

STEP Trial

Efficacy Analyses

HVTN Full Group Meeting
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Acknowledgements

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Merck

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- David Li
- Jonathan Hartzel

HVTN

- Steve Self
- Peter Gilbert

Efficacy Hypothesis

- Primary Hypotheses (Ad5 \leq 200 Stratum)
 - 1) Infection endpoint: Among subjects with baseline Ad5 titers \leq 200, those who receive the MRKAd5 HIV-1 gag/pol/nef vaccine will subsequently have a lower likelihood of acquiring HIV-1 infection compared to those who receive placebo

and/or
 - 2) Viral load endpoint: Among subjects with baseline Ad5 titers \leq 200 who subsequently become HIV-1 infected, those who receive the MRKAd5 HIV-1 gag/pol/nef vaccine will have a smaller average viral load set-point (HIV-1 RNA at ~3 months post-diagnosis) compared to those who receive placebo
- Secondary hypotheses were same as primary hypotheses, but in the overall study population (Ad5 \leq 200 and Ad5 $>$ 200 strata combined)

Two analysis populations

- Modified intent-to-treat (MITT) population includes all participants who:
 - Were HIV seronegative on day of randomization
 - Received at least one study injection
 - Best population for evaluating infection endpoint
- Per protocol (PP) population includes all participants who:
 - Were HIV seronegative at Week 12 study visit
 - Received at least the first 2 study injections in window
 - Were not "protocol violators"
 - Met entry criteria for study
 - Did not receive non-study vaccine (eg, flu shot) in prohibited window
 - Had a confirmatory visit following diagnosis of HIV infection
 - Did not receive ART before confirmatory visit
 - Best population for simultaneously evaluating both endpoints

Analysis strategy

- Event driven
 - Newly acquired HIV infection
 - Viral load (VL) 3 months post-diagnosis
- Planned interim analyses in addition to final analysis
 - 1st interim analysis triggered when 30 “per-protocol” events identified in Ad5 ≤ 200 stratum
 - Futility to be assessed at each interim analysis
 - p-value > 0.50 (1-tailed) for **EACH** endpoint
 - » Trend favoring placebo for each endpoint
 - » Likelihood of meeting either endpoint at final analysis is very low (conditional power <10%)

Statistical Power

- In Ad5 \leq 200 study population
 - With ~50 PP events, 80% power to detect 60% vaccine efficacy for acquisition endpoint
 - With ~30 PP events, 80% power to detect ~1-log reduction in VL 3 months post-diagnosis (first interim)
- In overall study population
 - With ~100 PP events, 80% power to detect 50% vaccine efficacy for acquisition endpoint
 - With ~60 PP events, 80% power to detect ~0.75-log reduction in VL 3 months post-diagnosis

Case split for infection endpoint
Primary analysis (Ad5 ≤ 200)

	Vaccine	Placebo
Total MITT cases	24	21
Cases <u>included</u> in PP efficacy analysis	19	11

Primary dataset reviewed by DSMB

Case split for infection endpoint Primary analysis (Ad5 ≤ 200)

	Vaccine	Placebo
Total MITT cases	24	21
Cases <u>included</u> in PP efficacy analysis	19	11

Subject Accounting between analysis populations

Cases <u>excluded</u> from PP efficacy analysis	5	10
⇓		
Diagnosed as HIV+ at or before week 12 visit	4	6
Discontinued before confirmatory visit	1	2
Received ART before confirmatory visit	0	1
Received non-study vaccine	0	1

Primary dataset reviewed by DSMB

HIV Incidence: Ad5 ≤ 200

Population	Group	N*	n	Person-years of Follow-up**	Incidence of HIV Infection	95% CI
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Per-Protocol	Vaccine	672	19	619	3.07	(1.85, 4.79)
	Placebo	691	11	622	1.77	(0.88, 3.16)

1 tailed p-value = 0.949 (for $VE_{INF} > 0$)

MITT	Vaccine	741	24	822	2.92	(1.87, 4.34)
	Placebo	762	21	836	2.51	(1.56, 3.84)

1-tailed p-value = 0.743 (for $VE_{INF} > 0$)

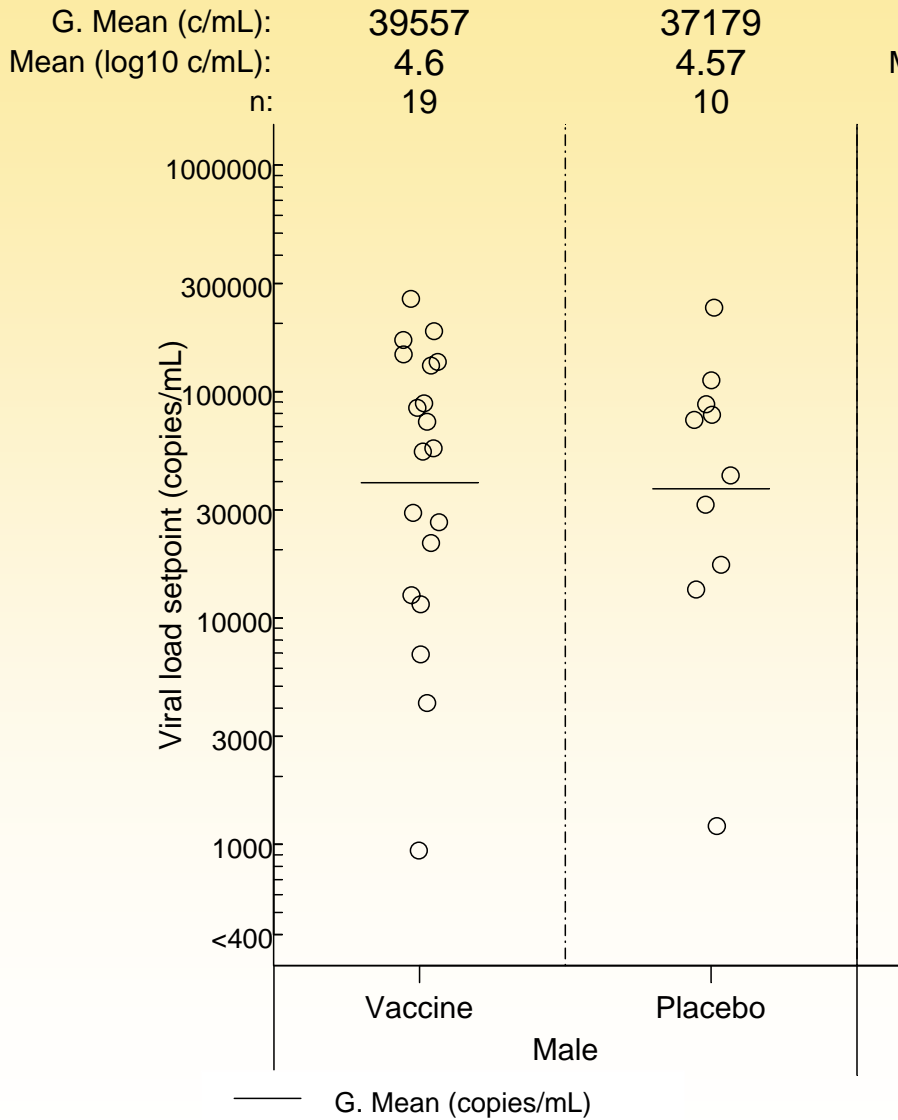
*N=Number in respective analysis population

**For the per-protocol population, follow-up time is defined as number of days from the day of the Week 12 visit to the last day of study follow-up for uninfected subjects and to the day of diagnosis for infected subjects.

For the MITT population, follow-up time is defined as number of days from the day of vaccination to the last day of study follow-up for uninfected subjects and to the day of diagnosis for infected subjects.

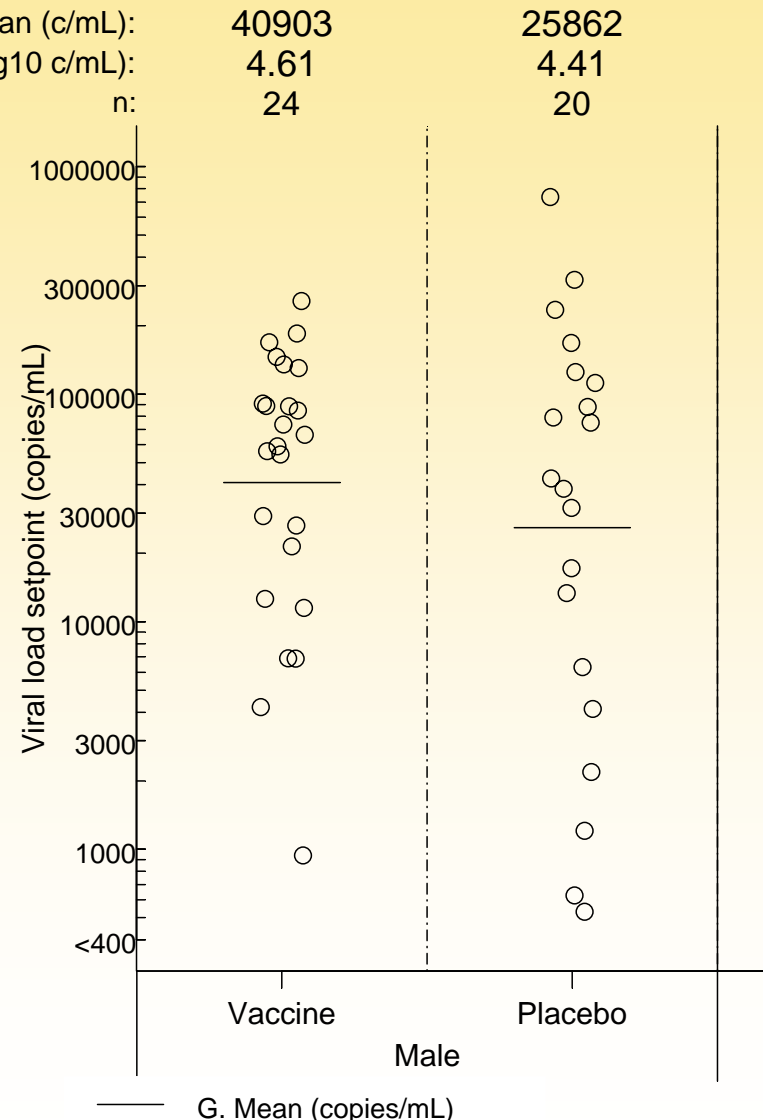
Viral Load Set-Points: $Ad5 \leq 200$

Per-protocol MITT



G. Mean (copies/mL)
1-tailed p-value = 0.528 (for $VE_{VL} > 0$)

There was 1 female infection: VLS = 20,207 c/mL (4.31 log10 c/mL)



G. Mean (copies/mL)
1-tailed p-value = 0.656 (for $VE_{VL} > 0$) 10

07-Nov-2007

Futility declared

- Futility cutoffs met at first interim analysis
 - p-value > 0.50 (1-tailed) for **EACH** endpoint
 - Trend favored placebo for each endpoint
 - Strongly suggests the vaccine neither prevents HIV infection nor reduces the amount of virus in those who became infected with HIV
- Based on these results, the DSMB recommended that
 - No further injections be administered in the trial
 - Volunteers be encouraged to return for all protocol visits and tests so that the investigators can fully evaluate whether there is an increased risk of infection in vaccine recipients over time
 - The trial Oversight Committee determine the appropriate steps and timing of release of trial results to volunteers, investigators, those conducting related trials, relevant agencies, and the public

Additional analyses

- Since futility had been declared by DSMB, the team felt it was justifiable to proceed (**cautiously**) with post-hoc analyses
 - Since there has only been 1 female case, all subsequent analyses will present males only
 - Additional analyses will focus on MITT population
 - Most conservative approach since does not exclude any post-randomization cases
 - Analyses in other Ad5 strata
 - Analyses of infection endpoint which include additional cases accrued since cut-off for first interim analysis
 - Focus on deciphering the reasons for lack of efficacy and the implications this has on broader population

All analyses which follow are post-hoc

Necessary steps prior to additional analyses

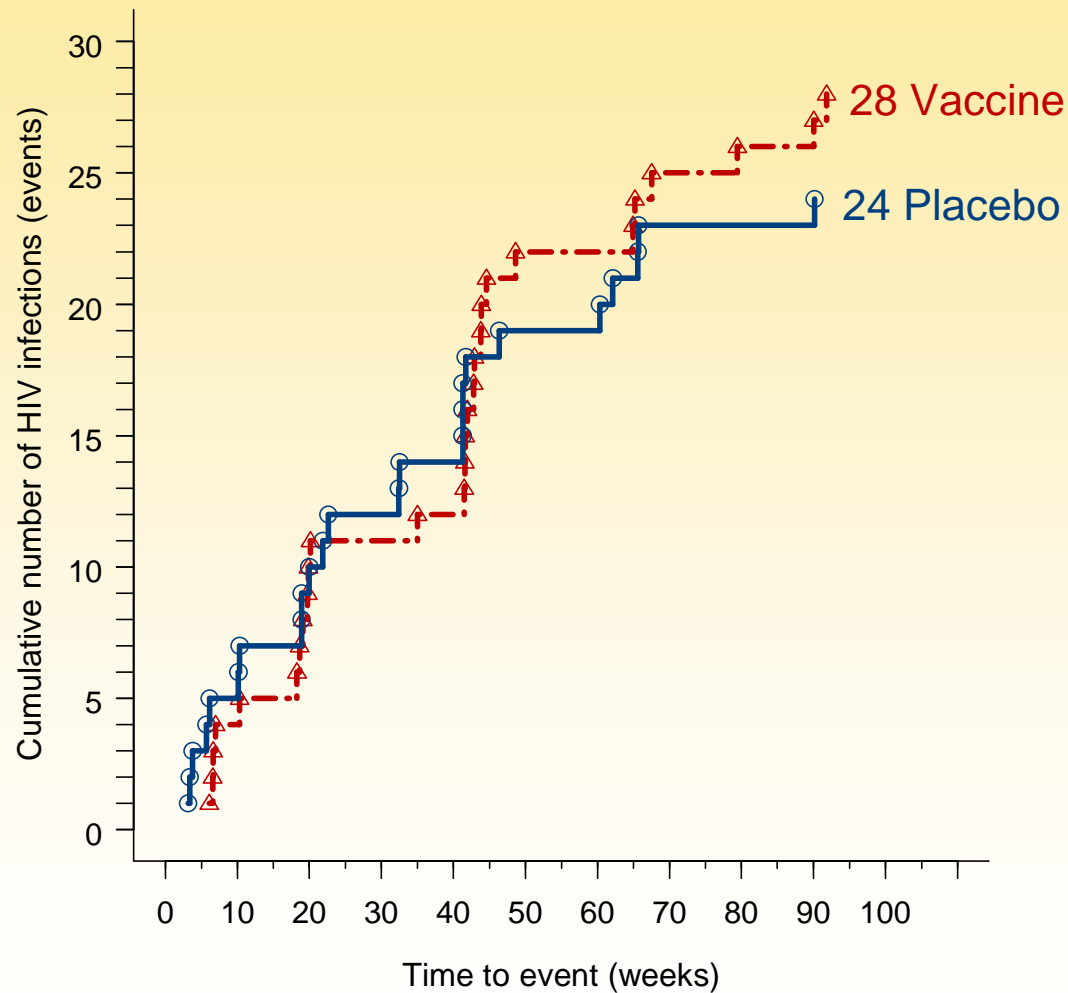
- Verify data integrity on additional cases
 - Not all data was included in frozen file used for interim analysis
- Complete adjudication process of additional cases
- Prioritize and complete additional lab assays
 - HIV diagnostic testing on additional cases
 - Key immunological assays
- Design, test, implement and review the programming and output of multiple, complex post-hoc statistical analyses

Cases included in additional analyses (Males only)

Ad5 \leq 200 male MITT cases included in 1 st interim analysis*	44
Additional Ad5 \leq 200 male MITT cases accrued through Oct 17, 2007	8
Total Ad5 $>$ 200 male MITT cases accrued through Oct 17, 2007	30
Total male cases accrued through Oct 17, 2007	82

*Primary dataset reviewed by DSMB, excluding the 1 female infection

Cumulative Number of HIV Infections: MITT population (males), Ad5 \leq 200



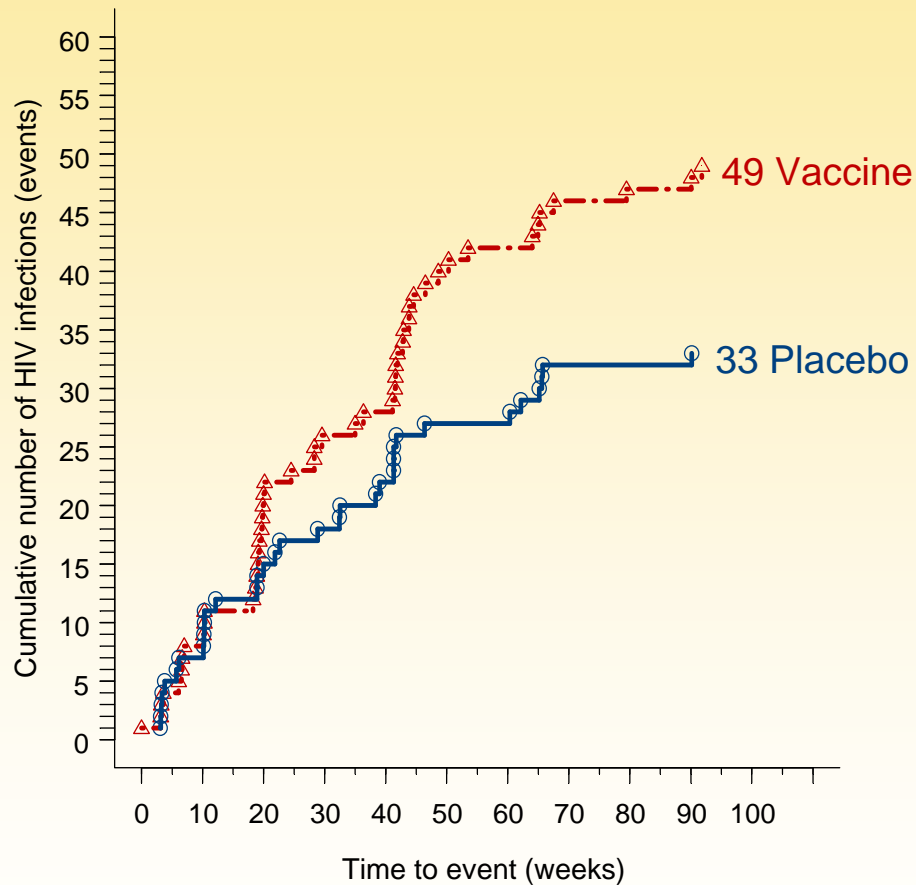
1-tailed p-value = 0.322 (for $VE_{INF} \neq 0$)

2-tailed p-value = 0.581 (for $VE_{INF} \neq 0$)

Cases accrued as of Oct 17, 2007

Cumulative Number of HIV Infections: MITT population (males)

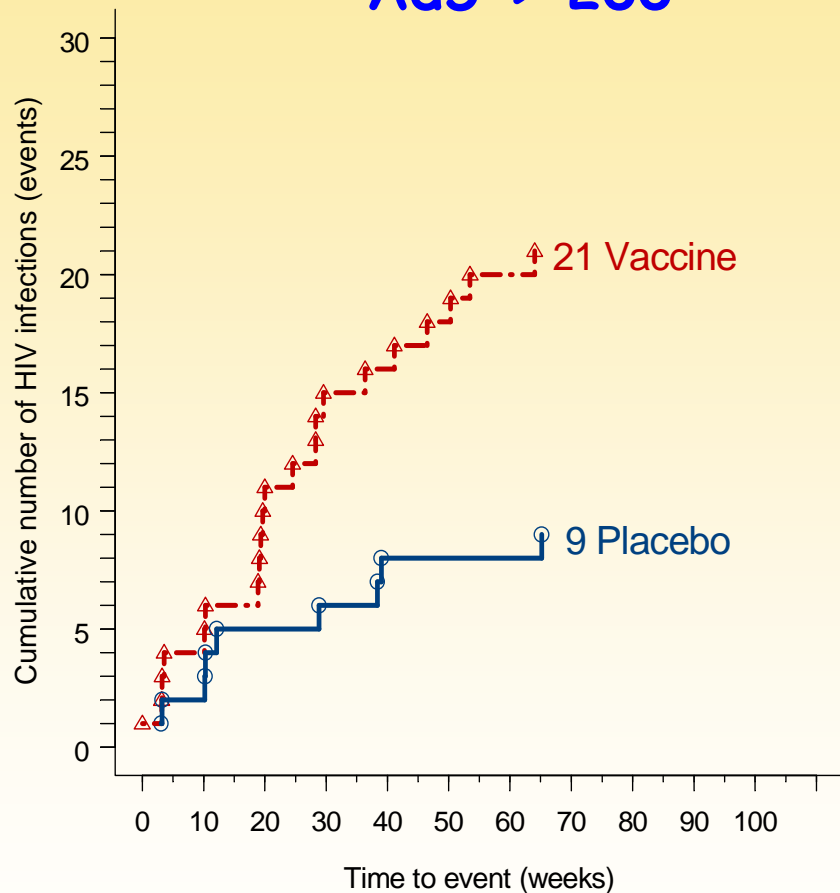
Overall



1-tailed p-value = 0.044 (for $VE_{INF} \neq 0$)

2-tailed p-value = 0.077 (for $VE_{INF} \neq 0$)

Ad5 > 200

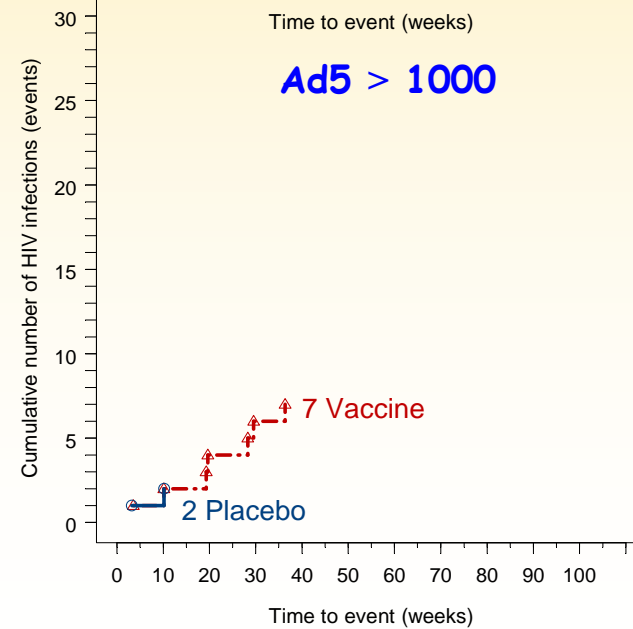
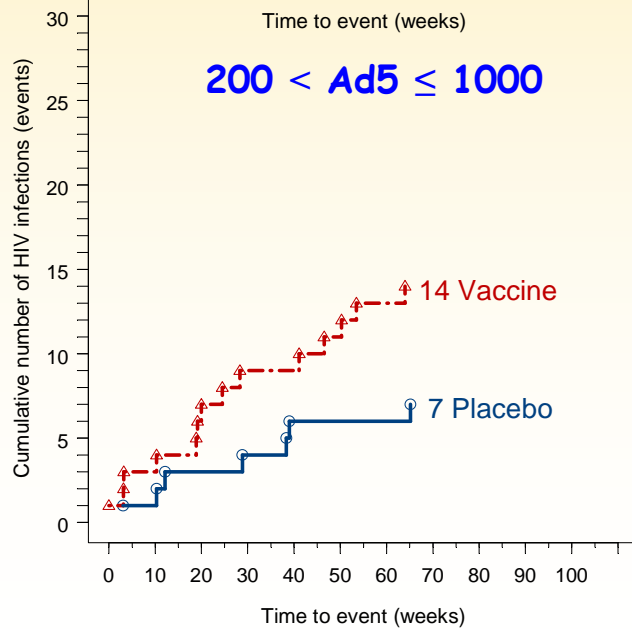
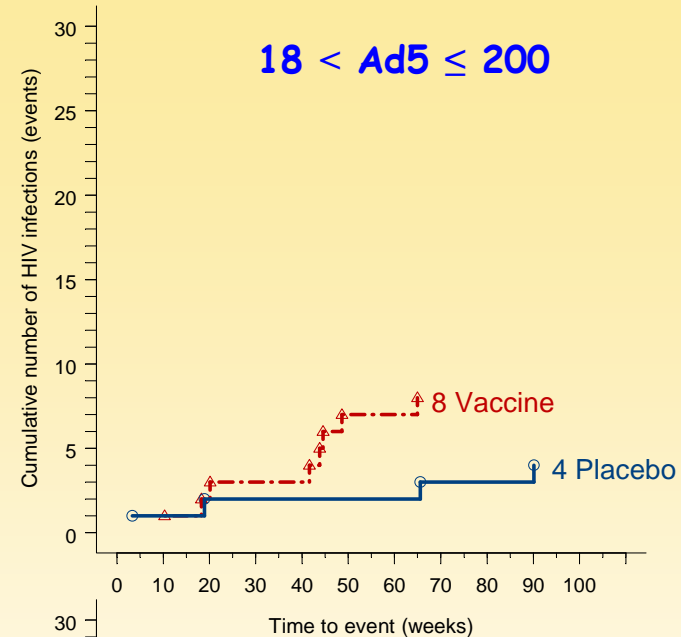
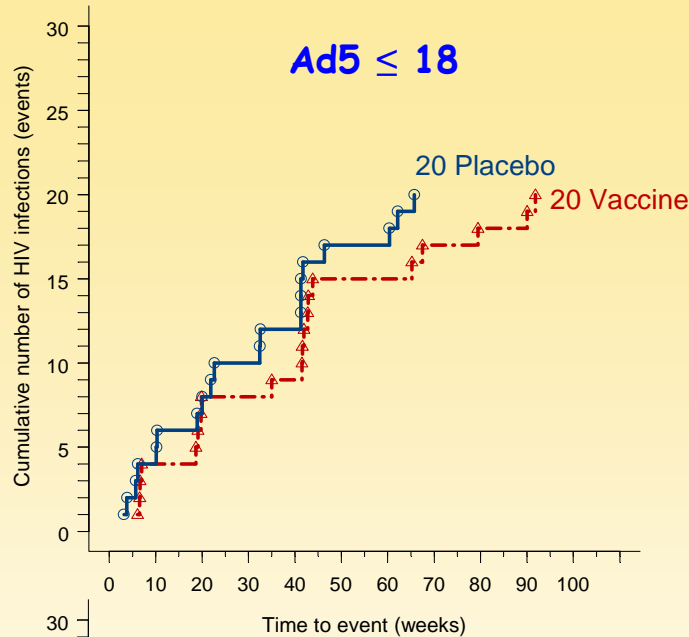


1-tailed p-value = 0.020 (for $VE_{INF} \neq 0$)

2-tailed p-value = 0.029 (for $VE_{INF} \neq 0$)

Cases accrued as of Oct 17, 2007

Cumulative Number of HIV Infections: MITT population (males)



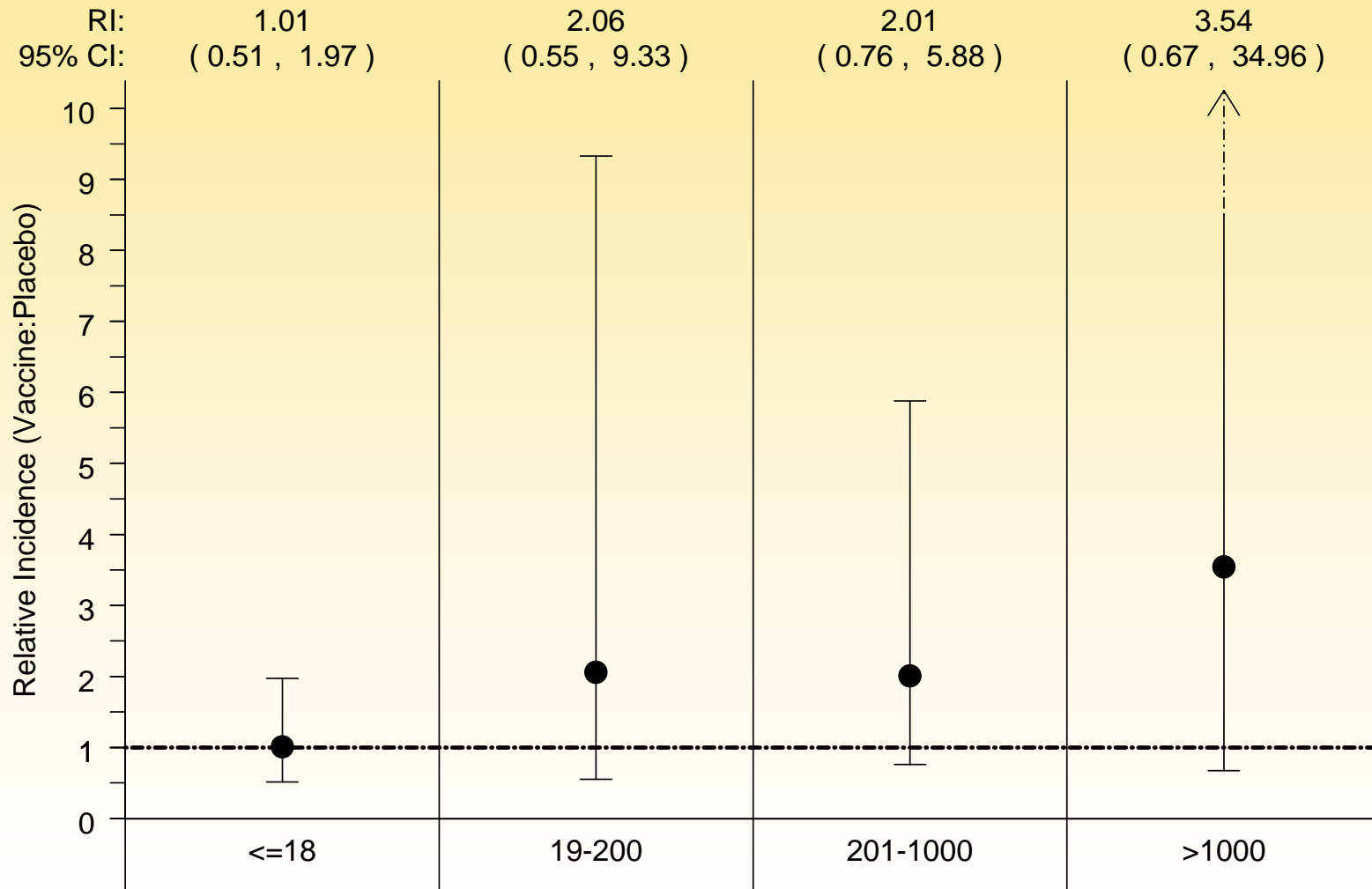
Cases accrued as of Oct 17, 2007

Incidence (95% CI) of HIV Infection MITT population (males)

Baseline Ad5 titer	Vaccine V	Placebo P	Relative Incidence (V:P)
≤ 18	4.0 (2.5, 6.3)	4.0 (2.5, 6.2)	1.0 (0.5, 2.0)
19-200	4.4 (1.9, 8.8)	2.2 (0.6, 5.5)	2.1 (0.6, 9.3)
201-1000	6.1 (3.3, 10.2)	3.0 (1.2, 6.2)	2.0 (0.8, 5.9)
> 1000	4.4 (1.8, 9.1)	1.2 (0.2, 4.5)	3.5 (0.7, 35.0)
≤ 18	4.0 (2.5, 6.3)	4.0 (2.5, 6.2)	1.0 (0.5, 2.0)
> 18	5.1 (3.4, 7.3)	2.2 (1.2, 3.8)	2.3 (1.1, 4.7)
≤ 200	4.2 (2.8, 6.0)	3.5 (2.3, 5.2)	1.2 (0.7, 2.1)
> 200	5.4 (3.3, 8.2)	2.3 (1.0, 4.3)	2.4 (1.0, 5.8)
Overall	4.6 (3.4, 6.1)	3.1 (2.1, 4.3)	1.5 (0.9, 2.4)

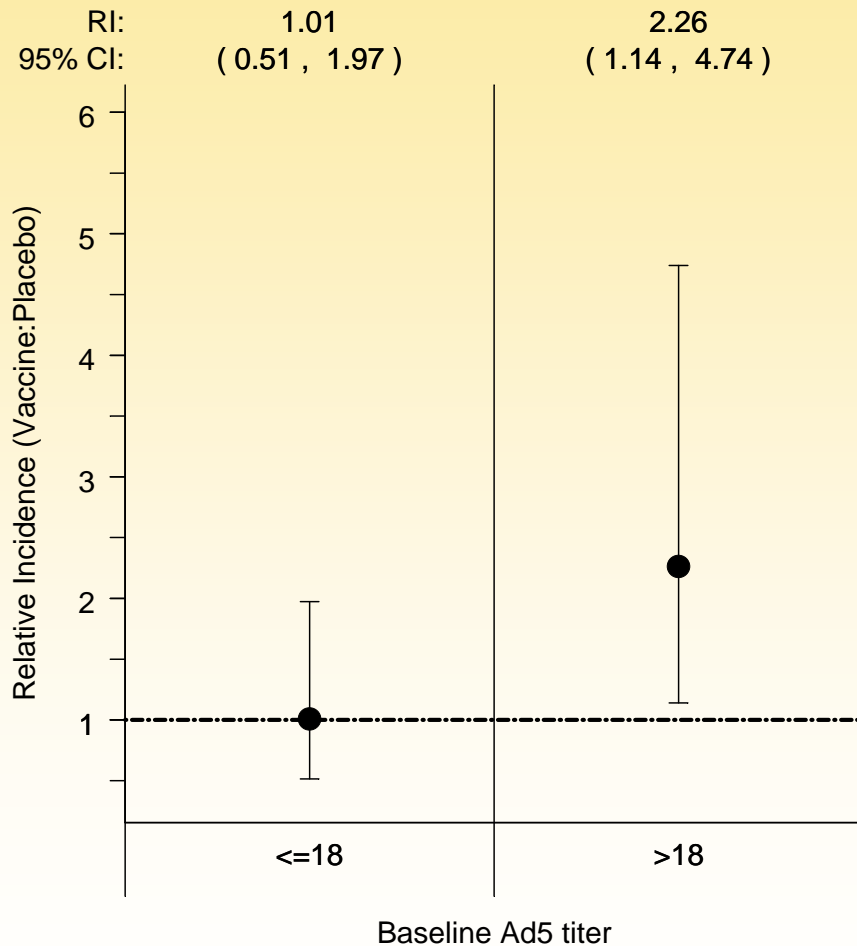
18 is the LOQ for the Ad5 titer assay; includes all HIV cases thru Oct 17, 2007

Relative Incidence of HIV infection (Vaccine:Placebo) MITT population (males)

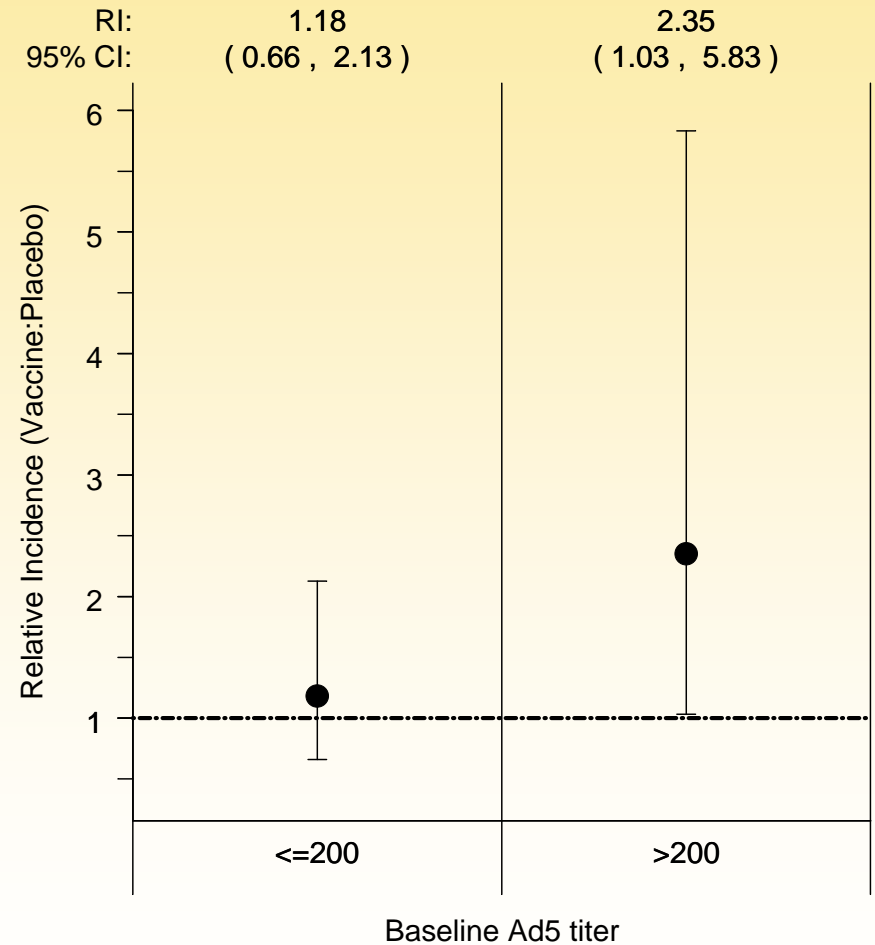


	# Events	# Risk	Mean follow-up in weeks	Baseline Ad5 titer
Vaccine:	20	382	67.2	8 [140, 66.9]
Placebo:	20	394	65.7	4 [142, 67.7]
				14 [229, 52.5]
				7 [229, 52.7]
				7 [163, 50.7]
				2 [157, 53.3]

Relative Incidence of HIV infection (Vaccine:Placebo) MITT population (males)



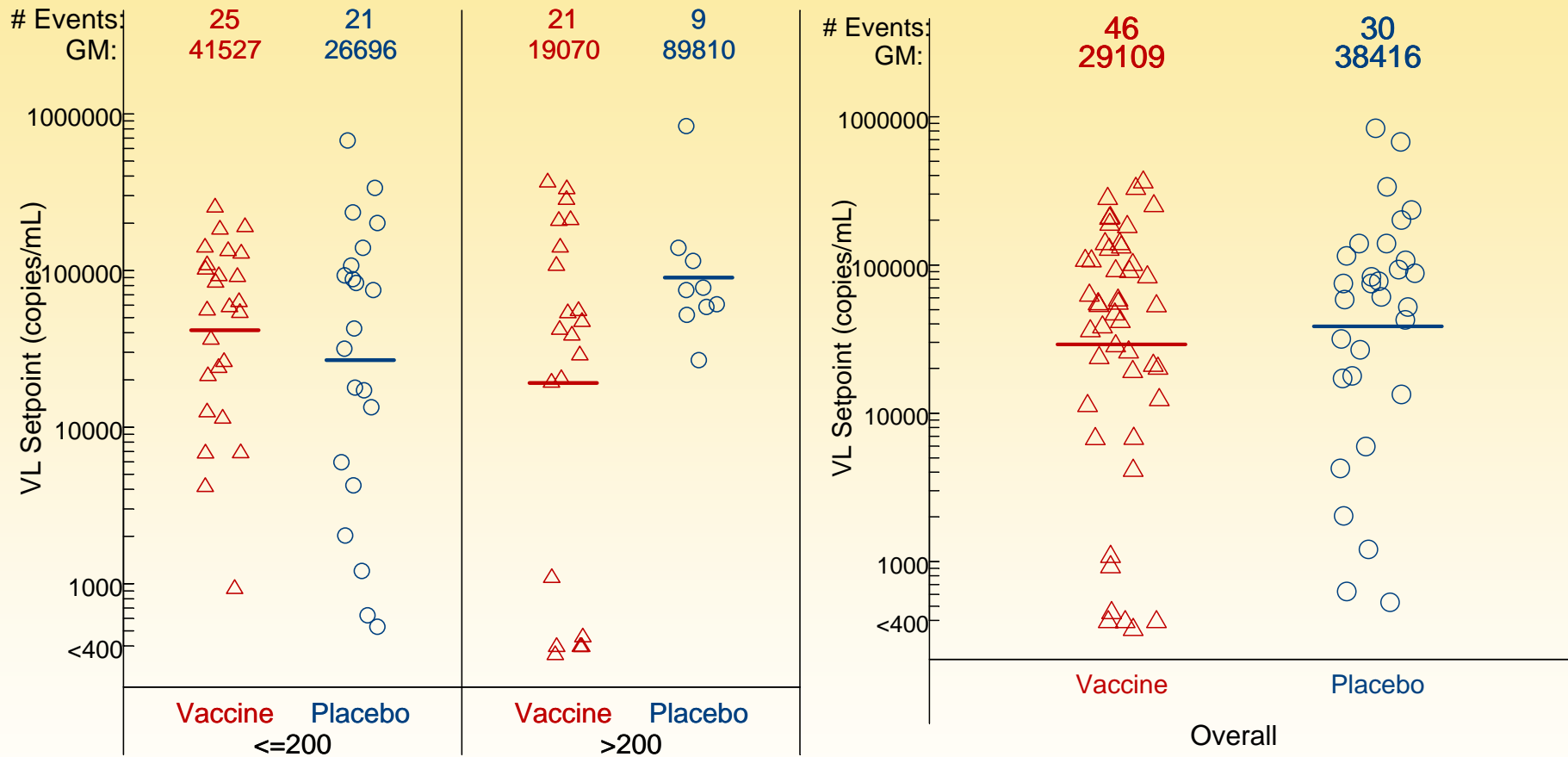
	# Events [# Risk, Mean follow-up in weeks]	
Vaccine:	20 [382, 67.2]	29 [532, 55.7]
Placebo:	20 [394, 65.7]	13 [528, 56.9]



	# Events [# Risk, Mean follow-up in weeks]	
Vaccine:	28 [522, 67.1]	21 [392, 51.7]
Placebo:	24 [536, 66.2]	9 [386, 52.9]

Viral Load Endpoint

Summary of VL Setpoint: **MITT** population (males)



For subjects with viral load setpoint data available as of Oct 17, 2007.

Summary of Efficacy Results: MITT population (males)

Baseline		HIV Infection Endpoint				Viral Load Endpoint	
		Case split		HIV rate(%/yr)		log10 copies/ml	
Ad5	N	V	P	V	P	V	P
≤ 200	1058	28	24	4.2	3.5	4.62	4.43
> 200	778	21	9	5.4	2.3	4.28	4.95
Overall	1836	49	33	4.6	3.1	4.46	4.58

V = vaccine, P = placebo

Data as of October 17, 2007

Immunogenicity results: Ad5 \leq 200

- Primary immunogenicity measure is unfractionated γ -interferon ELISPOT
 - ELISPOT responder: ≥ 55 SFC/ 10^6 PBMC and ≥ 4 -fold over negative control (mock)
- PBMC collected at Week 8, Week 30, Week 52 and Week 104 in all subjects
- Week 8 ELISPOT was run in "real-time" on a randomly selected 25% subset of all subjects and on all cases after they were identified
 - Other data currently being generated

Week 8 ELISPOT Responses

		% Responders		GM Elispot	
		Cases	Non-cases	Cases	Non-cases
≤200	N	19	143	19	143
	Gag	74%	76%	354	260
	Pol	63%	73%	627	463
	Nef	74%	70%	327	237
>200	N	13	173	13	173
	Gag	46%	54%	181	168
	Pol	38%	47%	296	241
	Nef	46%	51%	149	163

ELISPOT responder: ≥ 55 SFC/ 10^6 PBMC and ≥ 4 -fold over negative control (mock)

GM ELISPOT is for all subjects

Summaries based on 25% random subset of all subjects and all PP cases

Summary

- Study design and execution allowed timely assessment of both primary endpoints
- There was no evidence that vaccination prevented infection or lowered viral setpoint
- There were more infections in vaccinees than placebo recipients
 - This trend was more pronounced in participants with high baseline Ad5 titers
- Lack of efficacy did not appear to be explained by sub-optimal immune responses in vaccinees