

Adit Dhummakupt¹ Joseph Szewczyk¹, Shaun Barnabas², Mark Cotton², Robert Gorelick³, Suteeraporn Pinyakorn^{4,5}, Ellen Turk^{4,5}, Mark De Souza⁶, Nicola Cotugno^{7,8}, Frank Maldarelli⁹, Paolo Palma^{7,8}, Hans Spiegel¹⁰, Merlin Robb⁵, and Deborah Persaud¹ on behalf of the RV534 Study Group.

¹The Johns Hopkins University, Baltimore, MD, USA, ²Family Centre for Research with Ubuntu, Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg Academic Hospital, Cape Town, South Africa, ³Leidos Biomedical Research, Inc, Frederick MD USA, ⁴US Military HIV Research Program, CIDR, Walter Reed Army Institute of Research, Silver Spring, MD USA, ⁵Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD USA, ⁶SEARCH, Institute of HIV Research and Innovation, Bangkok 10330, Thailand, ⁷University of Rome Tor Vergata, Rome, Italy, ⁸Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, ⁹NCI Center for Cancer Research, NIH, Frederick, MD USA, ¹⁰Kelly Government Solutions, Contractor to NIH/NIAID/DAIDS, Bethesda, MD USA

BACKGROUND

In perinatal HIV-1, the latent reservoir is established early and precludes cure with antiretroviral therapy (ART) alone. Due to the difficulty of maintaining sustained virologic suppression on ART in children, additional therapeutic interventions are essential. Immunotherapy approaches that stimulate innate and adaptive responses may boost HIV-1-specific immunity, decrease the HIV reservoir, and enable ART-free remission. We conducted a study of the effects of the combination of a prime-boost HIVIS DNA and MVA-CMDR vaccine regimen with or without the toll-like receptor 4 agonist (delivered as the HPV vaccine Cervarix®) in children with HIV undergoing ART (RV534, HVRRICANE).

METHODS

Table 1: Study design, showing timing of vaccine administration and testing for virologic biomarkers

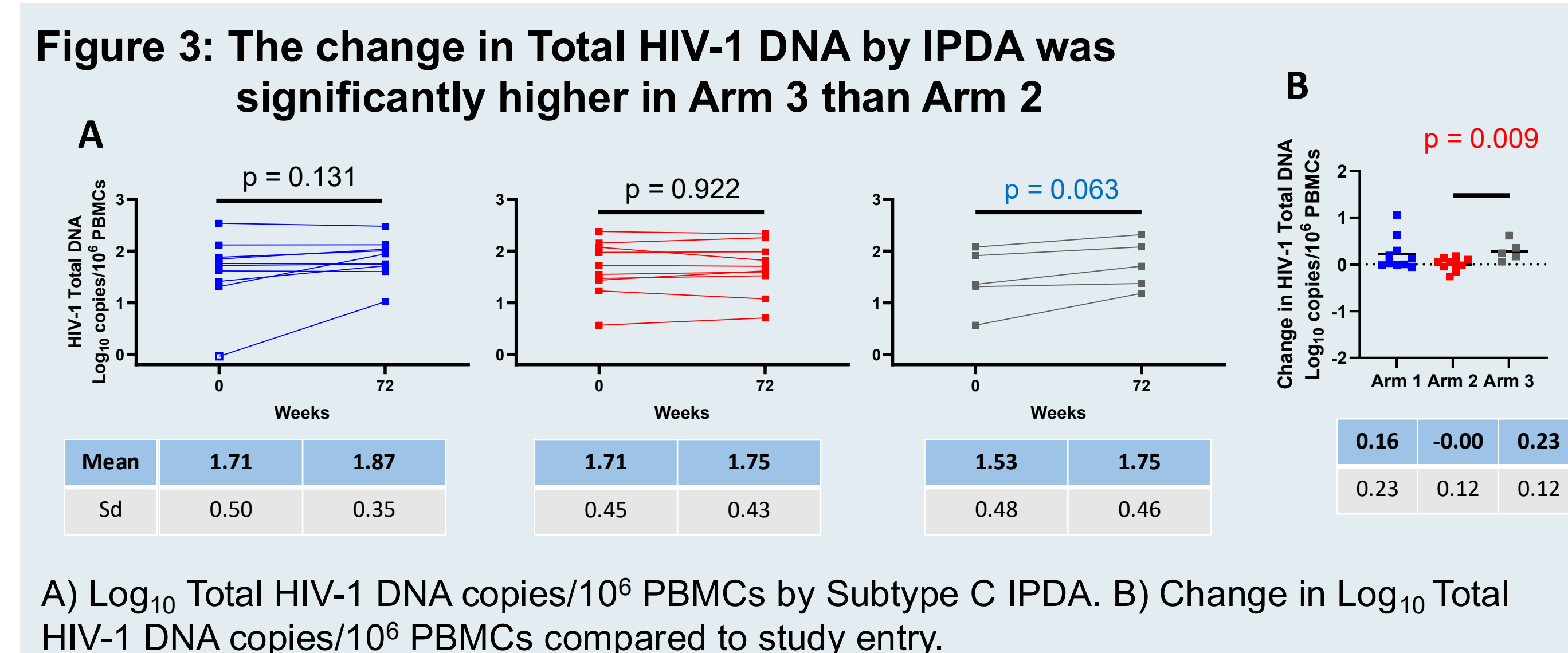
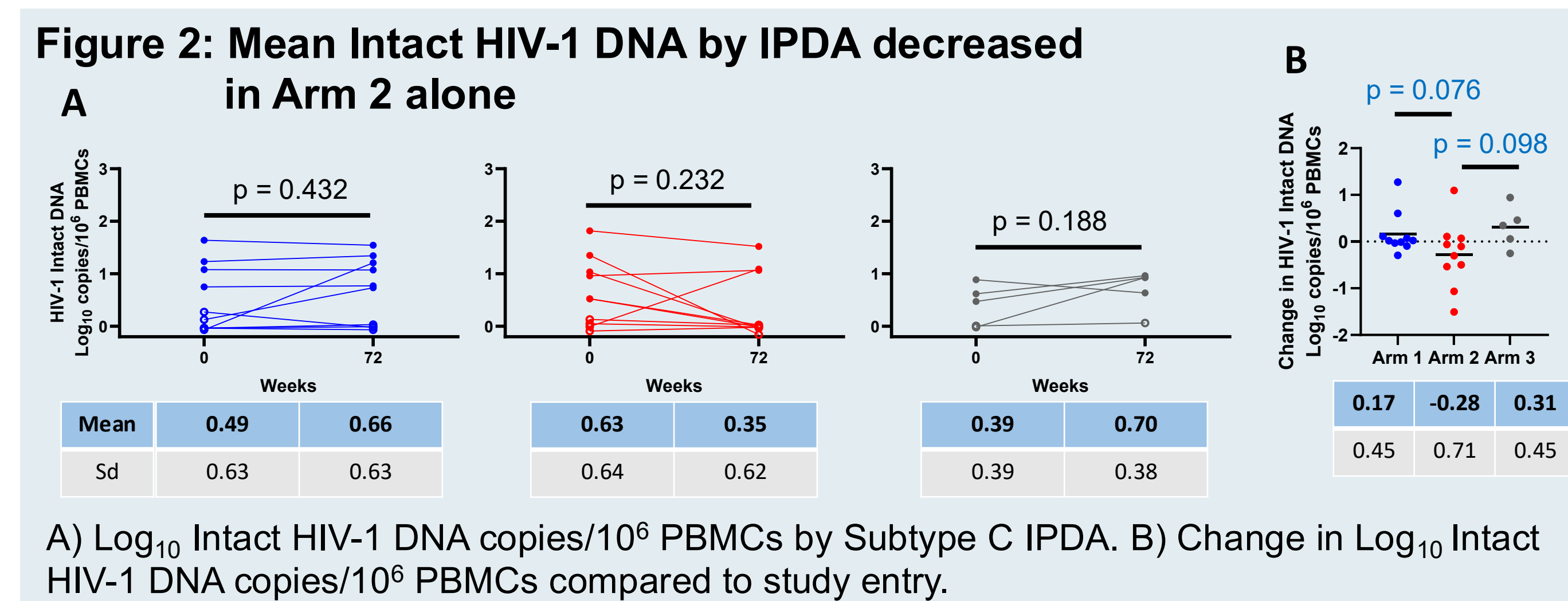
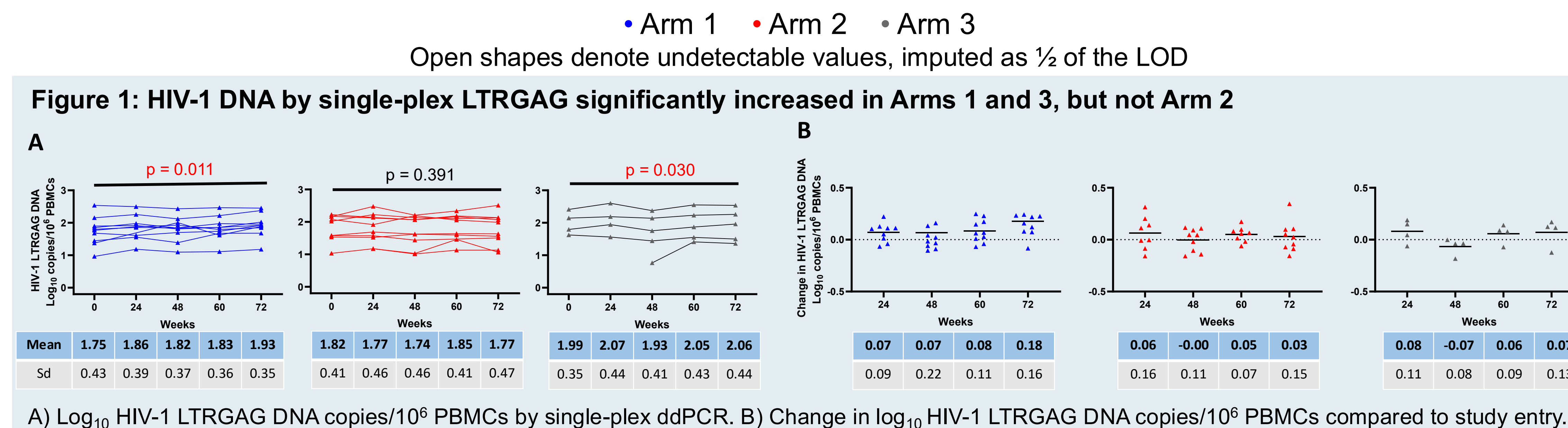
Weeks	0	4	24	36	48	60	72
Arm 1 (N=10)	HIVIS DNA	HIVIS DNA	MVA-CMDR	MVA-CMDR			
Arm 2 (N=10)	HIVIS DNA	HIVIS DNA	MVA-CMDR	MVA-CMDR			
Arm 3 (N=5)	Cervarix	Cervarix	Cervarix				
LTRGAG							
IPDA							
HMMC-gag							

Table 2: Participant demographics by arm

	Arm 1	Arm 2	Arm 3
Age, Median (IQR)	15 (15 - 16)	15 (15 - 16)	16 (15 - 16)
Sex, n(%), Male/Female	5 (50)/5 (50)	4 (40)/6 (60)	4 (80)/1 (20)

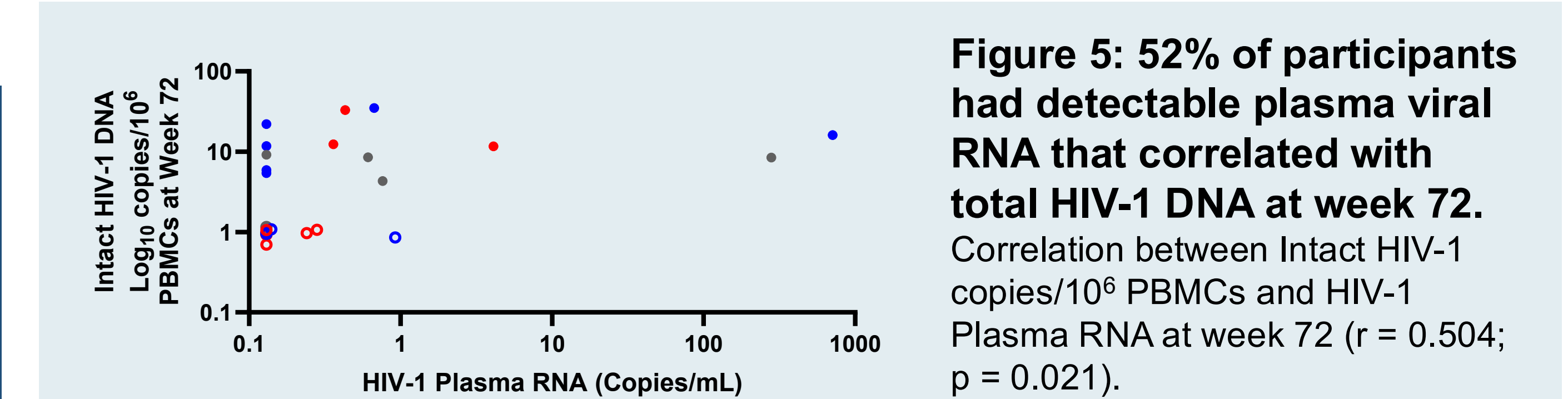
- 25 South African youths with perinatal HIV, on ART prior to 6 months of age, were randomized into one of 3 arms and were administered only the HIV vaccine regimen alone (Arm 1), the HIV vaccine regimen plus a TLR4 agonist administered as Cervarix® (Arm 2), or the Cervarix® vaccine alone (Arm 3) (Tables 1 & 2).
- HIV-1 DNA concentrations were determined with an LTRGAG, single-plex droplet digital PCR (ddPCR) assay¹.
- Intact and defective proviruses were quantified with an in-house, subtype C triplex ddPCR assay (*gag*, *pol* and *env*) based on the Intact Proviral DNA Assay (IPDA)².
- Intact and defective proviruses were successfully quantified with the subtype C IPDA in 21/25 (84%) of participants; individual primer/probes were developed for 4 participants with failed amplification (1 *gag*, 1 *pol*, 2 *env*).
- Low-level viremia (LLV) was quantified with a single copy HIV-1 RNA assay (HMMC-gag)³.

An HIV-1 therapeutic vaccine regimen in combination with a TLR4 agonist was more effective at reducing intact proviral load than either the HIV-1 Vaccines or TLR4 Agonist alone.



DISCLAIMERS

This study was performed by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. MD, USA and Stellenbosch University, Cape Town, South Africa. The study was sponsored by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. The study was funded by the Division of AIDS, National Institute of Allergy and Infectious Disease, NIH (Grant U01AI135941 and U1AI16566) and Fondazione PENTA for the treatment and care of children with HIV (and related diseases). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army, the Department of Defense, or HJF. The investigators have adhered to the policies for protection of human subjects as prescribed in AR-70-25.



CONCLUSIONS

- In youths with longstanding perinatal HIV-1, therapeutic HIV-1 vaccinations with HIVIS DNA followed by MVA/CMDR boost (Arm 1) or three doses of Cervarix® vaccine (Arm 3) led to increases in HIV DNA by single-plex LTRGAG ddPCR by Week 72 of study. HIV-1 DNA did not significantly change when the HIVIS DNA + MVA/CMDR regimen was co-administered with the TLR4 adjuvanted Cervarix® vaccine (Arm 2).
- The median intact HIV DNA load decreased in Arm 2, versus increases in both Arms 1 and 3. The proportion of intact proviruses increased in both Arms 1 and 3, but decreased with the combination of HIVIS DNA + MVA/CMDR and Cervarix® vaccinations (Arm 2). Decreases suggest immunotherapy with HIV vaccines combined with a TLR4 agonist may enhance antiviral responses.
- The study findings correlate with HIV-1-specific immune responses generated with vaccination (see Poster 0847)
- These findings support the potential for combining TLR-agonists with HIV-1 therapeutic vaccines to target proviral reservoirs after perinatal HIV-1 acquisition.

ADDITIONAL INFORMATION

- References
 - Powell L, Dhummakupt A, Siems L, Singh D, Le Duff Y, Uprety P, Jennings C, Szewczyk J, Chen Y, Nastouli E, Persaud D. Clinical validation of a quantitative HIV-1 DNA droplet digital PCR assay: Applications for detecting occult HIV-1 infection and monitoring cell-associated HIV-1 dynamics across different subtypes in HIV-1 prevention and cure trials. *J Clin Virol.* 2021 Jun.
 - Bruner KM, Wang Z, Simonetti FR, Bender AM, Kwon KJ, Sengupta S, Fray EJ, Beg SA, Antar AAR, Jenike KM, Bertagnoli LN, Capoferri AA, Kufera JT, Timmons A, Nobles C, Gregg J, Wada N, Ho YC, Zhang H, Margolick JB, Blankson JN, Deeks SG, Bushman FD, Siliciano JD, Laird GM, Siliciano RF. A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. *Nature.* 2019 Feb.
 - Somsouk M, Dunham RM, Cohen M, Albright R, Abdel-Mohsen M, Liegler T, Lifson J, Piatak M, Gorelick R, Huang Y, Wu Y, Hsue PY, Martin JN, Deeks SG, McCune JM, Hunt PW. The immunologic effects of mesalamine in treated HIV-infected individuals with incomplete CD4+ T cell recovery: a randomized crossover trial. *PLoS One.* 2014 Dec 29.
- Author Contact Information: Adit Dhummakupt, adhumma1@jhmi.edu, 720 Rutland Ave, Ross Building 1133, Baltimore, MD 21205

PLAIN LANGUAGE SUMMARY

When an HIV-1 vaccine regimen was combined with an HPV vaccine, intact HIV-1 DNA decreased more than either the HIV-1 vaccine or HPV vaccine alone after 72 weeks.