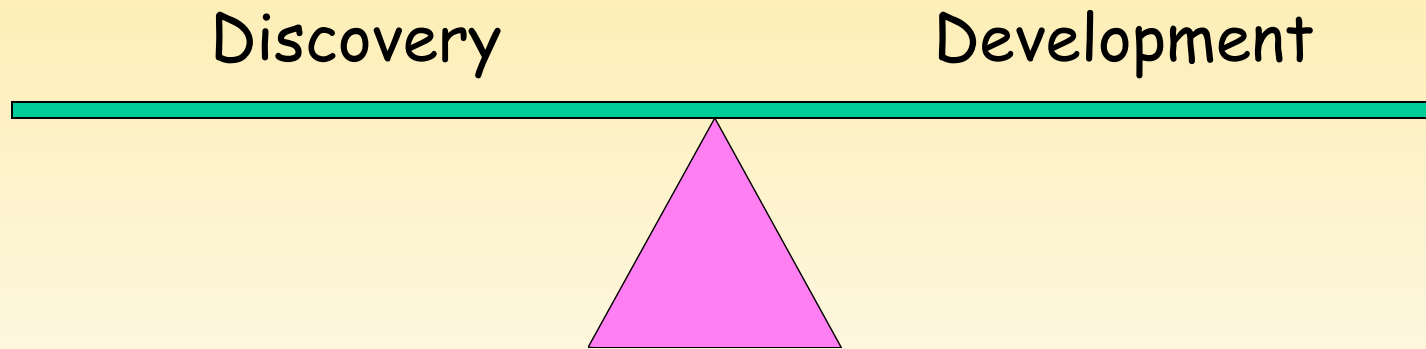


Next Steps:  
The role of efficacy trials in HIV  
vaccine discovery

Susan Buchbinder, MD

San Francisco Department of Public Health  
University of California, San Francisco  
HIV Vaccine Trials Network

# Purpose of efficacy trials



# Test-of concept trials: Step and Phambili

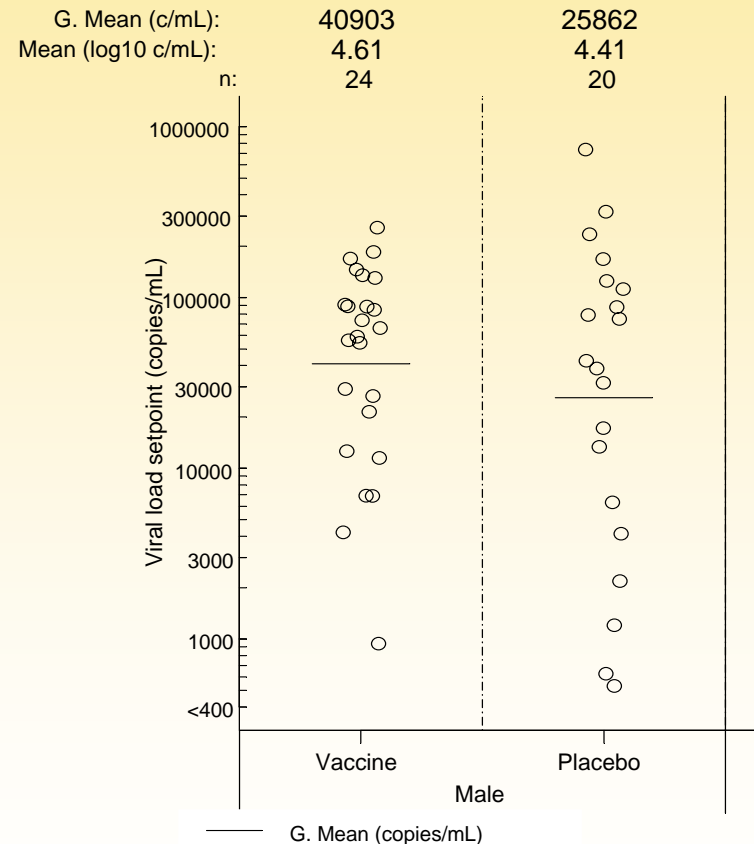
- Step (clade B)
  - Initially 1500 men and women, Ad5 NAb  $\leq$  200
  - Added 1500 men and women Ad5 NAb  $>$  200
- Phambili (clade C)
  - 3000 men and women across Ad5 NAb spectrum
- Questions:
  - "Suite" of test-of-concept trials allowed evaluation of several populations:
    - Baseline Ad5 NAb
    - Gender
    - Clade
  - Explore immune correlates

# Planned Step Interim Analysis: Sept 18, 2007

## MITT Analysis, Ad5 $\leq$ 200

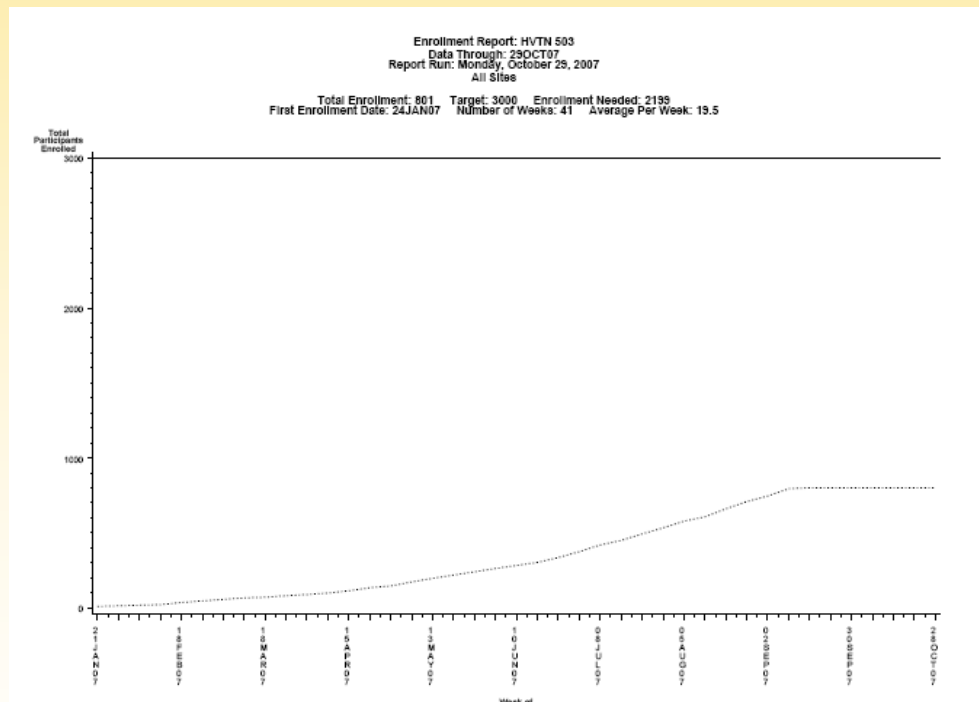
	Vaccine	Placebo
Infections	24	21
Person-years	822	836
Incidence	2.92	2.51

HIV Acquisition



Early viral RNA

# 19<sup>th</sup> September: Phambili

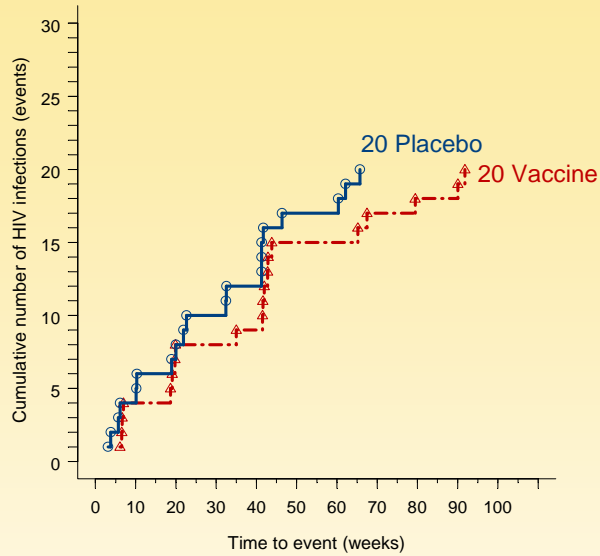


801 enrolled (45% female):

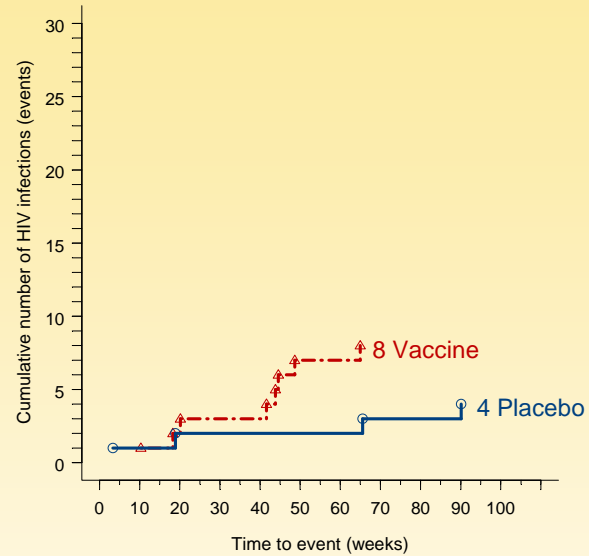
- 3 vaccinations/placebo: 58
- 2 vaccinations/placebo: 501
- 1 vaccination/placebo: 215

# Cumulative Number of HIV Infections: MITT population (males)

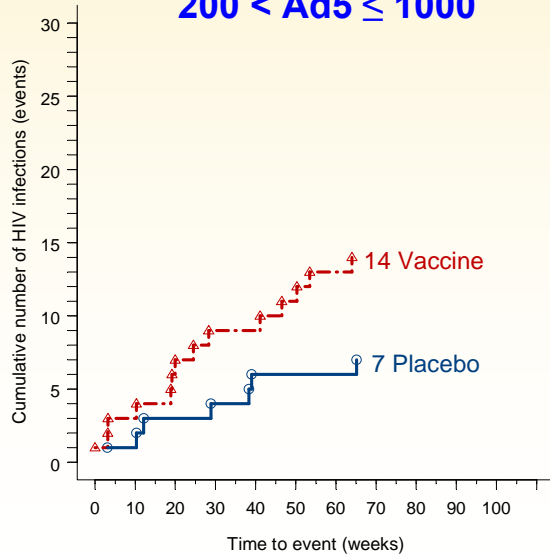
**Ad5  $\leq$  18**



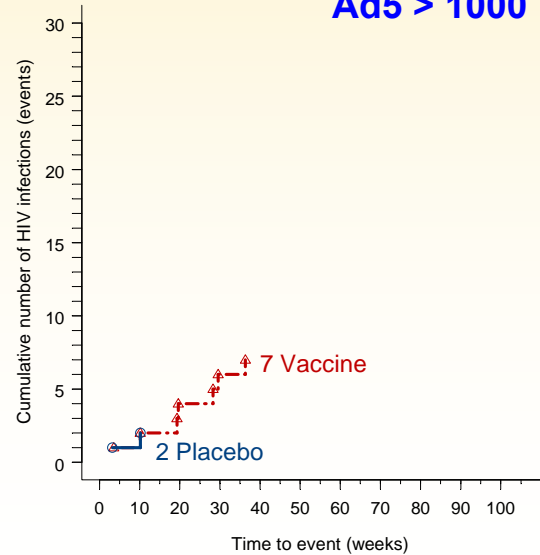
**18 < Ad5  $\leq$  200**



**200 < Ad5  $\leq$  1000**



**Ad5 > 1000**



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)
<b>Overall</b>	<b>4.6</b> (3.4, 6.1)	<b>3.1</b> (2.1, 4.3)	<b>1.5</b> (0.9, 2.4)

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

## Baseline characteristics by Ad5 status

Baseline characteristics	Ad5 <sub>&lt;18</sub> (n=746)	Ad5 <sub>&gt;18</sub> (n=1041)
Race (white)	71%	33%
Age (<30 years)	45%	59%
Location (North America)	87%	46%
History of STD	16%	13%
Unprotected insertive anal sex	63%	57%
Unprotected receptive anal sex	50%	50%
Any drug use	51%	37%
Injection drug use	2%	2%
# male sex partners (past 6 mos)	62%	59%
Circumcised	77%	40%

p<.05

Baseline Ad5 not associated with HIV in multivariate analysis (p=0.3)

## 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

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

<b>MODEL</b>	<b>Baseline Ad5</b>			
	<b>Ad5 ≤18</b> N=746	<b>Ad5 &gt;18</b> N=1041		
<b>Univariate</b>	1.0 (0.5, 1.8)	2.4 (1.2, 4.7)		
<b>Multivariate</b>				
<b>Model 1</b>	<b>1.1</b> (0.6, 2.0)	<b>2.7</b> (1.3, 5.5)		
<b>Model 2</b>	<b>1.1</b> (0.6, 2.0)	<b>3.1</b> (1.5, 6.5)		
<b>Model 3</b>	<b>0.8</b> (0.4, 1.6)	<b>2.6</b> (1.3, 5.4)		
<b>Model 4</b>	<b>0.8</b> (0.4, 1.6)	<b>2.7</b> (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)
<b>Multivariate</b>				
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 $\leq$ 18 N=746	Ad5 $>$ 18 N=1041	Yes N=999	No N=788
<b>Univariate</b>	1.0 (0.5, 1.8)	2.4 (1.2, 4.7)	1.0 (0.6, 1.7)	3.8 (1.5, 9.3)
<b>Multivariate</b>				
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
<b>Univariate</b>	0.7 (0.3, 1.4)	1.6 (0.7, 3.8)	3.3 (0.7, 16)	3.9 (1.3, 11)
<b>Multivariate</b>				
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.

## Ad5 immunity

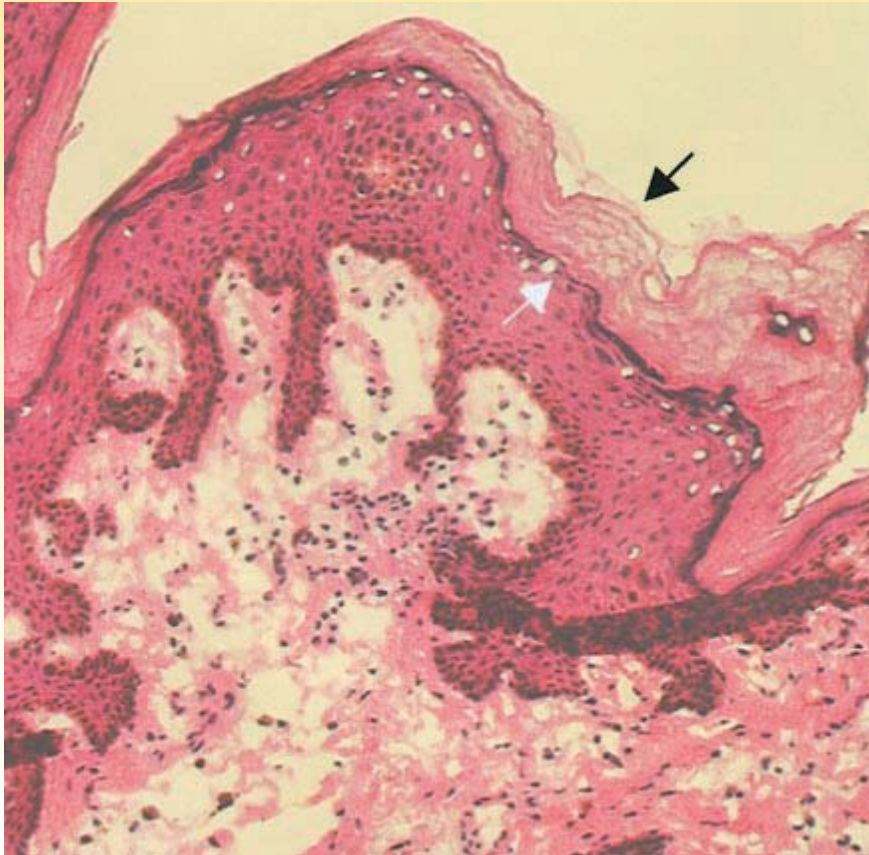
- Emphasized the importance of understanding natural and vaccine-induced immunity to vector
  - Limitation of NHP models
- Evaluate role of Ad5 immunity in HIV acquisition in other cohorts (HPTN 039, MACS)
- Studies to evaluate relationship of pre-existing Ad5 NAb and HIV- and Ad5-specific immune responses
  - Plenary overview (PL01-01)
  - Cytokines (OA05-04)
  - Systems biology (OA09-1)
  - Innate immunity (OA09-03)
  - Cross-reactive Ad5 binding Ab (P04-34)
- Relationship of results to other vectors

# Association of male circumcision (MC) with HIV acquisition risk

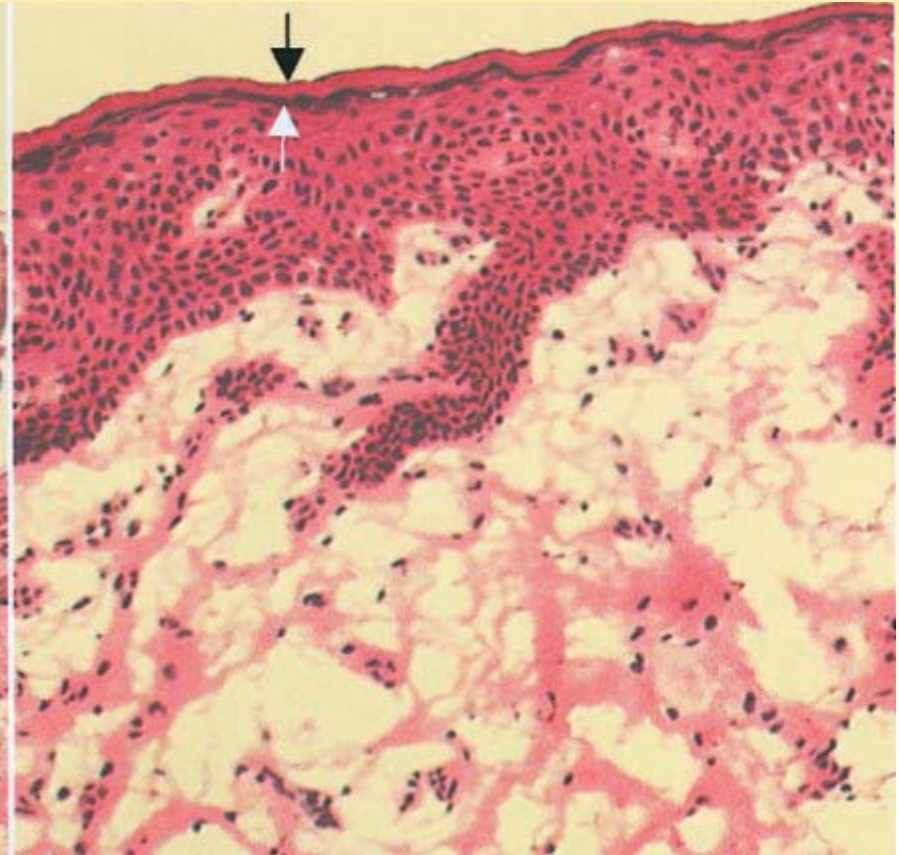
- Heterosexual men
  - Observational studies and 3 RCTs demonstrate MC reduces HIV acquisition risk > 50%
- Men who have sex with men (MSM)
  - Observational studies on association of MC with HIV mixed
  - Likely depends on mix of insertive vs. receptive anal sex
  - Insertive anal sex ~5x less risky than receptive anal sex
    - Studies in US MSM, ~10% of infxns attributable to lack of MC
- Laboratory studies demonstrate role of foreskin in HIV acquisition
  - Keratin layer thin in inner mucosa
  - Target cells abundant in foreskin
  - Possibilities for micro-abrasions

# Keratin in outer and inner foreskin

Patterson AJP 2002

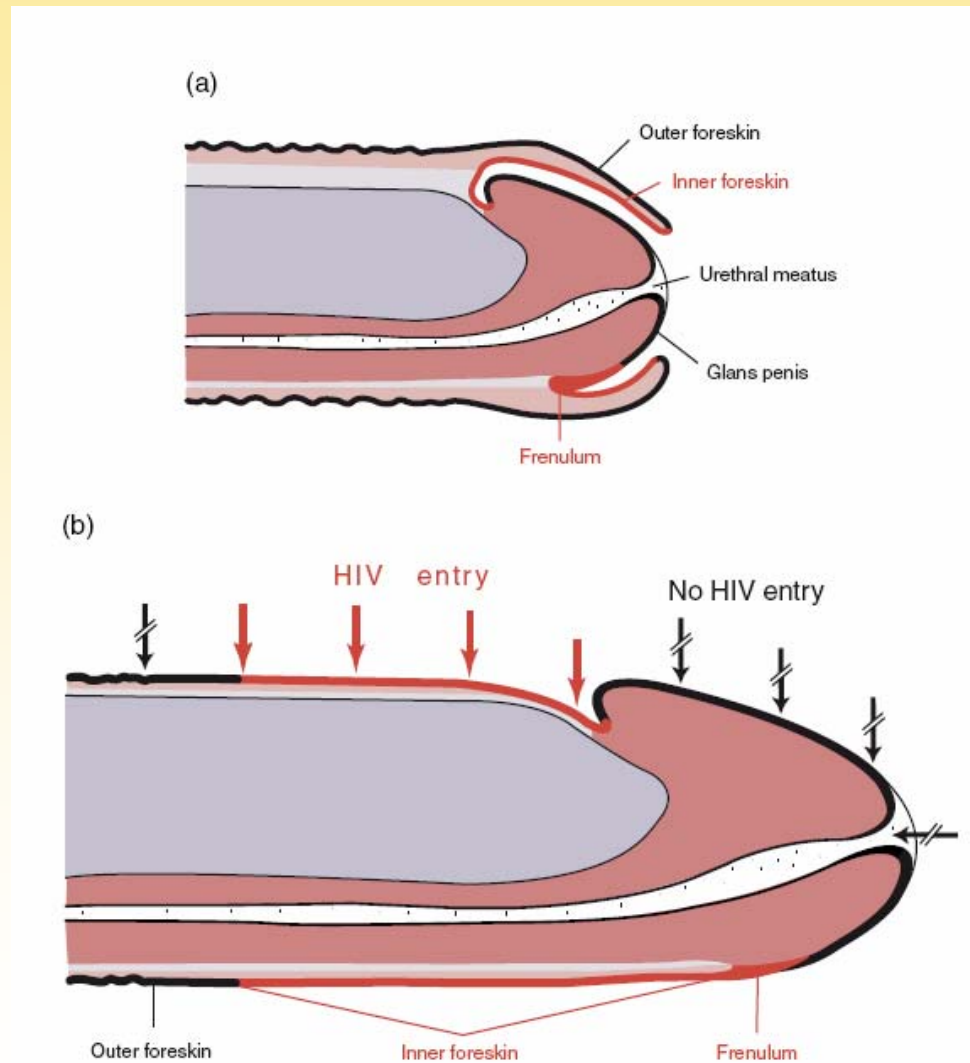


Outer foreskin



Inner foreskin

# Likely locations of HIV acquisition in uncircumcised penis



## Role of baseline unprotected insertive anal sex

Circumcised?	Unprotected <u>insertive</u> anal sex with HIV positive/unknown partner?	N	Hazard ratio (V:P)
Yes	No	359	1.1
Yes	Yes	640	0.9

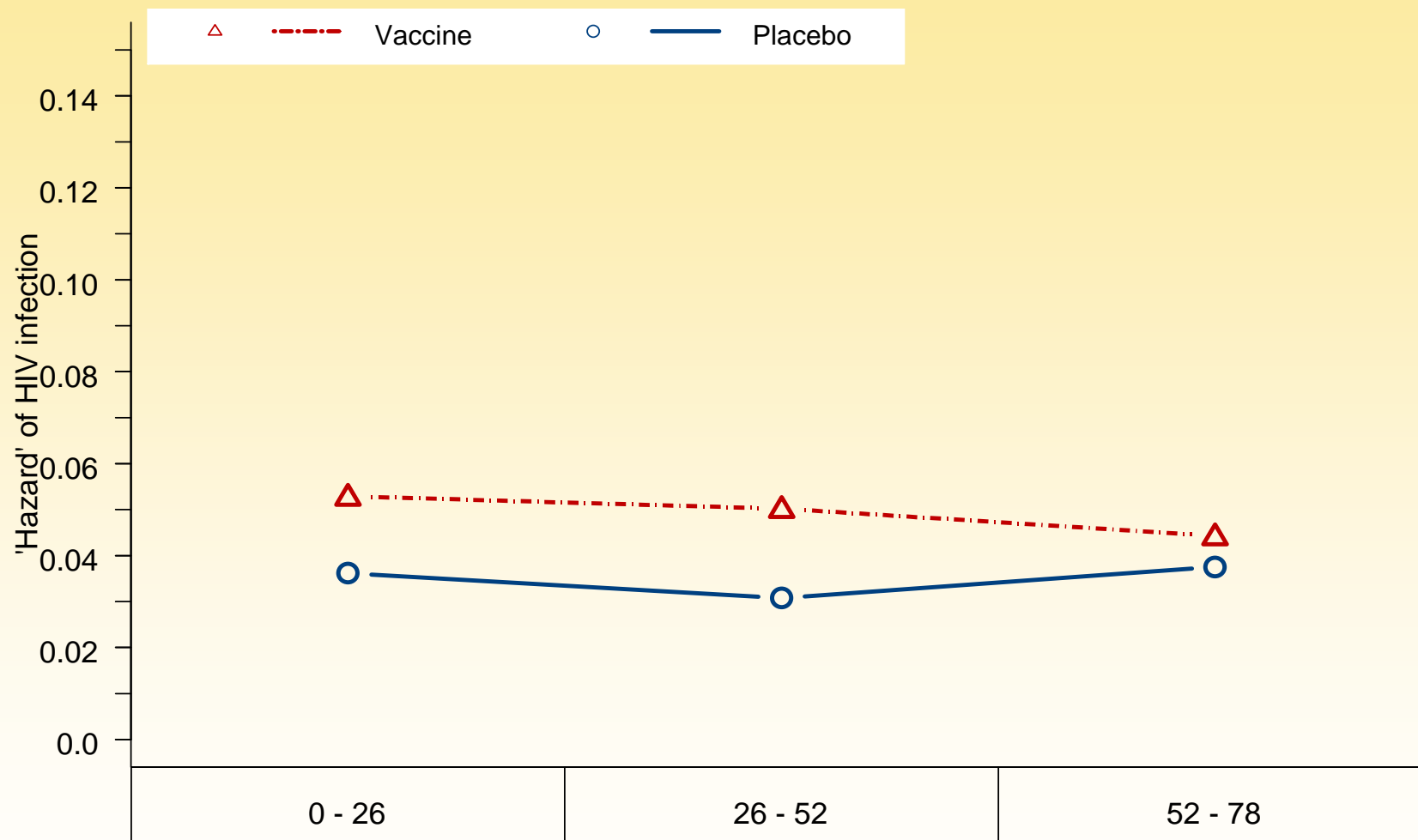
## Role of baseline unprotected insertive anal sex

Circumcised?	Unprotected <u>insertive</u> anal sex with HIV positive/unknown partner?	N	Hazard ratio (V:P)
Yes	No	359	1.1
Yes	Yes	640	0.9
No	No	359	2.5
No	Yes	429	6.1

## How might these associations of increased risk in uncircumcised men be explained?

- Potential confounders (being studied)
  - HSV-2, host genetics, sexual risk over time
  - Sexual networks
- Hypothetical: home activated target cells to foreskin (in Ad5 seropositives)
  - Make "less risky" sexual practice (insertive anal sex) riskier
- Next steps:
  - Evaluate cellular and mucosal specimens in Step/Phambili
  - Additional studies with other vectors in men awaiting circumcision
  - Further emphasis on reliable measures of mucosal immunity

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



# 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.

## Additional data on acquisition

- Follow-up of Step volunteers through 2009
  - Retention ~89% for both vaccinees and placebo recipients
  - Clinical course in infected pts: late-breaker (LB-01)
  - Additional infections analyzed within next several months
  - Additional specimens for laboratory study
    - Mucosal
    - Leukopheresis
  - Additional behavioral data (post-unblinding)
- Follow-up of Phambili participants
  - Presented as late-breaker (LB-02)
    - Evaluate effects in women

## Viral load analyses

- No overall impact on early viral load
- Additional studies
  - Overview presented
    - McElrath plenary
    - Studies underway through SRC (LB-33)
- Question of effects in subgroups
  - Among protective HLA subgroup, VL lower in vaccine than placebo? (P08-10)

# RV144

## Thai/USMHRP Trial

- Canarypox + gp120
- >16,000 men and women in community clinics
  - >100 endpoints
- 7 DMSB meetings to date
  - Safety and futility
- Timeline
  - Enrolled 10/03 - 12/05
  - Final visits 06/09
  - Results announced 10/09

# VRC Candidate HIV Vaccine

Months

0

1

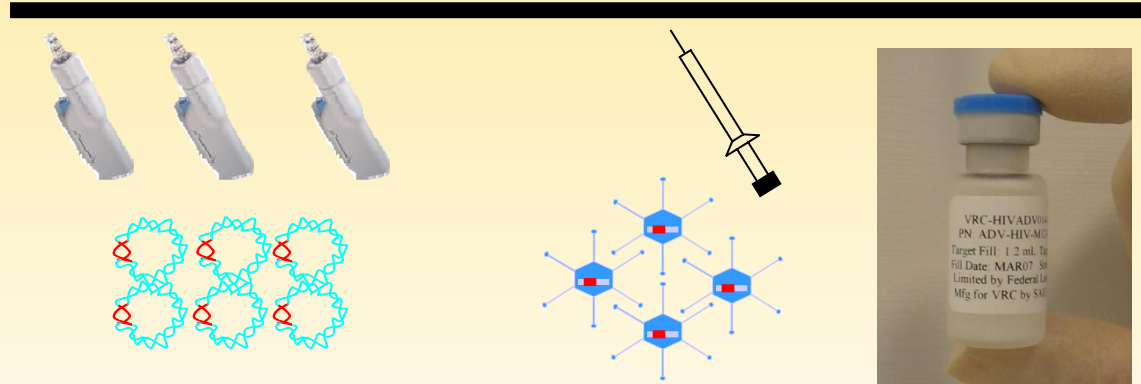
2

3

6

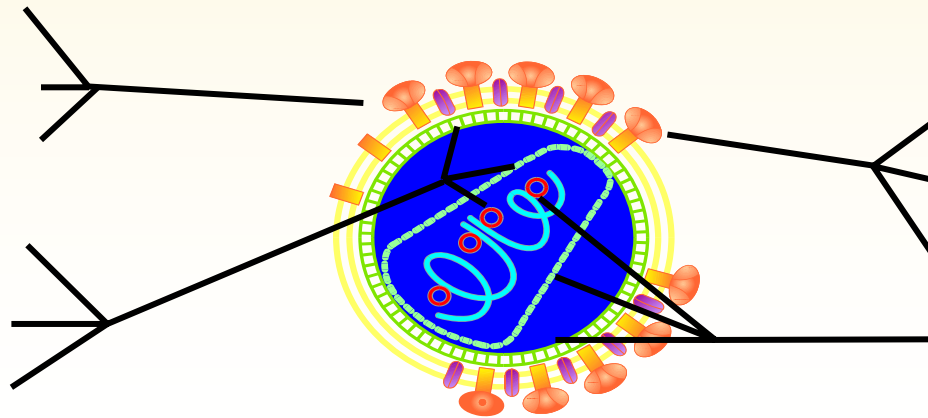
9

12



**CMV-R promoter**

Env A  
Env B  
Env C  
gag B  
pol B  
nef B



**rAd5**

Env A  
Env B  
Env C  
gag/pol B

## PAVE 100 set to launch Sept 2007...



**National Institute of Allergy and Infectious Diseases**  
**National Institutes of Health**

Based on the available scientific information, NIAID has decided that the VRC vaccine regimen did not warrant a trial of this size and scope and that PAVE 100 will not proceed. **However, NIAID will entertain a smaller, more focused clinical trial designed to answer one important question: Does the product have a significant effect on HIV viral load?** If such an effect is noted, then additional studies or expansion of the study to carefully examine immunological correlates could be performed.

**Excerpt from July 17, 2008 NIAID Statement  
“NIAID Will Not Move Forward with the  
PAVE 100 HIV Vaccine Trial”**

## HVTN 505 under development

- Focused test-of-concept trial to evaluate efficacy of DNA/Ad5 regimen on early viral load
- Trial limited to single population to maximize safety, focus efficacy evaluation
  - Ad5 seronegative
  - Circumcised
- US MSM
  - Ad5 seronegative MSM placebo recipients in Step trial had HIV incidence (4.6/100 py)

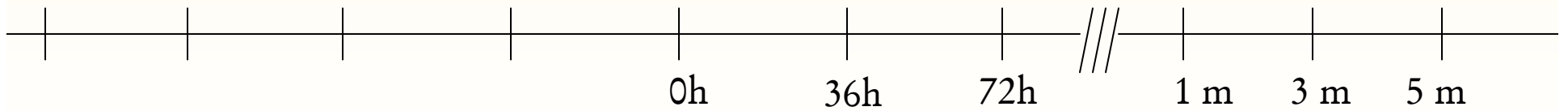
## Proportion of STEP US pts circumcised by race/ethnicity

	N	Circumcised	Uncircumcised	Unknown
White	781	89%	7%	4%
Black	117	79%	14%	7%
Latino	132	48%	48%	4%
Multi-racial	28	86%	14%	--
Other	47	70%	26%	4%

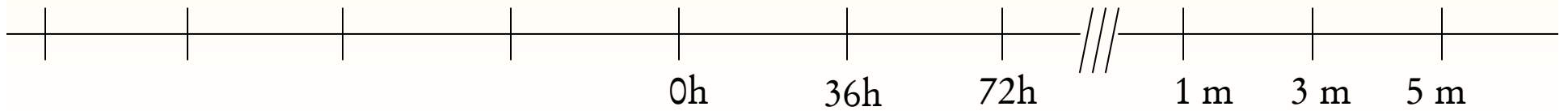
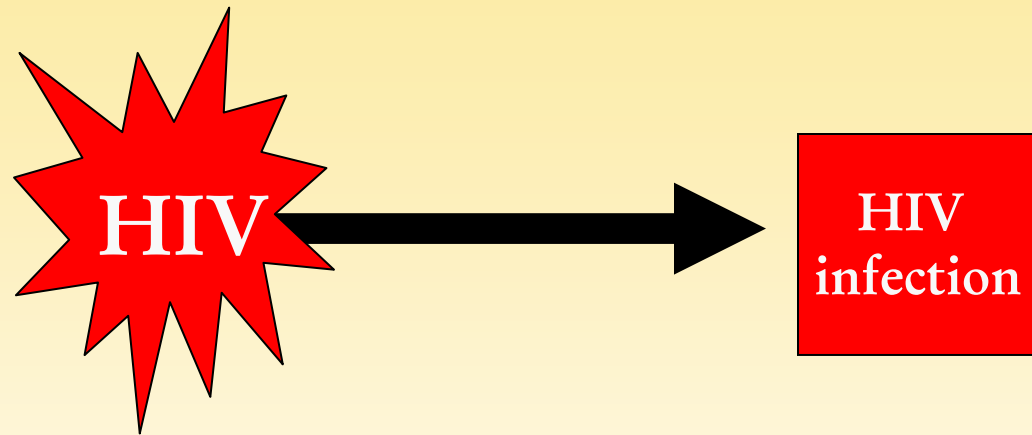
## Challenges in future trials

- Community education, mobilization
- Informed consent
- Impact of community roll-out of HIV interventions that lower HIV incidence in communities
  - ART
  - Male circumcision
- Impact of interventions that lower incidence in trial participants if become "standard"
  - E.g., Pre-exposure prophylaxis (PrEP)

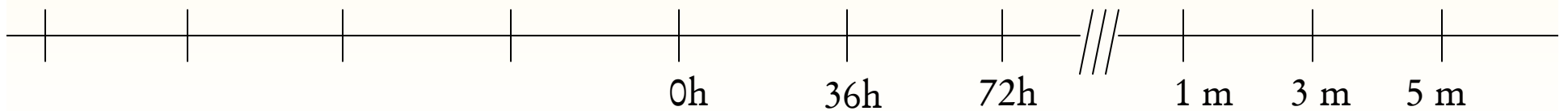
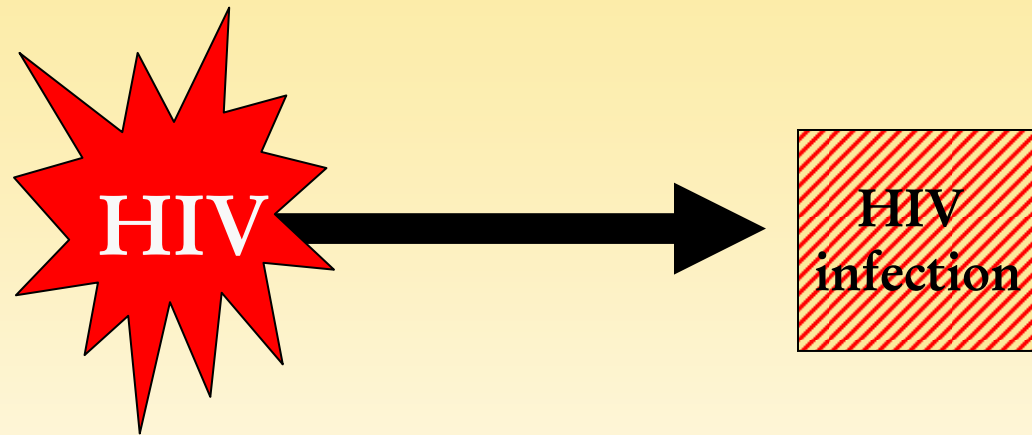
## Pre vs. Post-exposure prophylaxis



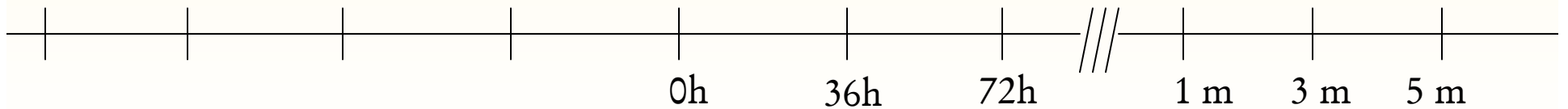
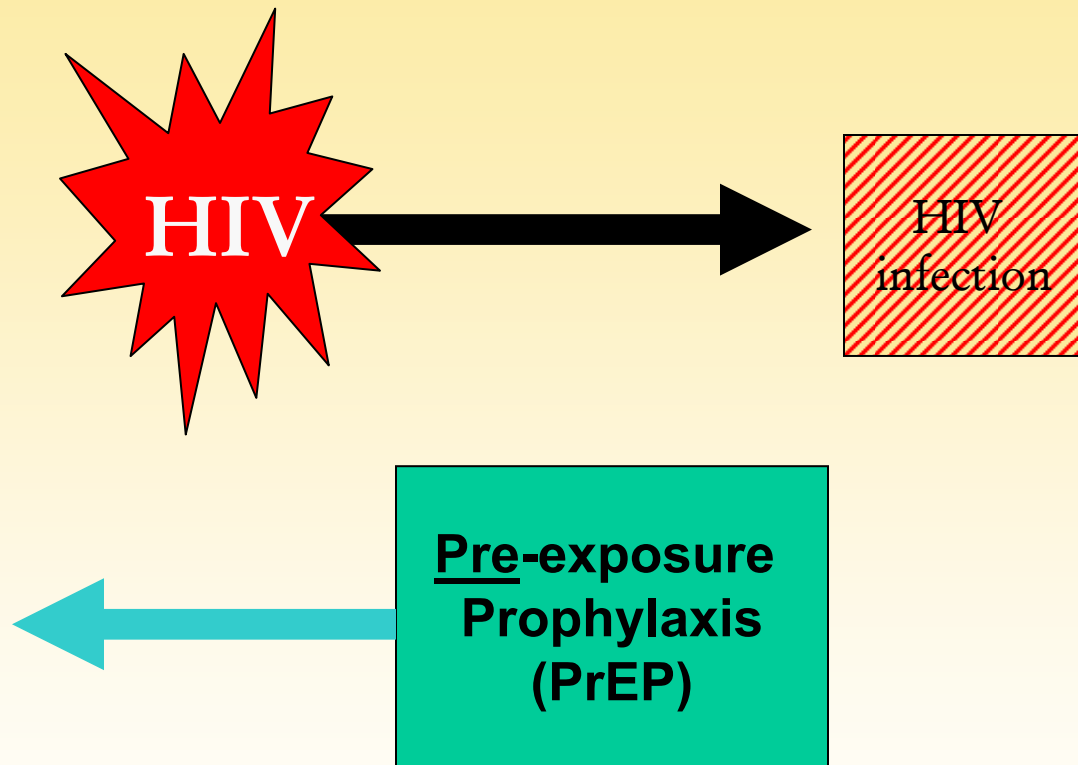
## Pre vs. Post-exposure prophylaxis



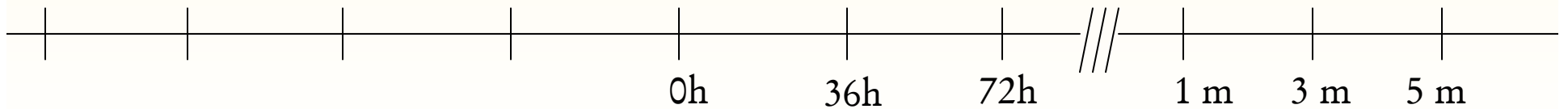
## Pre vs. Post-exposure prophylaxis



# Pre vs. Post-exposure prophylaxis



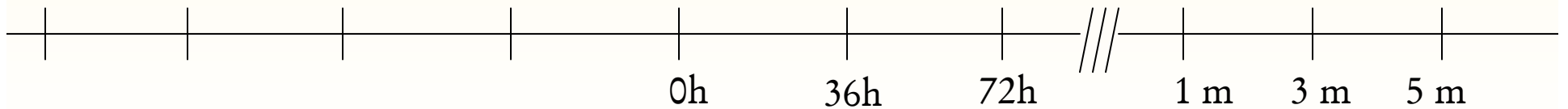
## Pre vs. Post-exposure prophylaxis



## Pre vs. Post-exposure prophylaxis



**Pre-exposure  
Prophylaxis  
(PrEP)**



# Pre-Exposure Prophylaxis trials (Current)

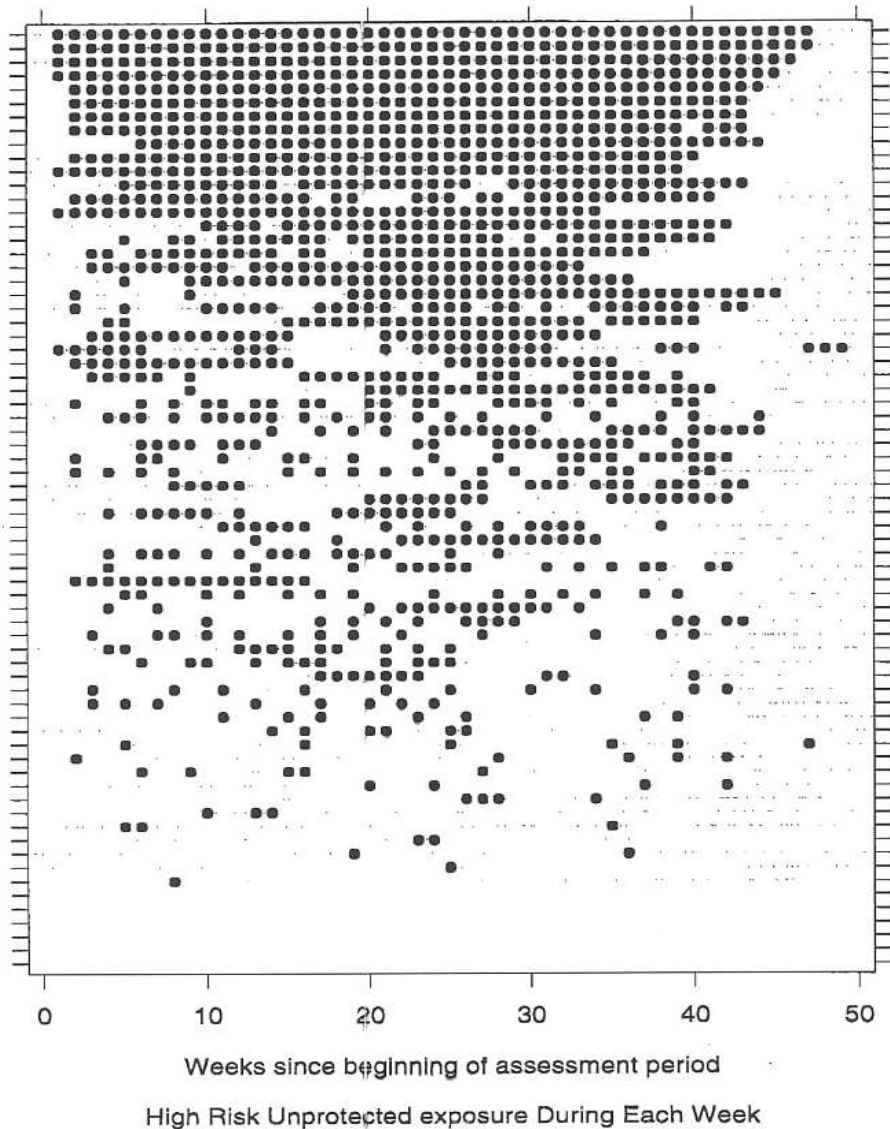
Sponsor/ Study Name	Product	Site	N	Study population	End date
CDC	Oral TDF	USA	400	MSM	2009
CDC	Oral TDF	Thailand	2400	IDU	2010
CDC	TDF/FTC	Africa	2000	Heterosexual men & women	2010
NIH iPrEX	TDF/FTC	S America, N America, Africa, Asia	3000	MSM	2010
UW Partners	Oral TDF vs. TDF/FTC	Africa	3900	Serodiscordant couples	2011
FHI FEM-PrEP	TDF/FTC	Africa	3900	Women	2012
NIH MTN VOICE	Vaginal tenofovir vs. oral TDF vs. TDF/FTC	Africa	4200	Women	2012

# Planning for PrEP trial results

- Hopeful, but cautious
- Need to understand results of trials
  - Efficacy for whom?
  - Why/when do breakthroughs occur?
  - Adherence?
  - Durability?
  - Risk compensation?
- Additional trials
  - Alternative drugs
  - Alternative dosing

## Changing Landscape

- Celebrate any breakthrough in effective prevention strategies
- All prevention efficacy trials tested against proven strategies
  - When efficacious vaccine, it will become standard
- PrEP: particular concerns about high efficacy but low access
- Focus vaccine efficacy trials on populations for whom existing strategies insufficient



- Calendar-based retrospective history on newly infected MSM
- “Susceptible” period from 3 months before last negative to first HIV positive test
- Each row represents a newly infected MSM
- Each dot represents a report of at least one unprotected anal or oral sex contact with HIV positive or unknown partner

# Opportunities

- Combination prevention approaches (Roundtable 01)
  - Evaluating synergies of vaccines with PrEP and/or microbicides
- Novel trial designs
  - Run in periods
  - Non-inferiority
  - "Structured prevention interruption"

## Summary

- Step and Phambili test of concept trials rapidly altered HIV vaccine field, contributing to discovery
  - 33 months after FPI, definitively addressed objectives
  - Raised important questions for the field couldn't have been anticipated or addressed in NHP models
  - Interesting leads about protection in subgroups
  - Rich source of data, specimens, and questions
- HIV prevention field is rapidly evolving
  - Promising interventions
  - Challenging trial designs
  - Ultimate goal - reduce new HIV infections and disease

# Acknowledgments

## The Step and Phambili Study Volunteers

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

# Acknowledgments

- Step and Phambili investigators, staff
- Larry Corey
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