

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

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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)

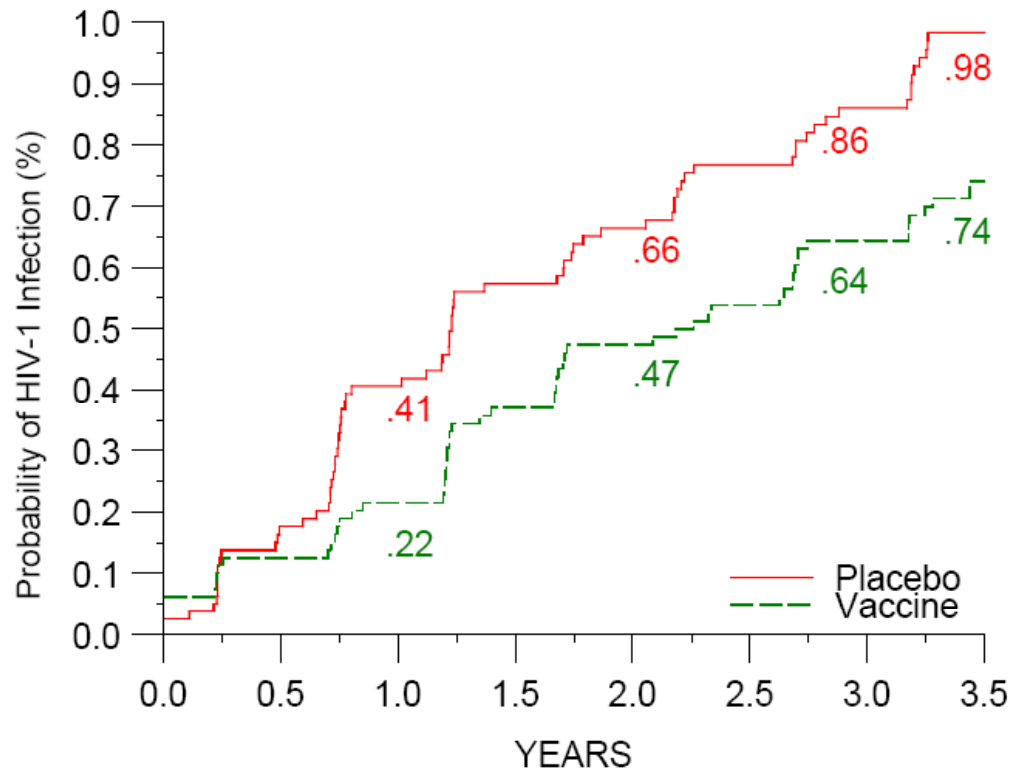
- All primary analyses were pre-specified prior to trial unblinding
- Study design considerations
 - Based on ITT analysis in HIV-uninfected subjects
 - Powered to reduce acquisition during the vaccination period by 25%
 - Powered to reduce post-vaccination acquisition by 50%
- mITT analysis was used 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



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

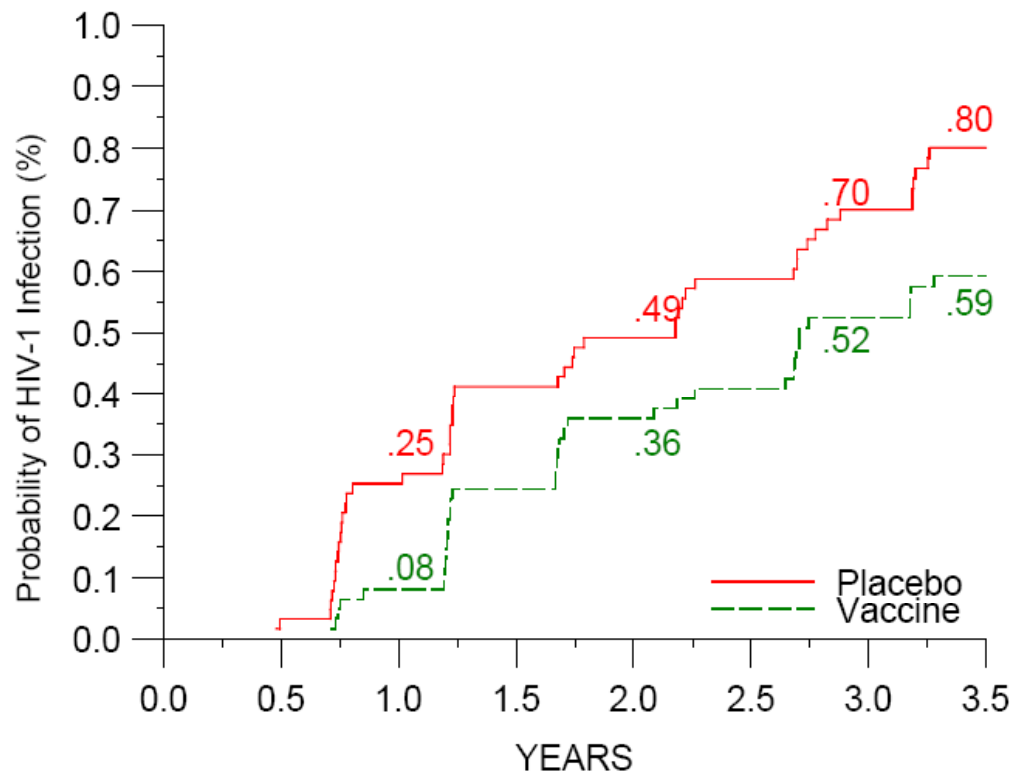
# at Risk	P 8200	7775	7643	7441	7325
	V 8202	7797	7665	7471	7347

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



36,720 person-years

86 infections

Vaccine infections: 36

Placebo infections: 50

VE: 26.2%

p=0.16

95% CI: -13.3, 51.9

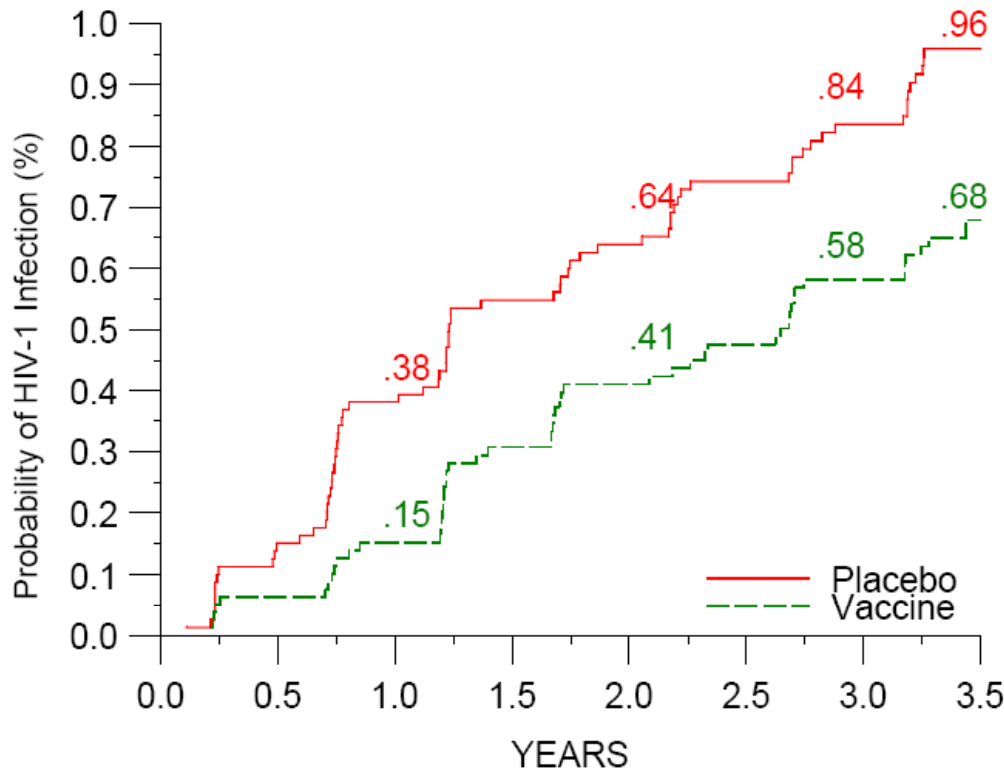
# at Risk	P	6366	6283	6220	6089	6002
	V	6176	6140	6068	5958	5874

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



52,985 person-years

125 infections

Vaccine infections: 51

Placebo infections: 74

VE: 31.2%

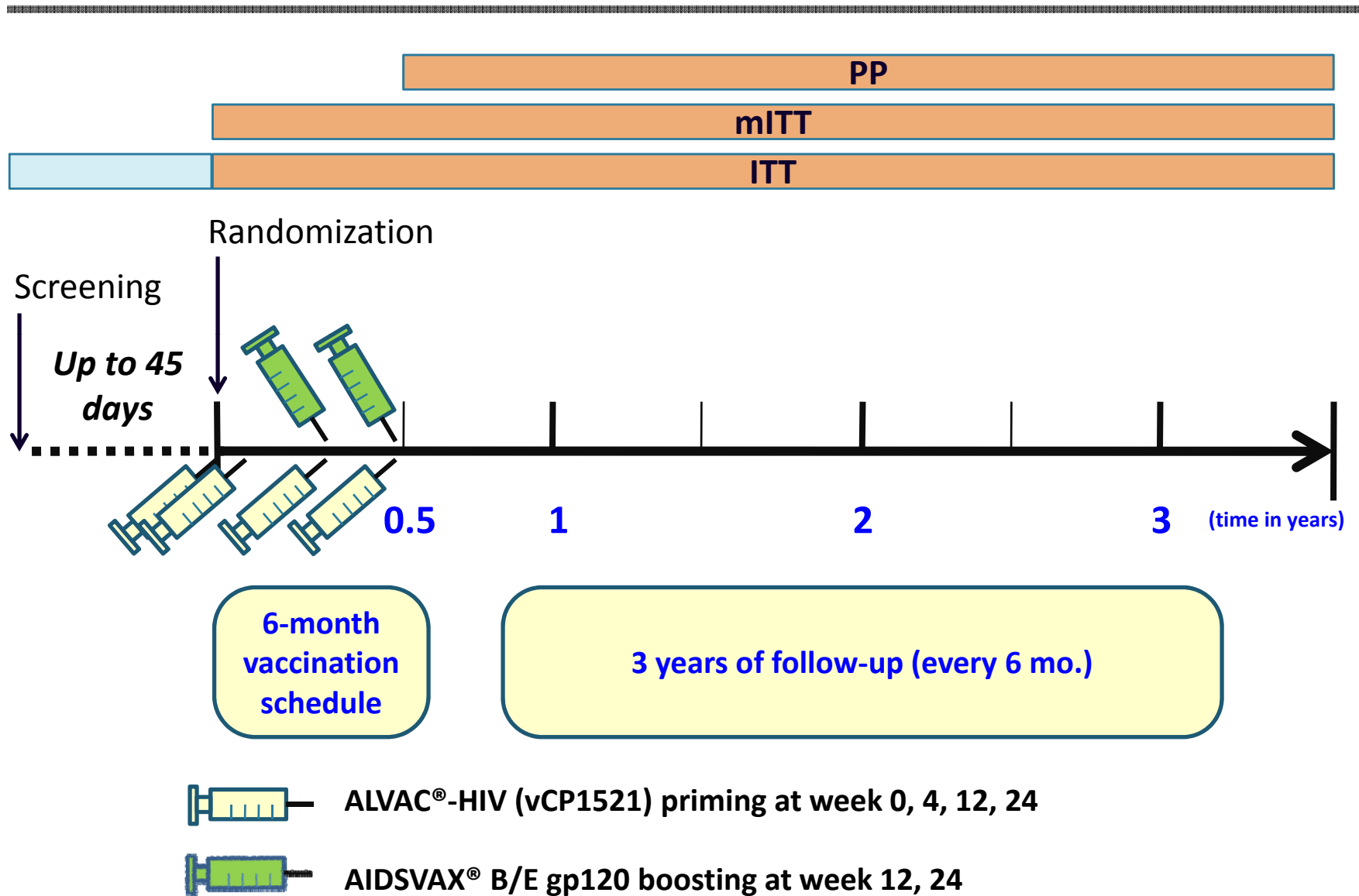
p=0.04

95% CI: 1.1, 52.1

(O'Brien-Fleming-adjusted)

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

Endpoint Accrual Timeframes



Summary of Analyses

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

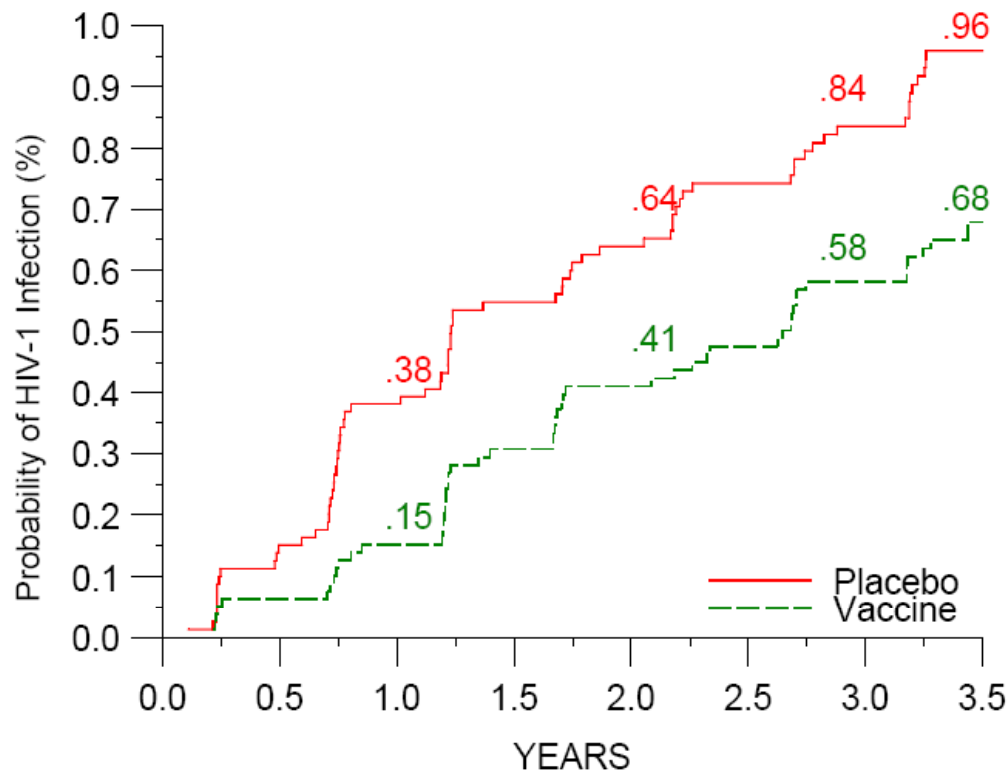
	Vaccine			Placebo			Treatment Effect	
	<i>N</i>	<i>Endpoints</i>	<i>PY Rate %</i>	<i>N</i>	<i>Endpoints</i>	<i>PY Rate %</i>	<i>Efficacy</i>	<i>95% CI</i>
Low	3,865	17	0.135	3,924	29	0.227	40.4%	-8.5, 67.2
Medium	2,369	12	0.157	2,292	22	0.299	47.6%	-6.0, 74.0
High	1,963	22	0.349	1,982	23	0.364	3.7%	-72.7,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

<i>month</i>	mITT		PP	
	<i>Events</i>	<i>Efficacy</i>	<i>Events</i>	<i>Efficacy</i>
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

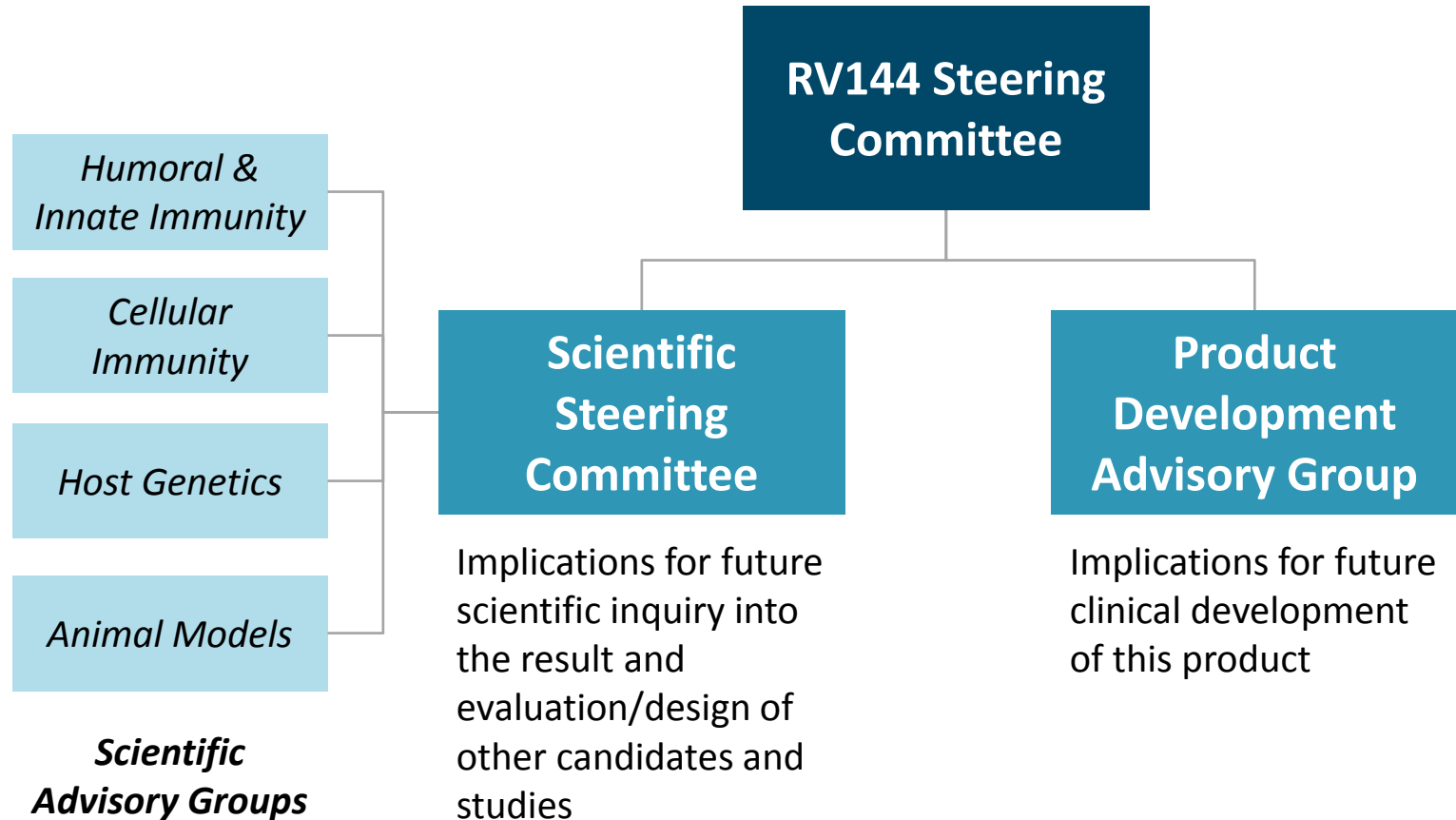
- The mITT analysis demonstrates a modest, statistically significant protective effect, and this is supported by the trends observed in the ITT and PP populations
- The mITT analysis is the most clinically relevant analysis as it:
 - Excludes volunteers with prior infection and reflects the study design 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

- **RV144 volunteers and community members**
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