GERMLINE-TARGETING SOSIP TRIMER IMMUNIZATIONS REDUCED POST-REBOUND SHIV LOADS IN INFANT MACAQUES

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BACKGROUND

- Globally, >1.4 million children are living with HIV.
- Life-long ART adherence predisposes children living with the virus to clinical complications.
- Adjunctive therapies to achieve ART-free viral suppression are urgently required.
- Immunization of HIV-naive rhesus macaques (RMs) with germline-targeting HIV SOSIP Env trimer elicited VRC01-like bNAb precursor responses *(Nelson et al 2024, Caniels et al 2024)*.
- **Hypothesis:** Administration of germline targeting HIV SOSIP trimer shortly after HIV infection will prime HIV-specific antibody responses and drive the expansion and maturation of specific B cell clonal lineages, **thereby resulting in a delay in time to rebound post-ATI**.

OBJECTIVES

Determine the impact of germline-targeting HIV SOSIP trimer immunization of SHIV-infected infant RMs on elicited antibody responses and viral rebound post-ART interruption (ATI).

RESULTS

Animal study design and plasma viral load (PVL)

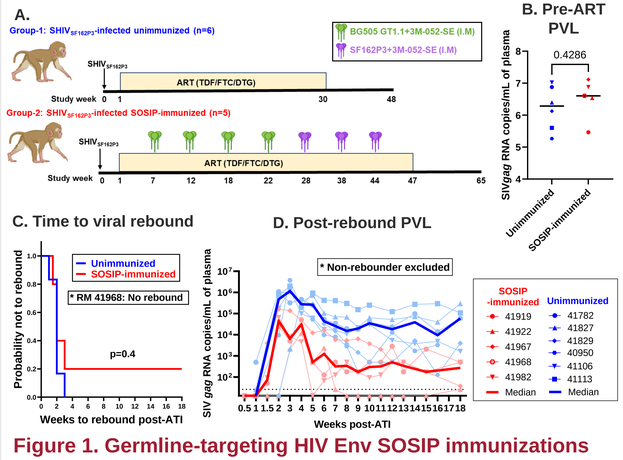
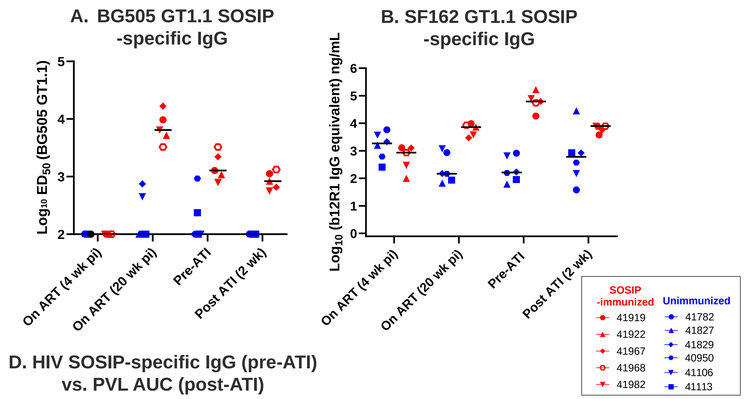


Figure 1. Germline-targeting HIV Env SOSIP immunizations control plasma viral load post rebound in infant RMs, yet do not delay viral rebound. (A) Oral $SHIV_{SF162P3}$ infection and SOSIP immunization of infant RMs. **(B)** PVL at ART start, **(C)** time to viral rebound, and **(D)** post viral rebound PVL in unimmunized (blue) and SOSIP-immunized (red) infant RMs. Mann-Whitney test (for B) or Log-rank test (for C) was performed using GraphPad Prism. Non-rebounder indicated in open symbol.

RESULTS

HIV Env SOSIP-specific IgG responses



D. HIV SOSIP-specific IgG (pre-ATI) vs. PVL AUC (post-ATI)

HIV Env trimer	rho	p
BG505 GT1.1	-0.65	0.04
SF162	-0.88	<0.001
246F3	-0.76	0.008
TRO11	-0.84	0.002
BJOX	-0.81	0.003
25710	-0.72	0.014
CH119	-0.68	0.025
CNE55	-0.71	0.015

Figure 2. SOSIP-immunized infant RMs developed higher magnitude HIV-specific IgG responses compared to unimmunized RMs. (A) BG505 GT1.1 SOSIP- **(B)** SF162 gp140 trimer- and **(C)** global HIV variant Env SOSIP-specific IgG responses in unimmunized (blue) and SOSIP-immunized (red) RMs. **(D)** Spearman correlation of HIV Env SOSIP-specific IgG responses pre-ATI with post-ATI plasma VL area under the curve (AUC). Statistical analysis was performed using GraphPad Prism. Non rebounder depicted using open circle.

Wk 4 pi: Pre-immunizations; Wk 20 pi: 2 wks post- 3rd GT1.1 immunization; Wk 24 pi: 2 wks post 4th GT1.1 immunizations; pATI: 30 wk pi (for unimmunized) and 46 wk pi (for SOSIP-immunized).

Virus-specific neutralizing antibodies

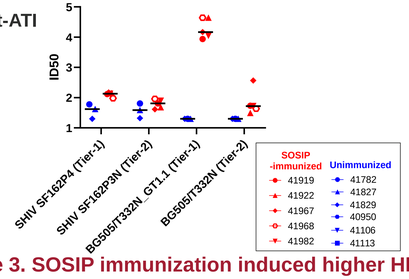
Autologous viruses

A. Pre-ATI

		Tier-1 viruses	
		SHIV SF162P4	BG505/T332N_GT1.1. ΔCT.His
SOSIP-immunized	41919	110	1.6
	41922	58	0.8
	41967	40	2
	41968	150	0.54
	41982	51	1.4

IC50 (μg/mL): >150; 100-150; 51-100; 21-50; 0-20

B. Post-ATI



CD4 binding site-specific bNAb precursor responses

C. On ART

		20 wks pi		24 wks pi		Pre-ATI	
		426c.TM	426c.TM.D279K	426c.TM	426c.TM.D279K	426c.TM	426c.TM.D279K
Unimmunized	41782	>164	>164	NA	NA	>164	NA
	41827	>164	>164	NA	NA	>164	NA
	41829	>164	>164	NA	NA	>164	NA
	40950	>164	>164	NA	NA	NA	NA
	41106	>164	>164	NA	NA	>164	NA
	41113	>164	>164	NA	NA	NA	NA
SOSIP-immunized	41919	>164	>164	>164	>164	>164	>164
	41922	>164	>164	>164	>164	>164	>164
	41967	>164	>164	>164	>164	>164	>164
	41968	>164	>164	>164	>164	>164	>164
	41982	31	>164	14	>164	67	110

IC50 (μg/mL): >150; 100-150; 51-100; 21-50; 0-20

D. Post-ATI

		2 wks post-ATI		10 wks post-ATI	
		426c.TM	426c.TM.D279K	426c.TM	426c.TM.D279K
Unimmunized	41782	<20	<20	<20	<20
	41827	<20	<20	<20	<20
	41829	<20	<20	<20	<20
	40950	<20	<20	NA	NA
	41106	NA	NA	NA	NA
	41113	NA	NA	NA	NA
SOSIP-immunized	41919	<20	<20	<20	<20
	41922	<21	<20	<20	<20
	41967	<22	<20	49	<20
	41968	32	<20	<20	<20
	41982	151	70	113	47

ID50: <20; 20-50; 50-100; >100

Figure 3. SOSIP immunization induced higher HIV-neutralizing antibody responses and developed VRC01-like bNAb precursor responses compared to unimmunized RMs. (A) Purified IgG from plasma pre-ATI and **(B)** plasma 2 weeks post-ATI was used to measure HIV-neutralizing antibody titers against autologous viruses. **(C)** Purified IgG from plasma on ART and **(D)** plasma post-ATI was screened for the development of VRC01-like CD4bs precursor bNAb responses using the 426c.TM virus, which engages germ line–reverted forms of VRC01 class bnAbs, and the CD4bs KO virus, 426c.TM.D279K. A 3-fold increase (purified IgG) or reduction (plasma) indicates the development of bNAb precursor response.

RESULTS

FcRn antibody treatment of the non-rebounder

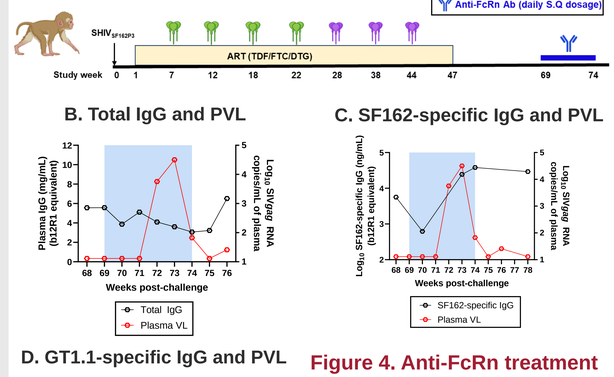


Figure 4. Anti-FcRn treatment resulted in viral rebound in the non-rebounder. (A) FcRn Antibody treatment of non-rebounder RM 41968. PVL and **(B)** total **(C)** SF162 trimer-specific and **(D)** BG505 GT1.1 SOSIP-specific IgG in the FcRn antibody-treated RM.

CONCLUSIONS

- Compared to unimmunized SHIV-infected RMs, germline-targeting HIV Env SOSIP-immunized SHIV-infected RMs:
1. Demonstrated similar time to viral rebound.
2. Had lower post-rebound plasma viral load, with 1 RM remaining aviremic long-term.
2. Developed more potent and broad HIV Env-specific plasma IgG responses, which correlated with post-ATI viral load.
3. Developed higher HIV-neutralizing antibody responses against autologous HIV strains.
4. 1/5 animals developed CD4 binding site-specific bNAb precursor responses (0/6 in unimmunized), which could not be detected post-viral rebound.
5. Virologic control achieved in the aviremic RM was dependent on total and HIV-specific IgG levels.

Clinical Implication: Identifying the correlates of SHIV control by a germline-targeting HIV Env SOSIP immunization strategy will guide the design of an effective HIV therapeutic vaccine to achieve ART-free viral suppression.

ACKNOWLEDGEMENT

This work was supported by the PAVE Martin Delaney Collaboratory UM1AI164566