

Post-Infection Cellular Immune Responses in Recipients Following ALVAC-HIV[®] + AIDSVAX[®] B/E Prime-boost Vaccination in the Thai Phase III Trial

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AIDS Vaccine Conference
October 20, 2009



RV152: Breakthrough infections [1]

- Participants

- Volunteers in RV144 (vaccine protocol) who become HIV-1 infected (> 90% enter RV152)

- Design:

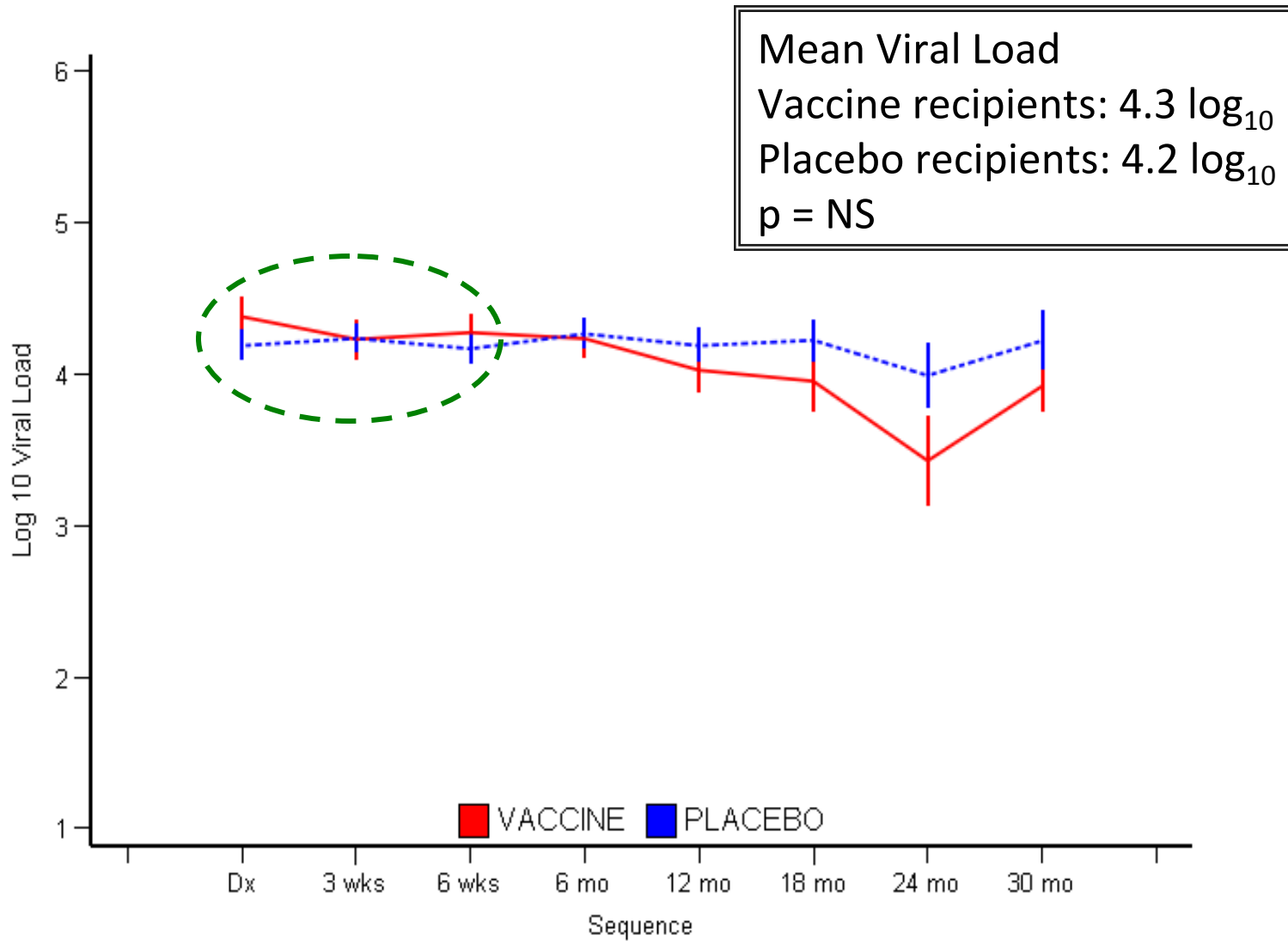
- Prospective cohort study of the clinical course of HIV-1 infection after vaccination (breakthrough infection).
- Participants and investigators will remain blinded

RV152: Breakthrough infections [2]

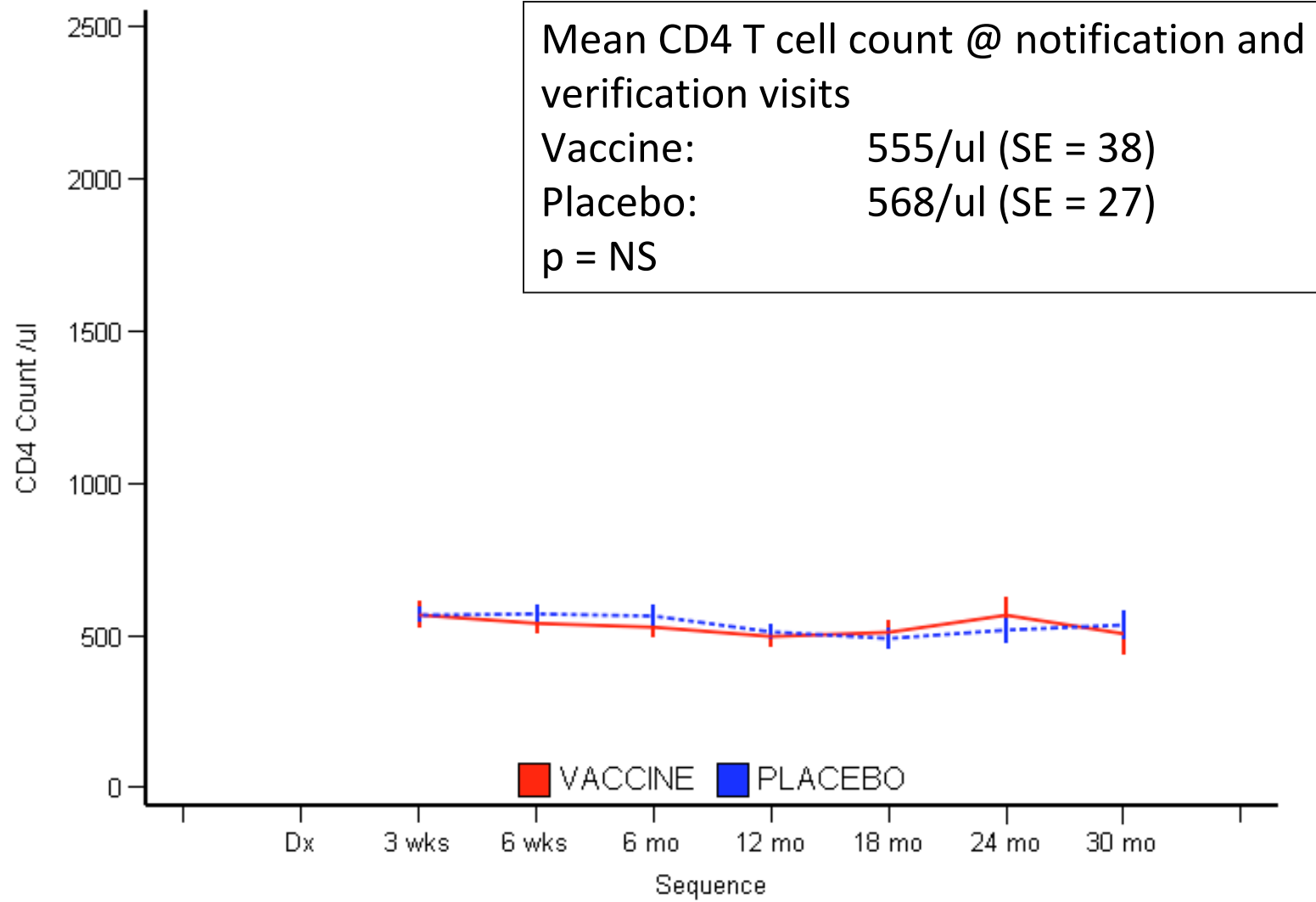
RV152 ENDPOINTS

- **Primary:** differences in a composite endpoint (AIDS-defining events, initiation of ARV, and CD4 count) between vaccine and placebo recipients who subsequently became infected with HIV.
- **Secondary:** Comparison of vaccine and placebo recipients for: long-term, AIDS-related endpoints, pre-ARV viral load and CD4+ counts, patterns of HIV-1 specific effector T-cell and B-cell immune responses, innate immune responses, breakthrough viruses, mucosal immune responses, host genetics and host restriction factors.

No difference in early post-infection viral load



No difference in post-infection CD4+ T cell count



RV152 Post-Infection Study

- Only persons who enrolled < 270 days from the estimated point of seroconversion were included in the analysis (N = 47)
 - HIV genotyping by MHA
 - ⁵¹Cr CTL
 - ELISPOT

Genotyping

- Methods
 - Plasma-based, multiregion hybridization assay MHA bce (Kijak et al) for the detection of B, C and CRF01_AE used. Assay probes 6 regions of the HIV genome
 - Definition of subtype:
 - At least 3 of 6 probes showed probe hybridization
 - Subtype B, C or CRF01_AE was assigned when probes from the same subtype hybridized in all regions
 - Recombinant assigned when 2 or more different subtype probes hybridized in different regions of the genome
- Vaccine E 18/23 (78%); Placebo E 19/22 (86%), $p = 0.83$

Methods – ^{51}Cr CTL

Measures CTL precursors expanded during IVS

Chromium Release CTL assay: Fresh PBMC

- Effectors: PBMC stimulated for 14 days with vaccinia (vCP2290) expressing HIV E *env* (TH023) and B *gag/pro* (IIIB)
- Targets: Autologous B-LCL expressing subtype E Env (TH023), B Gag/Pol or vaccinia in presence of excess cold targets
- T-cell phenotype assessed by CD8 or CD4 depletion
- Definition of CD8+ CTL positive:
 - At least 10% specific lysis at one E:T ratio
 - $\geq 50\%$ loss of specific lysis with CD8 depletion
 - $\geq 5\%$ specific lysis with CD4 depletion

Post-Infection ^{51}Cr CTL

Group	ENV	GAG/POL	ENV only	GAG/POL only	ANY
Placebo	7/23 (30.4%)	11/23 (47.8%)	3/23 (13.0%)	7/23 (30.4%)	14/23 (60.9%)
Vaccine	12/24 (50.0%)	7/24 (29.2%)	9/24 (37.5%)	4/24 (16.7%)	16/24 (66.7%)

Fisher's Exact (2-tailed)

	Vaccine	Placebo	P-value
Any	66.7%	60.9%	0.24
ENV	50.5%	30.4%	0.14
GAG	29.2%	47.8%	0.24

Although there are increased ENV responses in vaccinated and increased GAG responses in placebo, neither is statistically significant.

Methods: ELISPOT

Measures direct ex vivo IFN- γ secreting T cells

IFN- γ ELISPOT

- Cryopreserved PBMC
- Whole PBMC (10^5 /well) tested in matrix format with 92TH023 Env (165) or LAI Gag (120) peptides
- Definition of positive:
 - ELISPOT: at least 55 SFC/ 10^6 PBMC and 4 X Background

Post-Infection ELISPOT

Group	ENV	GAG	ENV only	GAG only	Any Response
Placebo	1/22 (4.5%)	9/22 (40.9%)	0/22 (0%)	8/22 (36.4%)	9/22 (40.9%)
Vaccine	7/21 (33.3%)	7/21 (33.3%)	4/21 (19.0%)	4/21 (19.0%)	11/21 (52.4%)

Fisher's Exact (2-tailed)

	Vaccine	Placebo	P-value
Any	52.4%	40.9%	0.55
ENV	33.3%	4.5%	0.02
GAG	33.3%	40.9%	0.75

There are significantly higher ENV ELISPOT responses in vaccinated and slightly higher GAG in placebo recipients.

^{51}Cr CTL - ELISPOT Concordance

Group	ENV	GAG	ENV only	GAG only	Any Response
Placebo	1/22 (4.5%)	6/22 (27.3%)	0/22 (0%)	3/22 (13.6%)	7/22 (31.8%)
Vaccine	6/21 (28.6%)	1/21 (4.8%)	3/21 (14.3%)	1/21 (4.8%)	8/21 (38.1%)

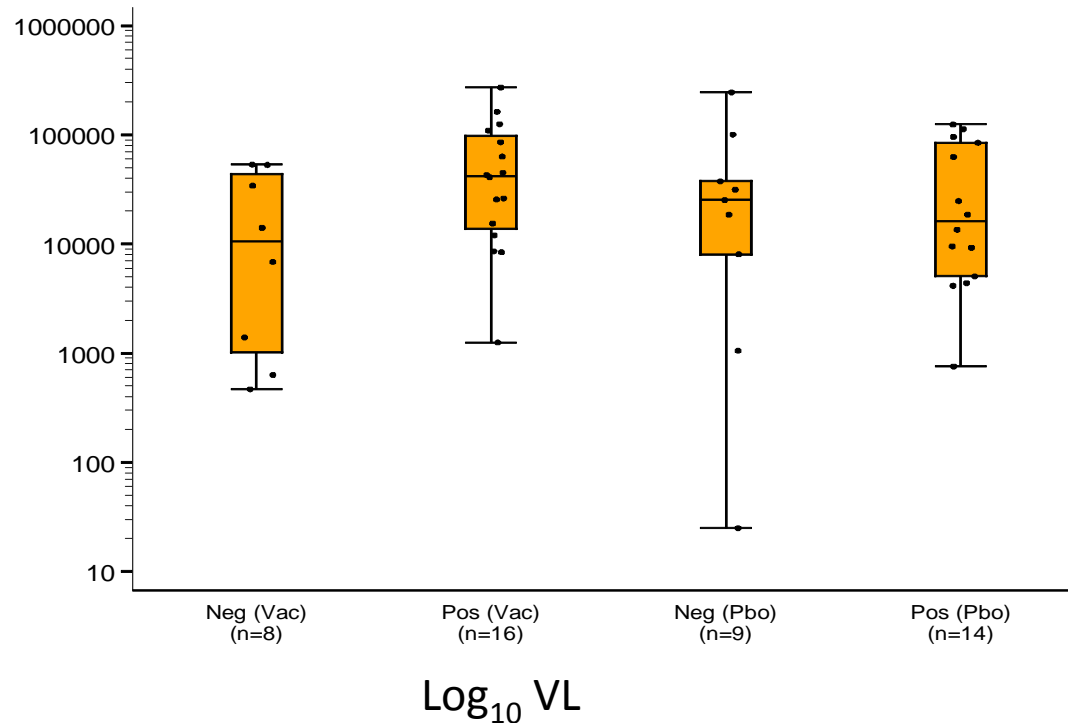
Fisher's Exact (2-tailed)

	Vaccine	Placebo	P-value
Any	38.1%	31.8%	0.75
ENV	28.6%	4.5%	0.04
GAG	4.8%	28.6%	0.09

In volunteers with positive CTL and ELISPOT, vaccine recipients had ENV responses ($p = 0.04$) and placebo recipients trended toward GAG responses ($p = 0.09$)

Viral Load and CTL status

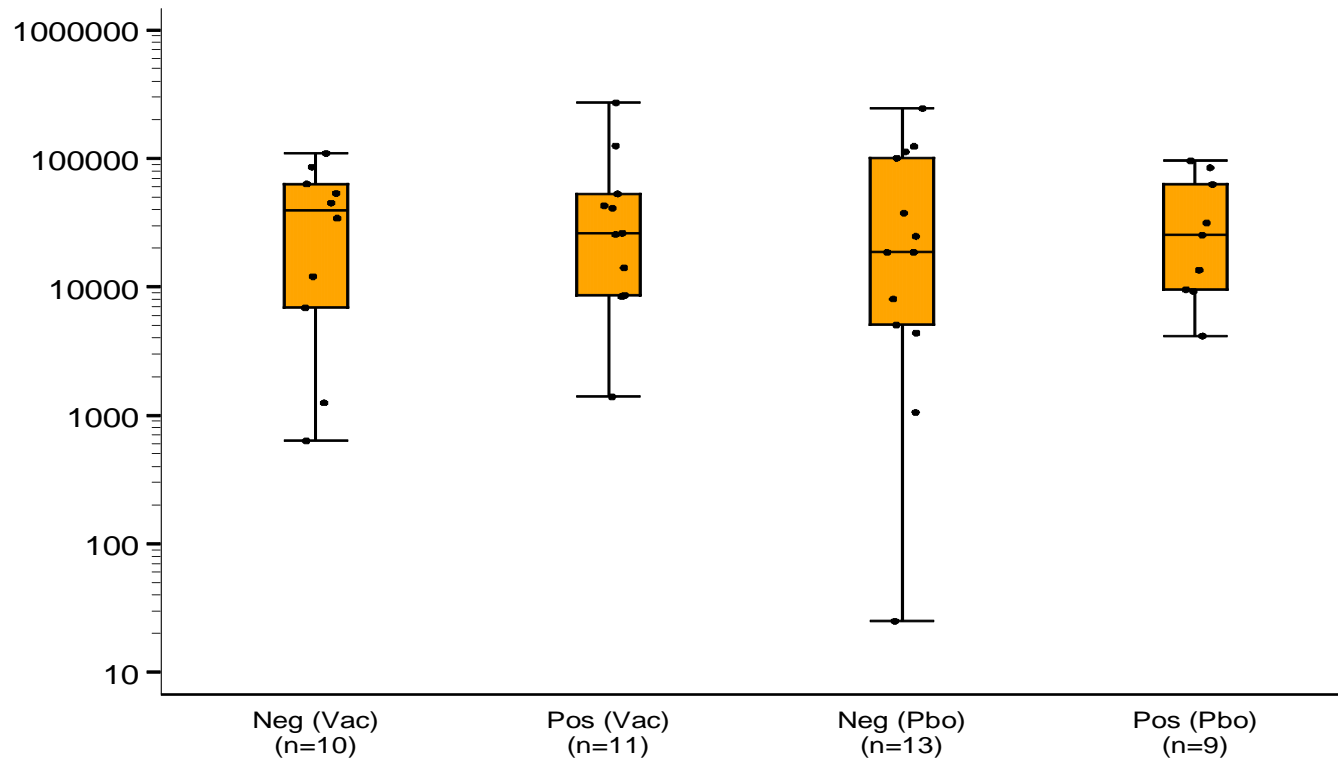
⁵¹Cr CTL are associated with a higher VL in vaccine recipients, not placebo.



	CTL-	CTL+	p-value*
Vaccine	3.82	4.53	0.08
Placebo	4.25	4.05	> 0.6

*Wilcoxon 2-sample

Viral Load and ELISPOT status



p = NS

Conclusions

- There was no vaccine effect on subtype distribution in the subset of volunteers evaluated in this study.
- ^{51}Cr CTL suggest that vaccine recipients show greater ENV responses and placebo recipients, like HIV infected persons, show more GAG/POL responses.
- ELISPOT, as seen with HIV uninfected vaccinees, shows a significantly higher level ENV responses compared to placebos.
- In persons showing concordant ^{51}Cr CTL and ELISPOT responses, the pattern of ENV predominance in vaccinees is again seen (60% for double positive / negative).
- CTL⁺ vaccine recipients have associated elevation in viral load compared to CTL⁻vaccinees ($p = 0.08$), and this effect was not seen in placebo recipients.