BNAB ESCAPE HIV-ENV VARIANTS IN ORALLY SHIV-INFECTED ART-TREATED INFANT MONKEYS

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BACKGROUND

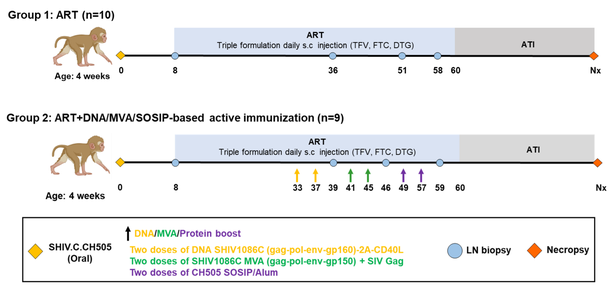
- 160,000 infants were infected with HIV in 2021 (UNAIDS), >50% during breastfeeding.
- Early life infection requires adherence to life-long ART predisposing children to long-term metabolic consequences and development of drug resistance.
- **Novel immune-based strategies in conjunction with ART are needed to achieve drug-free HIV remission.**
- Development of autologous virus-neutralizing antibodies via active immunization or broadly neutralizing antibody (bNAb) therapy can delay time to viral rebound after analytical treatment interruption (ATI).
- Development of viral variants that escape neutralizing antibody response limit the therapeutic potential of these strategies.

OBJECTIVES

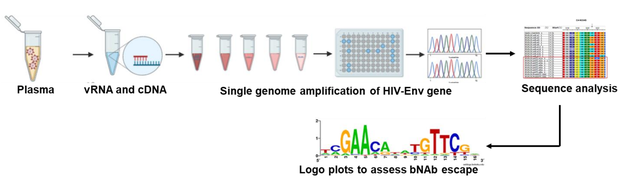
To map the bNAb escape mutations in orally SHIV-infected infant rhesus macaques (RMs) following ATI with and without therapeutic immunization

METHODS

Animal study design

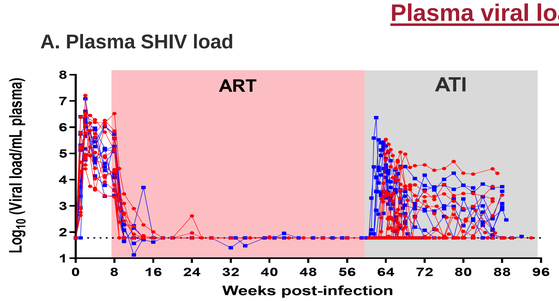


Single genome amplification and bNAb escape



RESULTS

Plasma viral load and time to viral rebound



Time to viral rebound

ART: 18 days (range 7-35 days)

ART+DNA/MVA/SOSIP: 14 days (range 7-168 days)

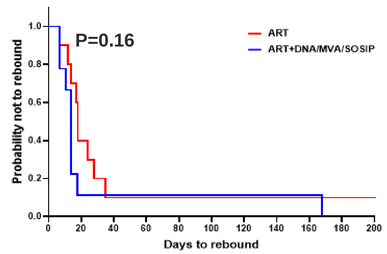


Figure 1. Comparable plasma viral load kinetics and time to viral rebound in ART only and ART+DNA/MVA/SOSIP vaccine groups (A) Plasma viral load of RMs from ART-only group (red) and ART+DNA/MVA/SOSIP vaccine group (blue) **(B)** Survival curve of time to viral rebound for infant RM's treated with ART-only (red) or ART+DNA/MVA/SOSIP vaccine (blue). P value was calculated using log-rank test (unadjusted).

Autologous SHIV neutralizing antibodies

A. Autologous virus neutralization pre-ART and post-ATI

B. Animals with detectable post-ATI autologous virus neutralization response

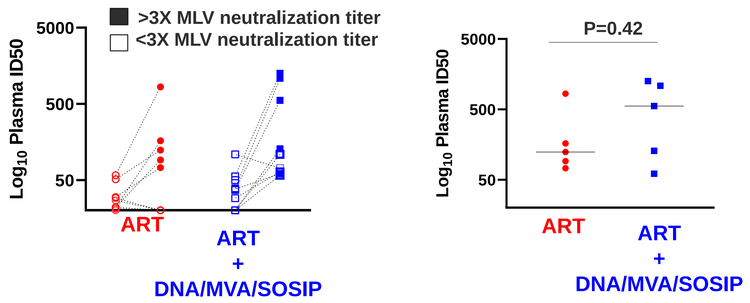
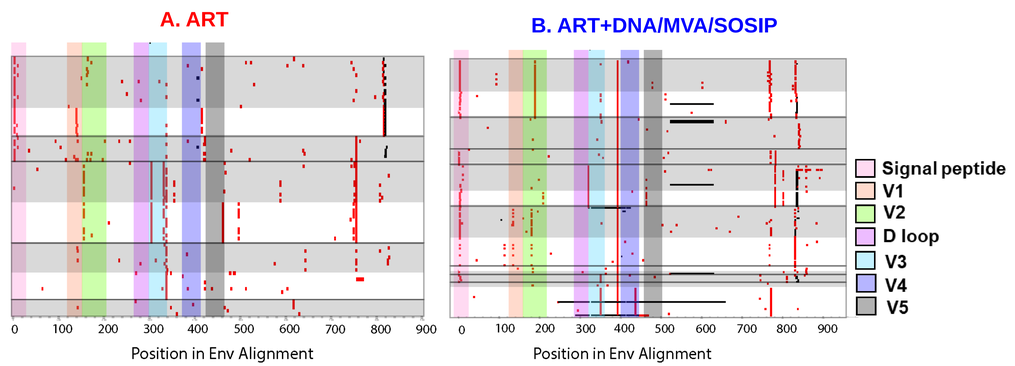


Figure 2. Slightly higher autologous virus neutralization response in ART+DNA/MVA/SOSIP group compared to ART only group (A) Autologous virus neutralization titers in ART only and ART+DNA/MVA/SOSIP vaccine groups pre-ART and 2-week post-ATI. 5/10 and 5/9 animals developed detectable autologous neutralizing antibody titers in ART and ART+DNA/MVA/SOSIP groups, respectively, post-ATI. Murine Leukemia Virus(MLV) neutralization served as a negative control and ID50 =3X MLV was the cut-off for detection of positive autologous neutralizing antibodies. **(B)** Median autologous virus neutralizing antibody titers in both groups for animals with detectable response. P value was calculated using Mann-Whitney test (unadjusted).

HIV envelope variants pre-ART and post-ATI

Figure 3. HIV-Env sequences pre-ART and post-ATI. Highlighter plots showing pre-ART (gray) and post-ATI sequences of RMs from **(A)** ART and **(B)** ART+DNA/MVA/SOSIP vaccine groups. Each box indicates one animal, red ticks indicate mutations compared to challenge virus, and black area indicates indels.



RESULTS

Detectable bNAb escape variants

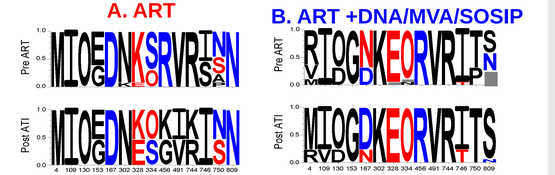


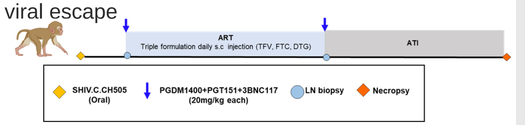
Figure 4. Logo plots of preART and postATI sequences at variable sites for two animals with the most variation from challenge virus. Pre-ART and Post-ATI logo plots for one animal in **(A)** ART and **(B)** ART+DNA/MVA/SOSIP vaccinated group. Residues are red if they confer resistance to one of the bNAb classes or blue if they confer sensitivity. O indicates a glycosylation site (*Bricault et al, 2019* and *Roark et al, 2021*).

CONCLUSIONS

- Comparable plasma VL kinetics and time to viral rebound post-ATI in ART and ART+DNA/MVA/SOSIP vaccine groups.
- Median autologous virus-neutralizing antibody titer slightly higher in the ART+DNA/MVA/SOSIP groups compared to ART only.
- Key mutations associated with bNAb escape:
  - **-Variability in site N334**
  - **-Variability in the signal peptide**
  - **-N130D (CD4bs-specific bNAb resistance)**
  - **-167N (V2-specific bNAb resistance)**
  - **-328K (V3- and CD4bs-specific bNAb resistance)**

Future Directions and clinical implications:

- HIV pseudoviruses with identified escape mutations to assess neutralization escape from bNAbs.
- Understanding bNAb and autologous virus neutralization escape variants developed upon treatment would facilitate the development of active and passive immunization regimens to minimize viral escape



FUNDING

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