Analysis of the HVTN 702 Phase 2b-3 HIV-1 vaccine trial in South Africa assessing RV144 antibody and T-cell correlates of HIV-1 acquisition

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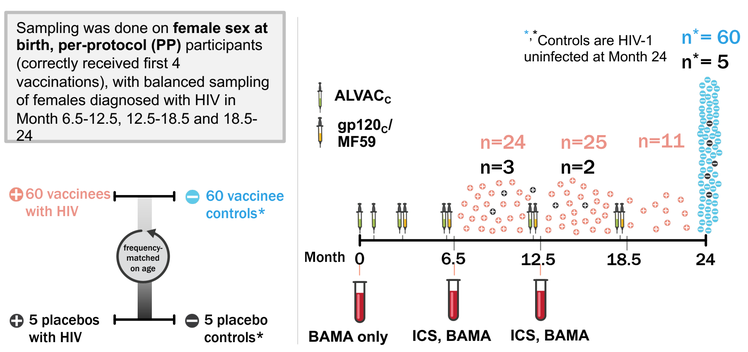
Background

Whether the immune correlates of HIV-1 acquisition identified in the Thai HIV-1 vaccine efficacy trial of an ALVAC/gp120 pox-protein vaccine regimen (RV144) generalize to other vulnerable populations is a critical question. Although the clade C-adapted vaccine regimen was not efficacious in preventing HIV-1 acquisition in South African participants, HVTN 702 (NCT02968849) provides a unique opportunity to answer this important question and to raise hypotheses regarding the observed lack of efficacy.

Methods

Limited case-control study design

Sampling was done on **female sex at birth, per-protocol (PP)** participants (correctly received first 4 vaccinations), with balanced sampling of females diagnosed with HIV in Month 6.5-12.5, 12.5-18.5 and 18.5-24



- HIV-1 specific CD4+ T-cell and binding antibody responses (bAb) measured by intracellular cytokine staining (ICS) and bAb multiplex assays (BAMA) 2 weeks post-fourth and fifth immunizations
- 3 primary endpoints assessed by Cox models as predictors of HIV-1:
  - Env-ZM96-specific CD4+ polyfunctionality score based on six markers (CD40L, IFN-γ, IL-2, TNF-α, IL-4, and IL-17a)
  - IgG bAb to A244 V1V2
  - IgG3 bAb to 1086.C V1V2
- 6 secondary endpoints:
  - polyfunctional CD4+ T-cell responses to other Env vaccine inserts
  - IgG bAbs to gp120 and Env consensus antigens
  - IgA score
- 206 exploratory endpoints: CD4+ T-cell and binding antibody responses
- Interactions among pre-specified primary and secondary endpoints also assessed using Cox models, with low/medium/high categories defined by tertiles.

Conclusions

- Previously-identified immune correlates of HIV-1 after ALVAC/gp120 vaccination were studied
- Polyfunctional CD4+ Env-ZM96 T cell responses correlated with HIV-1 vulnerability given qualitative IgG A244 V1V2 bAb response level
- Hypothesis raised that ALVAC/gp120 vaccination needs to induce high bAb V1V2 responses, in combination with polyfunctional CD4+ T cell responses, to achieve protection from HIV

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2. Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili 11 study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, 12 placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis 2011; 11:507-15.
3. Moodie Z, Dintwe O, Sawant S, Grove D, Huang Y, Janes H, Heptinstall J, Omar FL, Cohen K, De Rosa SC, Zhang L, Yates NL, Sarzotti-Kelsoe M, Seaton KE, Laher F, Bekker LG, Malahleha M, Innes C, Kassim S, Naicker N, Govender V, Sebe M, Singh N, Kotze P, Lazarus E, Nchabeleng M, Ward AM, Brumskine W, Dubula T, Randhawa AK, Grunenberg N, Hural J, Kee JJ, Benkeser D, Jin Y, Carpp LN, Allen M, D'Souza P, Tartaglia J, DiazGranados CA, Koutsoukos M, Gilbert PB, Kublin JG, Corey L, Andersen-Nissen E, Gray GE, Tomaras GD, McElrath MJ, Analysis of the HVTN 702 Phase 2b-3 HIV-1 vaccine trial in South Africa assessing RV144 antibody and T-cell correlates of HIV-1 acquisition risk, The Journal of Infectious Diseases, 2022.

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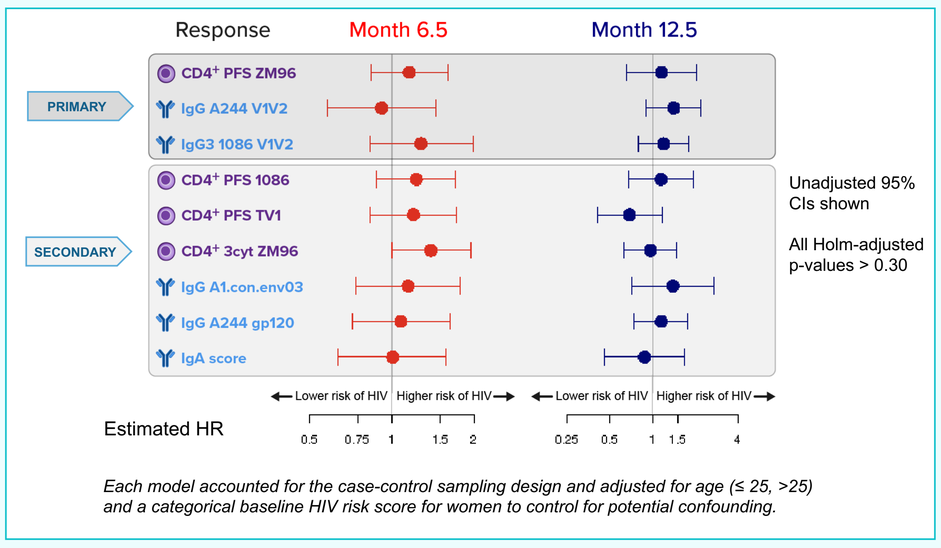
Results

Fig 1. No significant associations between any T-cell or bAb response and HIV-1 acquisition



Each model accounted for the case-control sampling design and adjusted for age (≤ 25, >25) and a categorical baseline HIV risk score for women to control for potential confounding.

Fig 2. Possible hypotheses for lack of VE in HVTN 702

Possibly because HVTN 702 vaccine

- Induced insufficient protective immune responses
- Continuing diversification of V1V2 loop in RSA
- Has different mechanism of action
- Is not protective

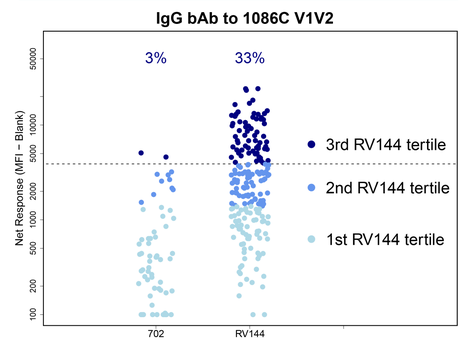


Table 1. Significant qualitative interactions among immune responses: IgG A244 V1V2 and various measures of CD4+ T cell polyfunctionality correlate with HIV-1 acquisition.

CD4+ response (magnitude)	IgG A244 V1V2	HR (95% CI)	Unadjusted p	Adjusted p
CD4+ PFS ZM96	Low (-)	2.20 (1.20, 4.04)	<0.0001	0.0017
	Medium	0.84 (0.41, 1.71)		
	High (+)	0.40 (0.26, 0.63)		
CD4+ PFS 1086	Low (-)	3.59 (1.99, 6.46)	<0.0001	0.0002
	Medium	1.06 (0.55, 2.04)		
	High (+)	0.42 (0.23, 0.76)		
CD4+ PFS TV1	Low (-)	2.30 (1.36, 3.89)	0.0016	0.033
	Medium	0.83 (0.41, 1.71)		
	High	0.52 (0.24, 1.12)		
CD4+ IFNg+/IL2+CD40L+ZM96	Low (-)	3.20 (1.84, 5.56)	<0.0001	0.0001
	Medium	1.10 (0.64, 1.90)		
	High (+)	0.49 (0.28, 0.85)		

(+) Among vaccinees with **highest tertile IgG A244 V1V2 bAb** responses, vaccine-matched **CD4+ T-cell** endpoints were associated with **decreased HIV-1 vulnerability** with estimated hazard ratios=**0.40-0.49** per 1-SD increase in the respective CD4+ T-cell endpoint.

(-) Conversely, among those with l**owest tertile IgG A244 V1V2 bAb** responses, **CD4+ T-cell** endpoints were associated with **2.2 to 3.6-fold higher vulnerability to HIV-1.**

Fig 3. Probability of HIV-1 as a function of continuous CD4+ response depends on IgG A244 V1V2 level

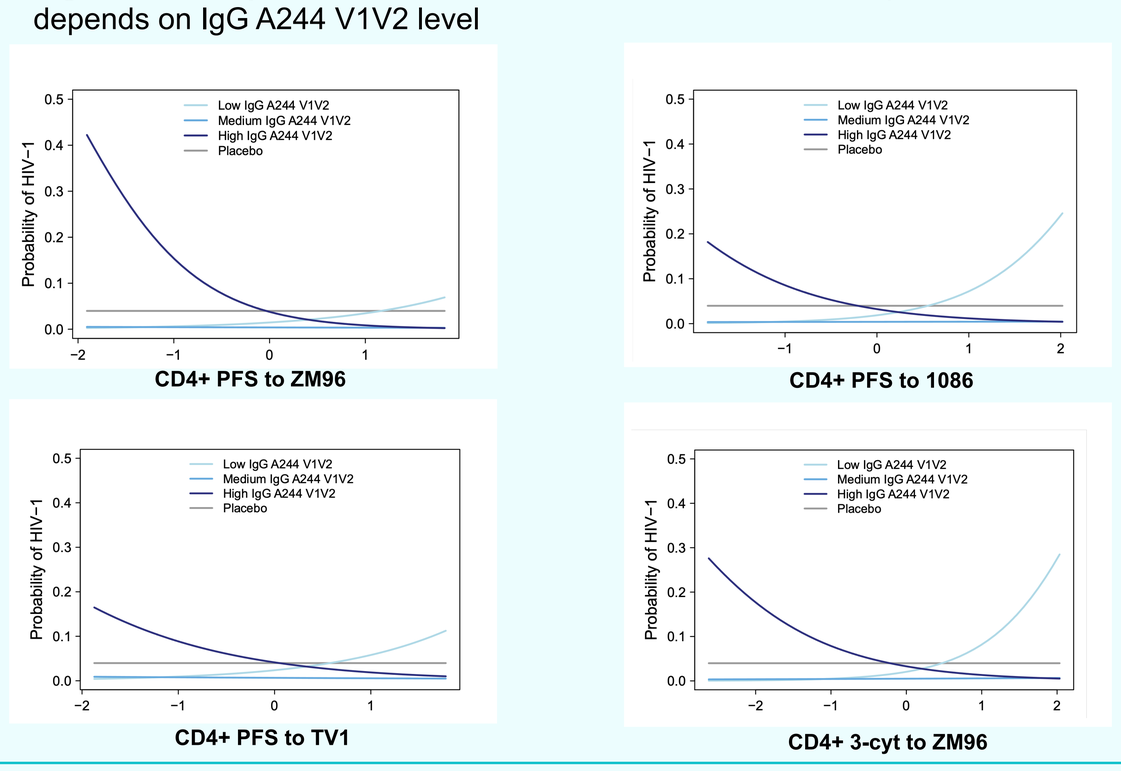


Table 2. HVTN 702 correlates results are consistent with RV144.

	IgG V1V2 responses and CD4+ responses correlate with HIV-1 protection	Interactions among immune responses
RV144	IgG V1V2 and CD4+ PFS were each strong enough to "stand alone" as independent CoRs	• IgG avidity, ADCC, nAb, CD4+ each inversely associated with HIV when IgA low • IgA, ADCC, avidity, and nAb each inversely associated when IgG V3.1 peptide microarray low
HVTN 702	The "right" combination of IgG V1V2 and CD4+ was needed: • CD4+ T cell responses coupled with high IgG V1V2 associated with decreased vulnerability to HIV • Low IgG V1V2 and strong CD4+ responses associated with increased vulnerability to HIV	CD4+ T cell responses inversely associated with HIV when IgG V1V2 high

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