Lenacapavir Plus bNAbs for People with HIV and Susceptibility to Either Teropavimab or Zinlirvimab

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Disclosures

- **Joseph J. Eron, MD:** Gilead Sciences (grants/contract payments, consulting fees),ViiV (grants/contract payments, consulting fees), Janssen Pharmaceuticals (grants, contract payments), Merck (consulting fees).
- **Paul P. Cook, MD:** Lilly (grants/contract payments), Seres Therapeutics (grants/contract payments), National Institutes of Health (grants/contract payments), Merck (grants/contract payments), ViiV Healthcare (grants/contract payments), Janssen Pharmaceuticals (grants/contract payments), and Gilead Sciences (grants/contract payments), Westat (data safety monitoring or advisory board participation).
- **Marina Caskey:** Gilead Sciences (advisory board participation)
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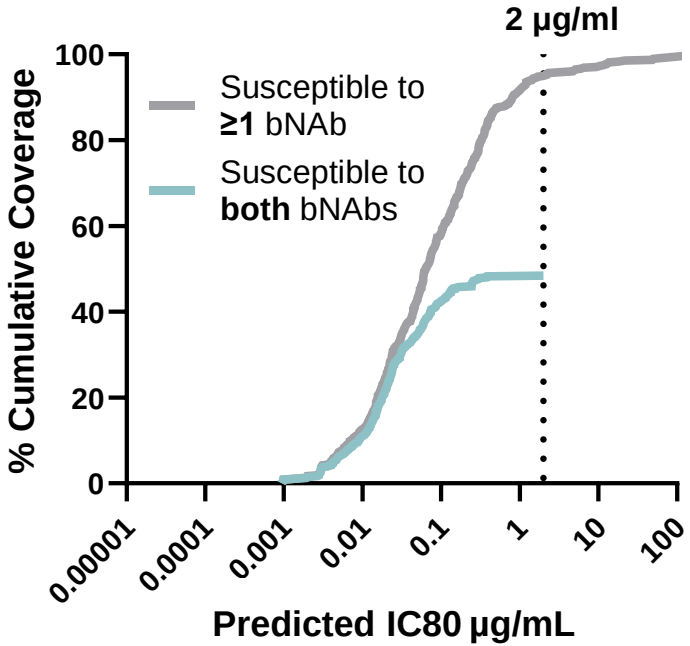
- **Megha L. Mehrotra, PhD**, **MPH**, **Hailin Huang, PhD, Laurie VanderVeen, PhD,** and **Sean E. Collins, MD, MS** are all employees and shareholders of Gilead.

Background

- Teropavimab (TAB) and zinlirvimab (ZAB) are broadly neutralizing antibodies (bNAbs) against the CD4-binding site of gp120 and a non-overlapping epitope on the V3 glycan of HIV-1 Env, respectively[1]
- Approximately 50% of clade B viruses are highly susceptible to both TAB and ZAB with a 90% inhibitory concentration (IC90) ≤2 µg/mL, while over 90% are highly susceptible to either TAB or ZAB[2]
- TAB and ZAB have extended half-lives that allow for dosing every 6 months[1]
- Lenacapavir (LEN) is a first-in-class, small molecule capsid inhibitor with high potency and a long half-life that can be administered subcutaneously every 6 months and is indicated in heavily treatment-experienced people with HIV-1 (PWH)[3]

bNAb Susceptibility Breadth[4]

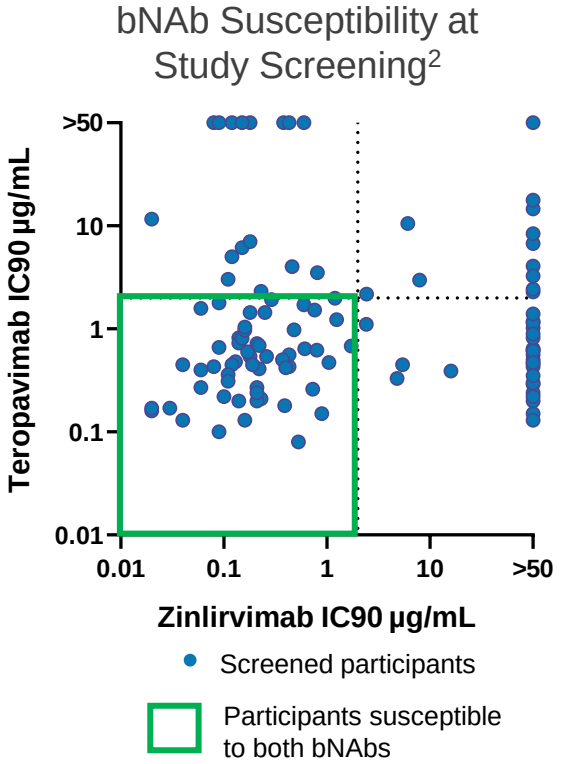


1. Gautam R, et al. *Nat Med* 2018; 24(5): 610-6. 2. Selzer L, et al. Presented at CROI 2023. Poster 580. 3. Sunlenca® Prescribing Information, available at https://www.gilead.com/-/media/files/pdfs/medicines/hiv/sunlenca/sunlenca_pi.pdf (accessed February 2024). 4. Estimated coverage given predicted IC90 closely resembles coverage given IC80 shown here. Data from CATNAP CombiNAber (Yoon H, et al. *Nucleic Acid Res*. 2015;43:W213-9, Wagh K, et al. *PLoS Pathog*. 2016 Mar30;12(3)) using 479 Clade B viruses.

Background

- In a Phase 1b study (NCT04811040), a single dose of the long-acting combination of LEN, TAB, and ZAB maintained virologic suppression (VS) for 6 months in 18/20 participants with HIV-1 highly susceptible to both bNAbs[1]

- The optimal threshold for required bNAb sensitivity to achieve efficacy in the context of HIV-1 treatment has not been established



bNAbs, broadly neutralizing antibodies; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

1. Eron J, et al. *Lancet HIV* 2024; Advanced online publication. https://doi.org/10.1016/S2352-3018(23)00293-X. 2. Selzer L, et al. Presented at CROI 2023. Poster 580.

Background and Objective

- In a Phase 1b study (NCT04811040), a single dose of the long-acting combination of LEN, TAB, and ZAB maintained virologic suppression (VS) for 6 months in 18/20 participants with HIV-1 highly susceptible to both bNAbs[1]

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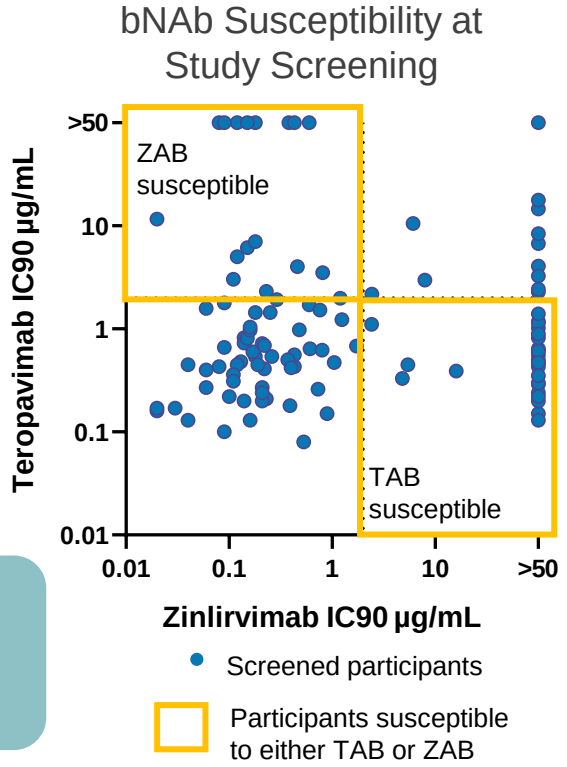
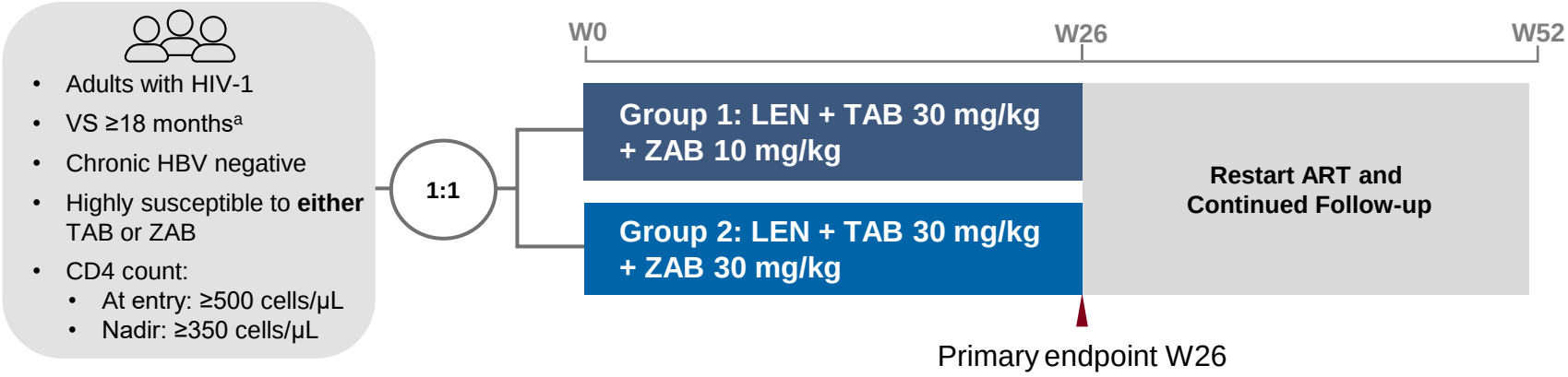


Objective: To evaluate safety and efficacy of LEN + TAB + ZAB in virologically suppressed participants highly susceptible to **either** TAB or ZAB, **but not both** bNAbs

bNAbs, broadly neutralizing antibodies; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

1. Eron J, et al. *Lancet HIV* 2024; Advanced online publication. https://doi.org/10.1016/S2352-3018(23)00293-X.

Study Design



Participants

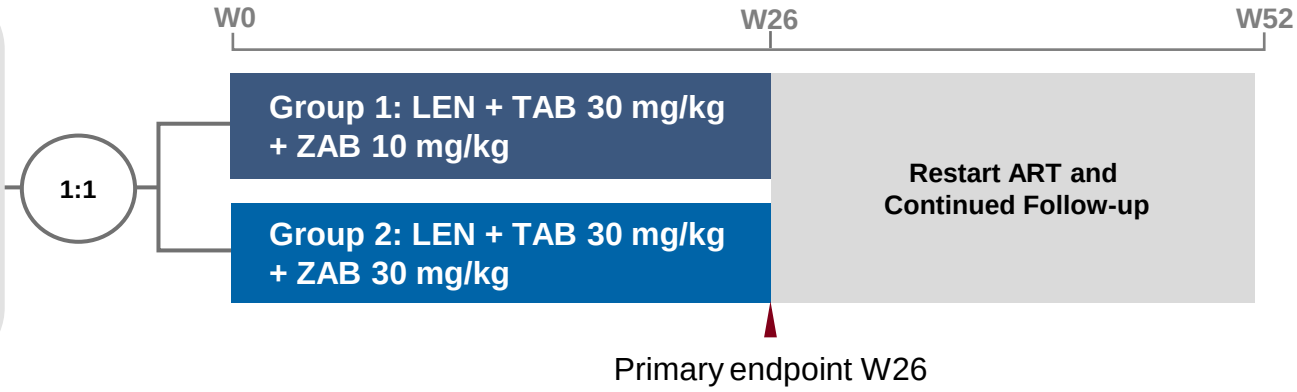
- After primary cohort sensitive to both bNAbs completed study, a cohort of participants with susceptibility to **either** TAB **or** ZAB was enrolled
- bNAb susceptibility defined as IC90 ≤2 µg/mL by PhenoSense mAb Assay (Monogram Biosciences)
- Randomization to treatment groups was stratified by bNAb susceptibility (TAB or ZAB)

[a]Previous virologic failure was allowed if participants were VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **IC90**, 90% inhibitory concentration; **LEN**, lenacapavir; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Study Design

- Adults with HIV-1
- VS ≥18 months[a]
- Chronic HBV negative
- Highly susceptible to **either** TAB or ZAB[b]
- CD4 count:
  - At entry: ≥500 cells/µL
  - Nadir: ≥350 cells/µL



	Day 1	Day 2
LEN oral 600 mg		
LEN SC 927 mg		-
TAB IV 30 mg/kg		-
ZAB IV 10 mg/kg or 30 mg/kg		-

Primary Endpoint:

- Safety and tolerability at Week 26

Secondary Endpoints:

- Efficacy: HIV-1 RNA <50 and ≥50 c/mL at Week 26 (FDA Snapshot)
- PK of LEN, TAB, and ZAB

[a]Previous virologic failure was allowed if participants were VS (HIV-1 RNA ≤50 copies/mL) for ≥18 months prior to screening; [b]bNAb susceptibility defined as an IC_{90} ≤2 µg/mL by PhenoSense mAb Assay (Monogram Biosciences). **ART,** antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **IV**, intravenous; **LEN**, lenacapavir; **SC**, subcutaneous; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Participant Disposition and Susceptibility

Randomized (N=11)

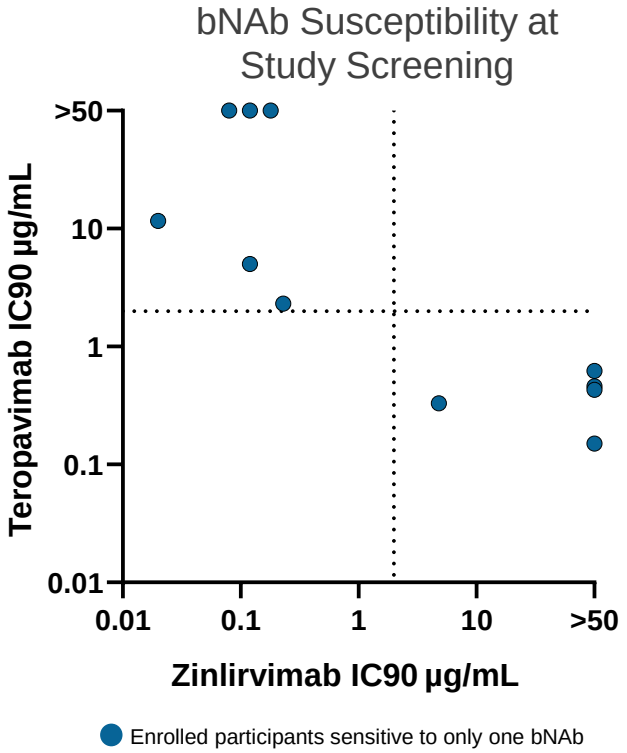
Received LEN + TAB + ZAB 10 mg/kg (n=5)
- Susceptible to TAB (n=2)
- Susceptible to ZAB (n=3)

Received LEN + TAB + ZAB 30 mg/kg (n=6)
- Susceptible to TAB (n=3)
- Susceptible to ZAB (n=3)

Prematurely discontinued study drug (n=1)
- Protocol violation (chronic HBV) restarted ART
- Included in safety analysis
- VS at discontinuation

Completed treatment regimen W26 (n=4)[a]

Completed treatment regimen W26 (n=6)



[a]1 and 3 participants were susceptible to TAB and ZAB, respectively

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **HBV**, Hepatitis B virus; **LEN**, lenacapavir; **TAB**, teropavimab; **VS**, virologic suppression; **W**, Week; **ZAB**, zinlirvimab.

Baseline Characteristics

	LEN + TAB + ZAB 10 mg/kg (n=5)	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=11)
Age (years), median (range)	49 (28–63)	51 (29–57)	49 (28–63)
Female sex at birth, n	2	1	3
Race, n			
Black	2	2	4
White	3	3	6
Other	0	1	1
Hispanic or Latino ethnicity, n	2	1	3
Weight (kg), median (range)	86.4 (67.6–104.5)	86.3 (84.2–117.6)	86.4 (67.6–117.6)
CD4 cell count (per mL), median (range)	861 (449–1916)	942 (673–1196)	916 (449–1916)
Duration of baseline ART (years), median (range)	2.5 (1.0–5.5)	4.9 (3.1–6.4)	3.7 (1.0–6.4)
Time since HIV-1 diagnosis (years), median (range)[a]	16 (5–25)	13.5 (3–24)	16 (3–25)

[a]These data are self-reported by the participant

ART, antiretroviral therapy; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Safety and Tolerability

Event, n	LEN + TAB + ZAB 10 mg/kg (n=5)	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=11)
Any adverse event (AE)	3	5	8
Any-grade AEs occurring in ≥2 participants			
Injection site induration	0	3	3
COVID-19	1	1	2
Injection site erythema	0	2	2
Injection site pain	0	2	2
Injection site nodule[a]	1	1	2
Injection site pruritis	0	2	2
SAE[b]	1	0	0
AEs leading to discontinuation	0	0	0

- 5 participants had treatment related AEs – all were Grade 1 injection site reactions related to LEN administration
- No infusion-related reactions occurred with bNAb administration
- There were no Grade ≥3 treatment-emergent laboratory abnormalities

[a]All nodules resolved by Week 26; [b]Soft tissue infection (Grade 3), not related to study drug or procedure.
LEN, lenacapavir; **SAE**, serious adverse event; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Viral Suppression at Week 26

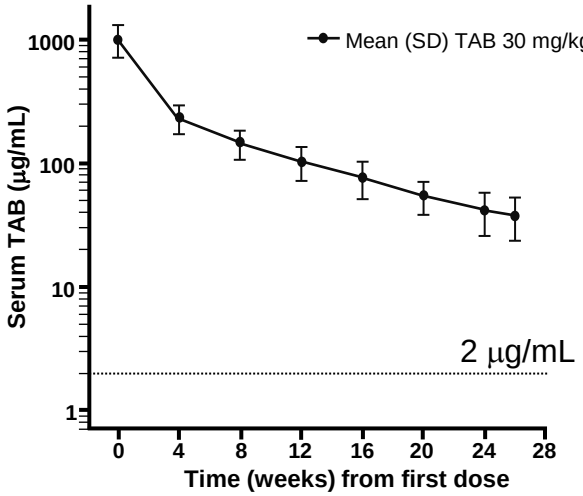
	LEN + TAB + ZAB 10 mg/kg (n=4)[a]	LEN + TAB + ZAB 30 mg/kg (n=6)	Total (N=10)
HIV-1 RNA ≥50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**0** (0; [0, 46])	**2** (20; [3, 56])
HIV-1 RNA <50 copies/mL, **n** (%; [95% CI])	**2** (50; [7, 93])	**6** (100; [54, 100])	**8** (80; [44, 98])

- Eight out of 10 participants remained virologically suppressed with HIV-1 RNA <50 copies/mL 6 months after dosing
- All participants in the higher dose group (n=6; ZAB 30 mg/kg) remained suppressed at Week 26

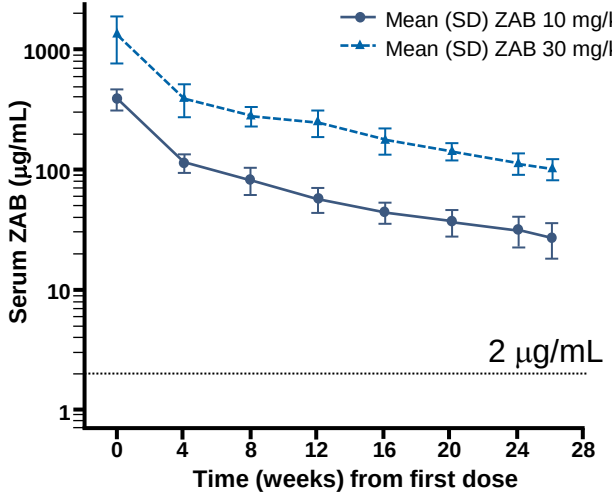
[a]One participant restarted ART prior to Week 26 due to a protocol violation (chronic HBV) and is excluded from the efficacy analysis.
HBV, hepatitis B; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

Mean (SD) Drug Concentrations Over Time

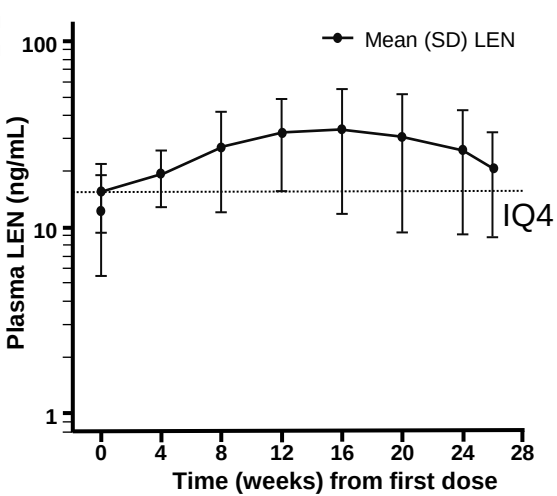
Mean (SD) TAB Concentrations



Mean (SD) ZAB Concentrations



Mean (SD) LEN Concentrations



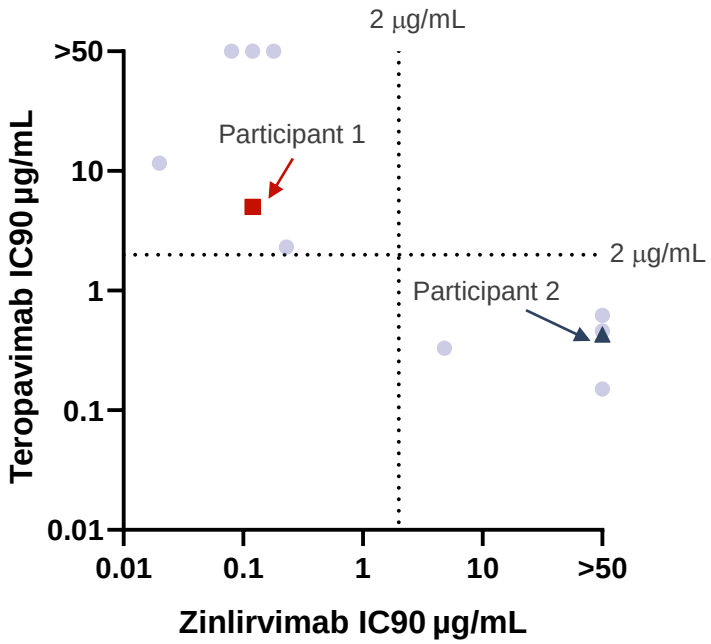
- TAB and ZAB exhibited average half-lives of approximately 70 and 82 days, respectively
- LEN concentrations were consistent with published treatment data[1]
- Treatment-emergent anti-drug antibodies (ADA) against ZAB occurred in one participant at Week 52. No participant had treatment-emergent ADA against TAB

IQ4, 4 x inhibitory quotient = 15.5 ng/mL**; LEN**, lenacapavir; **SD**, standard deviation; **TAB**, teropavimab; **ZAB**, zinlirvimab.

1. Eron J, et al. *Lancet HIV* 2024; Advanced online publication

Participants with Virologic Rebound

bNAb Susceptibility at Study Screening



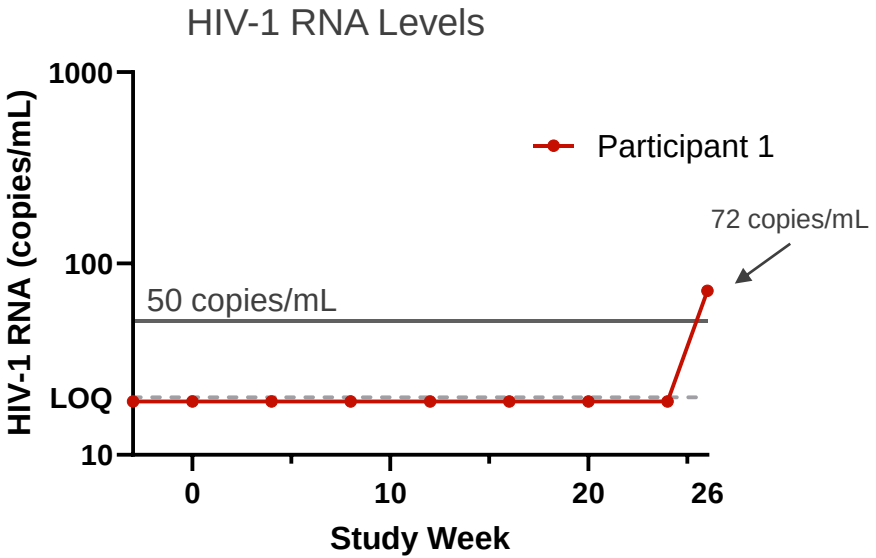
Participant Characteristics at Baseline

	Participant #1	Participant #2
Age, years	36	60
Sex	Male	Female
Weight, kg	86.4	89.7
CD4 count, cells/µL	449	1916
TAB IC90, µg/mL	5.02	**0.43**
ZAB IC90, µg/mL	**0.12**	>50

- LEN, TAB, and ZAB PK was within the range observed for other participants in Group 1

[a]Resistance was conducted using genotypic and phenotypic analyses of HIV-1 envelope and capsid.
LEN, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

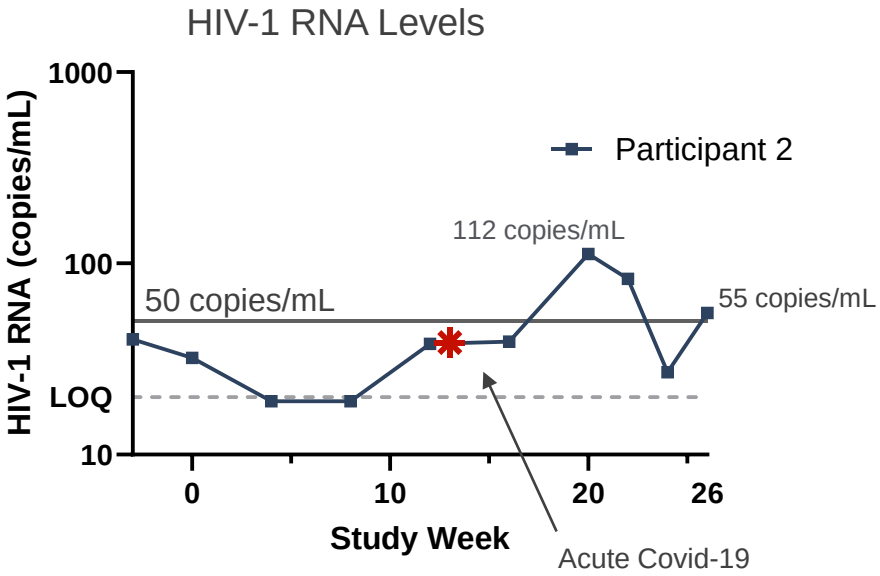
Participants with Virologic Rebound



- All participants restarted baseline ART at Week 26, per protocol
- Participant 1 restarted baseline ART at Week 26, prior to confirmatory HIV-1 RNA testing

ART, antiretroviral therapy; **LOQ**, limit of quantification

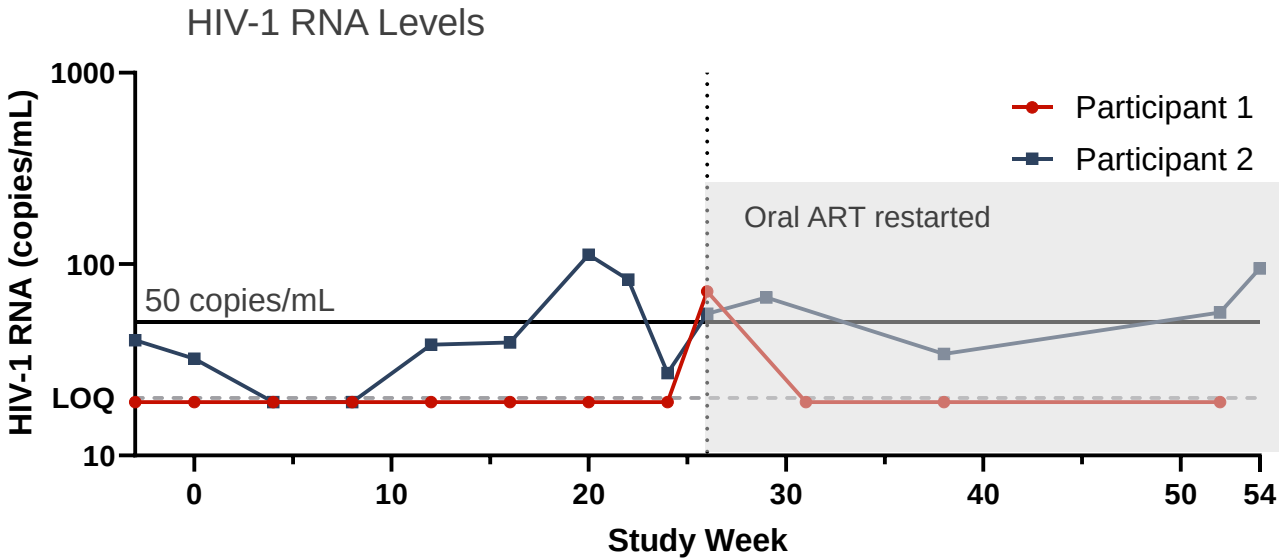
Participants with Virologic Rebound



- Participant 2 had virologic rebound at Week 20 after acute COVID-19 at Week 13. They continued on study treatment without additional intervention and restarted ART at Week 26

ART, antiretroviral therapy; **LOQ**, limit of quantification

Participants with Virologic Rebound



- Participant 1 resuppressed by the following visit after restarting oral ART
- Participant 2 continued to have low-level, detectable HIV-1 RNA after restarting oral ART
- Neither participant had detectable treatment-emergent resistance to study drugs

ART, antiretroviral therapy; **LOQ**, limit of quantification

Conclusions

- In participants highly susceptible to only one bNAb, the long-acting combination of LEN + TAB + ZAB was safe and well-tolerated
  - The most common AEs were Grade 1 injection site reactions related to LEN. There were no other treatment-related AEs
- One dose of the long-acting combination of LEN + TAB + ZAB maintained virologic suppression for 6 months in 8 out of 10 participants with HIV-1 highly susceptible to either TAB or ZAB, but not both
  - Two participants in the low dose ZAB (10 mg/kg) group had HIV-1 RNA between 50 – 100 copies/mL in the Week 26 snapshot window; no treatment-emergent resistance was detected
  - Other than a lower ZAB dose, no risk factors for virologic rebound were observed in participants with virologic rebound
  - All 6 participants in the higher dose group remained suppressed for 6 months after dosing
- More inclusive bNAb susceptibility criteria may be appropriate for treatment studies with LEN + TAB + ZAB when higher bNAb concentrations are maintained

AE, adverse event; **bNAb**, broadly neutralizing antibody; **LEN**, lenacapavir; **TAB**, teropavimab; **ZAB**, zinlirvimab.

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