CONSERVED-REGION MVA VACCINES REDIRECT HIV T-CELL IMMUNODOMINANCE IN PWH ON ART: *THE M&M STUDY*

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BACKGROUND

- We examined the safety and immunogenicity of MVA-vectored vaccines expressing highly conserved Gag and Pol regions of HIV. In prior studies, we found that T cell escape in these conserved regions is significantly lower than elsewhere in the HIV proteome[1].

Hypotheses:

- conserved-region vaccines will both increase anti-HIV T cell immunity and shift T cell immunodominance away from viral regions harboring escape variants.
- bivalent immunogens that increase coverage of global HIV diversity will more effectively boost and induce HIV-specific T cell responses in people living with HIV (PWH).

DESIGN & METHODS

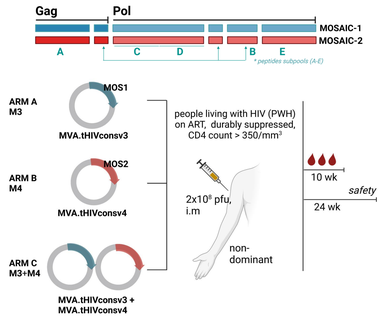
- First-in-human, double-blinded, randomized, Phase I study in PWH on ART with CD4 counts >350mm^2.
- Participants were vaccinated i.m with final dose of 2×10^8 pfu of either MVA.tHIVconsv3[2] (**M3**), MVA.tHIVconsv4[2] (**M4**), **M3**+**M4** or saline placebo in ratio of 7:7:7:3 (A)
- The vaccines, **M3** and **M4** express the same 6 conserved regions of HIV, in Gag and Pol and are called Mosaic-1 and **-**2 respectively (Fig **A**)
- Mosaic-1 and -2 *differ* by ~10% at the amino acid level.
- Ex vivo IFN-γ ELISpot was used to measure changes in HIV-specific T cell magnitude, breadth & immunodominance to peptides spanning Mosaic-1 and -2 and subpools (*A*-*E*).

RESULTS: SAFETY

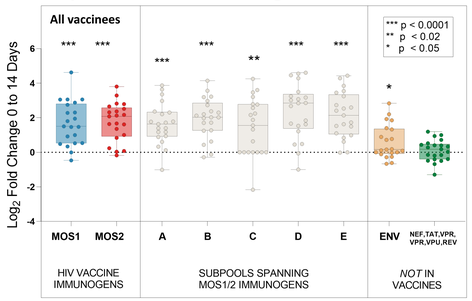
- Participant demographics: 17% women / 83% men, 54% Black / 41% White / 5% Unknown, age 21-60 years.
- The majority of adverse events (AEs) were grade 1 that mostly resolved with 24hr. Grade 3 or greater AEs probably associated with vaccine product resolved within 24hr. No AEs of special interest or serious AEs were reported over the study.

Intramuscular MVA-vectored vaccines expressing highly conserved mono- or bivalent HIV immunogens are safe in PLW on ART. A single MVA vaccination induced sustained increases of T cells targeting conserved HIV regions.

A.

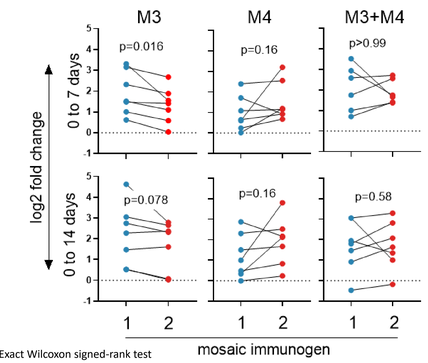


B. M3, M4 or M3+M4 vaccination significantly increased T cell responses to conserved regions of HIV in PWH



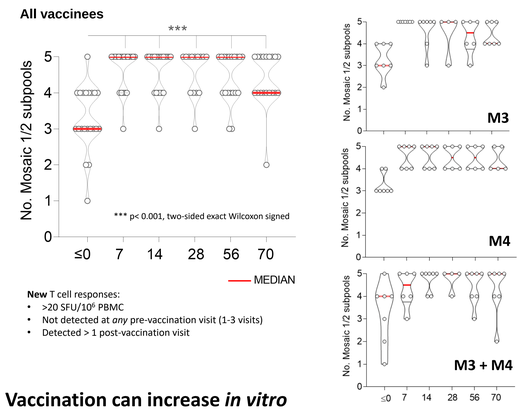
* Within arm fold change from 0-7 days and 0-14 days was also significant for all M3- M4 and M3+M4 arms, for both Mosaic-1 and Mosaic-2 antigens, p<0.05, exact 2-sided Wilcoxon signed-rank test Wilcoxon. No differences were observed between arms, p> 0.5, exact Wilcoxon rank-sum test

C. T cell responses to Mosaic-1 and Mosaic-2 immunogens significantly increased in all arms but with distinct patterns

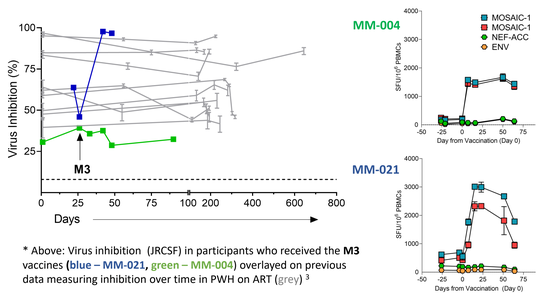


* Exact Wilcoxon signed-rank test

D. M3- M4- and M3+M4 vaccination increased the ex vivo T cell breadth against conserved HIV regions

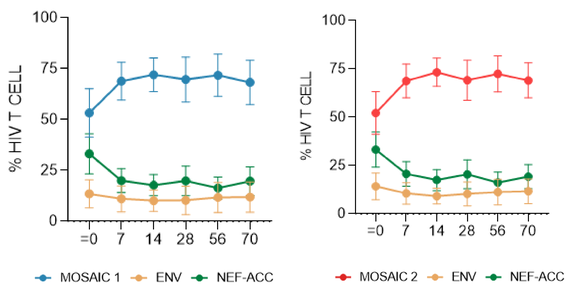


E. Vaccination can increase *in vitro* HIV inhibition



* Above: Virus inhibition (JRCSF) in participants who received the **M3** vaccines (**blue – MM-021, green – MM-004**) overlayed on previous data measuring inhibition over time in PWH on ART (grey) [3]

F. Vaccination (all arms) shifted T cell immunodominance to conserved HIV regions



RESULTS: T CELL MAGNITUDE

- Vaccination significantly increased T cell responses to both Mosaic-1 and Mosaic-2 immunogens within arms but not between arms **(**Fig **B**-**C**) .
- **M3** vaccination produced significant fold-changes to the Mosaic-1 immunogen whereas, **M4** vaccination favoured fold-changes to Mosaic-2. **M3**+**M4** vaccination did not favour either vaccine immunogen (Fig **C**).

RESULTS: T CELL BREADTH

- Vaccination (all vaccinees) significantly increased T cell breadth to both Mosaic-1 and Mosaic-2 immunogens that were sustained over the study (Fig **D**)
- No differences in breadth were observed between arms. Within arm increases in breadth were not significant.

RESULTS: CD8 T CELL VIRUS INHIBITION

- **M3** vaccination strongly increased in vitro inhibition of clade B JRCSF, but had not been consistent (Fig **E**)
- Planned studies will examine inhibition of autologous reservoir virus

RESULTS: T CELL IMMUNODOMINANCE

- Vaccination increased immunodominance of T cells targeted against both vaccine immunogens over the study period (Fig **F**).

NEXT STEPS:

- Ongoing studies will further delineate the immunogenicity of monovalent (**M3** or **M4**) vs bivalent (**M3**+**M4**) vaccination. Virologic studies (SCA, IPDA) are ongoing
- Phase I study of mosaic-1 and -2 immunogens in chimpadenovirus / MVA combination regimens *opens 2022, the 'CM Study'*

ADDITIONAL KEY INFORMATION

- Our sincere thanks to study participants, UNC clinical trial co-ordinators and support staff, our SMC Lucy Dorrell (ImmunoCore), Sharon Riddler (UPitt) and Hrishikesh Chakraborty (Duke). We also thank Alison Crook (U Oxford), Carmella Moody and team (RTI International), DAIDS staff particularly Steve Smiley. Funding - N.G. **U01 AI131310 ;** IRB: Study IGHID11810, Approval #18-2502

- [1] Warren et al eLIFE 2020; [2] Ondondo et al Mol Ther 2016; [3] Xu Frontiers in Immunol 2021