Improved Antibody Function After env-mRNA Vaccination During cART Does Not Control SHIV Post-ATI

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BACKGROUND

- Autologous neutralizing antibodies (aNAbs) have shown potential in delaying viral rebound by targeting the latent HIV reservoir upon viral reactivation.[1,2]
- **Hypothesis:** Therapeutic vaccines can induce or enhance both cellular and humoral immune responses.

Goals

To implement an env-mRNA vaccine regimen:
1. to improve quantitative and qualitative aNAb responses;
2. to delay viral rebound after ATI.

METHODS

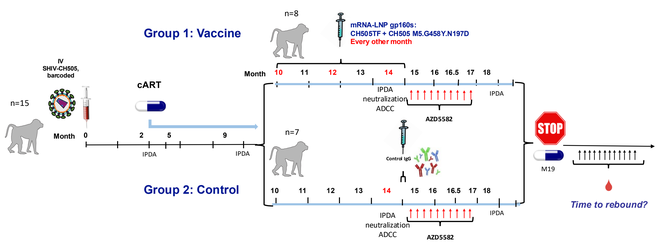


Figure 1: Schematic of study design.

The vaccine consist of HIV-1 CH505 gp160 trimers delivered by mRNA-LNP to elicit neutralizing antibodies (NAb) targeting the CD4-binding site (CD4bs) on HIV envelope.

- Plasma-purified IgG were tested for neutralization in TZM-bl assay, and antibody-dependent cellular cytotoxicity (ADCC) using CH505TF gp120-coated and infected cells. (PMID: 40151082)
- Ab responses were mapped using pseudovirus mutants in TZM.bl assay and electron microscopy-based polyclonal epitope mapping (EMPEM). (PMC6764681, PMC10860651)
- Viral reservoir was measured using the Intact Proviral DNA Assay (IPDA) and viremia by qPCR for 10 weeks after ATI. (PMC7944446)
- Exact Wilcoxon tests were used for analyses, without adjustment to the 0.05 alpha level for multiple comparisons.

RESULTS

1.The vaccine regimen improved quantitative aNAb responses.

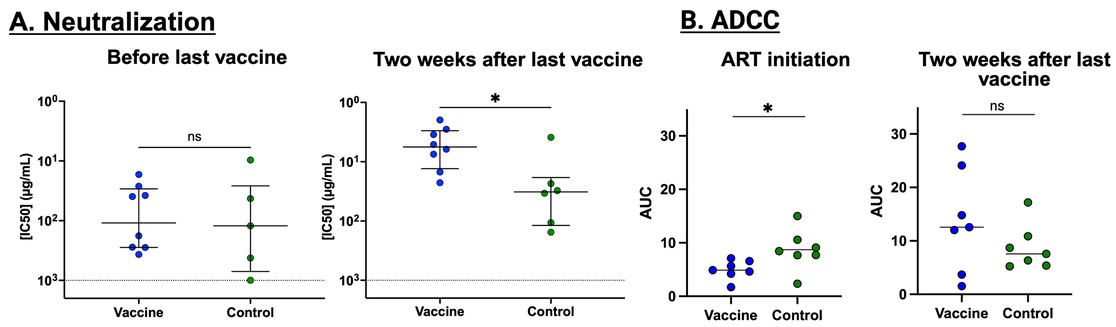


Figure 2: A. Anti-CH505.TF aNAb levels were higher two weeks post vaccination (IC50 median:5.64 µg/mL, IQR: 3.16-11.22) compared to the control group [(median:33.98 µg/mL, IQR: 23.38-154.60), p=0.01]. B. Vaccinated animals trended towards higher ADCC responses, reported as area under the curve (AUC), against gp120 coated targets compared to control animals (p=0.38). ADCC was undetectable against infected cells.

2.The vaccine regimen improved qualitative aNAb responses related to CD4bs CH235 lineage.

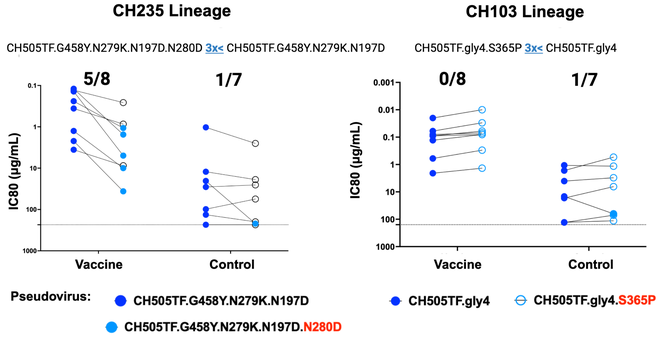


Figure 3: Plasma neutralization mapping revealed:

- CD4bs Abs indicative of CH235-like precursors detected in 5/8 RMs in the vaccine group compared to 1/7 in the control group.
- CH103-like Ab precursors were not detectable in the vaccine group and only in 1/7 RM in the control group.

3.The circulating reservoir was significantly lower in the vaccine group after immunization.

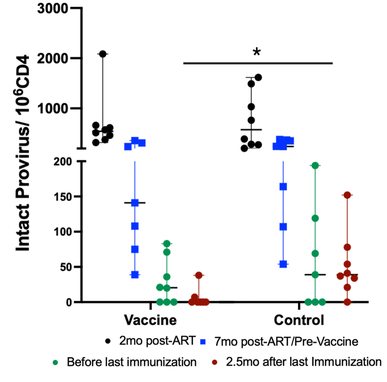


Figure 4: The reservoir size declined overtime and was lower in the vaccine group (median: 0 copies/million cells; IQR: 0-1.95) compared to the control group (median: 3.41 copies/million cells; IQR: 3.29-4.17; p = 0.01).

4. All RMs rebounded by 9w post-ATI and CD4bs responses detectable only in vaccine group.

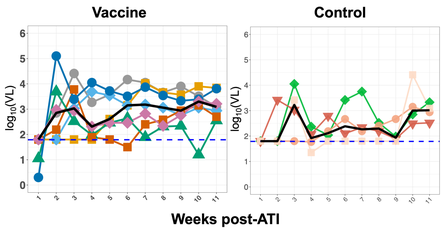


Figure 5: All RMs rebounded by 9 weeks. 8/9 and 4/7 had detectable VL at week 11 in the vaccine and the control group, respectively.

We observed no differences in time to rebound (vaccine: median 2 weeks, IQR 2-3; control: median 3 weeks, IQR 2-3; p = 0.14).

Time	Group	V1V3	CD4bs	C2C3	C3V5
Week 0: Time of ART interruption	Vaccine	y	y		
	Control	y			
Week 9: Time of for all rebound	Vaccine	y	y		
	Control	y			y
Week 11: Last time point of rebound	Vaccine		y		
	Control	y			y

Table 1. EMPEM: Among animals with detectable VL at wk 11, CD4bs Ab were present from pre-ATI and detectable until the last rebound measurement only in the vaccine group.

CONCLUSIONS

The vaccine regimen successfully:

1. boosted aNAb and ADCC responses,
2. and induced new specific anti-CD4bs responses.

Although lower circulating reservoir was detectable over time, all animals rebounded after ATI. Functional Ab responses did not correlate with VL after rebound.

1. These findings indicate need for therapeutic vaccine to further modify the specificity of Ab responses.
2. The contribution of T cells responses is under evaluation.

PLAIN LANGUAGE SUMMARY

This study tested a new HIV Envelope-based mRNA vaccine in an animal model and found that while it successfully increased the level and quality of the immune responses induced by the initial infection, these responses were not sufficient to prevent the virus from coming back after drug treatment was stopped. This suggests that vaccines can reshape immune responses in people living with HIV while receiving therapy, but they need to be carefully designed to prevent virus reactivation and rebound.

References
1. Bertagnolli et al. Proceedings of the National Academy of Sciences. 2020 Dec 15;117(50):32066-77. 2. Esmaeilzadeh et al. Science translational medicine. 2023 May 10;15(695):eabq4490.

Acknowledgements
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