Characterizing HIV Env Escape in Response to VRC07-523LS in a SHIV-Infected NHP Model

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Introduction: Despite success of antiretroviral therapy (ART), complimentary interventions for HIV prevention, treatment and cure are warranted, like broadly neutralizing antibodies (bnAbs). Our current study therefore characterizes mutations in the HIV *env* following administration of a CD4-binding site (CD4bs) bnAb in simian human immunodeficiency virus (SHIV)-infected nonhuman primates (NHP).

Methods: Six rhesus macaques (RM) were infected with an adapted clade C virus, SHIV.C.CH505.v2 (CH505.v2), and were viremic for 6 weeks. RMs received two doses of VRC07-523LS, at weeks 6 and 10. Using single genome sequencing, plasma *env* sequences were compared pre- and post-treatment. Env-specific pseudoviruses were generated containing escape mutations observed in *env* sequencing and assessed for susceptibility to VRC07-523LS and other less potent CD4bs bnAbs (VRC01 and 3BNC117) by TZM-bl neutralization assay.

Results: Following the first dose of VRC07-523LS, viral loads dropped across the cohort, but one animal droppped to undetectable at week 7, and then rebounded by week 8. To characterize viral evolution in the face of substantial antiviral effect, we obtained 59 *env* sequences from this animal collected pre- and post-bnAb. We found mutations in five regions of the putative VRC07-523LS epitope (N279S, N280D, N358D, R456S, and K460E). We then tested each mutation for its impact on VRC07-523LS activity. N280D, N279S, and R456S were sampled in other animals and had the greatest impact on bnAb activity; N280D conferred resistance to VRC07-523LS, as well as the less potent VRC01 and 3BNC117, while N279D and R456S demonstrated minimal change to VRC07-523LS, but significant decreases in potency to 3BNC117 and VRC01. The mutations N358D and K460E, which were not sampled in other animals, did not substantially change virus susceptibility to VRC07-523LS, 3BNC117 or VRC01.

Conclusion: Our SHIV.C.CH505.v2 NHP model system, which allows testing of one treatment across multiple outbred animals, improves understanding of how HIV responds to bnAbs in an *in vivo* system. Mutations within the putative bnAb epitope that were common across multiple animals impacted VRC07-523LS resistance substantially, while ones from a single animal exerted less effect on bnAb activity. The results from this study can inform future studies that combine other classes of bnAbs or next-generation CD4bs bnAbs.