Stable HIV-1 Autologous and Heterologous Virus Neutralization on Suppressive ART

301

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BACKGROUND

- Vaccine and cure regimens aiming to induce HIV-1 neutralizing antibodies (nAb) in people living with HIV-1 (PLWH) will benefit from a better understanding of the dynamics and durability of nAb during ART and reliable assay platforms to assess them.

METHODS

- We analyzed plasma and PBMC samples from 15 ACTG A5257 participants who initiated on ART at US sites:
  - median 40 years
  - 87% male
  - 33% Black
  - median pre-ART CD4 361 cells/mm³
- Longitudinal samples were collected pre-ART and at 1, 3 and ≥4 years (up to 10 years) during long-term ART suppression.
- To enable neutralization testing on ART, plasma IgG was purified with efficiency measured by spiked SIV mAb K11. IgG was reconstituted to the original plasma volume.
- Heterologous nAbs were measured against a 9-virus global reference panel. Results are expressed as the IgG dilution that neutralized 50% of each pseudovirus stock (ID50); ID50 >20 was considered a detectable response. Murine Leukemia Virus (MLV) served as control.
- Autologous pseudovirus stocks were prepared from Env expression vectors derived from pre-ART plasma and on-ART PBMC. Autologous nAbs were quantified using the PhenoSense mAb Assay platform.

RESULTS

Heterologous nAb responses to at least one virus were detected pre-ART in 9/15 participants (60%) vs 2/15 (13%) on ART at year 3 (p=0.02, McNemar) (Figure 1 Panel A).

Responses generally declined with ART, then remained stable. After 3 years on ART, no new heterologous responses were detected, and ID50 titers declined or remained stable within 3-fold assay variability (Figure 1 Panel B).

HIV-1 Autologous and Heterologous Virus Neutralization remain stable on suppressive ART supporting the use of these assays to measure on-ART vaccine-induced increases in HIV-1 nAb responses

Figure 1: Heterologous Longitudinal ID50 Results: 9-virus Global Panel

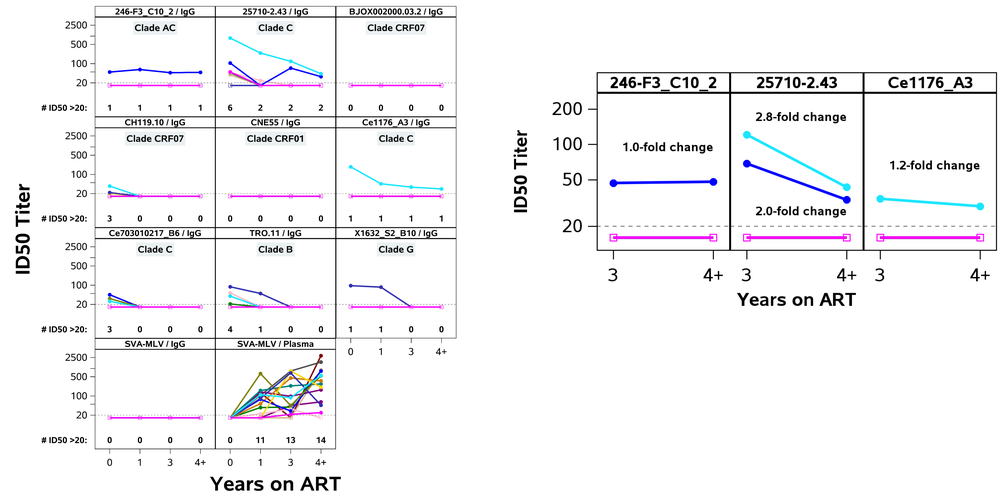
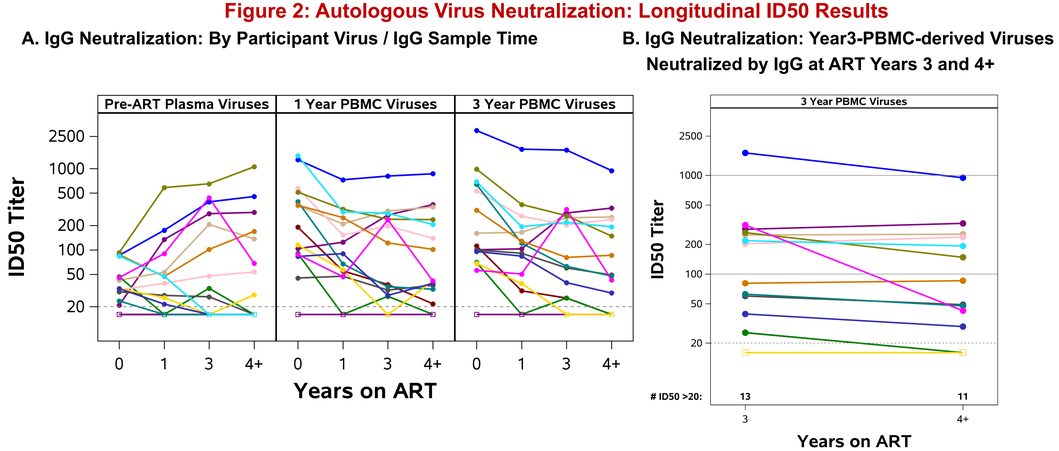


Figure 2: Autologous Virus Neutralization: Longitudinal ID50 Results



Each line represents an individual participant, displayed in the same color throughout
The dashed line represents the lowest dilution tested for the majority of samples (ID50 titer = 20)

RESULTS

13/15 (87%) participants had detectable autologous nAb responses to their pre-ART plasma pseudoviruses; detectable nAb ID50 titers ranged from 21-92 (Figure 2 Panel A). 13/15 (87%) also neutralized their autologous PBMC-derived viruses at 3 years on ART, with a median change after 3 years on ART of 0.76-fold (≈24% reduction) (≈15%/year reduction) and no >3-fold increases detected (Figure 2 Panel B).

CONCLUSIONS

- In PLWH, heterologous nAb are low-titer pre-ART and decline after ART initiation.
- Autologous nAb titers against PBMC provirus are readily detectable in most PLWH and decline gradually with ART.
- These results inform our understanding of HIV-specific nAb dynamics in PLWH before and during ART.
- They also delineate on-ART baseline levels of heterologous and autologous nAb in PLWH, and support the use of these assays to measure within-participant vaccine- or immunotherapy-induced increases in HIV-1 nAb responses.
- The heterologous assay requires less labor and can potentially document vaccine-induced increases in breadth, but many participants nAb will be below the limit of detection pre-intervention. The autologous assay is more labor intensive, but baseline activity on-ART should be measurable in most participants.

ADDITIONAL KEY INFORMATION

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- **Laboratory tests showed that in people living with HIV, neutralizing antibody responses against a person's own HIV as well as other strains of HIV remained stable after 3 years of effective antiretroviral therapy**
- **These results support use of these tests in clinical trials of HIV vaccine and cure strategies aiming to improve antibody responses in people living with HIV**