ChAdOx1.HIVconsvX and MVA.HIVconsvX Vaccination is Safe and Immunogenic in PWH on ART – *THE CM STUDY*

Cynthia Gay[1,2*], Yinyan Xu[2,3], Ann Marie Weideman[4,5], Fiona Shaw[2,3], Shayla Conrad[2,3], Sofia Mariano[2,3], Melissa Mischell[4,5], Caroline Baker[1,2], Susan Pedersen[1,2], JoAnn Kuruc[1,2], Alex Bradley[1,2], Taylor Whitaker[1,2], Ally Odom[6], Camryn Black[6], Lynn Harrington[6], Alison Crook[7], Lawrence Fox[8], Joseph Eron[1,2], David Margolis[1,2], Mehri McKellar[9], Emmanual Waterhouse[6,10], Michael Hudgens[3,4] Tomáš Hanke[8], Nilu Goonetilleke[2,3*]

1. Department of Medicine, University of North Carolina (UNC), Chapel Hill, NC, US 2. UNC HIV Cure Center, Chapel Hill, NC, US 3. Department of Microbiology & Immunology, UNC, Chapel Hill, NC, US 4. Biostatistics Core, Center for AIDS Research, UNC, Chapel Hill, NC, US 5. Department of Biostatistics, UNC, Chapel Hill, NC, US 6. Duke Human Vaccine Institute, Duke University, Durham, NC, U.S. 7. Nuffield Department of Medicine, University of Oxford, Oxford, UK 8. HIV Research Branch, Division of AIDS, NIAID, NIH, D.C., US 9. Duke Department of Medicine, Duke University, Durham, NC, US. 10. Duke Department of Pediatrics, Duke University, Durham, NC, US.

428

BACKGROUND

- Increasing the frequency of circulating T cells targeting the HIV reservoir will likely be needed for ART-free HIV remission in PWH.
- We examined the safety and immunogenicity of ChimpadenovirusOx1(ChAdOx1)- and 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 HIV regions but differ by 8% at the amino acid level[1] (**Fig A**).

HYPOTHESES

- Serial vaccination with ChAOx1- and MVA-vectored HIVconsvX vaccines will significantly increase the frequency of HIV-specific T cells in PWH on ART relative to baseline (average of pre-vaccination timepoints.)
- Since bivalent immunogens harbor more T cell epitopes, bivalent vaccine regimens will result in higher and broader frequencies of HIV-specific T cells in PWH on ART.

DESIGN & METHODS

- Phase 1, parallel design, double-blinded, randomized study in PWH suppressed on ART (≥24 months) with CD4 counts >350mm^2 (**Fig B**).

Group 1 C62-M4 N=8:
Day 0: 5x10^{10}vp ChAdOx1. HIVconsv62 (C62)
Day 28: 1.8x10^{8}pfu MVA.tHIVconsv4 (M4)

Group 2 C1C62-M3M4 N=8:
Day 0: 2.5x10^{10}vp ChAdOx1.tHIVconsv1 (C1) +2.5x10^{10}vp C62
Day 28: 1.0x10^{8}pfu MVA.tHIVconsv3 (M3) + 0.9x10^{8}pfu M4

Group 3 Placebo N=2: 0.9mL saline at Day 0 and 28

CM study participant demographics by treatment group

Study Group		C62-M4[1]	C1C62-M3M4[2]	Placebo	All
Age (years)	Median (IQR)	**58** (9.75)	**33.5** (22.5)	**50.50** (1.5)	**50**[3] (21.5)
Gender, N (%)	Male	6	8	1	15 (83.3)
	Female	2	0	1	3 (16.7)
Race, n (%)	Black/AA	4	2	2	8 (44.4)
	White	4	6	0	10 (55.6)
CD4 count (cells/mm^3)	Median (IQR)	785 (388.25)	998.5 (396.75)	1094 (16)	913 (454.5)
CD4:CD8 ratio	Median (IQR)	1.62 (0.69)	0.87 (0.23)	2.20 (0.29)	1.05 (1.00)
Years on ART	Median (IQR)	15.65 (7.18)	7.80 (8.95)	12.15 (2.35)	12.95 (9.23)

[1] Half of the **C62** vaccine was administered into the deltoid of each arm at Day 0 followed by half of the M4 vaccine in each arm at week 28.
[2] **C1** was administered in the deltoid of one arm at Day 0 followed by M3 vaccine in the same arm at week 28; **C62** was administered in the alternate arm at Day 0 followed by M4 vaccine in the same arm at week 28.
[3] 50 years was also the median age for vaccinees (n=16).
ART = antiretroviral therapy; IQR = interquartile range, AA = African American, CD4 count & ratio at screening

Monovalent (one immunogen) and bivalent (two immunogen) HIV vaccine regimens were compared in PWH on ART. Both regimens were safe and immunogenic.
The bivalent vaccine regimen produced a broader T cell response in participants favoring this approach for ART-free HIV remission strategies.

Table 1: Number (N) of participants who experienced a specific solicited adverse event (AE) by treatment group within 7 days of ChAdOx1 or MVA vaccination.

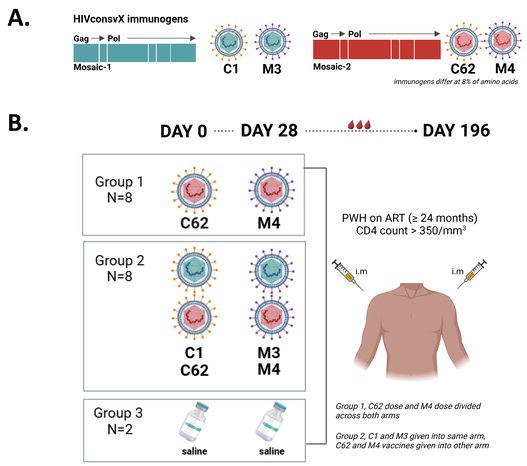
Adverse Event	Treatment Arm: C1C62-M3M4 (N=8)	C62-M4 (N=8)	Placebo (N=2)	Total
	N	N	N	N
Injection site pain[2]	8	5	1[1]	14
Fatigue	6	6	1	13
Headache	6	1	-	7
Malaise	4	2	-	6
Anorexia	3	1	1	5
Chills	3	1	-	4
Pyrexia	3	1	-	4
Myalgia	3	-	-	3
Injection site erythema[2]	-	2	-	2
Injection site warmth[2]	2	-	-	2
Injection site swelling[2]	-	2	-	2
Diarrhea	1	1	-	2
Injection site induration[2]	-	1	-	1
Injection site pruritus[2]	1	-	-	1
Hyperhidrosis	1	-	-	1
Nausea	1	-	-	1
Total	**8**	**7**	**1**	**16**

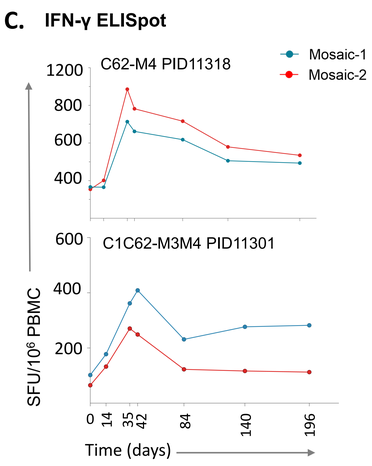
[1] Participant experienced injection site pain only in the right arm.
[2] Injection site AEs in right and left arm counted as separate events

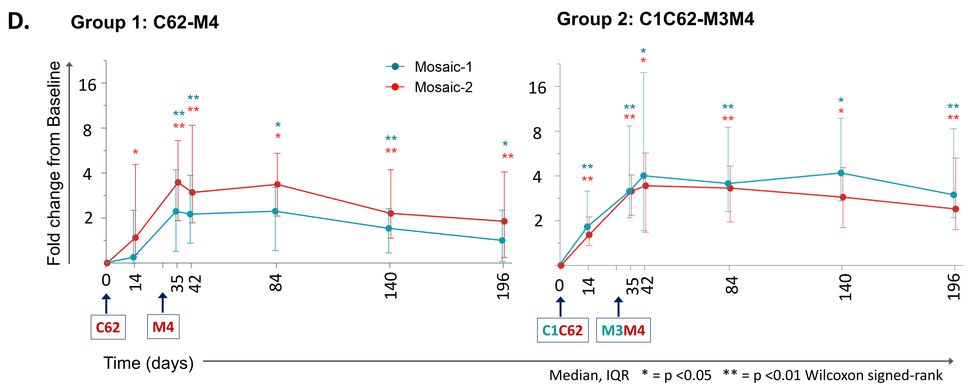
Table 2: Number of all solicited and unsolicited AEs by severity and relation to study product.

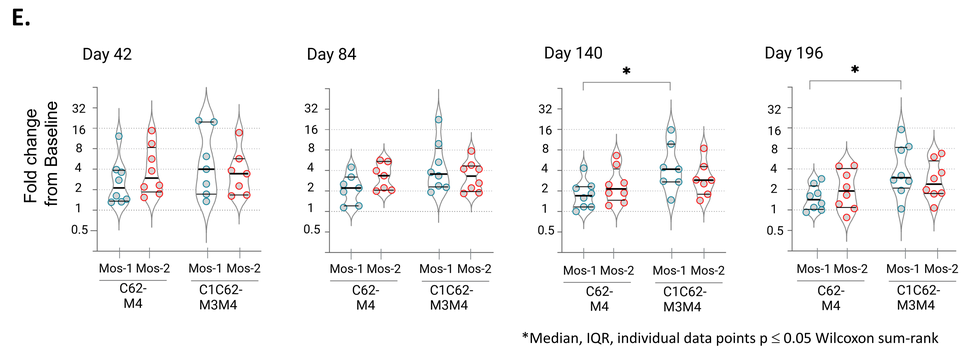
		Study Grade	Not related N	Possibly related N	Definitely N
C1C62-M3M4 (N=8)	Solicited	1 – Mild	-	41	17
		2 – Moderate	-	13	10
		3 – Severe	-	-	-
	Unsolicited	1 – Mild	2[1]	2	-
		2 – Moderate	25	1	-
		3 – Severe	2	-	-
C62-M4 (N=8)	Solicited	1 – Mild	-	19	12
		2 – Moderate	-	7	7
		3 – Severe	-	1[¥]	-
	Unsolicited	1 – Mild	4	1	-
		2 – Moderate	22	1	-
		3 – Severe	3	-	-
Placebo (N=2)	Solicited	1 – Mild	-	2	1
		2 - Moderate	-	-	-
		3 – Severe	-	-	-
	Unsolicited	1 – Mild	-	-	-
		2 – Moderate	2	1	-
		3 – Severe	5	-	-

There were no AEs > Grade 3; [1] Includes AE of Special Interest
[h] Injection Site AEs in the Right and Left Arm counted as separate AEs; [¥] A single Grade 3 treatment-related AE of fatigue was reported.









SAFETY ENDPOINTS

- Vaccination was safe with AEs mostly resolving within 24 hours (**Tables 1-2**).

IMMUNOGENICITY ENDPOINTS

- Both vaccine regimens, **C62-M4** and **C1C62-M3M4**, significantly increased frequencies of HIV-specific T cells targeting both Mosaic-1 and Mosaic-2 across post-vaccination timepoints (**Fig C-D**).
- Relative to the **C62-M4** group, T cell responses to Mosaic-1 were higher over the 6 months following **C1C62-M3M4** vaccination and significantly higher at Day 140 and Day 196 (**Fig D-E**).
- **C1C62-M3M4** produced the same fold-increase in T response to Mosaic-2 as **C62-M4** (**Fig D-E**).

CONCLUSION

- Serial vaccination with ChAOx1- and MVA-vectors expressing HIVconsvX immunogens is safe and immunogenic in PWH on ART.
- **C1C62-M3M4** produced higher fold increases in T cell response to Mosaic-1 than **C62-M4**, suggesting that *bivalent* HIVconsvX vaccination can induce a broader HIV-specific T cell response in PWH on ART.

NEXT STEPS

- We are examining the impact of vaccination on:
  - Other study endpoints, T cell breadth and immunodominance.
  - HIV-specific T cell proliferation and CD8 T cell inhibition of autologous reservoir virus.
- In our M&M Study (Poster **425**) we found that age and years on ART were independently associated with T cell response to MVA.HIVconsvX vaccination. *Post-hoc* analyses will include i) adjusting for age and years on ART within and between group comparisons, and ii) comparisons with M&M Study data.

ADDITIONAL KEY INFORMATION

- Our sincere thanks to study participants, UNC clinical trial co-ordinators and support staff, our SMC Liz Connicke (U Arizona), Zoe Moodie (UWashington) and Madhu Choudhary (UPitt). We also thank Carmella Moody and team (RTI International), DAIDS staff particularly Steve Smiley. Funding - N.G. **U01 AI131310 ;** IRB: Study IGHID12107, Approval #18-2502

- [1]Ondondo et al Mol Ther 2016