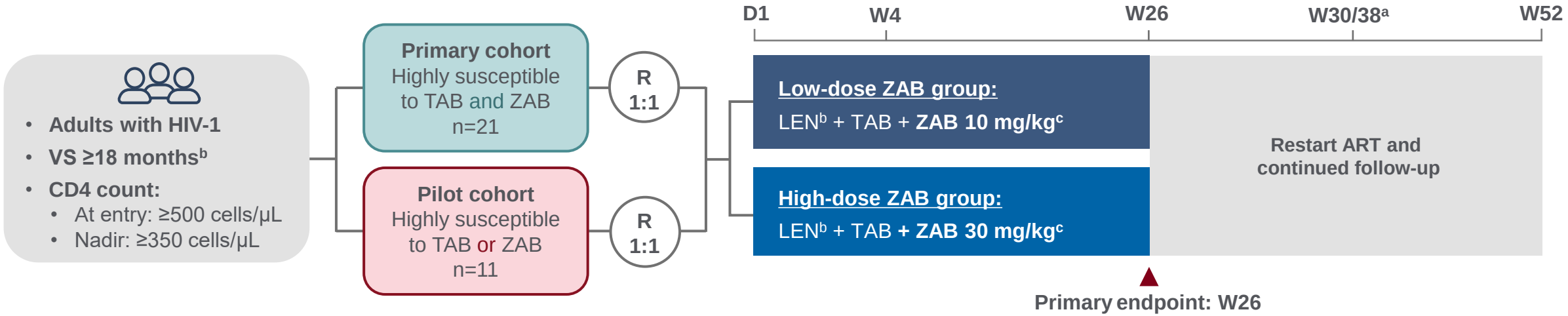
We report HIV-1-specific T cell responses in PWH receiving LEN, TAB, and ZAB in a Phase 1b study (NCT04811040)

ART, antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **LEN,** lenacapavir; **PWH,** people with HIV-1; **TAB,** teropavimab; **VS,** virologically suppressed; **ZAB,** zinlirvimab.

1. Xu Y, et al. *Mole Ther Meth & Clin Dev.* 2019;15:9–17. 2.Stevenson E, et al. *JCI Insight.* 2021;6(3):e142640. 3. Niessl J et al. *Nat Med*. 2020;26(2):222–7. 4. Rosas-Umbert M, et al. *Nature Commun.* 2022;13 6473. 5. Altaf M et al. Presented at CROI 2025. Poster 506. 6. Eron J et al. *Lancet HIV*. 2024;11(3):e146–e155. 7. Eron J et al. *J Infect Dis*. 2025; jiaf159.

Phase 1b Study Design

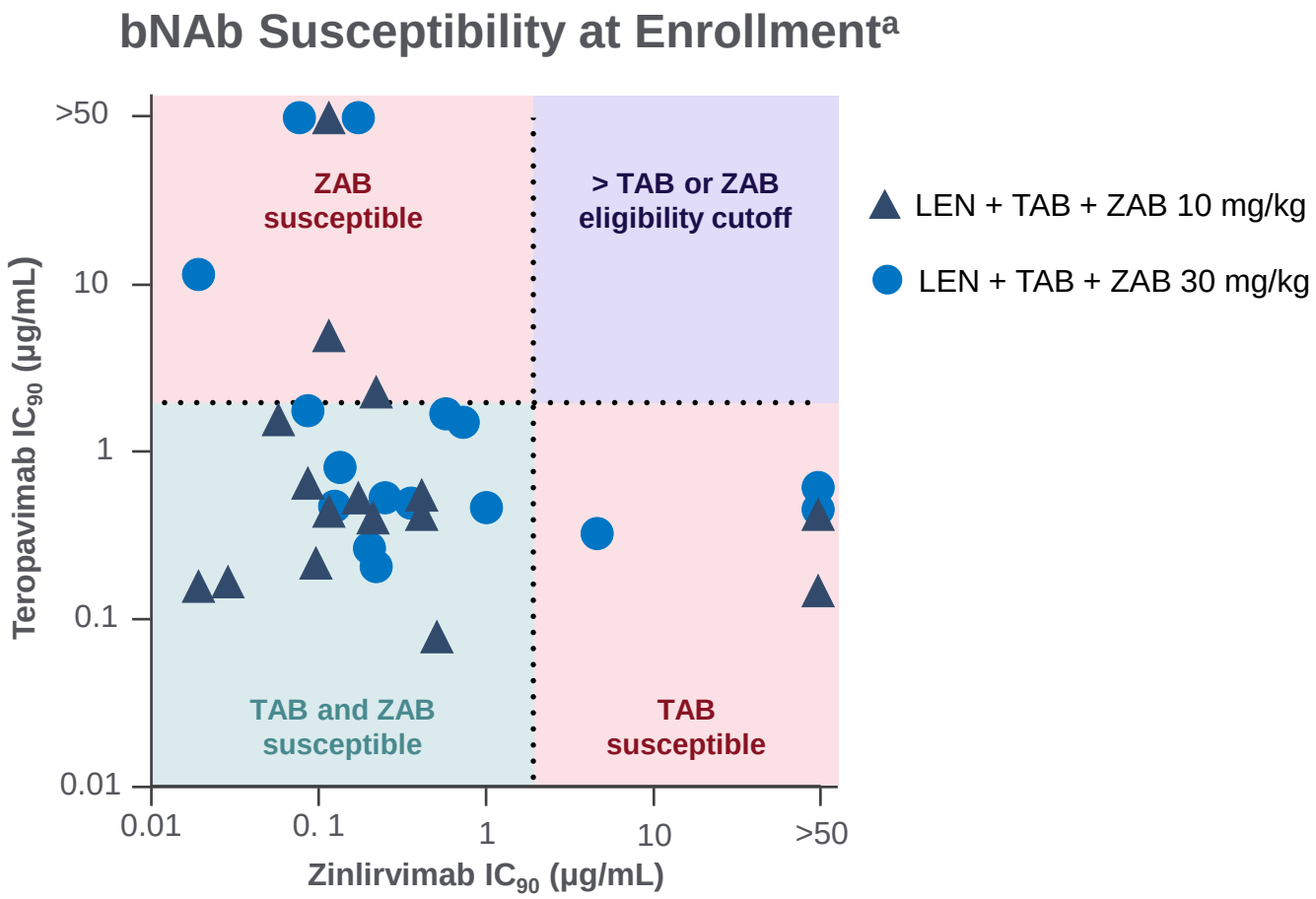
Randomized, blinded Phase 1b study assessing the safety profile and efficacy of a long-acting regimen LEN, TAB, and ZAB administered in two different doses



- **Primary endpoint:** efficacy at **Week 26 Safety** and **Efficacy** by FDA Snapshot Algorithm
- **Exploratory endpoint**: HIV-specific T-cell responses through **Week 52**

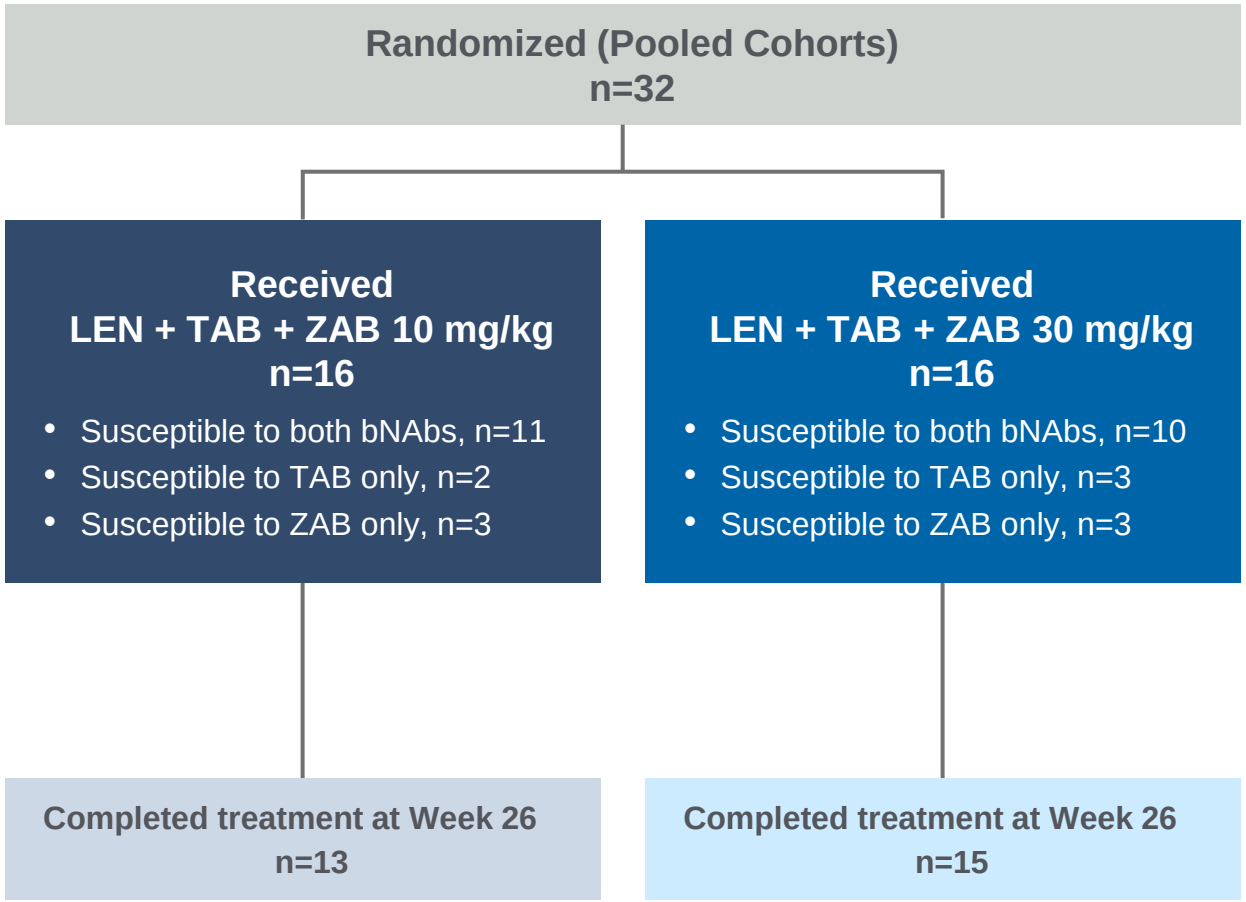
[a]Three subjects had samples collected at Week 30, while the (mutually exclusive) remainder were collected at Week 38. These timepoints are combined in the analysis for simplicity. [b]Previous virologic failure was allowed if participants had VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening. [c]TAB 30 mg/kg IV and ZAB 10 or 30 mg/kg IV on Day 1. bNAb susceptibility was defined as IC90 ≤2 µg/mL by PhenoSense® mAb Assay (Monogram Biosciences). **ART,** antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **D**, day; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **R,** randomized; **TAB,** teropavimab; **VS,** virologically suppressed; **W**, week; **ZAB,** zinlirvimab.

bNAb Susceptibility



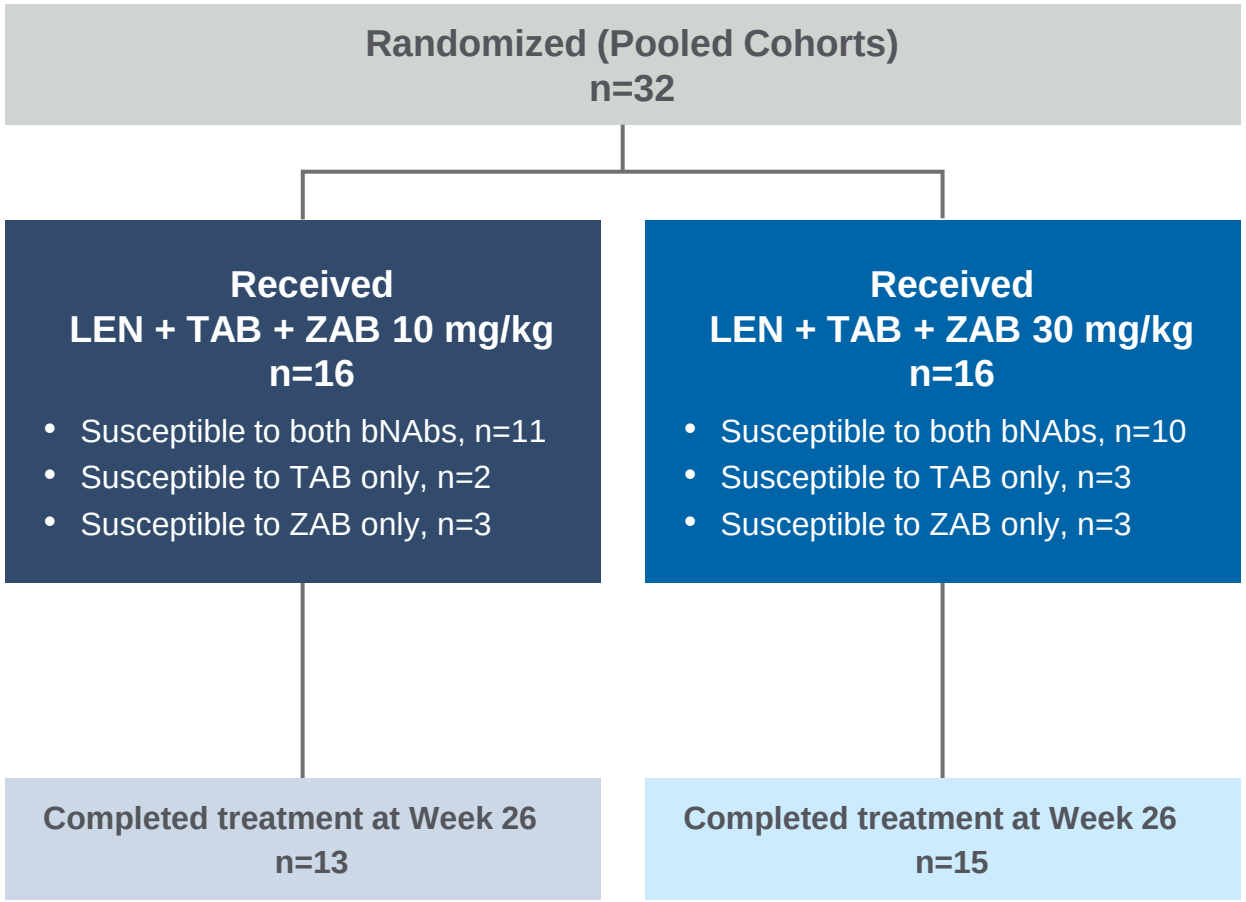
[a]By PhenoSense® mAb Assay (Monogram Biosciences).
bNAb, broadly neutralizing antibody; **IC_{90},** 90% inhibitory concentration; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Participant Disposition



ART, antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Participant Disposition and Baseline Characteristics



	LEN + TAB + ZAB 10 mg/kg (n=16)	LEN + TAB + ZAB 30 mg/kg (n=16)
Median (range) age, years	48 (28–63)	44 (25–59)
Female sex at birth, n (%)	2 (13)	4 (25.0)
Race, n (%)		
Asian	2 (13)	1 (6)
Black	3 (19)	4 (25)
White	10 (63)	8 (50)
Other	1 (6)	3 (19)
Hispanic or Latinx ethnicity, n (%)	6 (38)	4 (25)
Median (range) weight, kg	88 (59–150)	89 (60–143)
Median (range) CD4 cell count, cells/mL	821 (449–1916)	985 (667–1644)

ART, antiretroviral therapy; **bNAb,** broadly neutralizing antibody; **LEN,** lenacapavir; **TAB,** teropavimab; **ZAB,** zinlirvimab.

Phase 1b Primary Efficacy Results

Virologic Outcomes at Week 26 by FDA Snapshot Algorithm

	LEN + TAB + ZAB 10 mg/kg (n=14[a])	LEN + TAB + ZAB 30 mg/kg (n=16)
HIV-1 RNA ≥50 copies/mL, n % (95% CI)	**3** 21 (5; 51)	**0** 0 (0; 21)
HIV-1 RNA <50 copies/mL, n % (95% CI)	**11** 79 (49; 95)	**15** 94 (70; 100)
No virologic data in Week 26 window, n (%)	**0**	**1**[b] (6)

[a]Two participants were excluded from the efficacy analysis (did not receive the complete study regimen [participant decision], n=1, protocol violation, n=1). [b]Participant withdrew from the study after Week 12 (participant decision), with HIV-1 RNA <50 copies/mL at last available visit.

LEN, lenacapavir; **PWH,** people with HIV-1; **SC,** subcutaneous; **TAB,** teropavimab; **VS,** virologically suppressed; **ZAB,** zinlirvimab.

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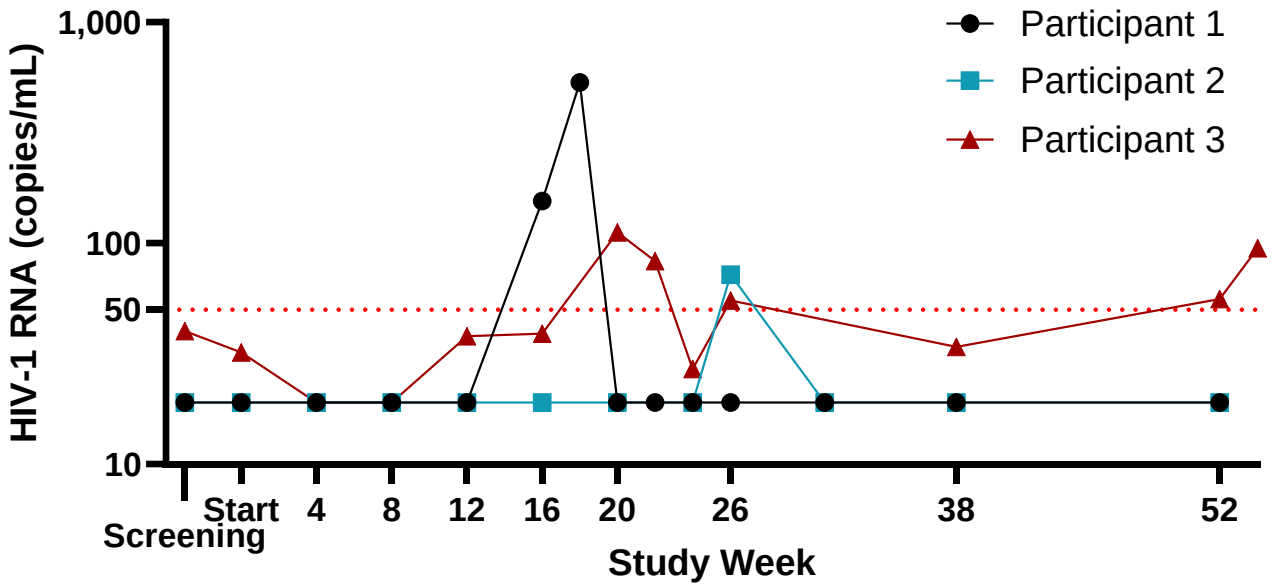
No virologic data in Week 26 window, n (%)	**0**	**1**[b] (6)

- Three participants from the low-dose ZAB group experienced low-level viremia (HIV-1 RNA ≥50 to <1000 copies/mL) during the 26 Week Snapshot Window[1,2]
- No participants in the high-dose ZAB group had virologic rebound 6 months after dosing[c]



[a]Two participants were excluded from the efficacy analysis (did not receive the complete study regimen [participant decision], n=1, protocol violation, n=1). [b]Participant withdrew from the study after Week 12 (participant decision), with HIV-1 RNA <50 copies/mL at last available visit. [c]For the ongoing Phase 2 trial (NCT05729568), a flat ZAB dose of 2550mg was selected based on the higher ZAB dosing group. **LEN,** lenacapavir; **PWH,** people with HIV-1; **SC,** subcutaneous; **TAB,** teropavimab; **VS,** virologically suppressed; **ZAB,** zinlirvimab.

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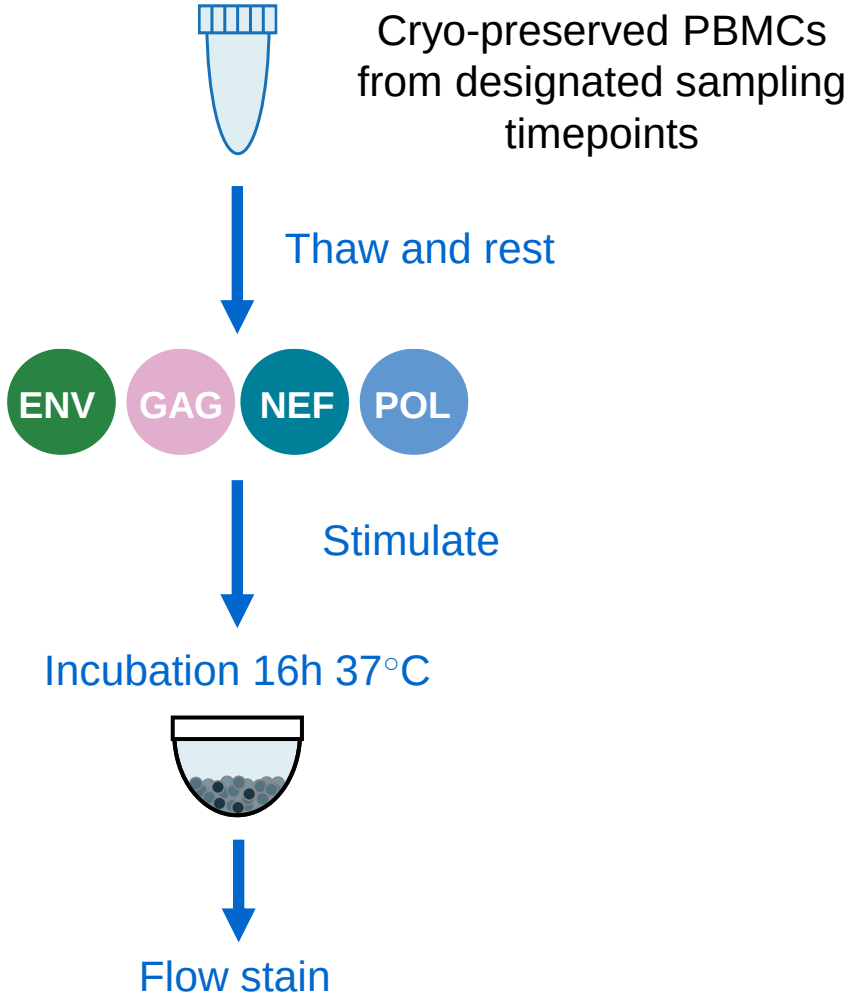
Phase 1b Exploratory Endpoint: HIV-specific T-cell responses

Exploratory Endpoint:

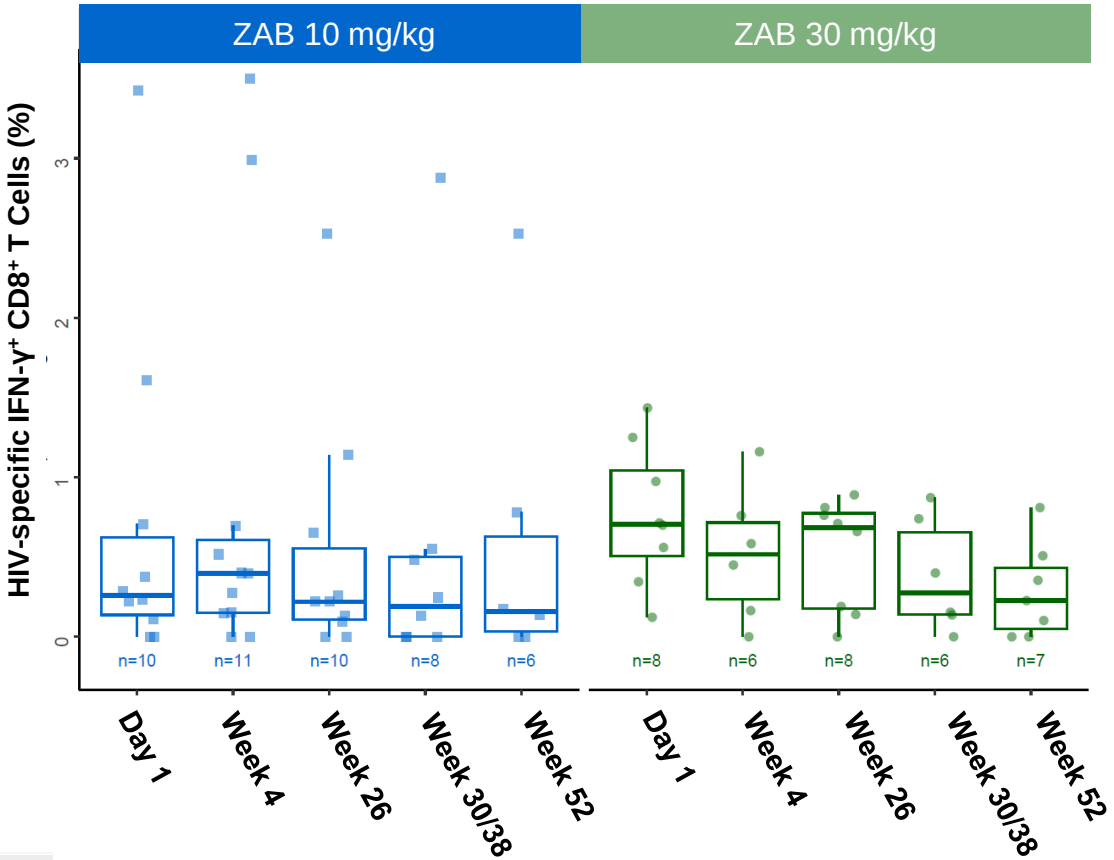
- Blood specimens were collected at baseline (Day 1) and Weeks 4 and 26 for both cohorts, as well as Weeks 30 or 38[a], and 52 for the primary cohort
- Cryo-preserved peripheral blood mononuclear cells (PBMCs) were isolated and stimulated *in vitro* with overlapping 15-mer peptide pools spanning Clade B HIV-1 consensus sequences[b], followed with intracellular cytokine staining and flow cytometry analysis to measure the frequency of HIV-specific T cells
- Only samples with 70% viability and $CD3^+$ T cell recovery ≥50,000 were analyzed and reported.
- Changes from baseline were assessed using Kruskal-Wallis tests and Wilcoxon Rank-sum test

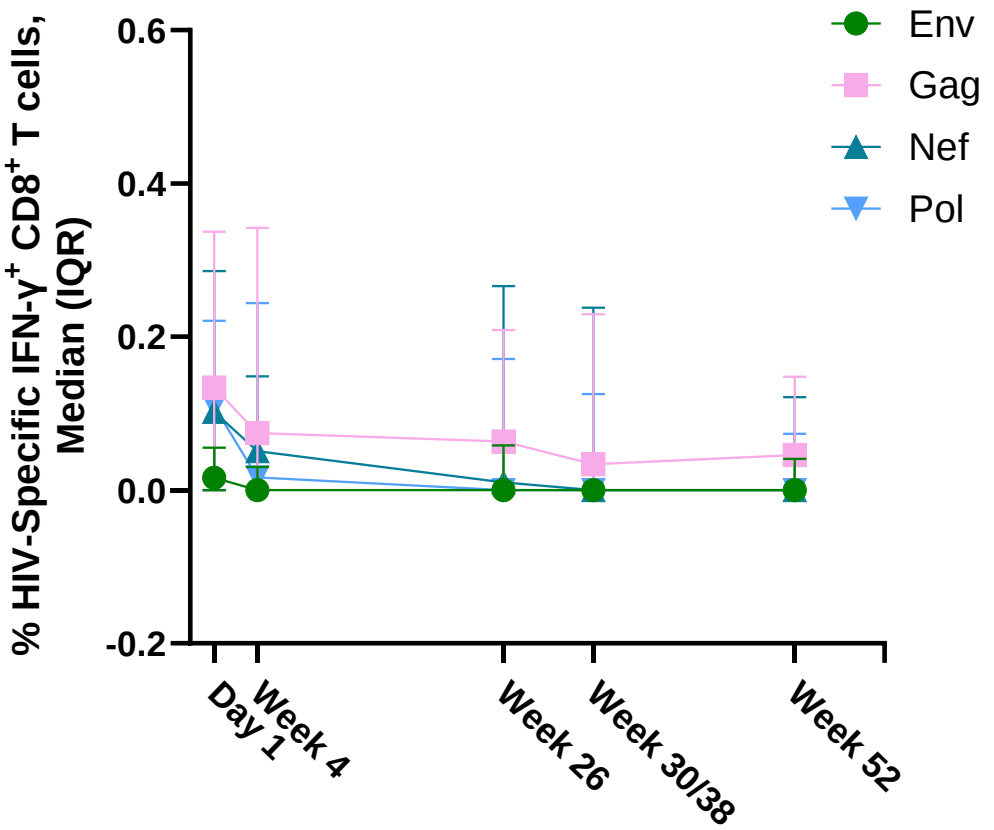


[a]Three subjects had samples collected at Week 30, while the (mutually exclusive) remainder were collected at Week 38. These timepoints are combined in the analysis for simplicity.
[b]The HIV-1 consensus sequence was identified by Jiani Li from Gilead Sciences which include updated LANL Clade B HIV-1 data base and Gilead Clade B HIV-1 data base in 2022; the peptide was clinical grade and synthesized at JPT.
PBMC, peripheral blood mononuclear cell

HIV-Specific IFN-γ+ CD8+ T Cells

- We observed no changes in HIV-specific IFN-γ+CD8+ T cells from baseline through Week 52
- No differences were observed when data were stratified by ZAB dose, peptide pool, or bNAb susceptibility



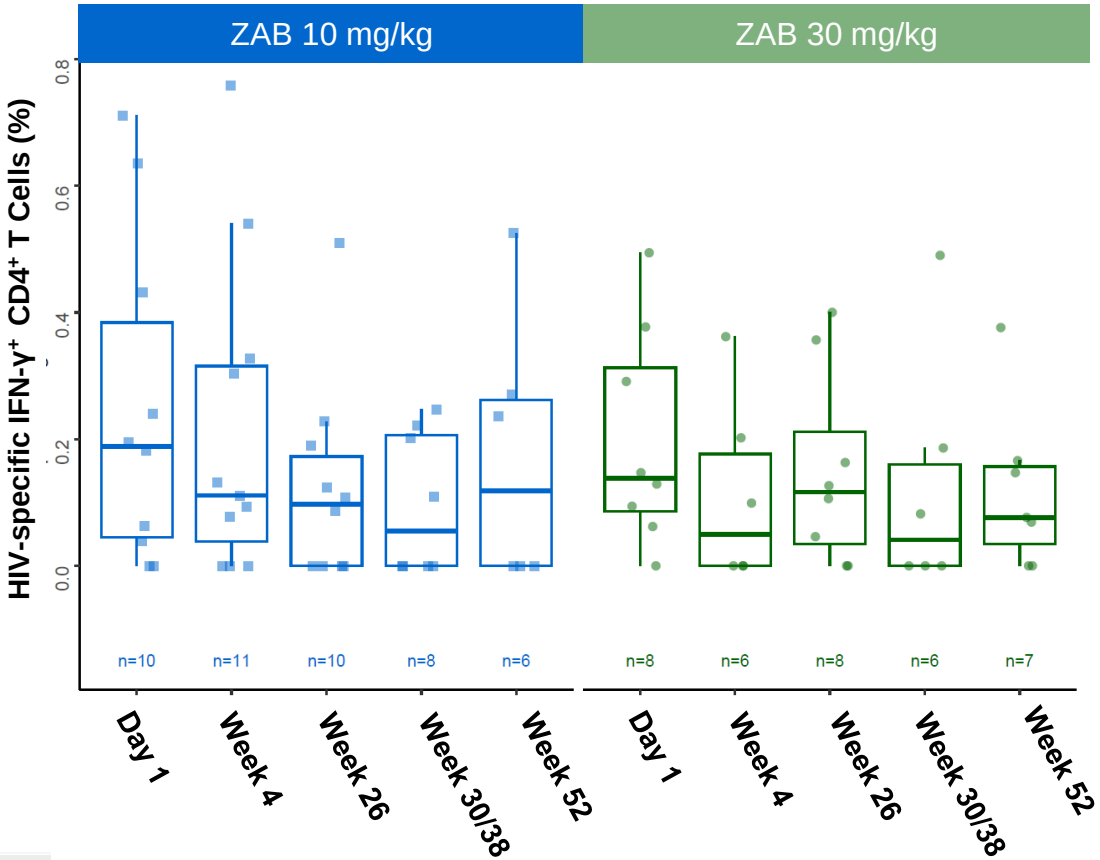


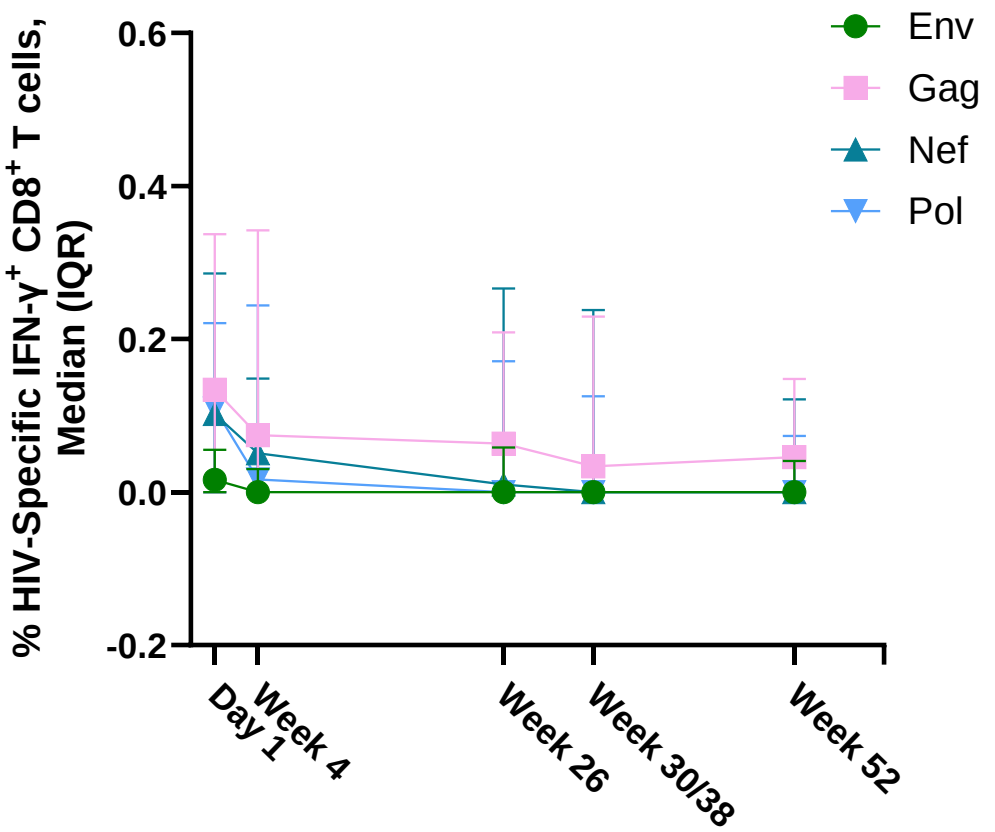
Data for the primary and pilot cohorts are combined; the pilot cohort was only followed to Week 26. The total % response is across all 4 peptide pools; all peptides were also examined individually and there was no significant difference.

bNAb, broadly neutralizing antibody; **IQR,** interquartile range; **TAB,** teropavimab; **ZAB,** zinlirvimab.

HIV-Specific IFN-γ⁺ CD4⁺ T Cells

- We observed no changes in HIV-specific IFN-γ⁺CD4⁺ T cells from baseline through Week 52
- No differences were observed when data were stratified by ZAB dose, peptide pool, or bNAb susceptibility





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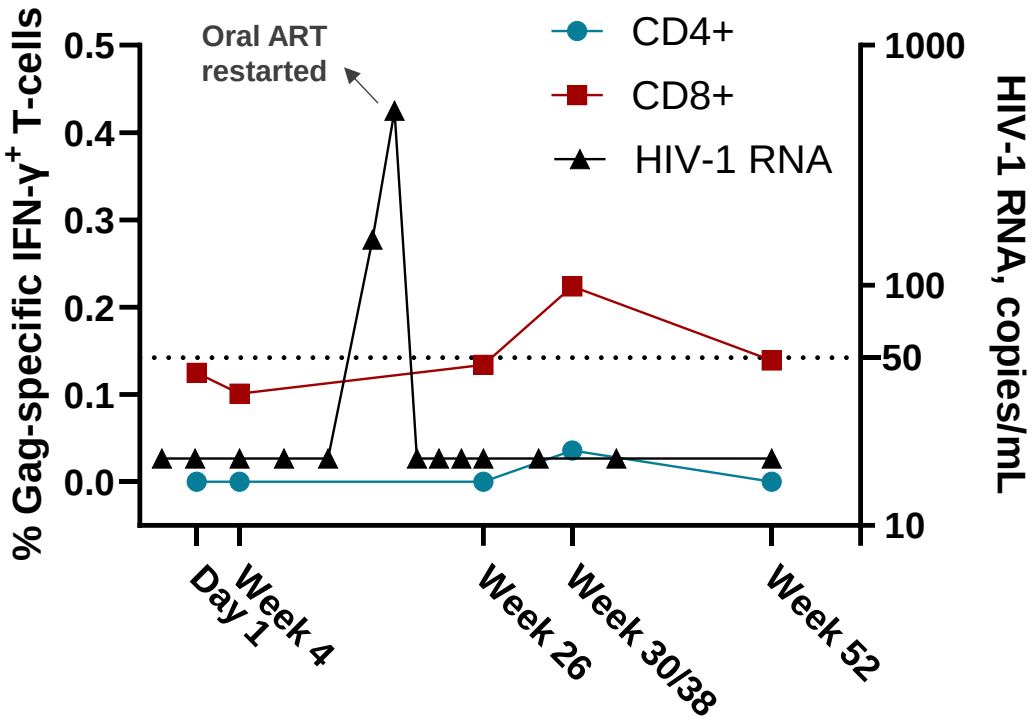
bNAb, broadly neutralizing antibody; **IQR,** interquartile range; **TAB,** teropavimab; **ZAB,** zinlirvimab.

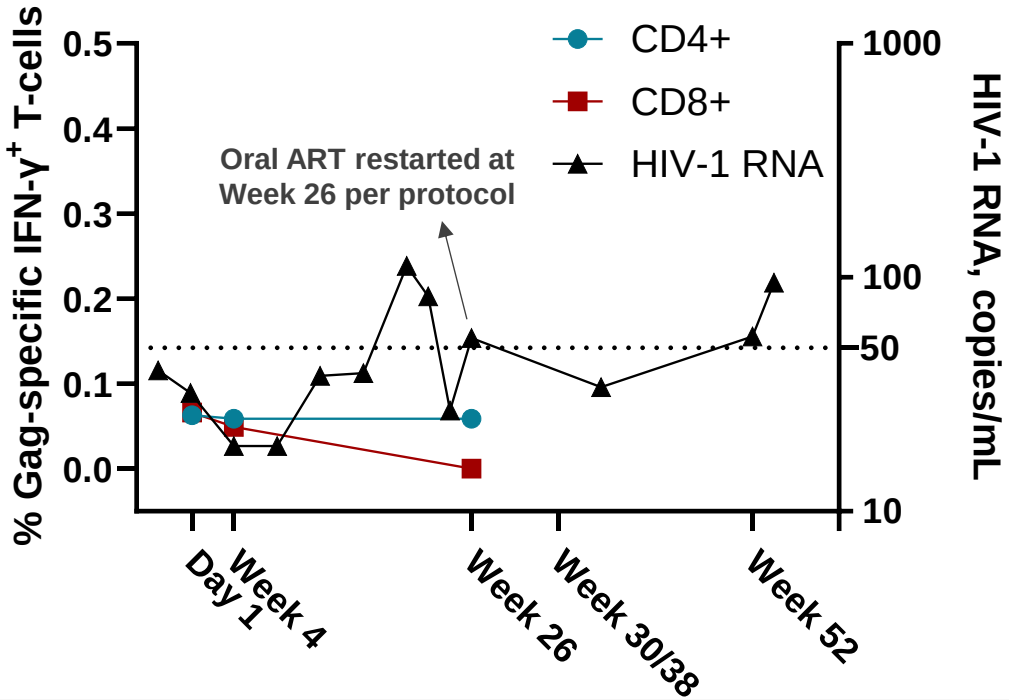
No Changes in HIV-specific IFN-γ+ T Cells in Participants With Transient Low-Level Plasma Viremia

- No durable changes in HIV-specific IFN-γ+CD8+ or IFN-γ+CD4+ T-cells were observed in two[a] participants who had transient low-level plasma viremia (50–1000 copies/mL) during study follow-up

Participant with viral rebound at Week 16



Participant with low-level detectable virus at various points through Week 26



[a]One participant had HIV-1 RNA 50–100 copies/mL at Week 26 and was missing CD4 and CD8 data at that timepoint, data not shown.
Dotted line indicates HIV-1 RNA 50 copies/mL.
ART, antiretroviral therapy; **VL,** viral load.

Conclusions

- We observed no increase from baseline in HIV-specific IFN-γ^{+}CD8^{+} or IFN-γ^{+}CD4^{+} T cell responses following LEN, TAB, and ZAB treatment in VS PWH
  - No increase was observed in two participants with transient low-level plasma viremia
- This data suggests that robust virologic suppression by LEN, TAB, and ZAB did not allow increased viral antigen expression, which in turn may have limited the expansion of HIV-specific T cells
- In contrast to studies that have dosed these bNAbs during viremia or observed virologic rebound during an analytic treatment interruption, when oral suppressive therapy was replaced with this novel combination, no evidence was observed for increased antigen production to a level needed to stimulate measurable T cell responses
- Our finding has implications for HIV-1 remission and cure studies, suggesting greater antigen exposure is required to elicit increases in HIV-specific T cell responses after bNAb administration

bNAb, broadly neutralizing antibody; **LEN,** lenacapavir; **PWH,** people with HIV-1; **TAB,** teropavimab; **VS,** virologically supressed; **ZAB,** zinlirvimab.

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