bNAb Sensitivity Does Not Fully Explain Post-Treatment Control in Early HIV–Treated Women During ATI

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Lisa Selzer[1], Krista Dong[2,3,4], Thumbi Ndung'u[4,5,6,7], Ross Martin[1], Xiaopeng Liu[1], Leonid Serebryannyy[8], Megha Mehrotra[1], Devi SenGupta[1], Romas Geleziunas[1], Christian Callebaut[1], Laurie A VanderVeen[1]

[1]Gilead Sciences, Inc., Foster City, CA, USA; [2]Harvard Medical School, Cambridge, MA, USA; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Ragon Institute of Mass General, MIT, and Harvard, Cambridge, MA, USA; [5]HIV Pathogenesis Programme, The Doris Duke Medical Research Institute, University of KwaZulu-Natal, Durban, South Africa; [6]Africa Health Research Institute, Durban, South Africa; [7]Division of Infection and Immunity, University College London, London, UK; [8]Vaccine Research Center, NIAID, NIH, Bethesda, MD, USA

Conclusions

- A combination regimen of 2 broadly neutralizing antibodies, VRC07-523LS and CAP256V2LS, and the toll-like receptor 7 agonist vesatolimod were evaluated in a Phase 2a HIV cure study in 20 acutely treated women with HIV-1 in South Africa from the Females Rising through Education, Support, and Health (FRESH) cohort
- In participants who started antiretroviral therapy very early (Fiebig stages I-III), there was minimal change in viral sequences comparing virus at detection/pre–antiretroviral therapy and post–rebound/analytical treatment interruption, suggesting rebound from a high frequency variant archived during acute infection
- CAP256V2LS susceptibility in rebound virus was associated with time to viral rebound and antiretroviral therapy restart, though broadly neutralizing antibody susceptibility alone does not fully explain the outcomes observed in this study
- Loss of broadly neutralizing antibody susceptibility was seen in only 2 out of 15 participants for whom post–rebound/analytical treatment interruption phenotypic data were available

Plain Language Summary

- HIV cure research is exploring new ways to control HIV using a combination of treatments
- One study tested 2 antibodies (proteins made by the immune system that can recognize viruses and block them from infecting cells) that work on many HIV strains together with a drug called vesatolimod in South African women who started HIV treatment very early after infection
  - Four out of 20 (20%) women were able to control HIV while staying off HIV medicines for over a year
- In most of the women, the virus that rebounded (came back) after stopping antiretroviral therapy was the same as the virus they had at the time of detection, suggesting the virus did not change or multiply because the women started antiretroviral therapy so early
- The virus in only 2 out of 15 women showed changes in how well it responded to the study antibodies after stopping treatment
- For 1 antibody, called CAP256V2LS, the virus's sensitivity (how easily it can be blocked) after stopping treatment was linked to how soon the virus came back and when women needed to restart treatment, with loss of sensitivity linked to the virus coming back more quickly and a shorter time to restarting treatment
- Sensitivity to antibodies used in this study alone did not fully explain why the virus in some women stayed under control after stopping treatment while the virus in other women came back

References: **1.** Deeks SG, et al. *Nat Med*. 2021;27:2085-98. **2.** Dong K, et al. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 9-12, 2025; San Francisco, CA, USA. Poster 105. **3.** Moldt B, et al. *J Acquir Immune Defic Syndr*. 2021;88:61-9. **4.** Yoon H, et al. *Nucleic Acids Res*. 2015;43:W213-9. **5.** Meng EC, et al. *Protein Sci*. 2023;32:e4792.

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Correspondence: Lisa Selzer, lisa.selzer1@gilead.com

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Introduction

- Combination therapies integrating immunomodulators and broadly neutralizing antibodies (bNAbs) may activate and harness host immune responses to support HIV control in the absence of antiretroviral therapy (ART)[1]
- Recently, in vitro studies have shown that the use of a combination of bNAbs that target different epitopes of HIV resulted in improved neutralization breadth and potency[1]
- In this Phase 2a HIV cure study (ClinicalTrials.gov Identifier: NCT05281510) 2 bNAbs, VRC07-523LS (VRC07) and CAP256V2LS (CAP256), were given in a sequential regimen with the toll-like receptor 7 agonist vesatolimod
  - This single-arm, open-label study was the first HIV cure trial in Africa, enrolling hyperacutely treated South African women from the Females Rising through Education, Support, and Health (FRESH) cohort
- 20% (4 out of 20) participants maintained post-treatment control until the end of the study without meeting ART restart criteria during 56 weeks of analytical treatment interruption (ATI)[2]

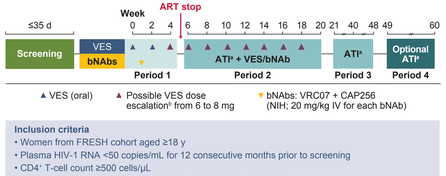
Objective

- To investigate changes in bNAb susceptibility when comparing rebound virus with HIV at detection/pre-ART

Methods

- Participants who were virally suppressed received 1 dose of both bNAbs on Day 7 and up to 10 doses of vesatolimod; ATI started on Day 35 and continued until Day 336 or until ART restart criteria were met (**Figure 1**)
- Plasma virus at HIV detection/pre-ART and post-rebound/ATI was genotyped using the GenoSure HIV envelope (Env) and phenotyped using PhenoSense HIV monoclonal antibody assays (Monogram Biosciences) for participants with HIV-1 RNA ≥50 copies/mL
  - Phenotypic susceptibility was defined as a 90% inhibitory concentration (IC_{90}) ≤5 µg/mL for VRC07 and an 80% inhibitory concentration (IC_{80}) ≤2 µg/mL for CAP256
- Genotypic signatures were used to determine predicted susceptibility to CAP256
  - Signatures were developed following previously described methodology.[3] Briefly, neutralization data, using a 50% inhibitory concentration threshold of 1 µg/mL to classify susceptible versus resistant viruses, combined with virus sequence information for 244 clade C viruses derived from the CATNAP[4] database were used to identify HIV Env amino acid positions important for susceptibility to CAP256; amino acid combinations with the highest positive predictive value and prevalence were chosen
- Images of HIV-1 Env in complex with CAP256 were created using University of California San Francisco ChimeraX[5] based on the Protein Data Bank structure 8FIS
- Spearman's correlation coefficient was calculated between VRC07 and CAP256 phenotypic susceptibility post-rebound/ATI versus ATI outcomes among participants with data available at viral rebound

Figure 1. Study Design



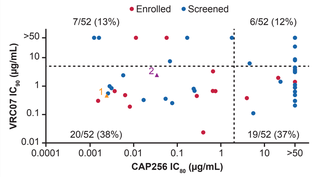
Inclusion criteria
- Women from FRESH cohort aged ≥18 y
- Plasma HIV-1 RNA <50 copies/mL for 12 consecutive months prior to screening
- $CD4^+$ T-cell count ≥500 cells/µL
- Documented history of viral susceptibility to CAP256 or VRC07[c]

[a]ART restart criteria included: plasma HIV-1 RNA ≥1000 copies/mL for 8 consecutive weeks and no drop of 0.3 log_{10} from the previous week, confirmed plasma HIV-1 RNA >100,000 copies/mL, confirmed $CD4^+$ T-cell count <350 cells/µL, pregnancy, participant request, or investigator or sponsor decision.
[b]If VES is well tolerated at 6 mg, participants may be dosed at 8 mg from the third dose onward with close monitoring.
[c]Viral susceptibility was defined as an IC_{90} ≤5 µg/mL for VRC07 and an IC_{80} ≤2 µg/mL for CAP256.
ART, antiretroviral therapy; ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; FRESH, Females Rising through Education, Support, and Health; IC_{80}, 80% inhibitory concentration; IC_{90}, 90% inhibitory concentration; IV, intravenous; NIH, National Institutes of Health; VES, vesatolimod.

Results

- Fifty-two women's viruses were screened for susceptibility to CAP256 and VRC07; viruses from 38% (20/52) were susceptible to both bNAbs, 37% (19/52) were susceptible to VRC07, and 13% (7/52) were susceptible to CAP256 (**Figure 2**)
- Of the 20 women found eligible (virus susceptible to ≥1 bNAb) and enrolled, 17 initiated ART during Feibig stage I, 2 during stages II/III, and 1 during stage V
- At HIV detection/pre-ART, 11 out of 20 participants' viruses were susceptible to both bNAbs, 7 out of 20 were susceptible to only VRC07, and 2 out of 20 were susceptible to only CAP256 (**Figure 2**)
- Out of the 20 participants, 19 met the criteria for resistance testing and 15 had available post-ATI phenotypic data; of these, 2 participants' viruses lost susceptibility to either VRC07 or CAP256 post-rebound/ATI relative to HIV detection/pre-ART virus
- Genotypic signatures to predict CAP256 susceptibility are shown in **Table 1**
  - The R166 D167 K169 signature had the highest probability of CAP256 susceptibility

Figure 2. bNAb Susceptibility at Enrollment and at Screening



The orange and purple triangles labeled "1" and "2" represent the 2 participants whose viruses lost susceptibility to either VRC07 or CAP256 post-rebound/ATI.
ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; IC_{80}, 80% inhibitory concentration; IC_{90}, 90% inhibitory concentration.

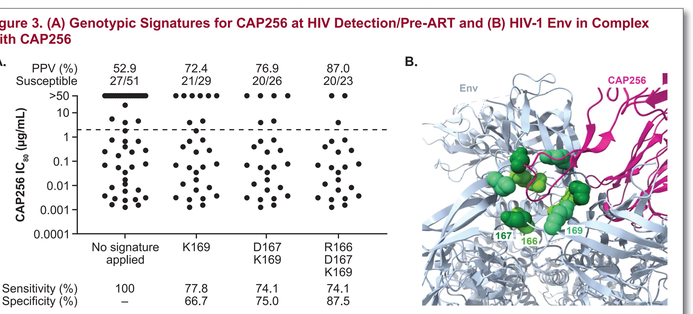
Table 1. Genotypic Signatures to Predict CAP256 Susceptibility[a]

Signature	PPV (%)
No signature	68
K169	81
D167 K169	83
R166 D167 K169	94

[a]Data are based on sequences in the CATNAP database.
PPV, positive predictive value.

- HIV detection/pre-ART genotypic and phenotypic susceptibility data were available for 51 participants who were screened (**Figure 3A**)
  - Genotypic signatures predicted phenotypic susceptibility of plasma viruses with high positive predictive value (87.0%), specificity (87.5%), and sensitivity (74.1%)
- Signature residues clustered around the V2 apex region of HIV-1 Env (**Figure 3B**)

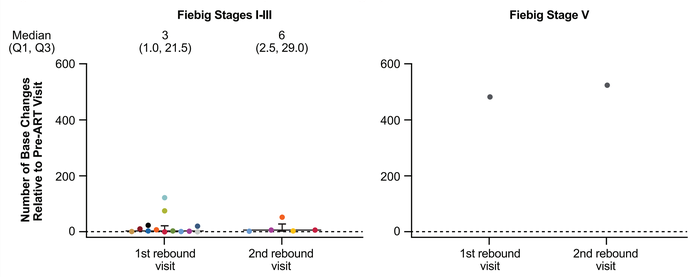
Figure 3. (A) Genotypic Signatures for CAP256 at HIV Detection/Pre-ART and (B) HIV-1 Env in Complex With CAP256



ART, antiretroviral therapy; IC_{80}, 80% inhibitory concentration; PPV, positive predictive value.

- Among those with post-ATI genotypic data (n = 15), HIV-1 Env sequences were highly conserved between HIV detection/pre-ART and post-rebound/ATI for participants in Fiebig stages I-III (**Figure 4**)

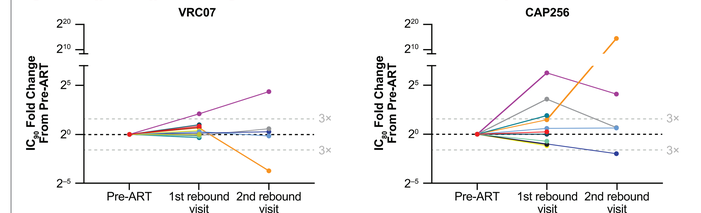
Figure 4. Pre-ART and Post-ATI Env Sequences Are Highly Conserved



Each colored dot represents 1 participant. This analysis was performed using a 15% variant threshold.
ART, antiretroviral therapy; ATI, analytical treatment interruption; Q1, Quartile 1; Q3, Quartile 3.

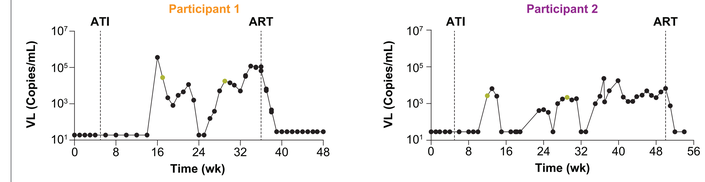
- Two participants' viruses (dual-bNAb sensitive at HIV detection/pre-ART) showed changes in post-rebound/ATI bNAb susceptibility (**Figure 5**)
  - The first developed resistance to CAP256 (IC_{90} >50 µg/mL) and increased susceptibility (15-fold IC_{90}) to VRC07 associated with S141P and K290K/S mutations and a V4 loop deletion (**Figure 6**)
  - The second showed a 76-fold IC_{80} increase to CAP256 with K176E and A561T mutations, followed by a 17-fold IC_{80} and a 21-fold IC_{90} increase to CAP256 and VRC07 from HIV detection/pre-ART, respectively, with additional mutations K97E, K186Q, and A561T (**Figure 6**)

Figure 5. IC_{80} and IC_{90} Fold Change From Pre-ART for VRC07 and CAP256 by Participant



Each colored line represents 1 participant. The orange and purple lines correspond to participants 1 and 2, respectively, whose viruses lost susceptibility to either VRC07 or CAP256 post-rebound/ATI.
ART, antiretroviral therapy; ATI, analytical treatment interruption; IC_{80}, 80% inhibitory concentration; IC_{90}, 90% inhibitory concentration.

Figure 6. VL Kinetics and Susceptibility to bNAbs

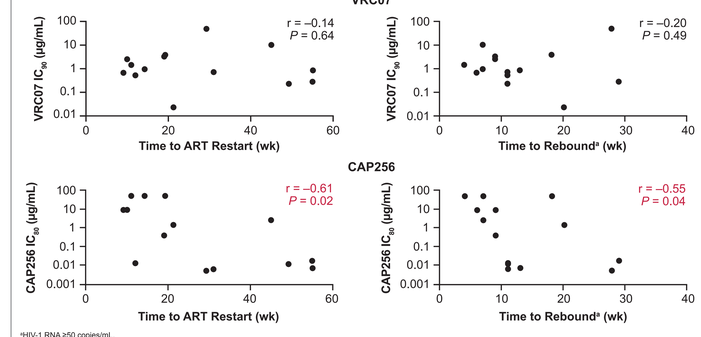


Participant (Fiebig Stage I)	Pre-ART VRC07 IC_{90} (µg/mL)	Pre-ART CAP256 IC_{80} (µg/mL)	Time (wk)	VL at VR (Copies/mL)	Rebound VRC07 IC_{90} (µg/mL)	Rebound CAP256 IC_{80} (µg/mL)	AA Changes From Pre-ART	Base Changes From Pre-ART
1	0.46	0.002	17	28,000	0.72	0.007	No change	7
			29	17,800	0.03	>50	S141P, K290K/S 13-AA deletion in V4 loop	52
2	2.38	0.03	12	2658	10.35	2.6	K178E, A561T	2
			29	2170	>50	0.6	K97E, K178E, K186Q, L397M, A561T	6

The green dots indicate when resistance testing was performed. This analysis was performed using a 15% variant threshold.
AA, amino acid; ART, antiretroviral therapy; ATI, analytical treatment interruption; bNAb, broadly neutralizing antibody; IC_{80}, 80% inhibitory concentration; IC_{90}, 90% inhibitory concentration; VL, viral load; VR, viral rebound.

- For participants with data at the first rebound visit (n = 14), CAP256 susceptibility post-rebound/ATI was correlated with time to rebound (P = 0.04) and time to ART restart (P = 0.02; **Figure 7**)

Figure 7. Time to ART Restart and Rebound[a] Correlates With CAP256 Susceptibility Post-Rebound/ATI



[a]HIV-1 RNA ≥50 copies/mL.
ART, antiretroviral therapy; ATI, analytical treatment interruption; IC_{80}, 80% inhibitory concentration; IC_{90}, 90% inhibitory concentration.