Introduction to the Science of HVTN 703/HPTN 081

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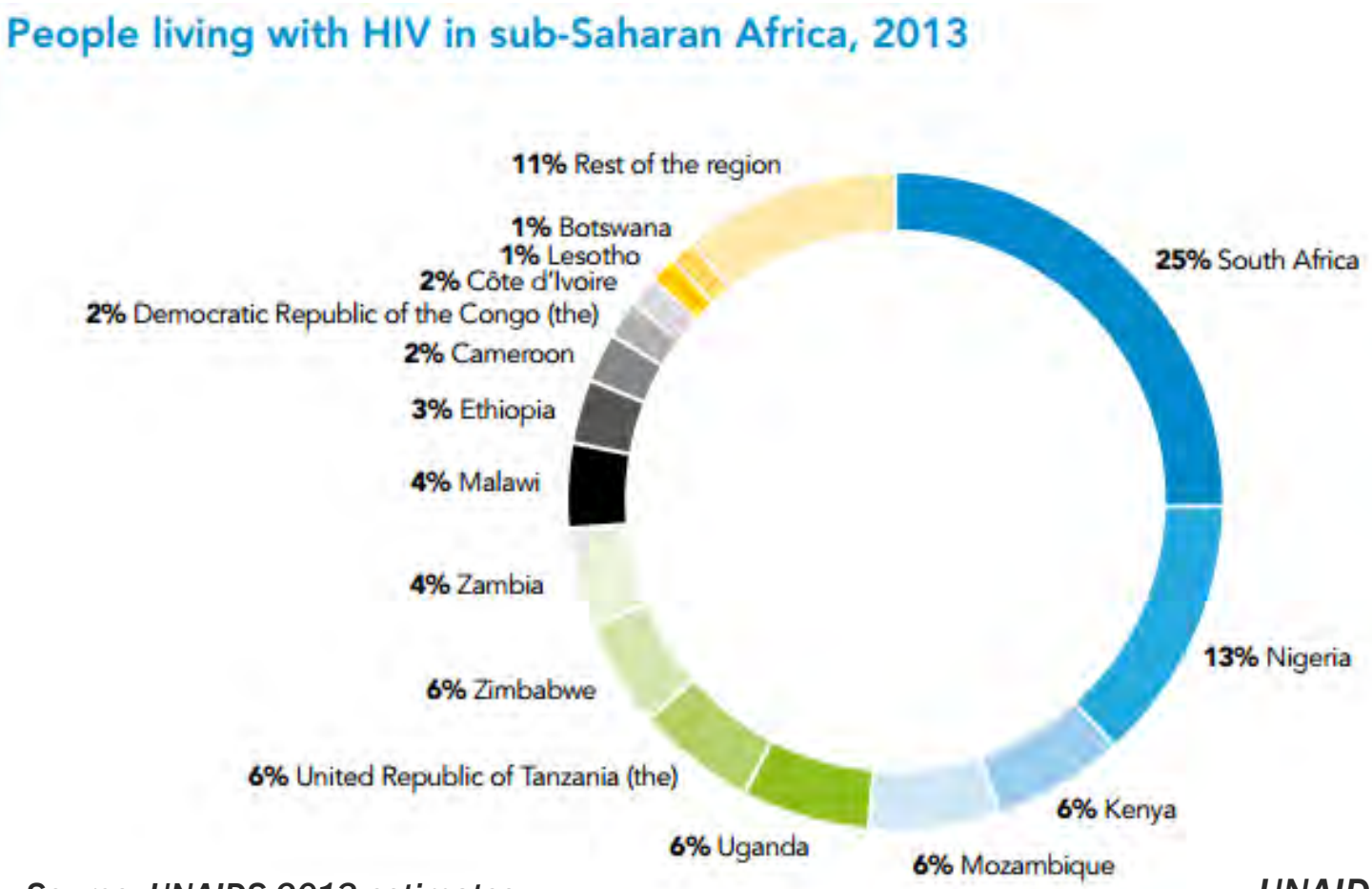
OUTLINE: AMP Science

- **HIV Prevention in sub-Saharan Africa**
- **The AMP Study: a brief introduction**
- **Antibodies: what they are & how they work**
- **Antibody Vocabulary: bnAbs, mAbs**
- **The AMP Study Antibody: VRC01**
- **And it all comes together: The AMP Study**
  - What questions does the AMP Study help answer?
  - What does the AMP Study ask of a participant?
- **Questions???**

Where is the HIV Prevention Field?
The Context for the AMP Study

- Despite many advances in prevention and treatment, the global HIV epidemic continues.
- Millions of new HIV infections occur every year.
- The current prevention toolbox is insufficient to curb the epidemic.
- We cannot treat our way out of the epidemic.

HIV in SSA: the Epidemic Goes On



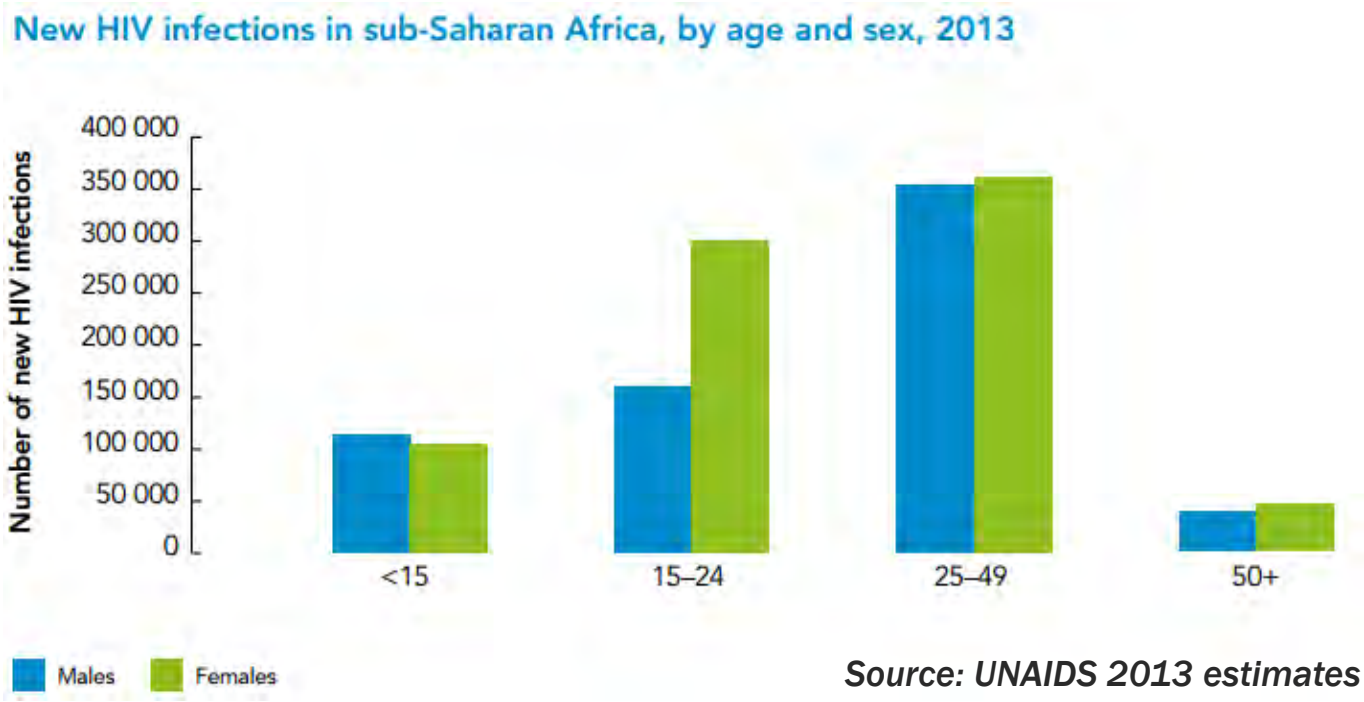
Source: UNAIDS 2013 estimates

UNAIDS Gap Report, 2014

HIV in SSA AMP Countries

Country	People living with HIV/AIDS	Adult (15-49 yr) Prevalence	Women with HIV/AIDS	Children with HIV/AIDS	AIDS Deaths
Botswana	300 000	23.4	160 000	15 000	4 200
Kenya	1, 600 000	6.2	800 000	220 000	62 000
Malawi	910 000	10.0	430 000	170 000	44 000
Mozambique	1, 400 000	11.3	750 000	200 000	74 000
SA	5, 600 000	17.3	2, 900 000	460 000	270 000
Tanzania	1, 800 000	5.6	760 000	230 000	84 000
Zimbabwe	1,200 000	14.9	600 000	200 000	58 000

HIV in SSA: the Epidemic Among Women



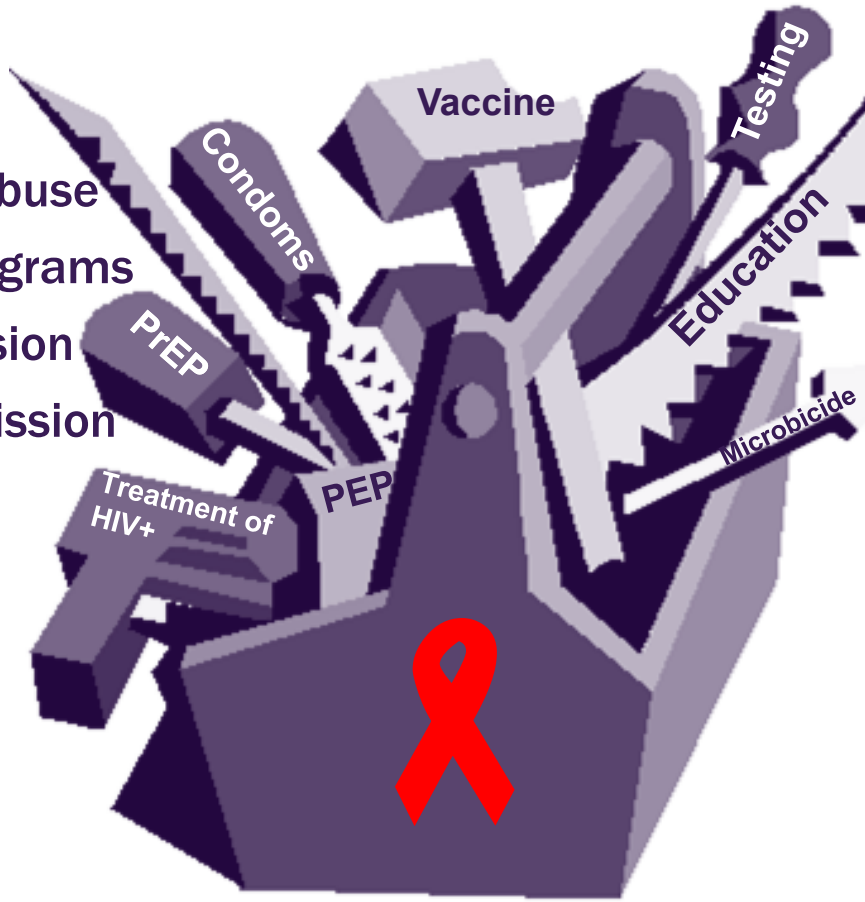
Source: UNAIDS 2013 estimates

- In 2013, of the 24.7 million people HIV infected in SSA >50% were women
- Young women are twice as likely to be infected as young men
- Women have fewer HIV prevention options than men

UNAIDS Gap Report, 2014

What Do We Have to Address the Epidemic?

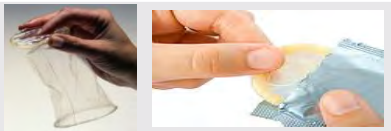
- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes, i.e. needle exchange programs
- Interruption of mother-to-child transmission
- Circumcision for female-to-male transmission
- HIV/STI Testing
- Antiretroviral treatment as prevention
- Post-exposure prophylaxis (PEP)
- Pre-exposure prophylaxis (PrEP)*
- Topical microbicides‡
- Vaccination‡



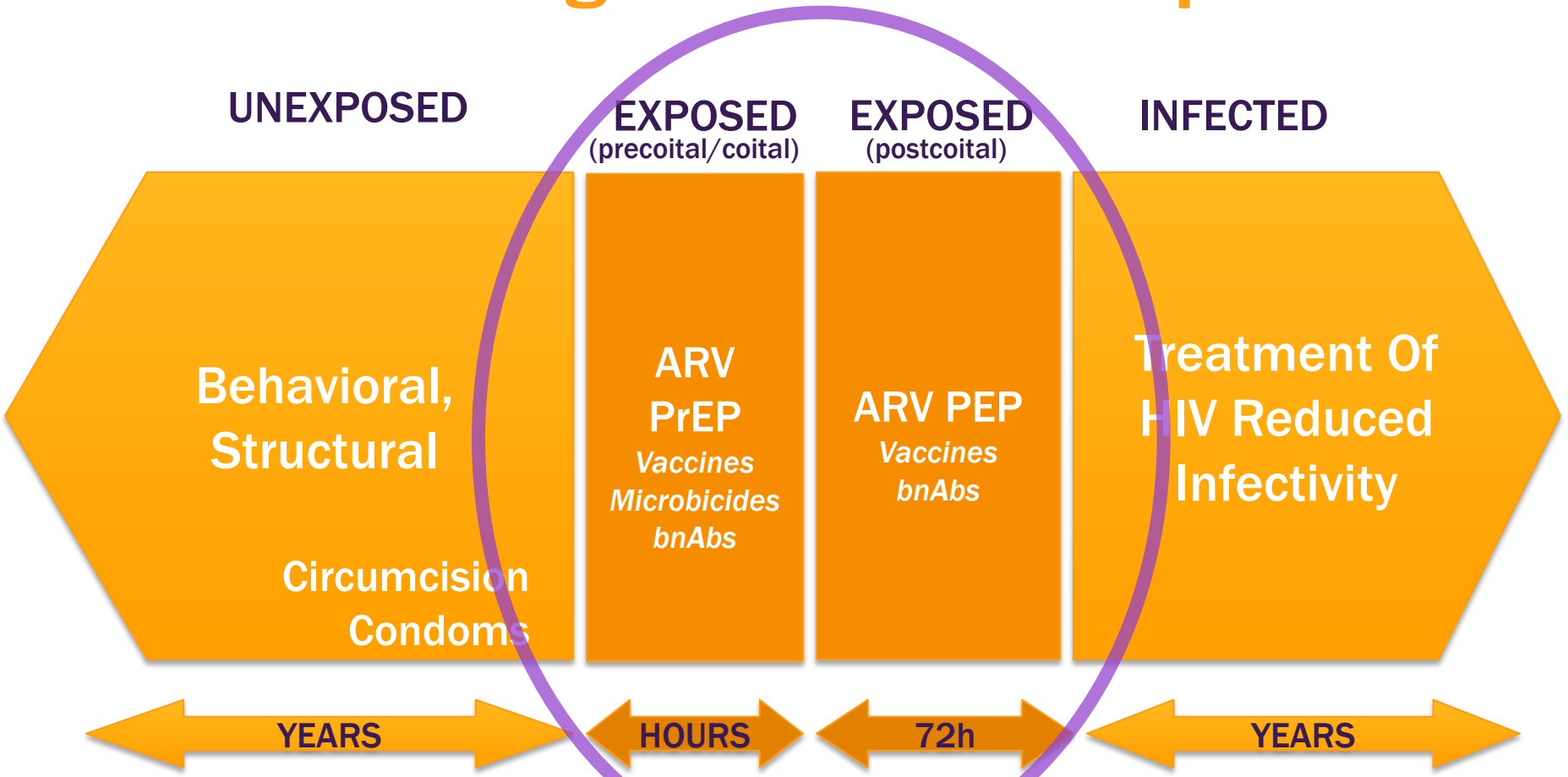
*Daily Truvada®; alternate regimens still in research ‡Still in research

With thanks to Carl Dieffenbach & Jeff Schouten

Consider an Analogy

PREGNANCY PREVENTION	HIV PREVENTION
Education & behavior modification	Education & behavior modification
Condoms 	Condoms 
Birth control pill 	PrEP 
"Morning-after pill" 	PEP 
Spermicide 	Topical microbicides 
Implantable birth control 	Antibody-mediated Prevention (bnAbs) 
Vasectomy/Tubal Ligation	Vaccination 

What is Missing to Address the Epidemic?



Thanks to Mike Cohen for this slide.
Cohen et al, JCI, 2008; Cohen IAS 2008

HIV Prevention in SSA Women: The Gap

- **HIV-1 prevention interventions demonstrated to be effective in reducing HIV-1 risk are inadequate**
  - **Condom use, HIV/STI testing** - Require participation/consent of male partner
  - **PrEP** - Achieving high adherence, especially among young SSA women, has been a central challenge (VOICE, Fem-PrEP)
  - **Microbicides** - Data suggest young SSA women wanted a product they could use to reduce their risk, but that microbicides did not fit into the realties of their daily lives (VOICE, FACTS 001)
- **Inadequate prevention options for women unable to negotiate safe sex practices**
- **Developing HIV-1 prevention options that SSA women can use remains a global concern**

The HVTN 703/HPTN 081 AMP Study: Filling the Gap

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.

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 VACCINE
TRIALS NETWORK

Another name for The AMP Study in SSA is

HVTN 703/HPTN 081

AMP Research Sites

AMP sub-Saharan Africa Sites

- Gabarone, 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

The HVTN 703/HPTN 081 AMP Study: Defining a new path forward

This is the first trial to assess if antibodies can be used to prevent HIV infection in women in sub-Saharan Africa, similar to how antibodies are used to prevent other infectious diseases.

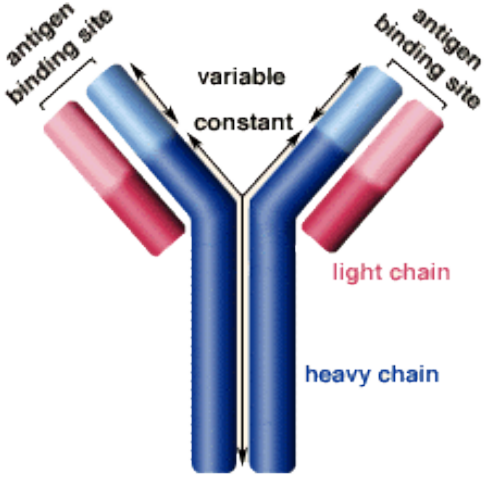
There is a Long History of Using Antibodies to Prevent Viral Infections

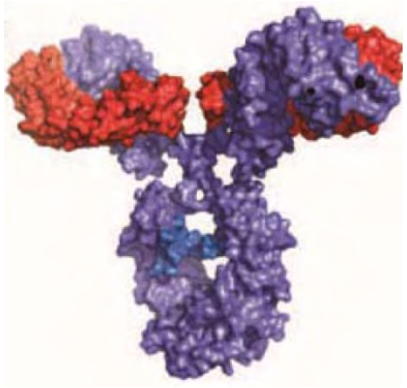
VIRUS	PRODUCT DESCRIPTION	INDICATION
Measles	Concentrated human gamma globulin	Prevention
Polio	Concentrated human gamma globulin	Prevention
CMV	Cytomegalovirus Immune Globulin	Prevention
Hepatitis A	Immune serum globulin (ISG)	Prevention (travel)
Hepatitis B	Hepatitis B Immune Globulin	Post Exposure
Rabies	Rabies Immune Globulin	Post Exposure
RSV	mAb (palivizumab) for prophylaxis of high risk infants	Prevention in High Risk Infants
VZ	Varicella Zoster Immune Globulin	Post Exposure

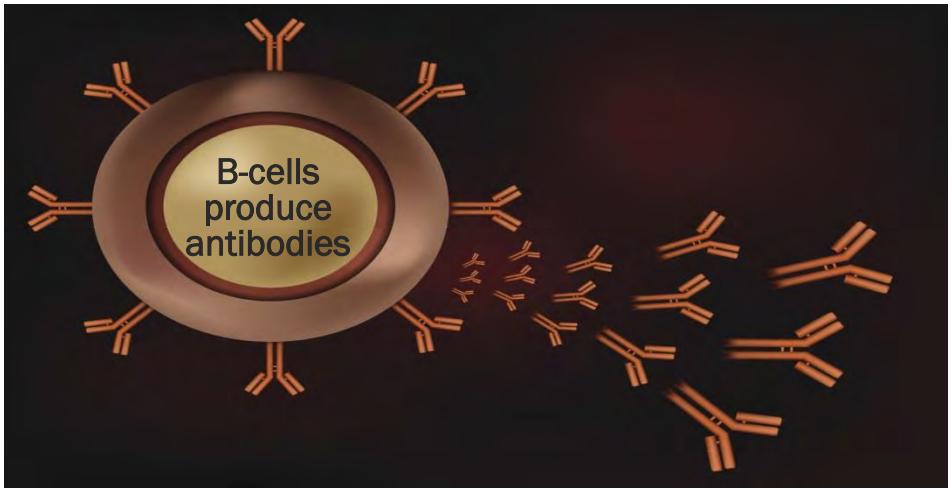
And, most effective vaccines induce antibodies that neutralize the pathogen.

Thanks to John Mascola for this slide.

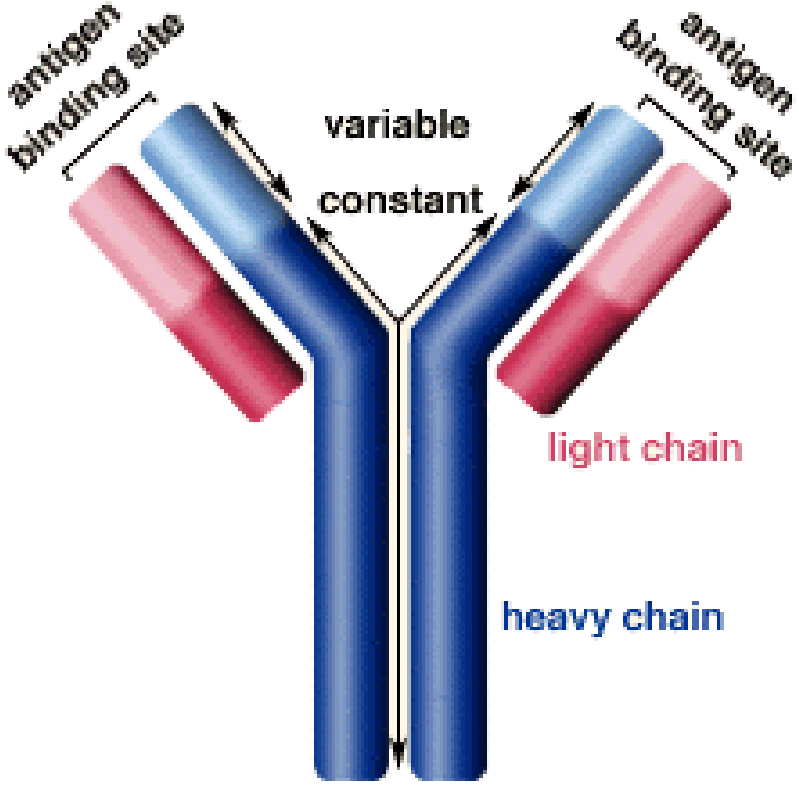
What is an Antibody?







How Does an Antibody Work?



NEUTRALIZATION

Binds to HIV & blocks its attachment to host cells

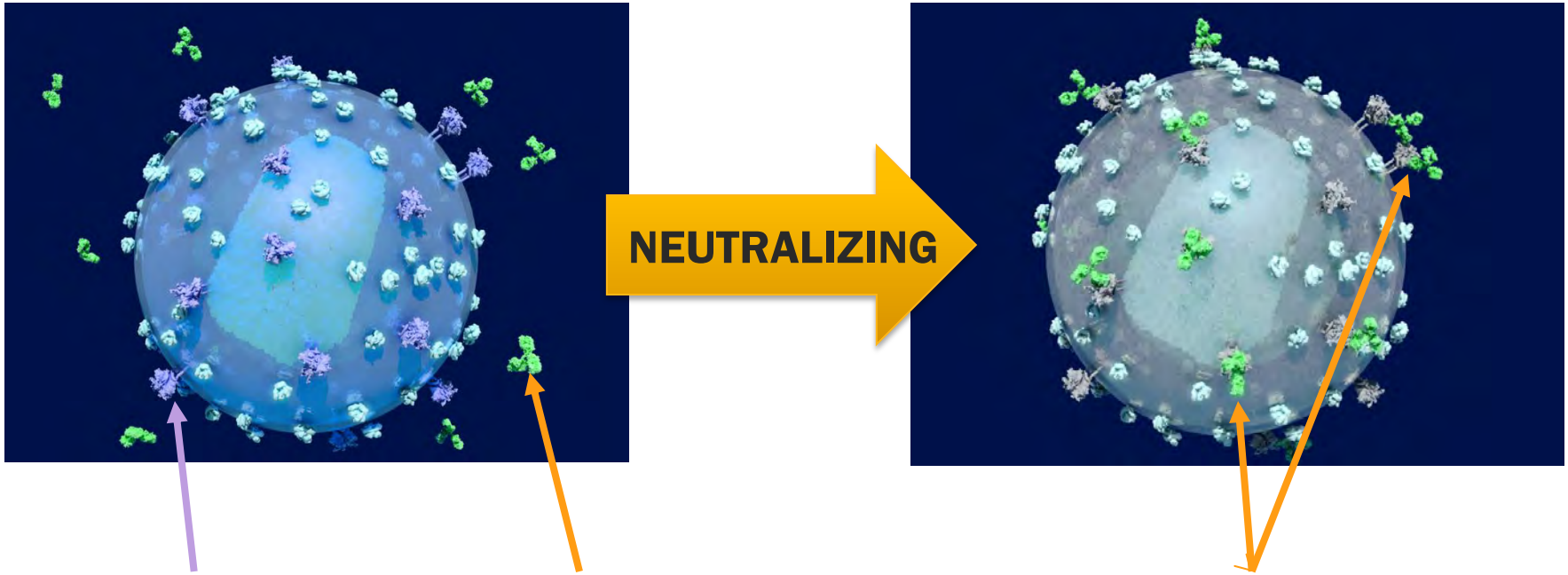
OPSONIZATION
("buttering the toast")

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

SENSITIZATION
("the lookout for the hitman")

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

Neutralizing Antibodies



Thanks to Lisa Donohue for these images.

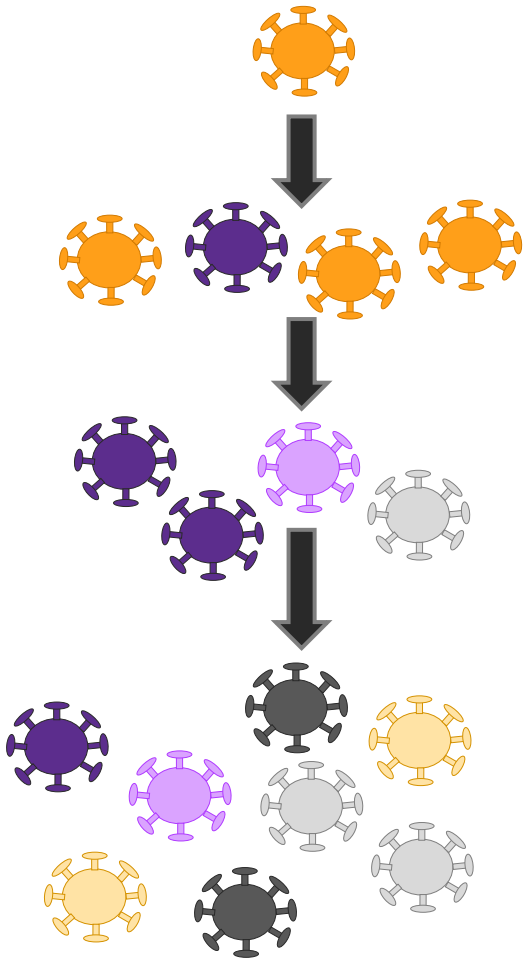
Neutralization Animation Goes Here

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

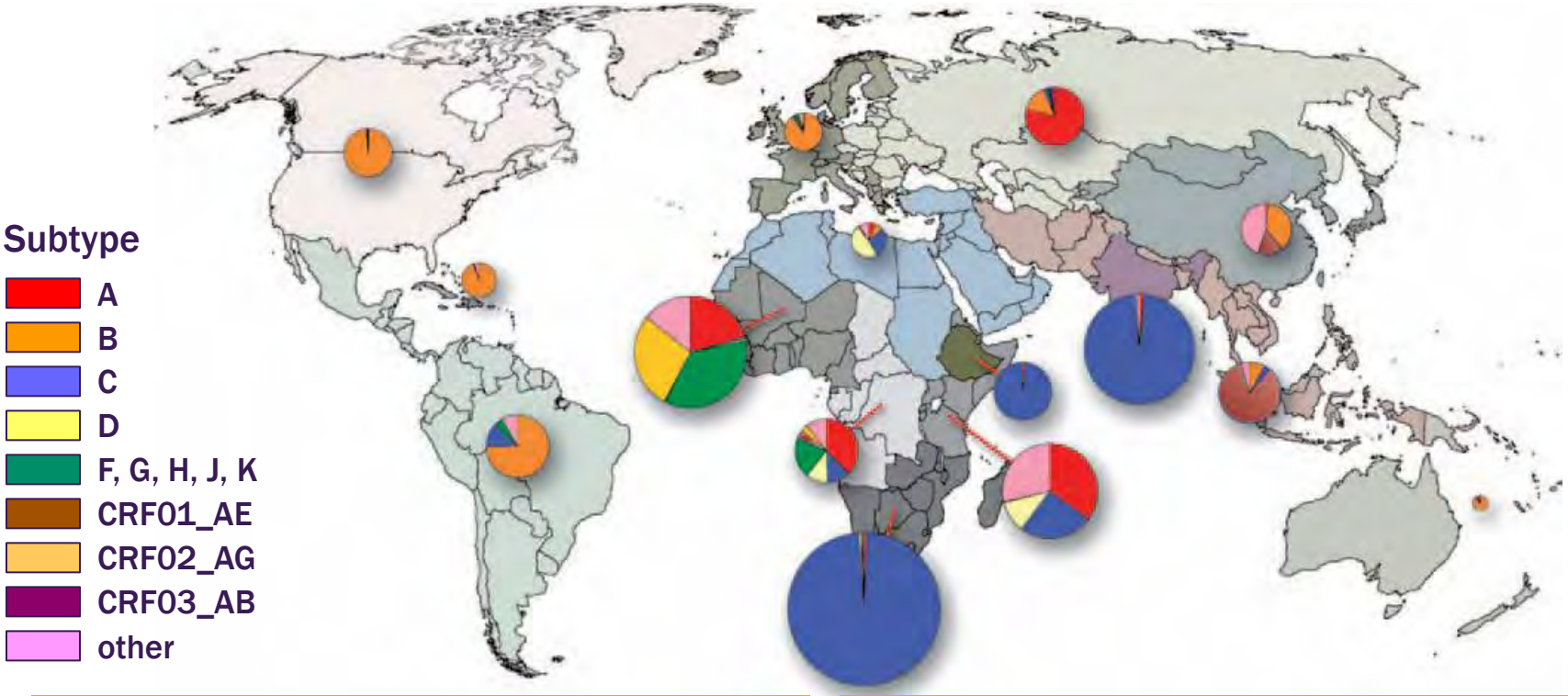
Produces BILLIONS of new virions a day

↑ Mutations with viral replication

Rapidly develop multiple lineages or "quasispecies"

HIV-1 Diversity Worldwide

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



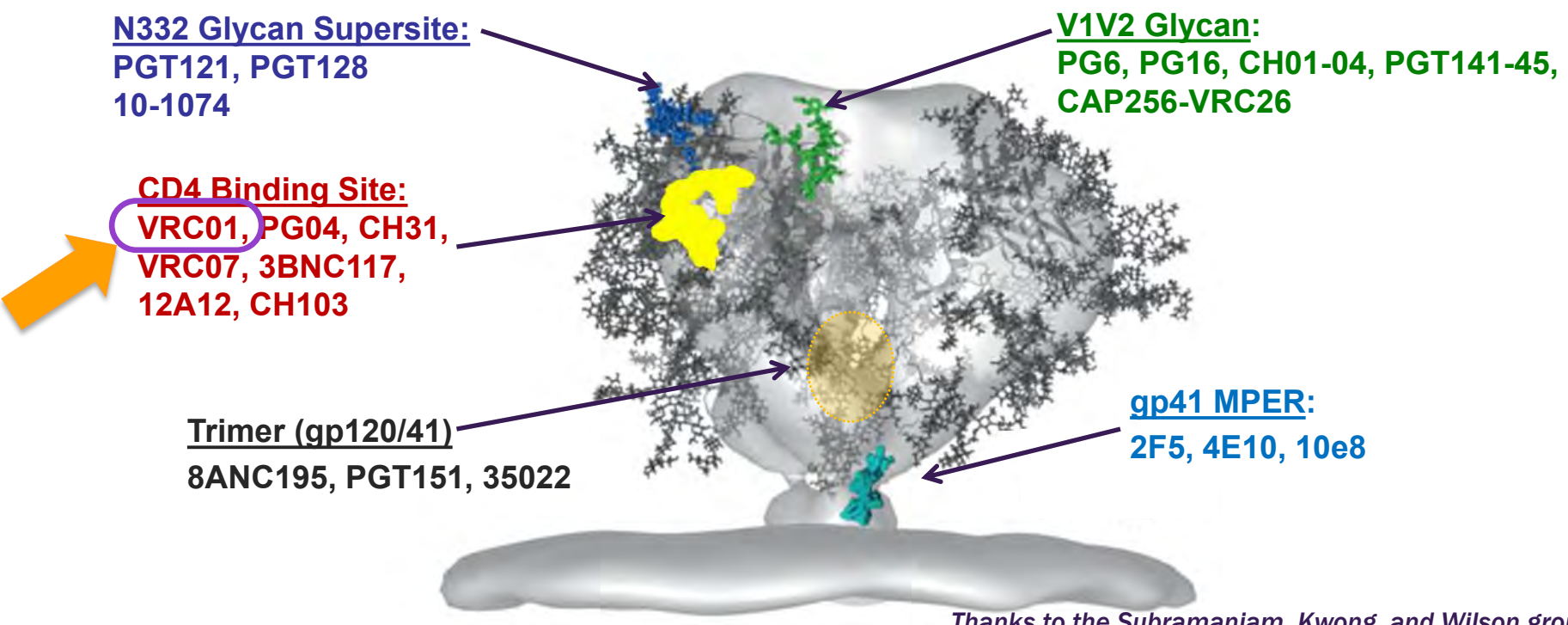
HIV genomes differ by 10-30%

Human genomes differ by about 0.1%

Hemelaar et al. 2004. WHO/UNAIDS.

What is a Monoclonal Antibody (mAb) 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



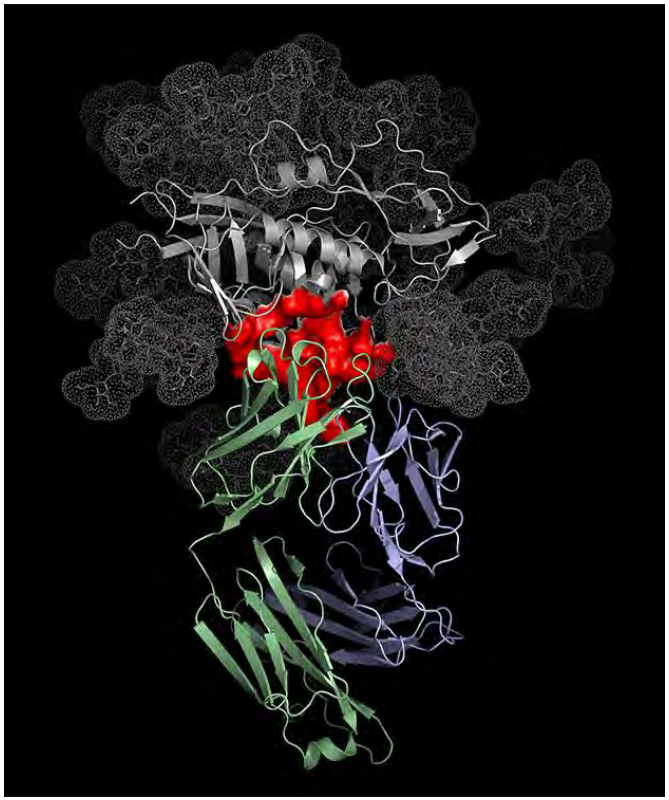
Thanks to the Subramaniam, Kwong, and Wilson groups.

OUTLINE: AMP Science

- ✓ HIV Prevention in sub-Saharan Africa
- ✓ The AMP Study: a brief introduction
- ✓ Antibodies: what they are & how they work
- ✓ Antibody Vocabulary: bnAbs, mAbs
- **The AMP Study Antibody: VRC01**
- **And it all comes together: The AMP Study**
  - What questions does the AMP Study help answer?
  - What does the AMP Study ask of a participant?
- **Questions???**

VRC01: The AMP Study Antibody

- 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.

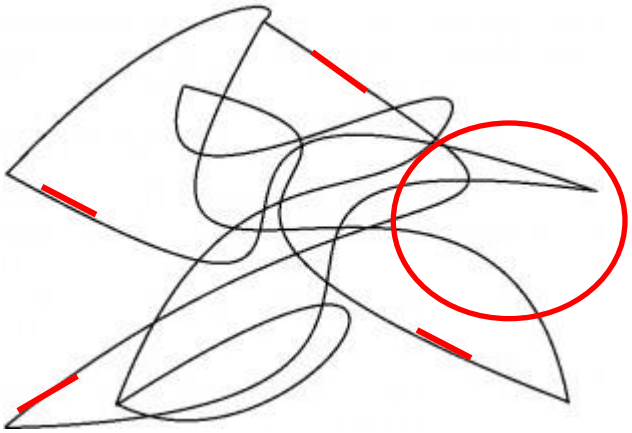


Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

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

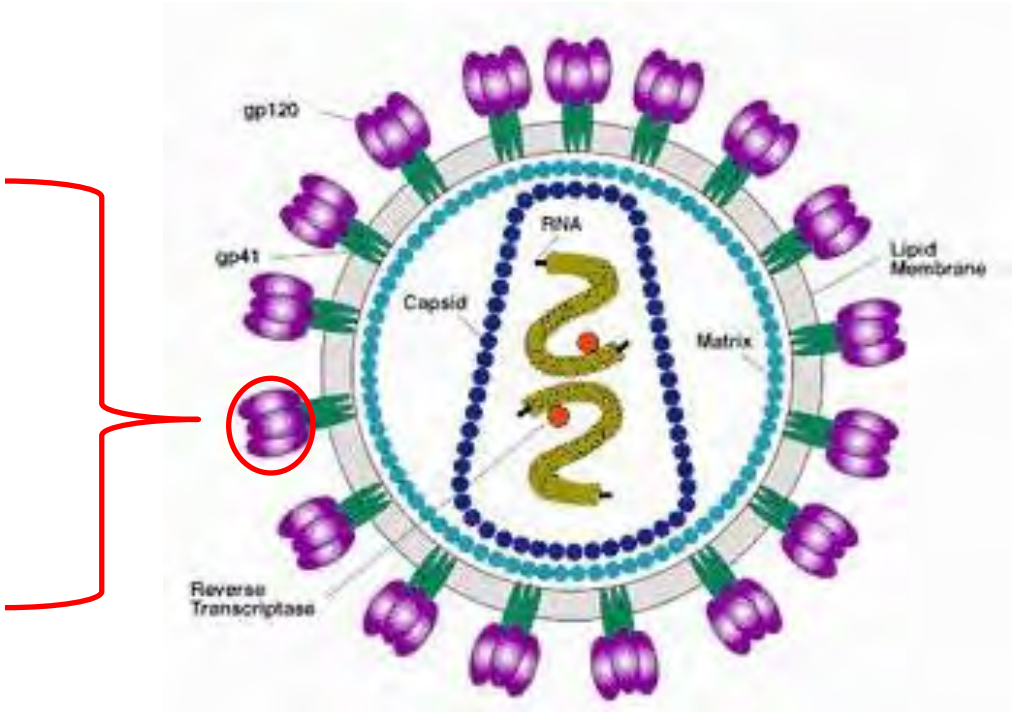


Image credit: NIAID

Why Evaluate VRC01?

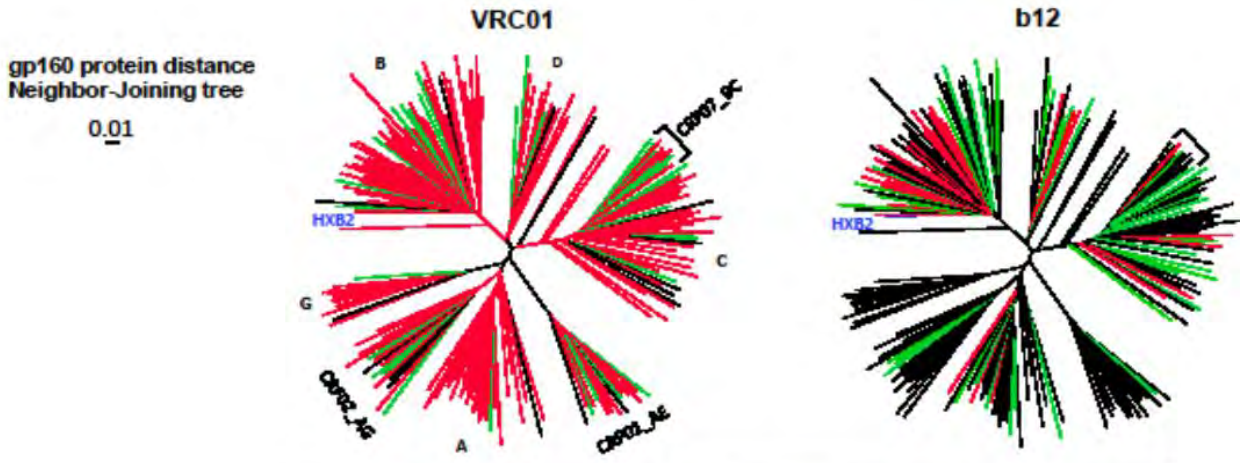
PREVENTION

- **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

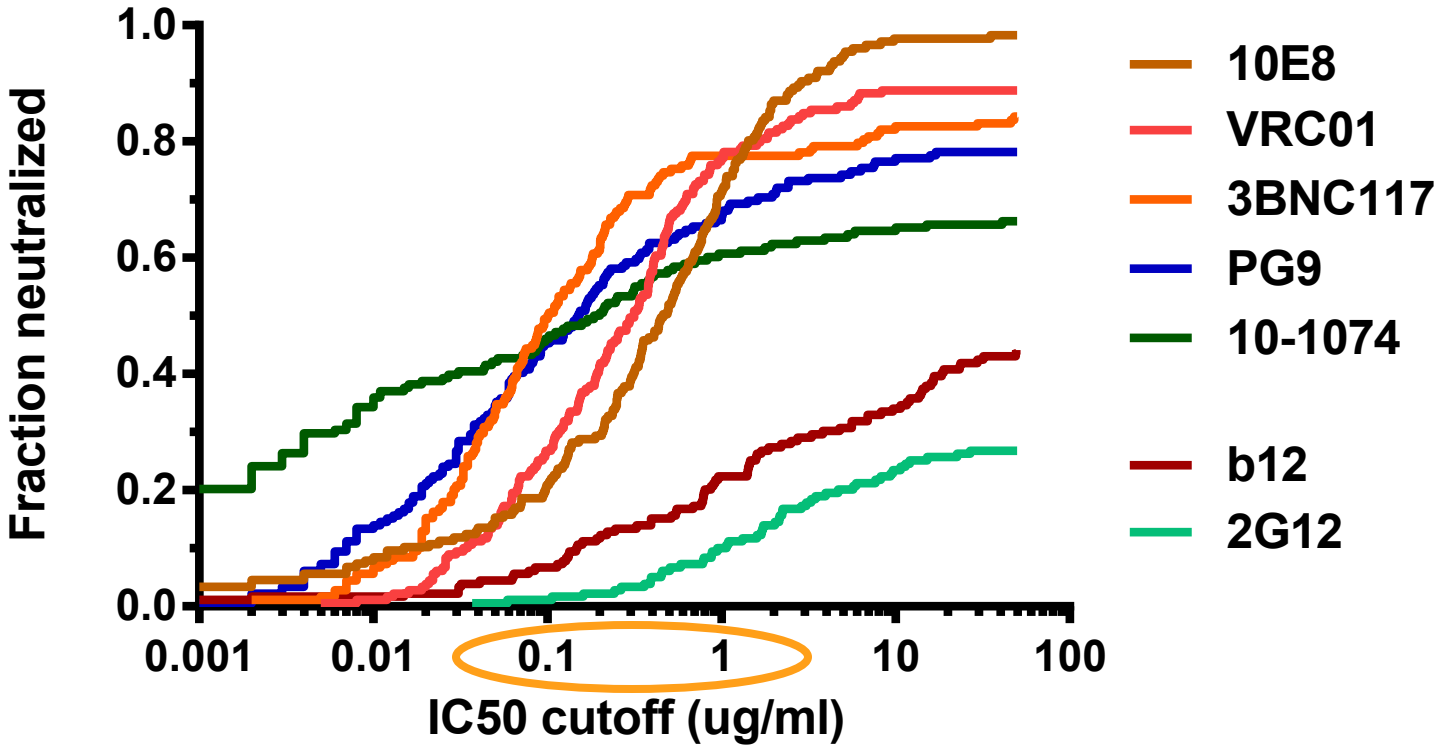


Virus clade	Number of viruses	IC_{50} < 50 µg/ml		IC_{50} < 1 µg/ml	
		VRC01	b12	VRC01	b12
A	22	100%	45%	95%	23%
B	49	96%	63%	80%	39%
C	38	87%	47%	66%	13%
D	8	88%	63%	50%	25%
CRF01_AE	18	89%	6%	61%	0%
CRF02_AG	16	81%	19%	56%	0%
G	10	90%	0%	90%	0%
CRF07_BC	11	100%	27%	45%	9%
Other	18	83%	33%	78%	6%
Total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

Tested Against 190 Different "Types" or Strains of HIV

Wu et al. Science. 2010

VRC01 is a Potent Antibody

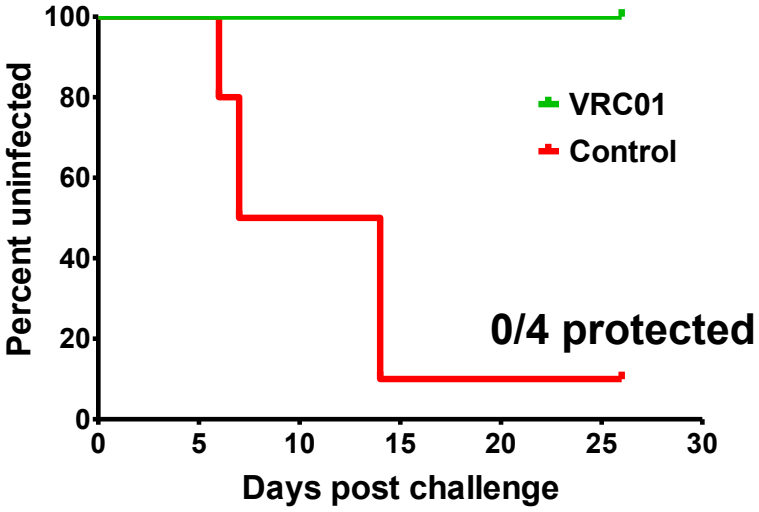


Thanks to David Montefiori & CAVD and Bob Bailer & NVITAL Laboratory

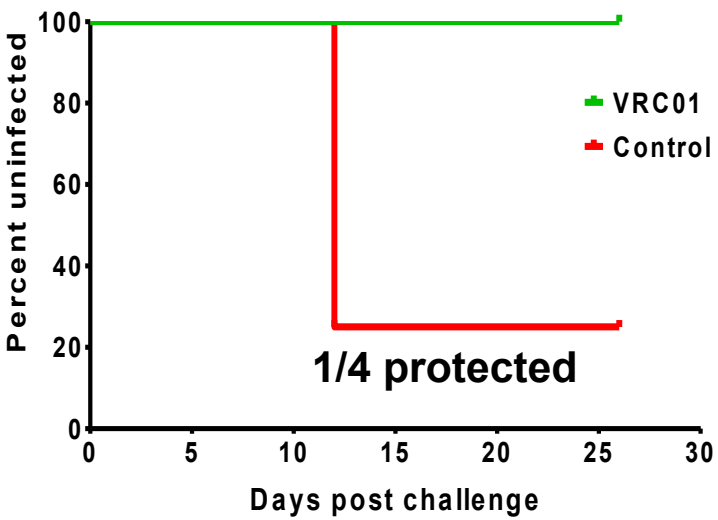
VRC01 in Preclinical (NHP) Trials

20 mg/kg infusion of VRC01

RECTAL CHALLENGE
4/4 PROTECTED



VAGINAL CHALLENGE
4/4 PROTECTED



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

- **3 Phase 1 trials: VRC601, VRC602, HVTN 104**
- **Safe, well-tolerated in >100 participants, >250 infusions**
  - No related serious “adverse events”
  - Mild adverse events only, which included mild lab changes in liver & kidney tests

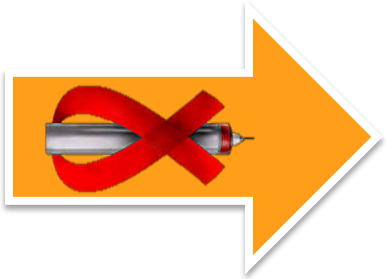
How Could VRC01 be a Prevention Tool?

- 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”

How Could VRC01 Help Us Find an HIV Vaccine?

No HIV vaccine has (yet) been able to teach the body to make (enough) neutralizing antibody to prevent HIV.

- How much neutralizing antibody is enough?
- How good are non-human "models" in the lab and in practical (NHP) studies?



ANSWERING THESE QUESTIONS CAN HELP US FIND A SAFE, EFFECTIVE HIV VACCINE MORE QUICKLY & LESS EXPENSIVELY.

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?

PrEP in the AMP Study

- US: PrEP as part of risk reduction counseling, including referral to PrEP providers & Truvada at no drug cost for interested ppts
- South America: PrEP Demonstration Projects for interested ppts
- Sub-Saharan Africa: WHO PrEP guidelines issued but PrEP not yet available in the public sector; work with stakeholders; respect in-country leadership & follow in-country guidelines as they evolve

AMP Study Design: HVTN 703/HPTN 081, version 1

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	800	500	1300	10 infusions total & Infusions every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	800	500	1300	
Control	800	500	1300	
Total	2400	1500	3900	

Study Schema for the AMP Study in sub-Saharan Africa

Planned version 2.0 of HVTN 703/HPTN 081 administratively splits the two cohorts into two regionally distinct protocols, providing for sovereign regulatory oversight in SSA, contributing local and regional expertise. Data is shared across the trials and trial design remains the same.

REGIMEN	Women in sub-Saharan Africa	
VRC01 10 mg/kg	500	10 infusions total & Infusions every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	500	
Control	500	
Total	1500	

The AMP Study in SSA: Selected Eligibility Criteria

- 18-50 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

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

STUDY DURATION: about 22 months

And Why Do We Ask This of Our Participants?

Because we want to END HIV…

- Whether through an antibody delivered by an IV
- Or through an HIV vaccine developed more quickly because of The AMP Study

…and our participants want to END HIV, too.

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THANK YOU!

HVTN 703/HPTN 081 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
STUDY

QUESTIONS?

SUPPLEMENTAL SLIDES

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 enrolment

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

Phase I Dose Escalation, Safety, and PK Studies VRC 601 & VRC 602

VRC 601:

IV or SC in HIV-Infected Adults

Group	N	Days 0 and 28
1	5	1 mg/kg IV
2	5	5 mg/kg IV
3	5	5 mg/kg SC
4	5	20 mg/kg IV
5	5	40 mg/kg IV
17 clinical visits and 28 PK blood draws per subject		

VRC 602:

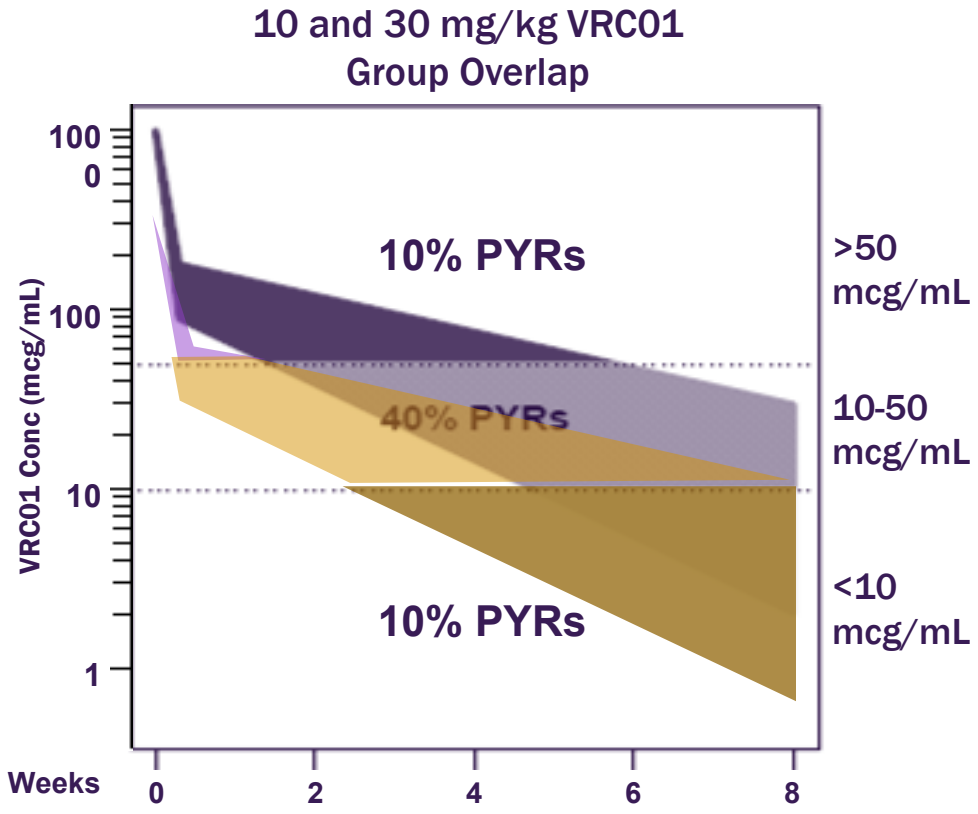
IV or SC in Healthy, HIV-Uninfected Adults

Group	N	Days 0 and 28
1	5	5 mg/kg IV
2	5	20 mg/kg IV
3	5	40 mg/kg IV
4	9	5 mg/kg or Placebo SC
16 clinical visits and 28 PK blood draws per subject		

Phase I Safety and PK Study: HVTN 104

		HVTN 104: Study product administration schedule in months (days)											
Gp	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	IV placebo for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01	SC pl for VRC01
4	12	VRC01 10mg/kg IV				VRC01 10mg/kg IV				VRC01 10mg/kg IV			
5	12	VRC01 30mg/kg IV				VRC01 30mg/kg IV				VRC01 30mg/kg IV			
Total	88	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered by needle and syringe injection											

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			