Efficacy Results from the Step Study
(Merck V520 Protocol 023/HVTN 502)

A Phase II Test-of-Concept Trial of the MRKAd5 HIV-1 Gag/Pol/Nef Trivalent Vaccine

CROI

February 5, 2008

Boston, MA

Rationale for Test of Concept HIV Vaccine Trial

- Cell-mediated immunity appears important in long-term control of viral replication
  - Animal models
  - Observational studies in humans (e.g., LTNP)

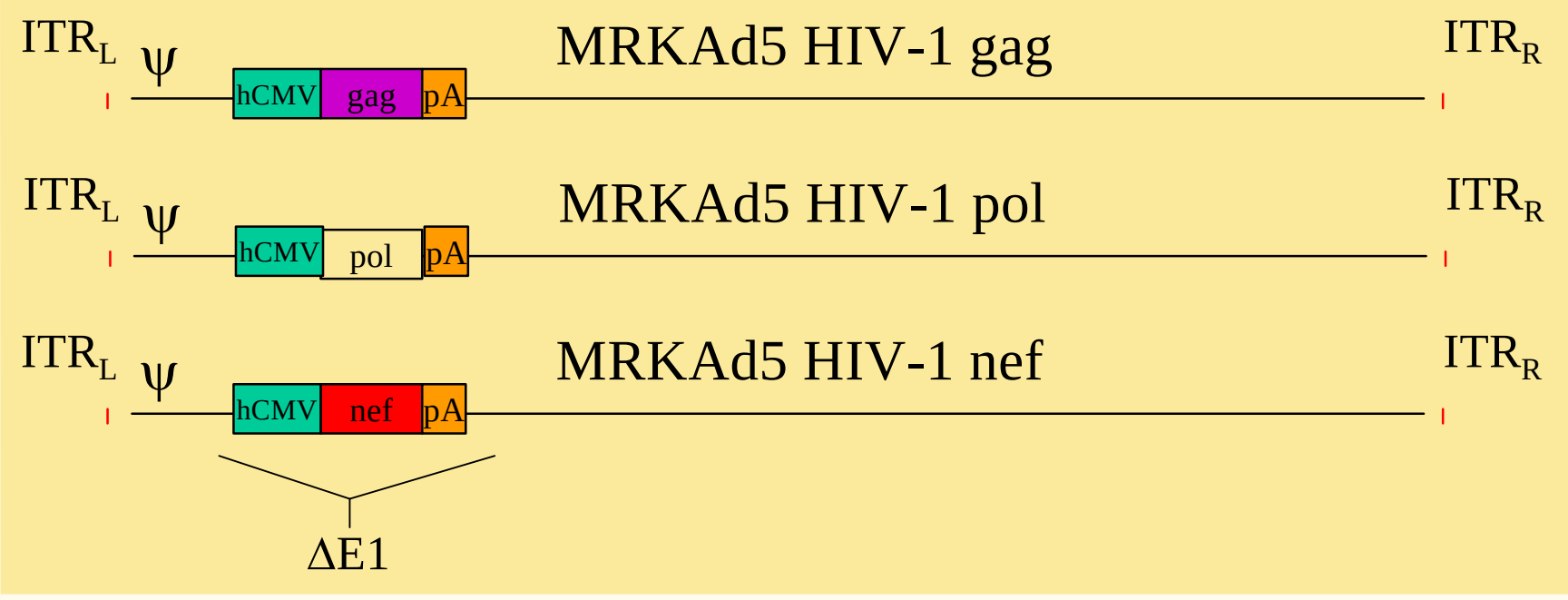
- Merck adenovirus type 5 (Ad5) trivalent vaccine immunogenic in Phase I trials

  ~80% IFN-γ ELISPOT if baseline Ad5 NAb ≤200

  ~60% IFN-γ ELISPOT if baseline Ad5 NAb >200

- Test of concept trial rather than Phase III
  - Preliminary assessment of efficacy
  - Smaller, faster

MRKAd5 trivalent vaccine



- Vaccine: 1:1:1 admixture of 3 Ad5 vectors
  - Encoded transgenes: codon-optimized, near-consensus clade B HIV-1 sequences
- Placebo: vaccine dilution buffer without Ad5

Trial Design

- 3000 high-risk HIV uninfected men and women
  - Initial study: 1500 pts w/ Ad5 NAb ≤200 (Dec 2004)
  - Modification: additional 1500 w/ Ad5 NAb >200 (July 2005)
  - Randomization stratified by Ad5 ≤18, 19-200, 201-1000, >1000

Primary hypotheses: Ad5 ≤200 subset

- Decrease in HIV acquisition and/or
- Lower viral load setpoint (~3 months post-diagnosis)

Secondary hypotheses: Total population

- Same as primary (Ad5 ≤200 and Ad5 >200 combined)

STEP
Study sites

Description of Baseline HIV Risk for Men and Women

Risk practices (previous 6 months)	Men N = 1850	Women N = 1150
# male sex partners		
0	3.9%	0.4%
1	4.2%	8.4%
2-4	32.5%	24.2%
5-9	23.9%	10.4%
10-19	14.9%	6.7%
≥ 20	20.7%	49.5%
Unprotected anal or vaginal sex	58.8%	74.6%
--With HIV positive sex partner	7.6%	4.5%
--With HIV unknown serostatus partner	34.1%	20.5%
Drug use	40.6%	51.0%

Analysis Strategy

- Event driven study
  - MITT (modified intention-to-treat): HIV negative at baseline, received ≥ 1 dose vaccine/placebo
  - PP (per protocol): HIV negative through week 12, received ≥ 2 doses in window, not protocol "violators"

- Interim analysis
  - First planned when 30 infections in Ad5 ≤200 stratum

- Pre-specified futility guidelines
  - p value >.50 for EACH endpoint
  - Unlikely to meet either endpoint at later time (< 10%)

HIV Incidence: Ad5 ≤ 200
Planned interim analysis

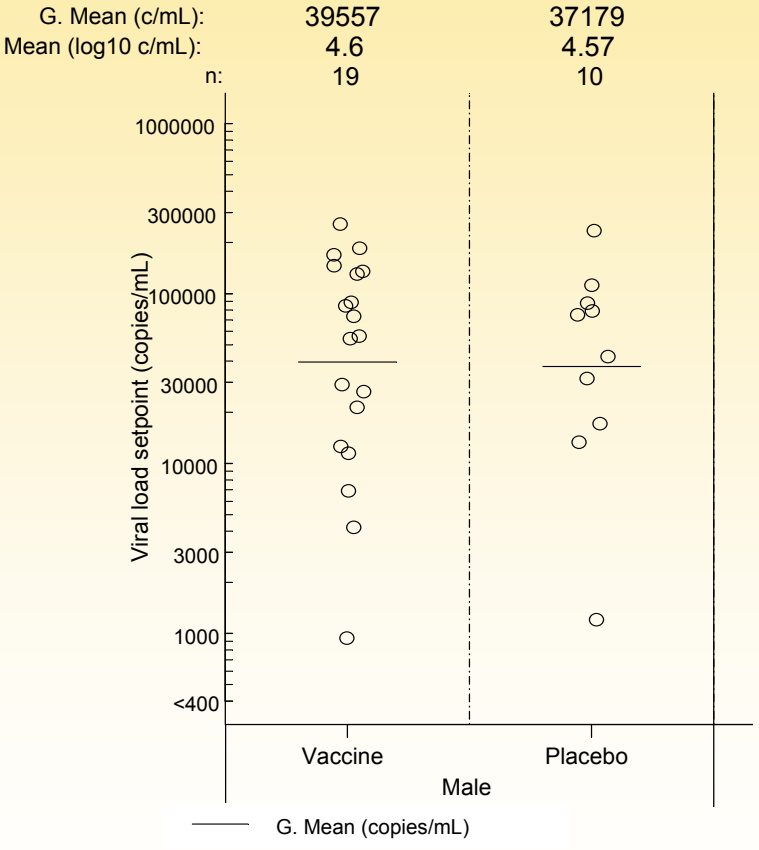
Population	Group	N*	n	Person-years of Follow-up**	Incidence of HIV Infection	95% CI
MITT	Vaccine	741	24	822	2.92	(1.87, 4.34)
	Placebo	762	21	836	2.51	(1.56, 3.84)
1-tailed p-value (beneficial effect) = 0.743 (for $VE_{INF} > 0$)						
Per-Protocol	Vaccine	672	19	619	3.07	(1.85, 4.79)
	Placebo	691	11	622	1.77	(0.88, 3.16)
1 tailed p-value (beneficial effect) = 0.949 (for $VE_{INF} > 0$)						

*N=Number in respective analysis population
** 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.
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.

Viral Load Set-Points: Ad5 ≤ 200

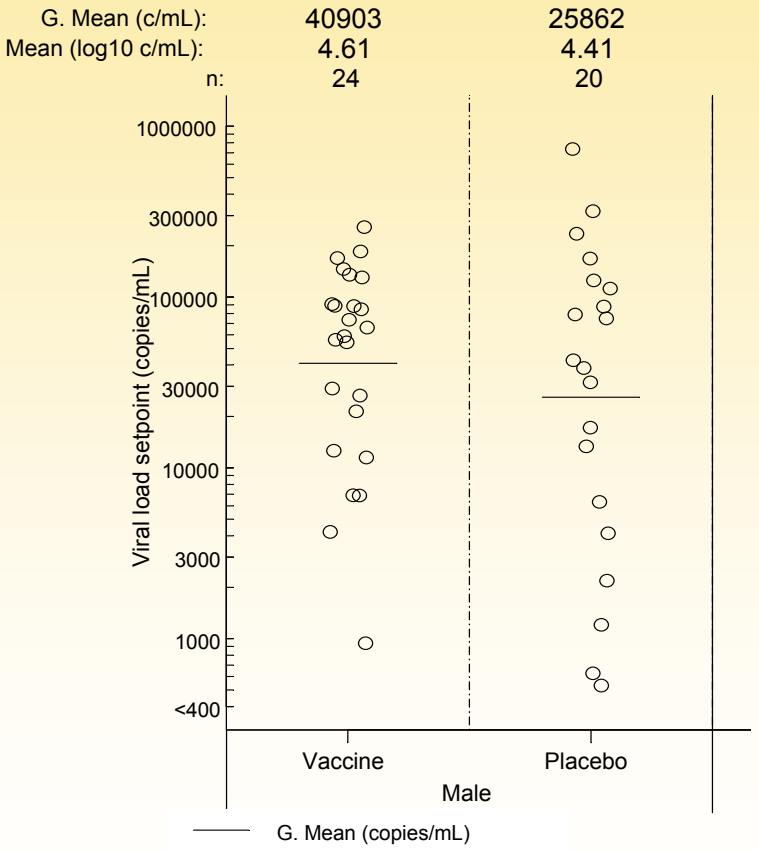
Planned interim analysis

Per-protocol



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

MITT



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

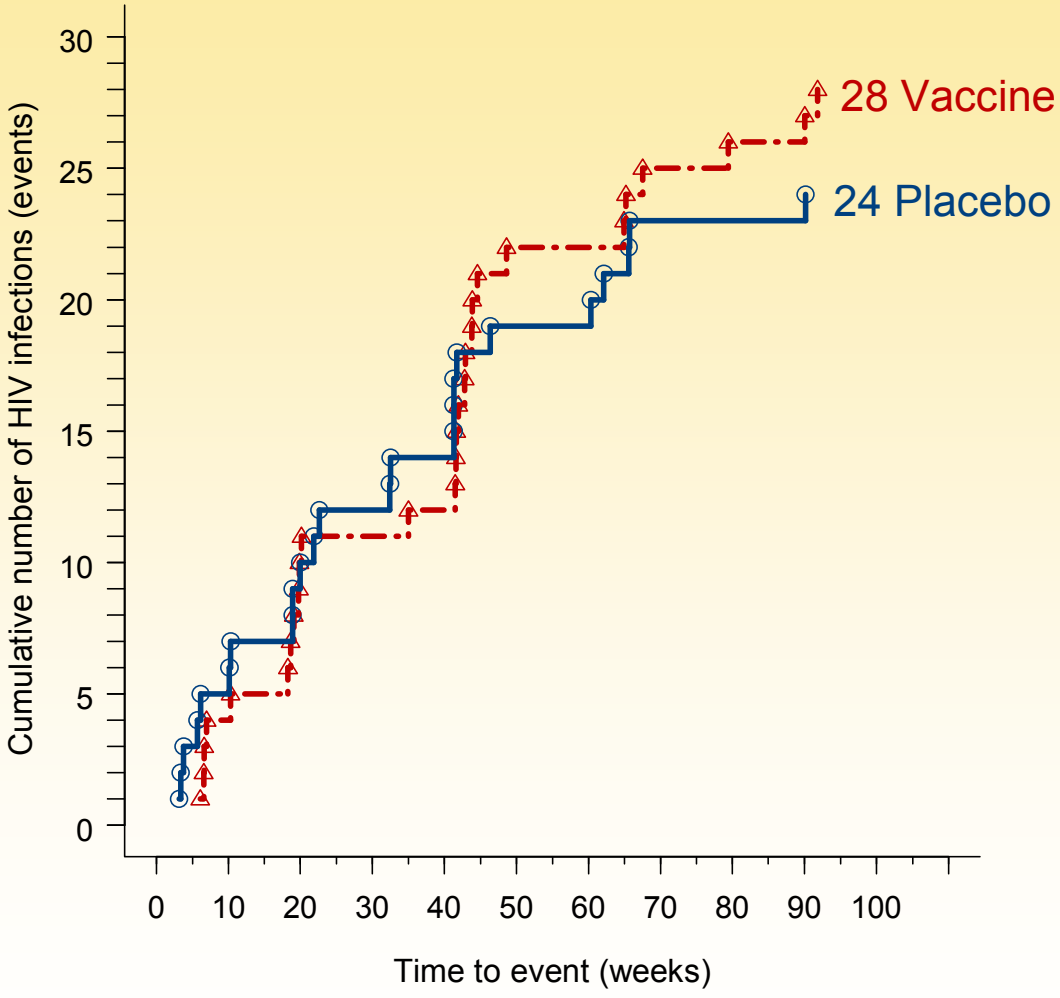
There was 1 female infection: VLS = 20,207 c/mL (4.31 log10 c/mL)

Number of cases included in post-hoc analyses (Males only)

Ad5 ≤ 200 male MITT cases included in **1st interim analysis***	44
Additional Ad5 ≤ 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



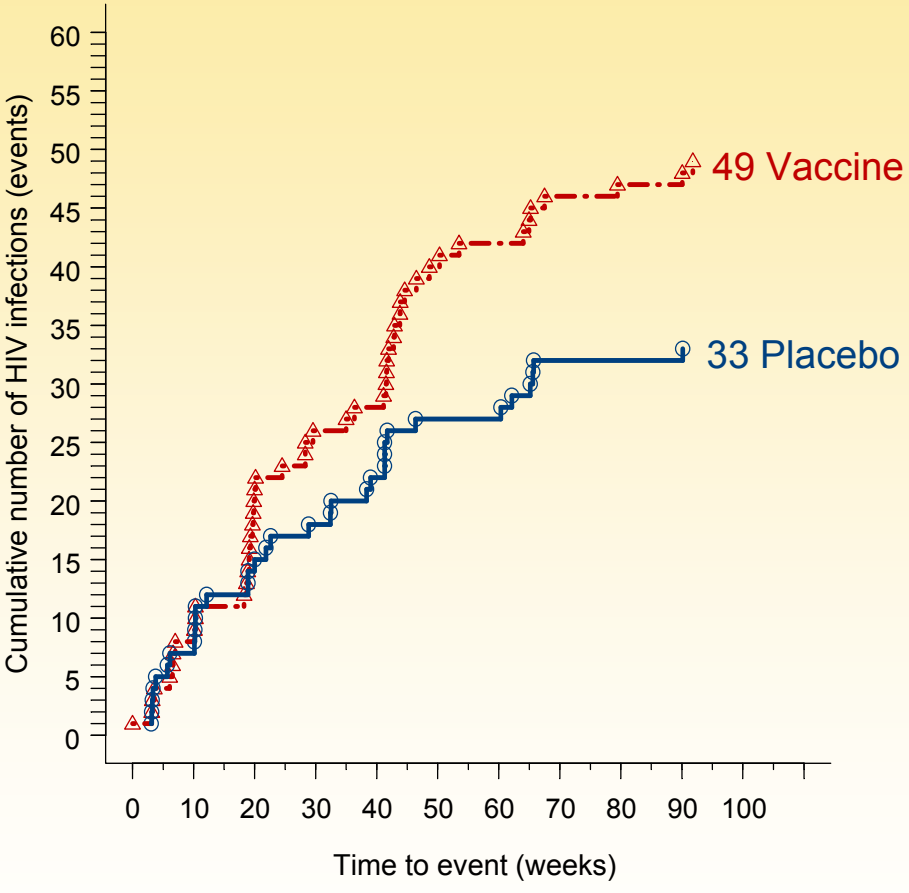
1-tailed p-value = 0.322 (for $VE_{INF} < 0$)

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)

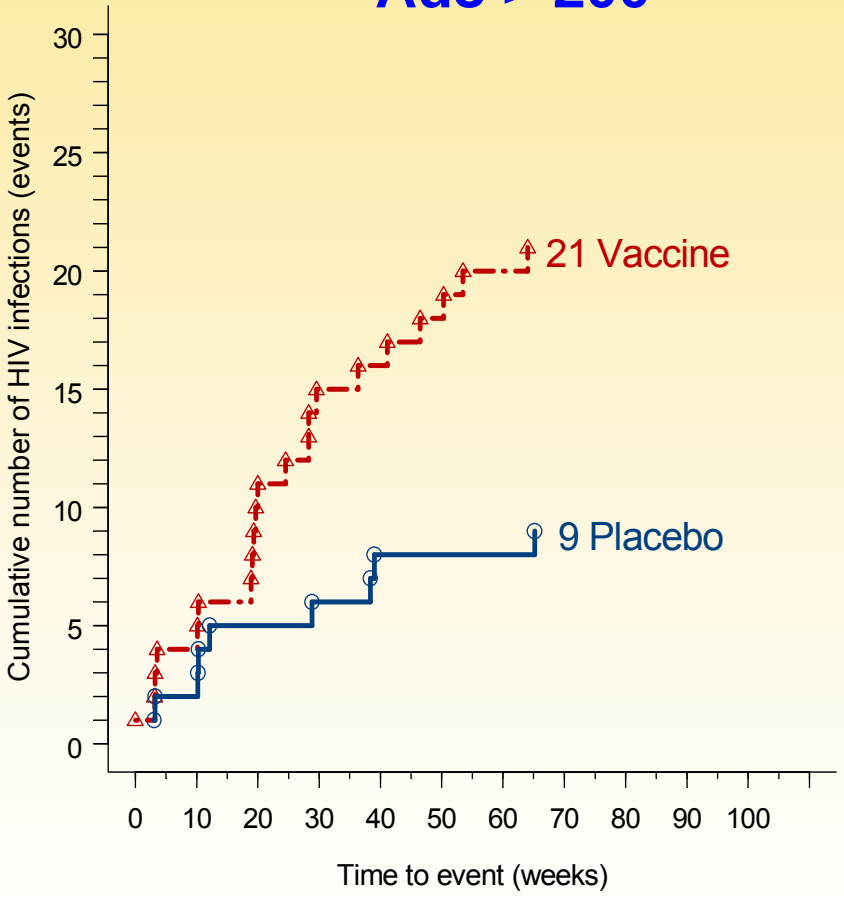
Overall



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

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

Ad5 > 200



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

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

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

Variables included in univariate/multivariate analyses

- Vaccine vs. placebo
- Baseline Ad5
- Circumcision (self-report)
- Age
- Race
- Region
- Baseline risk factors (previous 6 months)
  - # male sex partners
  - Unprotected receptive anal sex
  - Unprotected insertive anal sex
  - Substance use
  - Self-reported sexually transmitted infection

Variables included in univariate/multivariate analyses

- Vaccine vs. placebo
- Baseline Ad5*
- Circumcision (self-report)*
- Age
- Race
- Region
- Baseline risk factors (previous 6 months)
  - # male sex partners
  - Unprotected receptive anal sex
  - Unprotected insertive anal sex
  - Substance use
  - Self-reported sexually transmitted infection

*significant interaction with vaccine vs. placebo

Other variables associated with HIV acquisition

Variable	HR	95% CI	P value
Age (≤30)	1.9	1.2, 3.1	.008
Race (White)	0.5	0.3, 0.9	.023
Region (N. America)	3.1	1.4, 6.7	.004
Unprotected receptive anal sex w/ HIV+	2.3	1.2, 4.3	.01
Unprotected receptive anal sex w/ HIV unknown	2.8	1.7, 4.3	<.001
Unprotected receptive anal sex w/ HIV negative	1.6	1.0, 2.6	.035

Estimated Relative Risk of HIV Infection Vaccine : Placebo

(95% CI)

MODEL	Baseline Ad5			
	Ad5 ≤18 N=746	Ad5 >18 N=1041		
Univariate	1.0 (0.5, 1.8)	2.4 (1.2,4.7)		
Multivariate				
Model 1	1.1 (0.6, 2.0)	2.7 (1.3, 5.5)		
Model 2	1.1 (0.6, 2.0)	3.1 (1.5, 6.5)		
Model 3	0.8 (0.4, 1.6)	2.6 (1.3, 5.4)		
Model 4	0.8 (0.4, 1.6)	2.7 (1.3, 5.6)		

* Circumcision status was unknown for 49 (2.7%) men. All univariate and multivariate analyses are based on the Cox proportional hazards regression model for time-to-event data.

Estimated Relative Risk of HIV Infection
Vaccine : Placebo
(95% CI)

MODEL			Circumcision*	
			Yes N=999	No N=788
Univariate			1.0 (0.6, 1.7)	3.8 (1.5, 9.3)
Multivariate				
Model 1			1.0 (0.6, 1.8)	3.8 (1.6, 9.5)
Model 2			1.1 (0.6, 2.0)	4.1 (1.6, 10.4)
Model 3			0.9 (0.5, 1.6)	3.4 (1.4, 8.4)
Model 4			0.8 (0.5, 1.5)	3.6 (1.4, 9.2)

* Circumcision status was unknown for 49 (2.7%) men. All univariate and multivariate analyses are based on the Cox proportional hazards regression model for time-to-event data.

Estimated Relative Risk of HIV Infection Vaccine : Placebo

(95% CI)

MODEL	Baseline Ad5		Circumcision*	
	Ad5 ≤18 N=746	Ad5 >18 N=1041	Yes N=999	No N=788
Univariate	1.0 (0.5, 1.8)	2.4 (1.2,4.7)	1.0 (0.6, 1.7)	3.8 (1.5, 9.3)
Multivariate				
Model 1	1.1 (0.6, 2.0)	2.7 (1.3, 5.5)	1.0 (0.6, 1.8)	3.8 (1.6, 9.5)
Model 2	1.1 (0.6, 2.0)	3.1 (1.5, 6.5)	1.1 (0.6, 2.0)	4.1 (1.6, 10.4)
Model 3	0.8 (0.4, 1.6)	2.6 (1.3, 5.4)	0.9 (0.5, 1.6)	3.4 (1.4, 8.4)
Model 4	0.8 (0.4, 1.6)	2.7 (1.3, 5.6)	0.8 (0.5, 1.5)	3.6 (1.4, 9.2)

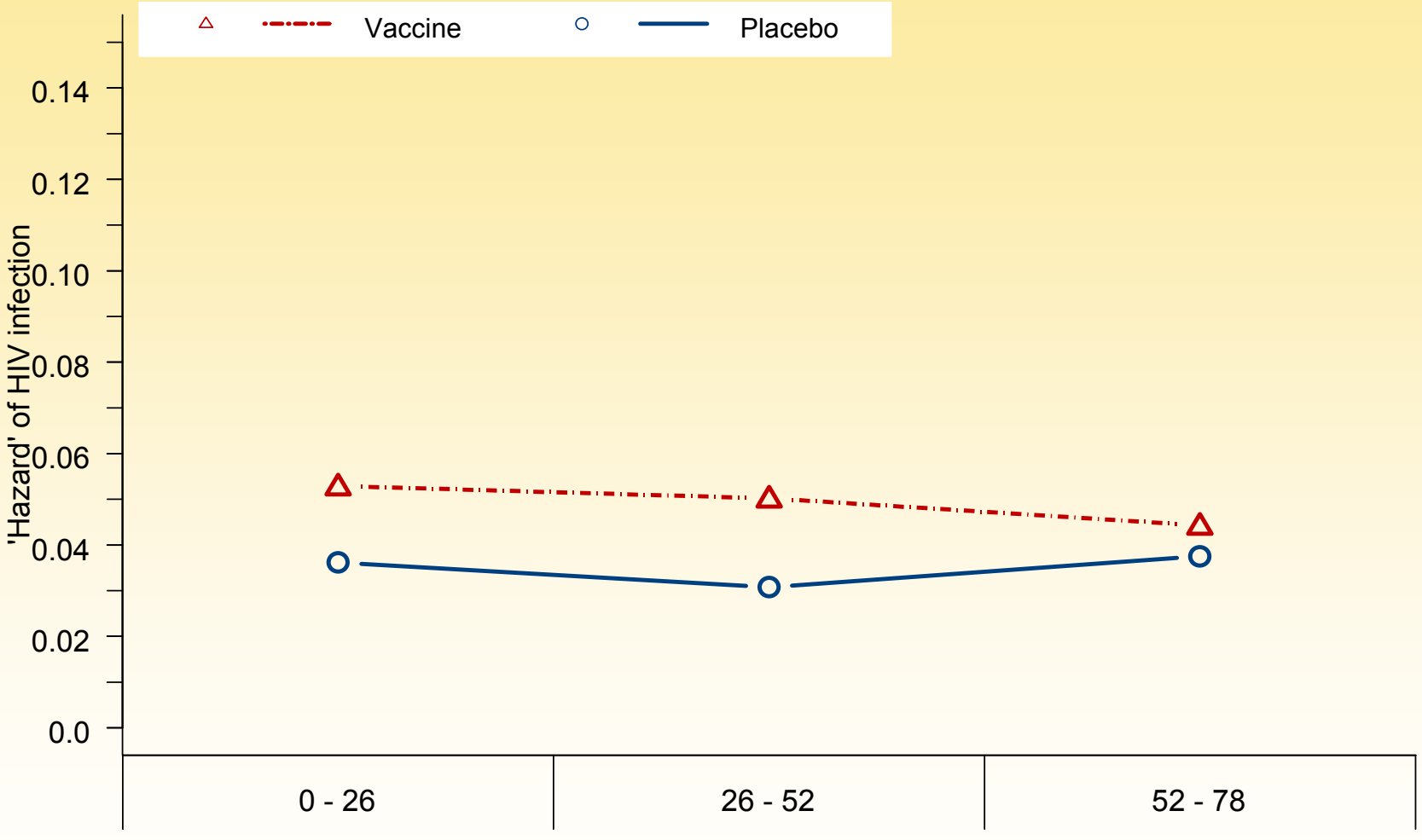
* Circumcision status was unknown for 49 (2.7%) men. All univariate and multivariate analyses are based on the Cox proportional hazards regression model for time-to-event data.

Estimated Relative Risk of HIV Infection
Vaccine : Placebo
(95% CI)

MODEL	Circumcised		Uncircumcised	
	Ad5 ≤18 N=578	Ad5 >18 N=421	Ad5 ≤18 N=168	Ad5 >18 N=620
Univariate	0.7 (0.3, 1.4)	1.6 (0.7,3.8)	3.3 (0.7, 16)	3.9 (1.3, 11)
Multivariate				
Model 1	0.8 (0.4, 1.6)	1.4 (0.6,3.2)	2.5 (0.8,8.0)	4.3 (1.7, 11.0)
Model 2	0.8 (0.4, 1.7)	1.7 (0.7,3.8)	2.4 (0.8,7.3)	4.8 (1.8, 12.6)
Model 3	0.6 (0.3, 1.2)	1.3 (0.6,3.0)	2.0 (0.6,6.3)	4.6 (1.8, 12)
Model 4	0.6 (0.3, 1.2)	1.4 (0.6,3.1)	2.1 (0.7,6.6)	4.2 (1.6, 11.1)

Men with unknown circumcision status (49, 2.7%) were excluded from analyses. All analyses are based on the Cox proportional hazards regression model for time-to-event data.

"Hazard" of HIV Infection: MITT population (males)
Crude estimation method using 26 week intervals



# Events [# Risk]	0 - 26	26 - 52	52 - 78
Vaccine:	23 [911]	16 [802]	7 [325]
Placebo:	16 [917]	10 [823]	6 [329]

Time interval of **estimated HIV infection** in weeks relative to randomization;
Summaries exclude 1 female infection (placebo group with Ad5 ≤ 18). MITT population includes all HIV cases diagnosed after baseline.

Summary

- Test of concept provided definitive results 33 months after first participant enrolled
  - Vaccine neither prevented infection nor lowered viral setpoint

- Greater number of infections in vaccine than placebo recipients
  - This trend appeared to be concentrated in Ad5 seropositive strata (randomization w/i strata)

Summary (cont.)

- Multivariate analyses reaffirm the trend toward an overall increase in HIV infection risk in vaccine vs. placebo recipients [estimated hazard ratio (HR) 1.6 to 2.0]

- Increased risk of HIV infection is most evident in uncircumcised men with pre-existing Ad5 immunity [estimated vaccine HRs 4.2 to 4.8].

- In contrast, no evidence of an increased risk in circumcised men without pre-existing Ad5 immunity [estimated vaccine HRs 0.6 to 0.8].

- Uncertainty about whether there is increased risk if either/or Ad5 seropositive or uncircumcised (one but not both risk factors)

Future directions and hypotheses

- Awaiting data on HSV-2 status, HLA typing, sexual network clustering, longitudinal risk
  - Additional multivariate analyses will be performed
- Possible mechanisms for potential increased HIV acquisition is being explored in laboratory studies
  - Studies in vaccine recipients and non-human primates
- Data being considered in developing protocols with other Ad5 vectored approaches

Acknowledgments

The Study Volunteers

For their dedication and commitment in the search for an HIV vaccine

STEP Study Protocol Team

- Sarah Alexander
- Susan Buchbinder
- Gail Broder
- Lisa Bull
- Danny Casimiro
- Ann Duerr
- Cheryl Ewing
- Dan Fitzgerald
- Paula Frew
- Lori Gabryelski
- Tirzah Griffin
- Soyon Im
- Dale Lawrence
- David Li
- Ellen MacLachlan
- Julie McElrath
- Devan Mehrotra
- Robin Mogg
- Dewayne Mullis
- Gabriela O'Neill
- Mary Pleier
- Michael Robertson
- Steve Self
- Rosario Leon
- Amanda Vettori
- Steve Wakefield
- Amy Zhou

Analyses

Special thanks to the team of biostatisticians who have worked relentlessly on preparing these analyses

Merck

- Devan Mehrotra
- Robin Mogg
- David Li
- Jonathan Hartzel

HVTN

- Peter Gilbert
- Steve Self

Organizations

- Merck
  - Keith Gottesdiener
  - Robin Isaacs
  - Mark Feinberg
- NIH
  - Carl Dieffenbach
  - Peggy Johnston
  - Jorge Flores
  - Alan Fix
- HVTN
  - Larry Corey