CROI
Conference on Retroviruses and Opportunistic Infections

Presentation 105

Evaluation of 2 Broadly Neutralizing Antibodies Plus Vesatolimod in Early-Treated South African Women With HIV-1 During Analytical Treatment Interruption

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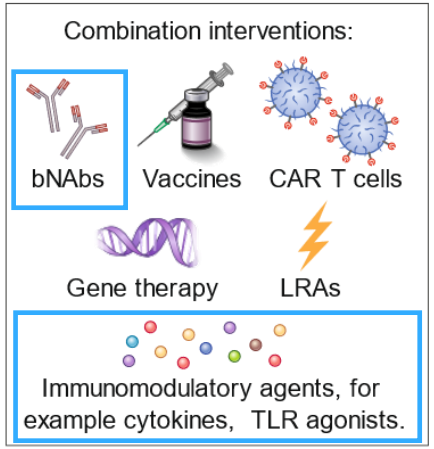
Disclosures

- Thumbi Ndung’u has received research grant funding and honoraria from Gilead Sciences, Inc.

Considerations for HIV Cure or Remission Trials

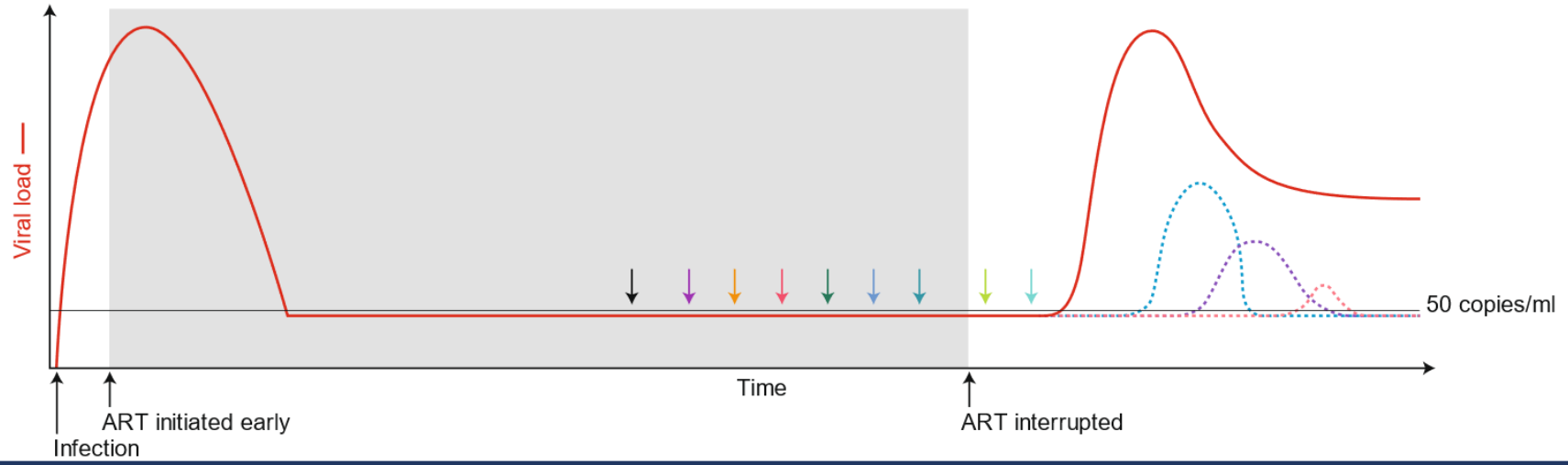
Impact of early ART:

- Reduced inflammation and immune activation
- Limited viral diversification
- Preserved functional immune responses
- Lower reservoir burden and complexity



Monitoring during ATI:

- Viral load (HIV RNA) every 2 weeks
- Immune responses, reservoir size and composition
- Clinical findings

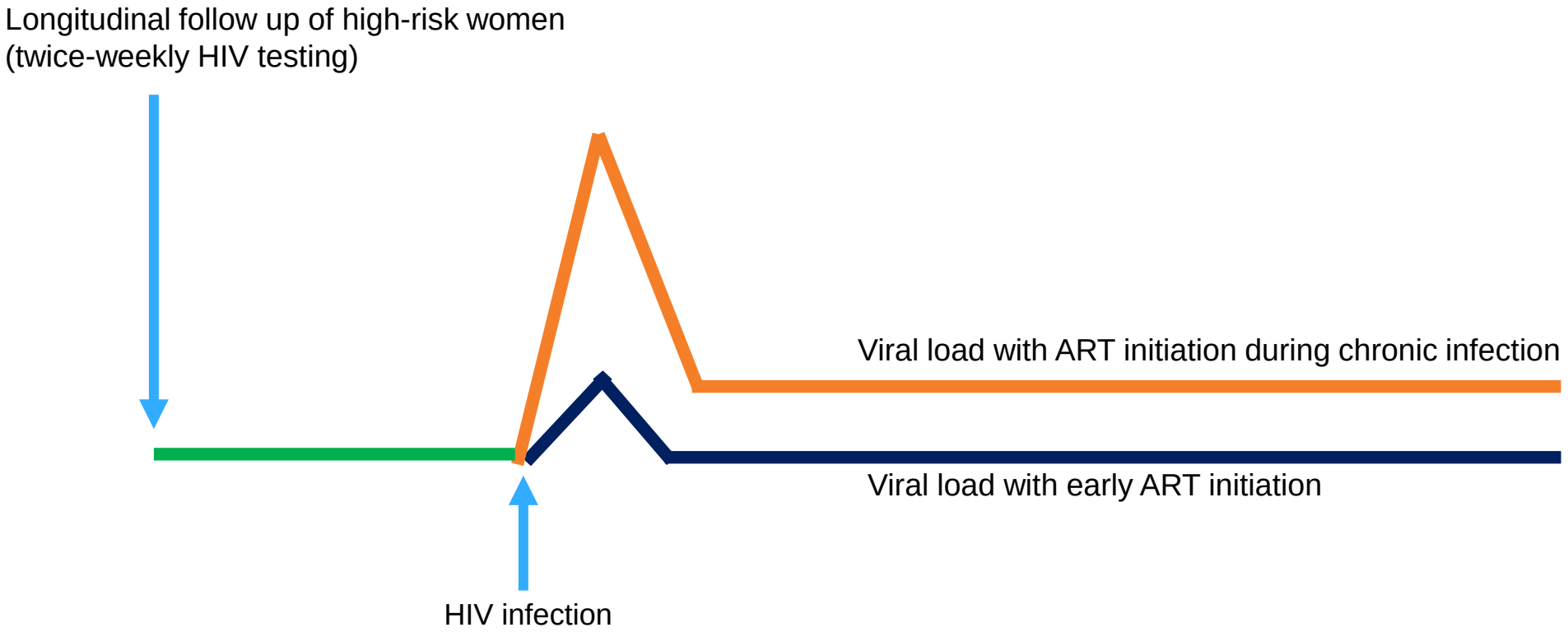


<u>Goal:</u> Significantly delay viral rebound or lower the viral set point

ART, antiretroviral therapy**; ATI**, analytical treatment interruption; **bNAb,** broadly neutralizing antibody**; CAR T**, chimeric antigen receptor T**; LRA**, latency-reversing agent; **TLR,** Toll-like receptor.
Deeks SG, et al. *Nat Med*. 2021;27:2085-98. Figure reproduced from Deeks et al 2021 with permission.

GS-US-382-5445: The First HIV Cure Trial in Africa Enrolled Hyperacutely Treated South African Women From the FRESH Cohort

FRESH cohort designed to detect hyperacute HIV infection



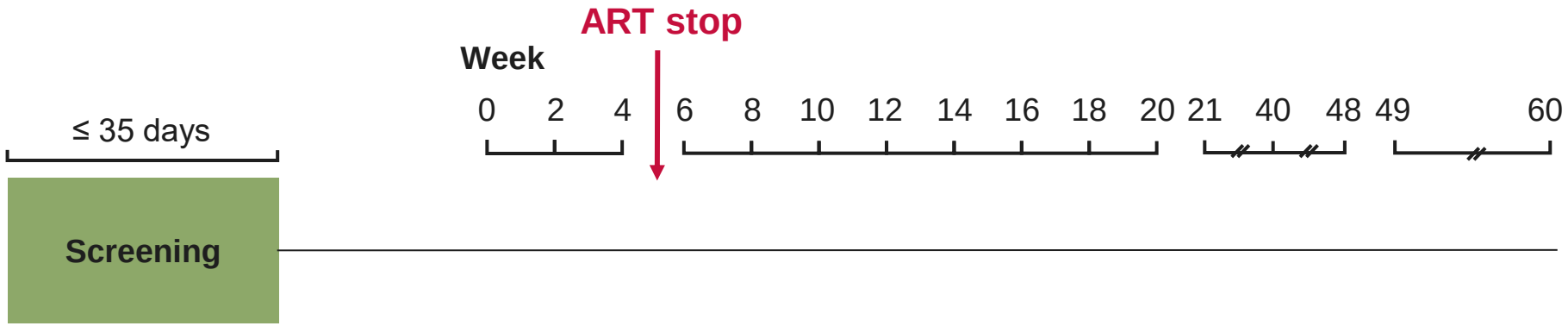
Participants in the trial began treatment at first detection of HIV

Collaborators: UKZN, Ragon Institute, NIH, CAPRISA. **Principal investigators:** Thumbi Ndung'u; Krista Dong.
ART, antiretroviral therapy**; FRESH**, Females Rising through Education, Support, and Health.
1. Dong KL, et al. *Lancet HIV*. 2018;5:e35-e44. 2. Ndung'u T, et al. *Sci Immunol*. 2018;3:eaau2798.

Single-Arm, Open-Label, Phase 2a Study

Inclusion criteria

- Females from FRESH cohort
- Virally suppressed on ART > 12 months
- Sensitive to at least 1 of the 2 bNAbs
- CD4+ T-cell count ≥ 500 cells/μL



<u>Objective:</u> Evaluate the safety, tolerability, and efficacy of VRC07-523LS + CAP256V2LS (bNAbs) and vesatolimod (VES; TLR7 agonist) during ATI

Results from a concurrent sociobehavioral study exploring site staff and participant experiences in the trial are expected in 2025. (PIs: Krista Dong and Karine Dubé)

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; **PI**, principal investigator; **TLR7**, Toll-like receptor 7.
NCT05281510.

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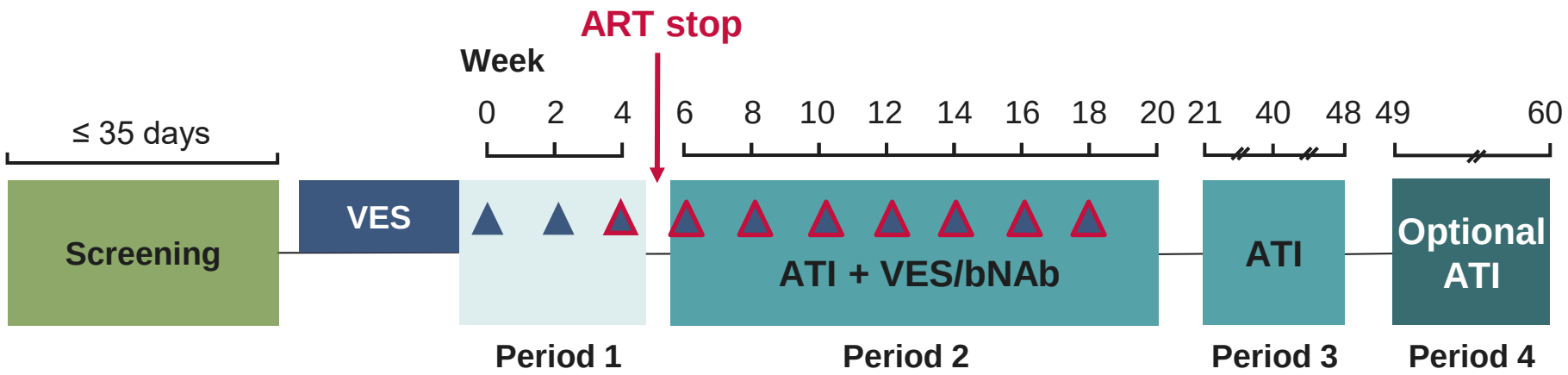

VES (oral) Possible VES dose escalation[a] from 6 to 8 mg

[a]If VES is well tolerated at 6 mg, participants can be dosed at 8 mg from the third dose onward with close monitoring.

ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; **VES**, vesatolimod.
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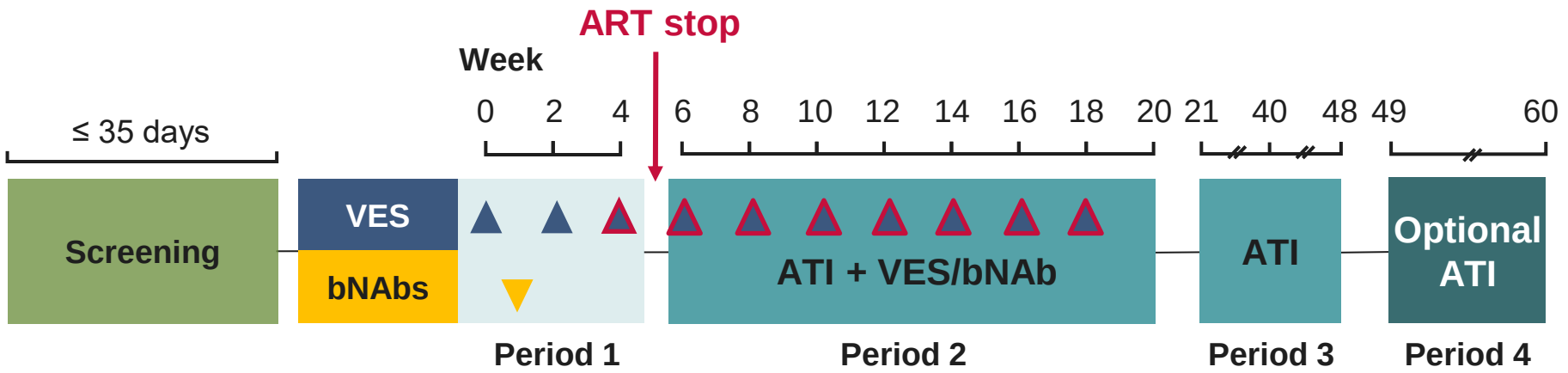

▲ VES (oral) ▲ Possible VES dose escalation[a] from 6 to 8 mg ▼ bNAbs: VRC07-523LS + CAP256V2LS (NIH) (20 mg/kg IV each bNAb)

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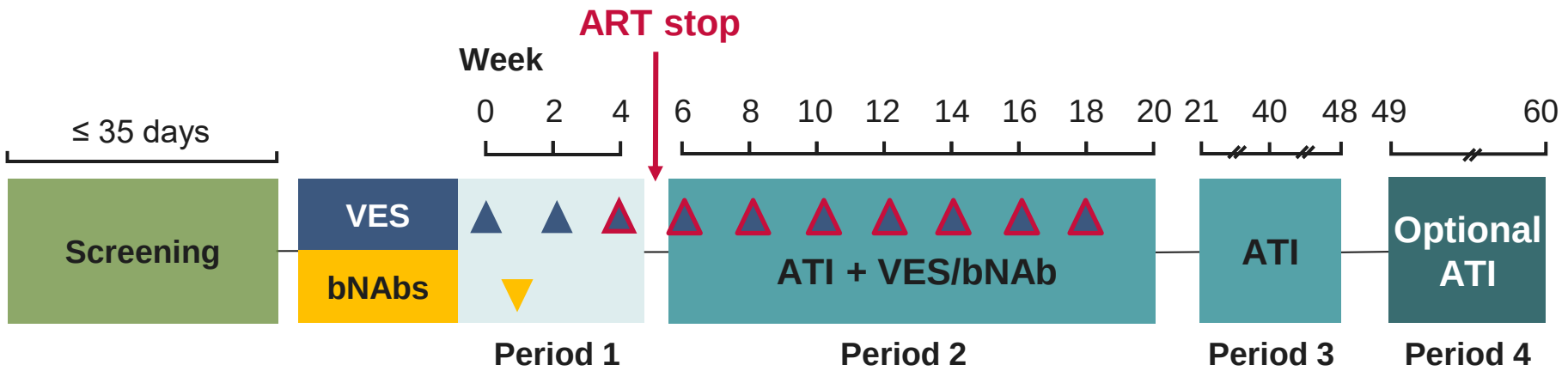

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Primary end point

Safety

- Proportion of participants with treatment-emergent AEs

Secondary end points

Efficacy

- Time to viral rebound (confirmed ≥ 50 copies/mL and ≥ 200 copies/mL)
- Viral load at end of ATI
- Time to ART resumption after ATI
- Proportion of participants who restarted ART at 48 weeks

Pharmacokinetics

- Serum PK and ADA for bNAbs

[a]If VES is well tolerated at 6 mg, participants can be dosed at 8 mg from the third dose onward with close monitoring.
ADA, antidrug antibodies**; AE,** adverse event; **ART**, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; **PK**, pharmacokinetics; **VES**, vesatolimod.
NCT05281510.

Single-Arm, Open-Label, Phase 2a Study

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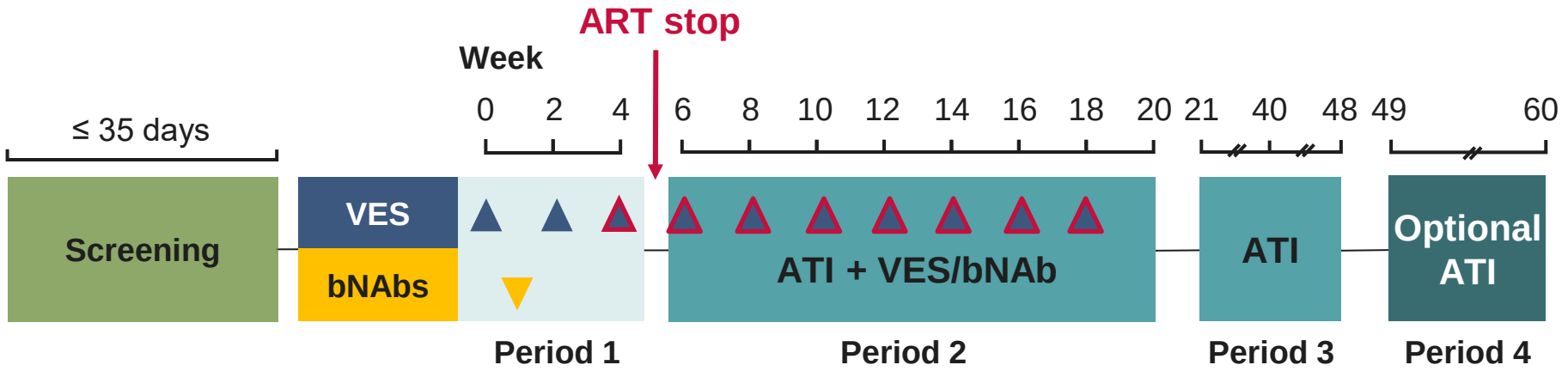


▲ VES (oral) ▲ Possible VES dose escalation[a] from 6 to 8 mg ▼ bNAbs: VRC07-523LS + CAP256V2LS (NIH) (20 mg/kg IV each bNAb)

ART restart criteria

- Plasma HIV-1 RNA measurements ≥ 1000 copies/mL for **8 consecutive weeks** without a drop of 0.3 $\log_{10}$ from previous week
- Confirmed plasma HIV-1 RNA > 100,000 copies/mL
- Confirmed CD4+ T-cell count < 350 cells/μL
- Pregnancy, participant request, or investigator/sponsor discretion due to other clinical criteria

During ATI, viral load was monitored every 2 weeks until initial rebound, then every week

[a]If VES is well tolerated at 6 mg, participants can be dosed at 8 mg from the third dose onward with close monitoring.

ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; **VES**, vesatolimod.
NCT05281510.

Baseline Characteristics

Characteristic	Enrolled Participants (N = 20)
CD4+ count at screening, cells/μL, median (range)	880 (520-1472)
Time to ART initiation, median (range), days	1 (0-3)
Time on ART before enrollment, median (range), years	6.9 (1.7-8.5)
Peak HIV-1 RNA before ART start, copies/mL, n (%)	
≥ 50 to < 2000	9 (45)
≥ 2000 to ≤ 5000	4 (20)
> 5000	7 (35)
Fiebig stage at ART initiation, n (%)	
I (HIV RNA+)	17 (85)
II (HIV RNA+ and p24+)	0
III (Ab+/WB-)	3 (15)
IV (Ab+/WB+/p31-)	0
Baseline bNAb susceptibility, n (%)	
Susceptible to both bNAbs	11 (55)
Susceptible to VRC07-523LS only	7 (35)
Susceptible to CAP256V2LS only	2 (10)

Minimal HIV exposure before starting ART and median time on treatment of almost 7 years

Ab, antibody**; ART**, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **WB**, western blot.

Safety Summary

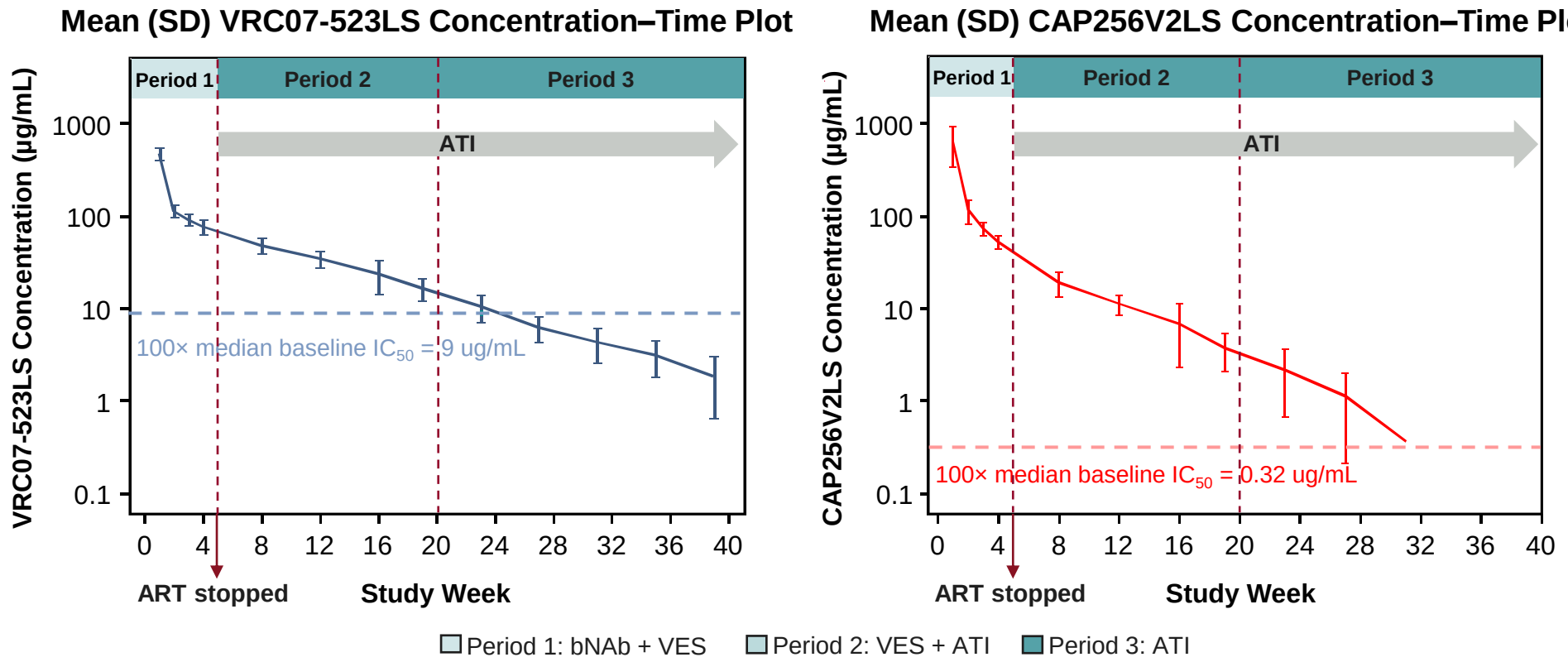
No. (%) of Participants	VES + VRC + CAP (N = 20)
TEAE	19 (95)
Study drug–related	18 (90)
TEAE grade 2 or higher	14 (70)
Study drug–related	8 (40)
TEAE grade 3 or higher	4 (20)
Study drug–related	2 (10)
SAE	2 (10)
Study drug–related	0
TEAE leading to premature discontinuation of study drug	1 (5)
Grade 1 cytokine release syndrome considered related to VES	1 (5)
TEAE leading to death	0

Overall, the study regimen was well tolerated;
Infusion related reactions were frequent (n=18, 90%), but mostly mild in severity

CAP, CAP256V2LS; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event; **VES**, vesatolimod; **VRC**, VRC07-523LS.

bNAb Concentrations

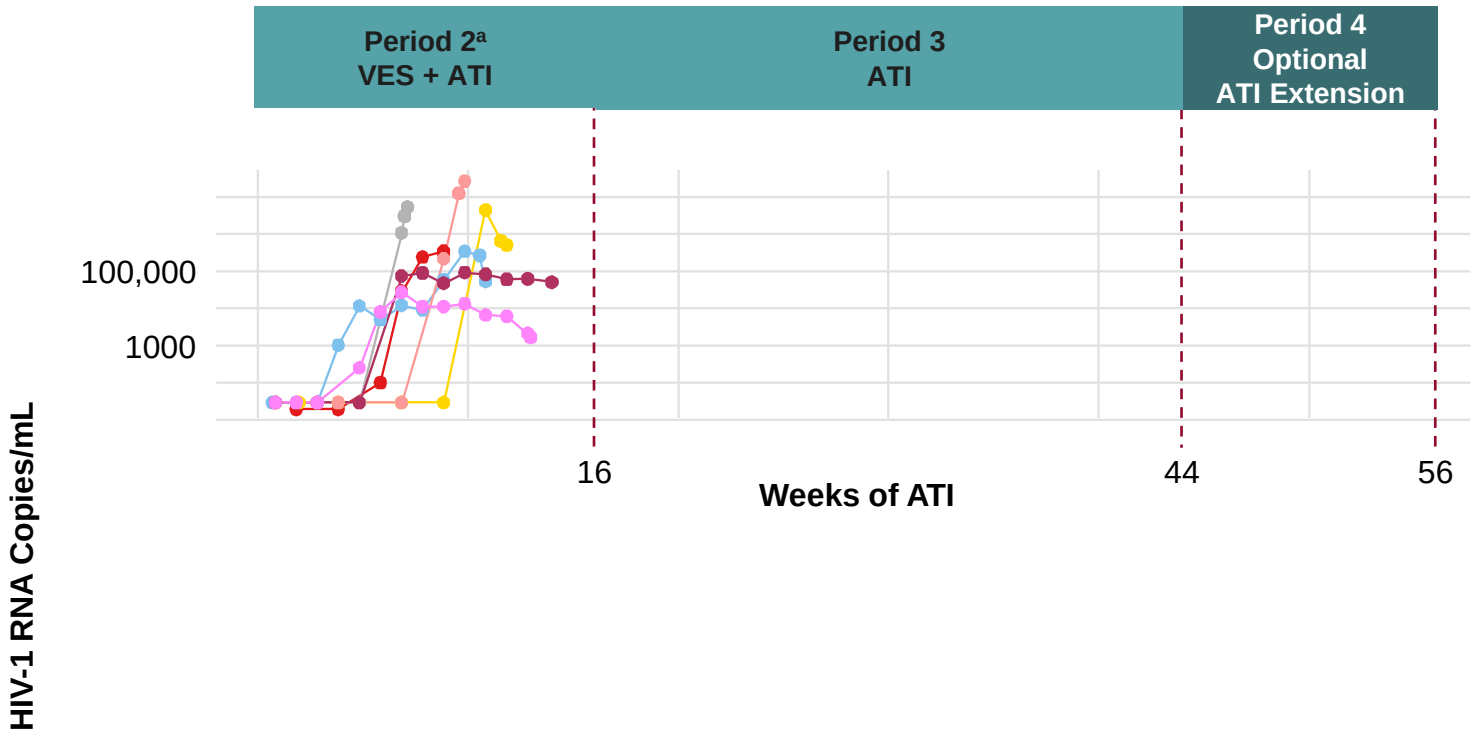
Single-dose VRC07-523LS and CAP256V2LS each administered as 20 mg/kg IV at week 1



As expected, mean bNAb concentrations remained above therapeutic levels through the end of Period 2

ART, antiretroviral treatment; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **IC_{50}**, half-maximal inhibitory concentration; **VES**, vesatolimod.

Three Distinct ATI Outcome Patterns

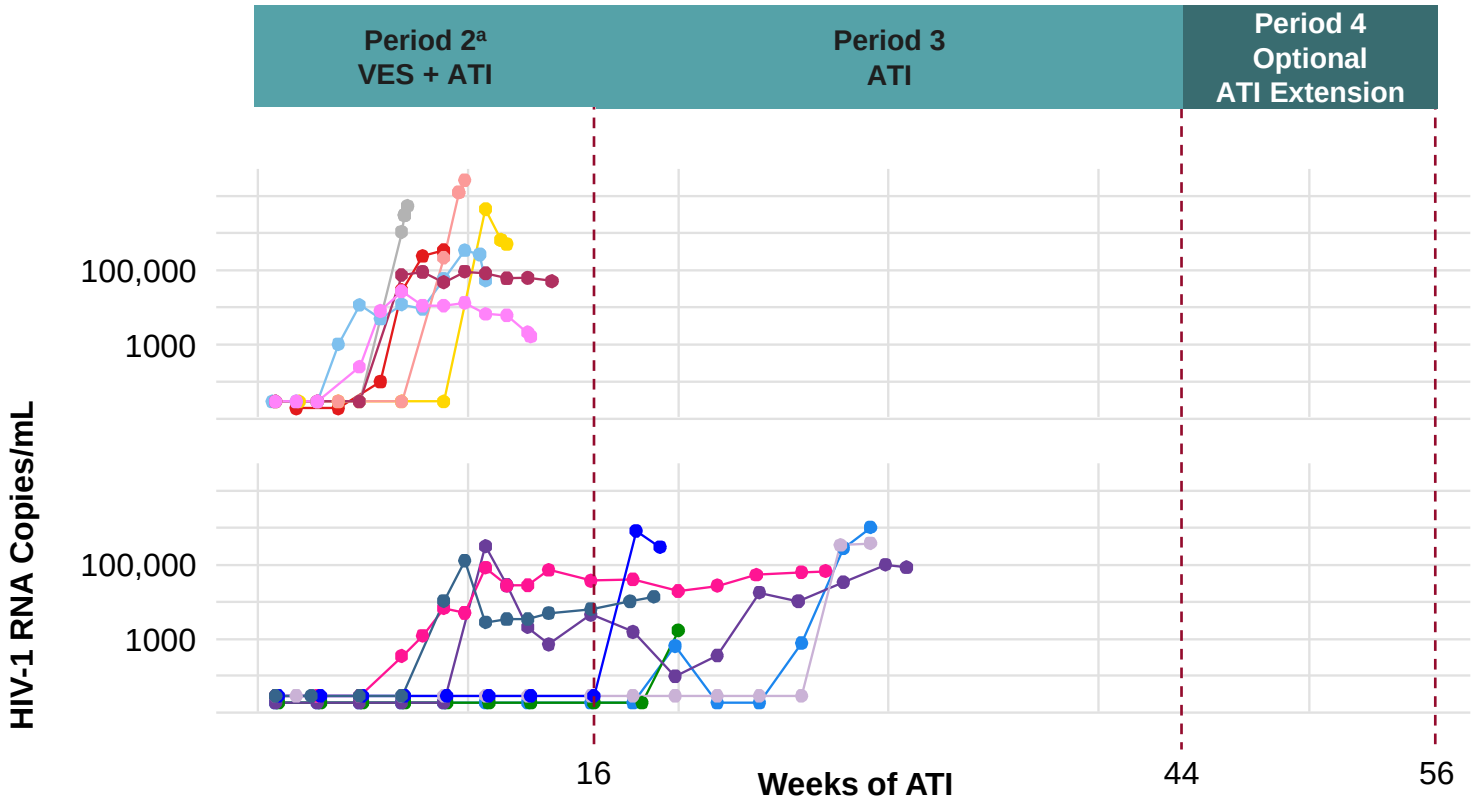


Group 1: Early ART Restart

- 7/20 (35%) participants restarted ART during Period 2

[a]bNAb concentrations remained above therapeutic levels for all participants throughout Period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **VES**, vesatolimod.

Three Distinct ATI Outcome Patterns

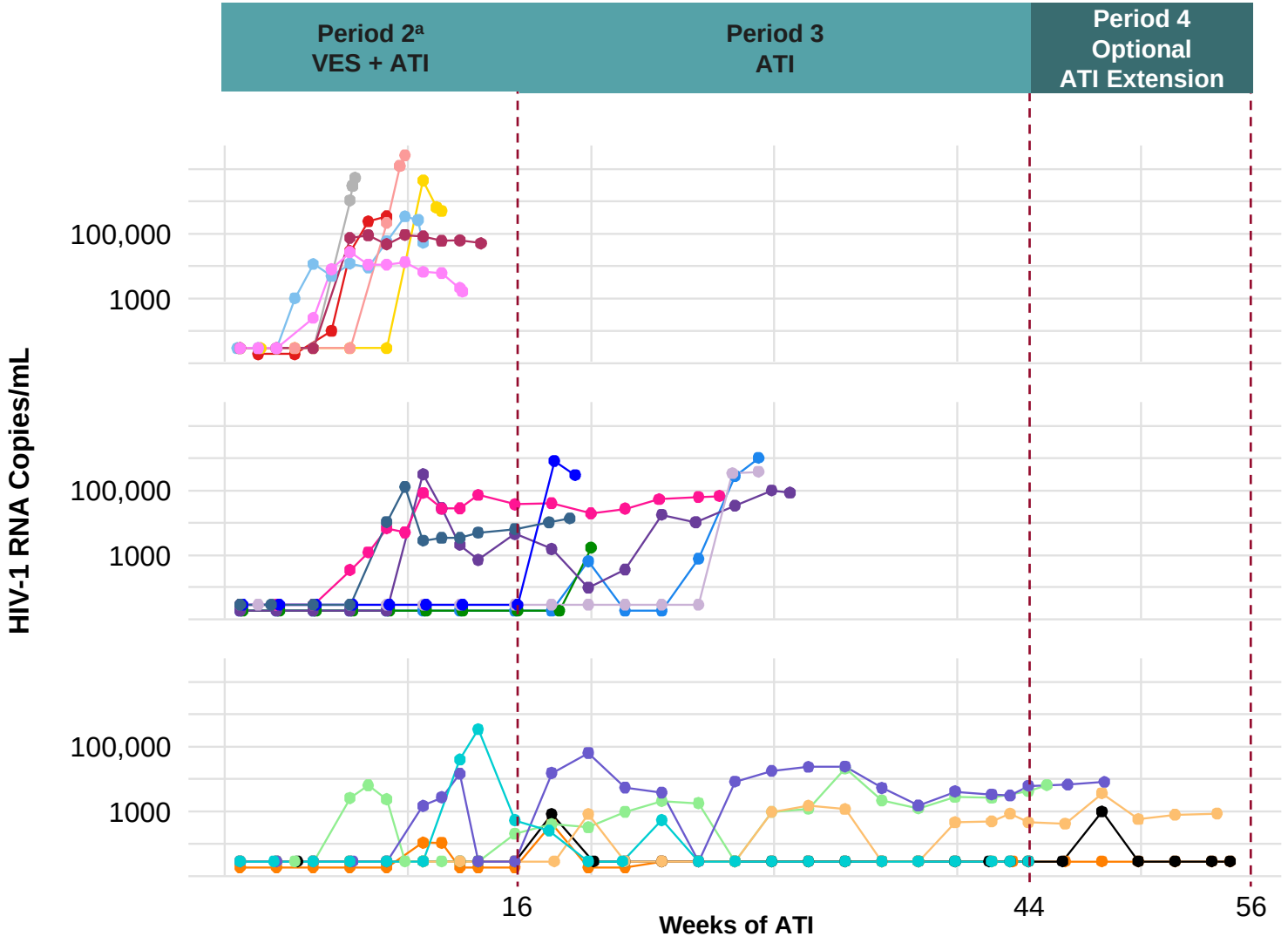


Group 2: Delayed ART Restart

- 7/20 (35%) participants restarted ART during Period 3

[a]bNAb concentrations remained above therapeutic levels for all participants throughout Period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **VES**, vesatolimod.

Three Distinct ATI Outcome Patterns

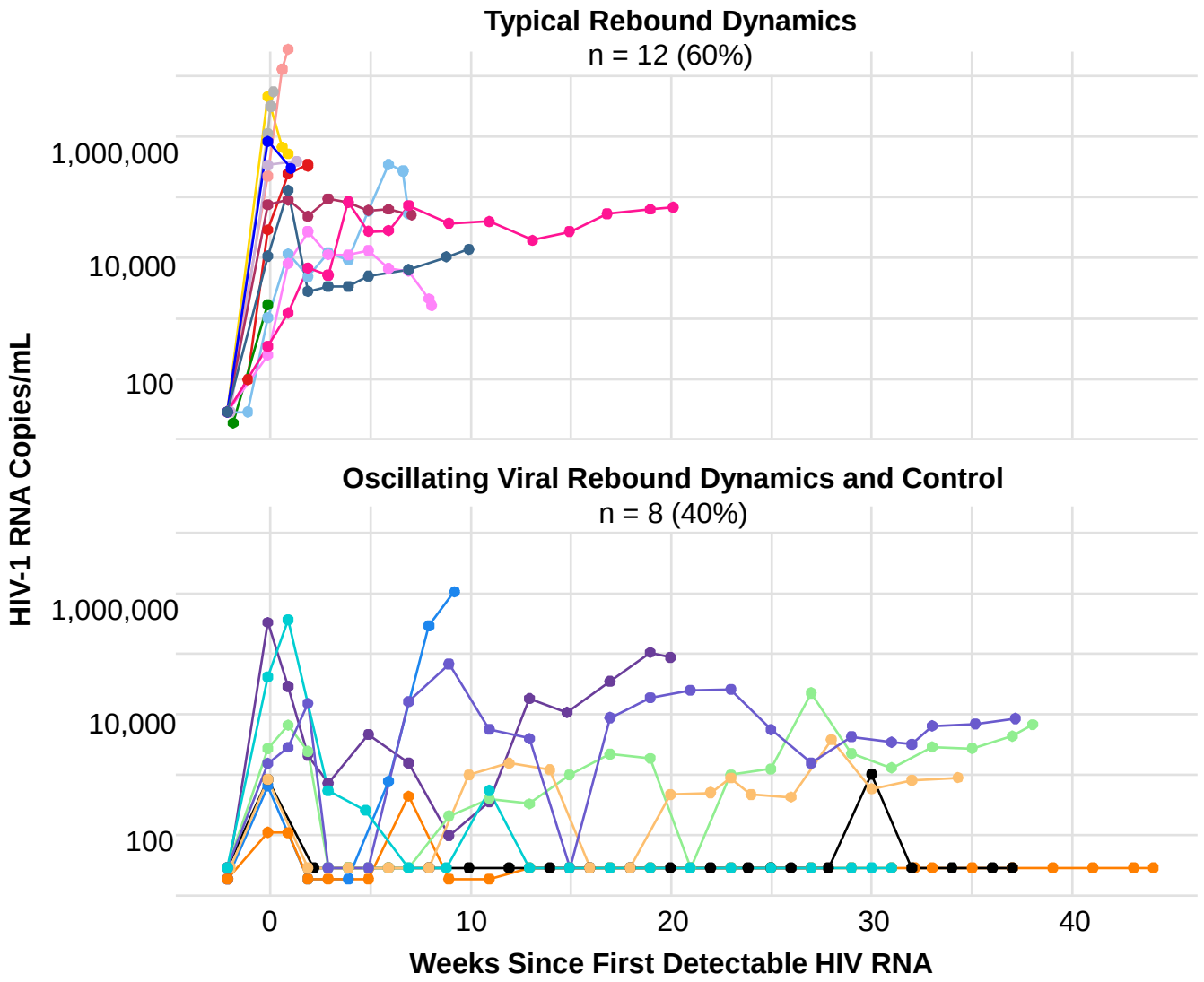


Group 3: Late ART Restart and Post-treatment Controllers

- 6/20 (30%) remained off ART through week 48 (44 weeks of ATI)
- 4/20 (20%) remained off ART through the end of study (55 weeks of ATI)
- Post-trial, the 4 controllers opted to remain off ART and in close follow-up
  - They are now off ART for a median of 1.5 years (range 1.2-2.4)

[a]bNAb concentrations remained above therapeutic levels for all participants throughout Period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **VES**, vesatolimod.

40% Had Oscillating Viral Rebound Dynamics



- The median time to viral rebound (≥ 50 copies/mL) after ATI was 11 weeks (95% CI, 7-18)
- 12 (60%) participants exhibited typical viral rebound dynamics once rebound occurred
- 8 (40%) participants exhibited atypical dynamics, including oscillation (re-suppression after initial rebound) and nonexponential growth

ATI, analytical treatment interruption.

Conclusions

- This first-in-Africa HIV cure trial demonstrates that complex cure studies can be successfully conducted in resource-limited settings with great unmet need via partnership with community and multisector collaborators
- The treatment regimen of VES, VRC07-523LS, and CAP256V2LS was well tolerated, with no serious study drug-related TEAEs reported
- 20% of participants achieved durable ART-free viral control and 40% experienced atypical rebound dynamics
  - While this regimen did not achieve durable control in all participants, ongoing analyses will inform the development of future cure approaches
  - Insights from an integrated sociobehavioral study will be critical for shaping the design and implementation of future HIV cure trials in diverse settings

ART, antiretroviral therapy; **TEAE,** treatment-related adverse event; **VES**, vesatolimod.

Acknowledgements

- We extend our thanks to the trial participants, their partners and family members, the study team at FRESH, HIV Pathogenesis Programme (HPP) core lab staff, counselors from University of KwaZulu-Natal (UKZN), HPP Community Advisory Board, and University Pathology Lab
- The NIH Vaccine Research Center contributed extensive knowledge on bNAb development, supplied the bNAbs and performed pharmacokinetic testing
- This study was funded by Gilead Sciences, Inc.
- Editing and production assistance were provided by Parexel, and funded by Gilead Sciences, Inc.

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bNAb, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; **HPP CAB**, HIV Pathogenesis Programme Community Advisory Board; **UKZN**, University of KwaZulu-Natal; **UPL lab**, universal pathology laboratory.