Poster #330LB

VRC01 infusion has no effect on HIV-1 persistence in ART-suppressed chronic infection

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Introduction

- ART blocks infection of new cells but has no impact on cells already infected with latent or transcriptionally active proviruses.
- Broadly neutralizing monoclonal antibodies (bnMAb) may promote clearance of viremia and cells expressing envelope through antibody-dependent cell-mediated cytotoxicity.
- A5342 evaluated whether the CD4-binding site bnMAb VRC01 affects multiple measures of HIV persistence in chronically-infected individuals on suppressive ART.

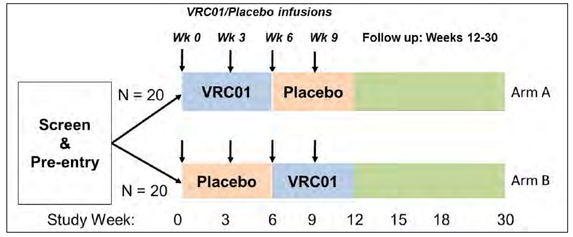
Objectives

- To assess the safety and tolerability of two IV infusions (40 mg/kg each) of bnmAb, VRCO1, administered 3 weeks apart in HIV-1 infected participants on effective ART.
- To examine the impact of VRC01 on the number of cells containing unspliced HIV-1 transcripts, as measured by the change in cell-associated (CA) HIV-1 RNA/DNA ratio in total CD4+ cells from entry to week 6 (primary study endpoint). Other virologic outcomes are describe below.

Methods

- Phase I, double-blind, randomized, placebo-controlled, parallel-arm study (Figure 1)
- All participants received 2 infusions of VRC01 (40 mg/kg)
- 40 participants were randomized equally to:
  - Arm A: VRC01 at Weeks 0 & 3; placebo at Weeks 6 & 9
  - Arm B: Placebo at Weeks 0 & 3; VRC01 at Weeks 6 & 9
- Study visits: Screen, Pre-entry, Entry (Week 0), Weekly for Weeks 1-12, and at Weeks 15, 18 and 30
- Blood samples from screen, entry, and weeks 3, 6, 9, and 12 were tested for multiple virologic outcomes including:
  - Plasma single copy HIV RNA assay (SCA) targeting integrase; the limit of detection ranged from 0.4 to 1 copies/ml, depending on the plasma volume availability (Cillo et al. J Clin Micro 2015)
  - Total CD4+ T cell-associated HIV RNA and DNA was measured by ultra-sensitive qPCR (Hong et al. J Clin Micro 2016)
  - Total PMA/ionomycin-induced virus production from CD4+T-cells; viral nucleic acid was quantified in supernatants by qPCR
- The primary analysis is the between arm comparison of changes in $\log_{10}$ transformed CA RNA/DNA ratio from BL to week 6 using Wilcoxon rank sum test at 10% significance level.
- Secondary analyses of within-participant changes from pre-VRC01 to post-VRC01 were compared using Wilcoxon signed rank test combining both arms.

Figure 1: Study Schema



Key inclusion/exclusion criteria:
- HIV-infected adults age 18-65 years
- CD4+ cell count ≥ 200mm^3
- Initiated ART in chronic infection with viral suppression to <LOD for ≥24 months (single isolated blip allowed)
- No current active HCV or HBV

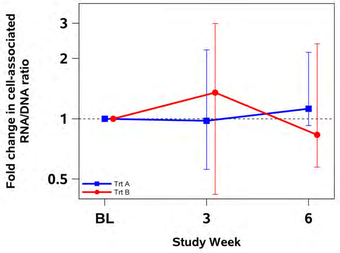
Table 1: Baseline Characteristics

	Arm A (N=20)	Arm B (N=20)	Total (N=40)
Age (years) Median (IQR)	45 (32, 54)	56 (50, 59)	52 (41, 58)
Sex (N, %) Male	17 (85%)	20 (100%)	37 (93%)
Race/Ethnicity (N, %)			
White, non-Hispanic	13 (65%)	14 (70%)	27 (68%)
Black, non-Hispanic	3 (15%)	4 (20%)	7 (18%)
Hispanic	4 (20%)	2 (10%)	6 (15%)
ART regimen at Entry (N, %)			
NNRTI + NRTIs	6 (30%)	5 (25%)	11 (28%)
PI + NRTIs	4 (20%)	6 (30%)	10 (25%)
InSTI + NRTIs	7 (35%)	6 (30%)	13 (33%)
Other	3 (15%)	3 (15%)	6 (15%)
CD4 cell count (cells/mm^3) Median (IQR)	701 (594, 952)	685 (535, 843)	696 (559, 889)
CD8 cell count (cells/mm^3) Median (IQR)	801 (490,1210)	617 (480, 744)	663 (490, 936)
CD4/CD8 Ratio Median (IQR)	0.9 (0.7, 1.2)	1.1 (0.9, 1.8)	1.0 (0.8, 1.4)

Results

Enrollment and Safety:
- 40 participants were randomized; 20 per arm. Median age was 52 y; median CD4+ T-cell count was 696 /mm^3 (Table 1). Two participants (1 from each arm) discontinued study prior to Week 12.
- Safety: VRC01, 40 mg/kg IV for 2 doses was safe and well tolerated. No treatment-related adverse events ≥grade 3 were reported during study follow up. One VRC01 infusion was held after 94% was administered due to Grade 2 rash, however the 2nd dose for this participant was well tolerated.

Virologic Outcomes (Table 2):
- No participants experienced virologic failure during the study.
- CAR/CAD ratio: No significant difference between VRC01 and placebo was observed for change from BL to week 6 (Figure below; median fold change: 1.12 vs. 0.83, p=0.16, 95% CI (0.75, 2.42)), or from pre-to post-VRC01 time points with both arms combined (1.24, 95% CI (0.83, 1.69), p=0.29).



- Residual viremia: At study entry, 22/40 (55%) participants had SCA ≥1 copy/ml. At week 6, there was no difference in the proportion with SCA ≥1 copy/ml between the arms (42% vs. 37%, p=1.0). The proportion ≥1 copy/ml was not statistically different for the pre- to post-VRC01 time points for both arms combined (p=0.59).
- Total stimulated virus production from CD4+ T-cells: The change in stimulated virus production was not statistically different between arms from BL to week 6 (-0.13 vs. 0.12 $\log_{10}$ RNA copies/ml; p=0.91), or from pre- to post-VRC01 time points with both arms combined (p=0.85).

TABLE 2: Virologic Outcomes

Parameter	Arm A	Arm B	p-value*	Arms A and B Combined		Change from Pre- to Post-VRC01	p-value**
Median (Q1, Q3)	Change from baseline to Week 6			Pre-VRC01 values	Post-VRC01 values		
Cell-associated HIV RNA/DNA ratio^	1.12 (0.92, 2.15)	0.83 (0.57, 2.37)	0.16	0.04 (0.02 0.08)	0.05 (0.02, 0.08)	1.24 (0.61, 2.15)	0.29
Cell-associated HIV RNA ($\log_{10}$ cps/10^6 CD4 cells)	0.08 (-0.23, 0.32)	-0.08 (-0.26, 0.29)	0.39	1.55 (0.99, 1.99)	1.48 (0.99, 2.10)	0.09 (-0.23, 0.32)	0.64
Cell-associated HIV DNA ($\log_{10}$ cps/10^6 CD4 cells)	-0.06 (-0.13, 0.06)	-0.01 (-0.08, 0.13)	0.30	2.93 (2.43, 3.15)	2.92 (2.51, 3.11)	-0.05 (-0.12, 0.06)	0.19
Stimulated Virus Production from total CD4+T-cells ($\log_{10}$ cps/ml)	-0.13 (-0.51, 0.92)	0.12 (-0.52, 0.30)	0.91	2.99 (2.06, 3.37)	2.66 (2.28, 3.41)	-0.10 (-0.51, 0.44)	0.85
	Week 6		p-value***				p-value****
Plasma HIV RNA ≥1 cp/ml by single copy assay (%)	8/19 (42%)	7/19 (37%)	1.0	16/38 (42%)	14/38 (37%)		0.59

^Changes in RNA/DNA ratios are shown as fold change calculated by dividing the RNA/DNA ratio at the later time point by the earlier time point
* Wilcoxon Rank Sum test ** Wilcoxon Signed Rank test *** Fisher's exact test **** McNemar's test

Discussion

- **In individuals with chronic ART-suppressed HIV infection, VRC01 infusions were safe and well tolerated.**
- **Two high-dose infusions of VRC01 did not affect virologic outcomes including:**
  - **Residual plasma viremia**
  - **Cell-associated HIV RNA/DNA levels**
  - **Total stimulated virus production from CD4+T-cells.**
- **Potential mechanisms being evaluated to explain the lack of response include viral resistance to VRC01, poor penetration of VRC01 to sites of virus expression, or inherent inability of VRC01 to clear virus particles or virus-expressing cells.**

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