

# 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???

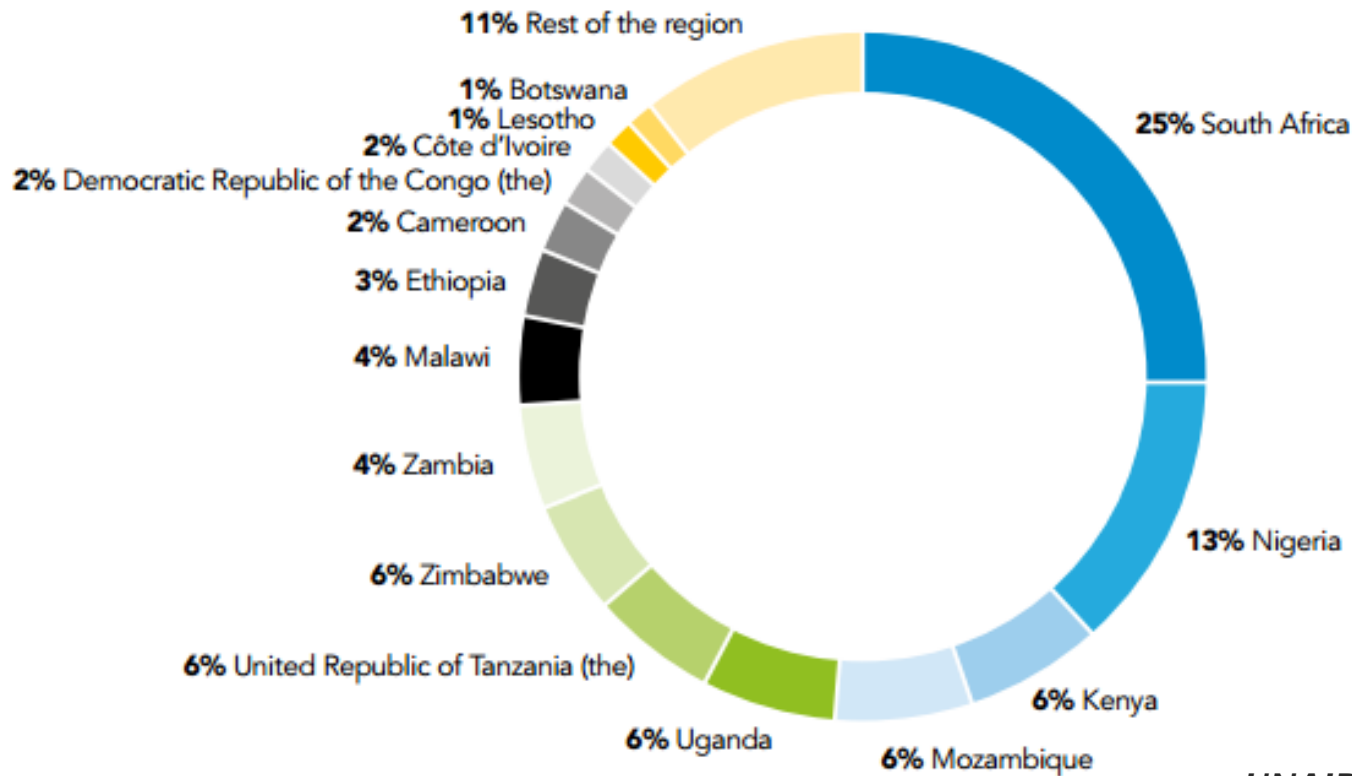
# Where is the HIV Prevention Field?

## 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

People living with HIV in sub-Saharan Africa, 2013



Source: UNAIDS 2013 estimates

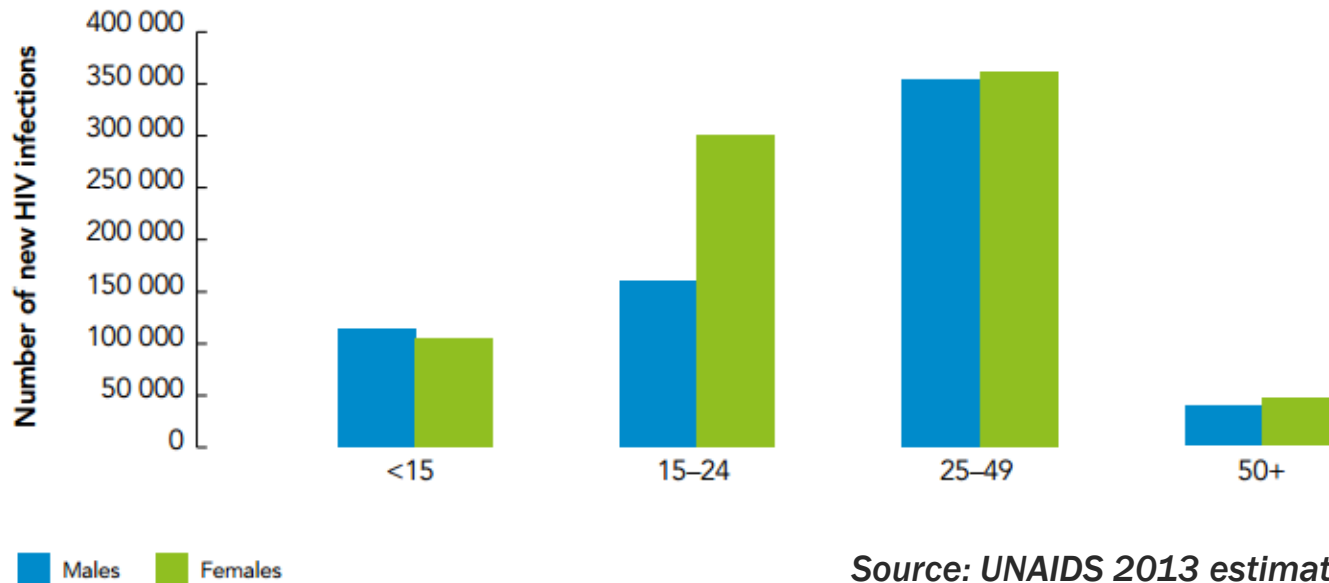
UNAIDS Gap Report, 2014

# 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

New HIV infections in sub-Saharan Africa, by age and sex, 2013



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<sup>†</sup>**
- **Intra vaginal rings<sup>†</sup>**
- **Vaccination<sup>†</sup>**














\*Daily Truvada®; alternate regimens still in research

<sup>†</sup>Still in research

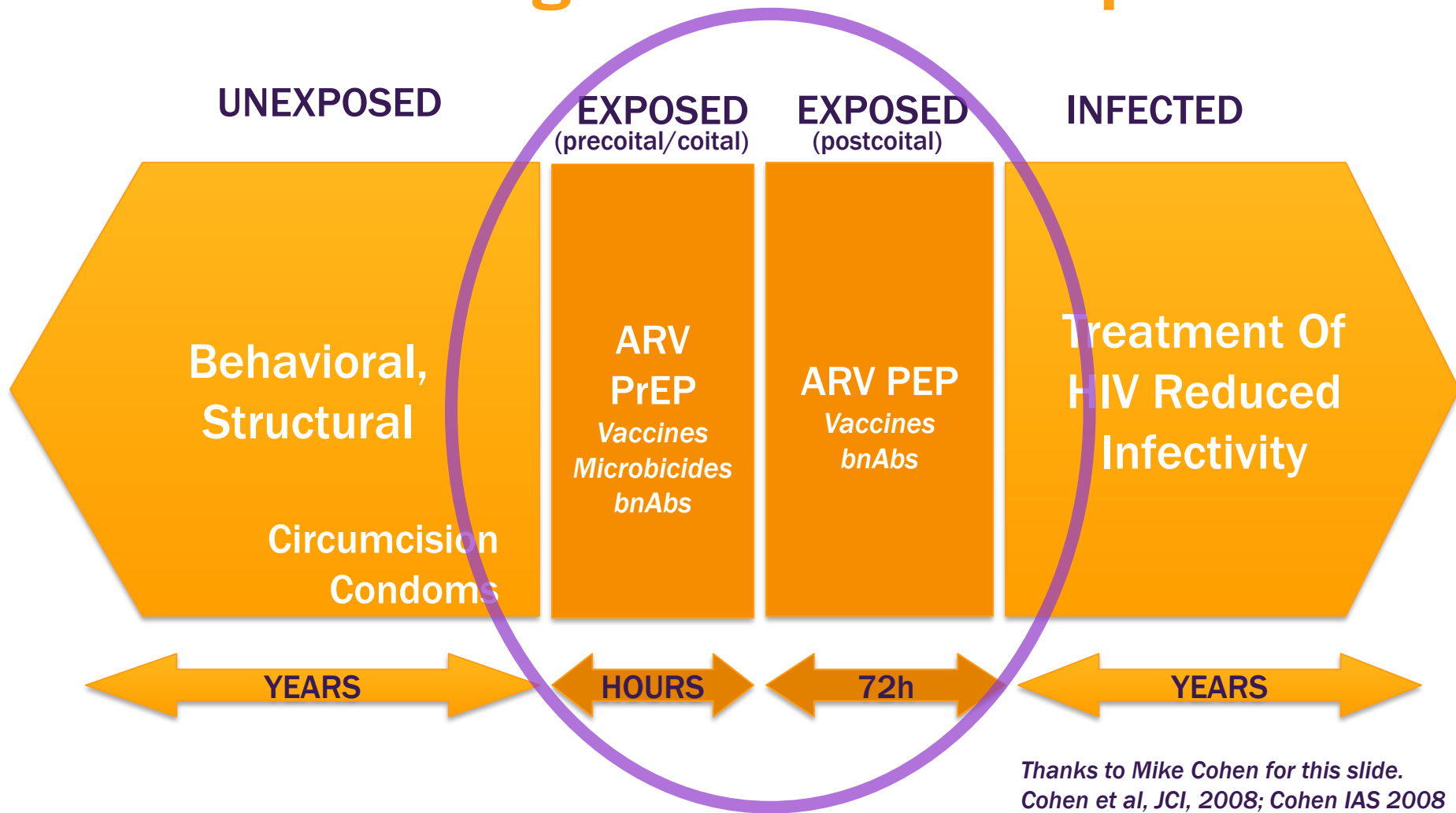
With thanks to Carl Dieffenbach & Jeff Schouten

# 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/IVRs** - Achieving high adherence, especially among young SSA women, has been a central challenge (VOICE, ASPIRE, The Ring Study )
  - **Microbicides** - Data suggest young SSA women wanted a product they could use to reduce their risk, but that microbicides did not fit into the realities 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.

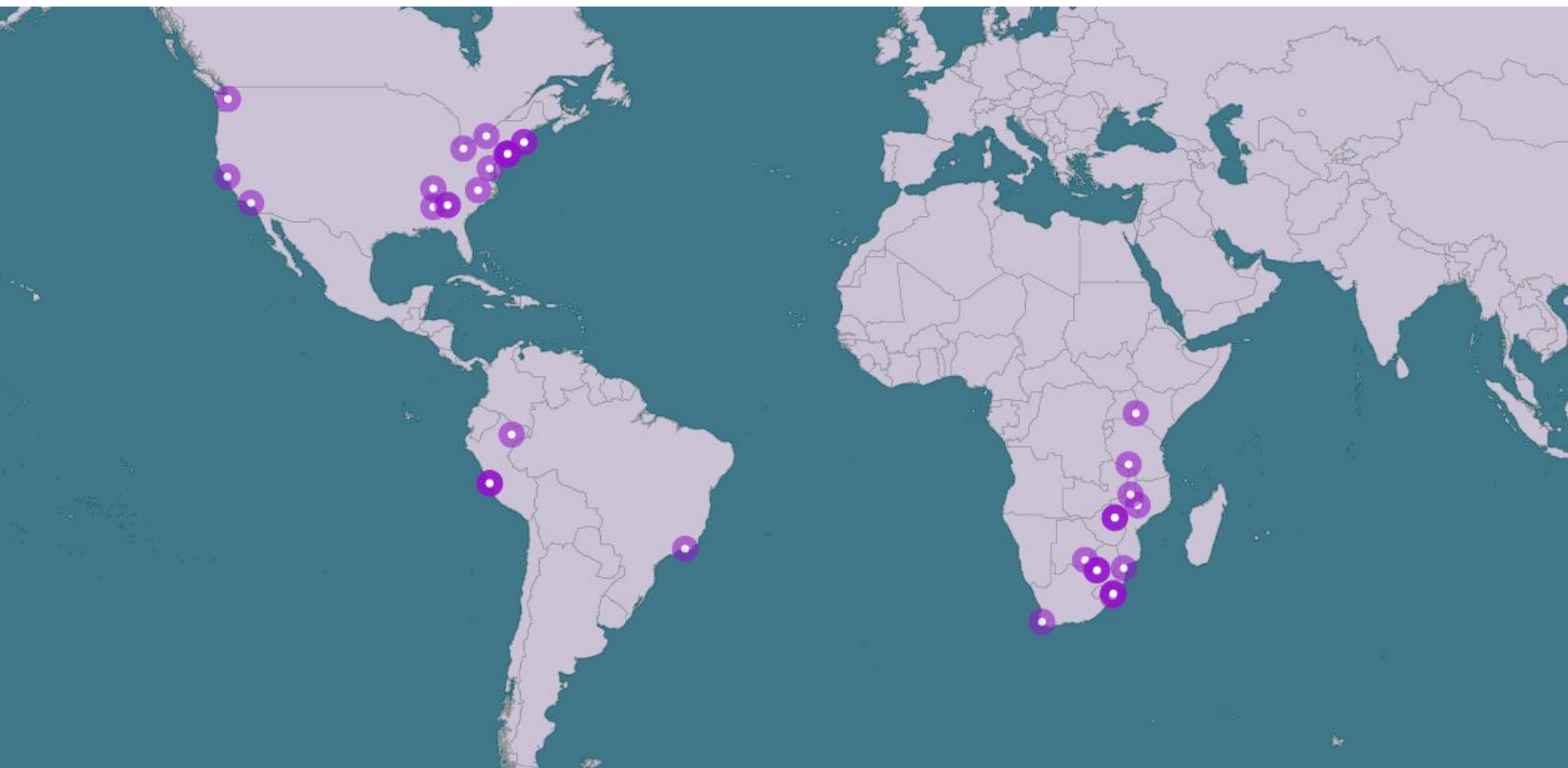


HIV VACCINE  
T R I A L S   N E T W O R K

Another name for The AMP Study in SSA is

**HVTN 703/HPTN 081**

# AMP Research Sites



# AMP in sub-Saharan Africa

7 Countries



15 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.**



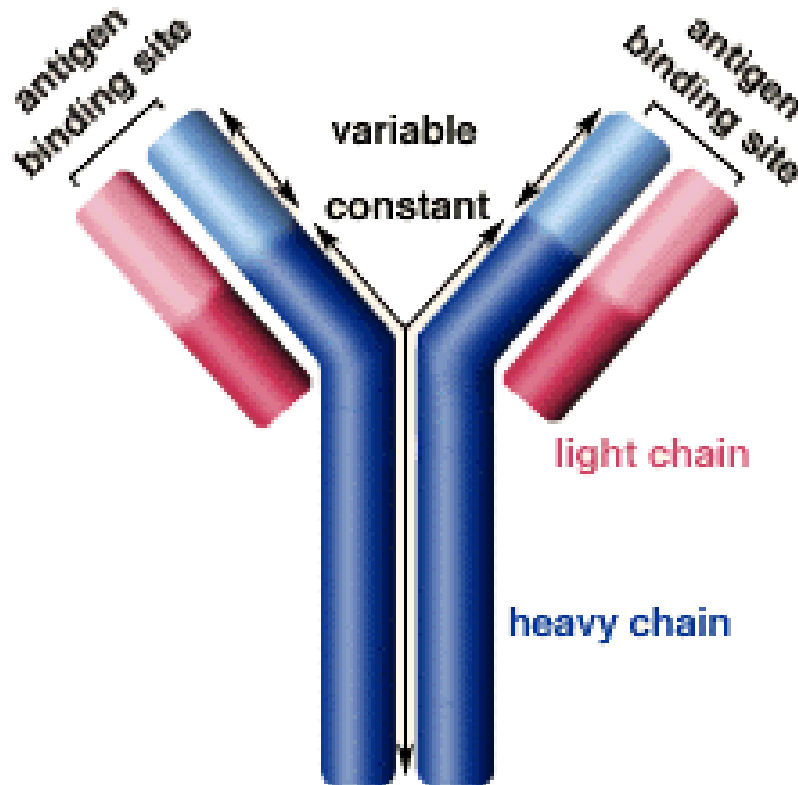
# There is a Long History of Using Antibodies to Prevent Viral Infections

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.*

# How Does an Antibody Work?



## NEUTRALIZATION

Binds to HIV & blocks its attachment to host cells

## OPSONIZATION

(“buttering the toast”)

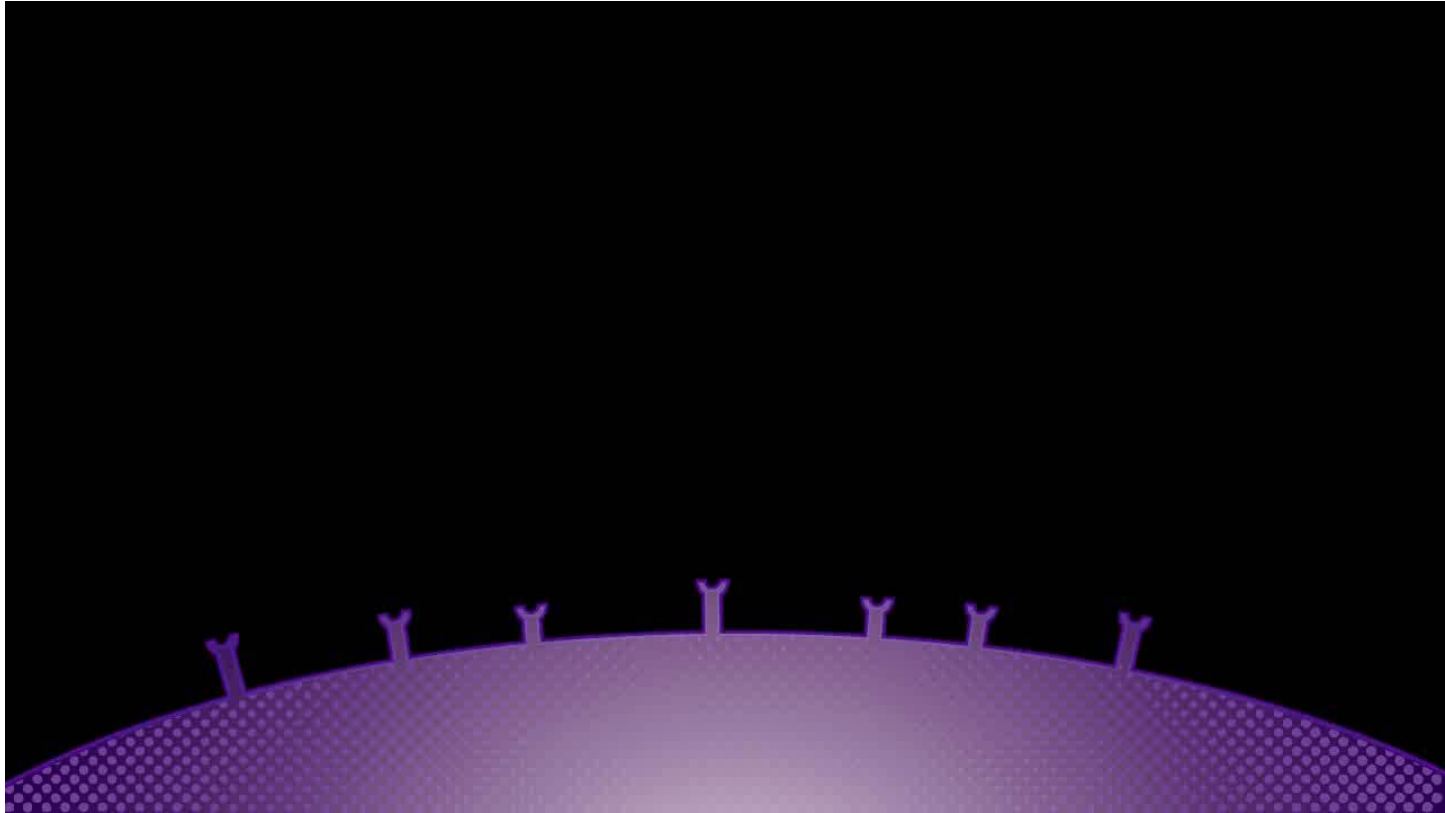
Binds to HIV, then binds to a macrophage; the macrophage then eats the HIV

## 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 Preventing HIV Infection



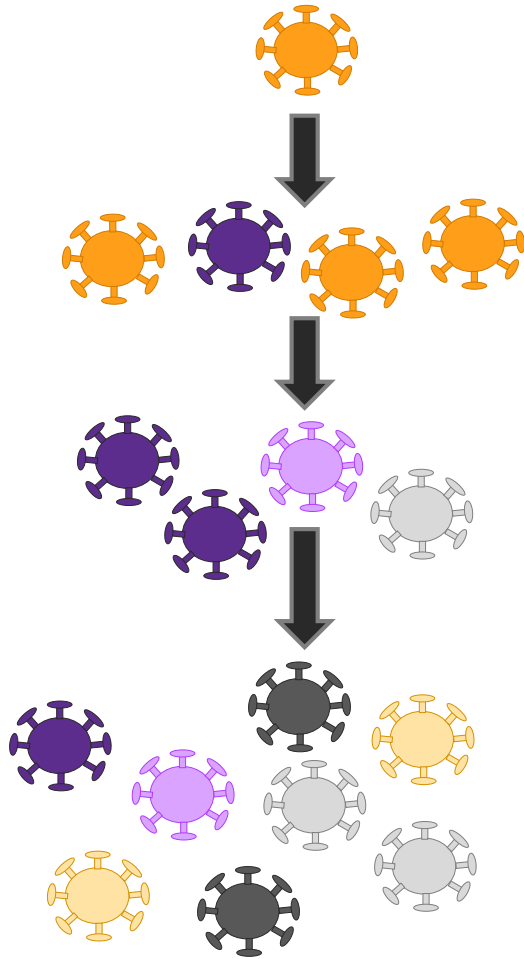
An example of a neutralising antibody is VRC01

# 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

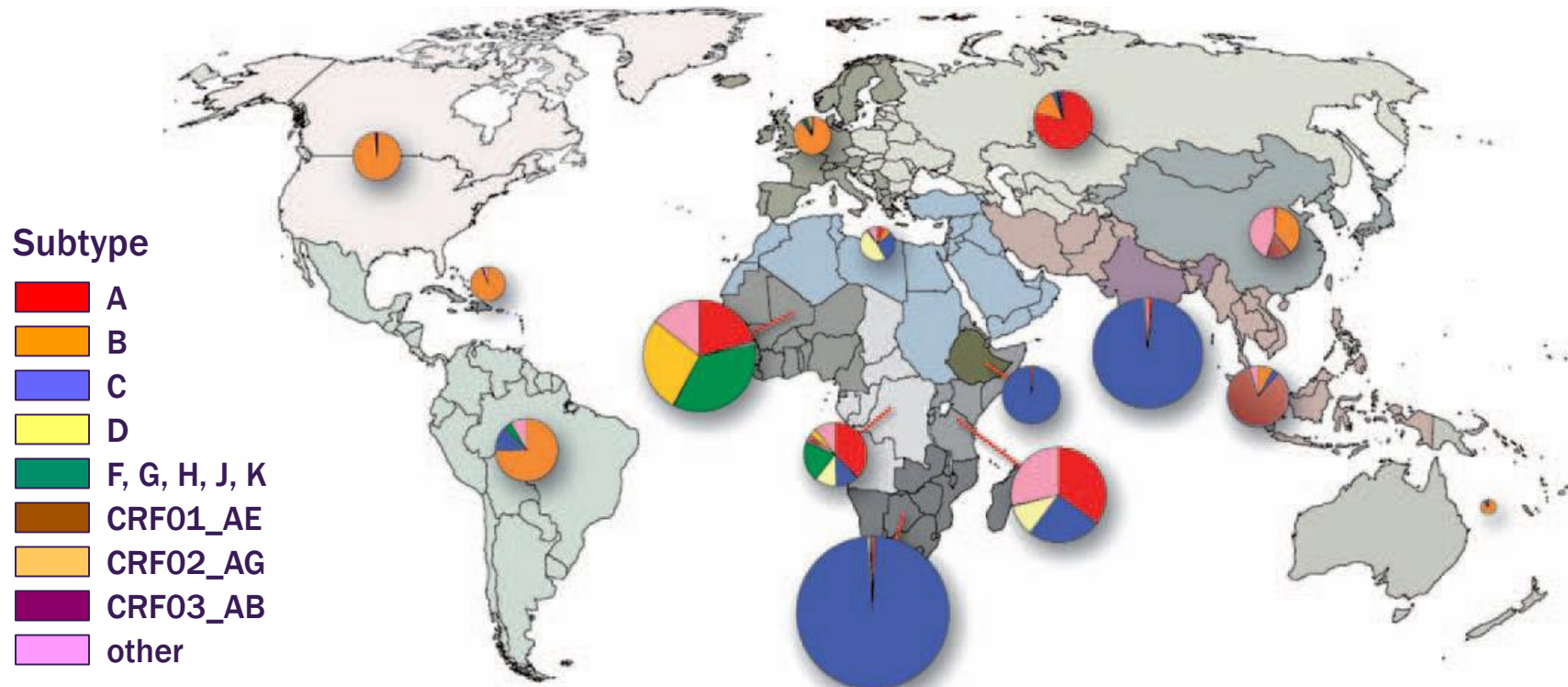
Produces BILLIONS of new virions a day

↑ 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%**

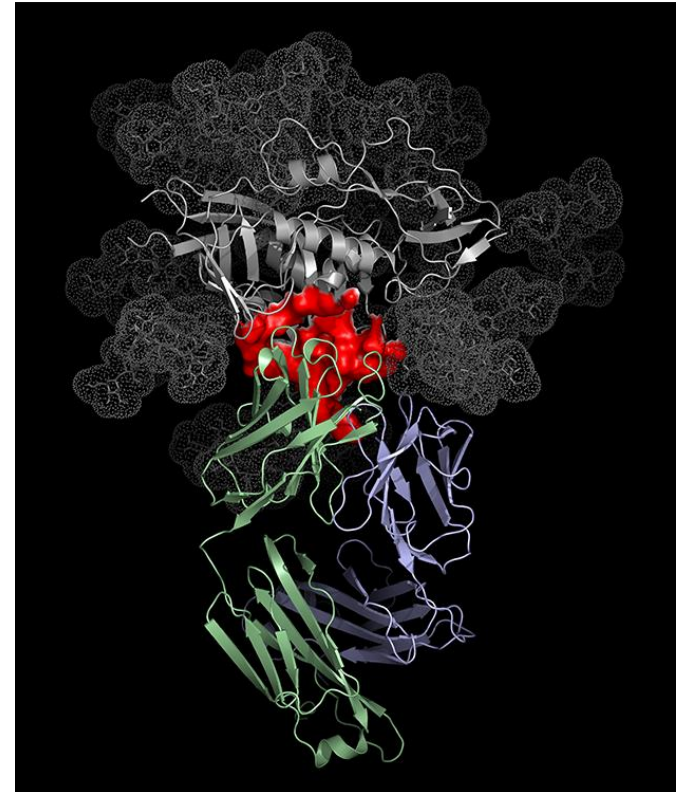
*Hemelaar et al. 2004. WHO/UNAIDS.*

# 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**
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- **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)



# Why Evaluate VRC01?

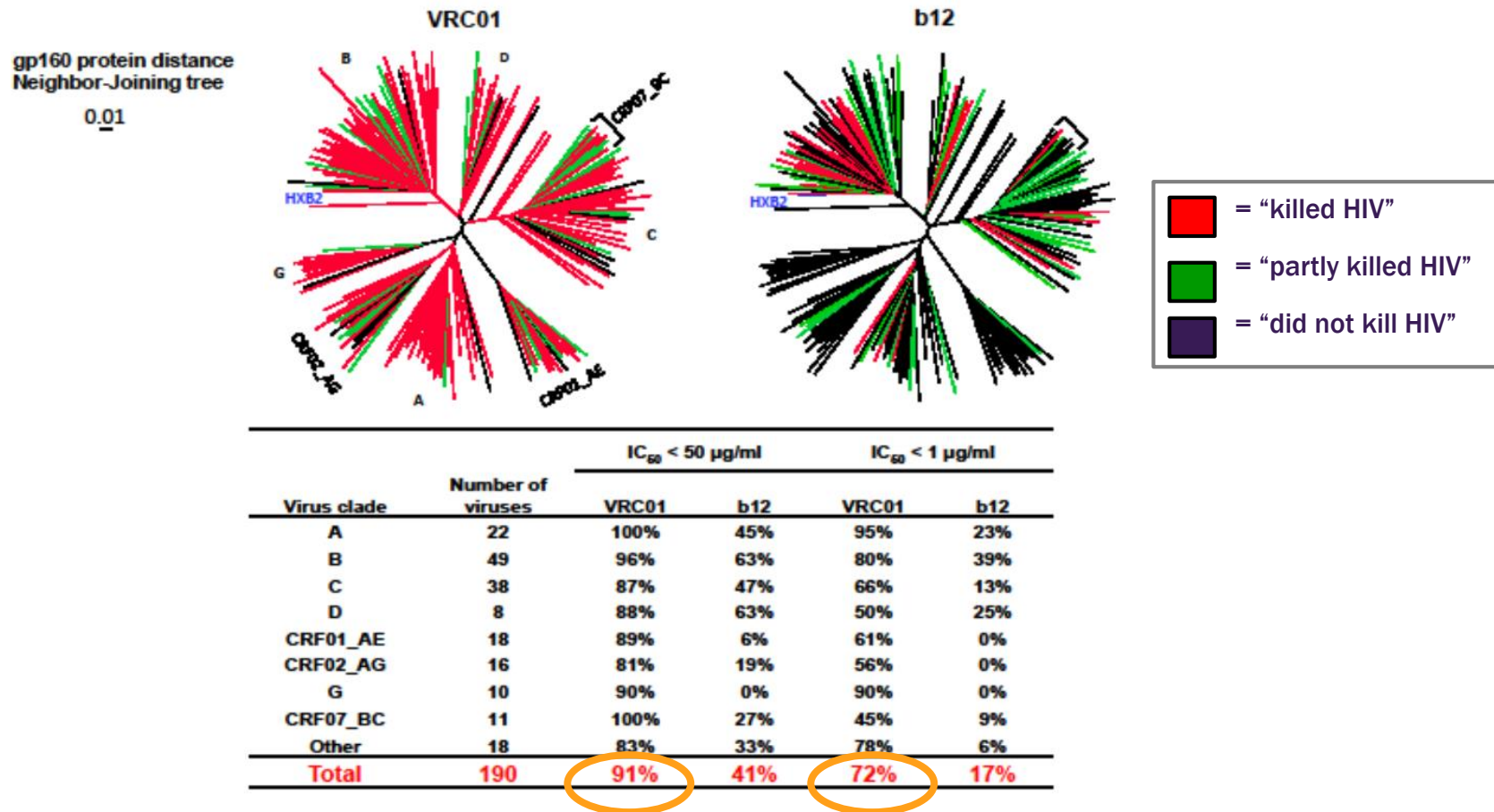
## PREVENTION

- **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

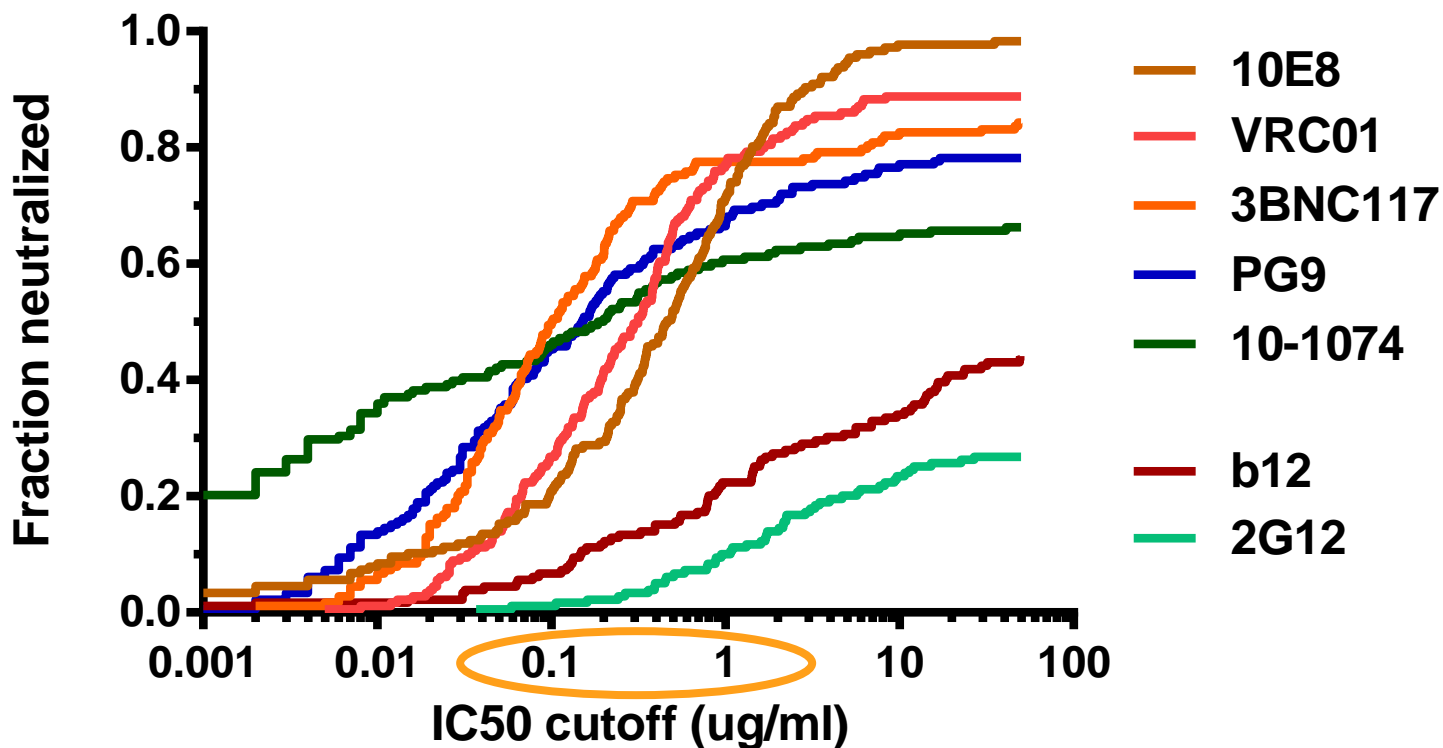
# VRC01 is a BROADLY NEUTRALIZING Antibody



Tested Against 190 Different "Types" or Strains of HIV

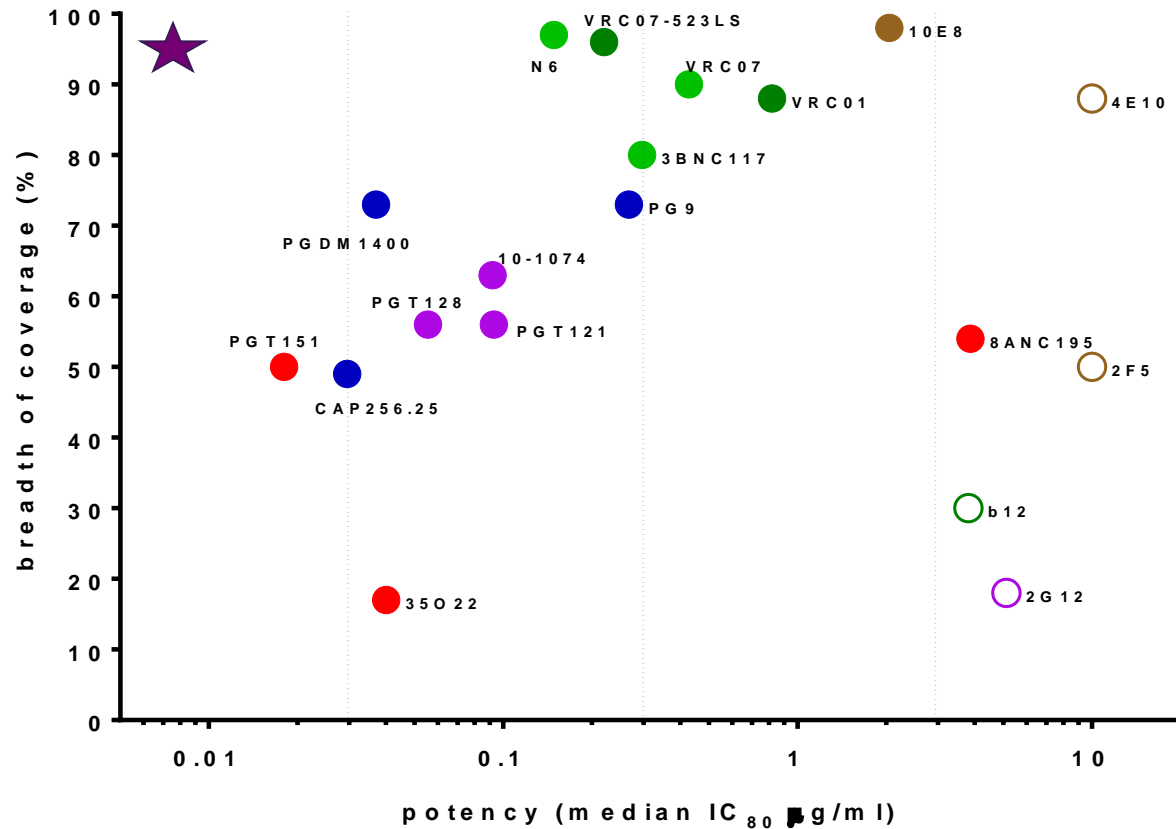
Wu et al. Science. 2010

# VRC01 is a Potent Antibody



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

# VRC01 is a Potent Antibody



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

# **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

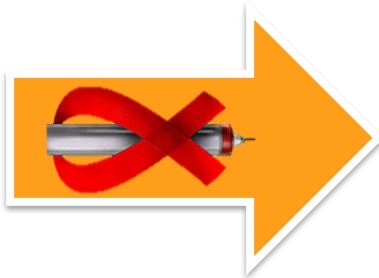
# How Could VRC01 be a Prevention Tool?

- 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?



# 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
VRC01 30 mg/kg	800	500	1300	
Control	800	500	1300	
<b>Total</b>	<b>2400</b>	<b>1500</b>	<b>3900</b>	Study duration: ~22 months

# 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
VRC01 30 mg/kg	500	
Control	500	
Total	1500	Study duration: ~22 months

# 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



# 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

# Conclusion

- Why do we care?
- Because we all want to **END HIV**...  
...and women in Africa want to **END HIV**, too.
- We want to empower African women



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# Review: AMP Science

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# THANK YOU!





# HVTN 703/HPTN 081 Protocol Team

- Chairs: Larry Corey & Mike Cohen
- co-Chairs: Sri Edupuganti & Nyaradzo Mgodl
- 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