

Age inversely correlates with T cell response to MVA.HIVconsvX vaccination in PWH on ART– *THE M&M STUDY*

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BACKGROUND

- In the U.S. over 50% of people with HIV (PWH) on antiretroviral therapy (ART) are over 50 years of age.
- We examined the safety and immunogenicity Modified Vaccinia Ankara (MVA) vectored vaccines expressing either one immunogen (monovalent) or two HIV immunogens (bivalent) in PWH on ART.
- The vaccine immunogens called Mosaic-1 and Mosaic-2 (collectively HIVconsvX), target the same conserved six HIV regions but differ by 8% at the amino acid level¹ (**Fig A**)

HYPOTHESES

- Single vaccination with MVA-vectored HIVconsvX vaccines, either alone or in combination, will increase:
 - HIV-specific T cell frequency
 - HIV T cell breadth

DESIGN & METHODS

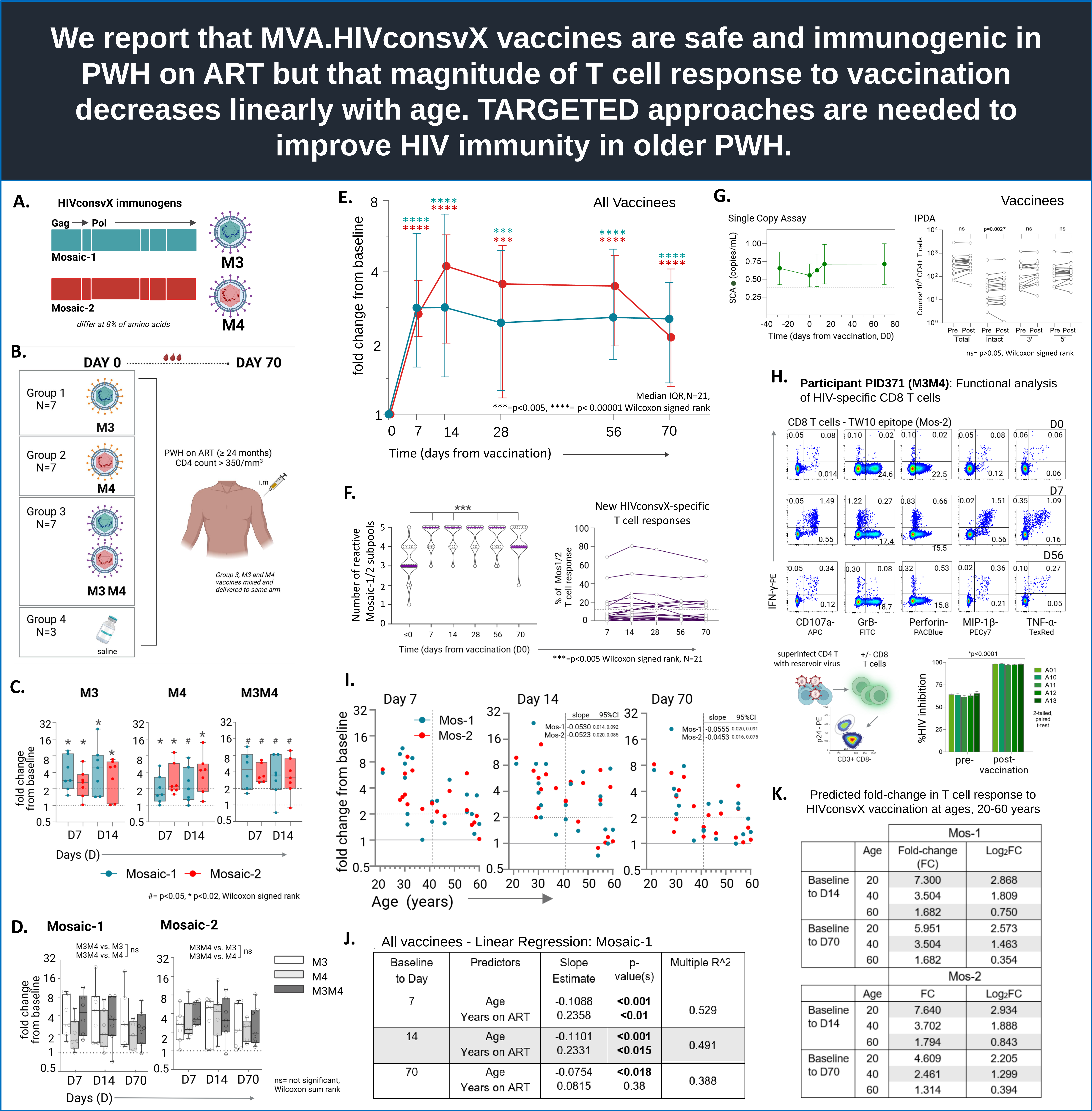
- Parallel design, double-blinded, randomized, Phase I study in PWH suppressed on ART (≥ 24 months) with CD4 counts $>350\text{mm}^2$ (**Fig B**).
- Participants were vaccinated intramuscularly (i.m) with final dose of 2×10^8 pfu of either MVA.tHIVconsv3 (**M3**), MVA.tHIVconsv4 (**M4**), **M3+M4** or saline placebo in ratio of 7:7:7:3.

M&M Study Demographics by Group						
		M3	M4	M3M4	Placebo	All
Age (years)	Median (IQR)	43 (15)	46 (22.5)	31 (18)	28 (15)	41 (24.3)
Gender, N (%)	Male	5	6	7	3	21(87.5)
	Female	2	1	0	0	3 (12.5)
Race, N (%)	Black/AA	3	4	5	1	13(54.2)
	White	3	3	2	2	10(41.7)
	Other/UK	1	0	0	0	1 (4.1)
CD4 count (cells/mm ³)	Median (IQR)	738 (150)	708 (280)	855 (308)	792 (274)	773.5 (307.5)
CD4:CD8		1.26	0.87	1.14	0.76	1.00
Years on ART	Median (IQR)	10.42 (3.75)	9.45 (6.29)	7.46 (6.38)	4.55 (4.31)	8.56 (4.97)

Age = age at enrollment. AA= African American, UK = unknown, CD4 count at screening

SAFETY ENDPOINTS:

- Most adverse events (AEs) were grade 1 and resolved with 48hr. 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.



IMMUNOGENICITY ENDPOINTS:

- Vaccination M3, M4 and M3+M3 regimens significantly increased the frequency T cells targeting HIVconsvX immunogens measured by IFN- γ ELISpot (**Fig C**).
- T cell response was not significantly different between regimens (**Fig D**). Overall (N=21), vaccination was highly immunogenic (**Fig E**).
- Vaccination significantly increased T cell breadth (**Fig F** left), identifying new T cell responses that, on average, were of low frequency, $\sim 11\%$ of total HIVconsvX-specific T cell response (**Fig F**, right).

VIROLOGY ENDPOINTS

- Vaccination did not impact low level viremia or frequency of total integrated DNA (**Fig G** left). A small increase in intact integrated DNA was observed (**Fig G** right) but did not correlate with fold-change in T cell response to vaccination (not shown).

POST-HOC ANALYSIS

- Increased frequency of HIVconsvX-specific T cells was associated with increased production of cytolytic molecules and increased inhibition of autologous reservoir virus (**Fig H**)
- Linear regression analysis identified :
 - inverse association between participant age and T cell frequency post-vaccination (**Fig I-J**)
 - positive association between years on ART and T cell frequency post-vaccination (**Fig J**)
- Modelling of these data suggests that, over a 20-year window, an individual would experience $\sim 50\%$ loss in T cell response to vaccination. (**Fig K**)

SUMMARY

- MVA vaccines expressing HIVconsvX immunogens are safe and immunogenic in PWH on ART.
- Future studies of these and other HIV T cell vaccines in PWH on ART must be designed to consider both the impact of age and years on ART that we propose as a surrogate of immune reconstitution

ADDITIONAL KEY INFORMATION

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¹Ondondo et al Mol Ther 2016