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Sensitivity of HIV-1 CRF01_AE envelopes to broadly neutralizing antibodies VRC07-523LS and PGDM1400LS

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Abstract

Background: Understanding the sensitivity of viral envelopes to broadly neutralizing antibodies (bNAbs) encoded within the reservoir is of major importance in evaluating efficacy in analytical treatment interruption (ATI) trials using bNAbs as an intervention in people living with HIV (PLWH). In this study, we assessed the sensitivity of viral envelopes (Envs) sequenced from RV254 participants for sensitivity to the bNAbs VRC07-523LS and PGDM1400LS.

Methods: Neutralization assays assessed Env sensitivity to the single bNAbs and a combination of the two. IC80s and IC50s of each mAb were determined and compared between the single mAbs and the combination of PGDM1400LS and VRC07-523LS. IC80 <1μg/mL were considered sensitive to bNAb neutralization.

Results: Despite more Envs displaying sensitivity to VRC07-523LS, PGDM1400LS displayed more potent neutralization. Nearly all Envs sensitive to either displayed increased sensitivity to the combination.

Conclusions: The combination provided increased coverage across viral Envs. CRF01_AE is Envs are sensitive to VRC07-523LS & PGDM1400LS, and these bNAbs may be used in ATI trials.

Methods

- 119 representative Envs sequenced and cloned from the viral reservoirs of 116 RV254 participants (85% CRF01_AE; 15% other subtypes/recombinant forms) who received early ART.
- Pseudoviruses (PSVs) harboring functional Envs were produced via transfection in 293T/17 cells with pSG3ΔEnv backbone.
- TZM-bl neutralization assays measured the sensitivity of each Env to VRC07-523LS, PGDM1400LS, and a combination of the two. Sensitivity of Envs was reported as IC50s and IC80s against single and combination mAbs.

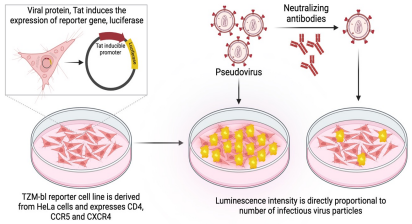

Figure 1: Neutralization Assays
TZm-bl cells that contain a luciferase reporter were added to a mixture of PSV and antibodies. Infected cells express luciferase which directly correlates to infectious particles.

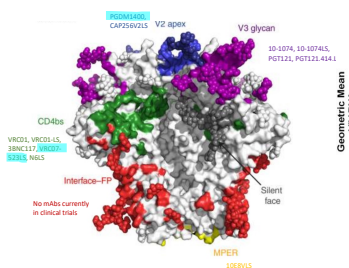

Figure 2: HIV Envelope epitopes
CD4 binding site (green) and V2 apex (blue) are distant, non-overlapping epitopes. VRC07-523LS and PGDM1400LS combinations create a complementary mechanism, targeting non-overlapping conserved and variable epitopes [1].

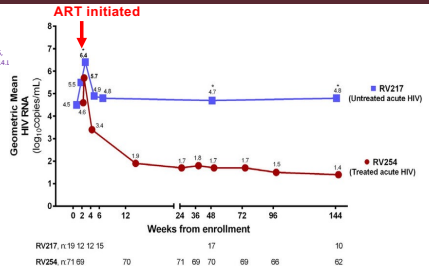

Figure 3: RV254 cohort
The RV254 cohort is comprised of individuals in Bangkok, Thailand who initiated ART immediately after they were identified as HIV-1 RNA+ during early acute infection. Viral reservoirs were measured by PCR assay during acute infection through chronic infection, providing evidence that early ART initiation (red line) resulted in significantly reduced acute viral loads and reduced setpoints compared to untreated individuals (blue line) [2].

Results

- IC50 sensitivity cut-off <1 μg/mL:
  - **PGDM1400LS** – 59% of Envs were sensitive (average=0.116 μg/mL); **VRC07-523LS** – 77% of Envs were sensitive (average=0.324 μg/mL); **Combination** – 87% of Envs were sensitive (average=0.217 μg/mL)
- IC80 sensitivity cut-off <1 μg/mL:
  - **PGDM1400LS** – 47% of Envs were sensitive (average=0.202 μg/mL); **VRC07-523LS** – 49% of Envs were sensitive (average=0.483 μg/mL); **Combination** – 63% of Envs were sensitive (average=0.293 μg/mL)

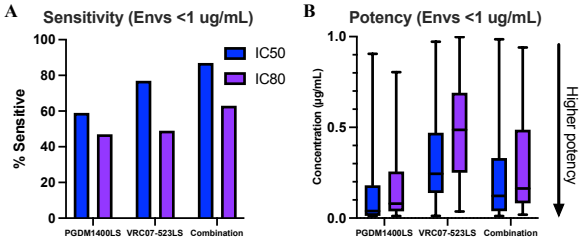

Figure 4: Participant Env Susceptibility to VRC07 and PGDM1400 Antibodies
(**A**) The proportion (% Sensitive) of Envs that were neutralized by single or combination mAbs at <1 μg/mL is represented for IC50 and IC80 cut-offs. (**B**) The average concentration of indicated mAb necessary to neutralize 50% or 80% of sensitive (<1 μg/mL) PSVs is shown. Env sensitivity to one bNAb was unrelated to the sensitivity to the other. However, the combination provided compensatory coverage, ultimately increasing sensitivity across the cohort.

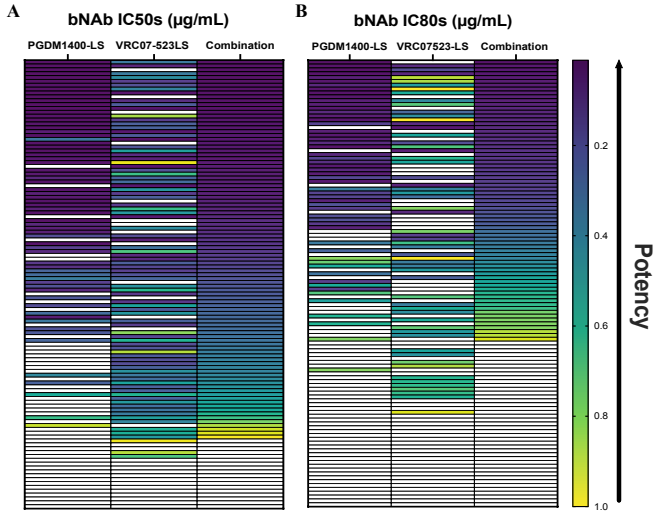

Figure 5: Sensitivity
A heatmap representing the IC50 (**A**) or IC80 (**B**) neutralization sensitivity of each representative mAb or combination of mAbs is shown. Potency (IC50/IC80) scores range from least sensitive in yellow (1 μg/mL) to most sensitive in dark purple (0.01 μg/mL). Cells in white are above the threshold of "sensitive" Envs established for this study (>1 μg/mL). PGDM1400LS demonstrated more potent neutralization across the screened Env candidates in comparison to VRC07-523LS. The VRC07-523LS and PGDM1400LS bNAb combination provided increased coverage across several viral Envs. IC80s suggests considerable potential of the combination to effectively neutralize a significant proportion of viral reservoirs in the RV254 cohort

Conclusions

- These data provide evidence that **CRF01_AE Envs sequenced from viral Env are sensitive to VRC07-523LS and PGDM1400LS** and may be used as candidate bNAbs in future Acute treatment interruption trials.
- The VRC07-523LS and PGDM1400LS **bNAb combination** provided increased coverage across several viral Envs and showed **complementary neutralization effects** in Envs that were not sensitive to single bNAbs.
- Additional studies are needed to confirm the optimal bNAb combinations for people living with CRF01_AE HIV-1 infection.
- This data provides further evidence supporting the need for the development of next-generation bNAbs.

References
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ACKNOWLEDGEMENTS
We would like to thank the study participants who committed so much of their time for this study. The participants were from the RV254/SEARCH 010, which is supported by cooperative agreements (W81XWH-18-2-0040) between the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., and the U.S. Department of Defense (DOD) and in part, by the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institute of Health (DAIDS, NIAID, NIH) (grant AA121058-001-01000). Antiretroviral therapy for RV254/SEARCH 010 participants was supported by the Thai Government Pharmaceutical Organization, Gilead Sciences, Merck and ViiV Healthcare.