



HIV VACCINE
TRIALS NETWORK

STEP Study: Summary of Results October

- Study Design
- Study Conduct
- Study Results
 - Primary Analyses
 - Secondary Analyses
 - Exploratory Analyses
- Conclusions



Study Design

The STEP Study was a model of successful trial design, planning, execution and monitoring:

- The trial results demonstrate the effectiveness of a Phase 2B Test of Concept design
 - Provided rigorous, rapid and efficient evaluation of the potential efficacy of the vaccine
 - Evaluated both HIV acquisition (VE_S) and set point viral load (VE_P surrogate) endpoints
 - Included rigorous monitoring plan meeting highest safety and ethical standards
 - Pre-defined stopping guidelines for potential stopping based on efficacy and futility
 - Endpoint-driven review by independent DSMB ensuring most timely assessment of results
 - Both efficacy endpoints fully monitored
 - Integrated monitoring of primary (TOC) and secondary (overall) analyses
 - Minimized exposure of participants to vaccine that would be found ineffective
 - Stratification by baseline Ad5 NAb titer provided
 - Rapid test of concept with efficient segue to rigorous test in overall population
 - Novel insights about the vaccine's potential effects



Study Conduct

- The clinical trial sites met all protocol milestones for enrollment and level of HIV risk for study cohort (HIV acquisition rate $\approx 3.8\%$ / yr)
- The clinical sites exceeded the pre-defined enrollment target of 25% women randomizing 1,150 women (38%)
- Retention rates and adherence to the protocol were at the highest level of clinical trial conduct



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Primary Safety and Immunogenicity Analyses

- In the stratum of subjects with $Ad5 \leq 200$
 - The vaccine is well-tolerated
 - The immunogenicity profile observed in Phase I and Phase II studies was confirmed



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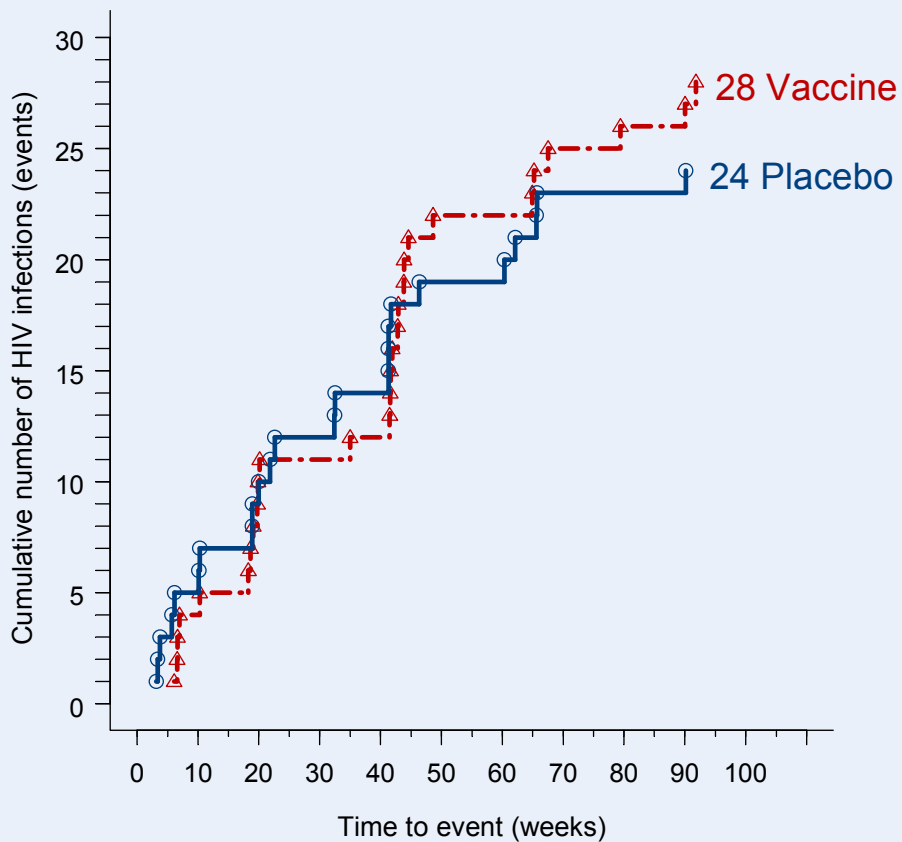
Primary Efficacy and Futility Analyses

- In the stratum of subjects with $Ad5 \leq 200$
 - There is no significant *decrease* in risk of HIV acquisition among vaccinees
 - There is no significant *decrease* in set point plasma viral load among vaccinees
 - The probability of observing a significant effect for either endpoint by end of trial estimated to be < 0.10 (futility)

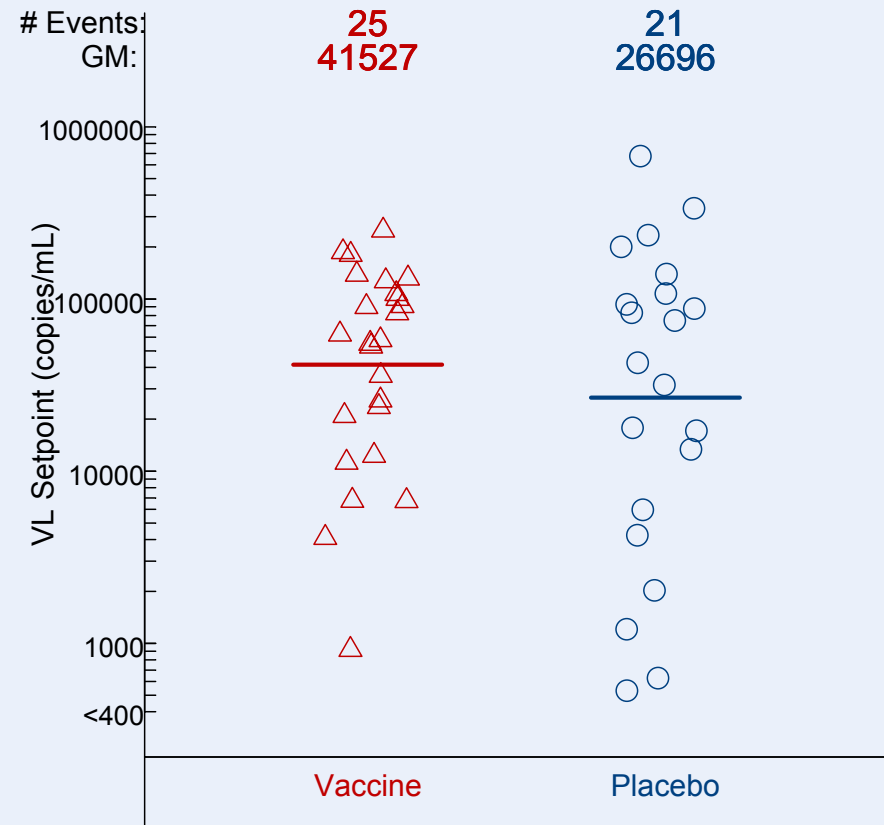


MITT Population (Males; Ad5 ≤ 200 Stratum)

Cumulative Number of HIV Infections



Viral Load Set Point





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Secondary Safety and Immunogenicity Analyses

- In the stratum of subjects with Ad5 > 200
 - The vaccine is well-tolerated
 - The immunogenicity profile observed in Phase I and Phase II studies was confirmed



Impact of Early Stopping

- Maintain same structure of pre-planned protocol-specified analyses (Secondary, Exploratory)
 - Secondary analyses of same hypotheses but “spend all α ”
 - Consider (post-hoc) 2-sided version of pre-planned secondary analysis
 - Exploratory analyses for description and hypothesis generation
- Careful of biases in effect estimates from stopped trials (regression to the mean)



Secondary Efficacy Analyses

- In overall population of subjects ($Ad5 \leq 200$ and $Ad5 > 200$)
 - There is no significant* *decrease* in risk of HIV acquisition among vaccinees
 - There is no significant* *decrease* in set point plasma viral load among vaccinees
- Post-hoc secondary analyses of *difference* in overall population of subjects ($Ad5 \leq 200$ and $Ad5 > 200$)?
 - There is no significant** *difference* in either risk of HIV acquisition ($p = 0.077$; 2-sided) or set point plasma viral load among vaccinees

* At final analysis of secondary hypothesis, $\alpha \approx 0.0125$ (1-sided; each endpoint)

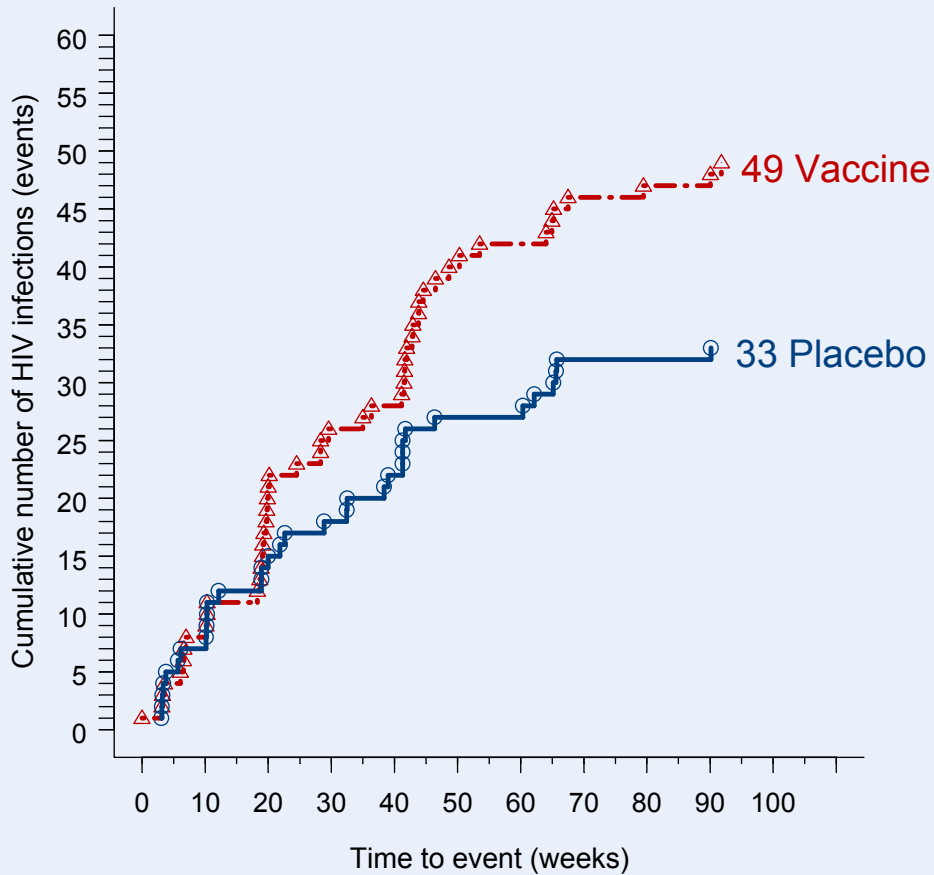
** At final analysis of secondary hypothesis, $\alpha \approx 0.025$ (2-sided; each endpoint)



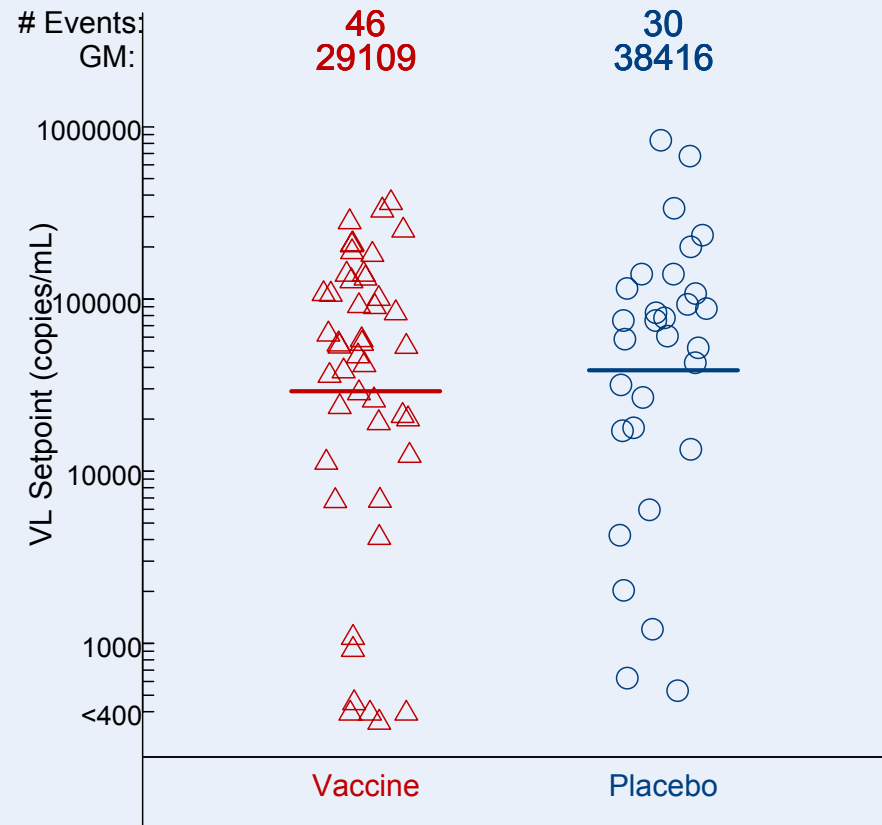
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MITT Population (Males; Pooled Across Ad5 Strata)

Cumulative Number of HIV Infections



Viral Load Set Point



Data as of Oct 17, 2007



Guidelines for Interpreting Results: Post-hoc and Exploratory Analyses

- Nominal statistical significance
 - Precise interpretation not possible
 - P-values that are *much* smaller than usual threshold values provide some indication of strength of evidence
 - Crude adjustment possible if multiplicity of tests defined
- Strong biological plausibility
- External validation
 - Independent confirmatory data
 - Primary role of exploratory analyses as “hypothesis generation”



Exploratory Analyses (males)

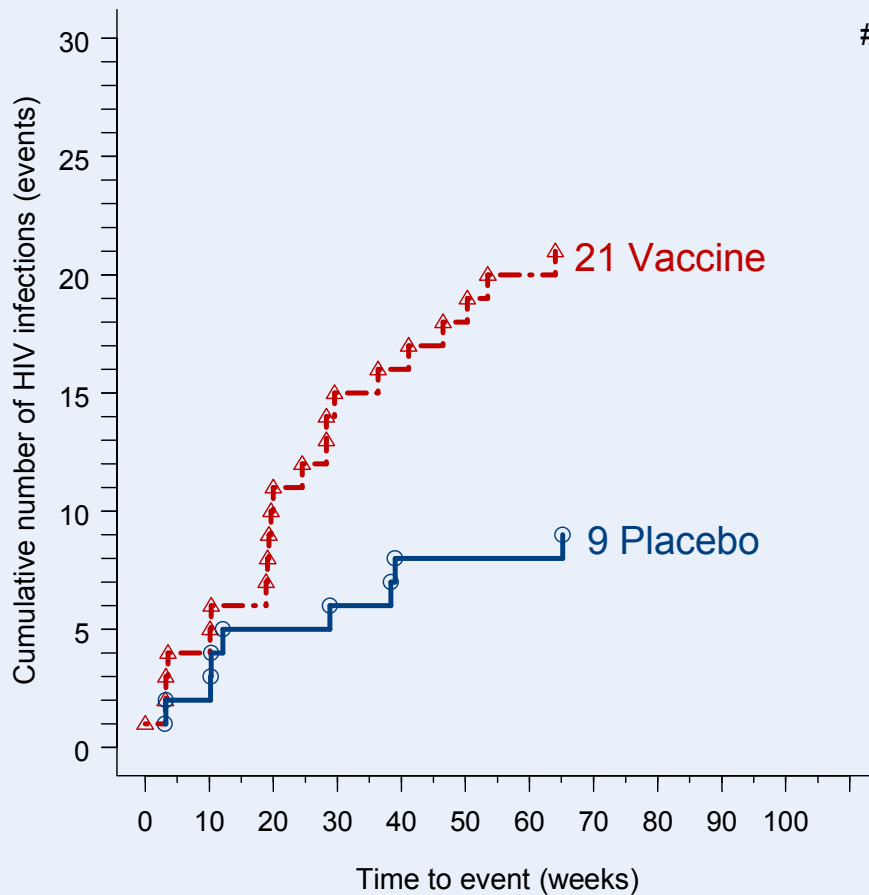
- In subgroup with Ad5 > 200, there is a trend for increased risk of HIV acquisition among vaccinees
 - Trend observed across range of Ad5 titers > 18
 - Trend is not “explained” in current analyses of potential confounders measured at baseline (eg, risk behavior, age, race, region, circumcision status)
 - Ability to statistically model trend may be limited by small numbers, heterogeneous population and correlations among potential confounders
 - Statistical significance of trend?
 - Nominal statistical significance is marginal ($p = 0.029$; 2-sided);
 - Compare to per-endpoint threshold of 0.025 and to multiplicity-adjusted threshold of ~ 0.0025 (assuming 10 exploratory subgroup analyses)



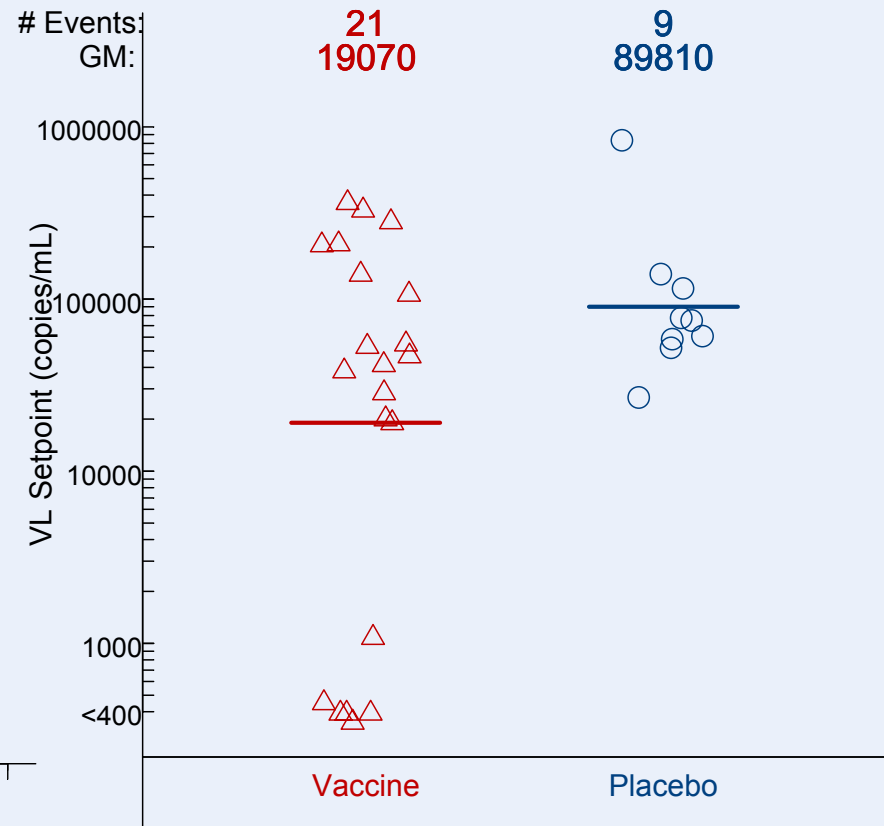
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Exploratory Analyses: MITT Population (Males; Ad5 > 200 Stratum)

Cumulative Number of HIV Infections



Viral Load Set Point



Data as of Oct 17, 2007



Conclusions

- Vaccine reactogenicity and immunogenicity was similar to that observed in Phase 1/2 trials program
- The vaccine provided no benefit in men with low or no prior immunity to Ad5 (baseline Ad5 titer ≤ 200).
- The vaccine provided no benefit in men overall (pooled strata Ad5 ≤ 200 and Ad5 > 200)



Conclusions

- In the subgroup of men with Ad5 > 200
 - A surprising trend towards increased rates of HIV acquisition among vaccinees was observed
 - Observed effects on HIV acquisition rates of some potential confounding variables are complex and somewhat confusing
 - The trend towards increased rates of HIV acquisition among vaccinees persists after statistical adjustment for potential confounders
 - Covariate analyses are not yet complete and some important potential confounders (e.g HSV-2 status) and laboratory studies are not yet available



Conclusions

- Interpretation of the observed trend in the high Ad5 subgroup is challenging and could possibly include mechanisms involving:
 - Biological effect of vaccination
 - Confounding by factors unrelated to vaccination
 - Chance
- When evaluating for potential harm
 - Statistical analyses are just one tool and statistical significance *per se* plays a different role than when evaluating for potential efficacy
 - Explanation of "chance" should be considered as an "explanation of exclusion"
- The observed trend towards increased risk among vaccinees in the high Ad5 subgroup must be taken very seriously
 - There are implications for the longer-term follow up of the STEP and Phambilli study participants
 - There are implications for the design and evaluation of other adenovirus-based vaccines



Conclusions

- Regardless of the mechanism for this trend in risk during the first year of follow up, important immediate questions to address are:
 - Does this potential increased risk for acquisition extend for a prolonged period of time?
 - Can we define cofactors that might explain or reduce this risk over time?



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A Couple of Final Thoughts

“The ability to support a tension that can occasionally become almost unbearable is one of the prime requisites for the very best sort of scientific research”

Thomas Kuhn,

The Structure of Scientific Revolutions



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A Couple of Final Thoughts

- The successful conduct of STEP was only possible with tremendous engagement and mutual commitment of study volunteers, investigators and sponsors.
- We must use our collective resources to answer the compelling scientific questions raised by the results of STEP in order to inform the path forward towards an effective HIV vaccine.
- The key to our success in this next set of challenges will be to renew our collective engagement and commitment... we owe this to our study volunteers and to ourselves.