Randomized Controlled Trial of VRC01 Monoclonal Antibody during Acute HIV Infection

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BACKGROUND

The VRC01 broadly neutralizing monoclonal antibody (bNAb), targeting the CD4 binding site of HIV-1, has been shown to decrease viremia in people with HIV-1 and prevent infection with neutralization-sensitive strains[1-3]. Administration of HIV-1 bNAbs to non-human primates during acute simian-human immunodeficiency virus infection also limits viremia with sustained viral control seen in some animals[4-6]. We investigated the **impact of a single intravenous VRC01 infusion in acute HIV-1 infection in individuals who initiated antiretroviral therapy (ART)** simultaneously or one week later.

METHODS

RV398 (NCT02591420) was a randomized placebo-controlled trial of 24 adults enrolled with acute HIV-1 infection in Thailand, Kenya, Uganda, and Tanzania. Eight participants were randomized to each of the three arms: 1) placebo infusion + immediate ART, 2) VRC01 40mg/kg + immediate ART, or 3) VRC01 40mg/kg + subsequent ART initiated on day 7. Infusions in arms 1 and 2 were blinded; study duration was 24 weeks. Initial ART consisted of TDF/FTC (or 3TC)/EFV. All participants provided written informed consent. Plasma HIV-1 RNA *env* was sequenced for each study participant at study enrollment and evaluated as Env-pseudotyped virus for neutralization sensitivity to VRC01 in the TZM-bl target cells.

Figure 1. Study locations

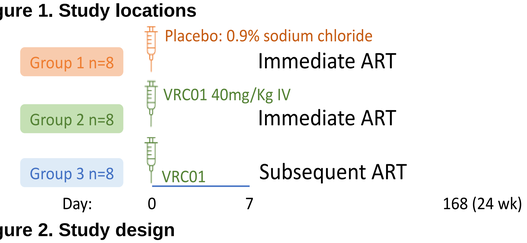

Figure 2. Study design

Primary objectives were to assess: 1) **VRC01 safety** in the setting of acute HIV-1 infection and 2) **virologic outcomes** mediated by VRC01 in the first 7 days. Exploratory objectives included viral neutralization sensitivity to VRC01.

Administration of **VRC01** bNAb with ART in acute HIV-1 infection is **safe** and **well tolerated**, with limited impact on acute HIV-1 plasma viremia.

RESULTS

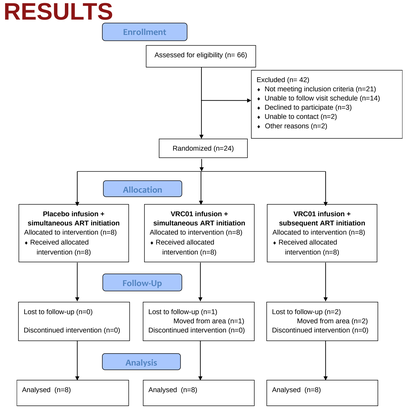

Figure 3. Trial profile

		Placebo + Immediate ART (N=8)	mAb Therapy + Immediate ART (N=8)	mAb Therapy + Subsequent ART (N=8)	Overall (N=24)
Origin	Thailand	5 (62.5%)	5 (62.5%)	5 (62.5%)	15 (62.5%)
	East Africa	3 (37.5%)	3 (37.5%)	3 (37.5%)	9 (37.5%)
Mean age (SD)		21.9 (4.6)	23.5 (3.2)	24.9 (2.5)	23.4 (3.6)
Gender	Cis-men	6 (75.0%)	4 (50.0%)	4 (50.0%)	14 (58.3%)
	Cis-women	2 (25.0%)	3 (37.5%)	2 (25.0%)	7 (29.2%)
	Transgender women	-	1 (12.5%)	2 (25.0%)	3 (12.5%)
Fiebig stages	I	1 (12.5%)	1 (12.5%)	1 (12.5%)	3 (12.5%)
	III	3 (37.5%)	3 (37.5%)	3 (37.5%)	9 (37.5%)
	III	2 (25.0%)	3 (37.5%)	1 (12.5%)	6 (25.0%)
	IV	1 (12.5%)	-	3 (37.5%)	4 (16.7%)
	V	1 (12.5%)	1 (12.5%)	-	2 (8.3%)
Viral Load, log(copies/mL)	Mean (SD)	5.8 (1.2)	5.7 (0.9)	5.6 (0.7)	5.7 (0.9)
CD4+ Count, cells/μL, n=7	Mean (SD)	595.7 (252.3)	500.8 (99.9)	411.0 (158.9)	502.5 (188.8)

Table 1: Summary of Categorical and Continuous Baseline Characteristics

VRC01 Safety: There was one grade 3 VRC01-related adverse event (AE), a transient AST elevation, and no VRC01-related serious adverse events (SAEs). Solicited AEs were mild or moderate.

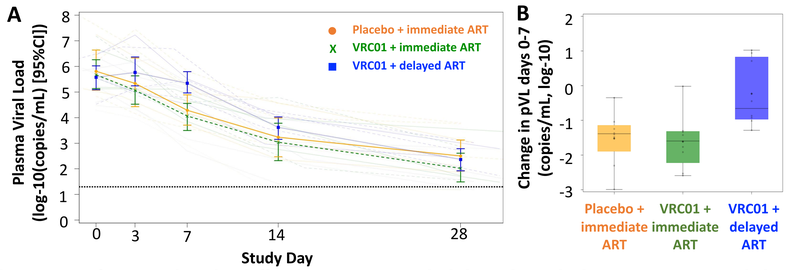

Figure 4. Plasma viremia following VRC01 administration during acute HIV-1 infection. A. Longitudinal log_{10} plasma viral load (mean and 95% CI) from baseline to study day 28 by treatment group. The dotted line indicates the limit of quantification (1.3 log_{10} copies/ml) **B.** Change in log_{10} plasma viremia over the first seven days.

Virologic outcomes: Immediate ART achieved more substantial viral load reduction by day 7 compared to the delayed ART arm in pairwise comparisons (p=0.007 and 0.003, respectively). The greatest reduction (mean log10; 95% CI) was observed in the VRC01 + immediate ART arm (-1.61; -2.10,-1.07) followed by placebo + immediate ART (-1.52; -2.08,-1.04) and VRC01 + delayed ART (-0.23; -0.82, 0.43).

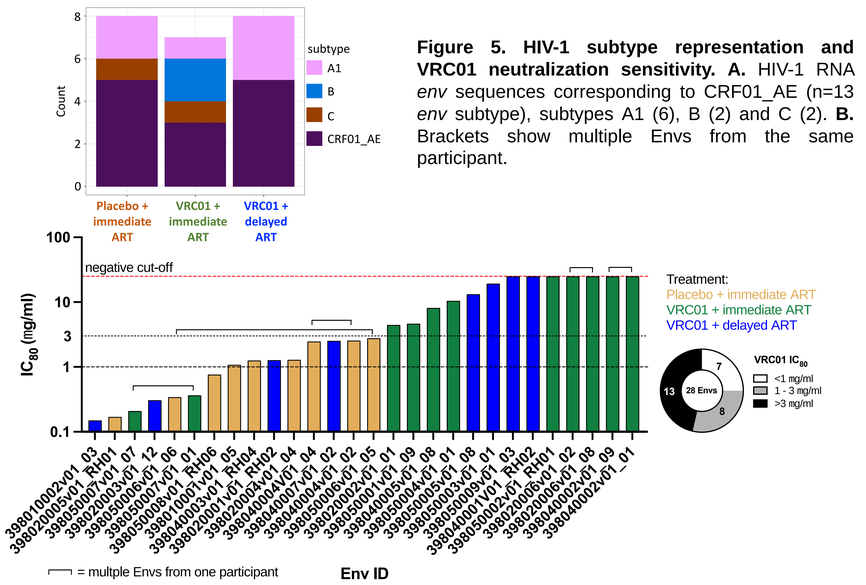

Figure 5. HIV-1 subtype representation and VRC01 neutralization sensitivity. A. HIV-1 RNA *env* sequences corresponding to CRF01_AE (n=13 *env* subtype), subtypes A1 (6), B (2) and C (2). **B.** Brackets show multiple Envs from the same participant.

Sequencing and Viral Neutralization Sensitivity: Viral sequencing of HIV-1 genomes at baseline from 23/24 infections reflected the geographic diversity of the participants. Fifteen Envs from 12 individuals (7 received placebo+immediate ART) were determined sensitive (IC80<1μg/ml) or intermediate sensitive (IC80 1 - 3μg/ml) to VRC01 at time of infusion.

CONCLUSIONS

Initial results demonstrate the **safety of VRC01 with ART** in acute HIV infection and the **feasibility of studying mAb interventions during AHI across diverse subtypes and geographies.** Modest VRC01 neutralization sensitivity of circulating viruses may have contributed to the limited impact of VRC01 on acute HIV-1 viremia.

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ACKNOWLEDGEMENTS

This work was supported in part by the US Army Medical Research and Development Command under Contract No. W81-XWH-18-C-0337 and by a cooperative agreement (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). Funding and trial sponsorship was provided by the Division of AIDS, NIAID, NIH.

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