

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med* 2009;361:2209-20. DOI: 10.1056/NEJMoa0908492.

Supplemental Material

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Methods

Study Details

The various persons contributed to study design as follows:

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Study Procedures

This section describes the test articles, the assays used to determine the vaccine immunogenicity, and the trial statistical analysis.

ALVAC-HIV (vCP1521) is a recombinant canarypox vaccine developed by Virogenetics Corporation (Troy, NY) and manufactured by sanofi pasteur (Marcy-l'Étoile, France). The recombinant canarypox was genetically engineered to express HIV-1 Gag and Pro (subtype B LAI strain) and CRF01_AE (subtype E) HIV-1 gp120 (92TH023) linked to the transmembrane

anchoring portion of gp41 (LAI). ALVAC Placebo (sanofi pasteur) was a sterile, lyophilized product consisting of virus stabilizer and freeze-drying medium reconstituted in 1 ml of 0.4% sodium chloride.

AIDSVAX® B/E (Global Solutions for Infectious Diseases, South San Francisco, CA), is a bivalent HIV gp120 envelope glycoprotein vaccine containing a subtype E envelope from the HIV-1 strain A244 (CM244) and a subtype B envelope from the HIV-1 MN produced in Chinese hamster ovary cell lines. The envelope glycoproteins, 300 µg of each, originally manufactured by Genentech, Inc., and further developed by VaxGen, Inc., are co-formulated with 600 µg of alum adjuvant. AIDSVAX placebo (VaxGen, Inc.) was 600 µg alum adjuvant.

Immunogenicity

Cell Preparation: Peripheral blood mononuclear cells (PBMC) were prepared using 8ml sodium citrate Vacutainer® Cell preparation tubes (CPT™) according to manufacturer's instructions (BD, Franklin Lakes, NJ). PBMCs were cryopreserved in RPMI medium (Sigma, St. Louis, MO) containing 20% heat-inactivated fetal-calf serum and 10% dimethylsulfoxide (DMSO; Sigma) in a Cryo 1°C freezing container (Nalgene, Rochester, NY). Cells were stored at $\leq -140^{\circ}\text{C}$.

Immunogenicity assessments were performed on cryopreserved specimens; average cell viability was >93%.

Interferon-gamma (IFN- γ) ELISpot and IFN- γ /Interleukin (IL)-2 Intracellular cytokine staining (ICS): PBMC were thawed and rested overnight prior to the assays. HIV peptides (New England Peptide, Gardner, MA) of 15-mer overlapping by 11 amino acids representing HIV

subtype E-Env (TH023; 162 peptides) and HIV subtype B-Gag (LAI; 120 peptides) were used for stimulation of PBMC. Two peptide sets were used as positive controls if there were sufficient cells: A commercial CMV pp65 peptide pool (JPT Peptide Technologies, Berlin, Germany), and the CEF pool representing immunodominant CD8⁺ T cell epitopes within cytomegalovirus (CMV), Epstein-Barr virus (EBV) and influenza was also used. All peptides were used at a final concentration of 1 µg/ml.²⁵

ELISpot Assay: Briefly, ninety-six-well hydrophobic polyvinylidene difluoride membrane-bottomed plates (Millipore) were coated over night at 4°C with anti-human IFN-γ monoclonal antibody (final concentration 5 µg/ml; Mabtech, Nacka Strand, Sweden). PBMC were re-suspended in RPMI (Invitrogen, Carlsbad, CA) supplemented with 10% normal human serum (Gemini Bio-products, Sacramento, CA), 2 mM L-Glutamine (Invitrogen), 50 µg/ml streptomycin and 50 U/ml penicillin (Invitrogen) and plated at a concentration of 2×10^5 /well. Wells containing PBMC and media only were supplemented with the equivalent concentration of DMSO and served as negative controls. Phytohemagglutinin (PHA; Sigma) was used as a positive control. PBMC plus peptide antigens or PHA were tested in 3 replicate wells. Negative controls were performed in quadruplicate. After incubation at 37°C in 5% CO₂ for 20 to 24 hours, PBMC were removed by washing with PBS/0.05% Tween-20 (Sigma). Captured IFN-γ was detected by incubation for 2 hours at 37°C with biotinylated anti-human IFN-γ monoclonal antibody (Mabtech) at 2 µg/ml in PBS/0.5% BSA. Following incubation plates were washed with PBS/0.05% Tween-20 and Avidin-Peroxidase-Complex (Vectastain Elite Kit) was added for 1 hour at room temperature. Unbound complex was removed by washing 6 times with PBS and the peroxidase staining was performed using AEC substrate (Vectastain AEC Kit) according

to the manufacturer's instructions. Spots were counted with a C.T.L. analyzer (Shaker Heights, OH) and software (version 4.0.19, C.T.L. Analyzers). Results are expressed as spot-forming cells (SFC)/ 10^6 PBMC. A positive IFN- γ response was defined as at least 55 SFC/ 10^6 PBMC (uncorrected) and at least 4 times the DMSO treated wells.²⁶

ICS Assay: PBMC were plated in a 96-well plate (1×10^6 /well). PBMC stimulation was performed in 10% FBS/RPMI media in the presence of 1 μ g/ml anti-CD28 and anti-CD49d and Brefeldin A (BD Biosciences, San Diego, CA) and stimulated with HIV and positive control peptide pools. PBMC supplemented with DMSO was used as a negative control. Staphylococcus Enterotoxin B (SEB; Sigma) was used as an additional positive control. After 6 hours of stimulation at 37°C, 5% CO₂ EDTA (20mM, Sigma) was added and incubated for 15 min. Subsequently PBMC were fixed and permeabilized using FACS Lysing Solution and FACS Permeabilizing Solution 2 (BD) according to the manufacturer's instructions. The following antibodies were added for 60 min at room temperature in the dark: CD4–fluorescein isothiocyanate (FITC), CD3-allophycocyanin (APC), IFN γ -phycoerythrin (PE), IL-2-phycoerythrin (PE) and CD8-PerCP-Cy5.5 (all BD Biosciences). PBMC were washed and fixed with 1% paraformaldehyde. Analysis was performed using a FACSCalibur flow cytometer (BD Immunocytometry Systems). Between 100,000 and 150,000 CD3⁺ lymphocytes were collected for each sample. Flow cytometry data were analyzed using FlowJo (version 8.8.6; TreeStar). Positive response was defined as $\geq 0.05\%$ and at least 3 times PBMC only.

HIV-specific Binding Antibody (BAb) Assays:

HIV-specific BAb were measured on frozen plasma using ELISA.

gp120 BAb ELISA: 96-well Immulon-2 plates were coated with 5µg/ml sheep affinity-purified anti-gp120 capture AB (Aalto, Bio Reagents, Dublin Ireland) in bicarbonate buffer (pH 9.6) and incubated overnight at 4°C. Plates were washed three times with phosphate buffered saline (PBS), and gp120 AG (MN or A244, kindly provided by Global Solutions for Infectious Diseases, San Francisco, CA) at a concentration of 1µg/ml in blocking buffer was added to half the plate, with the other half receiving dilution buffer only. Plates were incubated for 1h at 37°C, followed by three washes with PBS. Goat anti-human IgG peroxidase conjugate (Calbiochem, La Jolla, CA) diluted in blocking buffer was added to all wells and further incubated for 1h at 37°C. Plates were washed three times with PBS and ABTS Peroxidase Substrate system (Kirkegaard & Perry Laboratories, Gaithersburg, MD) added to wells for 30 minutes at 37°C. The absorbance was read at 405nm subtracting background at 650 nm. The OD was corrected for the corresponding wells containing no gp120 AG. Samples were screened for the presence of gp120 B and E antibodies at an initial dilution of 1:50. Non-reactive samples were assigned a reciprocal titer of 25. Reactive samples (optical density >0.200) were titrated further beginning at 1:100 at 2-fold dilutions. The reciprocal end-point titer was calculated as the greater OD value of either (2X Mean OD negative control + 2X SD) or 0.100.

p24 Binding AB ELISA: The ELISA procedure was that as described for gp120 BAb measurement, with the following exceptions: Immulon-2 plates were coated directly with 0.5 µg/ml recombinant HIV-1 p24 Gag AG (HIV-1 subtype B; Aalto Bio Reagents) in PBS and incubated overnight at 4°C. The OD was measured at 405nm subtracting background at 490nm. Samples were considered reactive on screening if the OD was >0.100

Lymphoproliferative Assay

The proliferative responses of subject PBMC were measured by incubating 1×10^5 cells per well in 96-well U-bottom plates with serial dilutions of envelope protein gp120MN and gp120A244 (10, 5, 1 µg/ml) (Global Solutions for Infectious Diseases) and serial dilutions of p24 (10, 5, 1 µg/ml) (ABL Inc., Kensington, MD); tetanus toxoid (Staten Serum Institute, Copenhagen, Denmark) was used at 5 µg/ml as a recall antigen. In a separate plate PBMC were cultured with 1, 4 and 16 µg/ml of PHA (Sigma Saint Louis, MO). After 3 days of incubation with PHA and 6 days with the antigens, cells were pulsed with 1 µCi/well of [3 H]-thymidine for 6 hr then harvested using the Filtermate 196 Harvester (Packard Bioscience Company, Meriden, CT) and counted in a TopCount NXT™ Microplate Scintillation and Luminescence counter (Packard Bioscience Company, Meriden, CT). The data are expressed as an LSI [Lymphocyte Stimulation Index = (PBMC cpm + antigen/mitogen) / (PBMC cpm+ medium)] to define antigen specificity. Individuals are arbitrarily designated as responders or non responders if their LSI is greater than or equal to 5.

Statistical Analysis

Sample size was designed to detect a vaccine-associated 25% decrease in the hazard rate during the vaccination period and 50% in the subsequent 3 years. A placebo arm infection rate of 0.34%/ year was assumed using the lower bound of the 95% confidence interval from a field study in Chon Buri of 20-30 year olds (M. Benenson, unpublished data). With up to 5% losses to follow-up per 6 month period, a total sample of 16,000 subjects provided 90% power using a two sided 5% Type 1 error rate, to detect vaccine efficacy (VE) >0.

Randomization used centrally generated permuted blocks of random sizes for a set of coded treatment labels that coincided with coded treatment stocks. Study pharmacists, independent of other site staff and blinded to the contents of the coded treatment stocks, maintained the randomization lists and prepared opaque syringes for clinic staff.

VE and its confidence interval (CI) were estimated from a proportional hazards analysis of time to infection with $VE = 100 \times (1 - \text{relative hazard of vaccine to placebo})$. A conservative single interim efficacy analysis, at two-thirds information time using O'Brien-Fleming stopping bounds and testing for VE 95% CI lower bound $>30\%$, was included in the plan. Analyses under alternative definitions of the infection time, adjusting for 4 pre-planned covariates, and an interval-censored analysis assuming underlying interval exponential failure were performed. Treatment effect heterogeneity was examined one at a time in a proportional hazards analysis via a test for interaction.

This trial is registered with Clinical Trials.gov, NCT00223080.

The Test of Understanding (TOU) was used to determine whether volunteers understood the trial and the pre trial information regarding HIV, experimental vaccines, and their rights as a volunteer. The volunteers used the Thai TOU.

Test Of Understanding for phase3 vaccine trial (set 1)

Date:

_____Month_____Year_____

PIN

Please read the instructions. This is a test of your understanding of HIV and the study. Please mark in the that your understanding. If the questions are unclear, please ask our staff before answering.

- | | | |
|--|-------------|--------------|
| 1. Vaccine is a thing that is used to protect from infectious diseases like polio and measles. | True | False |
| 2. AIDS is caused by a virus called HIV. | True | False |
| 3. HIV/AIDS can be transmitted from one person to another by having sex together or sharing needles for drugs. | True | False |
| 4. I will not get HIV infection from the experimental vaccine in this study. | True | False |
| 5. This study has been approved by the Ministry of Public Health. | True | False |
| 6. Some of the volunteers in this study will receive the experimental vaccine and others will receive placebo injections. | True | False |
| 7. Volunteers in the trial will know if they have received the experimental vaccine or the placebo during the trial. | True | False |
| 8. During the trial, the local research team will know whether I received the experimental vaccine or the placebo. | True | False |
| 9. The study vaccine may cause my blood to test positive for HIV, but this result does not necessarily mean that I have an HIV infection. | True | False |
| 10. Since this experimental vaccine may cause my blood to test positive for HIV, the research team will help to explain this situation, if needed. | True | False |
| 11. People participating in this vaccine trial can become infected with HIV if they practice risk behaviors for HIV infection. | True | False |
| 12. Women volunteers should avoid pregnancy all the period of 3.5 years of this study. | True | False |
| 13. There is no approved data that this experimental vaccine can | True | False |

protect humans from HIV infection.

- 14. If I have some side effects caused by the vaccine, the research team will insure that I get proper and free medical care. **True False**
- 15. After experimental vaccine injection in this study, some of the volunteers may feel pain at the site of injection or have fever which mostly will be gone within a day or two after the injection like other general vaccine. **True False**
- 16. I will be compensated for my time away from work, travel and meal expenses that result from my study visits. **True False**
- 17. Personal information which I give to the research team will not be disclosed to people who are not working on the vaccine study. **True False**
- 18. I will receive 10 vaccine injections during the study. **True False**
- 19. A blood specimen will be drawn by the research team at many of the visits during this study. **True False**
- 20. Although I am asked to complete the study, I can withdraw from the study at any time. **True False**

For staff only

Score: _____

Comments: _____

Staff signature and date:

แบบทดสอบความเข้าใจเกี่ยวกับโครงการศึกษาวัคซีนแอสตีทดลองระยะที่ 3 (ชุดที่ 1)

วันที่ _____ เดือน _____ พ.ศ. _____

กรุณาอ่านรายละเอียดก่อนทำแบบทดสอบ: แบบทดสอบนี้ ทำขึ้นเพื่อทดสอบความเข้าใจของท่านต่อโครงการฯ ที่ท่านเข้าร่วมเป็นอาสาสมัคร กรุณาทำเครื่องหมาย x ในช่อง ตามความเข้าใจของท่าน หากท่านไม่เข้าใจคำถาม กรุณาถามเจ้าหน้าที่ก่อนเขียนคำตอบ

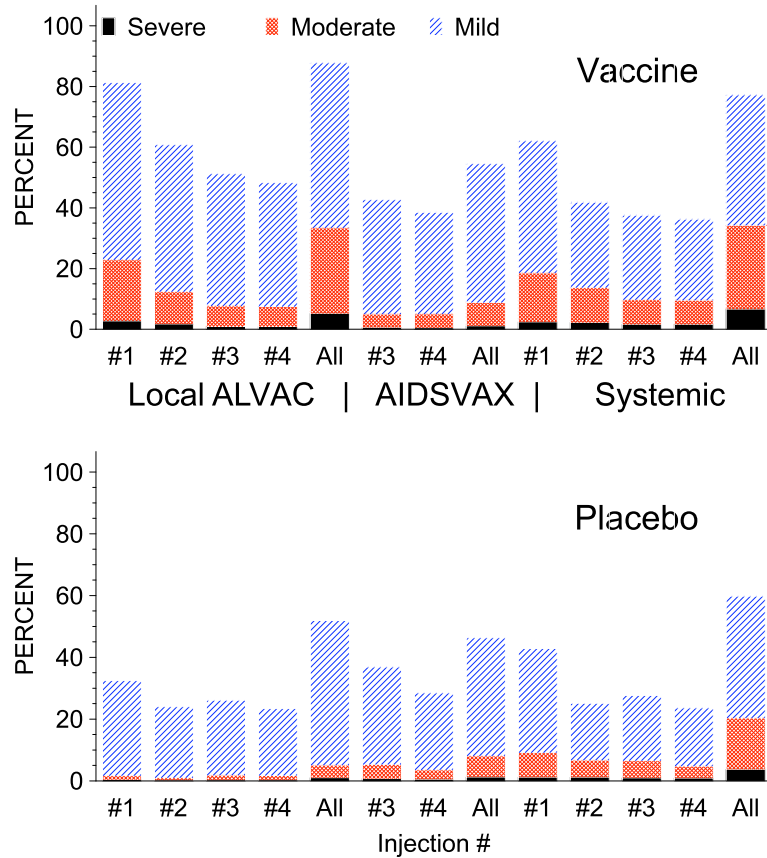
1. วัคซีนคือสิ่งที่ใช้สำหรับป้องกันโรคติดเชื้อต่างๆ เช่น วัคซีนป้องกันโรค โปลิโอและวัคซีนป้องกันโรคหัด ถูก ผิด
2. โรคเอดส์เกิดจากเชื้อไวรัสที่เรียกว่า เอชไอวี ถูก ผิด
3. เชื้อเอชไอวี (เอดส์) สามารถติดต่อจากคนหนึ่งไปยังอีกคนหนึ่งได้ โดยการมีเพศสัมพันธ์ หรือใช้เข็มฉีดยาเสพติดร่วมกัน ถูก ผิด
4. ข้าพเจ้าจะไม่คิดเชื้อเอชไอวี (เอดส์) จากการศึกษาวัคซีนทดลองที่ขึ้นในโครงการฯ นี้ ถูก ผิด
5. โครงการฯ นี้ได้รับความเห็นชอบจากกระทรวงสาธารณสุขแล้ว ถูก ผิด
6. อาสาสมัครในโครงการฯ บางรายจะได้รับการฉีดวัคซีนทดลอง และบางรายจะได้รับการฉีดยาเลียนแบบที่ไม่ใช่วัคซีน ถูก ผิด
7. ในระหว่างทำการวิจัย อาสาสมัครในโครงการฯ จะทราบว่าตนเองได้รับวัคซีนทดลอง หรือสารเลียนแบบที่ไม่ใช่วัคซีน ถูก ผิด
8. ในระหว่างทำการวิจัย คณะผู้วิจัยในพื้นที่จะทราบว่าข้าพเจ้าได้รับวัคซีนทดลอง หรือสารเลียนแบบที่ไม่ใช่ วัคซีน ถูก ผิด
9. วัคซีนทดลองในโครงการฯ อาจทำให้ผลตรวจเลือดหาการติดเชื้อเอชไอวี (เอดส์) ของข้าพเจ้าเป็นบวก แต่ผลบวกนั้นไม่ได้หมายความว่าข้าพเจ้ามีเชื้อเอชไอวี (เอดส์) ในร่างกาย ถูก ผิด
10. เนื่องจากวัคซีนทดลองในโครงการฯ อาจทำให้ผลตรวจเลือดหาการติดเชื้อเอชไอวี (เอดส์) ของข้าพเจ้าเป็นบวก ดังนั้นคณะผู้วิจัยจะช่วยให้ข้าพเจ้าอธิบายสิ่งที่เกิดขึ้นได้ ถ้าข้าพเจ้าต้องการความช่วยเหลือ ถูก ผิด
11. ผู้ที่เข้าร่วมโครงการฯ สามารถจะติดเชื้อเอชไอวี(เอดส์)ได้ อ้ายังมีกฎหมายที่เข้มงวดต่อการติดเชื้อเอชไอวี (เอดส์) ถูก ผิด
12. อาสาสมัครเพศหญิงควรหลีกเลี่ยงการตั้งครรภ์ตลอดระยะเวลา 5 ปีครึ่ง ที่อยู่ในโครงการฯ ถูก ผิด
13. ยังไม่มีข้อมูลว่าวัคซีนทดลองในโครงการฯ สามารถป้องกันการผลิตเชื้อเอชไอวี (เอดส์) ในคนได้จริง ถูก ผิด
14. ถ้าข้าพเจ้ามีอาการข้างเคียงที่เกิดจากการฉีดวัคซีนทดลองในโครงการฯ ทางคณะผู้วิจัยรับรองว่าข้าพเจ้าจะได้รับการดูแลรักษาที่เหมาะสม และไม่เสียค่าใช้จ่ายใดๆ ถูก ผิด
15. หลังการฉีดวัคซีนทดลองในโครงการฯ อาสาสมัครบางคนอาจมีอาการปวดบวมที่ฉีด หรือมีไข้ เป็นเวลา 1-2 วัน เหมือนกับการฉีดวัคซีนชนิดอื่นทั่วไป ถูก ผิด
16. ข้าพเจ้าจะได้รับค่าชดเชยสำหรับการเดินทาง ค่าเดินทางและค่าอาหาร เนื่องจากมาตามนัดของโครงการฯ ถูก ผิด
17. จะไม่มีการเปิดเผยข้อมูลส่วนตัวของข้าพเจ้าที่แจ้งไว้ต่อคณะผู้วิจัยให้แก่ผู้อื่นที่ไม่ได้ทำงานในโครงการฯ ถูก ผิด
18. ข้าพเจ้าจะได้รับการฉีดวัคซีนทดลองทั้งหมด 10 ครั้ง ระหว่างที่เข้าร่วมโครงการฯ ถูก ผิด
19. คณะผู้วิจัยจะแจกแจงผลของข้าพเจ้าหาต่อครั้งระหว่างที่เข้าร่วมโครงการฯ ถูก ผิด
20. ถึงแม้ว่าข้าพเจ้าจะออกจากรองให้อยู่ร่วมโครงการฯจนจบก็ตาม ข้าพเจ้าสามารถจะถอนตัวออกจากโครงการฯ ได้ทุกเวลา ถูก ผิด

สำหรับเจ้าหน้าที่เท่านั้น:

VERSION 01 May 2003

คะแนนที่ได้ = _____

เจ้าหน้าที่ _____



Supplemental Figure 1

Figure Legend

Local and systemic reactogenicity after ALVAC-HIV and AIDS VAX B/E vaccination.

- Shown in the upper panel are local reactogenicity after each ALVAC-HIV and AIDS VAX B/E vaccination (#1 - #4) and in total. Stacked bar graphs show severity: (blue diagonal bars, mild); red stipple (moderate); black (severe). Mild (Grade 1) is defined as: transient or mild discomfort; no limitation in normal daily activity. Moderate (Grade 2) is defined as: some limitation in normal daily activity. Severe (Grade 3) is defined as: unable to perform normal daily activity. The lower panel shows similar data for placebo recipients.

Supplemental Table 1A. Adverse events in RV144 by MedDRA coded system organ classification in vaccine and placebo recipients during the 30 post-vaccination interval and overall.

RV144
AE-Supplemental Table 1a

	All 30-Day Post Dose Intervals				All treatment emergent			
	Group				Group			
	VACCINE		PLACEBO		VACCINE		PLACEBO	
	n	%	n	%	n	%	n	%
ADVERSE EVENTS (SOC)								
Blood and lymphatic system disorders	8	0.1%	10	0.1%	38	0.5%	47	0.6%
Cardiac disorders	19	0.2%	18	0.2%	42	0.5%	46	0.6%
Congenital, familial and genetic disorders	2	0.0%	0	0.0%	19	0.2%	13	0.2%
Ear and labyrinth disorders	18	0.2%	16	0.2%	48	0.6%	53	0.6%
Endocrine disorders	3	0.0%	3	0.0%	35	0.4%	31	0.4%
Eye disorders	70	0.9%	80	1.0%	211	2.6%	218	2.7%
Gastrointestinal disorders	334	4.1%	366	4.5%	1089	13.3%	1077	13.1%
General disorders and administration site conditions	179	2.2%	148	1.8%	364	4.4%	325	4.0%
Hepatobiliary disorders	2	0.0%	1	0.0%	18	0.2%	18	0.2%
Immune system disorders	18	0.2%	7	0.1%	65	0.8%	60	0.7%
Infections and infestations	1162	14.2%	1181	14.4%	3174	38.7%	3192	38.9%
Injury, poisoning and procedural complications	639	7.8%	735	9.0%	2514	30.7%	2575	31.4%
Investigations	4	0.0%	6	0.1%	13	0.2%	11	0.1%
Metabolism and nutrition disorders	7	0.1%	2	0.0%	46	0.6%	47	0.6%
Musculoskeletal and connective tissue disorders	212	2.6%	203	2.5%	530	6.5%	498	6.1%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	0.0%	5	0.1%	16	0.2%	31	0.4%
Nervous system disorders	178	2.2%	211	2.6%	509	6.2%	560	6.8%
Pregnancy, puerperium and perinatal conditions	1	0.0%	2	0.0%	186	2.3%	195	2.4%
Psychiatric disorders	21	0.3%	21	0.3%	119	1.5%	115	1.4%
Renal and urinary disorders	6	0.1%	6	0.1%	40	0.5%	49	0.6%
Reproductive system and breast disorders	53	0.6%	52	0.6%	217	2.6%	206	2.5%
Respiratory, thoracic and mediastinal disorders	101	1.2%	94	1.1%	327	4.0%	308	3.8%
Skin and subcutaneous tissue disorders	382	4.7%	413	5.0%	619	7.5%	664	8.1%
Social circumstances	0	0.0%	0	0.0%	0	0.0%	1	0.0%
Surgical and medical procedures	2	0.0%	2	0.0%	13	0.2%	16	0.2%
Vascular disorders	10	0.1%	19	0.2%	51	0.6%	60	0.7%
Any AE	2658	32.4%	2736	33.4%	5625	68.6%	5685	69.4%

Supplemental Table 1B. Serious adverse events in RV144 by MedDRA coded system organ classification in vaccine and placebo recipients during the 30 post-vaccination interval and overall.

RV144
AE-Supplemental Table 1b

	All 30-Day Post Dose Intervals				All treatment emergent			
	Group				Group			
	VACCINE		PLACEBO		VACCINE		PLACEBO	
	n	%	n	%	n	%	n	%
SERIOUS ADVERSE EVENTS (SOC)								
Blood and lymphatic system disorders	0	0.0%	0	0.0%	2	0.0%	6	0.1%
Cardiac disorders	1	0.0%	2	0.0%	13	0.2%	12	0.1%
Congenital, familial and genetic disorders	0	0.0%	0	0.0%	16	0.2%	11	0.1%
Ear and labyrinth disorders	1	0.0%	1	0.0%	3	0.0%	3	0.0%
Endocrine disorders	0	0.0%	0	0.0%	3	0.0%	3	0.0%
Eye disorders	0	0.0%	0	0.0%	3	0.0%	0	0.0%
Gastrointestinal disorders	13	0.2%	11	0.1%	97	1.2%	94	1.1%
General disorders and administration site conditions	1	0.0%	2	0.0%	11	0.1%	23	0.3%
Hepatobiliary disorders	0	0.0%	1	0.0%	8	0.1%	6	0.1%
Immune system disorders	0	0.0%	1	0.0%	10	0.1%	13	0.2%
Infections and infestations	34	0.4%	37	0.5%	334	4.1%	359	4.4%
Injury, poisoning and procedural complications	67	0.8%	81	1.0%	512	6.2%	522	6.4%
Metabolism and nutrition disorders	0	0.0%	0	0.0%	4	0.0%	5	0.1%
Musculoskeletal and connective tissue disorders	0	0.0%	1	0.0%	9	0.1%	14	0.2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	0.0%	0	0.0%	9	0.1%	12	0.1%
Nervous system disorders	3	0.0%	5	0.1%	26	0.3%	23	0.3%
Pregnancy, puerperium and perinatal conditions	0	0.0%	2	0.0%	173	2.1%	177	2.2%
Psychiatric disorders	2	0.0%	4	0.0%	37	0.5%	40	0.5%
Renal and urinary disorders	1	0.0%	0	0.0%	12	0.1%	12	0.1%
Reproductive system and breast disorders	1	0.0%	2	0.0%	16	0.2%	12	0.1%
Respiratory, thoracic and mediastinal disorders	1	0.0%	3	0.0%	15	0.2%	15	0.2%
Skin and subcutaneous tissue disorders	2	0.0%	0	0.0%	8	0.1%	10	0.1%
Social circumstances	0	0.0%	0	0.0%	0	0.0%	1	0.0%
Surgical and medical procedures	0	0.0%	0	0.0%	4	0.0%	6	0.1%
Vascular disorders	0	0.0%	0	0.0%	2	0.0%	0	0.0%
Any SAE	126	1.5%	150	1.8%	1175	14.3%	1219	14.9%

Supplemental Table 1C. Deaths in RV144 by MedDRA coded system organ classification in vaccine and placebo recipients during the 30 post-vaccination interval and overall.

RV144
AE-Supplemental Table 1c

	All 30-Day Post Dose Intervals				All treatment emergent			
	Group				Group			
	VACCINE		PLACEBO		VACCINE		PLACEBO	
	n	%	n	%	n	%	n	%
DEATHS (SOC)								
Cardiac disorders	1	0.0%	1	0.0%	4	0.0%	4	0.0%
General disorders and administration site conditions	0	0.0%	1	0.0%	1	0.0%	7	0.1%
Infections and infestations	0	0.0%	0	0.0%	1	0.0%	8	0.1%
Injury, poisoning and procedural complications	9	0.1%	4	0.0%	61	0.7%	45	0.5%
Musculoskeletal and connective tissue disorders	0	0.0%	0	0.0%	0	0.0%	1	0.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	0.0%	0	0.0%	4	0.0%	1	0.0%
Nervous system disorders	0	0.0%	0	0.0%	1	0.0%	1	0.0%
Pregnancy, puerperium and perinatal conditions	0	0.0%	0	0.0%	1	0.0%	0	0.0%
Psychiatric disorders	0	0.0%	0	0.0%	10	0.1%	6	0.1%
Renal and urinary disorders	0	0.0%	0	0.0%	1	0.0%	1	0.0%
Respiratory, thoracic and mediastinal disorders	0	0.0%	0	0.0%	1	0.0%	0	0.0%
Social circumstances	0	0.0%	0	0.0%	0	0.0%	1	0.0%
All	12	0.1%	6	0.1%	85	1.0%	75	0.9%