Susceptibility to anti-HIV bnAbs is concordant in pre-ART plasma and on-ART PBMC samples: ACTG NWCS413

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Abstract

Background: Pre-existing resistance is a barrier to the efficacy of broadly neutralizing antibodies (bnAbs) for treatment and cure of HIV infection. We aimed to determine the range of baseline susceptibilities to bnAbs in clinical development and to assess the PhenoSense HIV nAb Assay's predictive capacity in plasma virus and proviral DNA samples.

Methods: HIV envelopes derived from pre-ART plasma and PBMCs from 1 and 3 years of ART from each of 65 chronically HIV-infected participants of the ART naïve trial A5257 were tested for neutralization sensitivity to seven bnAbs (VRC01, VRC07.523LS, 3BNC117, N6, 10-1074, CAP256-VRC26.25, 10E8) using the PhenoSense nAb assay, which generates pseudovirions from plasma vRNA or PBMC proviral DNA-derived HIV envelopes. PBMCs from 9 participants at entry to A5340, which evaluated VRC01 during ART interruption, were also tested. Rank-based Spearman Correlation and Fisher's exact tests were used for statistical analyses.

Results: Participants' median CD4 count was 350 cells/mm^3 and 40% had a baseline VL >100,000 copies/ml. IC50s varied more than 3 logs for each bnAb, but pre-ART plasma, year 1 and 3 PBMC values were highly correlated (Spearman r= 0.62-0.95, P<0.001 for all), with modestly lower IC50s in the later PBMC samples. Susceptibilities within the CD4 binding site bnAbs were correlated (r=0.71-0.86, P<0.001 for pre-ART plasma). No relationship was found between bnAb classes, a except modest correlation between CD4bs bnAbs and 10-1074 (r= 0.29-0.4, P=0.002-0.023).
Among the A5340 samples, VRC01 IC50s from entry PBMCs correlated with published pre-ART plasma IC50s available for 5 participants (Spearman r=0.9, P=0.04). In 9 participants with entry PBMCs, VRC01 IC50s did not significantly correlate with time to rebound (Spearman r=-0.35, P=0.37), but IC50<0.5 µg/mL was associated with delayed time to rebound (>8 weeks) (P=0.0278).

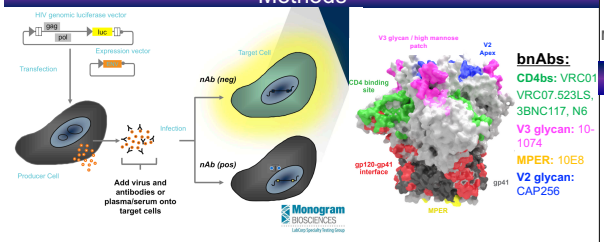
Conclusions: We found a wide range in baseline neutralization susceptibilities to clinically relevant bnAbs with highly correlated values across plasma and PBMC-derived samples over 3 years of ART. In A5340, PhenoSense nAb susceptibilities on entry PBMCs were similar to published pre-ART values and IC50<0.5 µg/mL was associated with delayed rebound after ATI. Results support the utility of screening for neutralization susceptibility prior to therapeutic bnAb use and suggest PhenoSense nAb PBMC testing may be a valid approach in suppressed individuals.

Participants and Samples

- 3 samples each from 65 participants of A5257[1], a large ART efficacy trial conducted at US sites between 2008-2014
- Samples: Pre-ART plasma, PBMCs from 1 and 3 years of ART suppression
- A5257 (subgroup) participant characteristics:
  - 88% were male, 63% white, with median age of 37 years.
  - Baseline VL was >100,000 copies/ml in 40%
  - median CD4 count was 353 cells/mm^3.
- Entry PBMC samples from 9 participants of A5340[2], a Phase I clinical trial of VRC01

[1]Lennox et al., *Ann Int Med* 2014; [2]Bar et al., *NEJM* 2016

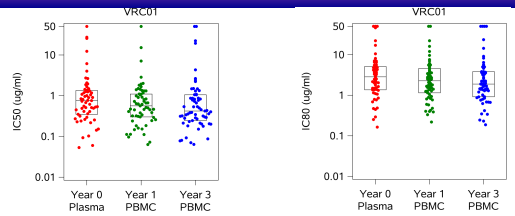
Methods



PhenoSense HIV nAb Assay[3] **bNAb Panel**

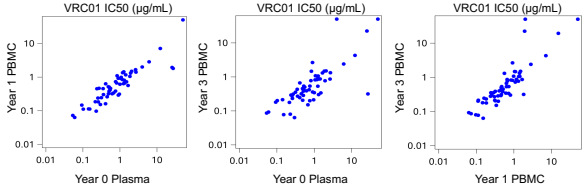
[3]Richman et al., *PNAS* 2003; Trimer adapted from McCoy and Burton, *Immuno Rev* 2017

Results: VRC01



- IC50 ranged from <0.1 to >50 µg/mL; IC80 ~0.3 to >50 µg/mL
- 75% for pre-ART plasma: 1.3 µg/mL; PBMCs: 1.0 µg/mL

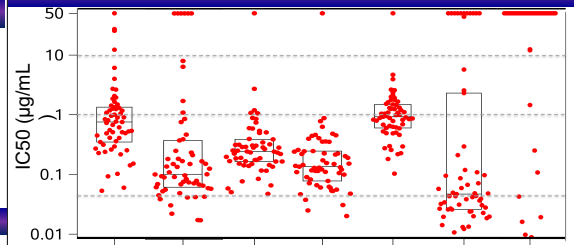
Results: Correlations between samples



Plasma and PBMC samples' IC50s correlate (Spearman r= 0.78-0.91; P<0.001)

- Within sample comparisons for all bnAbs r= 0.64-0.98; P<0.001
- Pre-ART plasma < Year 1 PBMC ≤ Year 3 PBMCs

Results: IC50s of Pre-ART Plasma



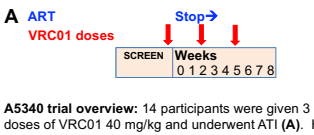
Med IC50: (µg/mL)	VRC01	3BNC117	N6	VRC07.523	10E8	10-1074	CAP256
	0.758	0.103	0.243	0.135	0.921	0.047	50.0

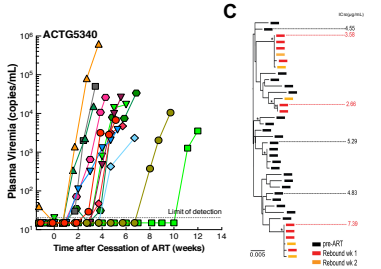
Results: Sensitivity Thresholds for Year 1 PBMCs

bnAb	IC50 < 1 ug/mL N (%)	IC50 < 10 ug/mL N (%)	IC80 < 1 ug/mL N (%)	IC80 < 10 ug/mL N (%)
VRC01	43 (70.49%)	59 (96.72%)	14 (22.95%)	56 (91.80%)
3BNC117	53 (86.89%)	57 (93.44%)	47 (77.05%)	53 (86.89%)
N6	59 (96.72%)	60 (98.36%)	43 (70.49%)	59 (96.72%)
VRC07-523LS	59 (96.72%)	60 (98.36%)	52 (85.25%)	60 (98.36%)
10-1074	48 (78.69%)	50 (81.97%)	45 (73.77%)	49 (80.33%)
10E8	50 (81.97%)	60 (98.36%)	9 (14.75%)	59 (96.72%)

bnAb combinations	IC50 < 1 ug/mL N (%)	IC80 < 1 ug/mL N (%)
VRC01 + 10-1074	36 (59.02%)	11 (18.03%)
3BNC117 + 10-1074	45 (73.77%)	37 (60.66%)
N6 + 10-1074	46 (75.41%)	31 (50.82%)
VRC07-523LS + 10-1074	47 (77.05%)	40 (65.57%)
10E8 + 10-1074	39 (63.93%)	7 (11.48%)

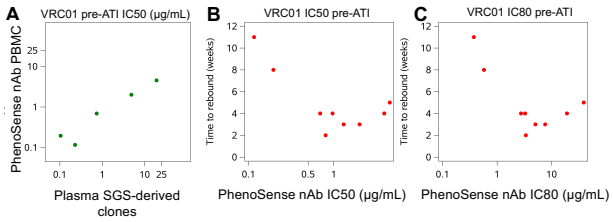
Results: Correlation with assays and outcomes in A5340[2]





A5340 trial overview: 14 participants were given 3 doses of VRC01 40 mg/kg and underwent ATI **(A)**. High levels of VRC01 were achieved and viral rebound followed **(B)** with modest delay vs. historical controls.

VRC01 resistance analysis overview: SGS Envs from pre-ART plasma and rebound plasma were tested for sensitivity to VRC01 in TZM.bl assay. Pre-existing resistance to VRC01 was identified in participants with early viral rebound **(C)**.



A. Phenosense nAb and published TZM.bl assay results. In 5 participants with available samples, the VRC01 IC50s derived from pre-ATI samples were highly correlated. Phenosense nAb from entry PBMCs (Y axis) and pre-ART plasma SGS-derived Envs in the TZM.bl assay (3-6 clones, X axis) (Spearman r=0.9, P=0.04).

B & C. Phenosense nAb and time to rebound in A5340. In 9 participants with entry PBMCs, VRC01 IC50s did not significantly correlate with time to rebound (Spearman r=-0.35, P=0.37). IC50 > 0.5 µg/mL and IC80 >1 µg/mL were associated with rapid rebound (2-5 weeks) (P=0.0278, Fisher's exact test).

Conclusions

- In samples from recently treated US ACTG trial participants, we found a wide range in baseline neutralization susceptibilities to individual and combinations of clinically relevant bnAbs.
- Values were highly correlated across plasma and PBMC-derived pseudovirions over 3 years of ART.
- In A5340, a pilot efficacy trial of VRC01, Phenosense nAb values were similar to published values from SGS-derived Env pseudoviruses and IC50<0.5 µg/mL was associated with delayed rebound.
- **Results support the utility of screening for bnAb susceptibility prior to therapeutic bnAb use and suggest PhenoSense nAb PBMC testing may be a valid approach.**
- The PhenoSense nAb assay is pending CLIA/CAP compliant validation and will be used to screen participants for entry into A5357 (VRC01.LS and Cabotegravir) and A5364 (3BNC117.LS and 10-1074.LS), and other bnAb clinical trials.

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