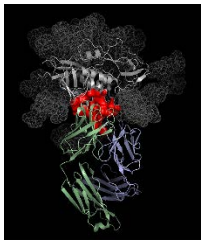
Antibody Mediated HIV Prevention: The AMP Studies



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MTN Regional Meeting
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Outline of this Presentation

- VRC01 monoclonal antibody
- AMP Trial Design considerations
  - Study Population
  - Selection of sample size
  - Selection of dose and schedule of VRC01
- Eligibility criteria
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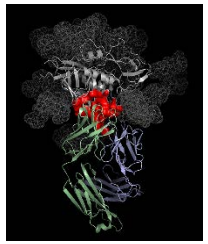
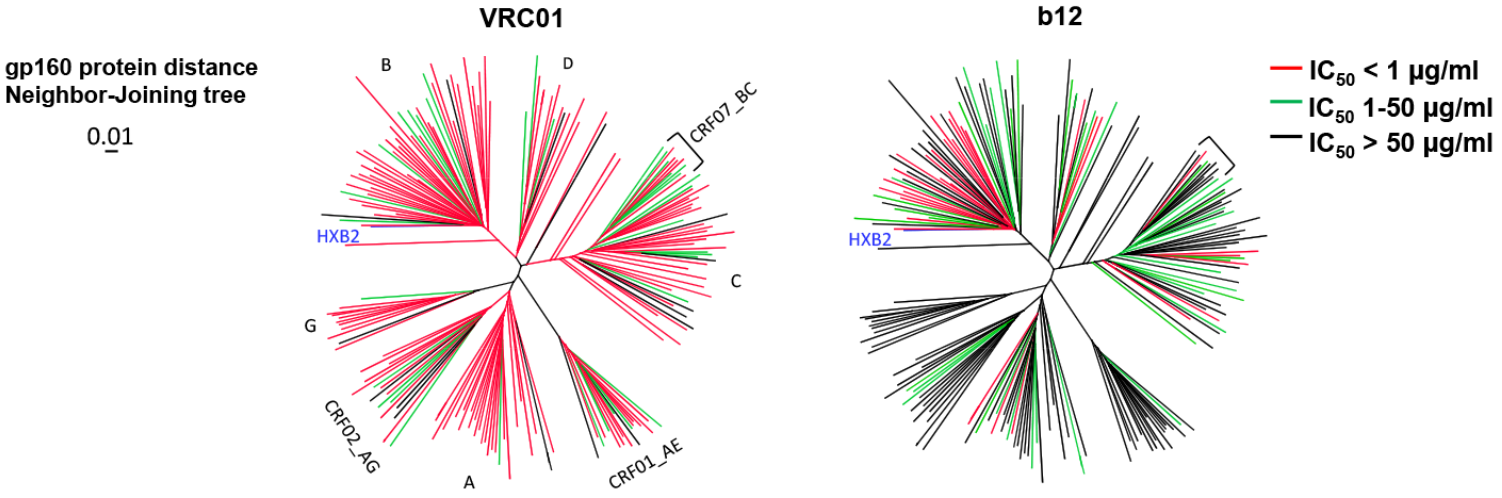
VRC01: Passive Antibody Protection

- Antibodies have been isolated which can neutralize a broad range of HIV strains in vitro
- Hope for antibody-mediated prevention (AMP) of HIV.
- The first antibody to enter advanced human clinical trials is VRC01
- Discovered in an elite viral controller
- Developed by John Mascola & colleagues at the Vaccine Research Center of the National Institutes of Health
- It is a human monoclonal antibody targeting the HIV-1 CD4 binding site.



VRC01 is Broadly Neutralizing



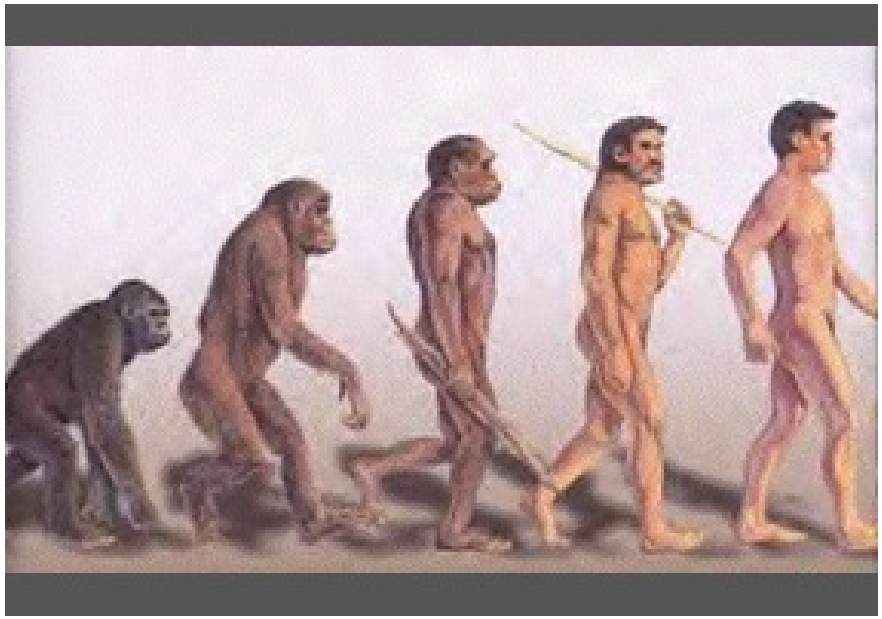
Virus clade	Number of viruses	IC50 < 50 µg/ml		IC50 < 1 µg/ml	
		VRC01	b12	VRC01	b12
A	22	100%	45%	95%	23%
B	49	96%	63%	80%	39%
C	38	87%	47%	66%	13%
D	8	88%	63%	50%	25%
CRF01_AE	18	89%	6%	61%	0%
CRF02_AG	16	81%	19%	56%	0%
G	10	90%	0%	90%	0%
CRF07_BC	11	100%	27%	45%	9%
Other	18	83%	33%	78%	6%
Total	190	91%	41%	72%	17%

Panel of 190 Diverse Viral Isolates

Thanks to Barney Graham and Wu et al. Rational design of envelope identifies broadly neutralizing human monoclonal Antibodies to HIV. Science. 2010

VRC01 demonstrated protection in animal studies

VRC01:
From NHP to Human Studies



VRC01 has acceptable human safety profile

- VRC601
- VRC602
- HVTN 104
- HVTN 703/ HPTN 081
- HVTN 704/HPTN 085

VRC01: Safety and Tolerability

- **Studied in Phase 1 trials: VRC601, VRC602, HVTN104**
  - VRC 601 : dose escalation and PK study of IV and SC in HIV infected individuals
  - VRC 602: dose escalation and PK study of IV and SC in HIV uninfected individuals
  - HVTN 104: safety and PK study of VRC01 in HIV uninfected individuals
- **>100 participants; >250 IV infusions of VRC01**
- **Overall, safe and well-tolerated**

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The AMP Studies:

AMP = Antibody Mediated Prevention

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

Two harmonized protocols:

HVTN 704/HPTN 085

(2700 MSM and TG in the Americas)

HVTN 703/HPTN 081

(1500 Women in sub-Saharan Africa)

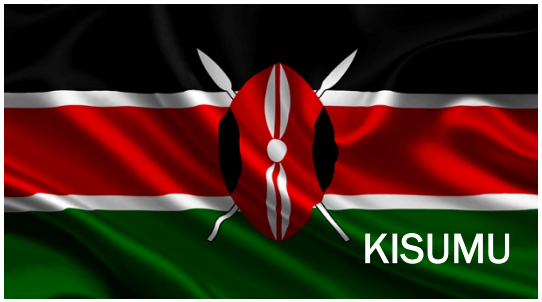
AMP Study Population: 2 Cohorts

Cohort	Antibody (VRC 01) 10mg/kg	Antibody (VRC 01) 30mg/kg	Placebo	Total Population
Americas: **United States, Peru & Brazil** MSM & TG people (Clade B)	900	900	900	2,700
Southern Africa: **Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe** Heterosexual women (Clades A, C, D, & CRFs)	500	500	500	1,500
Total	1,400	1,400	1,400	4,200

AMP Study Research Sites

(As of Sep, 2016)

AMP in sub-Saharan Africa



7 Countries

15 Sites

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 in the Americas
  - 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

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.

The AMP Studies: 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

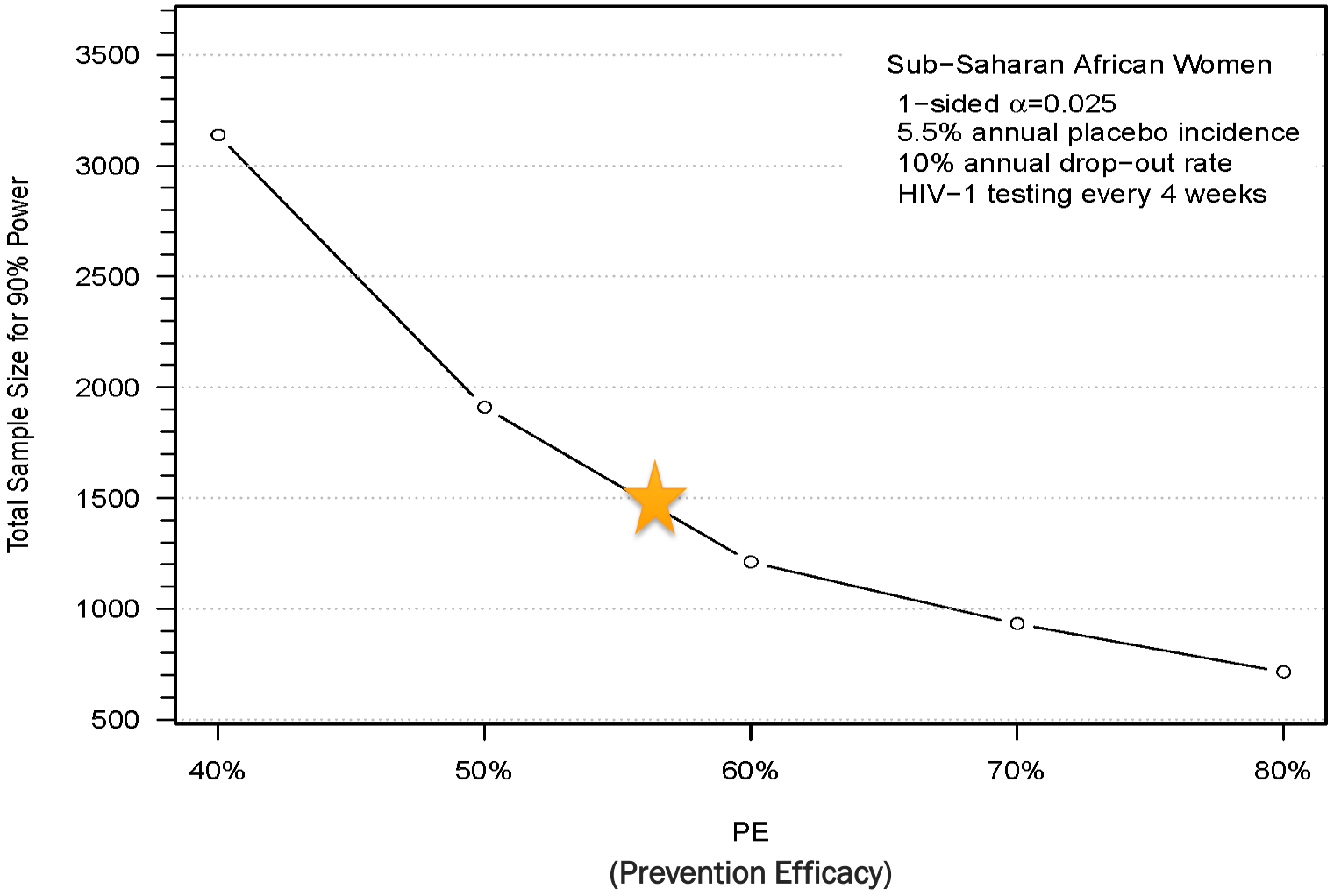
SECONDARY

- **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 viral sequences in infected people
  - VRC01 neutralization sensitivity of, & effector functions against, HIV strains from infected trial participants

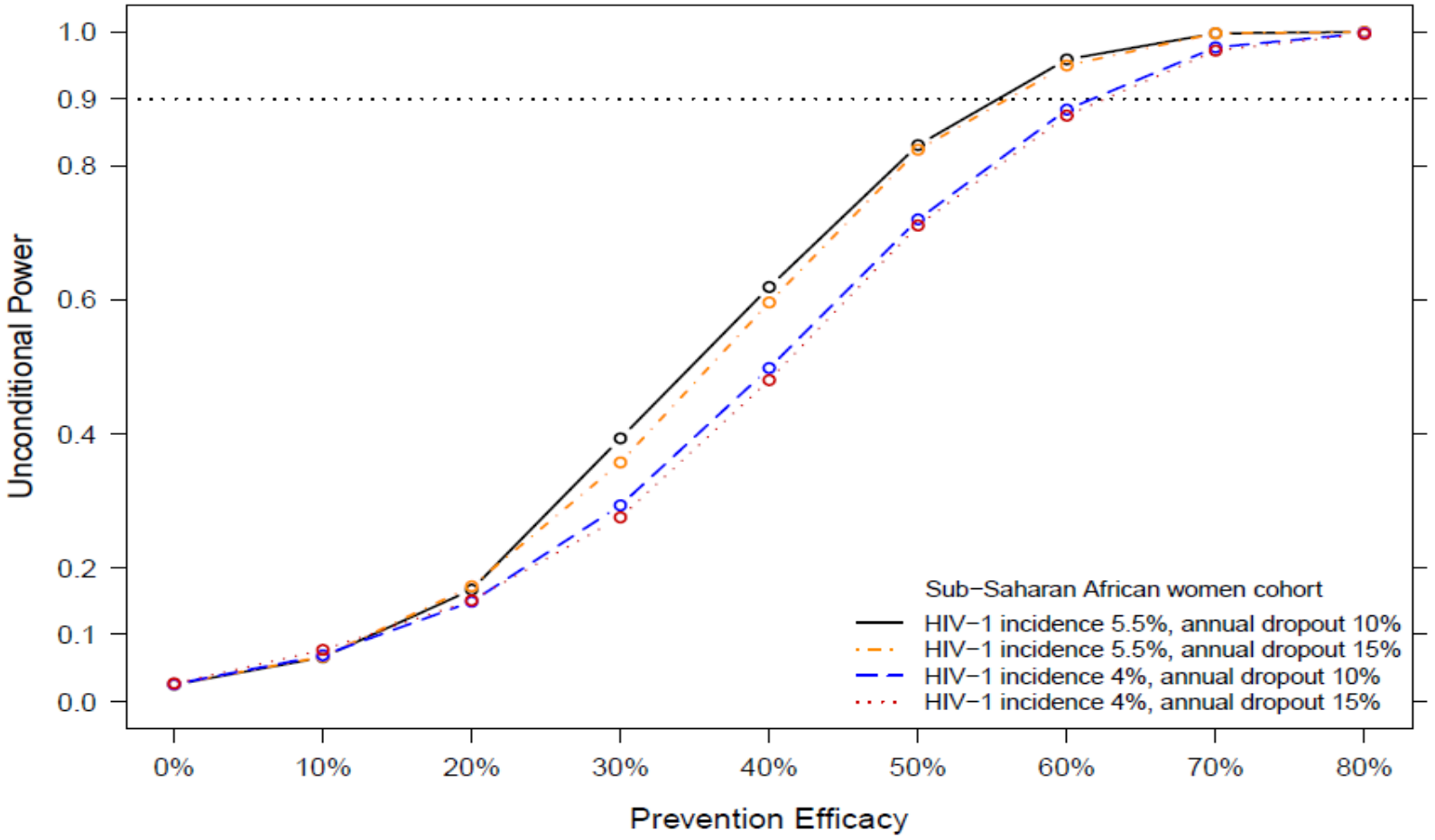
Assumptions for Sample Size Calculations

- 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



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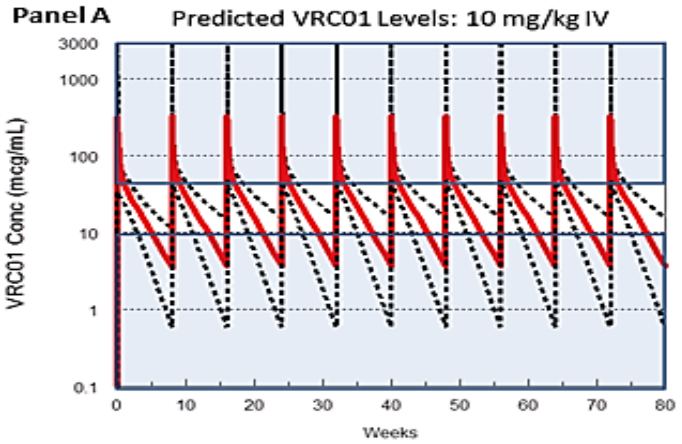
Study Schema for The AMP Studies

REGIMEN	HVTN 704/HPTN 085 MSM & TG in the Americas	HVTN 703/HPTN 081 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	

Predicted VRC01 serum concentrations at 2 doses (10mg/kg and 30mg/kg)

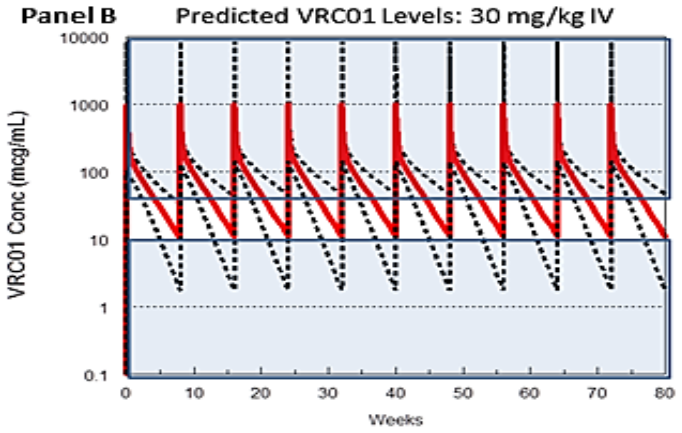


>50 mcg/mL

10-50 mcg/mL

<10 mcg/mL

10 mg/kg VRC01 group: Predict (50%, 40%, 10%) PYRs in (Low, Medium, High) zones



>50 mcg/mL

10-50 mcg/mL

<10 mcg/mL

30 mg/kg VRC01 group: Predict (10%, 40%, 50%) PYRs in (Low, Medium,

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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

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**

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AMP Trial Monitoring

- Early feasibility check
  - After ~25% of participants have completed their week 32 visit, infusion feasibility assessment will be conducted and reported to DSMB
  - 80% or more of participants must remain engaged in the trial
- Monitoring for harm, non-efficacy, high efficacy
- Monitoring for operational futility
- Interim safety assessment

Interim Safety Assessment

- An interim safety assessment will be performed through the Week 24 visit for the first 450/300 enrolled participants.
- Plan to slow enrollment during periods of FDA review and the pre-specified interim safety analysis
- Infusions for those 450/300 participants will continue while the interim safety assessment is conducted.
- 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.

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AMP SSA Study Update

As of September 19, 2016

- Protocol opened May 9, 2016 (N=1500)
- First participant enrolled: May 17, 2016
- Site Activation Status:
- Sites activated: Soweto CRS, eThekwini CRS, Vulindlela CRS, Groote Schuur CRS, WRHI CRS, Gaborone CRS, Chatsworth CRS
- Sites not yet activated: Parirenyatwa CRS, Seke South CRS, Spilhaus CRS, Kisumu CRS, Blantyre CRS, Lilongwe, Maputo CRS, Mbeya CRS
- Number currently enrolled (received VRC01/control): 122
- Number randomized (not yet received VRC01/control): 12

AMP Americas Study Update

As of September 19, 2016

- Protocol opened March 31, 2016 (N=2700)
- First participant enrolled April 6, 2016
- All US sites have been activated
- South America site activation status:
- Sites not yet activated: Barranco, Via Libre, San Miguel, Iquitos, Rio
- Number currently enrolled (received VRC01/control): 473
- Number randomized (not yet received VRC01/control: 12

Interim Safety Assessment

- Enrolment Slow-Down in the Americas
- Planned operational aspect of the trial
- Pre-specified in the protocol
- Is not based on any safety concerns

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AMP Studies: Summary

- 1st Phase 2b studies with an IV intervention for HIV prevention in men, women, & TG
- 1st efficacy trials with an anti-HIV mAb
- Cross-Network collaboration: HVTN & HPTN
- Global trials in 2 cohorts on 3 continents
  - 2700 MSM + TG in North & South America (Clade B)
  - 1500 Women in sub-Saharan Africa (Clades C, A, D)
- > 750 infusions in > 500 participants*
- VRC01 has demonstrated a strong safety profile

*as of September 2016

Why Antibodies?

- Reasonable likelihood that antibodies will work
- Likely to be safe and well tolerated
- Because we want to PREVENT HIV…
  - Whether through an mAb
  - Or through an HIV vaccine
  - Or through an intra-vaginal ring
  - Or through oral PrEP
  - Or through a long acting injectable agent

"The secret is to gang up on the problem (HIV), rather than compete against each other" - *adapted,* Thomas Stallkamp

Thank you!

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, Manuel Villaran, Sinead Delany-Moretlwe
- Social & Behavioral Scientist: Michele Andrasik
- DAIDS Protocol Pharmacist: Scharla Estep
- Regional Medical Liaison: Simba Takuva
- 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, Evangelyn Nkwopara
- Regulatory Affairs Representative: Meg Brandon
- Communications Representatives: Jim Maynard & Eric Miller
- Community Engagement Representatives: Gail Broder, Jonathan Lucas, Jontraye Davis
- Clinic Coordinators: Deb Dunbar, Lilian Saavedra, Elaine Sebastian
- CAB Representatives: Likhapha Faku, Mark Hubbard, Jim Wick
- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab

AMP sub-Saharan Africa Sites

- Gaborone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Cape Town, RSA
- Durban (2 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Mbeya, Tanzania

AMP Americas* Sites

United States

- Atlanta, GA (2 clinic locations)
- Birmingham, AL
- Boston, MA (2 clinic locations)
- Chapel Hill, NC
- Cleveland, OH
- Los Angeles, CA
- Nashville, TN
- Newark, NJ
- New York City, NY (4 clinic locations)
- Philadelphia, PA
- Rochester, NY
- San Francisco, CA
- Seattle, WA
- Washington, DC

South America

- Peru
  - Lima (3 CRSs)
    - Barranco
    - San Miguel
    - Via Libre
  - Iquitos
    - Association Civil Selva Amazonica
- Brazil
  - Rio de Janeiro– IPEC-Fiocruz

**And Lausanne, pending Swiss Medic approval*