IMPACT OF VACCINE-ELICITED CD8⁺ T CELLS ON SIV DYNAMICS

Cristina Ceriani[1], Kathryn A. Nary[1], Diane G. Carnathan[1], Rama R. Amara[1], Guido Silvestri[1,2], Maud Mavigner[1,3]

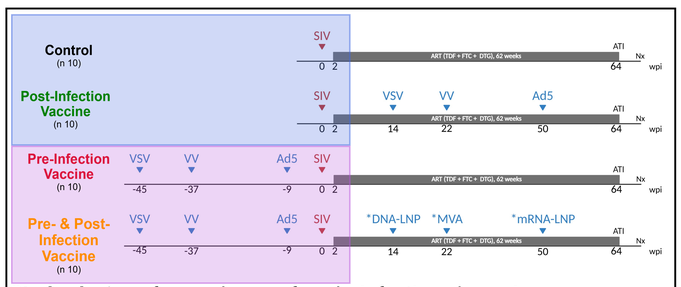
[1] *Division of Microbiology and Immunology, Emory National Primate Research Center, Emory University, Atlanta.* [2] *Department of Pathology & Laboratory Medicine, Emory School of Medicine, Emory University, Atlanta.* [3] *Department of Pediatrics, Emory School of Medicine, Emory University, Atlanta.*

BACKGROUND

Enhancing immune-mediated clearance of latently-infected cells is a key strategy for achieving an HIV cure. Here we evaluated CD8+ T cell responses to a potent vaccine regimen administered to rhesus macaques (RMs) prior to SIV infection and/or after viral suppression mediated by antiretroviral therapy (ART) to define how vaccine-elicited immune responses impact SIV reservoir establishment and maintenance.

METHODS

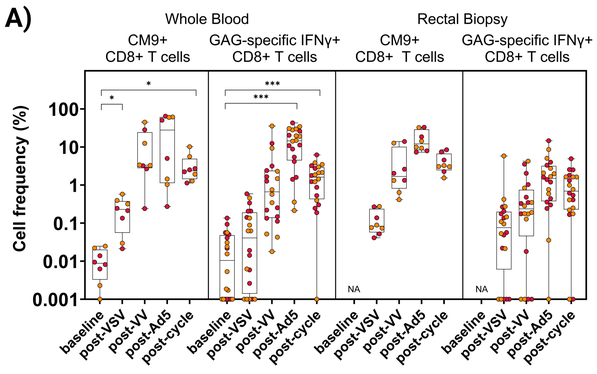
Forty RMs were infected intravenously with SIVmac239M and treated with ART initiated two weeks post-infection (wpi). RMs were divided into four groups, each including 10 RMs: control (treated with ART only), vaccinated pre-infection, vaccinated after viral suppression, vaccinated pre-infection and after viral suppression.



Study design: for analyses of early infection dynamics, groups were combined into two cohorts based on vaccination status at the time of infection: unvaccinated (control + post-infection vaccine) and vaccinated (pre-infection vaccine + pre- & post-infection vaccine). wpi, weeks post-infection; ART, antiretroviral therapy; ATI, analytical treatment interruption; Nx, necropsy.

The vaccination regimen consisted of heterologous viral vector (HVVs) immunizations with Vesicular stomatitis virus (VSV), Vaccinia virus (VV), and Adenovirus type 5 (Ad5) vectors expressing SIV-Gag with the exception of the second vaccination for Group "Pre- & Post-infection vaccine" that included lipid nanoparticle DNA (DNA-LNP), Modified Vaccinia Ankara (MVA) and RNA-LNP vectors. Immune responses in peripheral blood (PB) and rectal biopsies (RB) were monitored at one week after each vaccine and 5 weeks after completion of the full vaccination cycle (post-cycle). Groups were balanced for age, sex and Mamu-A*01 MHC genotype. All animals were Mamu-B*08 and B*17 negative. Plasma viral loads (PVL) were monitored twice weekly during the early dynamics phase, followed by once monthly.

RESULTS



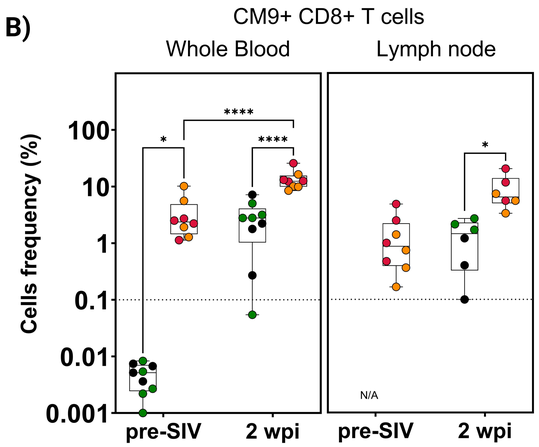
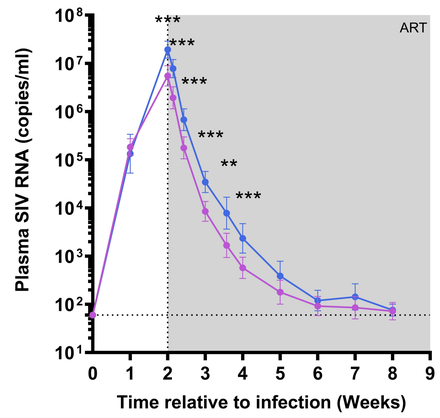


***Figure 1:* Vaccination with SIV gag HVV prior to SIV infection resulted in:**
(A) The expansion of SIV-specific CD8+ T cells in both peripheral blood (PB) and rectal tissues as compared to baseline. This immune response peaked one week after the last immunization and contracted within the next 4 weeks (post-cycle).
(B) Higher frequencies of SIV-specific CD8⁺ T cells in PB (P<0.001) and lymph node (p<0.05) at 2 wpi as compared to unvaccinated RMs.
(C) Lower PVL following SIV infection, between 2 to 4 wpi (P<0.01) as compared to unvaccinated RMs. For this analysis animal groups were defined as unvaccinated (control + post-infection vaccine) and vaccinated (pre-infection vaccine + pre- & post-infection vaccine).

unvaccinated (control + post-infection vaccine)
vaccinated (pre-infection vaccine + pre- & post-infection vaccine)

Pre-infection vaccination induced expansion of SIV-specific CD8+ T cells leading to a **lower plasma viral load** following SIV infection at 2 to 4 weeks post-infection as compared to unvaccinated RMs.



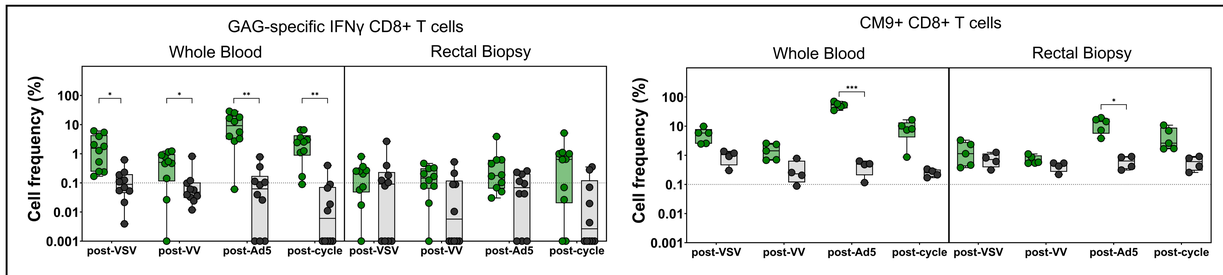


Figure 2: Vaccination with SIV gag HVV after SIV infection and ART-suppression resulted in higher frequencies of SIV-specific CD8⁺ T cells in PB and rectal tissues as compared to control (treated with ART only) RMs.

control
post-infection vaccine

CONCLUSIONS

Our results demonstrate robust SIV-specific CD8+ T cells responses induced by vaccination administered prior to SIV infection or after viral suppression mediated by ART. While vaccination during ART did not enhance viral control after ATI, ART has not yet been interrupted in RMs vaccinated pre-infection that showed lower PVL during acute infection and ART initiation. Monitoring of viral dynamics post-ATI in this group as well as reservoir characterization in all RMs will establish the ability of vaccine-elicited cells to alter SIV persistence.

PLAIN LANGUAGE SUMMARY

Antiretroviral therapy (ART) can control HIV/SIV but does not eliminate infected cells that hide in the body. In this study, we vaccinated rhesus macaques either before or after SIV infection and found that the vaccine generated strong virus-specific CD8+ T cell responses; animals vaccinated before infection showed lower virus levels early after infection. Ongoing analyses will determine whether these vaccine-induced immune responses can reduce long-term viral persistence and improve control after stopping ART.

ACKNOWLEDGEMENTS: We thank all animal care and veterinary staff at the Emory National Primate Research Center (ENPRC), the ENPRC Flow Cytometry Core, Emory CFAR Virology and Molecular Biomarkers Core, and Gilead for providing ART; The presented work was supported by UM1 AI169662 and P51OD011132 .

Contact information: cristina.ceriani@emory.edu