RV 144

Immunogenicity of ALVAC-HIV (vCP1521) and AIDSVAX B/E Prime Boost Vaccination in RV144, Thai Phase III HIV Vaccine Trial

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Background

- Vaccinated subjects received recombinant ALVAC-HIV (vCP1521) priming with AIDSVAX B/E (VaxGen gp120 B/E) boosting
  - ALVAC: expresses subtypes E (TH023: gp120)/B (TM gp41) *env* and B *gag/pro* (LAI)
  - AIDSVAX: gp120 subtypes B (MN) and E Env (CM244) (AIDSVAX)
- ALVAC administered at 0, 1, 3 and 6 months and AIDSVAX at 3 and 6 months
- Previous Phase I/II trial using identical immunization regimen was performed with 61 volunteers (vaccine: placebo ratio 3:1) and cellular and humoral immunogenicity were assessed. (Nitayaphan et al., JID, 2004)

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Objectives

- Assess cellular and humoral immunogenicity induced by the RV144 vaccine regimen in a random subset of volunteers who remained HIV seronegative
  - Assess the frequency and magnitude of HIV specific T cell responses induced by ALVAC-HIV and AIDSVAX B/E by ELISpot, intra-cellular cytokine staining and antigen-specific lymphoproliferation (LPA)
  - Assess humoral immunogenicity induced by ALVAC plus AIDSVAX using binding antibody assays
- In instances where identical assays used, compare the frequency of immune responses observed in RV144 with those seen in the earlier phase I/II trial (RV135)

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RV144 Immunogenicity – Study Flow

Randomized list (EMMES)
Laboratory blinded to vaccine status

	200 participants	200 participants	200 participants	
	IFN-γ ELISpot	IFN-γ/IL-2 ICS	LPA	gp120/p24 BAb
Months	0 and 12	0 and 12	0 and 6.5	
Antigens	gp160 (92TH023) - 162 peptide pool p24 (LAI) - 120 peptide pool		A244 and MN gp120 IIIB p24	A244 and MN gp120 BH10 p24
Match	ALVAC (vCP1521)		AIDSVAX/ALVAC	

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Methods

- All specimens processed within 8 h of venipuncture
- Validated assays performed on archived specimens: $\bar{X}$ 4.5 years (3.1-5.7)
- IFN-g ELISpot and IL-2/ IFN-g ICS

  Definition of positive:
  - ELISpot: at least 55 SFC/Million PBMC and 4 X Background (media only)
  - ICS: At least 3 X Background and frequency of $\geq$0.05% gated events
- Ag-specific LPA performed using reduced carboxymethylated gp120 (E and B) and p24 (subtype B)

  Definition of positive:
  - LSI of $\geq$ 5 at post-vaccination visit and at least 3-X increase over baseline visit
- Binding Antibody assays performed by ELISA:
  - gp120 ELISA used an Ab derived from subtype B to capture gp120 Ag of both subtypes (CM244 and MN)
  - p24 ELISA was performed by direct binding of Ag to plate

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Study Arm for Immunogenicity Assays

Assay

Status (N)	ELISpot	ICS	Binding Ab/LPA
Vaccinee (443)	157	144	142
Placebo (155)	41	56	58

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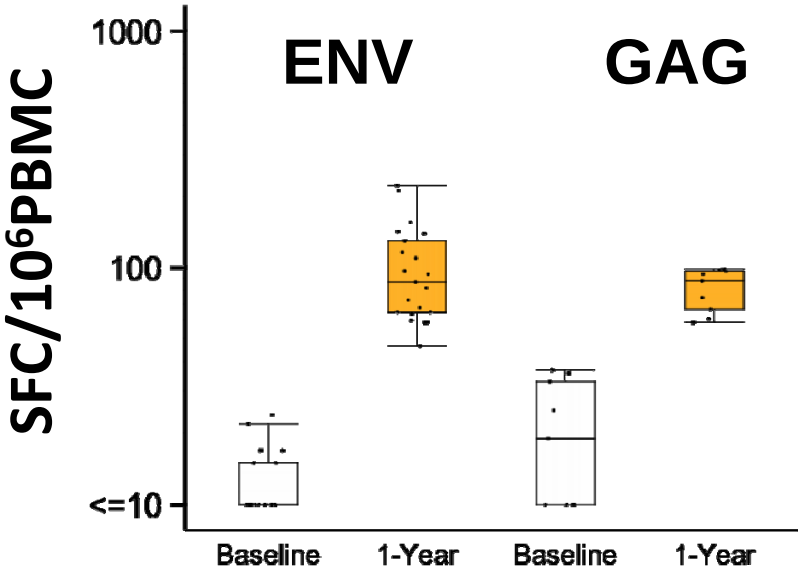
ELISpot responses – Vaccinees

6 months post-final vaccination

Antigen(s)	*Frequency (%)*
Env Only	17/152 (11)*
Gag Only	6/148 (4)
Env + Gag	3/151 (2)
Any HIV	26/152 (17)**



*** P<0.05;**P<0.01 versus Placebo (N=38)**

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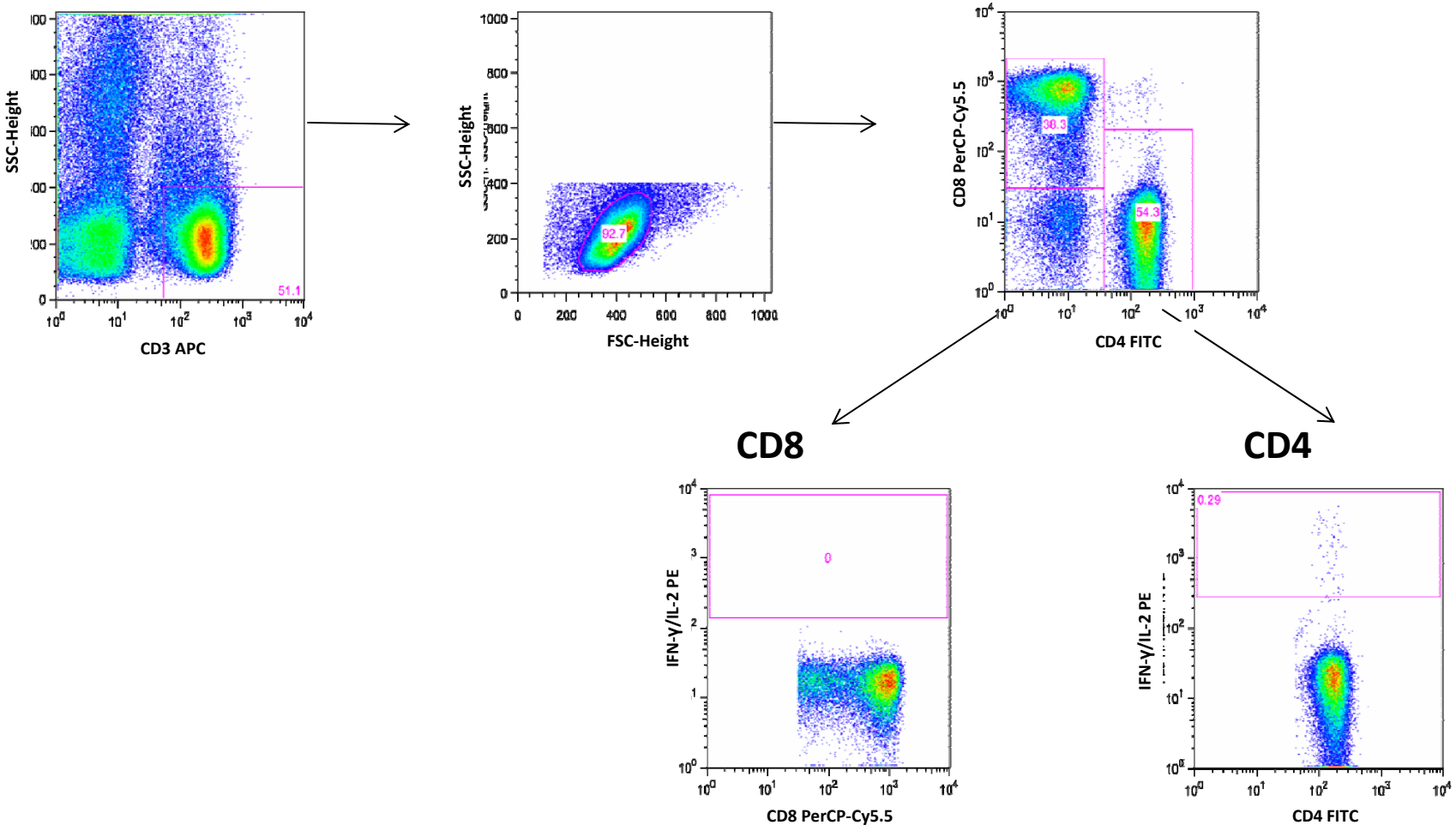
ICS—Gating Strategy



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IFN-γ/IL-2 ICS

6 months post-final vaccination

	Frequency (%)			
	CD4		**CD8**	
Antigen	**V**	**P**	**V**	**P**
Env Only	45/142 (32) *	1/54 (2)	5/133 (4)	4/52 (8)
Gag Only	0/144	0/56	3/136 (2)	1/53 (2)
Env + Gag	2/142 (1)	0/54	0/131	0/51
Any HIV	**47/142 (33)***	**1/54 (2)**	**8/131 (6)**	**5/51 (10)**

***P <0.0001 compared to placebo**

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Ag-Specific Lymphoproliferation

2 weeks post-final vaccination

	Frequency (%)	
Antigen	**Vaccinee**	**Placebo**
gp120 E (A244)	61/68 (90)	4/24 (17)
gp 120 B (MN)	51/57 (89)	4/21 (19)
p24	31/56 (55)	3/22 (14)

P<0.001 compared to placebo group - all Antigens

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Binding Antibody

2 weeks post-final vaccination

Antigen	***Frequency (%)***	***Reciprocal GMT***
B gp120	140/142 (99)	31207 (800-204800)
E gp120		14558 (200-204800)
B p24	74/142 (52)	138 (50-1600)

P<0.0001 compared to placebo group - all Antigens

Phase I/II versus RV144

Assay	***RV 135 (2000-2002)***		***RV144 (2003-2009)***	
	B	**E**	**B**	**E**
ELISpot	17%		17%	
CD8 CrCTL	10%			
LPA	53%	51%	61%	75%
P24 EIA	50%		52%	
Gp120 EIA	100%	96%	99%	99%

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Summary

- Direct ex vivo cellular immunogenicity assessed by cytokine production at 6 months following completion of immunization was CD4-mediated, but CD8 responses following in vitro stimulation not assessed
- The vaccine regimen induced robust CMI as measured by LPA responses to HIV subtypes B and E Env and more moderately to p24 at 2 weeks post immunization
- CI responses overall were predominantly to HIV Env

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Summary (2)

- vCP1521 induced CD4 and antibody responses to the HIV-1 Gag antigen
- Induction of humoral immune responses was robust to both subtypes of HIV-1 gp120 and less so to p24
- Both CMI and humoral immune responses were comparable to the earlier phase I/II trial
- Future work - Further definition of responding CD4 T cells, neutralizing antibody, ADCC and innate immunity

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Acknowledgments

The 16,402 study participants

- **TRRC**
  - Bessara Nuntapinit
  - Sirinan Madnote
  - Panadda Swangsinth
  - Susan Mason
- **Thai Ministry of Public Health**
  - Nakorn Premsri
  - Chawetsan Namwat
- **AFRIMS**
  - Chirapa Eamsila
  - Nantana Khaochalad
  - Patricia Morgan
  - Michael Benenson
- **Vaccine Trial Centre**
  - Punnee Pitisuttithum
- **MHRP, Rockville**
  - Jennifer Malia
  - Sheila Peel
  - Linda Jagodzinski
  - Victoria Polonis
  - Lisa Reilly
- **Sanofi-Pasteur**
  - John McNeil
  - Lucy Gisonni-Lex
  - Sanjay Gurunathan
- **HVTN**
  - John Hural
- **IAVI**
  - Josephine Cox
- **DAIDS/NIH**
  - Peggy Johnston
  - Philip Renzullo

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The NEW ENGLAND JOURNAL of MEDICINE

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

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