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Presentation # PS07.1

Safety and Analytical Treatment Interruption Outcomes in a Clinical Trial of 2 Broadly Neutralizing Antibodies Plus Vesatolimod in Early-Treated South African Women With Clade C HIV-1

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Disclosures

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Introduction

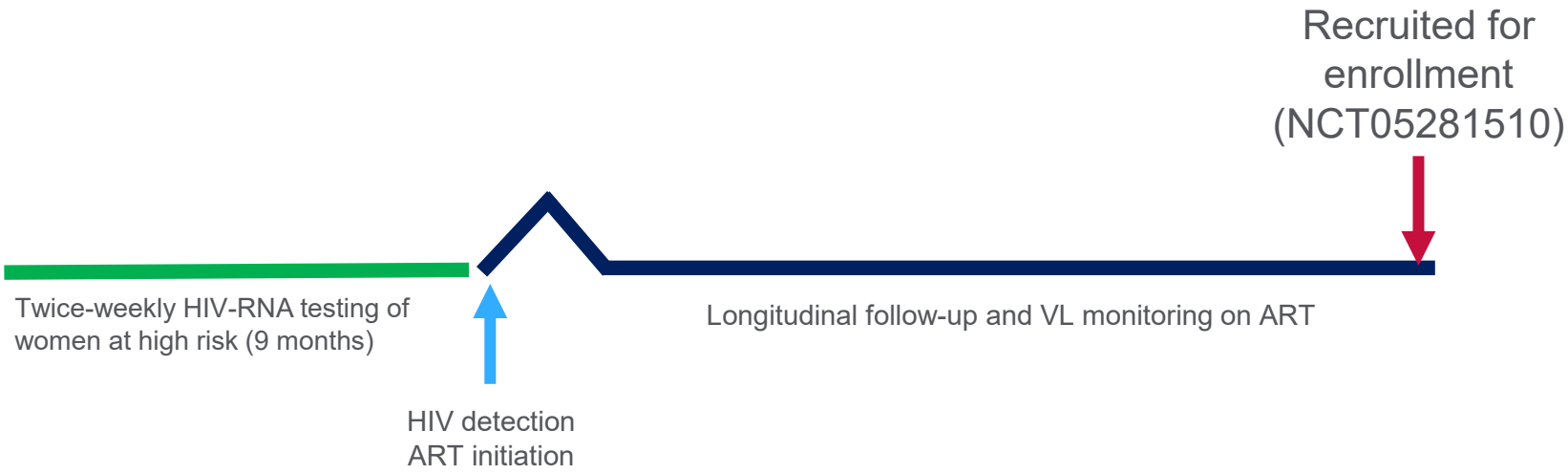
- **Balancing participant risk/benefit** in HIV cure trials that include investigational drug combinations and analytical treatment interruptions (ATI) is of paramount importance
- We assessed the **incidence of treatment-related adverse events** (TRAEs) based on how long participants remained off ART in an open-label study of 2 broadly neutralizing antibodies (bNAbs), VRC07-523LS and CAP256V2LS, combined with an oral Toll-like receptor-7 (TLR7) agonist, vesatolimod (VES), in young women with virally suppressed clade C HIV-1 in Durban, South Africa
- This study (NCT05281510), conducted in the Females Rising through Education, Support, and Health **(FRESH) cohort**, is the **first HIV cure trial in Africa**, with a unique population of early-treated women[1,2]

ART, antiretroviral therapy.

1. Dong K, et al. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2025; March 9-12; San Francisco, CA, USA. 2. Dong K, et al. Presented at the 13th IAS Conference on HIV Science; July 13–17, 2025; Kigali, Rwanda.

Recruitment of Women From the FRESH Cohort

FRESH cohort designed to detect and treat hyperacute HIV infection in young women in Durban, South Africa.[1,2] ART was initiated a median of 1d after detection by HIV-RNA



Collaborators: UKZN, Ragon Institute, NIH, CAPRISA. **Principal investigators:** Thumbi Ndung'u; Krista Dong. NCT05281510 (GS-US-382-5445). **ART,** antiretroviral therapy; **FRESH**, Females Rising through Education, Support, and Health. 1. Ndung'u T, et al. *Sci Immunol*. 2018;3:eaau2798. 2. Dong K, et al. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2025; March 9-12; San Francisco, CA, USA.

Background on Safety of bNAbs and Vesatolimod

First HIV cure study to test a combination of 2 bNAbs plus VES

Dual bNAbs

- **VRC07-523LS** and **CAP256V2LS**
  - Predicted to have excellent coverage in clade C viruses, the most common HIV-1 subtype in South Africa[1]
- **Binds to *Env*-expressing cells**
  - Directly kills infected cells
  - May also induce T-cell immunomodulatory effects[1-3]
- **Well tolerated**, most common adverse events are mild to moderate infusion-related reactions[2,3]
- **First study to administer both bNAbs together**

VES

- **TLR7 agonist**
  - Stimulates innate immune responses and induces ISG expression and production of proinflammatory cytokines and chemokines[4-6]
- Across 8 clinical trials, **VES was generally well tolerated**
  - Mild to moderate flu-like symptoms, including cytokine release syndrome (CRS), may occur, typically after the first or second dose of VES[5-7]
  - Only 1 participant experienced grade 3 CRS after receiving VES + elipovimab, an investigational effector-enhanced bNAb, on the same day. The event resolved completely[7]
  - Staggered dosing with bNAbs, adaptive clinical monitoring, and tailored dose escalation is warranted when VES is administered in combination with other agents

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **ISG**, interferon- stimulated gene; **PWH**, people with HIV; **TLR7**, Toll-like receptor 7; **VES**, vesatolimod. 1. Doria-Rose NA, et al. *J Virol*. 2016;90(1):76-91. 2. Gaudinksi MR, et al. *Lancet HIV*. 2019;6:e667-79. 3. Caskey M. *Curr Opin HIV AIDS*. 2020;15:49-55. 4. Borducchi EN, et al. *Nature*. 2018;563:360-4. 5. Riddler SA, et al. *Clin Infect Dis*. 2021;72:e815-24. 6. SenGupta D, et al. *Sci Transl Med*. 2021;13:eabg3071. 7. Riddler SA, et al. *Infect Dis Ther*. 2024;13:2285-99.

Screening

Inclusion: virally suppressed on ART for > 12 mo; sensitive to at least 1 of the 2 bNAbs[1]

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

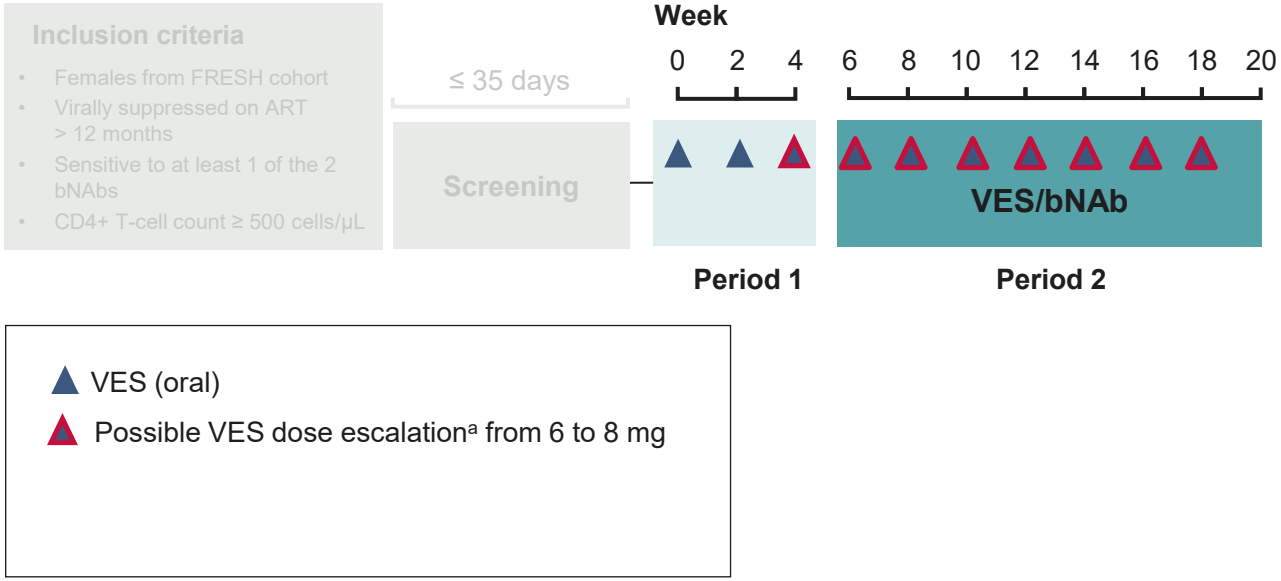
≤ 35 days

Screening

ART, antiretroviral therapy; **bNAb**, broadly neutralizing antibody; **FRESH**, Females Rising through Education, Support, and Health; NCT05281510. 1. Dong K, et al. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2025; March 9-12; San Francisco, CA, USA.

VES Dosing

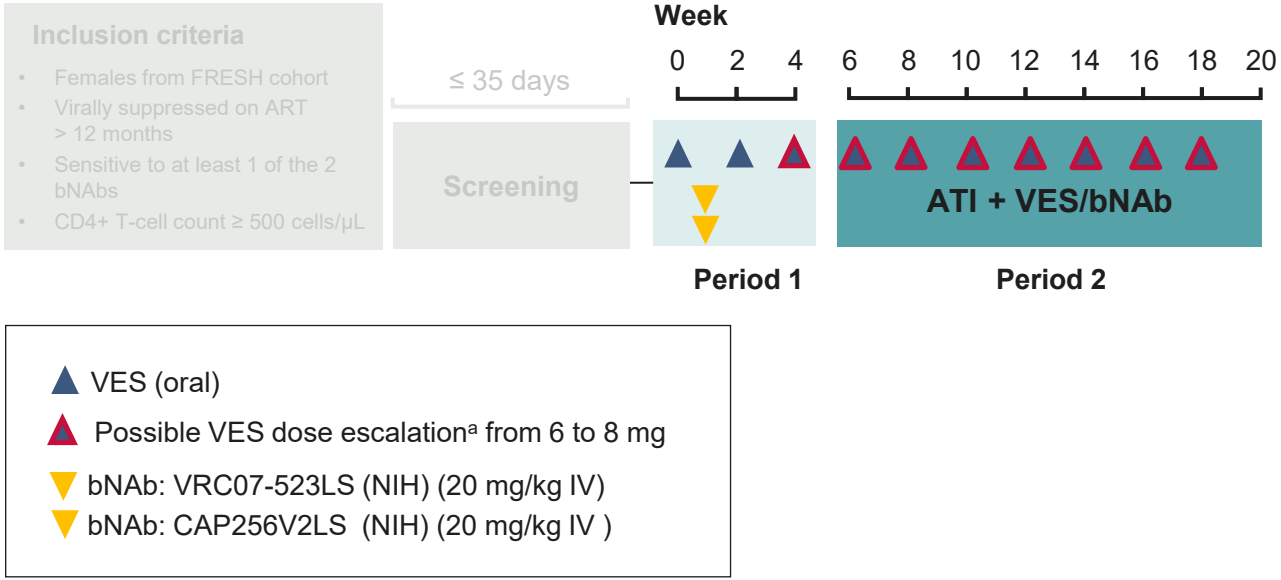
Up to **10 oral doses of VES** administered every 2 w; **dose escalation** and adaptive monitoring



[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.

bNAb Dosing

The **bNAbs** (VRC07-523LS and CAP256V2LS) were infused sequentially; given 1 w after the first VES dose



[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; **IV**, intravenous; **NIH**, National Institutes of Health; **VES**, vesatolimod. NCT05281510.

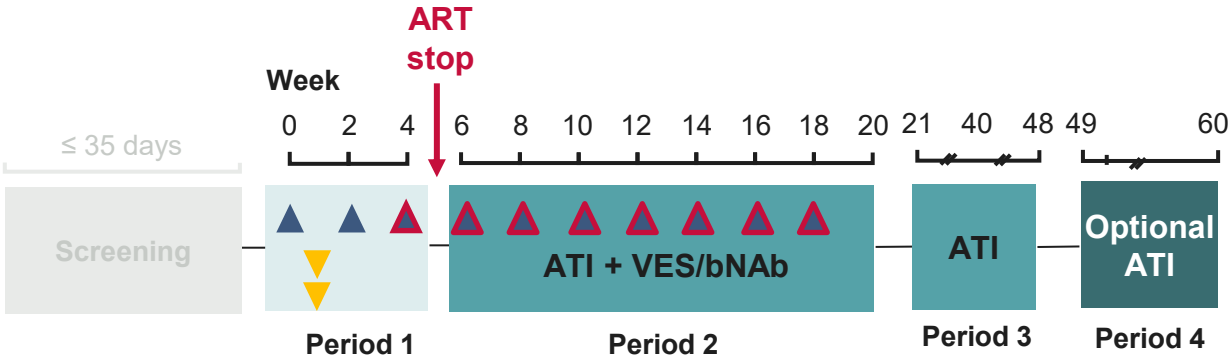
ATI Period

ART was stopped at w 5 with close VL monitoring of ART for up to 55 w

ART restart criteria: HIV-1 RNA ≥ 1000 copies/mL for 8 consecutive weeks without a drop of 0.3 log10 from the previous week, confirmed HIV-1 RNA > 100,000 copies/mL, or confirmed CD4+ T-cell count < 350 cells/µL

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



▲ VES (oral)

▲ Possible VES dose escalation[a] from 6 to 8 mg

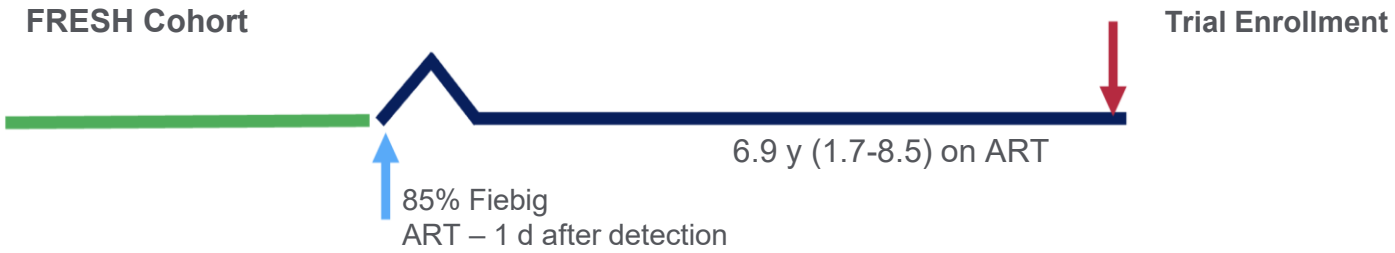
▼ bNAb: VRC07-523LS (NIH) (20 mg/kg IV)

▼ bNAb: CAP256V2LS (NIH) (20 mg/kg IV)

[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; **IV**, intravenous; **NIH**, National Institutes of Health; **VES**, vesatolimod; **VL**, viral load. NCT05281510.

Baseline Characteristics

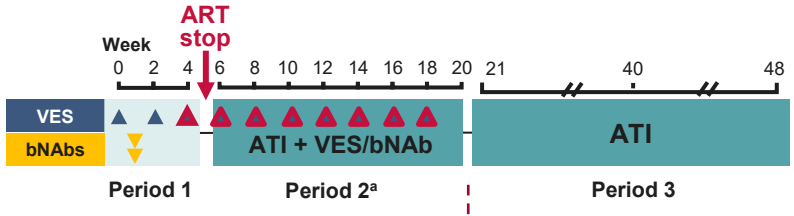
N = 20 virally suppressed young Black women living with HIV-1 clade C

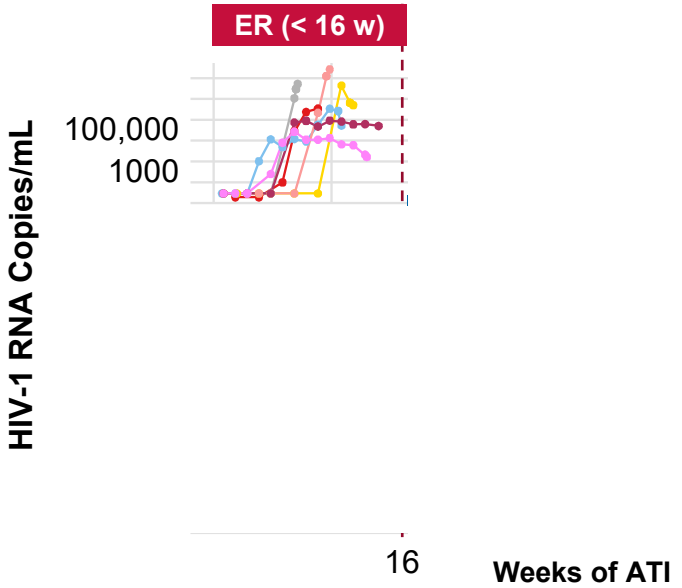


Baseline Characteristics	Participants (N = 20)
Age, median (range), years	26 (23-32)
Baseline HIV-1 RNA, copies/mL	< 30
Baseline CD4⁺ T cells, median (range), cells/μL	776 (323-1252)
Fiebig stage I at detection, n (%)	17 (85%)
Time on ART before enrollment (range), years	6.9 (1.7-8.5)

ART, antiretroviral therapy.

Three Distinct ATI Outcomes Based on Time to ART Restart

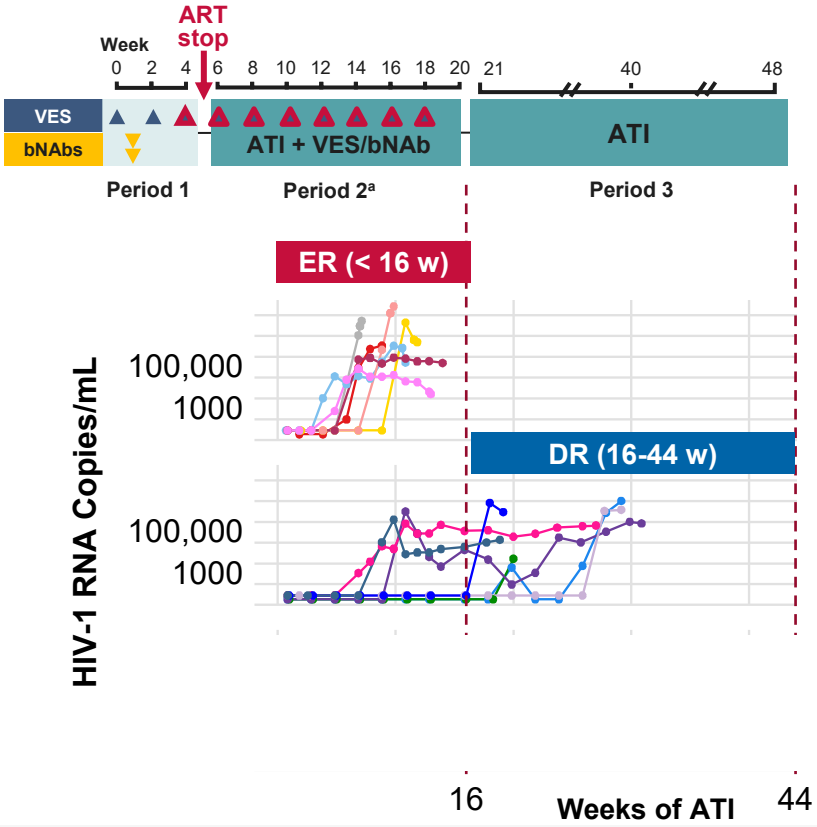




N = 7 (35%) – Early ART restart (ER)

Colored lines represent individual study participants.
[a]bNAb concentrations remained above therapeutic levels for all participants throughout period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **VES**, vesatolimod.

Three Distinct ATI Outcomes Based on Time to ART Restart

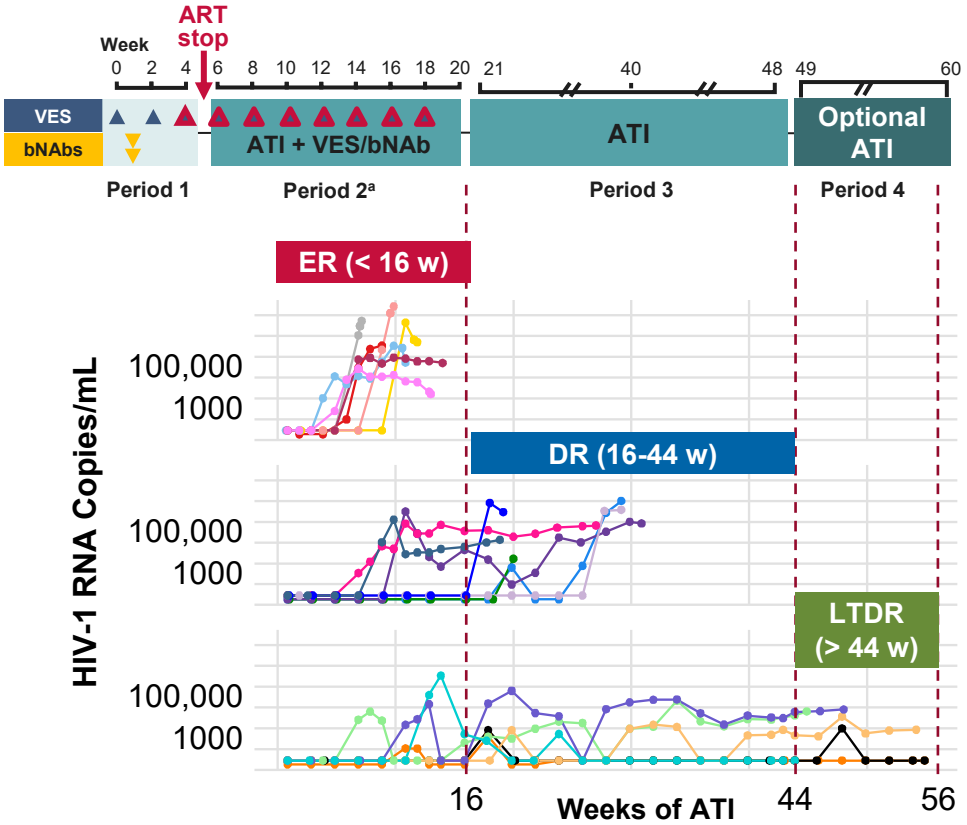


N = 7 (35%) – Early ART restart (ER)

N = 7 (35%) – Delayed ART restart (DR)

Colored lines represent individual study participants.
[a]bNAb concentrations remained above therapeutic levels for all participants throughout period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **VES**, vesatolimod.

Three Distinct ATI Outcomes Based on Time to ART Restart



N = 7 (35%) – Early ART restart (ER)

N = 7 (35%) – Delayed ART restart (DR)

N = 6 (30%) – Long-term delayed ART restart (LTDR), includes 4 participants who remained off ART until the end of the trial at > 55 w and continued off ART after the trial for ~2 years

Colored lines represent individual study participants.
[a]bNAb concentrations remained above therapeutic levels for all participants throughout period 2.
ART, antiretroviral therapy; **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **VES**, vesatolimod.

Regimen Was Well Tolerated (No Serious TRAEs)

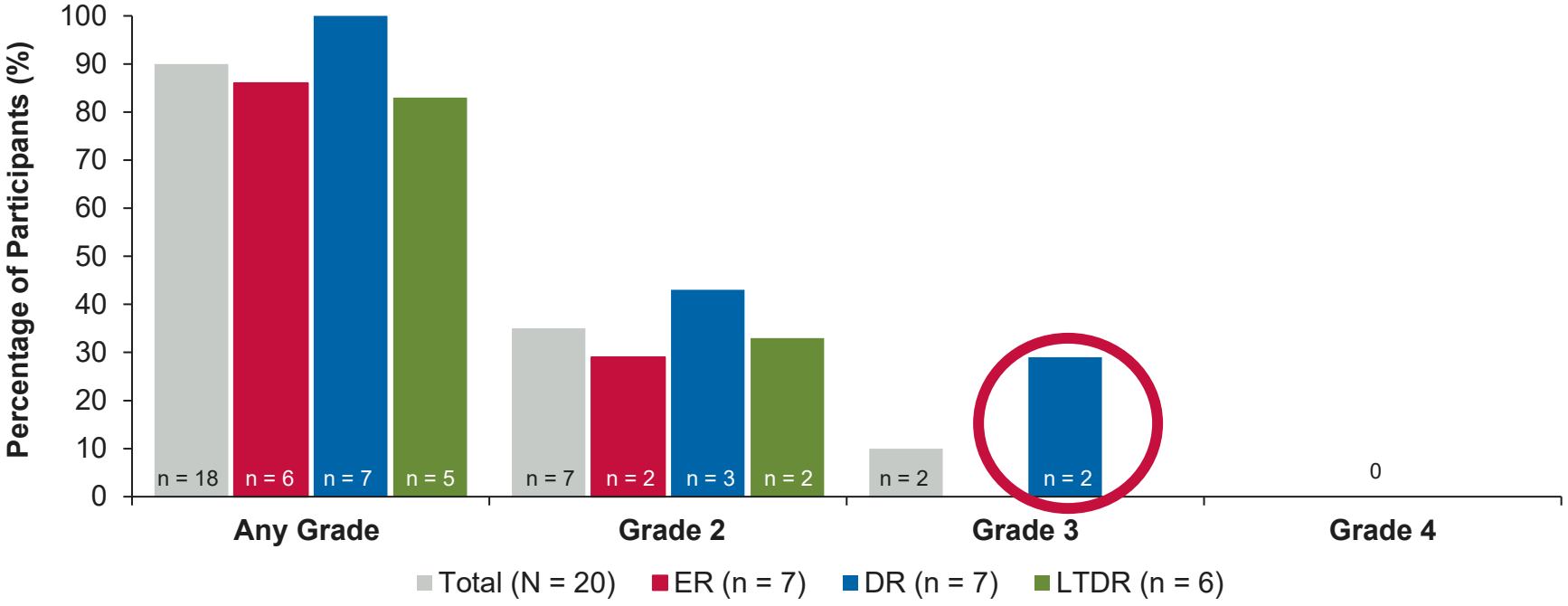
	ER (N = 7)	DR (N = 7)	LTDR (N = 6)	Total (N = 20)
TRAEs	6 (86)	7 (100)	5 (83)	**18 (90)**
Most common TRAEs (≥ 25%)				
Infusion-related reaction	6 (86)	7 (100)	5 (83)	**18 (90)**
Headache	6 (86)	3 (43)	4 (67)	**13 (65)**
Tachycardia	1 (14)	5 (71)	2 (33)	**8 (40)**
Fever	3 (43)	4 (57)	0	**7 (35)**
Chest discomfort	1 (14)	2 (29)	2 (33)	**5 (25)**
Serious TRAEs[a]	0	0	0	**0**
Requiring early drug discontinuation				
Grade 1 CRS	0	1 (14.3)	0	**1 (5)**

- Similar percentage of TRAEs across the 3 ATI outcome groups
- Infusion-related reactions were common (90%), but mostly mild and all resolved within 48 h
- No fever in LTDR group vs 43% of ER, 57% of DR participants
- DR group had a grade 1 CRS considered related to VES, resolved completely without treatment

[a]Serious TRAEs as assessed by the investigator. Adverse events coded according to MedDRA version 27.1. Severity grades defined by Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Antiviral Toxicity Grading Scale, version 01 April 2015. CTCAE v5 grading scale was used to grade AEs determined to be CRS or IRRs. **ATI**, analytical treatment interruption; **CRS**, cytokine release syndrome; **CTCAE**, National Cancer Institute Common Terminology Criteria for Adverse Events; **ER**, early restart (< 16 weeks); **DR**, delayed restart (16-44 weeks); **LTDR**, long-term delayed restart (> 44 weeks); **TRAE**, treatment-related adverse event.

TRAEs Were Mostly Mild

DR group had 2 participants who experienced grade 3 TRAEs (fever and chills)



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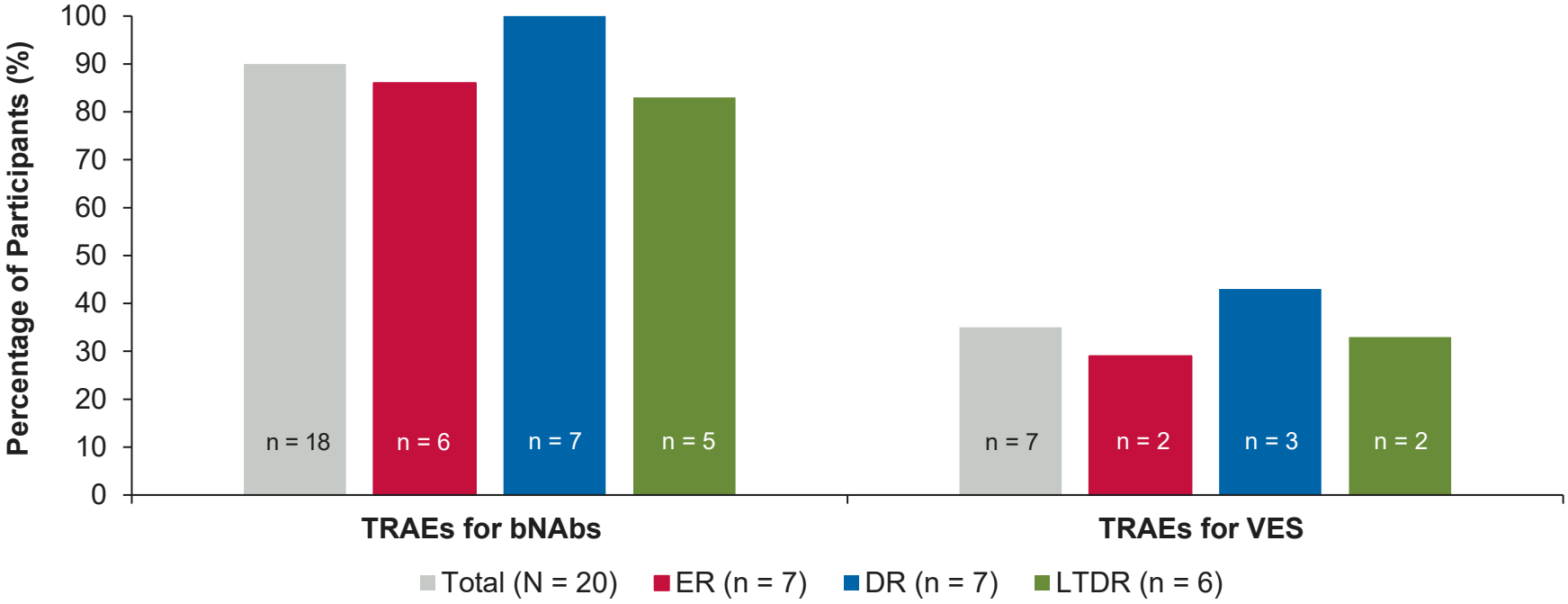
ATI, analytical treatment interruption; **ER**, early restart (< 16 weeks); **DR**, delayed restart (16-44 weeks); **LTDR**, long-term delayed restart (> 44 weeks); **TRAE**, treatment-related adverse event.

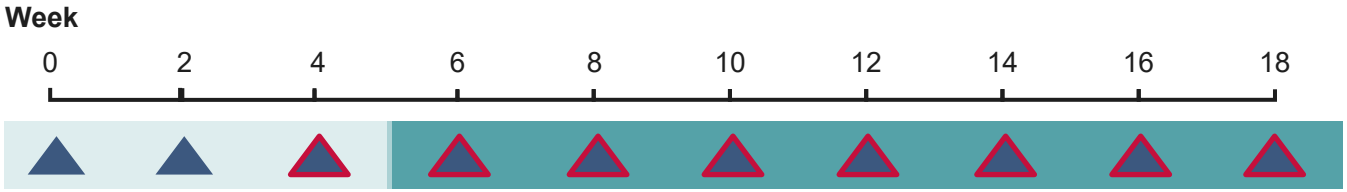
bNAbs – More TRAEs Compared With VES

TRAEs after bNAbs (83%-100%), **compared with VES** (28%-43%)



Adverse events coded according to MedDRA version 27.1. **ATI**, analytical treatment interruption; **bNAb**, broadly neutralizing antibody; **ER**, early restart (< 16 weeks); **DR**, delayed restart (16-44 weeks); **IRR**, infusion-related reaction; **LTDR**, long-term delayed restart (> 44 weeks); **TRAE**, treatment-related adverse event; **VES**, vesatolimod.

VES – Most TRAEs Were Associated With the First Dose



No. who had TRAEs after each VES dose[a]	4	1	2	0	2	0	0	2	0	0
Early	1 headache	1 headache	1 rash+pruritis		1 dizziness					
Delayed	2 headache; fever		1 CRS[b]					1 body pain		
Long-Term Delayed	1 headache				1 headache			1 headache+ tachycardia		

▲ VES (oral)

▲ VES dose escalation from 6 to 8 mg

[a]TRAEs recorded between 0-3 days relative to VES dose. [b]Signs and symptoms of CRS included pyrexia, tachycardia, headache, bone pain, and chills. Adverse events coded according to MedDRA version 27.1.
CRS, cytokine release syndrome; **ER**, early restart (< 16 weeks); **DR**, delayed restart (16-44 weeks); **LTDR**, long-term delayed restart (> 44 weeks); **TRAE**, treatment-related adverse event; **VES**, vesatolimod.

bNAb Infusion – Most Common TRAEs Were Mild IRRs

All IRRs occurred on the same day as infusion

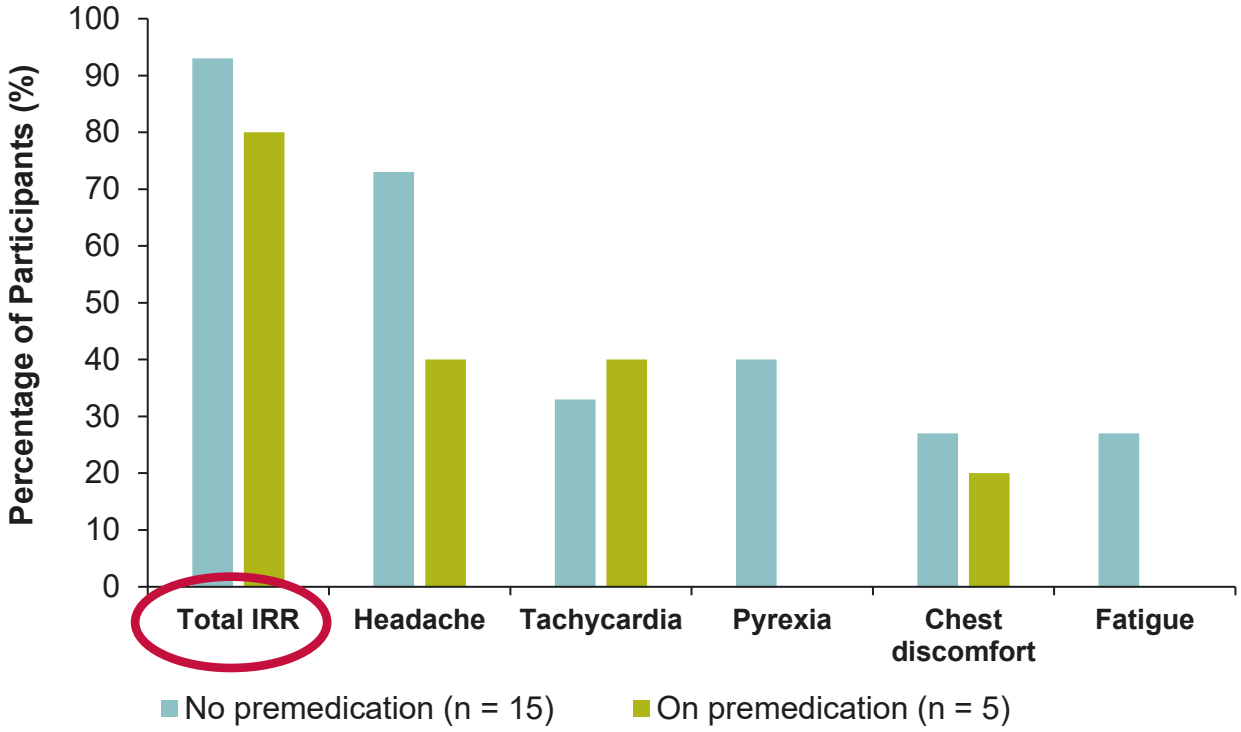
TRAEs (in > 1 participant)	No. of TRAEs for bNAbs			
	ER	DR	LTDR	Total
Grade 1	**28**	**21**	**16**	**65**
Infusion related reaction	6	5	5	16
Headache	5	2	3	10
Tachycardia	1	4	2	7
Fever	3	2	0	5
Chest discomfort	1	2	2	5
Fatigue	3	1	0	4
Nausea	3	0	1	4
Chills	0	2	0	2
Neutropenia	2	0	0	2
Pruritus	0	1	1	2
Vomiting	2	0	0	2
Grade 2	2	5	2	9
Headache	1	1	1	3
Infusion related reaction	0	2	0	2

Most common IRR TRAEs after bNAb infusion:

- **ER group**: IRR TRAEs including headache, fever, fatigue, and nausea
- **DR group**: tachycardia
- **LTDR group**: notably fewest overall TRAEs

Adverse events coded according to MedDRA version 27.1.
bNAb, broadly neutralizing antibody; **ER**, early restart (< 16 weeks); **DR**, delayed restart (16-44 weeks); **IRR**, infusion-related reaction; **LTDR**, long-term delayed restart (> 44 weeks); **TRAE**, treatment-related adverse event.

Premedication Decreased Infusion-Related Reactions (IRR)



- Given the incidence of IRRs in the first 15 participants, paracetamol was administered to the remaining 5 participants before the bNAbs infusion
- Premedication reduced the frequency of IRRs and some associated signs and symptoms such as headache, fever, and fatigue

Adverse events coded according to MedDRA version 27.1. Premedication defined as receipt of paracetamol on the same day as bNAb (VRC and CAP) administration. IRRs reported in > 20% participants were included.
bNAb, broadly neutralizing antibody; **IRR**, infusion-related reaction.

Conclusions

- 30% of early-treated virally suppressed women in this study controlled HIV for > 44 w without ART[1]
  - Four (20%) remained in follow-up after the end of the study, off ART for ~2 y
- The combination regimen was well tolerated (no serious TRAEs)
  - Majority of TRAEs for VES were mild/moderate and occurred after the first dose (same as previous studies)[2]
  - IRRs after bNAbs were common; premeds reduced the frequency of IRRs and some signs and symptoms such as headache, fever, and fatigue
  - Staggered dosing, close monitoring, adaptive dose escalation, and premedication are effective strategies to minimize AEs
- All participants successfully completed this complex trial
- Women are motivated to participate in HIV cure trials
- This combination of dual bNAbs + VES was shown to be safe in early-treated women in South Africa, offering insights into potential risk mitigation strategies for future HIV cure studies

AE, adverse event; **ART**, antiretroviral therapy; **bNAb**, broadly neutralizing antibody**; IRR,** infusion-related reaction; **TRAE**, treatment-related adverse event; **VES**, vesatolimod.

1. Dong K, et al. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2025; March 9-12; San Francisco, CA, USA. 2. Riddler SA, et al. *Infect Dis Ther.* 2024;13:2285-2299.

Acknowledgments

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- We thank the **NIH Vaccine Research Center** (VRC) who contributed extensive knowledge on bNAb development and supplied the bNAbs (HT Lucio Gama)
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