RV 144

Primary and Subgroup Analyses of the Thai Phase III HIV Vaccine Trial

Nelson L. Michael, MD, PhD
Colonel, Medical Corps, United States Army
Director, US Military HIV Research Program (MHRP)
Walter Reed Army Institute of Research

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Outline

- Primary Populations (Statistical Analysis Plan)
  - Intent-to -Treat (ITT)
  - Per Protocol (PP)
  - Modified Intent-to-Treat (mITT)

- Subgroup Analyses (Statistical Analysis Plan)
  - Time and duration of protective effect
  - Overall HIV risk group stratification
  - Specific HIV behavioral risk stratification

Primary Populations (Statistical Analysis Plan)

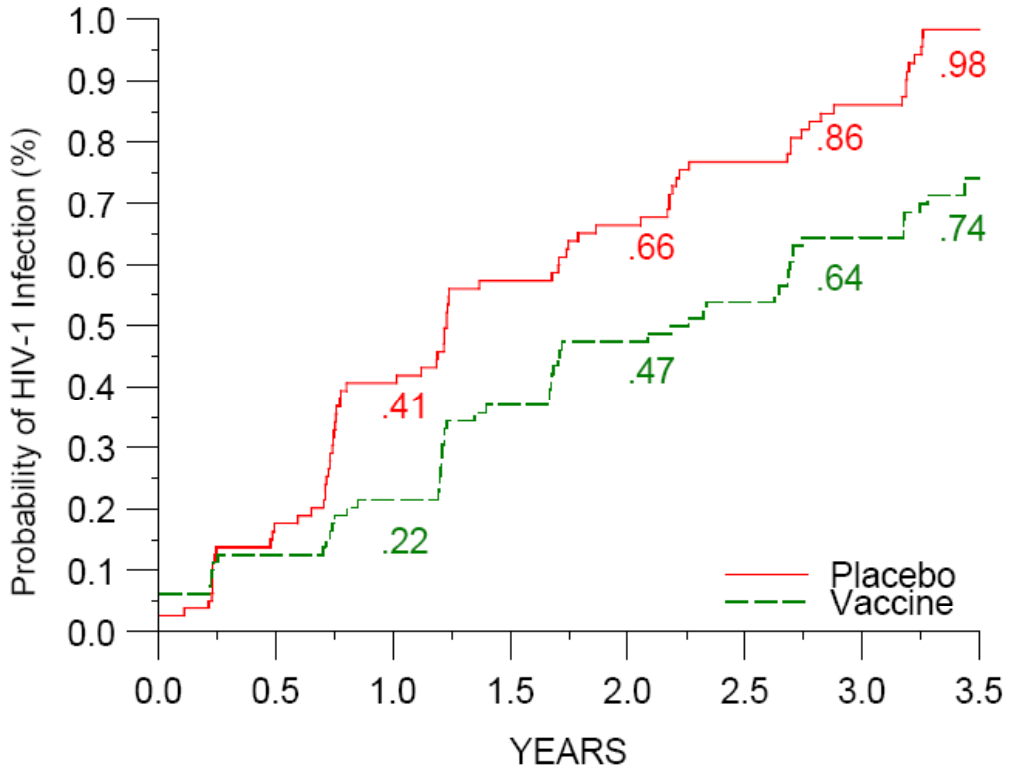
- All primary analyses were pre-specified prior to trial unblinding
- Study design considerations
  - Based on ITT analysis in HIV-uninfected subjects
  - Powered to reduce acquisition during the vaccination period by 25%
  - Powered to reduce post-vaccination acquisition by 50%
- mITT analysis was used by the independent Data and Safety Monitoring Board to judge trial futility throughout the study and efficacy at the Interim Analysis

Intent-to-Treat (ITT)

- Examines all subjects, ***regardless of HIV infection status***, who were randomized to either vaccine or placebo arm (16,402 subjects analyzed)
- Includes 7 HIV infected subjects (5 vaccine, 2 placebo) discovered to be HIV infected ***at baseline*** by look-back analysis

Efficacy (ITT)

Cumulative # Infections	Placebo	32	52	67	76
	Vaccine	17	37	50	56



# at Risk	P	8200	7775	7643	7441	7325
	V	8202	7797	7665	7471	7347

52,985 person-years

132 infections
(7 prevalent)

Vaccine infections: 56
Placebo infections: 76

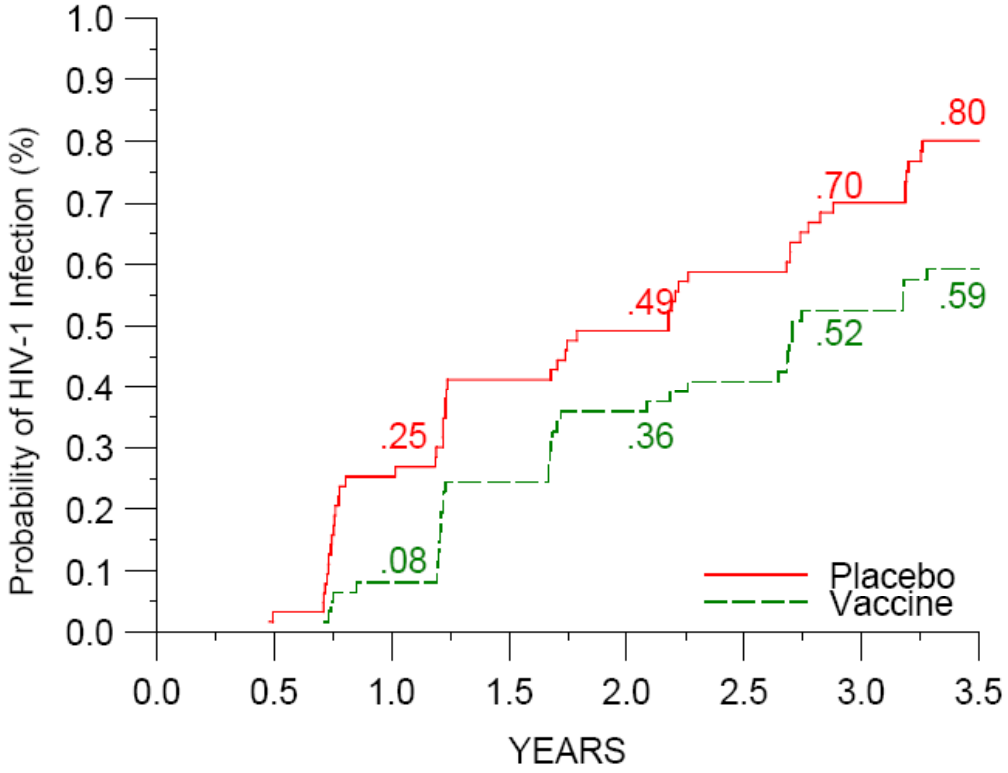
VE: 26.4%
p=0.08
95% CI: -4.0, 47.9

Per Protocol (PP)

- 12,542 subjects analyzed
- Excludes 3,853 subjects who were included in the mITT
  - 2,422 who did not receive all six study injections
  - 1,412 who received any injection "out of window"
  - 19 for other protocol violations
- Excludes first 6 months (14%) of the 42-month trial period
- ***Excludes 39 HIV-infected subjects (15 vaccine, 24 placebo), reducing the number of endpoints by 31%***

Efficacy (PP)

Cumulative # Infections	Placebo	16	31	44	50
	Vaccine	5	22	32	36



# at Risk	P	6366	6283	6220	6089	6002
	V	6176	6140	6068	5958	5874

36,720 person-years

86 infections

Vaccine infections: 36
Placebo infections: 50

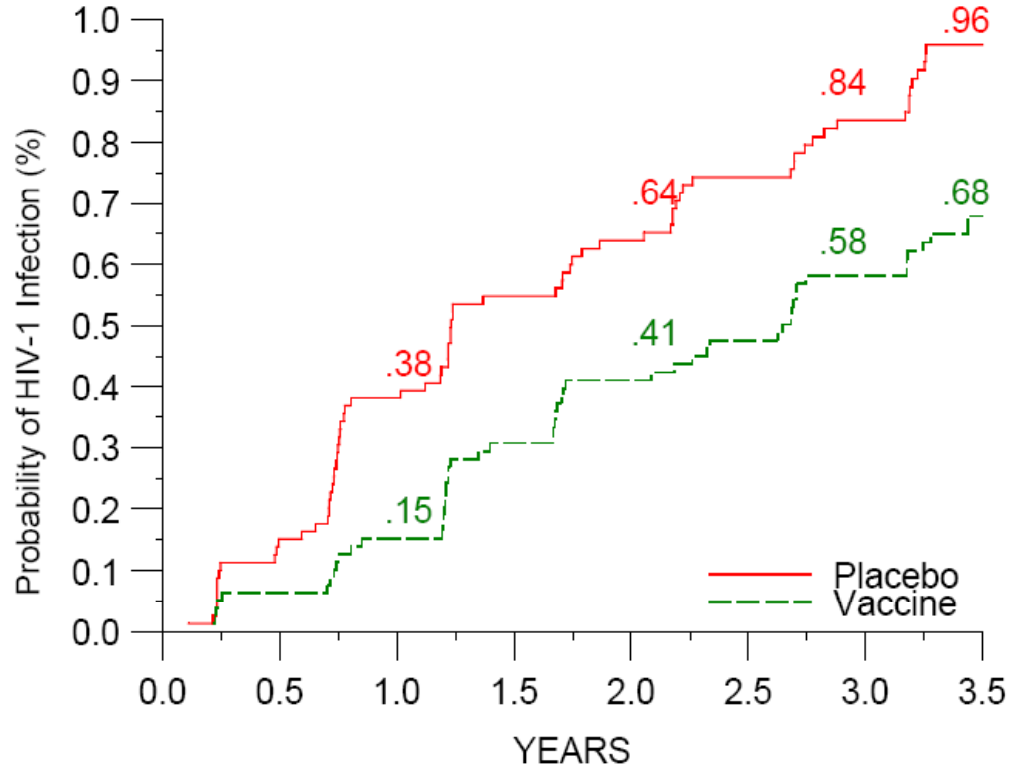
VE: 26.2%
p=0.16
95% CI: -13.3, 51.9

Modified Intent-to-Treat (mITT)

- Examines all ***HIV-uninfected subjects*** who were randomized
- This was a pre-specified analysis in the Statistical Analysis Plan
  - Primary analysis for DSMB examinations throughout the trial

Efficacy (mITT)

Cumulative # Infections	Placebo	30	50	65	74
	Vaccine	12	32	45	51



# at Risk	P	8198	7775	7643	7441	7325
	V	8197	7797	7665	7471	7347

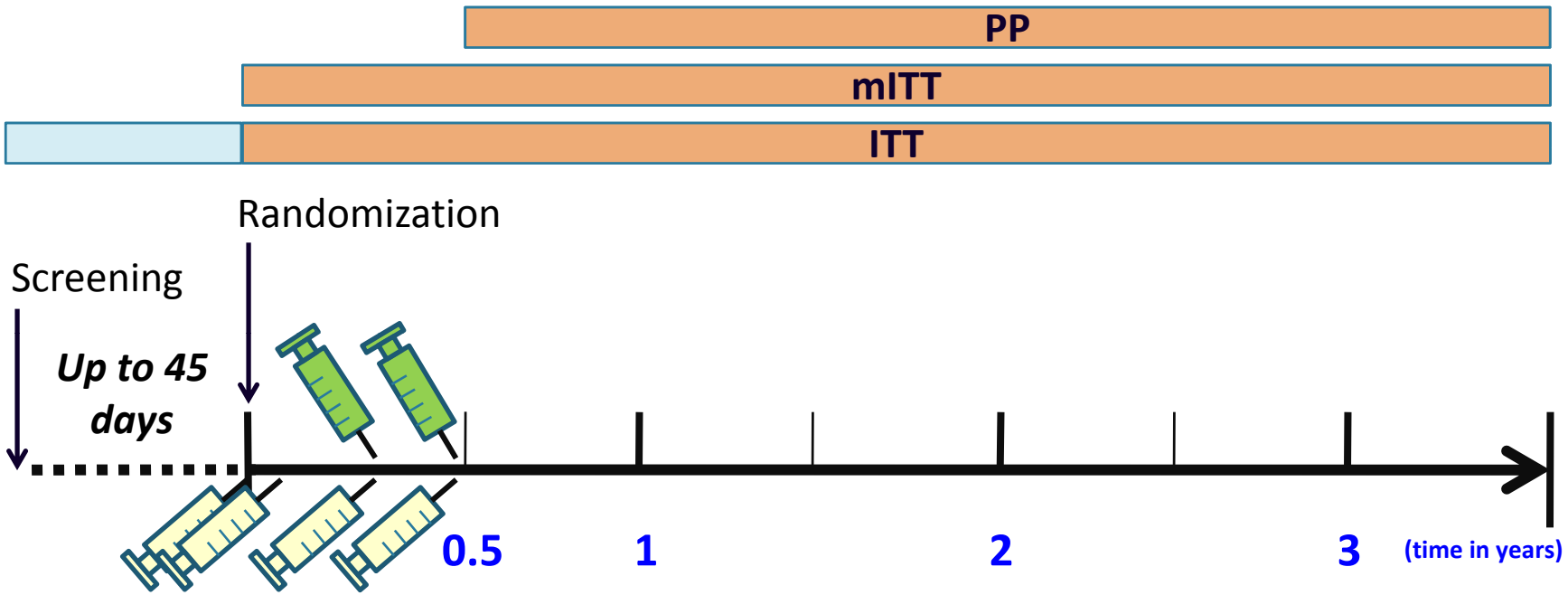
52,985 person-years

125 infections

Vaccine infections: 51
Placebo infections: 74

VE: 31.2%
p=0.04
95% CI: 1.1, 52.1
(O'Brien-Fleming-adjusted)

Endpoint Accrual Timeframes



6-month vaccination schedule

3 years of follow-up (every 6 mo.)

ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24

Summary of Analyses

	ITT	mITT	PP
N (# subjects)	16,402	**16,395**	12,542
Person years	52,985	**52,985**	36,720
Vaccine/Placebo (event #)	56 / 76	**51 / 74**	36 / 50
Vaccine efficacy	26.4%	**31.2%**	26.2%
2-sided p value	0.08	**0.04**	0.16
95% confidence interval	-4.0, 47.9	**1.1, 51.2**	-13.3, 51.9

Includes 5 vaccine and 2 placebo recipients who were HIV positive at baseline

Decreased event numbers, lower precision

Risk-stratified Treatment Effects (mITT)

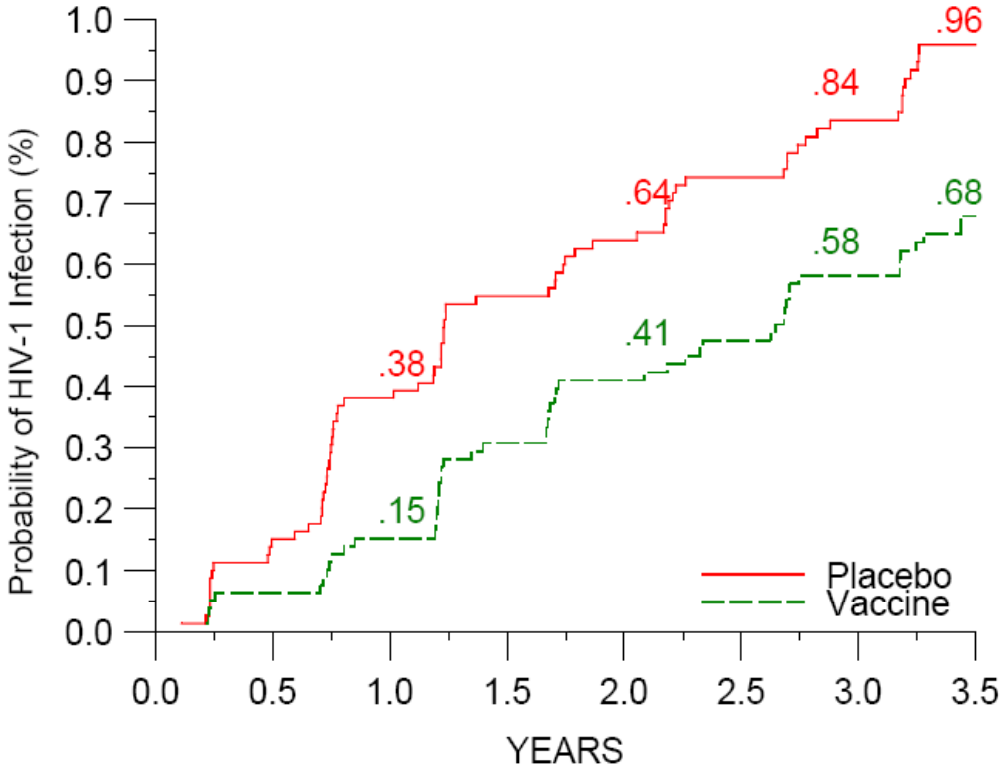
	Vaccine			Placebo			Treatment Effect	
	N	*Endpoints*	*PY Rate %*	*N*	*Endpoints*	*PY Rate %*	*Efficacy*	*95% CI*
Low	3,865	**17**	**0.135**	3,924	**29**	**0.227**	**40.4%**	-8.5, 67.2
Medium	2,369	**12**	**0.157**	2,292	**22**	**0.299**	**47.6%**	-6.0, 74.0
High	1,963	**22**	**0.349**	1,982	**23**	**0.364**	**3.7%**	-72.7, 46.3

VE for each risk category was statistically similar

Exploratory Risk-stratified Analysis

- The point estimate of VE in high-risk volunteers was very low with very large confidence intervals
  - Of the 125 infections
    - 12 infections were seen in same-gender sex risk
    - 2 infections were seen in CSW
    - Zero infections were seen in IDU
  - Of these 14 events, half occurred in each treatment group
- The point estimates of VE in lower risk, heterosexual volunteers were higher with very large confidence intervals
- These observations are exploratory and hypothesis-generating

Efficacy (mITT):
Evidence for Early, Waning Protective Effect?



52,985 person-years

125 infections

Vaccine infections: 51
Placebo infections: 74

VE: 31.2%
p=0.04
95% CI: 1.1, 52.1
(O'Brien-Fleming-adjusted)

Cumulative Vaccine Efficacy Over Time

(Kaplan-Meier-based estimates)

	mITT		PP	
month	***Events***	***Efficacy***	***Events***	***Efficacy***
6	**16**	**54%**	n/a	n/a
12	**42**	**60%**	21	68%
18	**67**	**44%**	41	41%
24	**82**	**36%**	53	27%
30	**95**	**36%**	62	31%

When tested, efficacy did not decrease with time

Conclusions

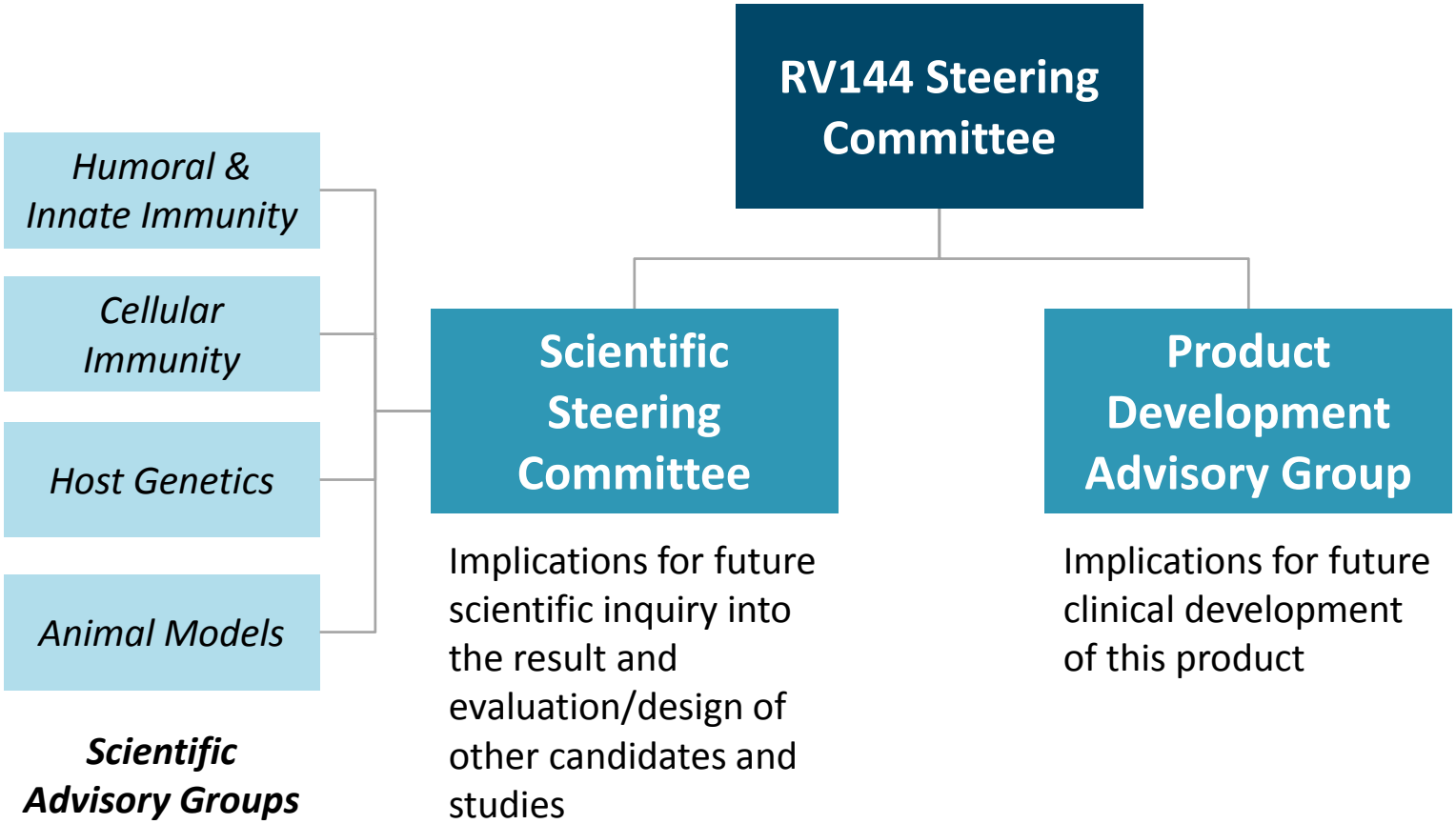
- The mITT analysis demonstrates a modest, statistically significant protective effect, and this is supported by the trends observed in the ITT and PP populations
- The mITT analysis is the most clinically relevant analysis as it:
  - Excludes volunteers with prior infection and reflects the study design and protocol
  - Does not assume that all four vaccinations are important
  - Does not assume that timing of all 4 vaccinations is critical
  - Limits bias compared to PP

Questions

Subgroup analyses are provocative but not statistically robust; inferences require caution

- Was the modest protective effect limited to non-high risk individuals?
- Was the modest protective effect early and non-durable?
- As neither ALVAC-HIV nor AIDSVAX was previously tested for efficacy in this population, what is their respective contribution to the observed effect?

Towards a Correlate



These groups have been appointed and have already begun to convene

Acknowledgements

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