Women and AMP in Africa Study Design Discussion

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AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:

The AMP Studies:

HVTN 704/HPTN 085

(2700 MSM and TG in the Americas)

HVTN 703/HPTN 081

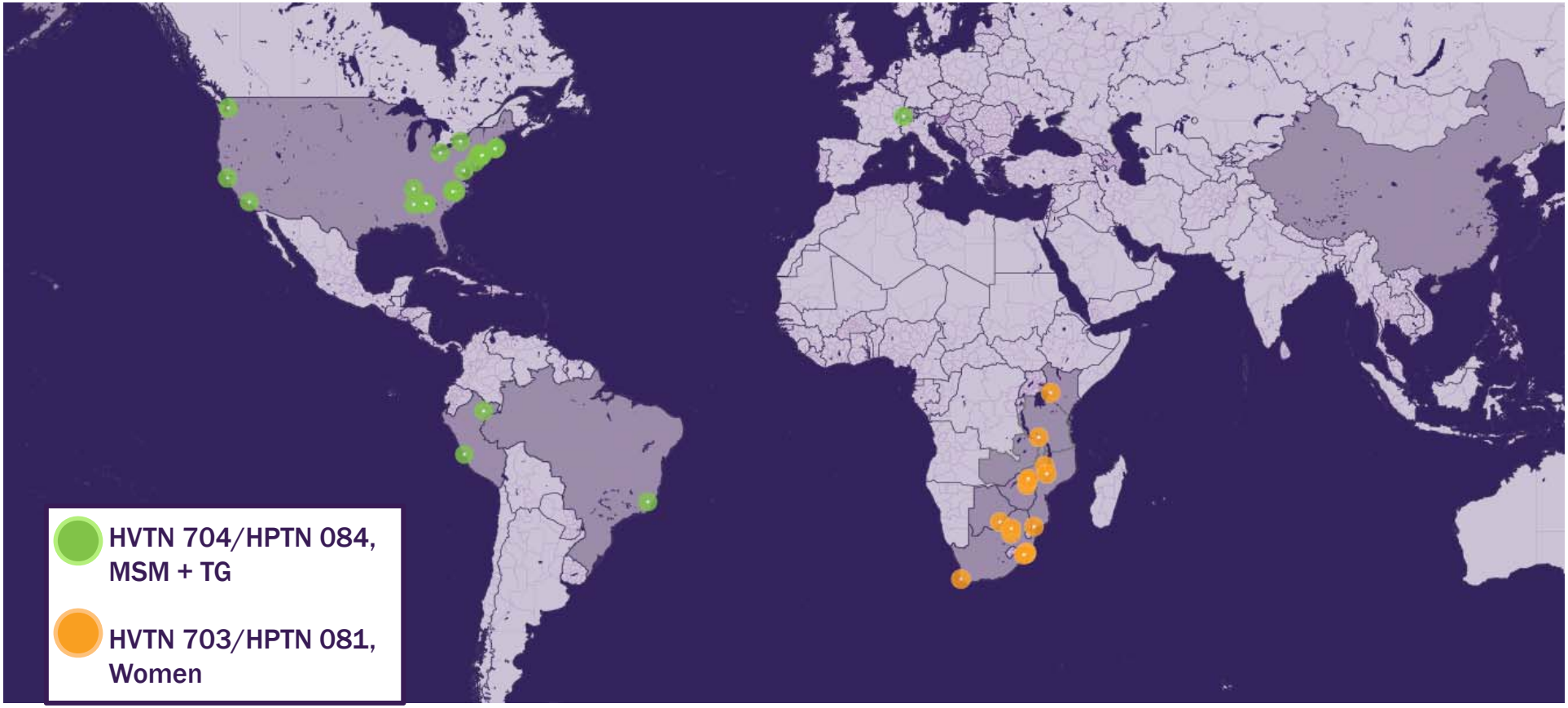
(1500 Women in sub-Saharan Africa)

The AMP Studies

Being conducted by the
HIV Vaccine Trials Network and the
HIV Prevention Trials Network,
in partnership with their combined clinical trial sites.

AMP Study Research Sites

(As of January, 2017)



HPTN
HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK

The AMP Study: Objectives & Endpoints

PRIMARY

- **Safety & Tolerability of VRC01 infusion**
  - Reactogenicity, AEs, SAEs, discontinuation rates
- **Efficacy to prevent HIV infection**
  - HIV infection by week 80 in those HIV-negative at enrollment

SECONDARY

- **Develop a marker(s) of VRC01 that correlates with the level and antigenic specificity of efficacy**
  - Serum VRC01 concentration
  - Serum mAb effector functions
  - Breakthrough HIV infection sequences
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants

The Main AMP Study Questions

- Is the VRC01 antibody safe to give to people?
- Are people able to "tolerate" the antibody without becoming too uncomfortable?
- Does the antibody lower people's chances of getting infected with HIV?
- If the antibody does lower people's chances of getting infected with HIV, how much of it is needed to provide protection from HIV?

Study Schema for The AMP Studies

HVTN 704/HPTN 085

HVTN 703/HPTN 081

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	500	1300	10 infusions total - given every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	900	500	1300	
Control	900	500	1300	
Total	2700	1500	4200	

MSM+TG AMP Schema: HVTN 704/HPTN 085

			Infusion schedule (Weeks) [A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80♦	W92†
Group 1	VRC01 10 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		
	Total:	2700 (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 control)												

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.
† Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 450 enrolled participants. Infusions for those 450 participants will continue while the interim safety assessment is conducted. Following enrollment of the 450th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete, reviewed by the DSMB, and submitted to the US FDA. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory.

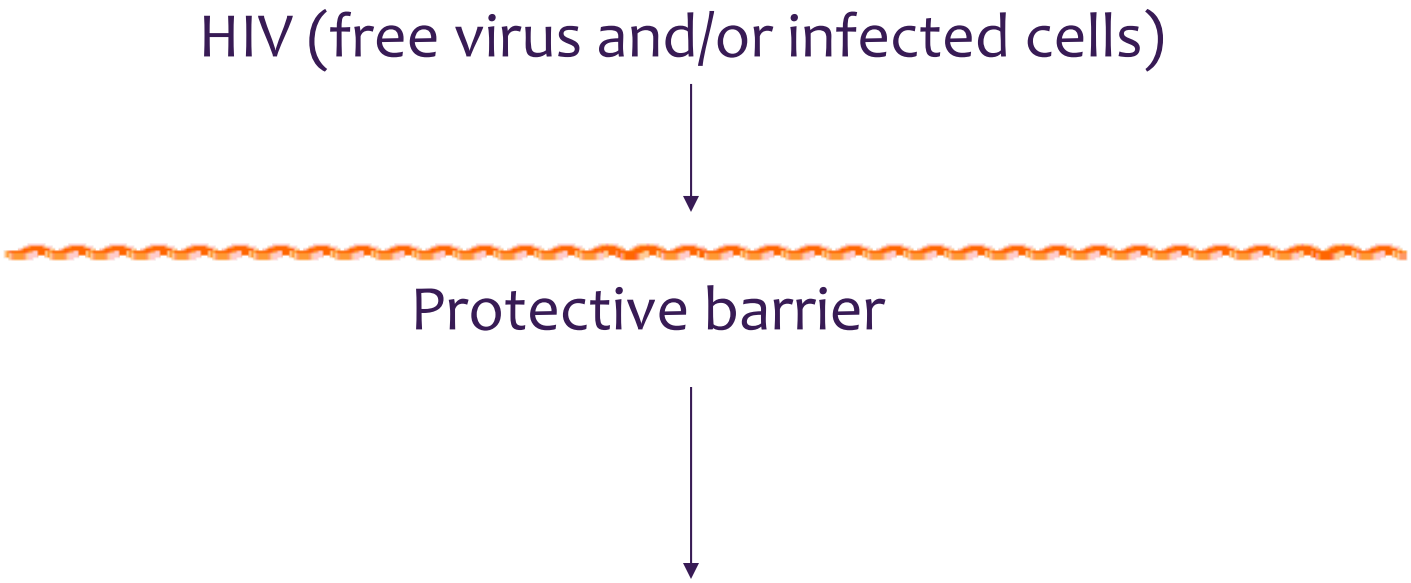
SSA Women AMP Schema: HVTN 703/HPTN 081

			Infusion schedule (Weeks) [A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80♦	W92†
Group 1	VRC01 10 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	500	C	C	C	C	C	C	C	C	C	C		
	Total:	1500 (500 VRC01 30 mg/kg; 500 VRC01 10 mg/kg; 500 control)												

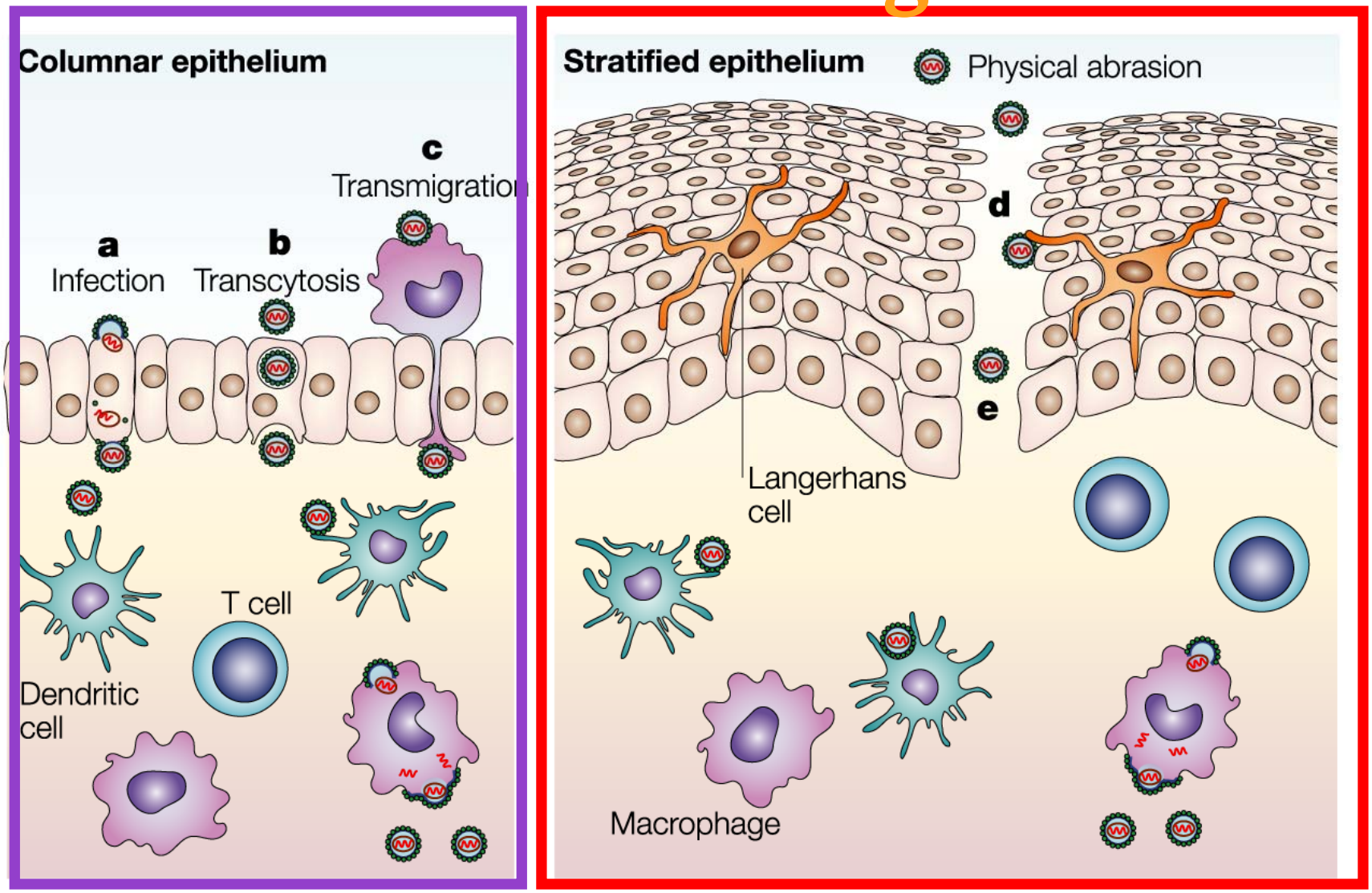
♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.
† Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

*An interim safety assessment will be performed through the Week 24 visit for the first 300 enrolled participants. Infusions for those 300 participants will continue while the interim safety assessment is conducted. Following enrollment of the 300th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete and reviewed by the DSMB. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory. Data from VRC01 administration in HVTN 704/HPTN 085 may inform the safety assessment in HVTN 703/HPTN 081.

A Model for Discussing HIV Risk



A Model for Discussing HIV Risk



Shattock and Moore 2003

What increases the risk of HIV infection?

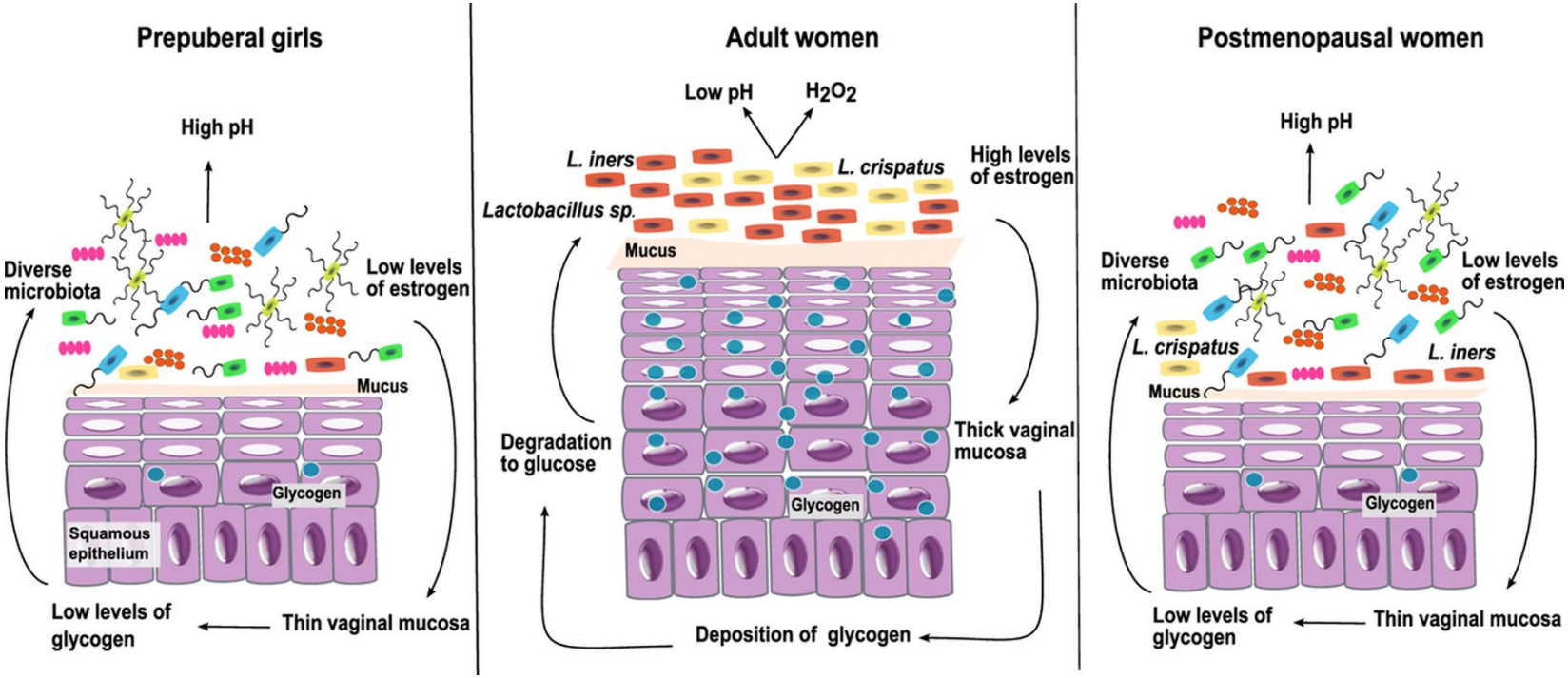
Mechanism	Examples
Increased amount of HIV	Increased viral production Type of body fluid
Breakdown of natural barrier	Trauma Inflammation Immune, genetic factors (?) Hormonal contraception
Larger pool of susceptible cells	Inflammation Genetic factors

Why are young women so vulnerable to HIV?

- Low sexual frequency but high risk sex
- ? Partners are recently infected men 5-10 years older
- Low condom use
- Biologic vulnerability of the genital tract, potentially including:
  - Ectopy - larger surface area of vulnerable cells exposed?
  - Increased HIV co-receptors in cervical cells
  - Recent HSV-2 infection
  - Intra-vaginal practices
  - Trauma during sex

Caelum, C, 2016

Changes in the vaginal mucosae during different stages of a woman's life



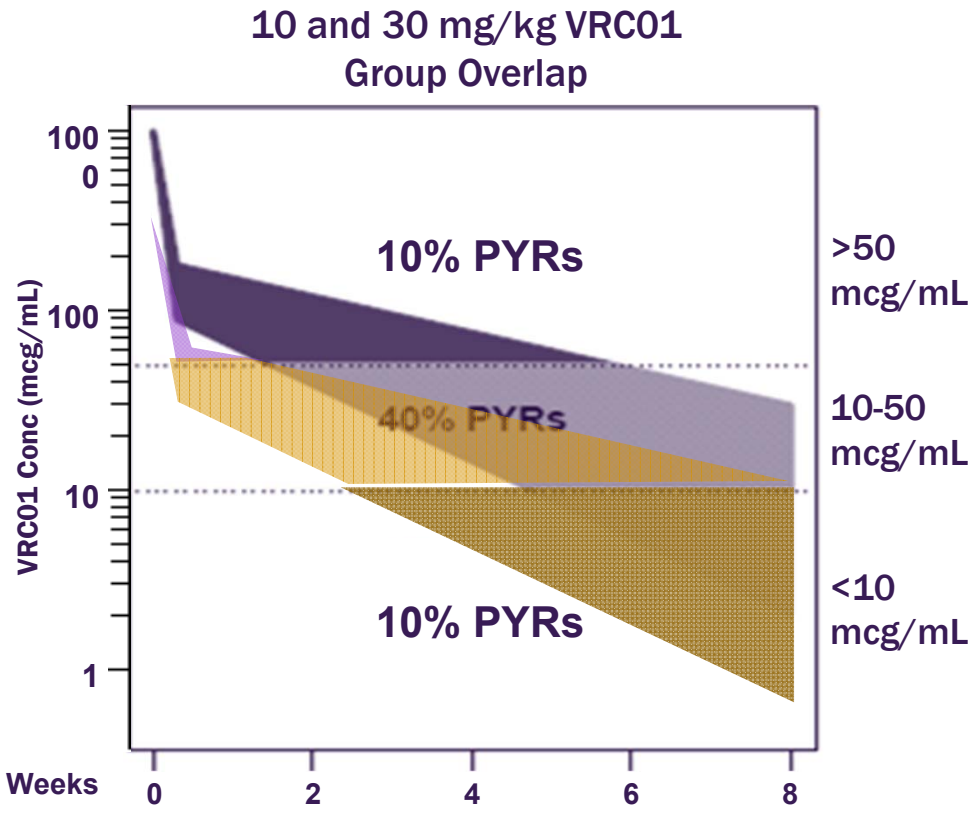
Rationale for 2 Cohorts

- As these are Test-of-Concept trials we selected the two populations in which novel biomedical interventions are needed
  - MSM + TG
  - Heterosexual women in sub-Saharan Africa
- We suspect that route of acquisition and genital tract immunology and anatomy may influence the distribution of VRC01 and potential efficacy

Rationale for 3 Arms

- The primary analysis compares the combined VRC01 group vs. control, therefore having similar sample size as a 2-arm trial
- Assessment of PE at two doses provides data for modeling how PE would change given a new dose and/or schedule
- Multiple doses improves assessment of correlates of protection

Two Dose Groups: Overlapping Serum Concentrations



	10 mg/kg	30 mg/kg	Overlap
High (>50 mcg/mL)	10% PYRs	50% PYRs	**10% PYRs**
Medium (10 to 50 mcg/mL)	40% PYRs	40% PYRs	**40% PYRs**
Low (<10 mcg/mL)	50% PYRs	10% PYRs	**10% PYRs**
Total Overlap = 60% PYRs or Person Years at Risk			

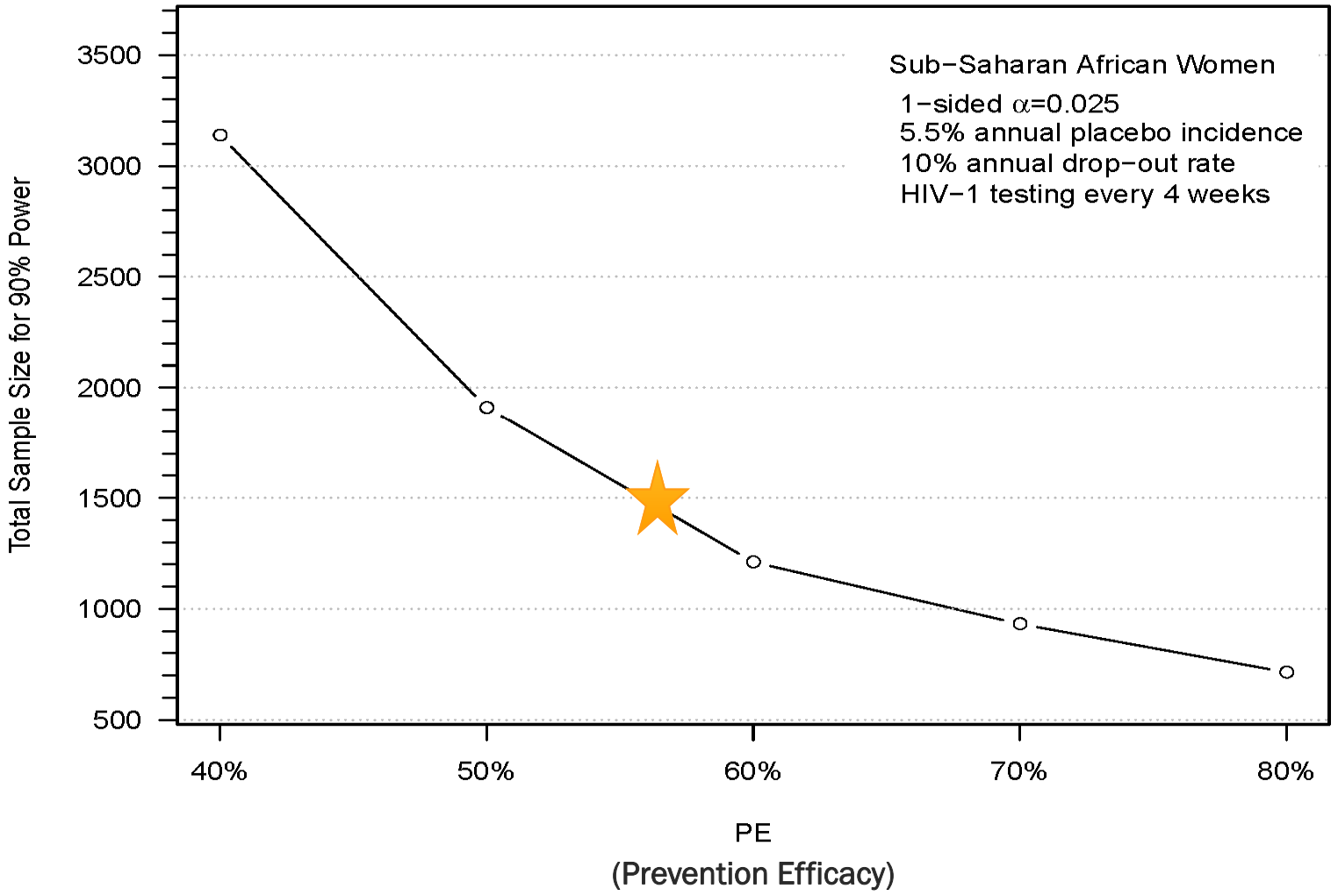
Trial Design Rationale

- Passive administration of VRC01 antibody will reduce acquisition of HIV infection in high risk populations
- Doses selected will determine the activity of the antibody across a range of serum concentration in diverse populations across multiple geographic regions of the world
- Level of VRC01 antibody required for protection will vary by type of sexual exposure
- Concentration of antibody in serum will be directly associated with the rate of protection; that is, higher levels of antibody will give greater rates of protection than lower levels
- Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization.

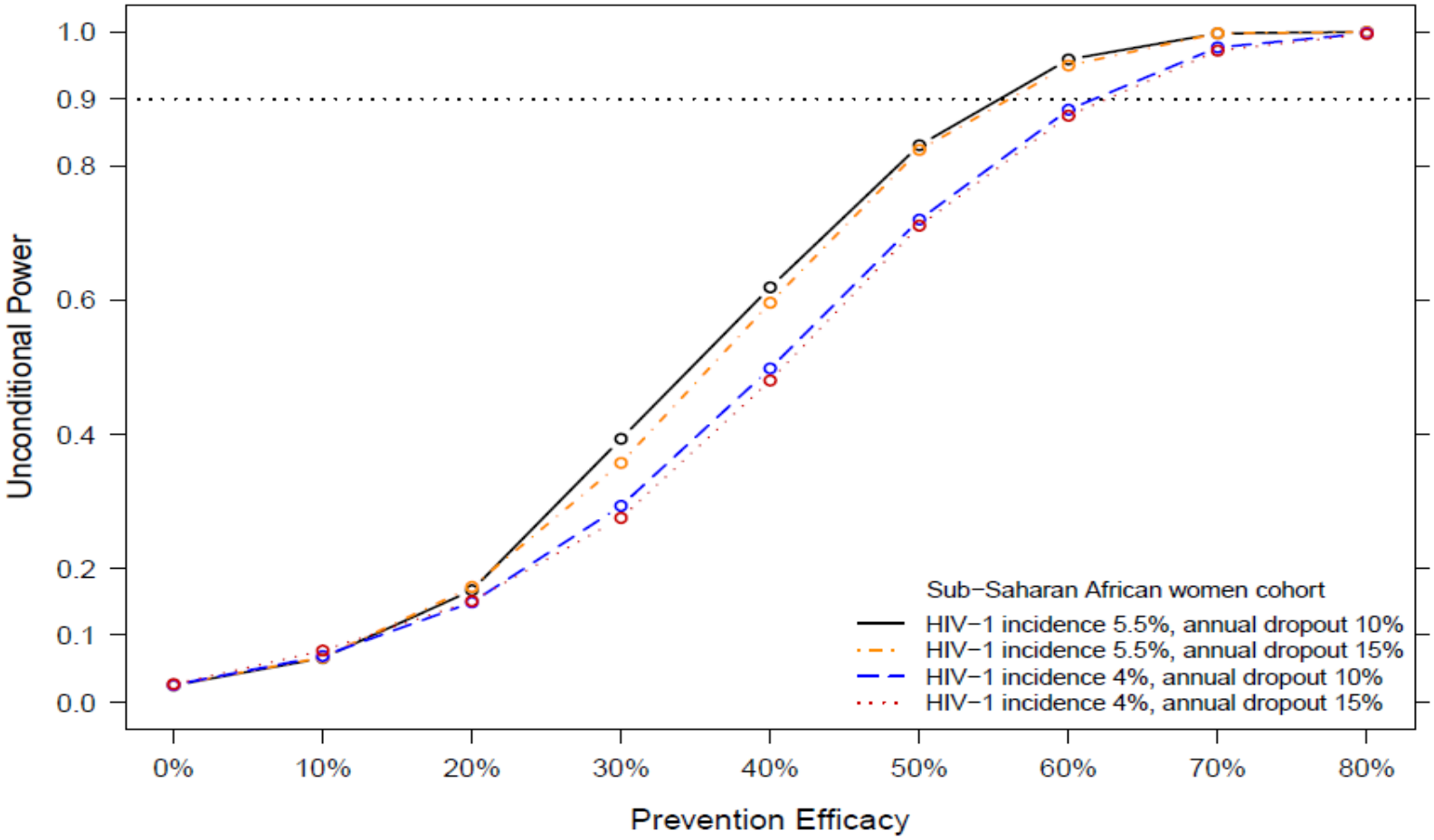
Assumptions for Sample Size Calculations

- The two trials have identical statistical designs and analysis plans
- Each trial powered to detect 60% (vs. 0%) prevention efficacy
- Incidence
  - 5.5% annual HIV-1 incidence in the sub-Saharan African women placebo group
  - 3% annual HIV-1 incidence in the MSM+TG placebo group
- ~30 month uniform accrual period
- Q4-weekly visits for HIV-1 diagnostic tests
- 10% annual dropout incidence in each study group

Sample size selection for SSA women



Sample size & power calculations are robust over a range of HIV incidence & dropout assumptions: WOMEN



HVTN 704/HPTN 085: Select Eligibility Criteria

- **Men & transgender people who have sex with men, 18-50 years of age**
- **HIV uninfected**
- **Risk behavior related criteria:**
  - Male or TG who has had condomless anal intercourse with ≥ 1 male or TG partner(s) or any anal intercourse with ≥ 2 male or TG partners in the past 6 months
  - All volunteers in a mutually monogamous relationship with an HIV(-) partner for > 1 year are excluded.
- **Volunteers with clinically significant medical conditions are excluded**

HVTN 703/HPTN 081: Select Eligibility Criteria

- Heterosexual Women, 18-40 years of age
- HIV uninfected
- Risk behavior related criteria:
  - Female who has had vaginal or anal intercourse with a male partner in the past 6 months
  - All volunteers in a mutually monogamous relationship with an HIV(-) partner for > 1 year are excluded.

- Volunteers with clinically significant medical conditions are excluded

AMP Study Procedures

- **IV**: receive an IV over a 30-60 minute period every 8 weeks (10 times total)
- **Blood draw**: get a blood draw at the clinic every 4 weeks (includes an HIV test)
- **STI testing**: get STI testing (urine and rectal swabs) about every 6 months
- **Questionnaires**: complete questionnaires about sexual behavior & general health every 4-8 weeks

STUDY DURATION: about 22 months

AMP Studies: Summary

- 1st large scale, phase 2b studies with an IV intervention for HIV prevention in men & women
- 1st efficacy trials with an anti-HIV mAb
- Cross-Network collaboration: HVTN & HPTN
- Global trials in 2 cohorts on 4 continents
  - 2700 MSM + TG in North & South America (Clade B)
  - 1500 Women in sub-Saharan Africa (Clades C, A, D)

AMP Protocol Team

- Chairs: Larry Corey & Mike Cohen
- co-Chairs: Sri Edupuganti & Nyaradzo Mgodi
- Protocol Team Leader & Core Medical Monitor: Shelly Karuna
- DAIDS Medical Officers: Marga Gomez & David Burns
- Statisticians: Allan DeCamp, Deborah Donnell, Peter Gilbert, Michal Juraska, Nidhi Kochar
- Laboratory Representatives: John Hural, Sue Eshleman, On Ho, David Montefiori, Vanessa Cummings, Estelle Piwowar-Manning
- VRC Representatives: Julie Ledgerwood, Barney Graham, John Mascola
- Investigator Representatives: Ken Mayer, LaRon Nelson, Erica Lazarus
- Social & Behavioral Scientist: Michele Andrasik
- DAIDS Protocol Pharmacist: Katherine Shin
- Regional Medical Liaisons: Simba Takuva & Robert De La Grecca
- Clinical Safety Specialist: Maija Anderson
- Protocol Development Manager: Carter Bentley
- FHI360/HPTN LOC Director: Niru Sista
- Senior Research Clinician: Phil Andrew
- Clinical Research Manager: Liz Greene
- Clinical Trials Manager: Carissa Karg
- SDMC Representatives: Lynda Emel, Gina Escamilla
- Regulatory Affairs Representative: Meg Brandon
- Communications Representatives: Jim Maynard & Eric Miller
- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Deb Dunbar, Ana Rimachi, Christie Heiberg
- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab


THANK
YOU