

STEP Trial

Exploring hypotheses for
differential HIV acquisition rates

HVTN Full Group Meeting
November 7, 2007

Why more infections in high Ad5 group in vaccine compared with placebo?

- 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? (Julie/Danny)
 - Is this response concentrated in high Ad5 group?
- Does this effect persist? (Peter)

1. Baseline characteristics

Vaccine and placebo groups well matched within strata (males)

Baseline Characteristics	Baseline Ad5 Titer			
	≤200		>200	
	Vaccine (n=522)	Placebo (n=536)	Vaccine (n=392)	Placebo (n=386)
Location: US	72.6%	73.7%	44.1%	43.8%
Race: White	59.2%	61.9%	34.7%	33.7%
Age: ≤30 yrs old	49.4%	47.2%	58.7%	59.3%
IV Drug Use	2.1%	2.1%	1.8%	3.4%
Any Drug Use	47.9%	45.1%	38.3%	38.9%
Unprotected Anal Receptive Sex	51.0%	50.4%	49.2%	48.4%
Unprotected Anal Insertive Sex	61.3%	60.6%	59.4%	56.7%
History of STD	15.1%	13.6%	16.6%	11.1%
Circumcision status: Yes	65.5%	65.1%	40.6%	38.6%
No	31.6%	31.2%	58.4%	58.8%
No Data	2.9%	3.7%	1.0%	2.6%

Notes for slide 4: baseline differences

- Within each Ad5 stratum (≤ 200 , >200), vaccine and placebo recipients well-matched on measured baseline variables
 - Several variables not yet measured (HSV-2 status, HLA types) have not yet been compared within strata
- Between strata, low and high Ad5 populations are different, as previously shown in Dan Fitzgerald's slides

2. Changes in risk over time

Why would change in risk be different in vaccine and placebo groups?

Double-blinded, so for differences to occur, need:

1. Some participants must correctly "guess" at whether they got vaccine or placebo
 - Based on symptoms from injections or
 - HIV antibody tested outside of study
2. Participants who believe they received vaccine must behave differently than participants who believe they got placebo

No obvious difference in perception of treatment assignment, high Ad5 group

"Do you think you got vaccine or placebo?"

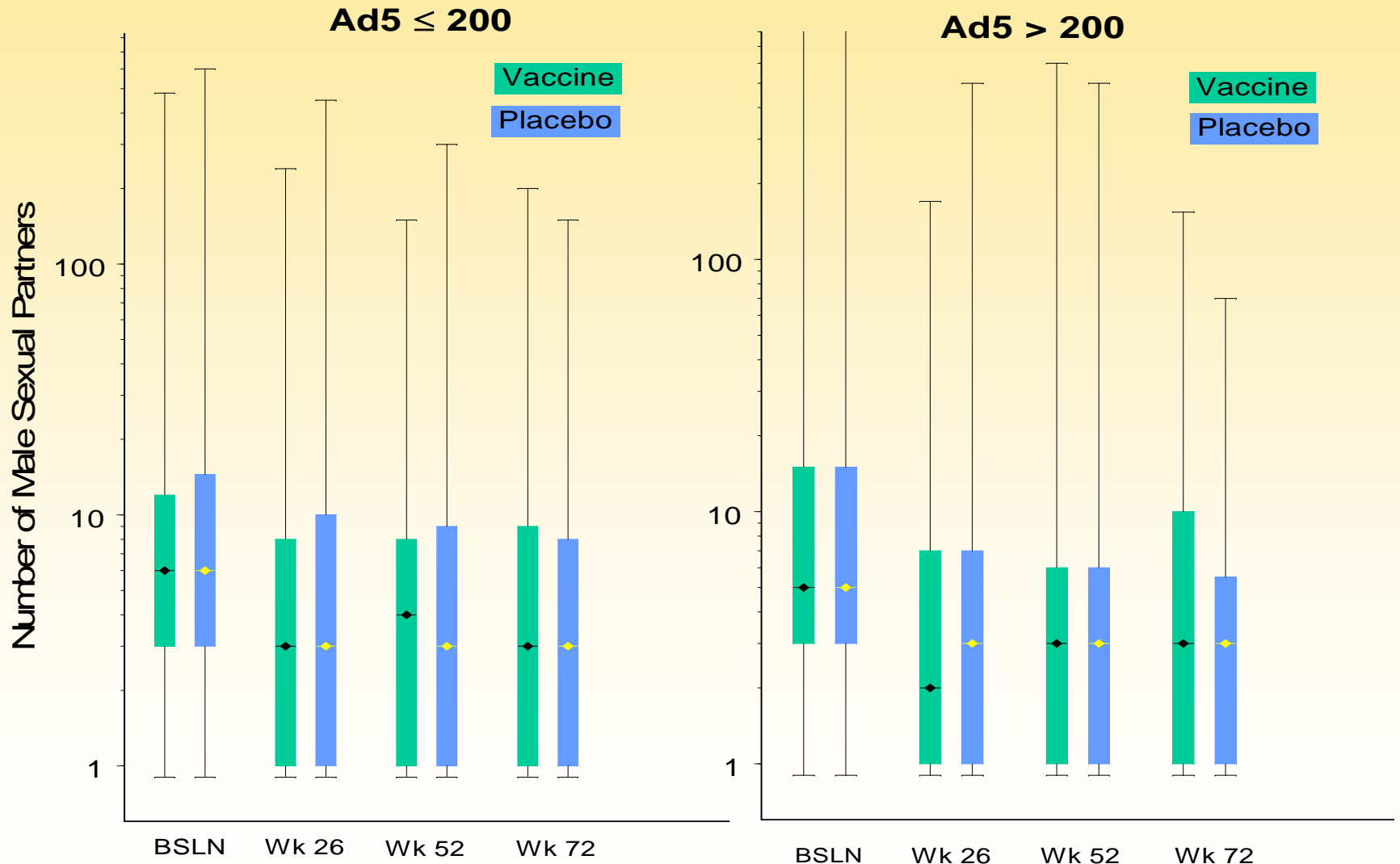
(Data on N = 867 subjects)

Perception of Treatment Received ↓	Actual Treatment Received			
	Ad5 ≤ 200		Ad5 > 200	
	Vaccine (N = 224)	Placebo (N = 203)	Vaccine (N = 221)	Placebo (N = 219)
"Not Sure"	111 49.6%	116 57.1%	130 58.8%	133 60.7%
"Placebo"	44 19.6%	50 24.6%	36 16.3%	40 18.3%
"Vaccine"	69 30.8%	37 18.2%	55 24.9%	46 21.0%
TOTAL	224 100%	203 100%	221 100%	219 100%

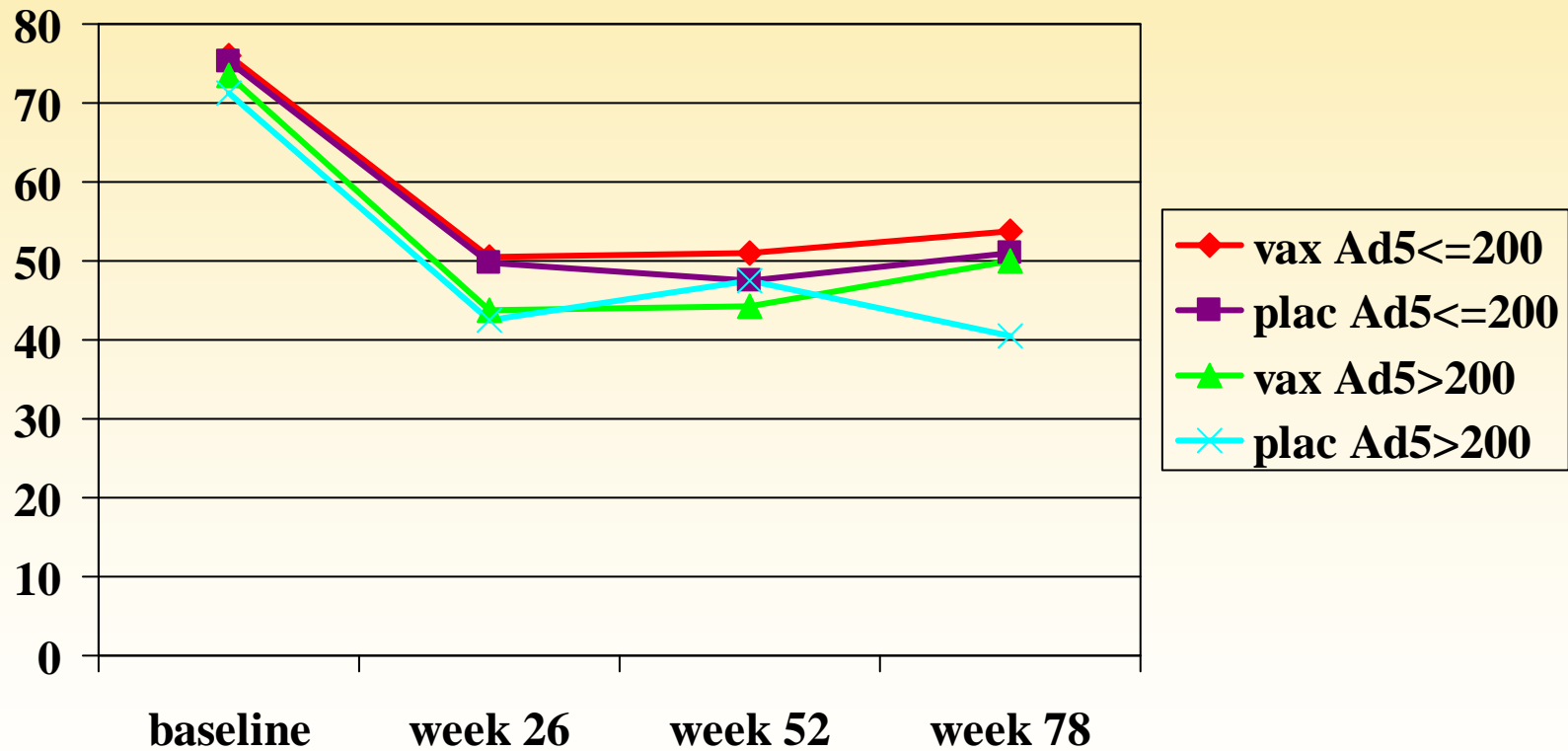
N = number of subjects with data for analysis, recent addition to questionnaire

Number male sex partners (males)

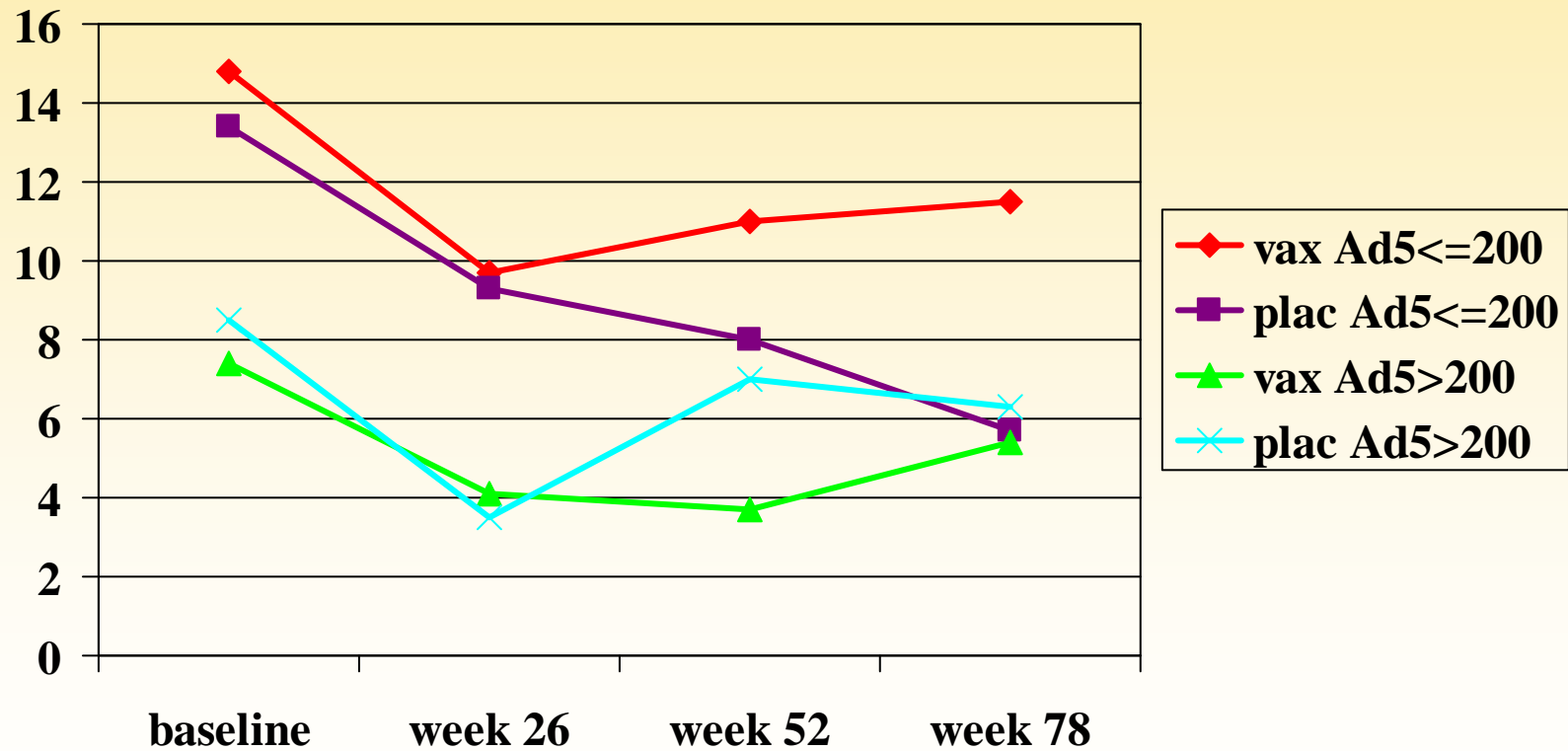
(median, 25-75%, range)



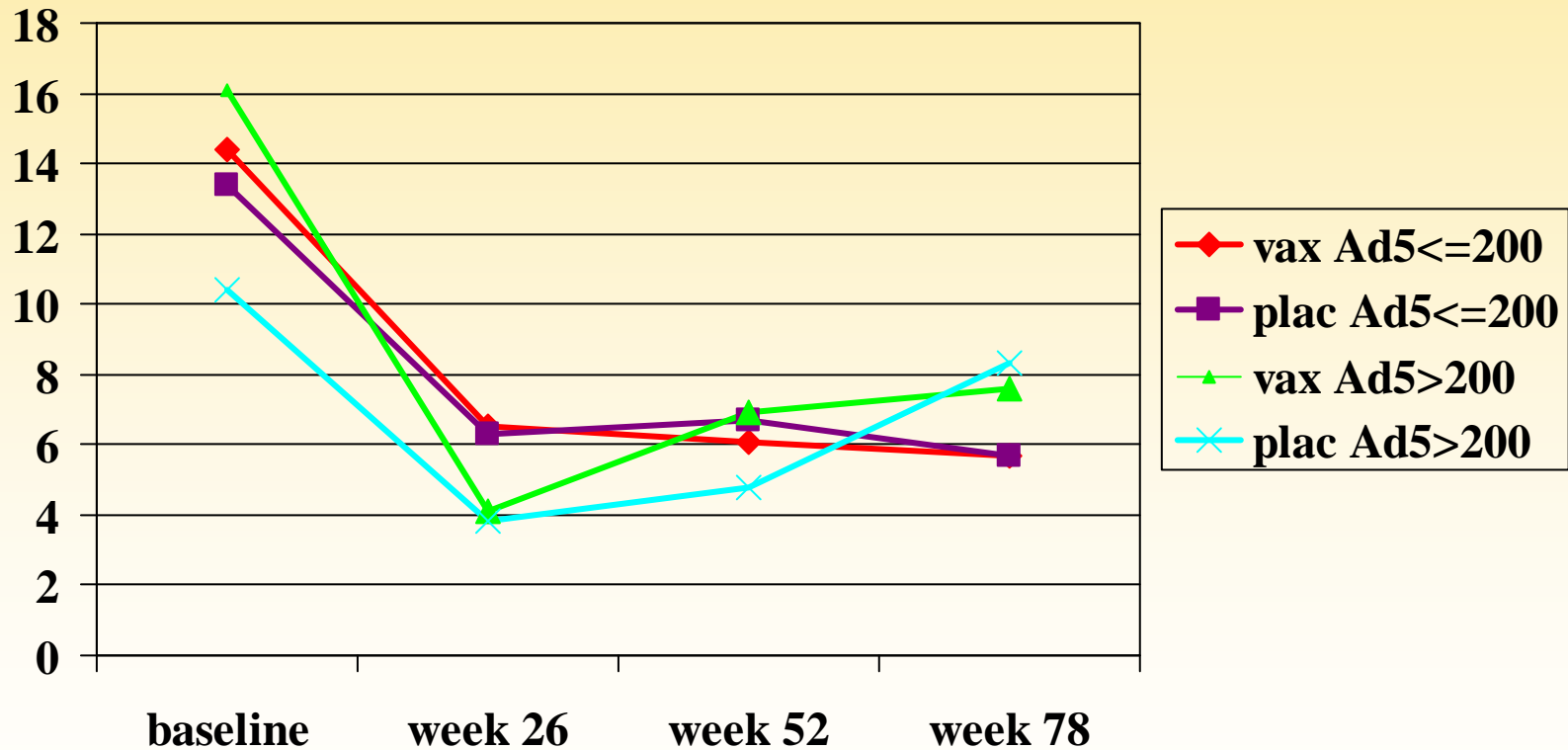
% males reporting unprotected anal sex Prior 6 months



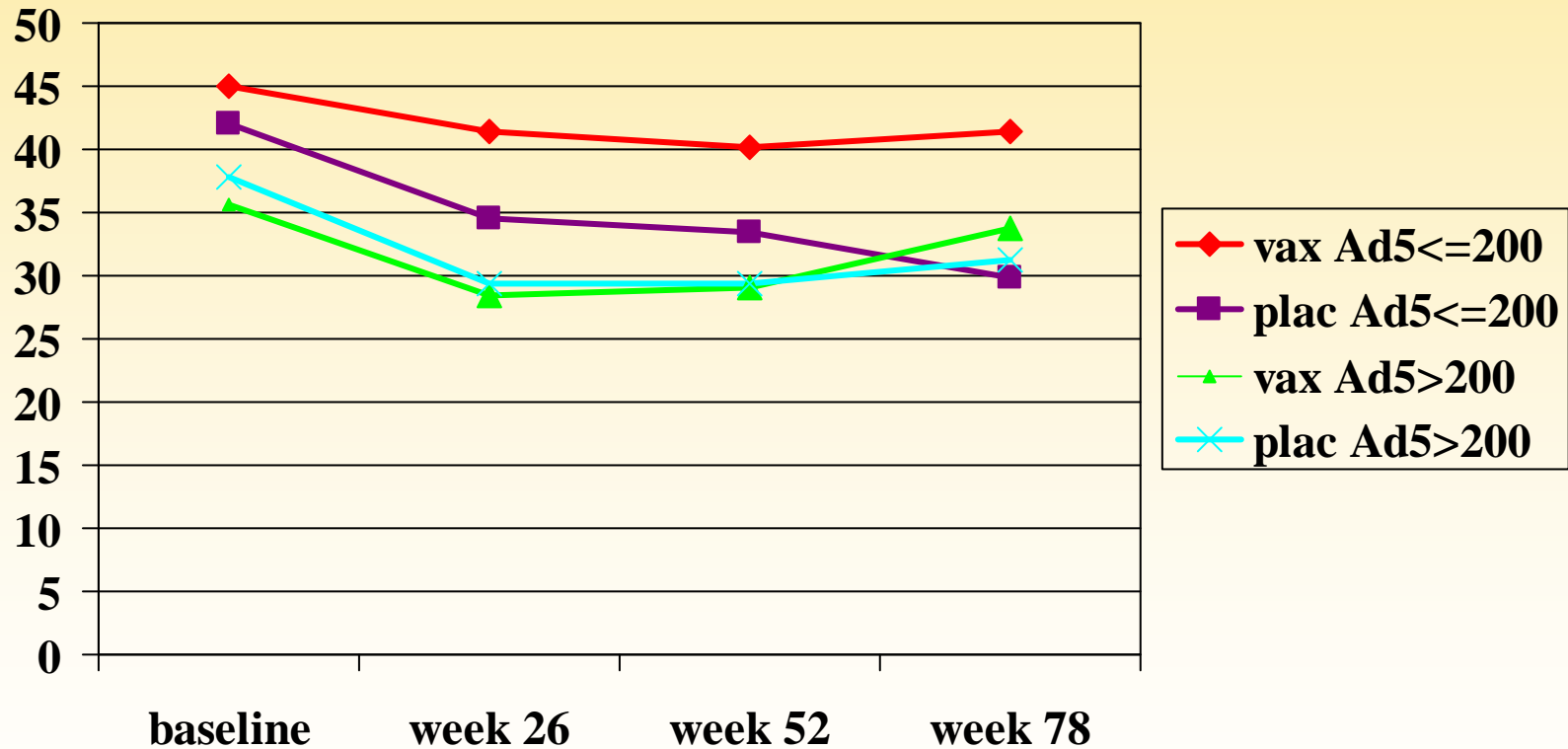
% men, unprotected anal sex with HIV+ Prior 6 months



% men with self-reported STI Prior 6 months



% men reporting recreational drug use Prior 6 months



Summary of behavioral risk

- Risk declines over time for most behaviors
 - Encouraging, given risk reduction counseling
- On some measures, more risk in low Ad5 than high Ad5 group
 - Another indication that the low and high Ad5 populations may have differences unrelated to the vaccine
- No evidence of differences in knowledge of treatment assignment or risk in high Ad5 vaccine vs. placebo
 - Modest differences seen only in low Ad5 group

3. Chance (small numbers)

What does chance mean when looking at potential harm?

- When looking for beneficial effect, want to avoid concluding that a difference exists if the difference in number is due to chance (sampling)
 - Focus on low p value, dismiss results if they do not show big enough difference to conclude differences are real
- But, when looking for potential harm, pay attention even if p value is not significant
 - Explanation of "chance" should always be considered, but is "explanation of exclusion"

HIV Incidence (95% CI) in males

MITT population

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
19-200	4.4 (1.9-8.8)	2.2 (0.6-5.5)	2.0
201-1000	6.1 (3.3-10.2)	3.0 (1.2-6.2)	2.0
>1000	4.4 (1.8-9.1)	1.2 (0.2-4.5)	3.5

Notes for slide 17: HIV incidence

- Participants randomized within 4 Ad5 strata, therefore should be well-matched
- Within strata, number of infected participants relatively small and follow-up time relatively short, so large confidence intervals

Notes for slides 20-22

- Numbers in red (n) represent number of infected participants and numbers in black (N) represent number of participants included in that analysis
- Rows delineate participants with different baseline characteristics. Because numbers within each Ad5 stratum are small, best to focus on total numbers within row, rather than within strata

HIV Infections by Age Group: MITT Cases (males)

Age		Ad5 ≤ 200		Ad5 > 200		TOTAL	
		Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
≤ 30 yrs	n	14	15	14	4	28	19
	N	258	253	230	229	488	482
>30 yrs	n	14	9	7	5	21	14
	N	264	283	162	157	426	440
TOTAL	n	28	24	21	9	49	33
	N	522	536	392	386	914	922

HIV Infections by Race/Ethnicity: MITT Cases (males)

Race/ethnicity		Ad5 ≤ 200		Ad5 > 200		TOTAL	
		Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Hispanic	n	2	1	6	0	8	1
	N	39	42	43	50	82	92
Black	n	3	4	2	1	5	5
	N	53	51	41	40	94	91
Multi	n	6	3	5	2	11	5
	N	104	100	160	149	264	249
White	n	16	13	8	5	24	18
	N	309	332	136	130	445	462
Other	n	1	3	0	1	1	4
	N	17	11	12	17	29	28
TOTAL	n	28	24	21	9	49	33
	N	522	536	392	386	914	922

Individual group sizes

HIV Infections by Circumcision: MITT Cases (males)

Circumcised		Ad5 ≤ 200		Ad5 > 200		TOTAL	
		Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Yes	n	16	20	10	6	26	26
	N	342	349	159	149	501	498
No	n	11	4	11	2	22	6
	N	165	167	229	227	394	394
No data	n	1	0	0	1	1	1
	N	15	20	4	10	19	30
TOTAL	n	28	24	21	9	49	33
	N	522	536	392	386	914	922

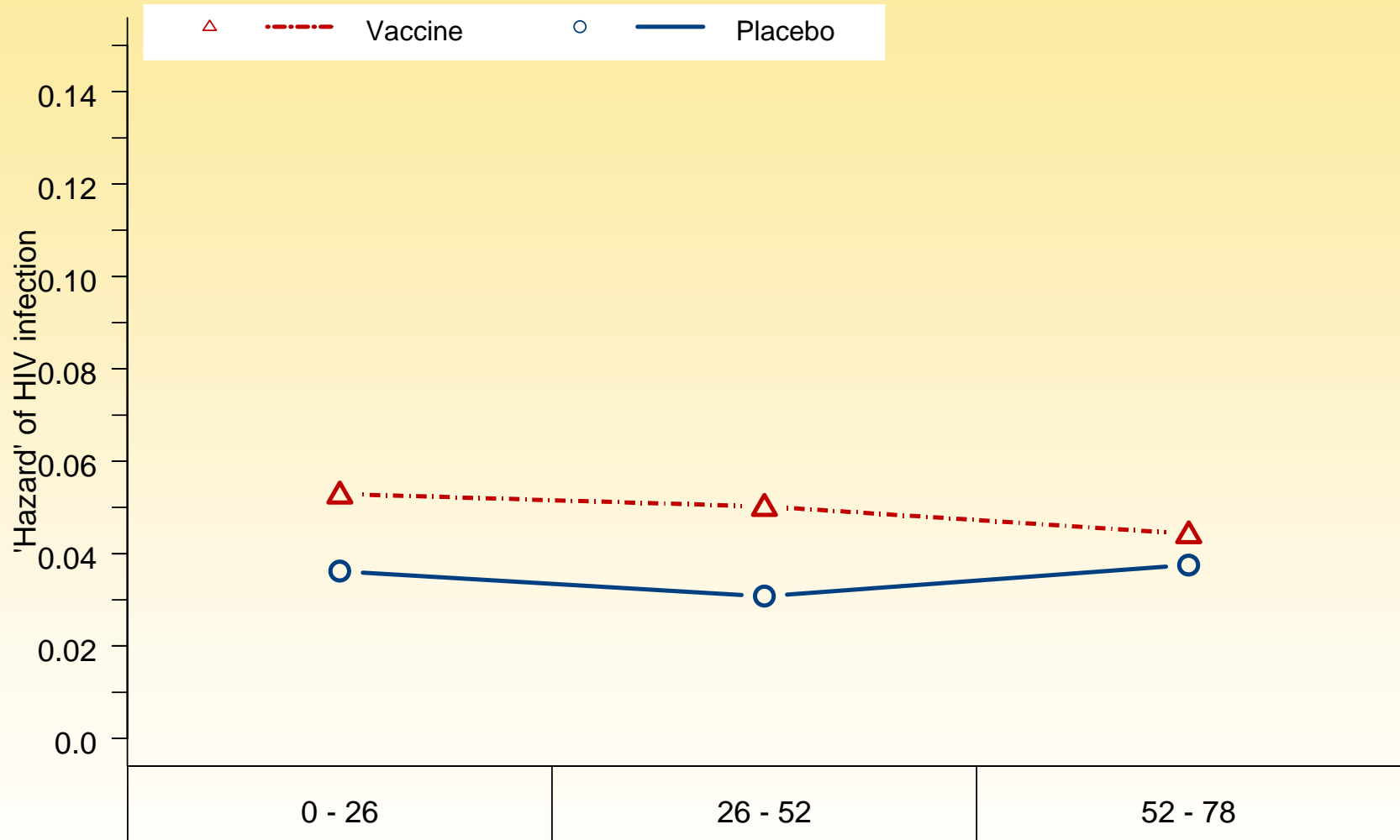
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Summary of slides 20-22

- Larger number of infections in vaccine compared with placebo for
 - Both age categories (≤ 30 , > 30 years)
 - Major racial/ethnic groups (white, multi-racial)
- Too few data to draw conclusions about most racial/ethnic groups
- Relationship of circumcision status to other demographic characteristics (geography, race/ethnicity, Ad5 status) is complex, and underscores the challenge in interpreting individual covariates in isolation

"Hazard" of HIV Infection: MITT population (males)

Rates of HIV infection relatively level for both vaccine and placebo



Events [# Risk]

Time interval (weeks)

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. 12-Nov-2007

Is the effect seen in high Ad5 group due to chance?

- Effect, if real, appears to be concentrated in high Ad5 stratum
- Could chance explain this?
 - Is incidence high in vaccine group or low in placebo group? (Complicated by differences between populations)
 - Study protocol not designed to look at combined data at 1st interim analysis, nor designed to look at high Ad5 separately
- Explore:
 - Biological plausibility through laboratory studies
 - Persistence of differences through ongoing follow-up

To whom do these results apply?

- No evidence of increased infection in women, heterosexual men, but insufficient data to assess
- Small numbers for subgroup analyses
 - Ad5 status correlated with geography, race/ethnicity, circumcision - difficult to tease apart
 - Multivariate analyses will attempt to evaluate when additional data on all major covariates available
 - Multivariate analysis useful for generating hypotheses, will not provide definitive information

Acknowledgments

The Study Volunteers

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

STEP Study Sites

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