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Antibody Mediated HIV Prevention

An Overview

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HPTN CWG Plenary 1
12 June 2016

Disclosures

- No financial disclosures

Antibodies and Viral Infections

- Long history of use of antibodies against viral infections

Long History of Using Antibodies to Prevent Viral Infections

Pathogen	Product Description	Indication
Measles	Concentrated human gamma globulin	Prevention
Polio	Concentrated human gamma globulin	Prevention
CMV	Cytomegalovirus Immune Globulin	Prevention
Hepatitis A	Immune serum globulin (ISG)	Prevention (travel)
Hepatitis B	Hepatitis B Immune Globulin	Post Exposure
Rabies	Rabies Immune Globulin	Post Exposure
RSV	mAb (palivizumab) for prophylaxis of high risk infants	Prevention in high risk Infants
VZIG	Varicella Zoster Immune Globulin	Post Exposure

And, most effective vaccines induce antibodies that neutralize the pathogen.

Thanks to John Mascola for this slide.

Antibodies and Viral Infections

- Long history of use of antibodies against viral infections
- But what is an antibody?
- How do antibodies work?

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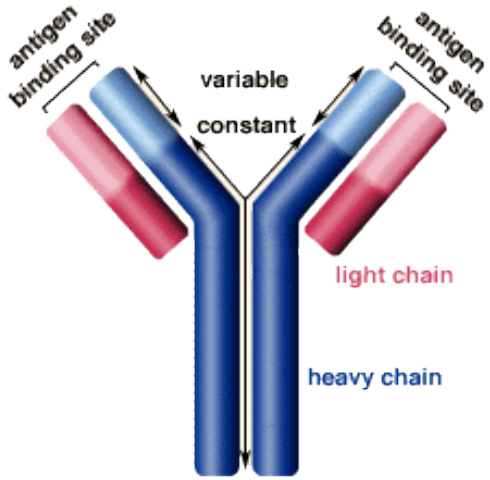
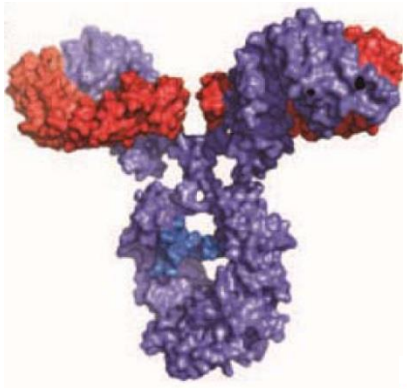
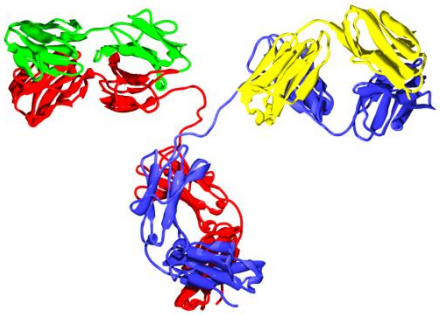
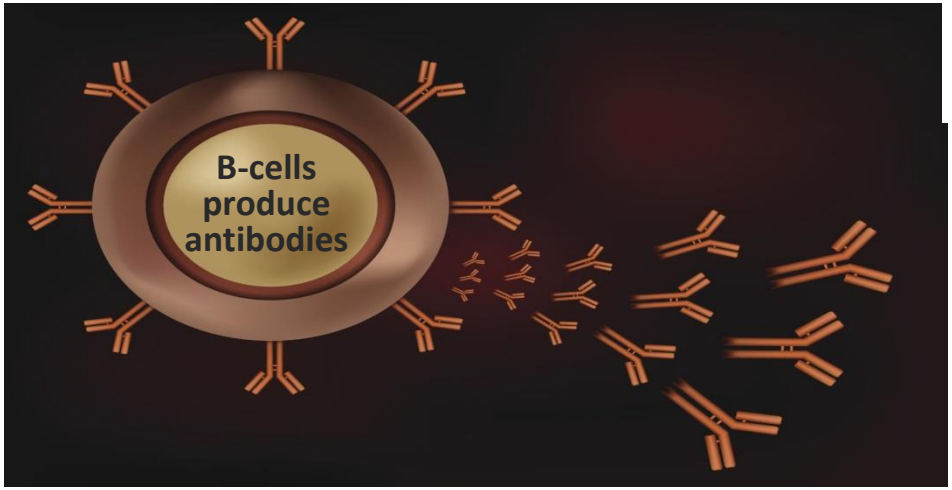
What is an Antibody?



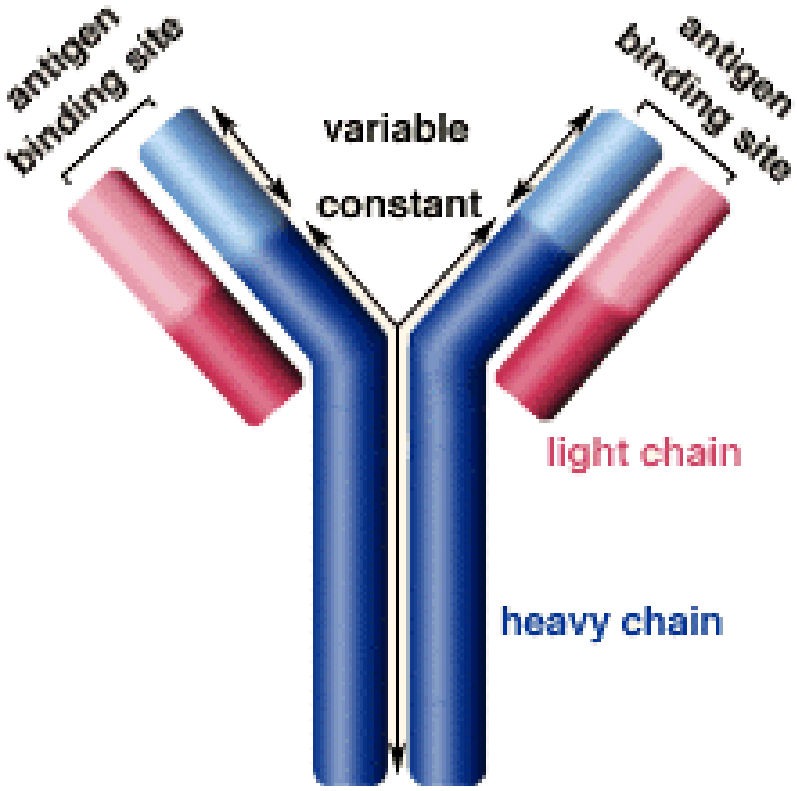




NIAID



How Do Antibodies Work?



NEUTRALIZATION

Binds to Ag & blocks its attachment to host cells

OPSONIZATION
("buttering the toast")

Binds to Ag, then binds to a macrophage; the macrophage then eats the HIV

SENSITIZATION
("the lookout for the hitman")

Binds to Ag, then binds to an NK cell; the NK cell then spills its "poison" to kill Ag

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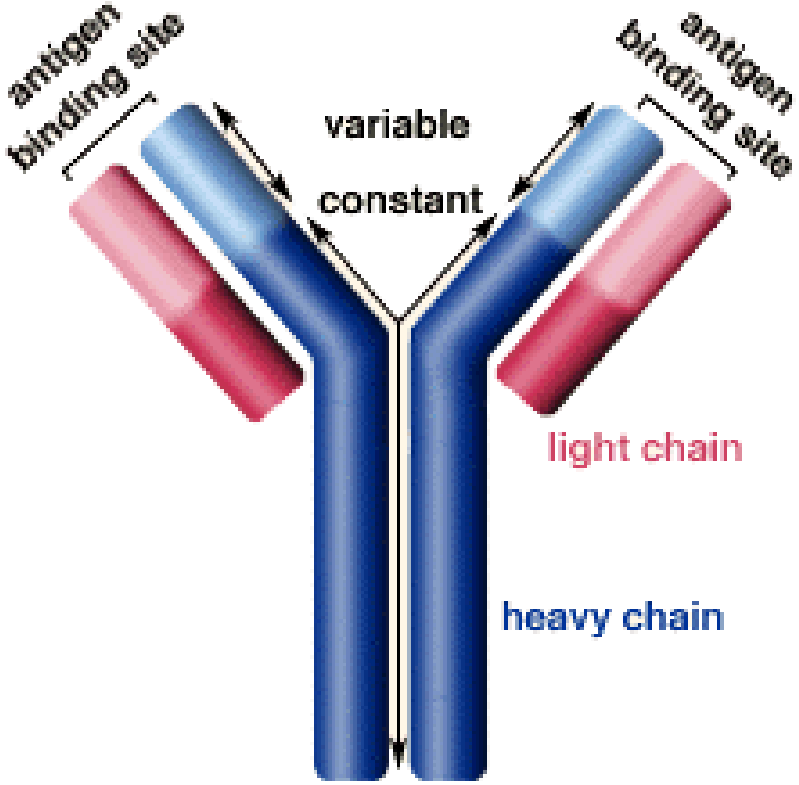
Can Antibodies be used to prevent HIV?

Antibodies and HIV

- Concept of using antibodies against HIV-1 follows naturally from knowledge gained from many viral diseases
- Antibodies have potential to block HIV-1 replication through multiple mechanisms.
- Antibodies exert immune pressure on the virus leading to escape

How Do Antibodies Work?



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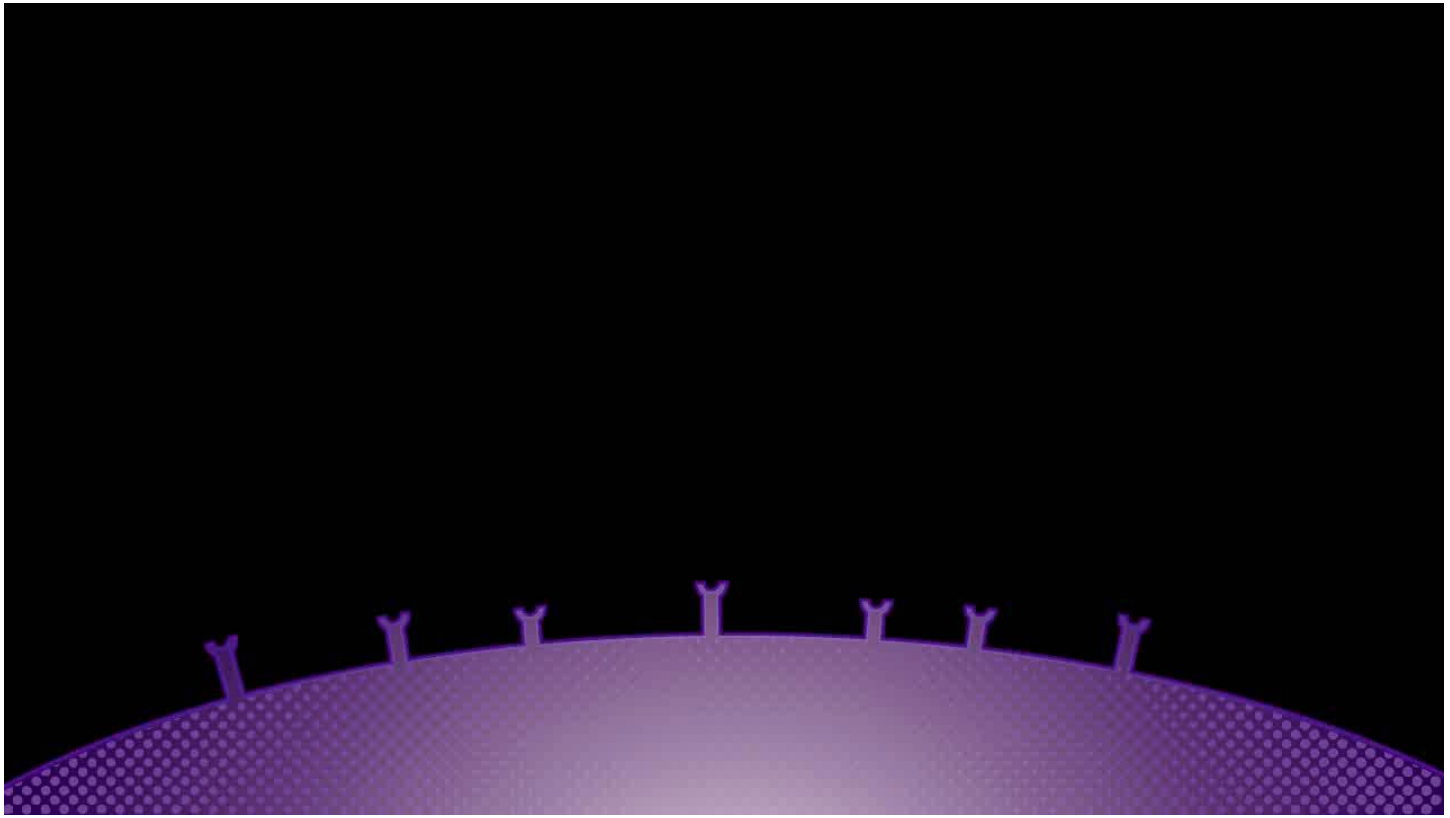
Neutralizing Antibodies Preventing HIV Infection



An example of a neutralising antibody is VRC01

The Antibody Response to HIV-1

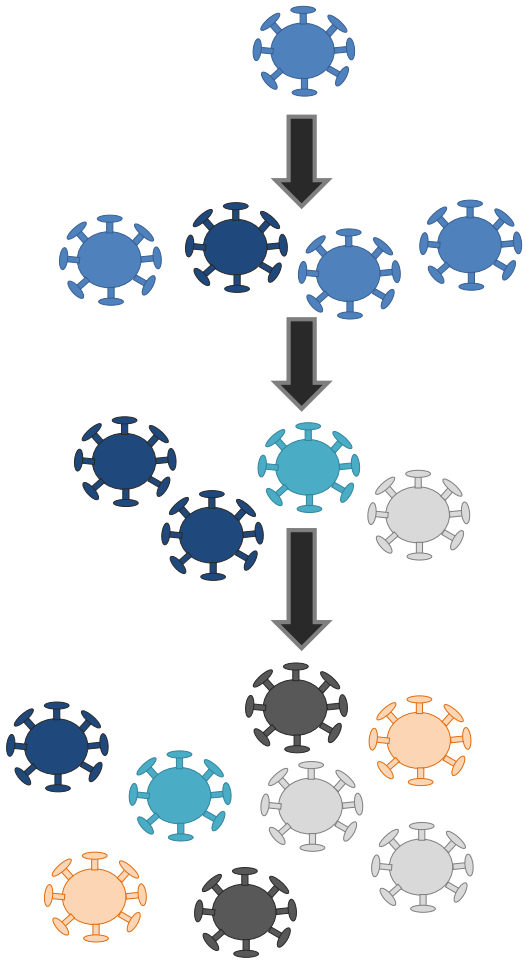
- B-cell responses to HIV-1 develop within approx. 1 week of detectable viraemia
- Initially – Ag-Ab complexes
- Circulating anti-gp41 antibodies within days
- Circulating anti-gp120 antibodies weeks later
- These binding antibodies do not have a detectable effect on viraemia
- Neutralising Abs against the infecting strain aka autologous strain appear months later – but are not able to neutralise more divergent viruses
- Autologous nAbs drive immune escape because contemporaneous viruses are less sensitive to autologous nAbs than earlier strains
- Hence need for bNAbs

What is a BROADLY Neutralizing Antibody?

A “bnAB”: an antibody that neutralizes a lot of different types of strains of HIV.

And why do we care…?

HIV Diversity Within an Individual



Usually 1 HIV strain in a new infection

("Transmitted-founder")

Replicates within about 24hrs

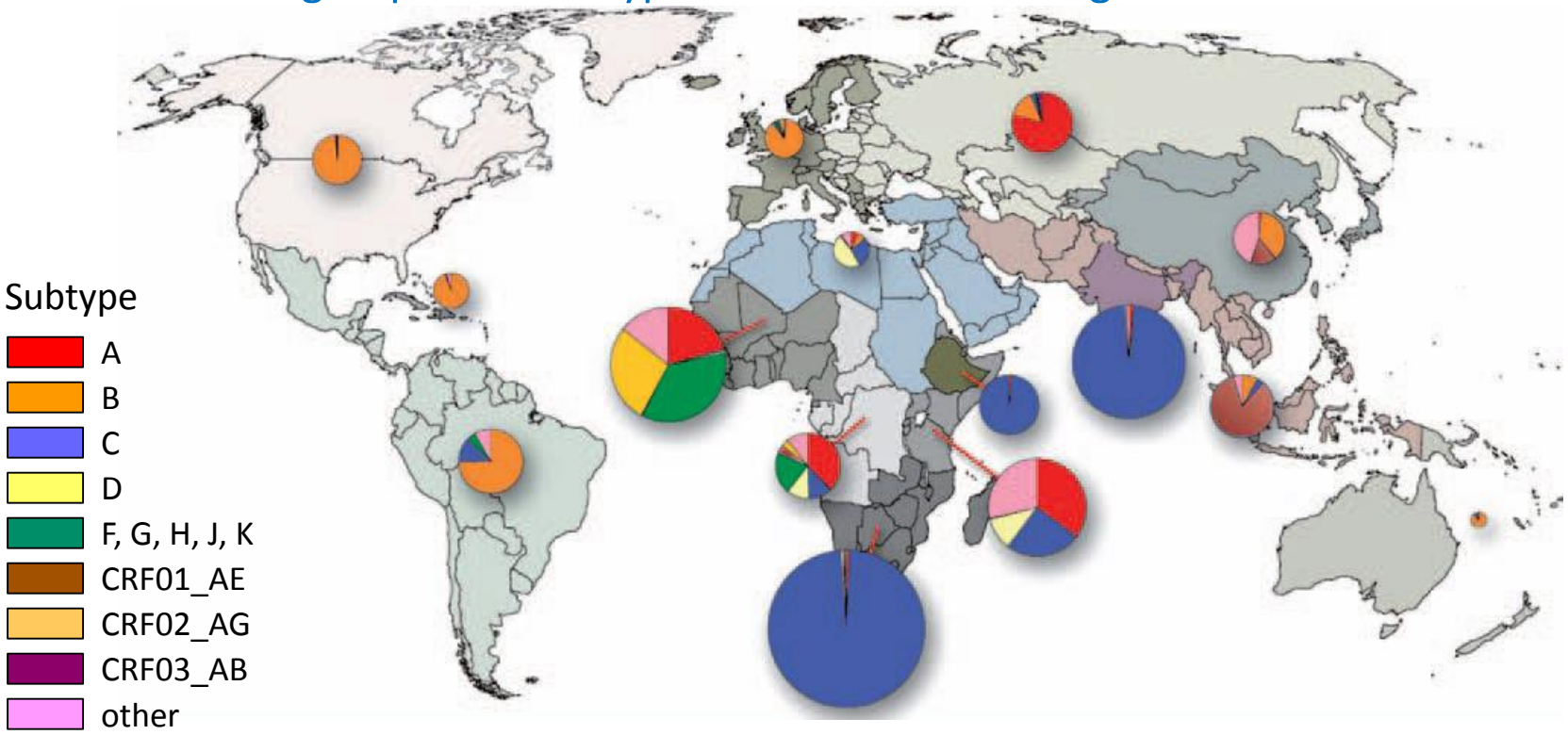
Produces BILLIONS of new virions a day

Mutations with viral replication

Rapidly develop multiple lineages or "quasispecies"

HIV-1 Diversity Worldwide

HIV-1 group M: 9 subtypes & several circulating recombinant forms



HIV genomes differ by 10-30%

Human genomes differ by about 0.1%

Hemelaar et al. 2004. WHO/UNAIDS.

HIV-1 Antibodies

- Neutralizing antibodies (NAbs) typically play a key role in controlling viral infections and contribute to the protective effect of many successful vaccines.
- Compelling data in experimental animal models that NAbs can prevent HIV-1 acquisition
- No similar data in humans
- Role in controlling established infection in humans is also limited

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Introducing VRC01

What is a monoclonal Antibody to HIV?

- A single type ("clone") of antibodies often found in the blood of long-term non-progressors, then made in a lab
- Bind to different parts of the HIV gp120 envelope protein

VRC01

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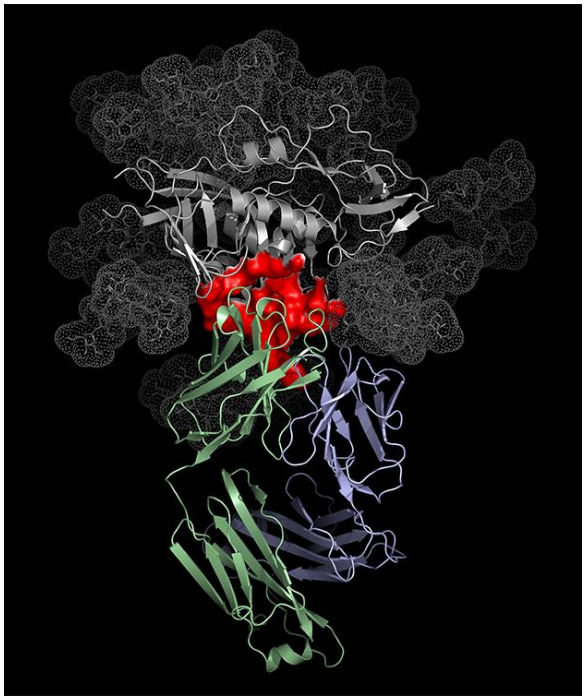
VRC01

- Broadly Neutralizing (“bnAb”)
- Monoclonal (“mAb”)
- Antibody
- Discovered by scientists at the US NIH
- In the lab, it has been able to block HIV in about 90% of the different types of HIV that it has been tested against.

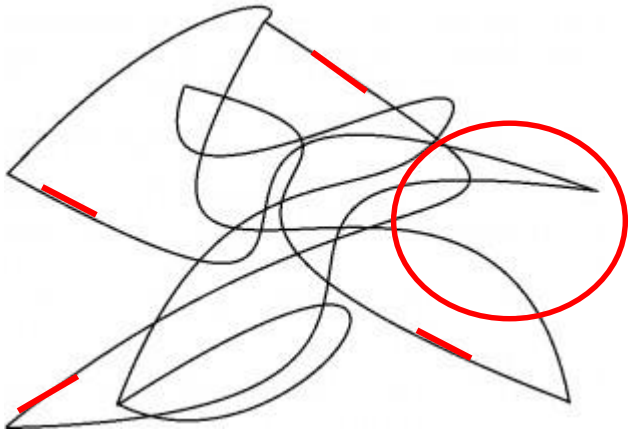


Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

Photo: NIAID/NIH Vaccine Research Center (VRC)

VRC01 Attaches to the CD4 Binding Site on gp120

The GP 120 Protein



Red lines = linear epitopes
Red circle = the CD4 binding site

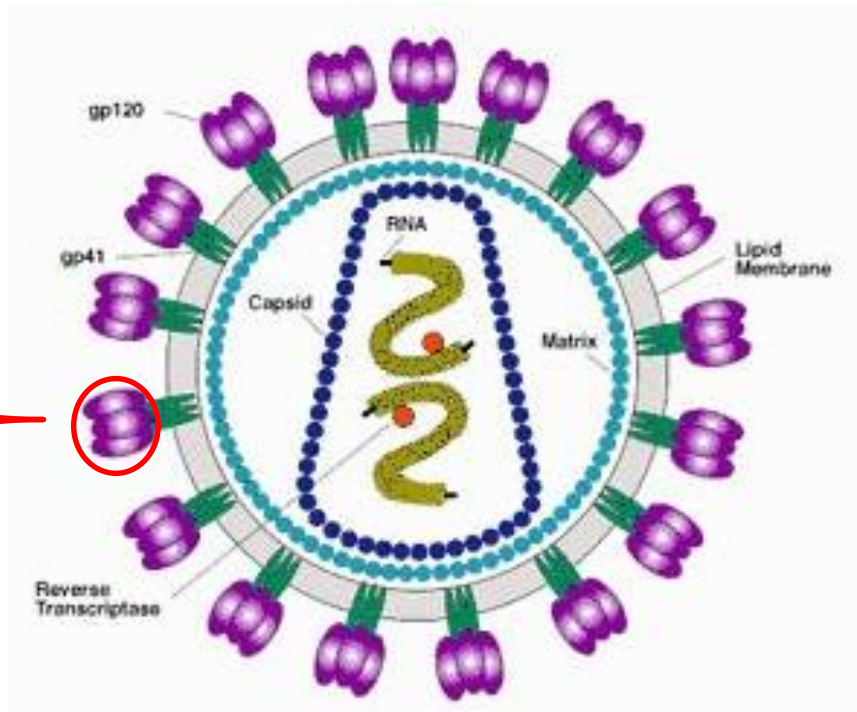


Image credit: NIAID

Why evaluate VRC01?

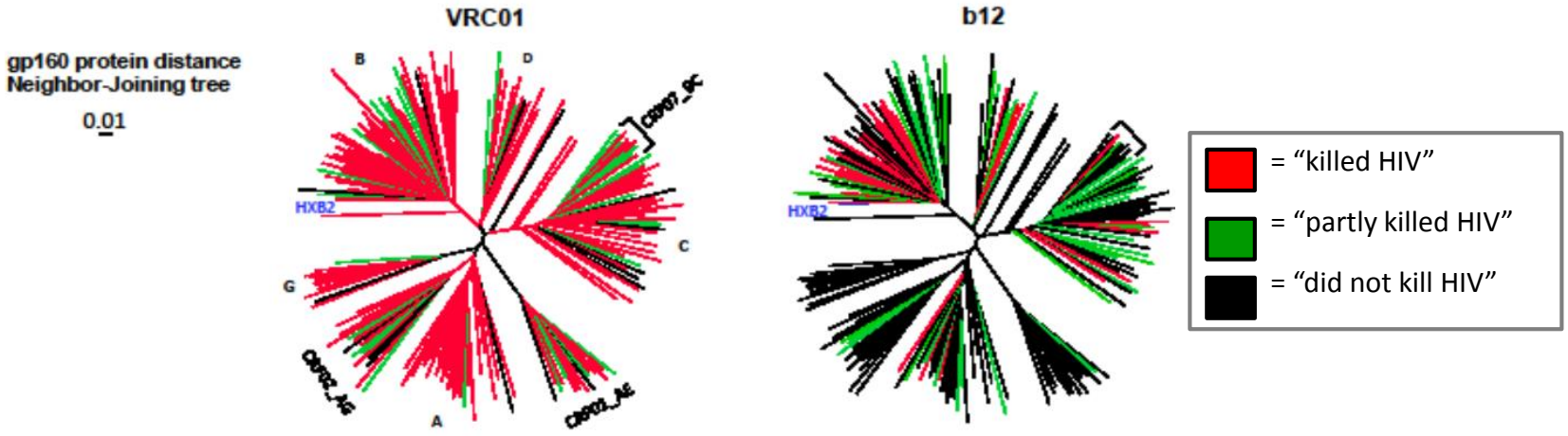
PREVENTION

- Promising antibody for **HIV prevention**
  - Broadly neutralizing & potent in lab studies
  - Good results in early studies
  - May supplement other prevention approaches

HIV VACCINE

- Move the **HIV vaccine** search forward
  - Teach us the amount of antibody a vaccine may need to elicit to prevent HIV
  - Help us find a safe, effective HIV vaccine more efficiently

VRC01 is a BROADLY NEUTRALIZING Antibody

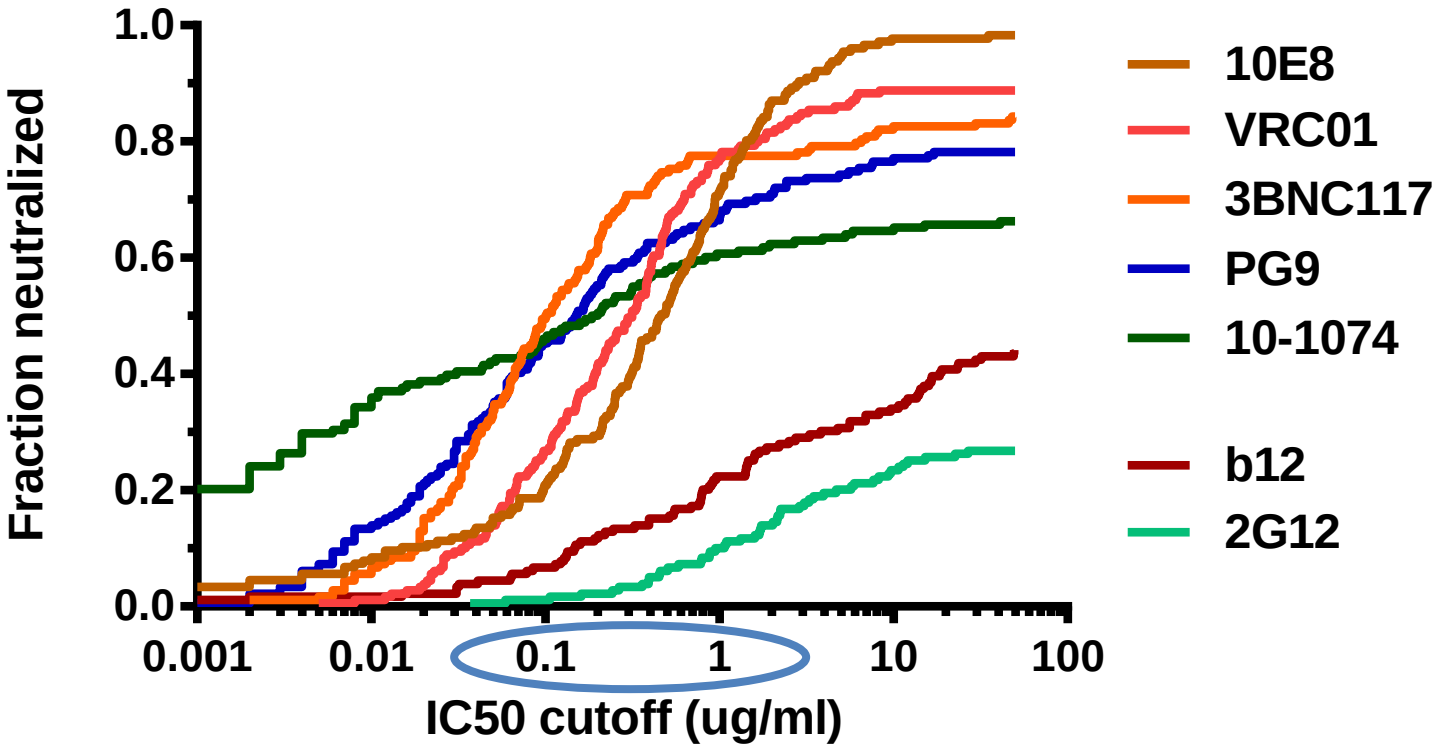


Virus clade	Number of viruses	IC_{50} < 50 µg/ml		IC_{50} < 1 µg/ml	
		VRC01	b12	VRC01	b12
A	22	100%	45%	95%	23%
B	49	96%	63%	80%	39%
C	38	87%	47%	66%	13%
D	8	88%	63%	50%	25%
CRF01_AE	18	89%	6%	61%	0%
CRF02_AG	16	81%	19%	56%	0%
G	10	90%	0%	90%	0%
CRF07_BC	11	100%	27%	45%	9%
Other	18	83%	33%	78%	6%
Total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

Tested Against 190 Different "Types" or Strains of HIV

Wu et al. Science. 2010

VRC01 is a Potent Antibody

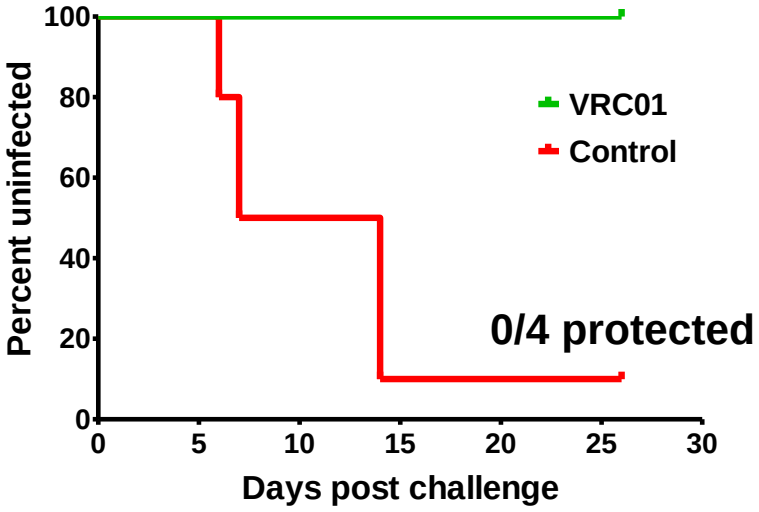


Thanks to David Montefiori & CAVD and Bob Bailer & NVITAL Laboratory

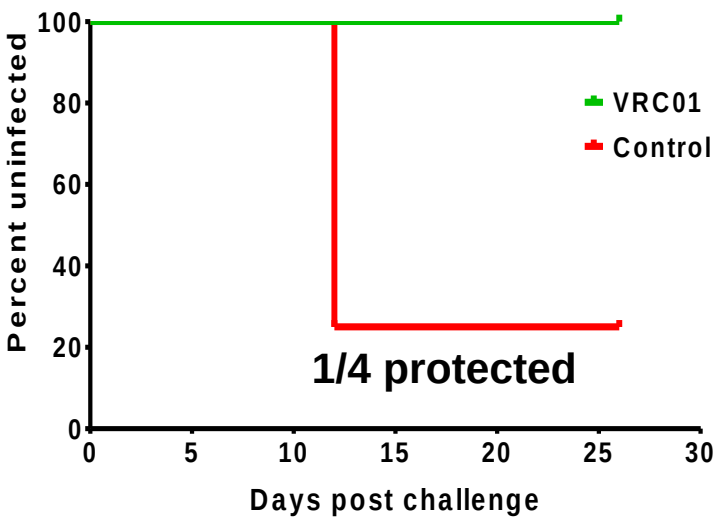
VRC01 in Preclinical (NHP) Trials

20 mg/kg infusion of VRC01

RECTAL CHALLENGE
4/4 PROTECTED



VAGINAL CHALLENGE
4/4 PROTECTED



VRC01: VRC01 in Phase 1 Clinical (Human) Trials: Safe and Well-tolerated

- 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

How Could VRC01 be a Prevention Tool?

- Cover a period of risk for newborns (during & right after birth, during breastfeeding)
- Cover the “tail” of long-acting PrEP injection
- Cover the ramp-up period of an HIV vaccine regimen
- Combine with other mAbs in a prevention “cocktail”

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Introducing AMP

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AMP STUDY

AMP = Antibody Mediated Prevention

This is the idea of using an antibody made by scientists and giving it to people directly, i.e. using an intravenous (IV) infusion, to prevent HIV infections.

Two harmonized protocols:

HVTN 704/HPTN 085 (MSM and TG in the Americas)

HVTN 703/HPTN 081 (Women in sub-Saharan Africa)

Who is Doing the AMP Study?

The study is being conducted by two groups, the HIV Vaccine Trials Network and the HIV Prevention Trials Network.

HIV Prevention Trials Network

HIV VACCINE
TRIALS NETWORK

Rationale for Study Design

- 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; and
- Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization.

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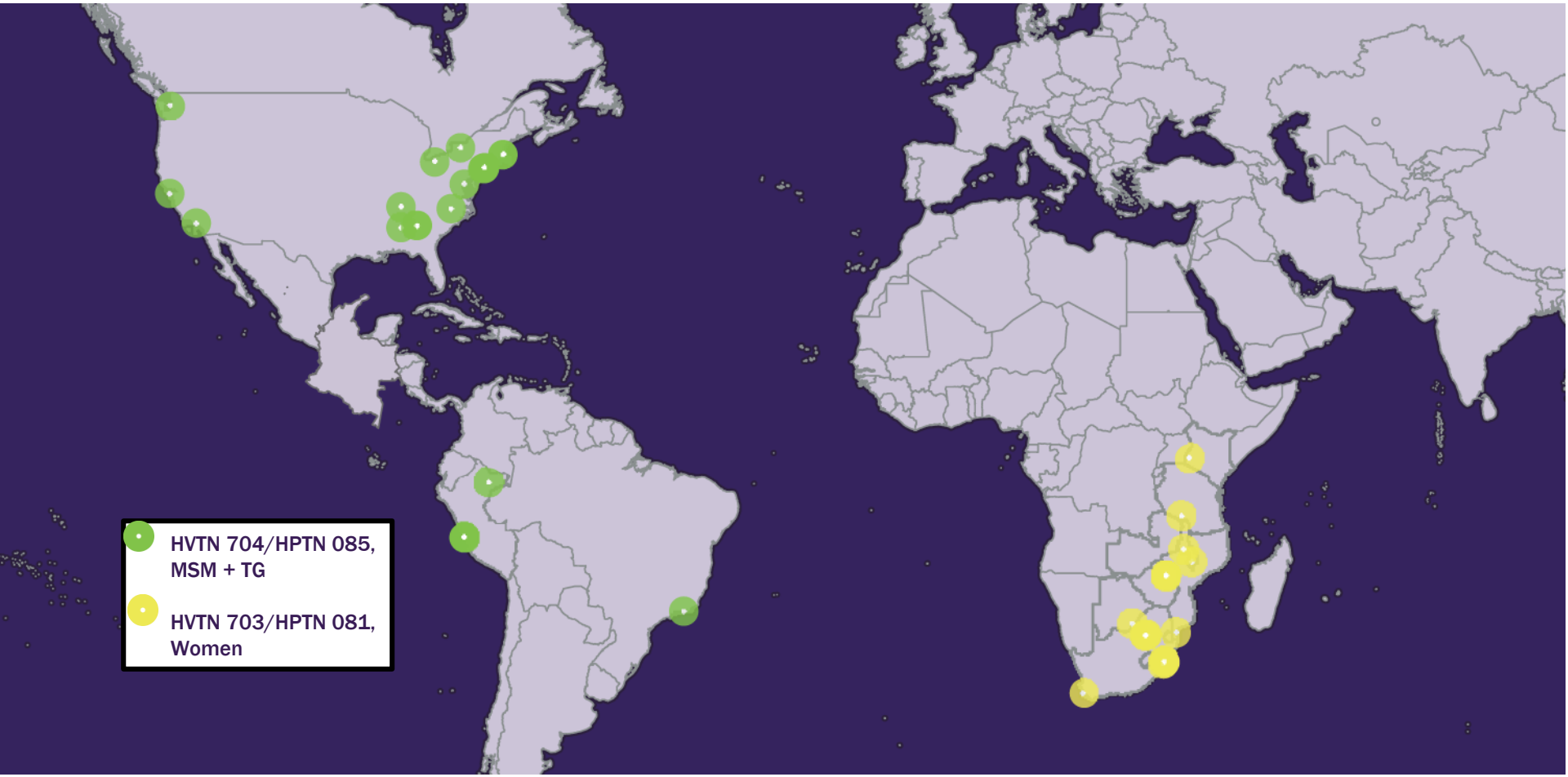
AMP Studies: Research Sites



AMP 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

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Study Schema for The AMP Study

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	500	1400	10 infusions total & Infusions every 8 weeks
VRC01 30 mg/kg	900	500	1400	
Control	900	500	1400	
Total	2700	1500	4200	Study duration: ~22 months

The AMP Study: Selected Eligibility Criteria

- **General and Demographic Criteria**
- 18-50 years of age
- **HIV-Related Criteria:** HIV uninfected
- Lab
- Risk behavior related criteria:
  - In the Americas: 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 Africa: female who has had vaginal or anal intercourse with a male partner in the past 6 months
  - All volunteers in a monogamous relationship with an HIV(-) partner for > 1 year are excluded.
- Volunteers with clinically significant medical conditions are excluded

The AMP Study: Objectives

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 and to provide insight into mechanistic correlates of protection**
  - Serum VRC01 concentration
  - Serum mAb mediated neutralization and Fc effector functions to panels of HIV-1 Envs
  - Breakthrough HIV viral sequences in infected people
  - 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?

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What Will an AMP Participant Need to Do?

- 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 & cervicovaginal swabs) at enrolment and thereafter as indicated
- Questionnaires: complete questionnaires about sexual behavior & general health every 4-8 weeks
- Comprehensive HIV Prevention Package

STUDY DURATION: about 22 months

Monitoring of the AMP Trials

- Early feasibility check
  - After ~120 participants have completed Week 32 visit, infusion feasibility will be conducted by assessing discontinuation and drop out rates
  - 80% or more of 120 participants need to remain engaged in the trial
- Safety assessment/slow down once enrollment reaches n=450 participants
- Monitoring for harm, non-efficacy, high efficacy
- Monitoring for futility to assess prevention efficacy

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AMP STUDY

Site Activation Status - HVTN 704/HPTN 085

Study Opened March 31, 2016

Sites activated (58%)	• Nashville, San Francisco, Philadelphia, Birmingham, Columbia-NYBC, Columbia-P&S, Rochester, Seattle, Atlanta–Hope Clinic, Boston-Brigham, Boston-Fenway, Cleveland, Columbia–Harlem, Chapel Hill
Sites not activated	• Atlanta–Ponce de Leon, Columbia–Bronx, LA, New Jersey, Washington DC/GWU
Activation n/a training June 5-10	• Iquitos, Lima-Barranco CRS, Lima-San Miguel CRS, Lima Via Libre CRS, Rio-IPEC-Fiocruz CRS

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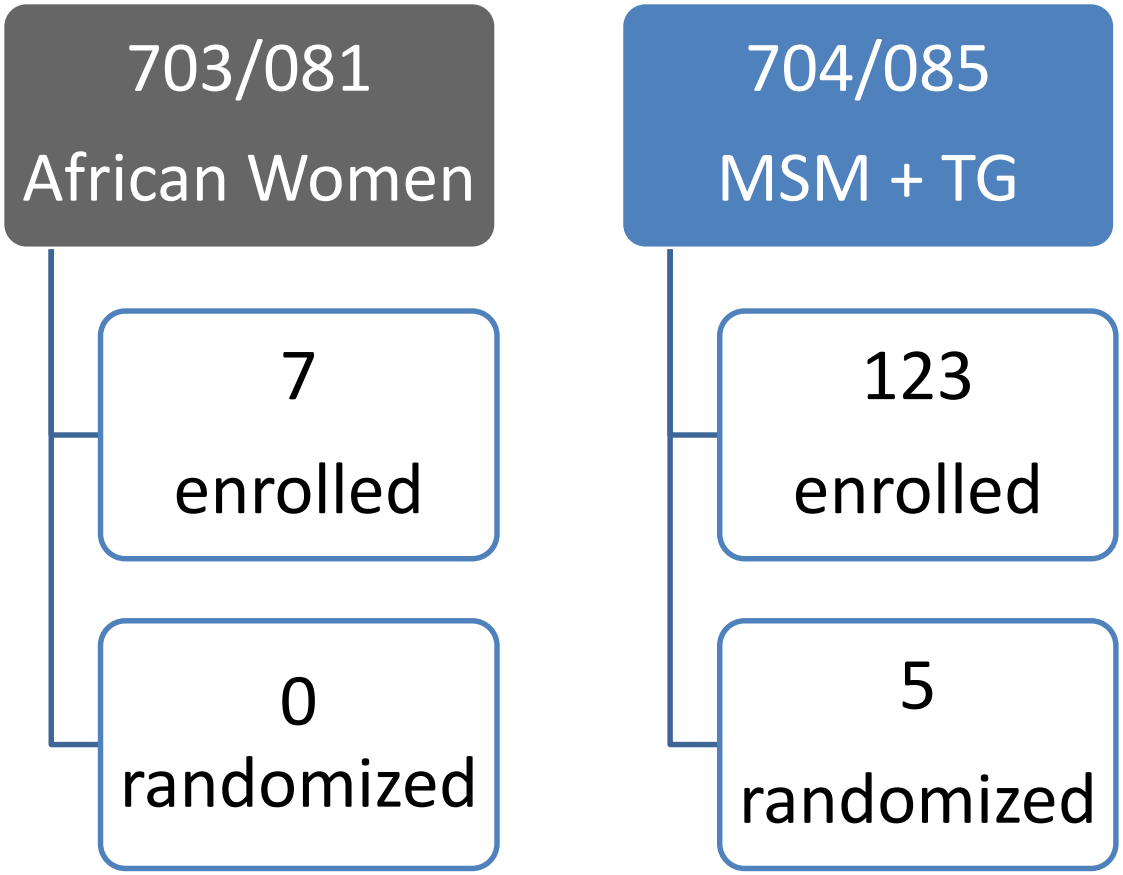
Site Activation Status - HVTN 703/HPTN 081

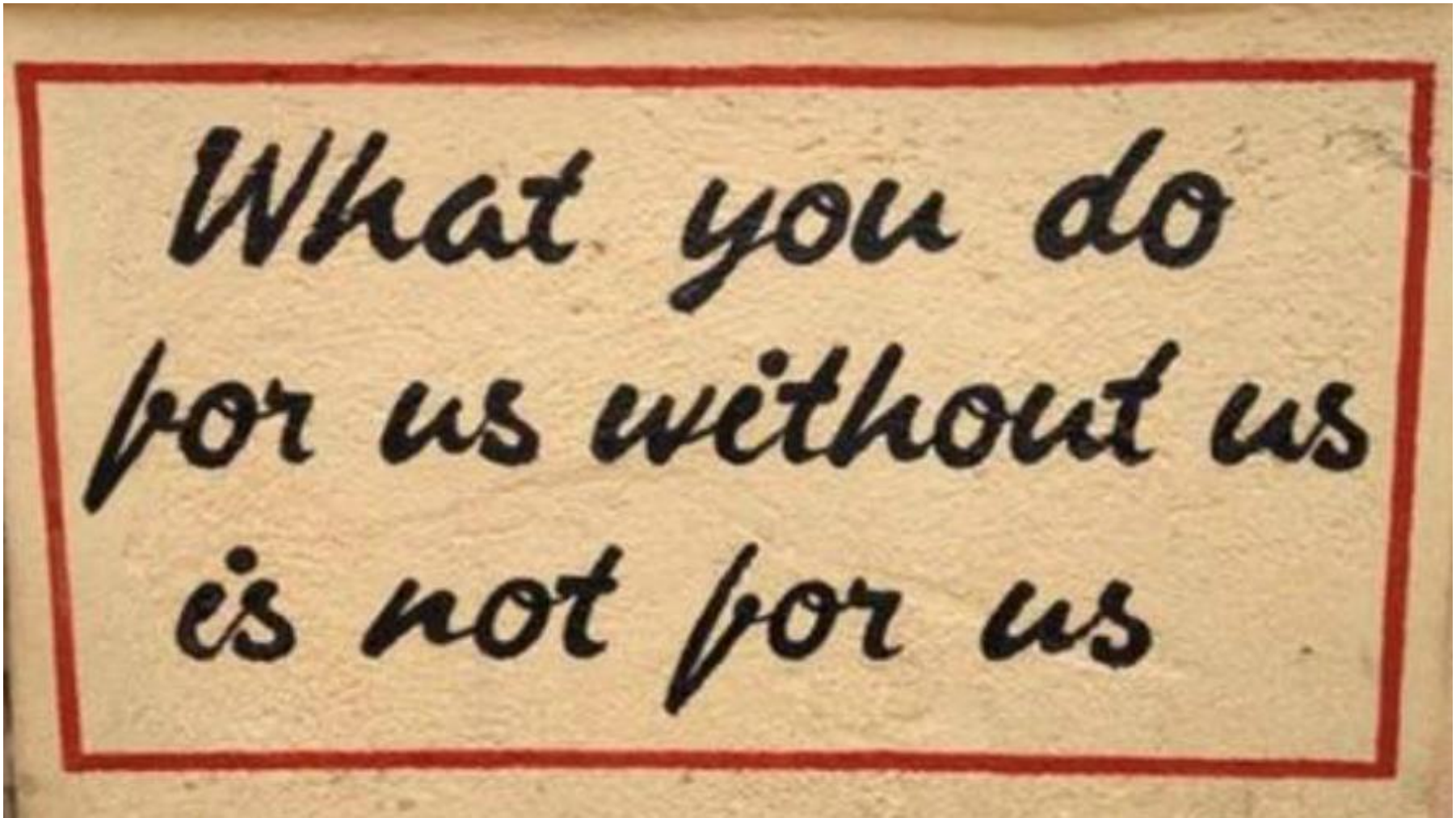
Study Opened May 9, 2016

Sites activated (20%)	• Soweto CRS, eThekwini CRS, Vulindlela CRS
Sites not activated	• Groote Schuur CRS, Chatsworth CRS, Gabarone, Parirenyatwa CRS, Seke South CRS, Spilhaus CRS, WRHI CRS, Kisumu CRS
Activation n/a training August 1-5	• *Blantyre CRS, Lilongwe, Maputo CRS, Mbeya CRS*

Enrollment Updates as of 06 June 2016



Community Engagement Activities



Community Engagement Activities

- Community Engagement Units – HVTN/HPTN Cores
- Animated Videos
- Study has its own web sites –
  www.ampstudy.org
  www.amstudy.org.za
  www.ampstudy.org.br
- Community Engagement, Recruitment and Retention activities at the CRSs
- Media Engagement

VRC01: Take Home Messages

- The VRC01 antibody is not made from live HIV, killed HIV, or HIV-infected human cells.
- It cannot cause HIV infection or AIDS.
- The antibody is made in a laboratory, using the same kinds of processes used to make other medicines.
- Laboratory tests have shown that the VRC01 antibody can prevent many different strains of HIV from infecting cells.
- VRC01 also prevented animals from getting infected.
- The AMP study will help us learn if the VRC01 antibody will prevent HIV infection in people

The AMP Studies: Summary

- 1st large scale, phase 2b studies with an intravenous biomedical intervention for HIV prevention in men and women
- 1st efficacy trials with a monoclonal antibody against HIV
- Cross-Network collaboration between HVTN & HPTN
- Global trial in 2 cohorts on 3 continents
  - 2,700 MSM + TG in North & South America (Clade B)
  - 1,500 Women in sub-Saharan Africa (Clade C)
- First participant enrolled in the US on April 6, 2016
- First participant enrolled in SAA on May 17, 2016

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The 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

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