Vesatolimod Pharmacodynamic Responses in a Trial of Vesatolimod and Broadly Neutralizing Antibodies in Early-Treated South African Women With Clade C HIV-1

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Conclusions

- This study (GS-US-382-5445) conducted in the Females Rising through Education, Support, and Health (FRESH) cohort is groundbreaking as the first HIV cure trial in Africa, with a unique population of early-treated women presumed to have HIV reservoirs of limited size and diversity
- Vesatolimod (VES) induced consistent pharmacodynamic (PD) responses, including upregulation of interferon-stimulated genes (ISGs) and VES PD cytokines post first dose, in Black female participants in this small study, suggesting a similar PD effect in this population compared with previously studied populations
- While overall VES PD responses were similar across analytical treatment interruption (ATI) outcome categories, higher MMP3 and CXCL9 levels after first VES dose were associated with longer time off antiretroviral treatment (ART) and cumulative time of plasma viral load ≤ 400 copies/mL during ATI
- Interpretation of these findings is limited due to the small sample size, but may suggest a gender or cohort-specific effect

Plain Language Summary

- Developing an HIV cure is a priority for ending the global epidemic and requires studies to test new interventions to ensure they are safe and effective in populations most affected by HIV
- It is important to include women in these studies because they are equally affected by HIV but rarely enrolled in HIV clinical trials. This is especially true for young women in sub-Saharan Africa, who have the highest HIV infection rates in the world
- In this study we enrolled 20 young Black women with HIV-1 in Durban, South Africa. The aim was to evaluate an experimental drug called vesatolimod, in combination with 2 broadly neutralizing antibodies, to better understand how it works in the body and to find out whether it might affect control of HIV without antiretroviral treatment (ART)
- The study showed that 30% of the women who received the experimental combination were able to control HIV for more than 44 weeks after stopping their ART
- Vesatolimod boosted immune responses in the women, including expression of genes associated with viral suppression, and some specific responses were associated with participants maintaining better ART-free viral control
- This clinical trial is important because it showed that women are willing and able to participate in HIV cure trials. Additionally, as the first HIV cure trial conducted in Africa, it showed that complex cure studies can be successfully conducted in resource-limited settings where there is a great need for an HIV cure

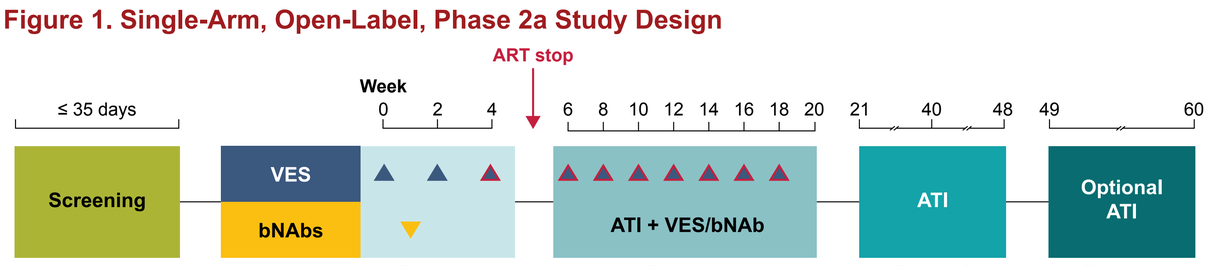
Background

- VES is an oral Toll-like receptor-7 (TLR7) agonist that acts as an immunomodulator, and when administered alone, induces ISG expression and production of proinflammatory cytokines and chemokines[1-3]
- VES is being evaluated for use in combination with therapeutic vaccines and/or broadly neutralizing antibodies (bNAbs) as part of a strategy for HIV cure.[3-6] However, VES PD responses in women have not been extensively assessed
- In the first HIV cure trial conducted in Africa (GS-US-382-5445; NCT05281510), the safety and efficacy of a regimen of VES combined with 2 bNAbs, VRC07-523LS and CAP256V2LS, was evaluated in a cohort of virologically suppressed women with clade C HIV-1[6]
- The primary and key secondary results showed that the regimen was generally safe and well tolerated, and that 30% of women in the trial were able to maintain viral control for ≥ 44 weeks while off ART during an ATI[7]
- Here, we present an exploratory analysis of the association between VES PD responses and ATI outcomes in the GS-US-382-5445 trial

Methods

- This study enrolled 20 early-treated, virally suppressed young Black women, aged ≥ 18 years, from the FRESH cohort in Durban, South Africa. Participants had been on ART for ≥ 12 months, had CD4$^+$ T-cell counts ≥ 500 cells/μL, and harbored virus that was sensitive to at least 1 of the 2 bNAbs (assessed by Monogram PhenoSense assay)
- Participants received up to 10 oral doses of VES every 2 weeks (6 mg for 2 doses and up to 8 mg thereafter) and a single dose of VRC07-523LS and CAP256V2LS (20 mg/kg each) was given intravenously 1 week after the first VES dose (**Figure 1**)
- Participants paused ART at week 5 and remained off ART until meeting ART restart criteria:
  - HIV-1 RNA ≥ 1000 copies/mL for 8 consecutive weeks without a drop of 0.3 $\log_{10}$ from the previous week, confirmed HIV-1 RNA > 100,000 copies/mL, or confirmed CD4$^+$ T-cell count < 350 cells/μL
  - In the ATI period, HIV-1 RNA was monitored every 2 weeks during viral suppression and weekly after viral rebound
- Plasma samples for VES pharmacokinetics (PK) were collected at predose and up to 48 hours after VES dose 1
- Blood samples for VES PD (ISG mRNA expression and serum cytokine levels) were collected at predose, 24 hours postdose, and 7 days after VES doses 1, 5, and 10
  - ISG expression was analyzed using a real-time quantitative polymerase chain reaction assay
- The associations between ATI outcomes and VES PD responses and other inflammatory cytokines were evaluated using a Cox proportional hazards model and Spearman's correlation
- ATI outcomes included first time to plasma HIV-1 RNA ≥ 1000 copies/mL, time off ART up to 55 weeks of ATI, and cumulative time with plasma HIV-1 RNA ≤ 400 copies/mL

Figure 1. Single-Arm, Open-Label, Phase 2a Study Design



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

[a]If VES was well tolerated at 6 mg, participants could be dosed at 8 mg from the third dose onward with close monitoring.
ART, antiretroviral therapy; ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; VES, vesatolimod.
NCT05281510.

Results

Participants

- The study population comprised young women (median age 26 years) with HIV-1 RNA < 30 copies/mL and median CD4$^+$ T-cell count (range) of 776 (323-1252) cells/μL at day 0
- Seventeen of 20 (85%) participants were classified as Fiebig stage I at ART initiation; median time to ART initiation post-detection was 1 day, and median time on ART before enrollment was 6.9 years

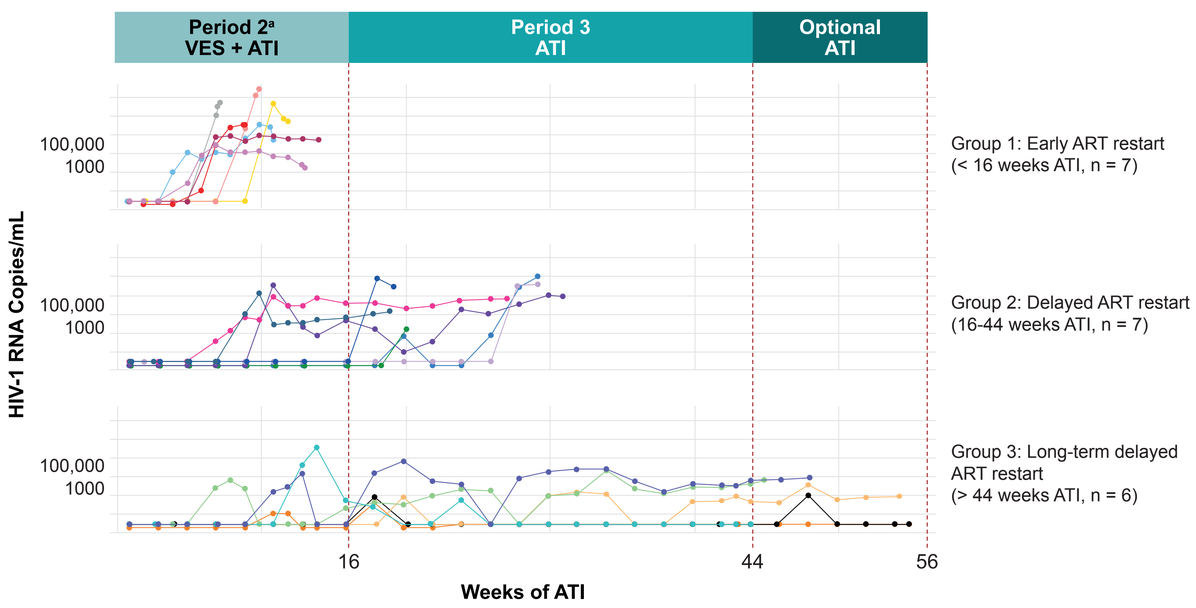
VES Dosing

- All 20 participants (100%) received at least 3 VES doses, 19 (95%) at least 6 VES doses, and 9 (45%) all 10 VES doses
  - Ten participants discontinued VES due to viremia (> 5000 copies/mL) and 1 due to adverse events

ATI Outcomes

- During ATI, viral rebound (≥ 50 copies/mL) occurred at a median of 11 weeks, with ART restart at a median of 24.2 weeks
- Three distinct ATI outcome patterns were observed based on how long participants remained off ART: early restart (< 16 weeks, n = 7 [35%]), delayed restart (16-44 weeks, n = 7 [35%]), and long-term delayed restart (> 44 weeks, n = 6 [30%]) (**Figure 2**). Four participants (20%) remained off ART for > 60 weeks

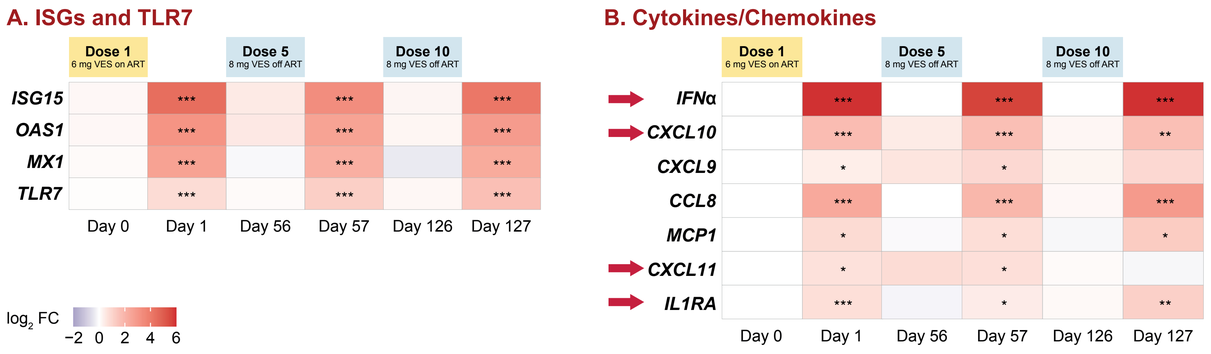
Figure 2. ATI Outcomes: Time to ART Restart



[a]Broadly neutralizing antibody concentrations remained above therapeutic levels for all participants throughout period 2.
ART, antiretroviral therapy; ATI, analytical treatment interruption; VES, vesatolimod.

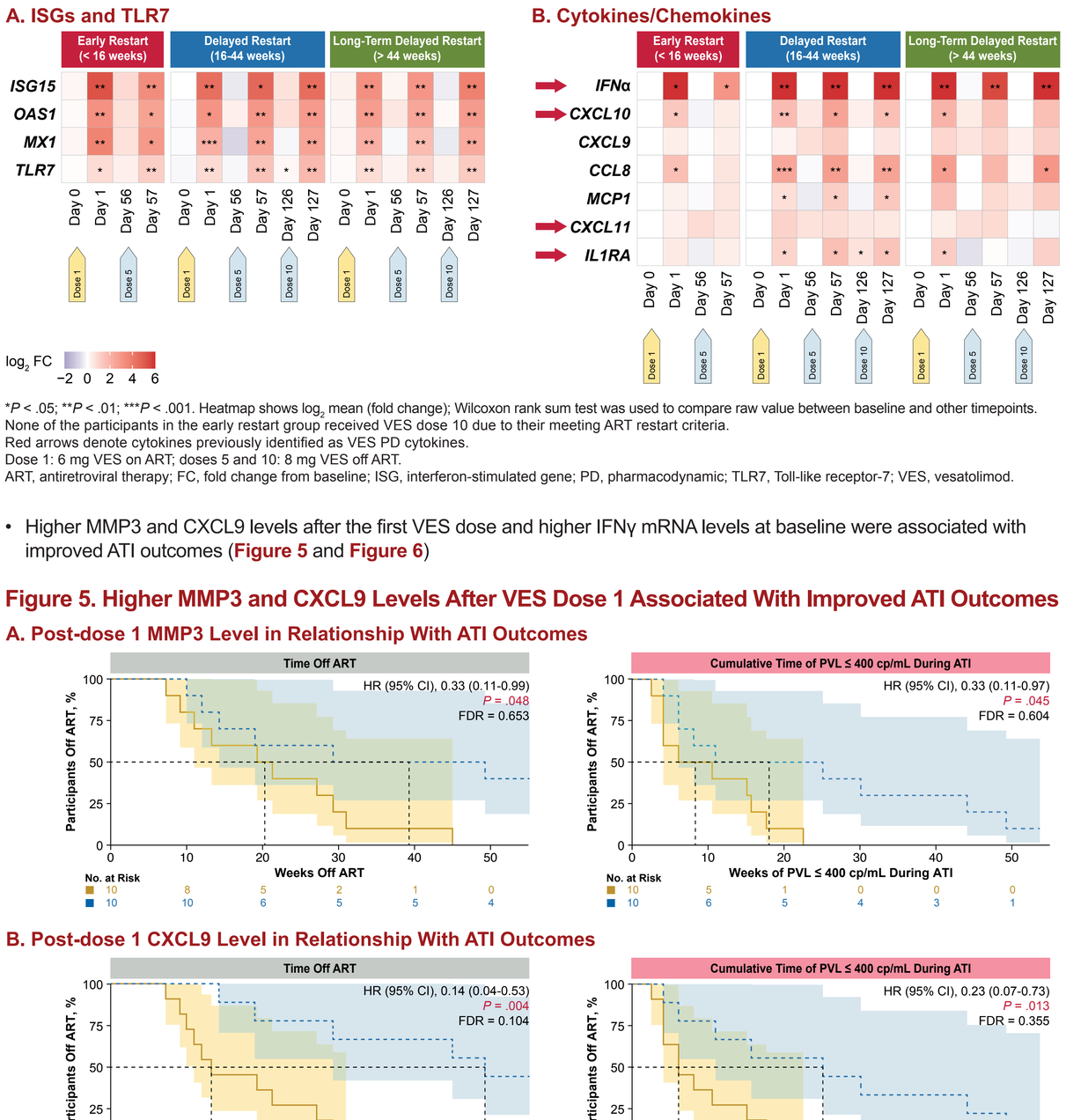
- Consistent upregulation of ISGs (ISG15, OAS1, MX1), TLR7, VES PD cytokines (IFNα, IL1RA, CXCL10, CXCL11), and other chemokines (CXCL9, CCL8, MCP1) were observed after each VES dose, with no increase in fold change from baseline after dose escalation (**Figure 3**)
- VES PD responses, including upregulation of ISGs, TLR7, cytokines, and chemokines, were similar across ATI outcomes (**Figure 4**)

Figure 3. Consistent Upregulation of VES PD Response and TLR7 Across Multiple Doses



*P < .05; **P < .01; ***P < .001. Heatmap shows $\log_2$ mean (fold change); Wilcoxon rank sum test was used to compare raw values between baseline (pre-dose) and other timepoints.
Red arrows denote cytokines previously identified as VES PD cytokines.
ART, antiretroviral therapy; FC, fold change from baseline; ISG, interferon-stimulated gene; PD, pharmacodynamic; TLR7, Toll-like receptor-7; VES, vesatolimod.

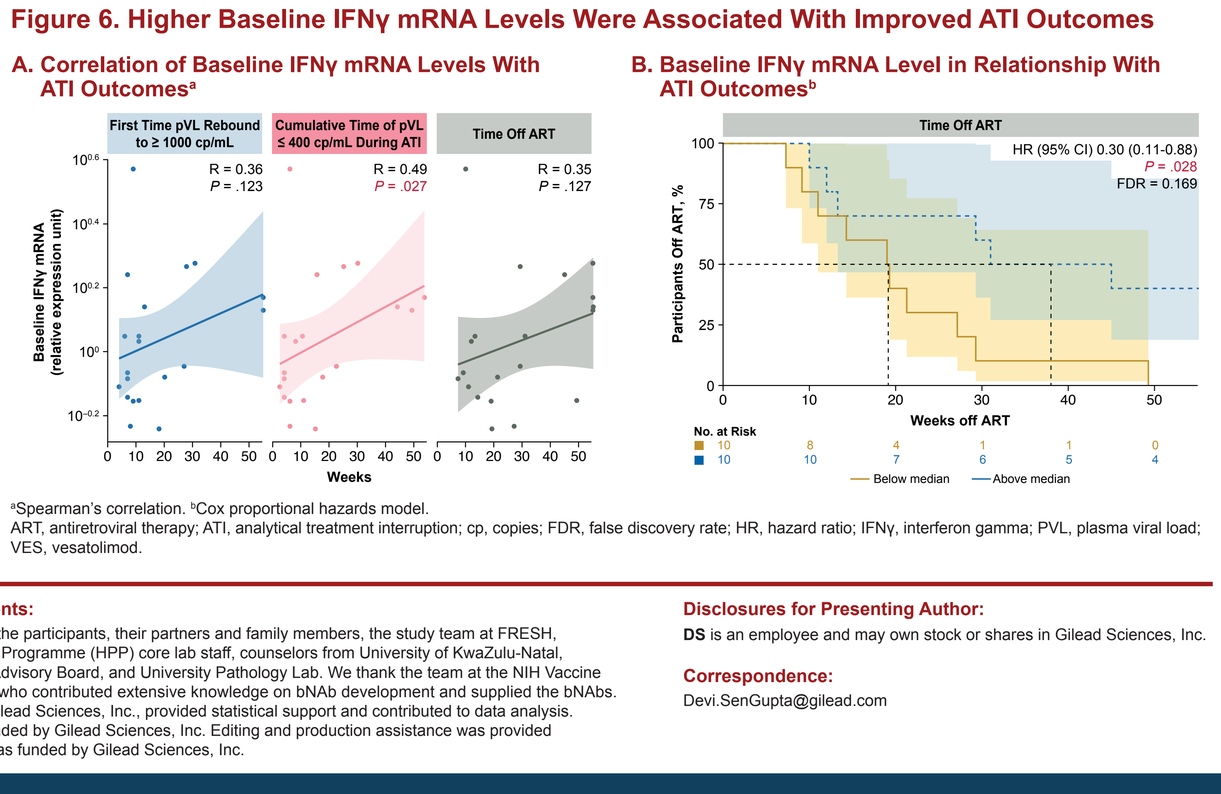
Figure 4. Similar Upregulation of VES PD Response and TLR7 Across ATI Outcomes



*P < .05; **P < .01; ***P < .001. Heatmap shows $\log_2$ mean (fold change); Wilcoxon rank sum test was used to compare raw value between baseline and other timepoints.
None of the participants in the early restart group received VES dose 10 due to their meeting ART restart criteria.
Red arrows denote cytokines previously identified as VES PD cytokines.
Dose 1: 6 mg VES on ART; doses 5 and 10: 8 mg VES off ART.
ART, antiretroviral therapy; FC, fold change from baseline; ISG, interferon-stimulated gene; PD, pharmacodynamic; TLR7, Toll-like receptor-7; VES, vesatolimod.

- Higher MMP3 and CXCL9 levels after the first VES dose and higher IFNγ mRNA levels at baseline were associated with improved ATI outcomes (**Figure 5** and **Figure 6**)

Figure 5. Higher MMP3 and CXCL9 Levels After VES Dose 1 Associated With Improved ATI Outcomes



Cox proportional hazards model.
ART, antiretroviral therapy; ATI, analytical treatment interruption; cp, copies; CXCL9, chemokine (C-X-C motif) ligand 9; HR, hazard ratio; FDR, false discovery rate; MMP3, matrix metalloproteinase 3; PVL, plasma viral load; VES, vesatolimod.

Figure 6. Higher Baseline IFNγ mRNA Levels Were Associated With Improved ATI Outcomes

[a]Spearman's correlation. [b]Cox proportional hazards model.
ART, antiretroviral therapy; ATI, analytical treatment interruption; cp, copies; FDR, false discovery rate; HR, hazard ratio; IFNγ, interferon gamma; PVL, plasma viral load; VES, vesatolimod.

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