

The STEP Study

Summary

Press Briefing
November 7, 2007

Summary

- Step is 3000 person db, pbo, rand study in subjects at high risk for HIV infection, designed to test the efficacy of the merck Ad5 trivalent vaccine
- As previously reported, vaccination in this trial (and a related trial called phambili) were discontinued due to an interim analysis that demonstrated no efficacy for the vaccine. This interim analysis was performed in a subgroup of participants with low baseline immune responses to Adenovirus 5 (or Ad5), a group that was expected to have the best chance of demonstrating efficacy
- These results are being presented here today in Seattle in an open scientific forum. This is a short summary of the information presented, with the first half of my presentation focusing on the data leading to a decision of futility, and the second half presenting additional data in the larger study population.

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 **\sim 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

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

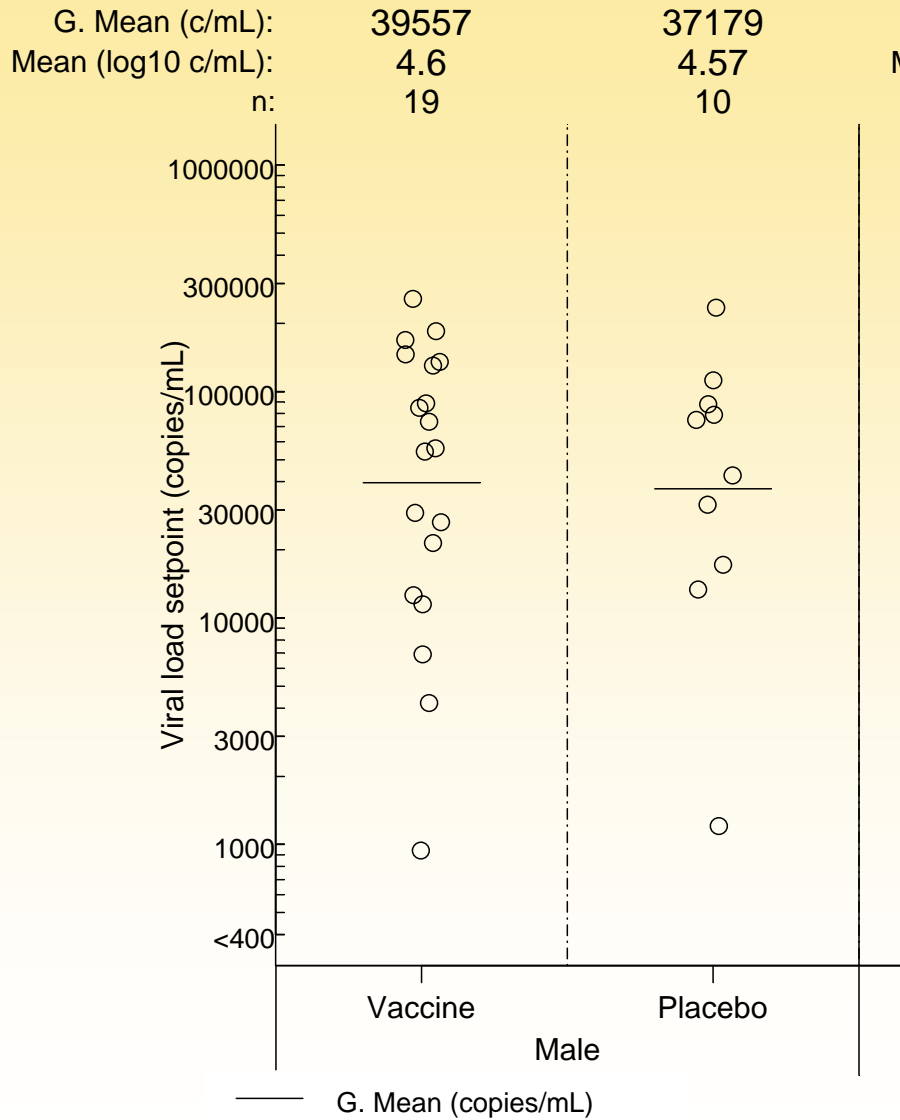
Cases <u>excluded</u> from PP efficacy analysis	5	10
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Diagnosed HIV+ at or before week 12 visit	4	6
Discontinued before confirmatory visit	1	2
Received ART before confirmatory visit	0	1
Received non-study vaccine	0	1

Primary dataset reviewed by DSMB

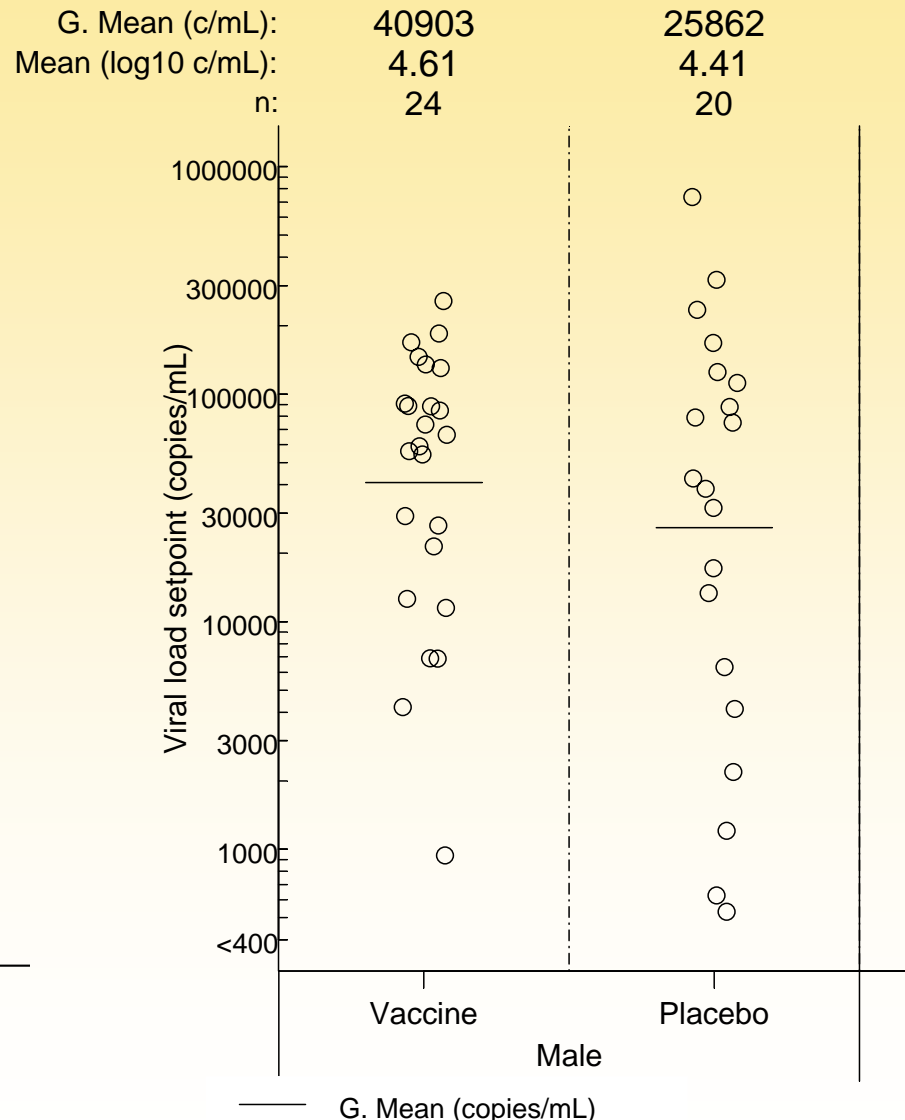
Viral Load Set-Points: $Ad5 \leq 200$

Per-protocol

MITT



1-tailed p-value = 0.528 (for $VE_{VL} > 0$)



1-tailed p-value = 0.656 (for $VE_{VL} > 0$)

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

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

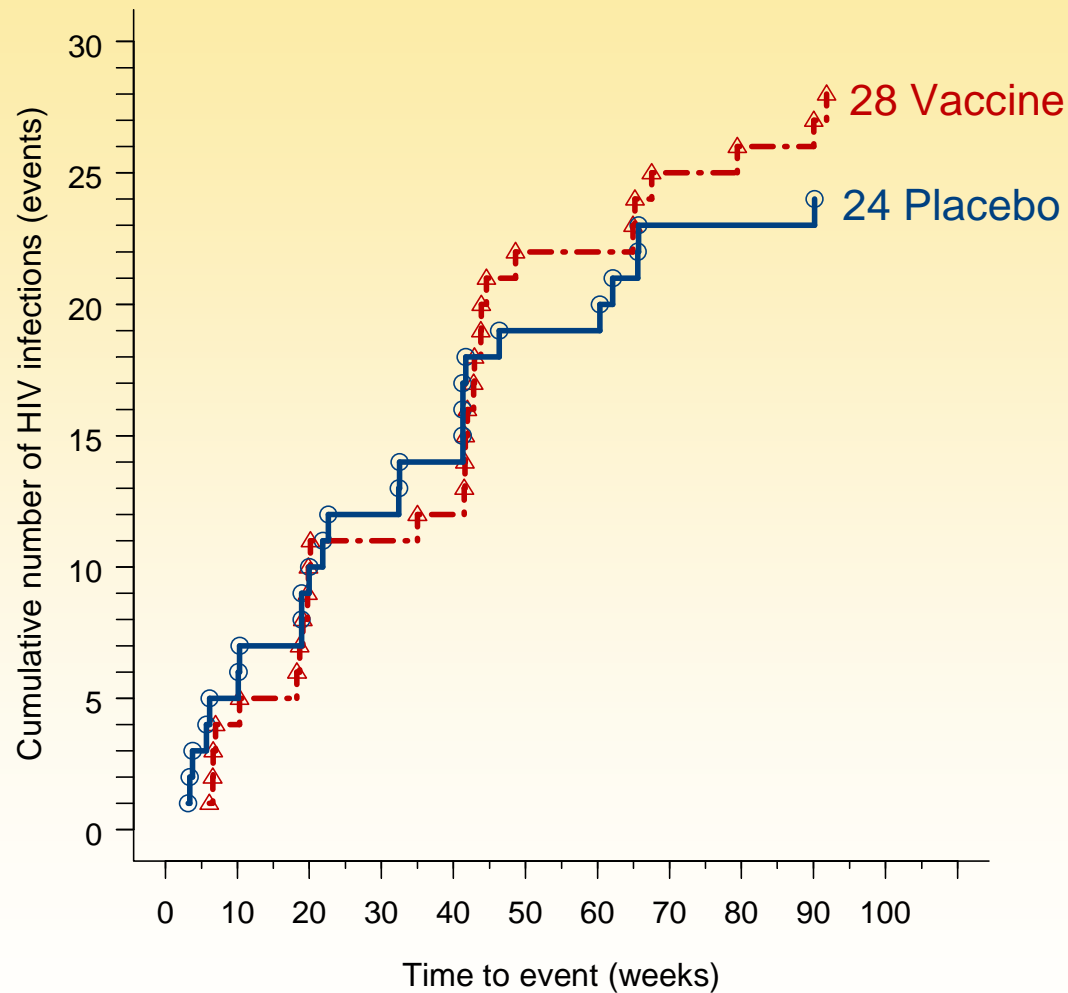
All analyses which follow are post-hoc

Cases included in additional analyses (Males only)

Ad5 \leq 200 male MITT cases included in 1st 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 ≤ 200



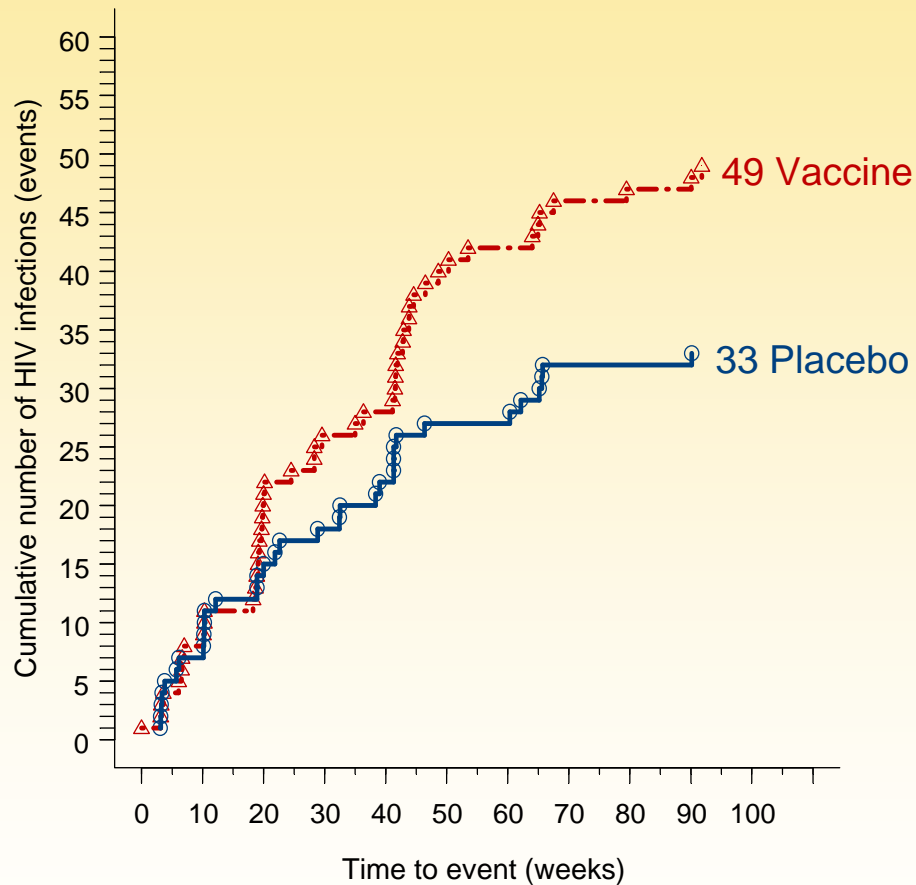
1-tailed p-value = 0.322 (for $VE_{INF} \neq 0$)

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)

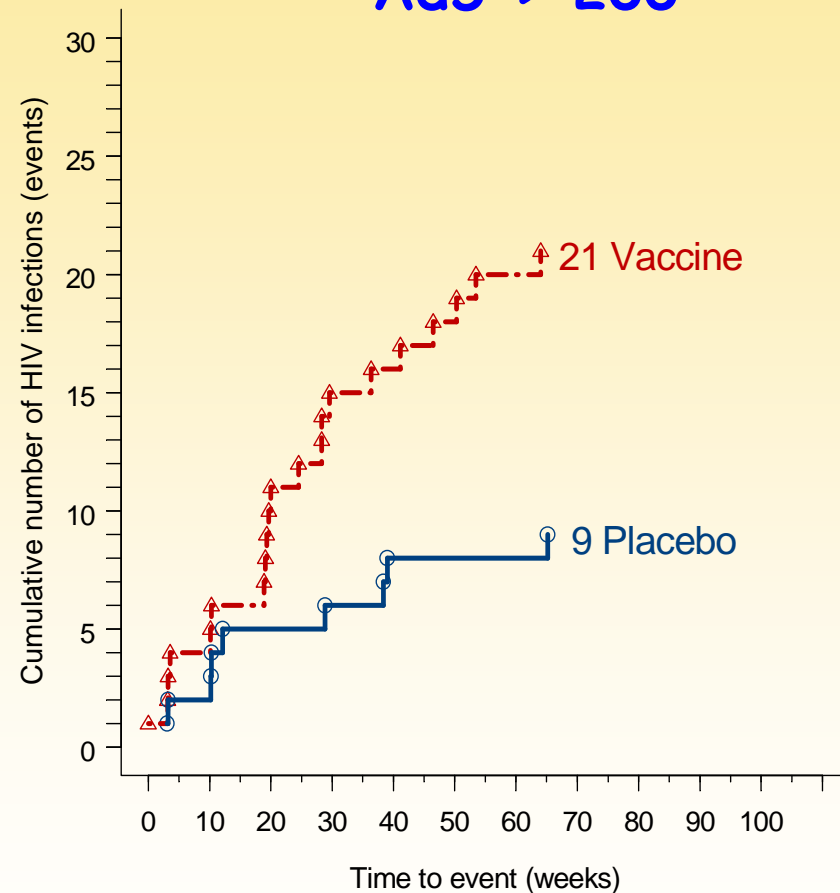
Overall



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

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

Ad5 > 200

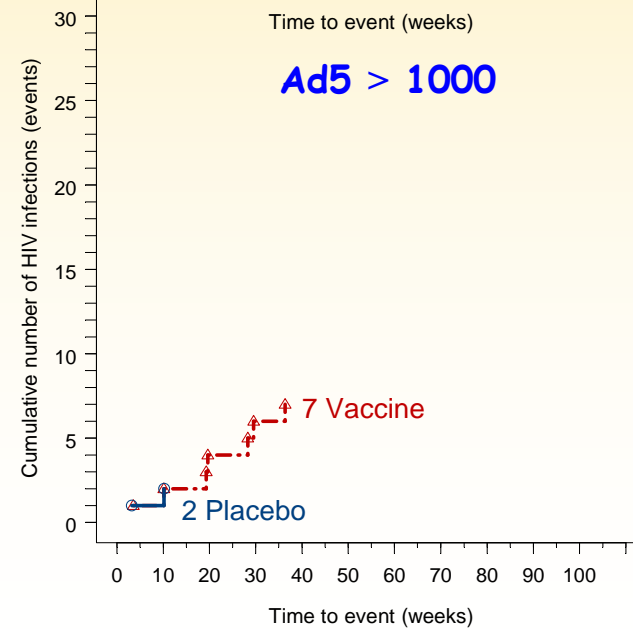
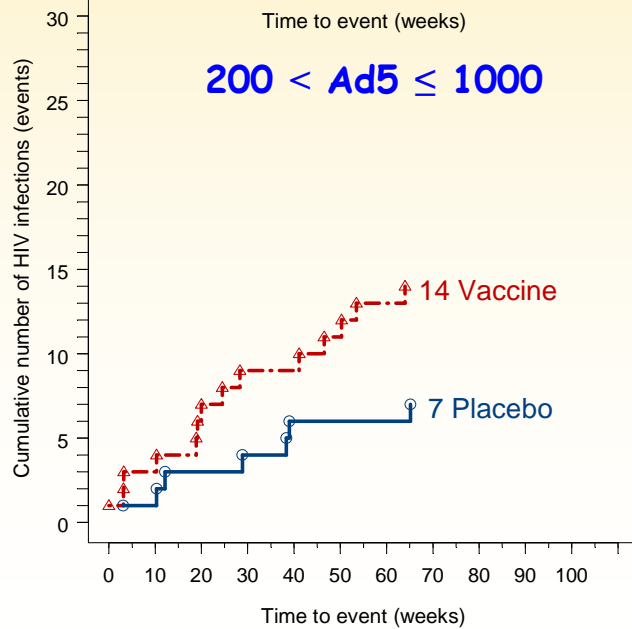
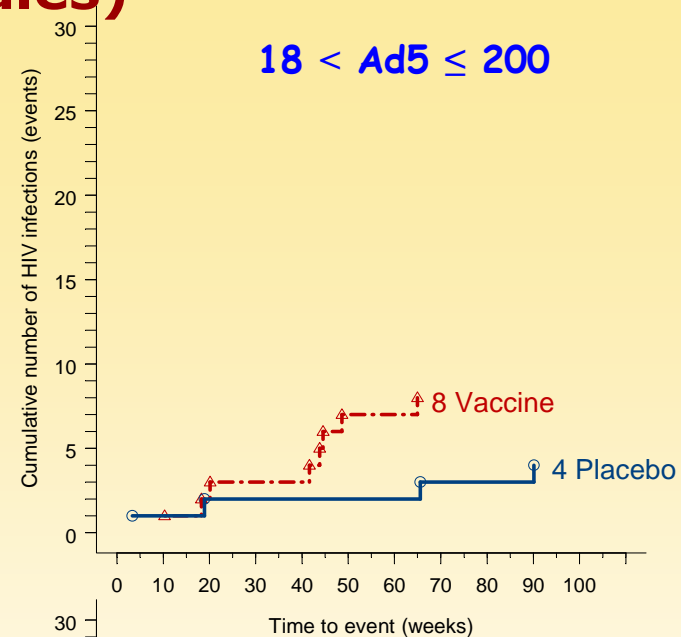
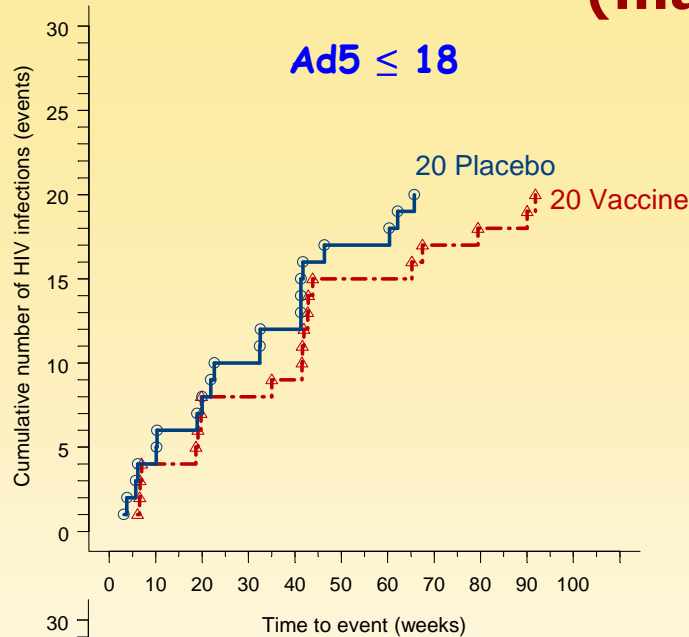


1-tailed p-value = 0.020 (for $VE_{INF} \neq 0$)

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

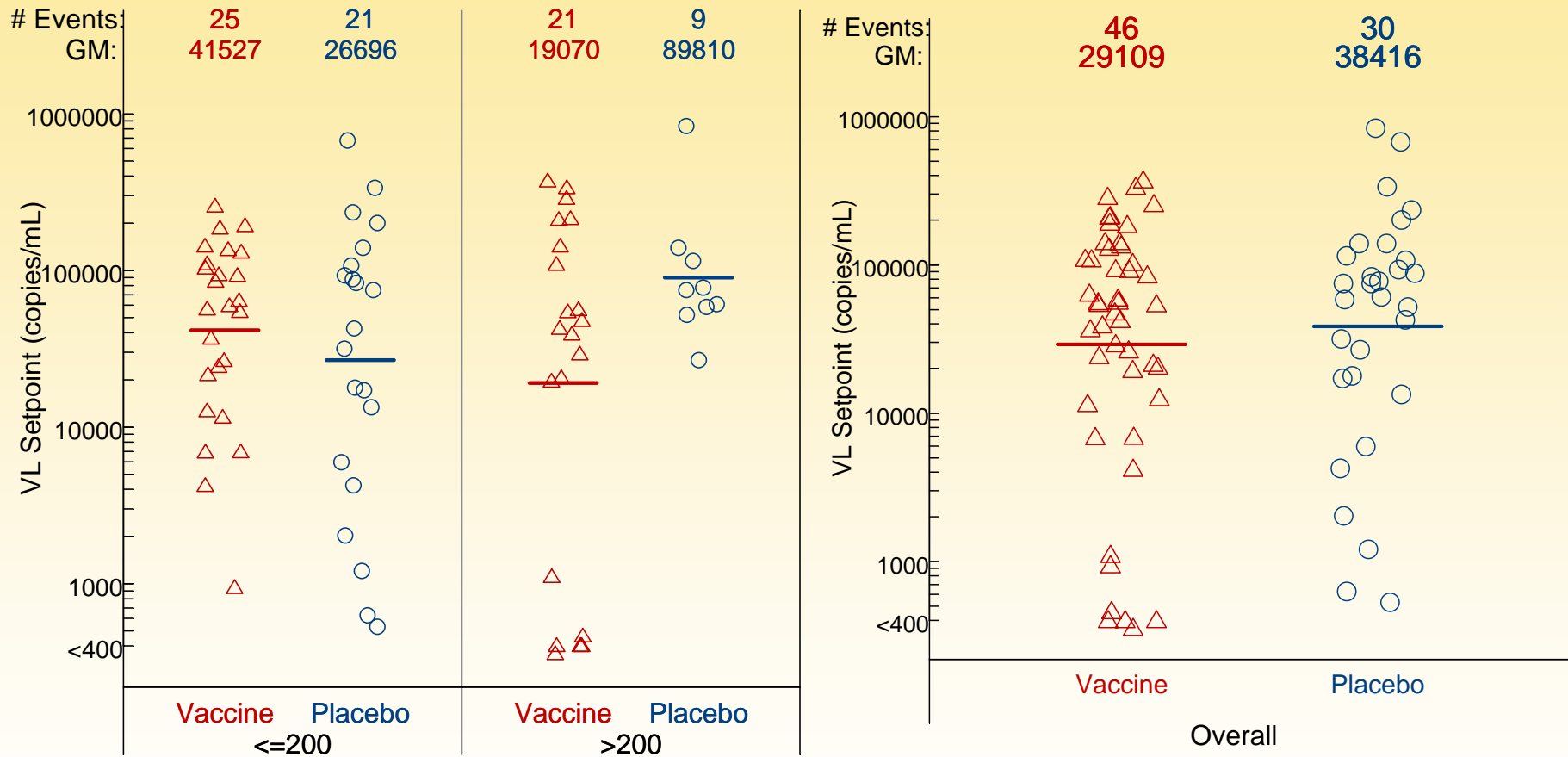
Cases accrued as of Oct 17, 2007

Cumulative Number of HIV Infections: MITT population (males)



Cases accrued as of Oct 17, 2007

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	
		Case split		HIV rate(%/yr)		Endpoint	
		Ad5	N	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

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 lack of immune responses in vaccinees

Why could vaccine group have higher # of HIV infections in high Ad5 group?

- The differences between vaccine and placebo could be unrelated to the vaccine
 1. Differences at baseline between the groups
 2. Differences in risk over time
 3. Chance (small number of infections)
- The differences could be due to vaccine
 - Is there an immune response that correlates with this risk?
 - Is this response concentrated in high Ad5 group?
- **Explore:**
 - Biological plausibility through laboratory studies
 - Persistence of differences through ongoing follow-up

Q&A

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