Introduction to the Science of HVTN 703/HPTN 081

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Collaborative Research Program
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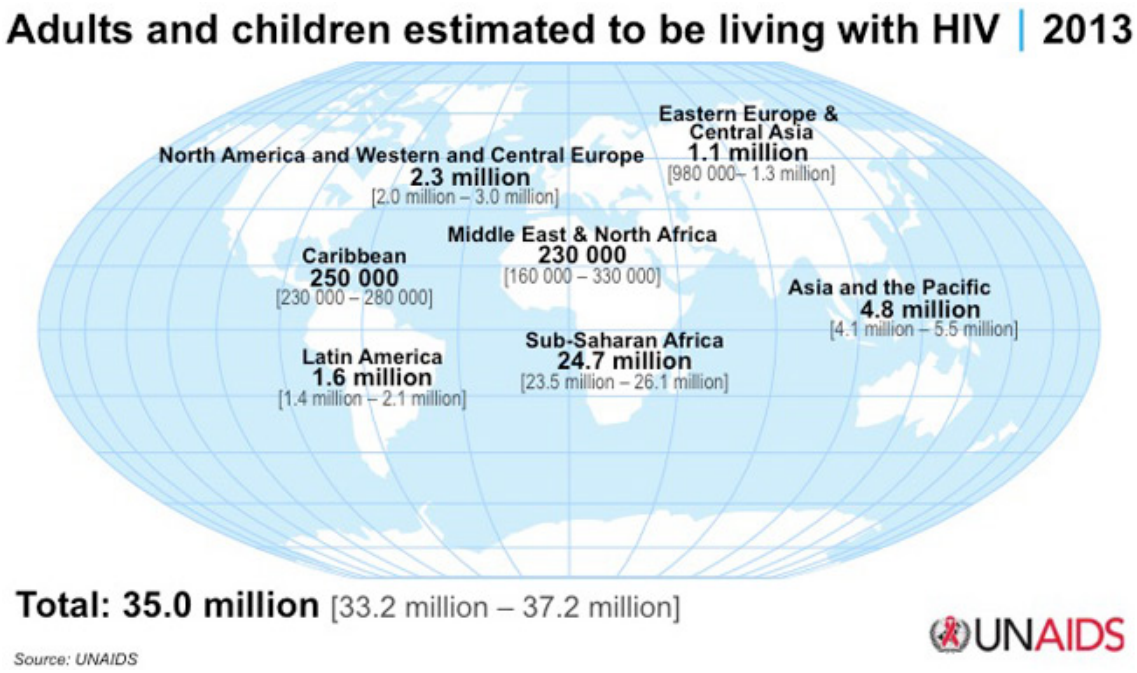
OUTLINE: AMP Science

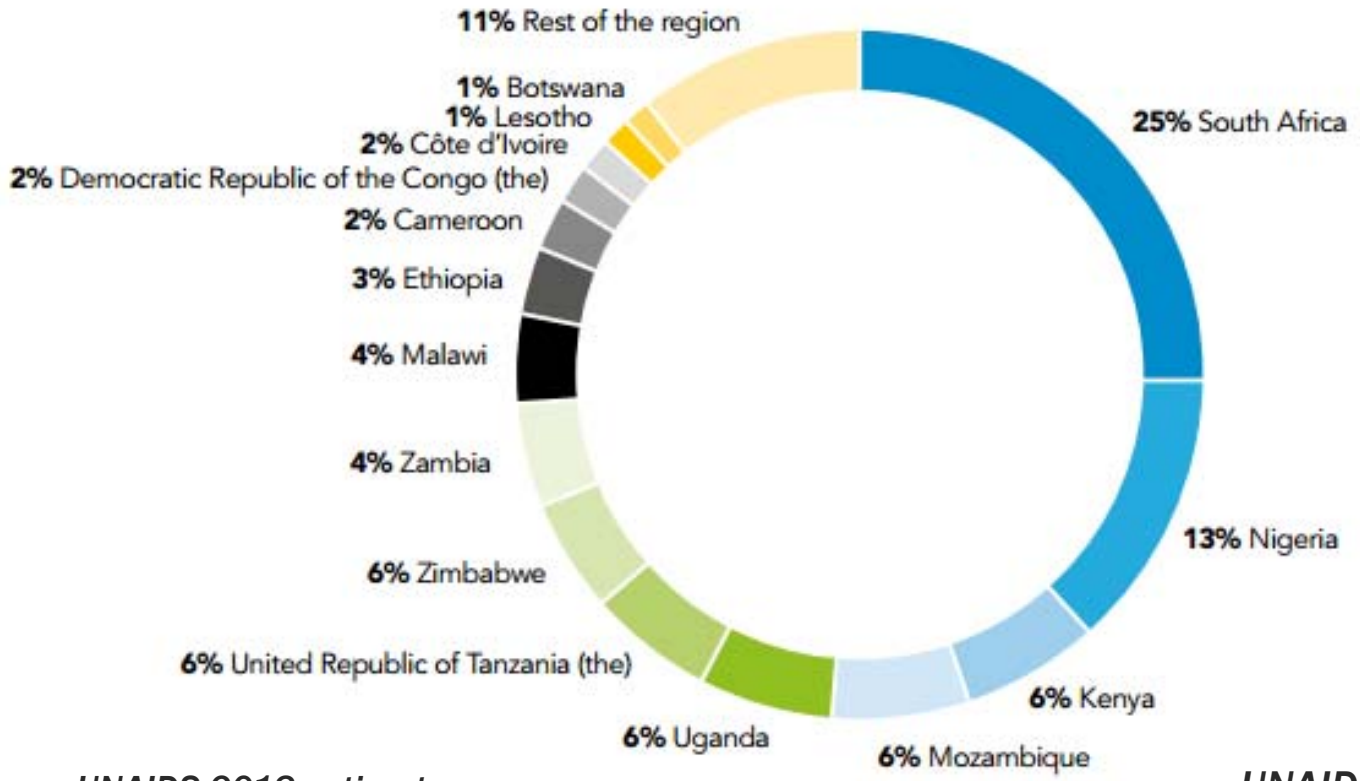
- The Epidemic in sub-Saharan Africa
- HIV Prevention in sub-Saharan Africa
- The AMP Study: a brief introduction
- Antibodies: what they are & how they work
- Antibody Vocabulary: bnAbs, mAbs
- The AMP Study Antibody: VRC01
- And it all comes together: The AMP Study
  - What questions does the AMP Study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

The Global HIV/AIDS Epidemic



HIV in SSA: the Epidemic Goes On

People living with HIV in sub-Saharan Africa, 2013



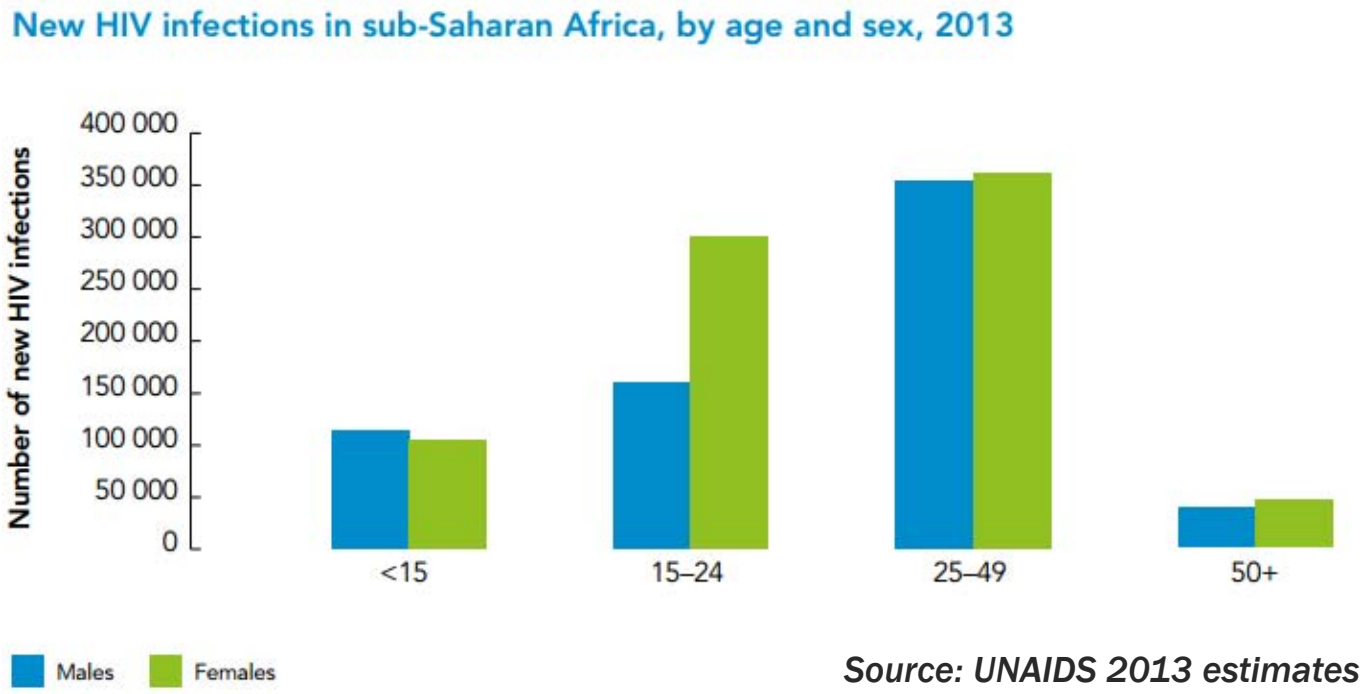
Source: UNAIDS 2013 estimates

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



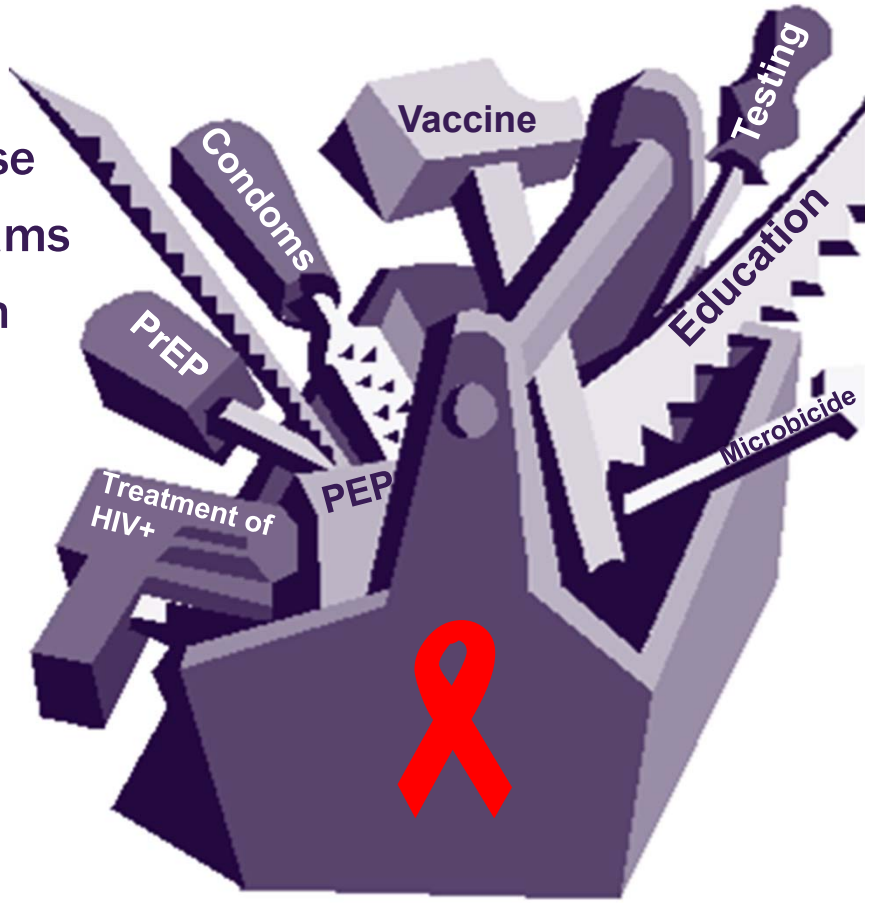
Source: UNAIDS 2013 estimates

- 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
- Male 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

Overview of HIV Prevention Intervention Trials

Previous, on-going and planned Research

Oral PrEP, vaginal rings, and injectables

HPTN
HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK

Pre-exposure Prophylaxis (PrEP) for HIV Prevention

- Daily pill (a combination ARV marketed as Truvada) approved for prevention of acquisition of HIV in guidelines
- The WHO has recommended oral PrEP for HIV-negative people at substantial risk of HIV
- Many trials contributed towards these recommendations
- Phase III PrEP trials used daily oral tenofovir-based pills:

✓ **Potent:** Broad and potent activity (all HIV subtypes)

✓ **Safe:** Favorable safety and tolerability

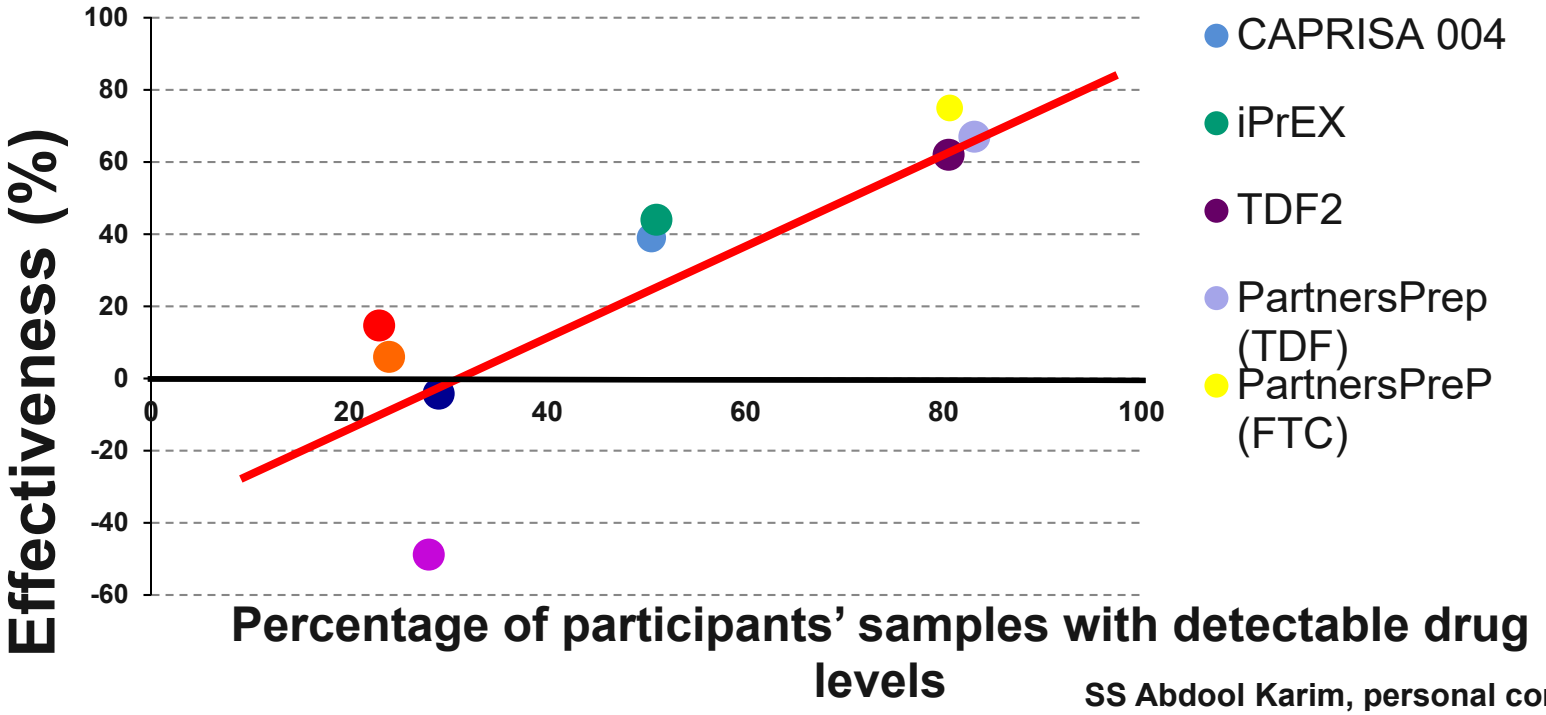
✓ **Easy:** Low pill burden, no food restrictions, few drug interactions

The Oral PrEP Landscape

- Studies have proven that daily use of an ARV tablet (PrEP) is very effective in preventing HIV.

- However, PrEP studies among African women did not have similar results
- Possible reasons for this:
  - Varying adherence,
  - Varying levels of genital inflammation
  - Suboptimal vaginal tenofovir levels
  - Low HIV risk perception
- Lack of interest in HIV prevention
  - Inability to take a daily pill
- Lack of motivation in a placebo-controlled trial with an unproven product

Must take PrEP for it to work



SS Abdool Karim, personal comm

Which approaches can optimize uptake and adherence with PrEP among young women in Southern Africa?

PrEP in Young Women

- HPTN 067/ADAPT Study: Comparison of daily & non-daily PrEP dosing in African women - Demonstrated Young women in Africa will take oral PrEP
- HPTN 082/HERS - Assess proportion and characteristics of young women who accept vs. decline oral PrEP at enrollment

What are the Alternatives to Oral PrEP?

The Dapivirine Vaginal Ring

- The dapivirine ring was developed by the International Partnership for Microbicides (IPM)
- The ring contains an ARV -- dapivirine -- to offer women potentially longer-acting protection against HIV
- It is the first vaginal ring being tested for HIV prevention
- The ring is designed to be worn for a month at a time
  - The ring slowly releases dapivirine into the cervix and vagina over the month it is worn

Why test a vaginal ring for HIV prevention?

Longer Acting:

A monthly product may help with consistent use

Higher adherence → increased effectiveness

Ease of Use:

Flexible ring, can be self-inserted

Little or no impact on sexual activity

Safety:

Studies have shown the ring is safe to use and has very few side effects

Privacy:

Vaginal rings can be inserted and removed in private

Rarely felt by women or male partners

ASPIRE & The Ring Study

- **Overall, the dapivirine vaginal ring resulted in a 27% and 31% reduction in the rate of HIV acquisition, compared to placebo**
- **HIV protection differed significantly by age**
- **Adherence was strongly related to age**
  - Blood samples and used ring testing showed that younger women were less adherent to the ring
- **Protection was strongly linked to adherence**

The Next Steps

	IPM 032	MTN-025
Primary Objective	Long-term safety and Adherence	
Follow-up Regimens	Initially 1-monthly Routinely 3-monthly (2 additional rings)	
Treatment Regimen	1-monthly ring replacement	
Progress	On-going	

What about long acting injectable PrEP in HIV-1 prevention?

HPTN 076

- A Phase 2 Phase II Safety, and Acceptability of an Investigational Injectable Product, TMC 278 LA for PrEP
- 132 USA, SSA, 18 – 45 years
- 2 : 1 active RPV: placebo randomization
- 4-week oral lead-in phase
- Direct observed therapy to assure oral drug exposure prior to long-acting dosing
- Then a series of 6 injections of 1200mg each at 8-week intervals
- Followed by a 32-week observational period during drug 'washout.'

HPTN 076

- TMC278 LA IM injections administered every eight weeks in this clinical trial cohort of African and US women were safe, overall well tolerated and acceptable.
- Data from this study support further development of injectable agents for PrEP.

Cabotegravir

- HPTN 077 - A Phase 2a Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, Cabotregravir, in 200 HIV-uninfected Men and Women 18-65 years – SSA, USA, Brazil
- Ends January 2018
- HPTN -084 A Phase 3 Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women
- 3,600 SSA 18 – 45 years

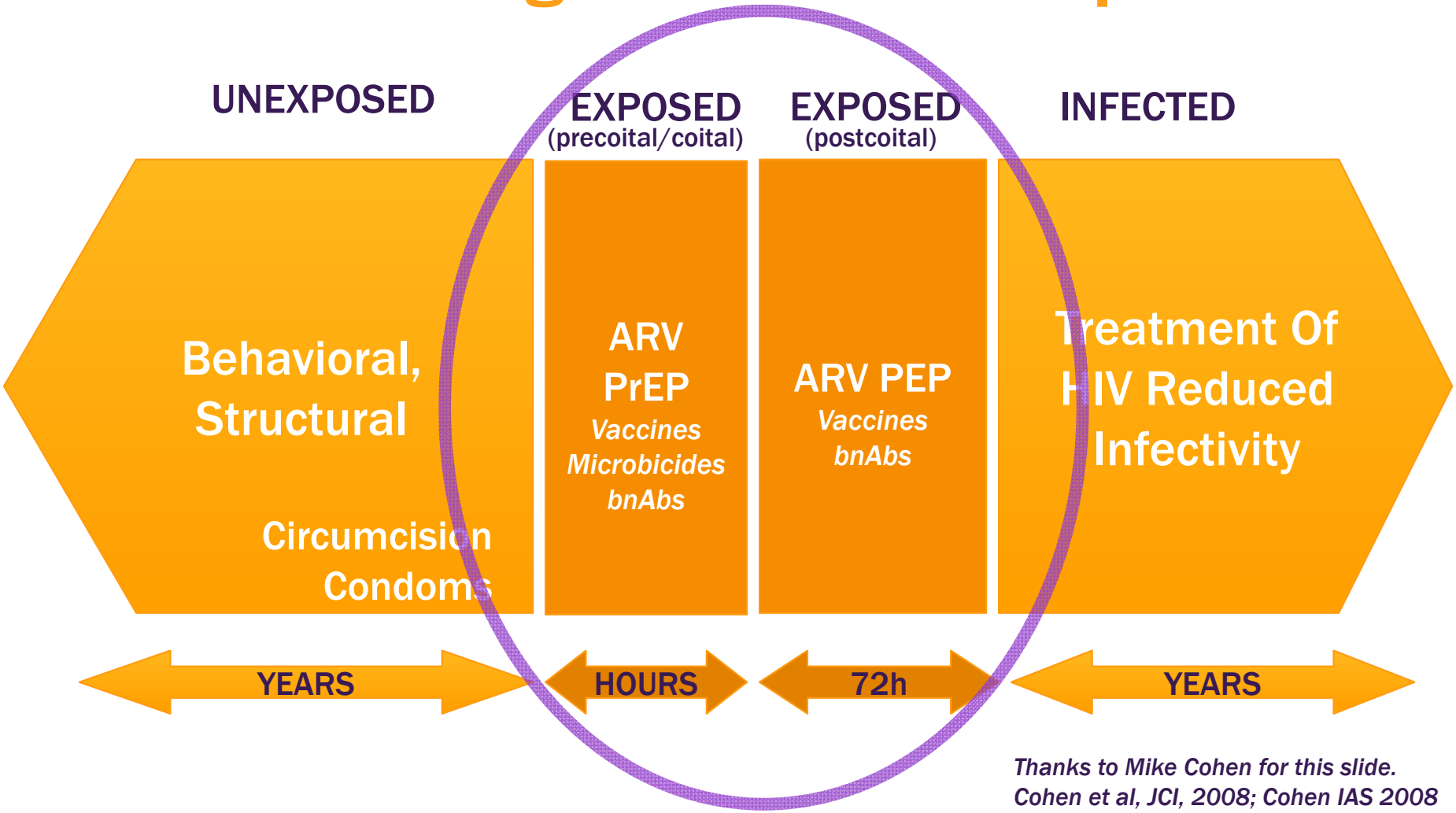
Injectables - Summary

- PrEP effectiveness compromised by need for regular adherence
- Effective injectable LA formulations represent the next generation of PrEP.
- Obviate the need for a daily or peri-coital pill-taking activity
- Do not entirely solve adherence problems
- Need for oral lead-in phase
- Long tail phase – may pose a challenge

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 the microbicides tested 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**

What is Missing to Address the Epidemic?



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

Can antibodies be used to prevent HIV-1 infections?

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

AMP = Antibody Mediated Prevention

This is the idea of using an antibody made in the lab 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 Prevention Trials Network

HIV VACCINE TRIALS NETWORK

Another name for The AMP Study in SSA is

HVTN 703/HPTN 081

HVTN703/HPTN 081 AMP Study
Research Sites in Africa

AMP in sub-Saharan Africa

7 Countries

21 Sites

AMP sub-Saharan Africa Sites

- Gabarone, Botswana
- Kisumu, Kenya
- Blantyre, Malawi
- Lilongwe, Malawi
- Maputo, Mozambique
- Harare (3 clinics), Zimbabwe
- Mbeya, Tanzania
- Cape Town, RSA
- Durban (4 clinics), RSA
- Johannesburg, RSA
- Soweto, RSA
- Vulindlela, RSA
- Rustenberg
- Klerksdorp
- Pretoria
- Tembisa

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

This is the first trial to assess if antibodies can be used to prevent HIV infection, similar to how antibodies are used to prevent other infectious diseases.

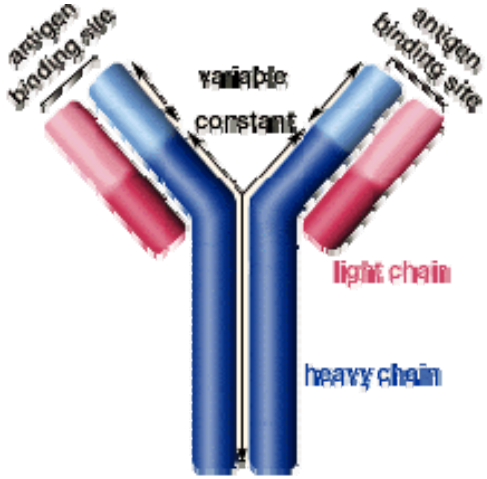
There is a Long History of Using Antibodies to Prevent Viral Infections

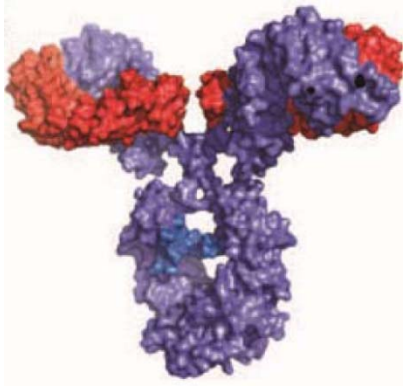
VIRUS	PRODUCT DESCRIPTION	INDICATION
Measles	Concentrated human gamma globulin	Prevention
Polio	Concentrated human gamma globulin	Prevention
CMV	Cytomegalovirus Immune Globulin	Prevention
Hepatitis A	Immune serum globulin (ISG)	Prevention (travel)
Hepatitis B	Hepatitis B Immune Globulin	Post Exposure
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

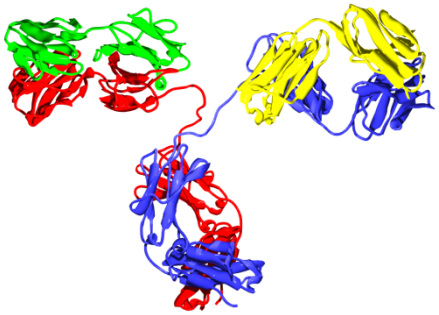
And, most effective vaccines induce antibodies that neutralize the pathogen.

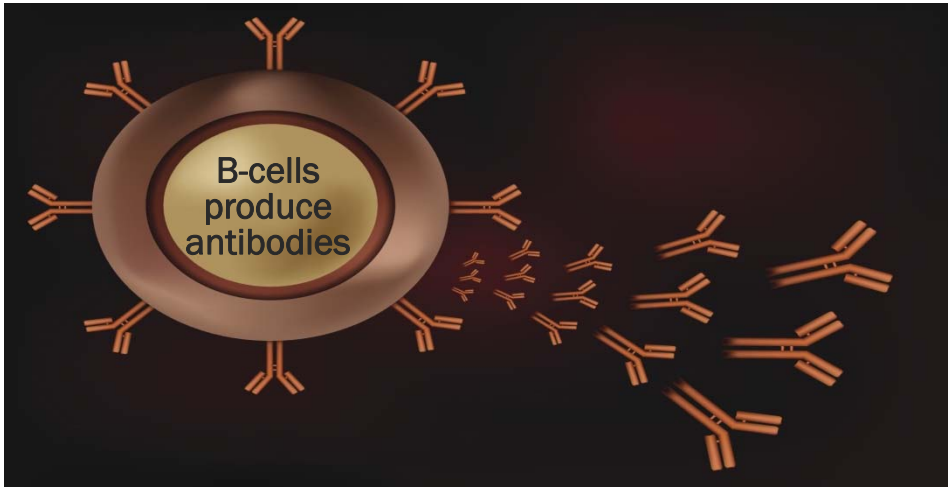
Thanks to John Mascola for this slide.

What is an Antibody?

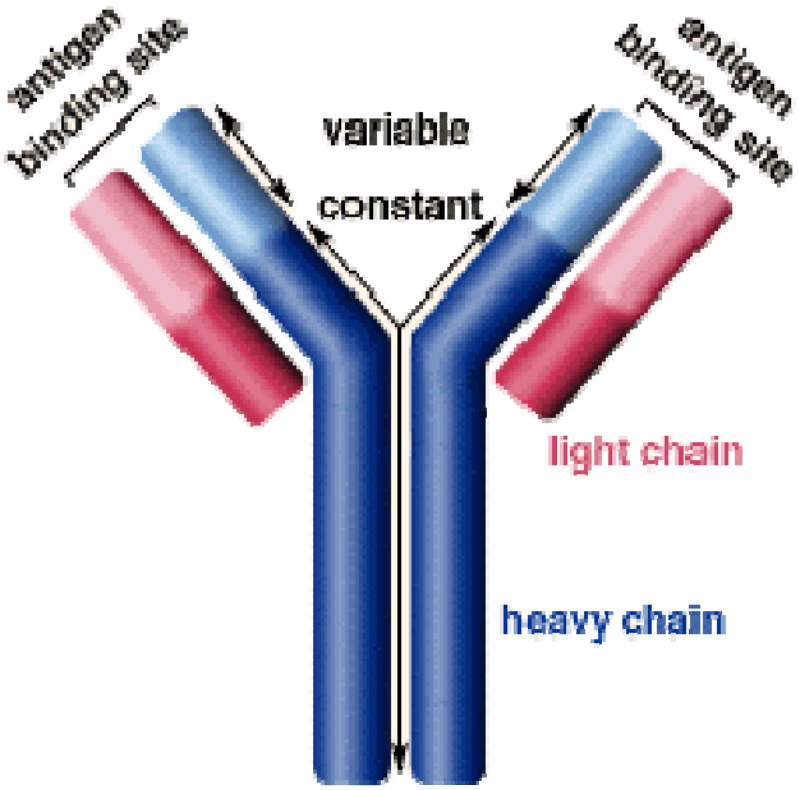








How Does an Antibody Work?



NEUTRALIZATION

Binds to HIV & blocks its attachment to host cells

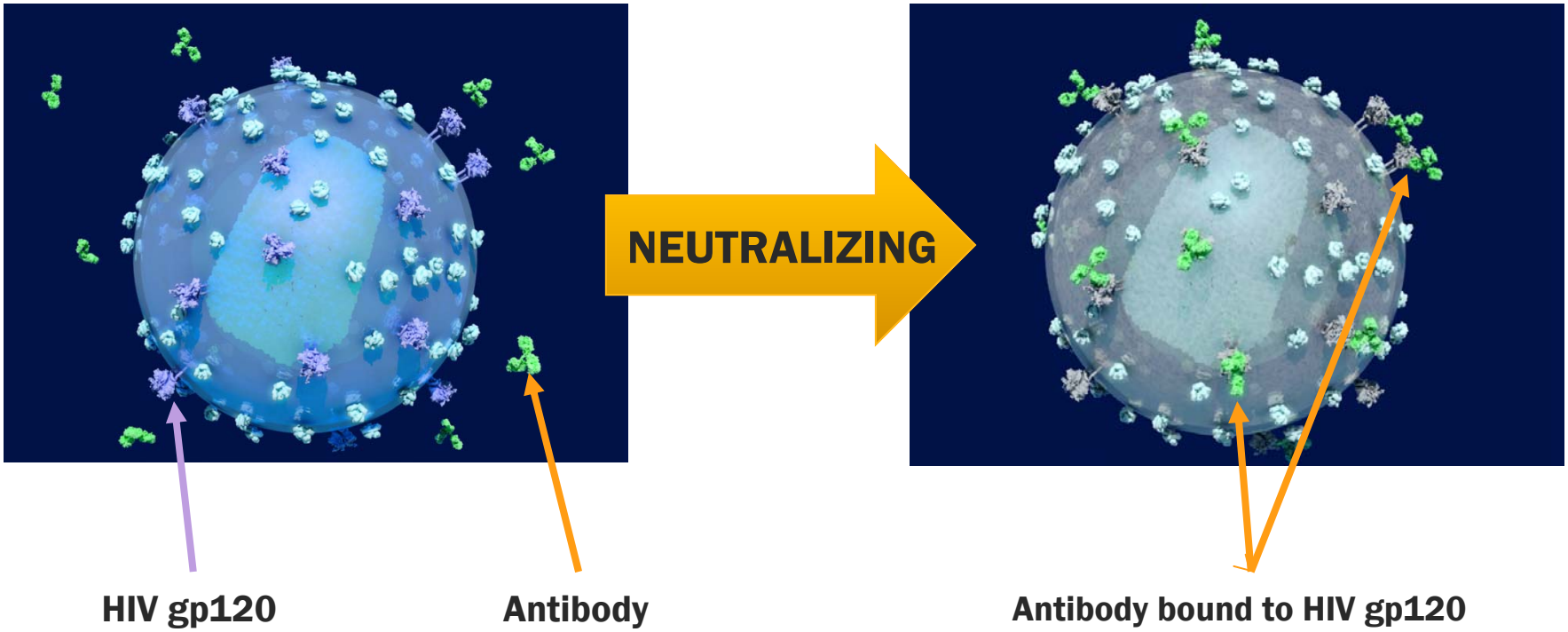
OPSONIZATION
("buttering the toast")

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

SENSITIZATION
("the lookout for the hitman")

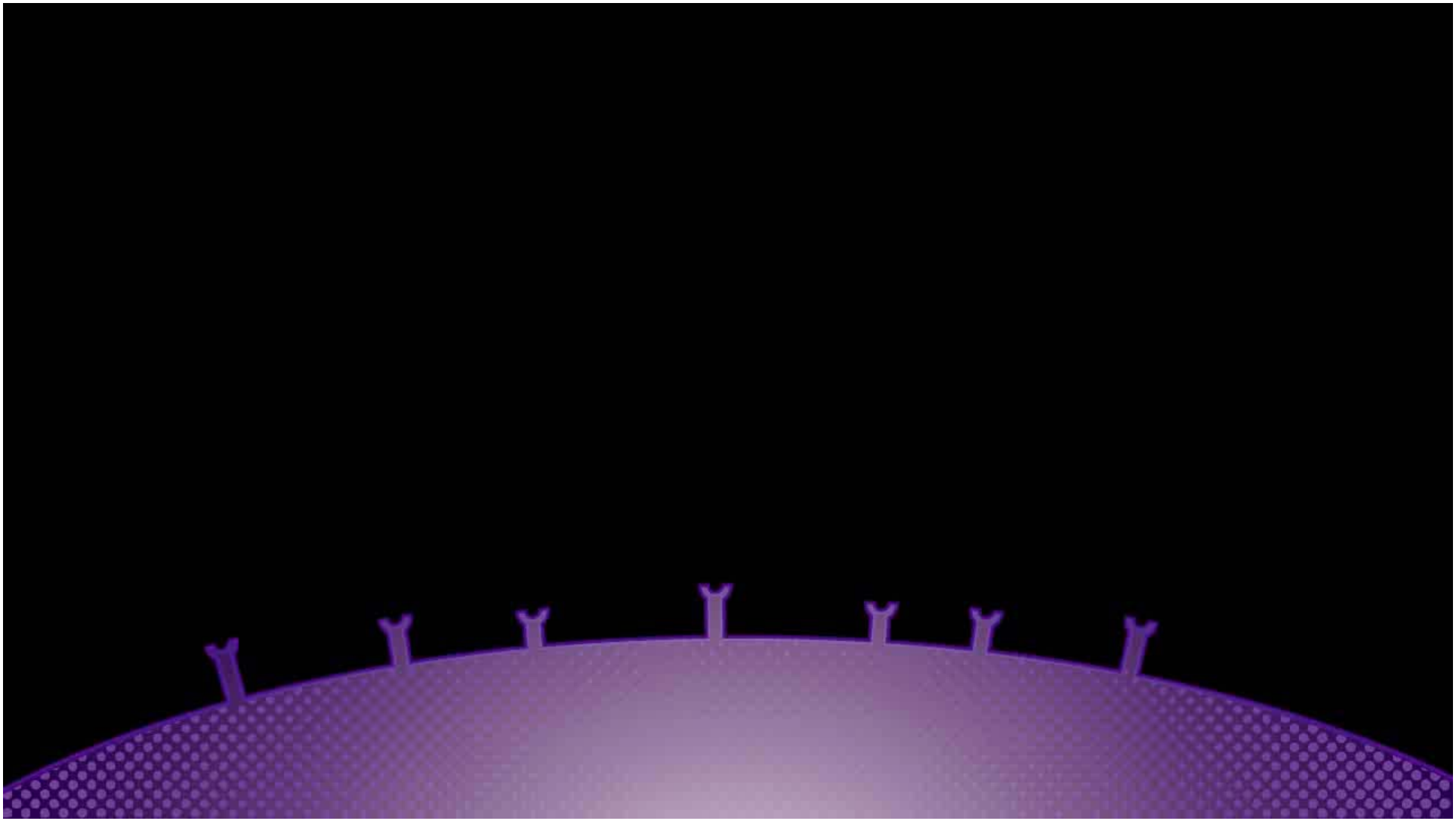
Binds to HIV, then binds to an NK cell; the NK cell then spills its "poison" to kill HIV

Neutralizing Antibodies



Thanks to Lisa Donohue for these images.

Neutralizing Antibodies Preventing HIV Infection



HPTN
HIV Prevention
Trials Network

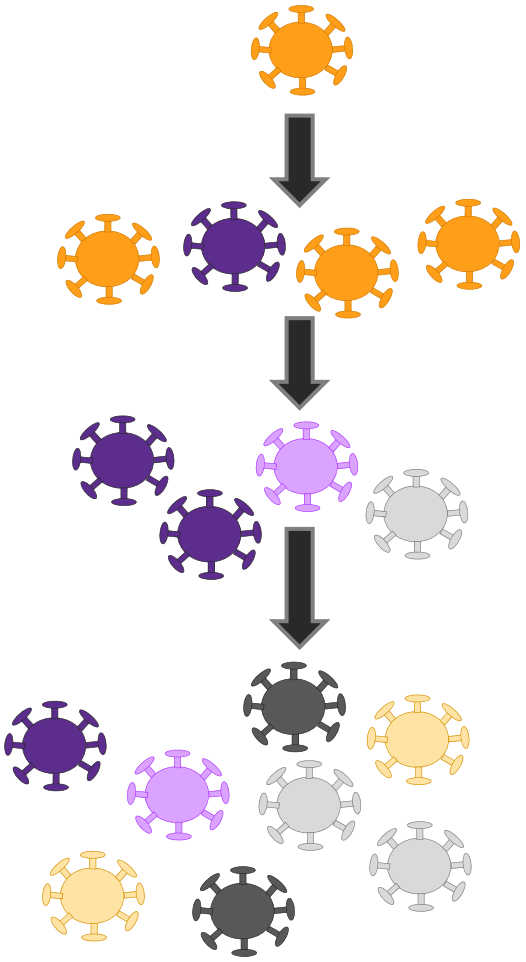
HIV VACCINE
TRIALS NETWORK

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

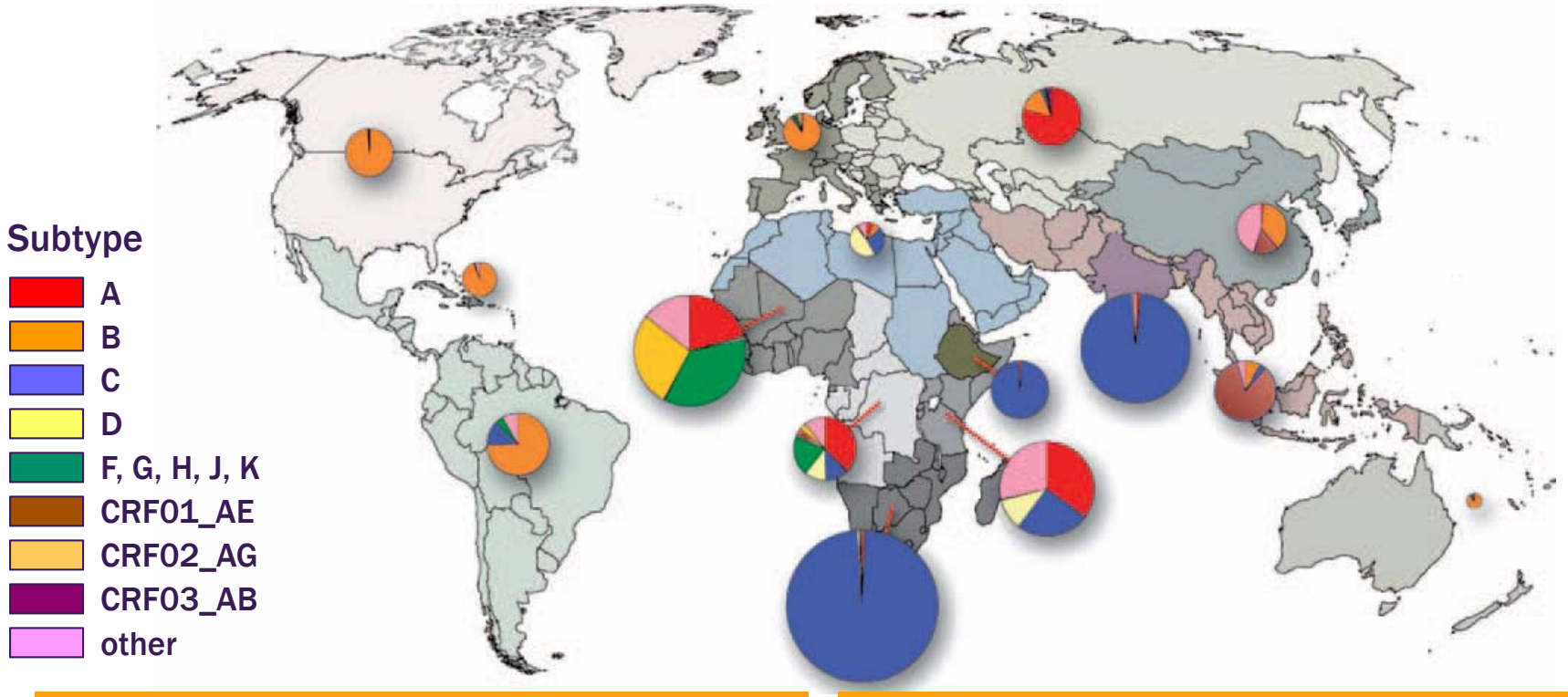
Produces BILLIONS of new virions a day

↑ mutations with viral replication

Rapidly develop multiple lineages or "quasi-species"

HIV-1 Diversity Worldwide

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



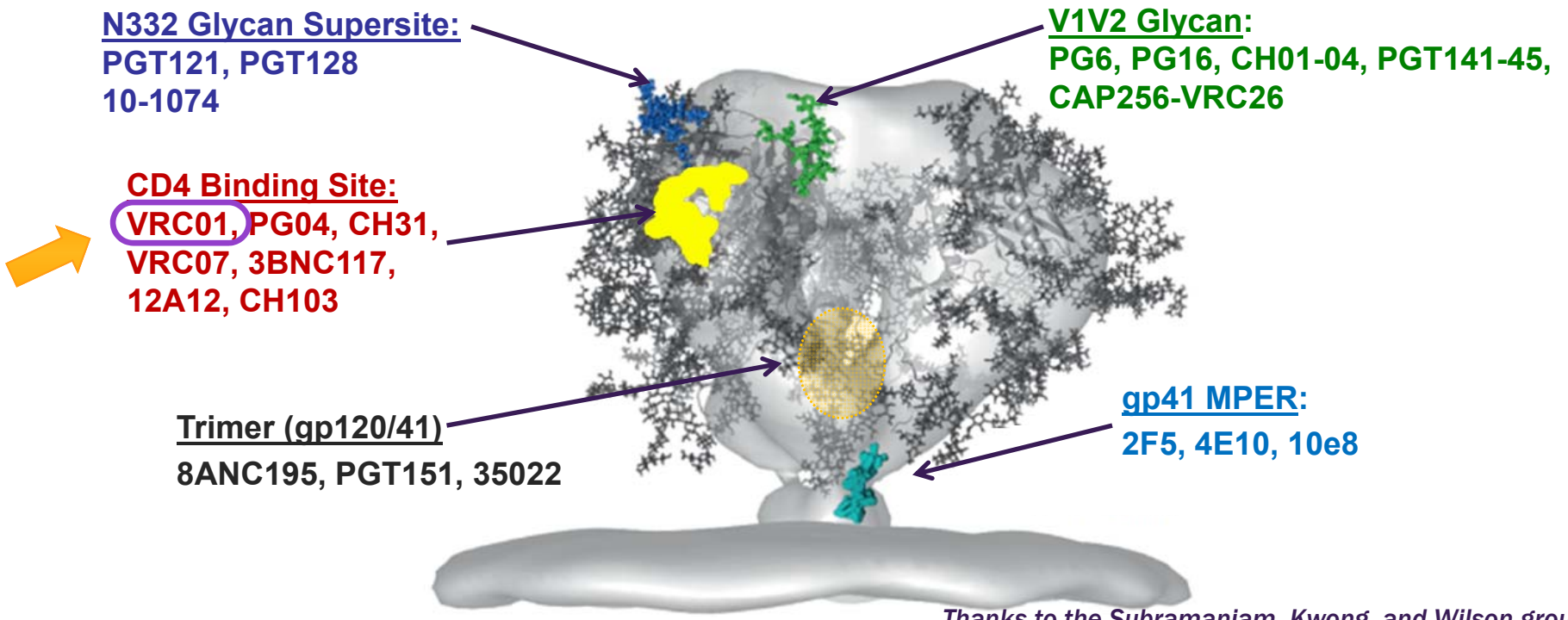
HIV genomes differ by 10-30%

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



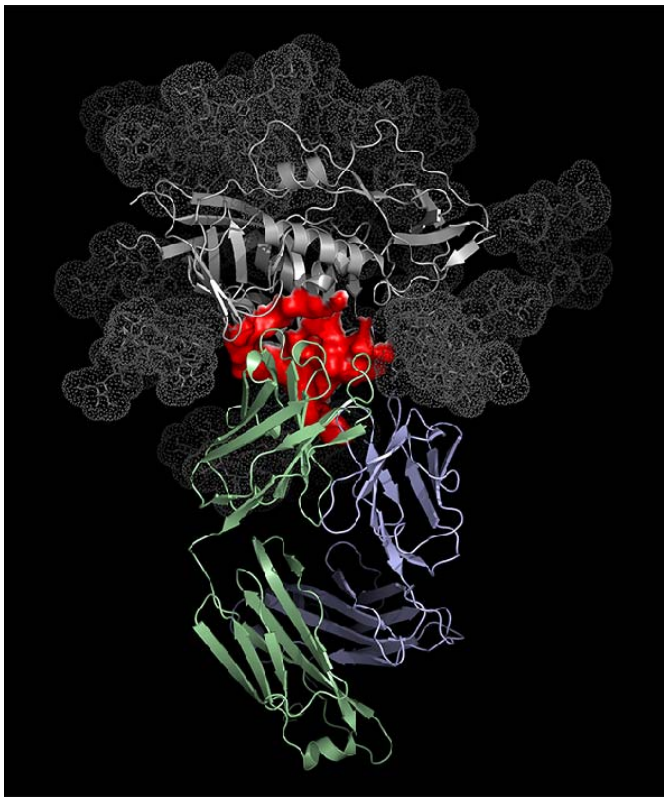
Thanks to the Subramaniam, Kwong, and Wilson groups.

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.

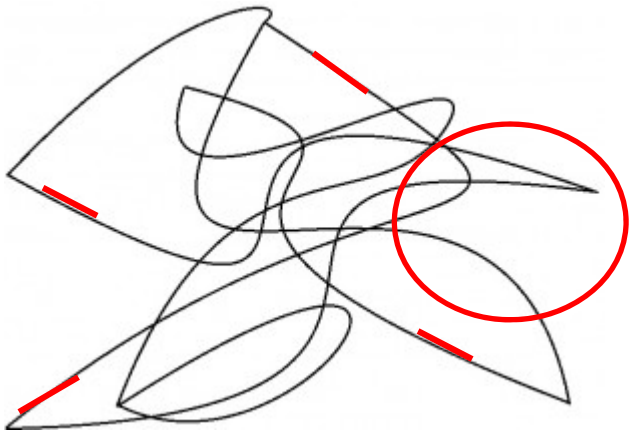


Gray: gp120
Red: CD4 binding site (CD4bs)
Purple & Green: VRC01 attached to the CD4bs

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

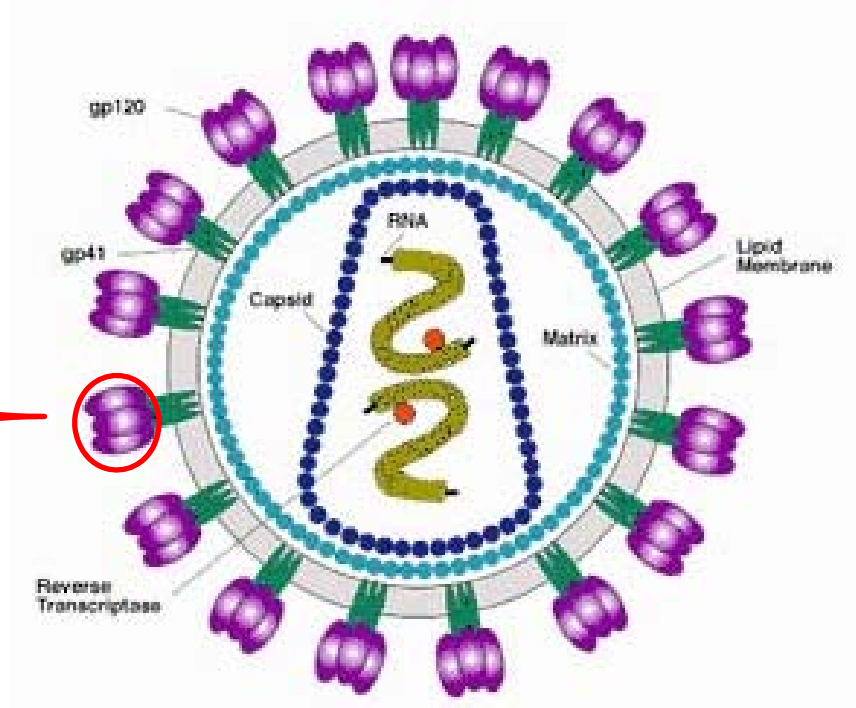


Image credit: NIAID

Why Evaluate VRC01?

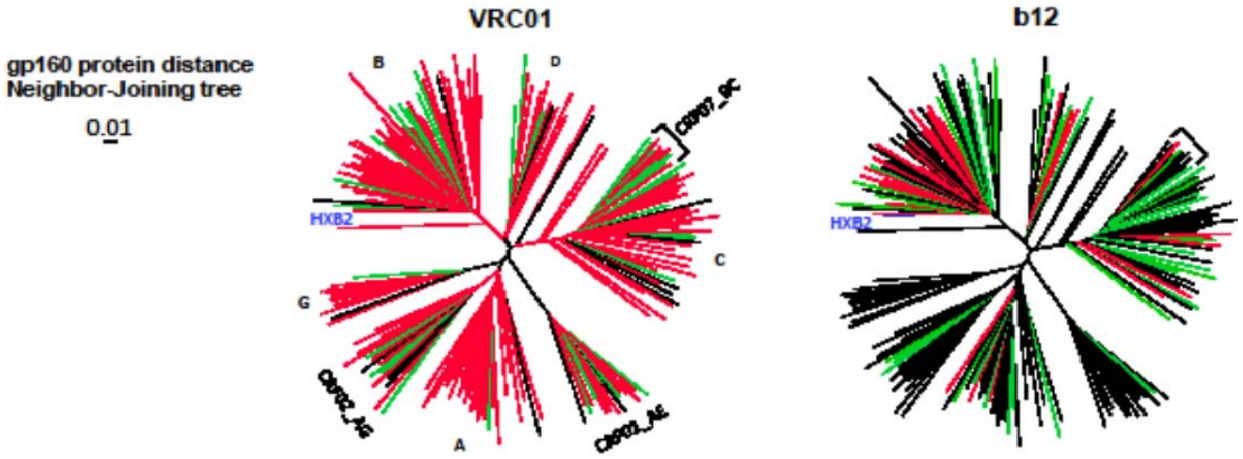
PREVENTION

- **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



= "killed HIV"

= "partly killed HIV"

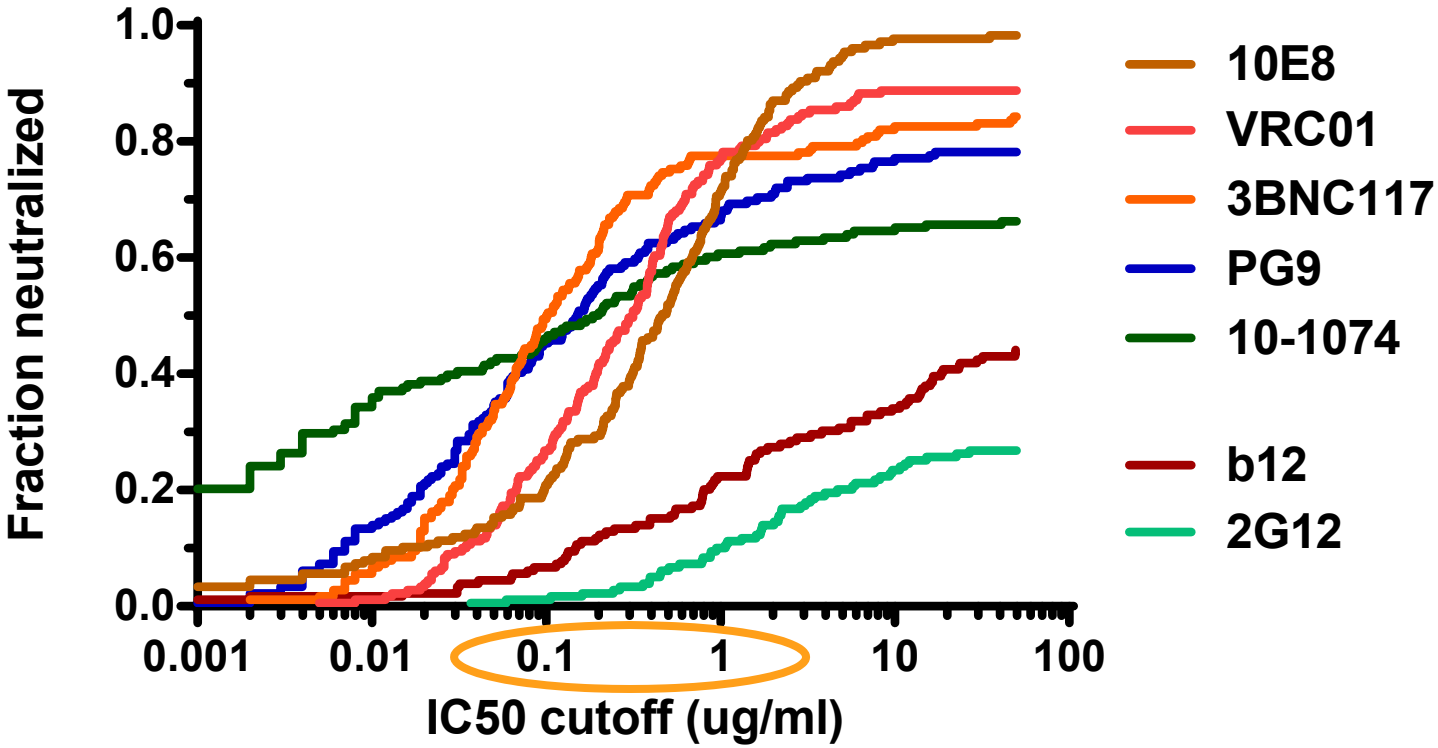
= "did not kill HIV"

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	[illegible]	33%	[illegible]	6%
Total	190	91%	41%	72%	17%

Panel of 190 Diverse HIV "Strains"

Wu et al. Science. 2010

VRC01 is a Potent Antibody

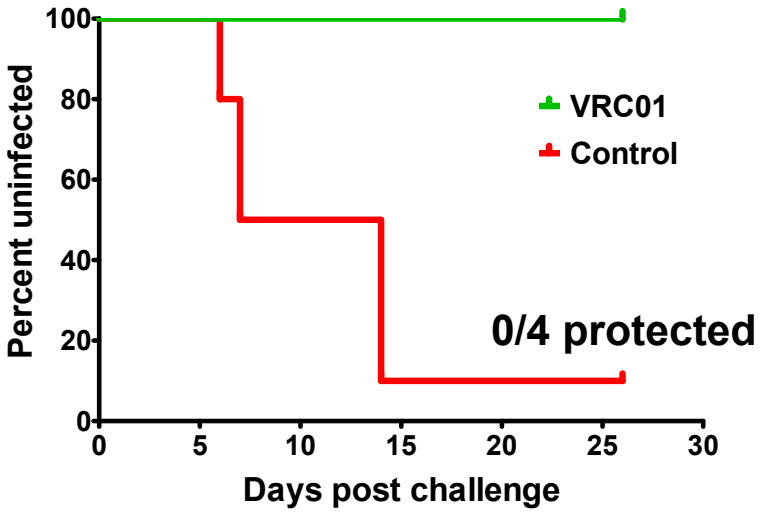


Thanks to David Montefiori & CAVD and Bob Bailer & NVITAL Laboratory

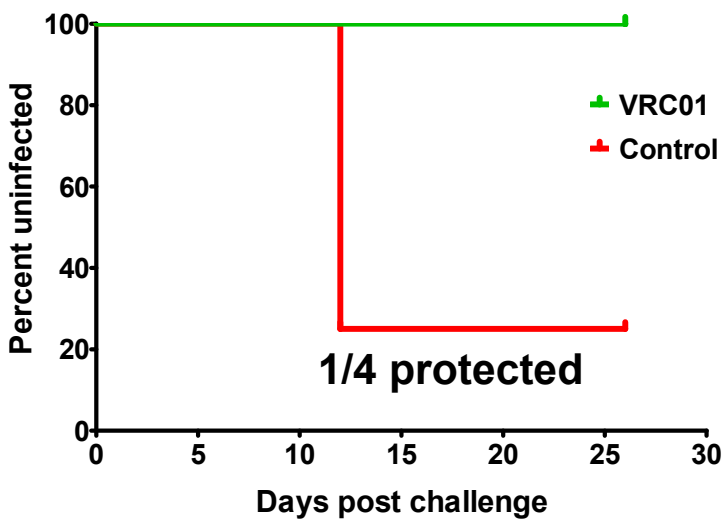
VRC01 in Preclinical (NHP) Trials

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
  - No serious “adverse events”
  - Mild adverse events only, which included mild lab changes in liver & kidney tests

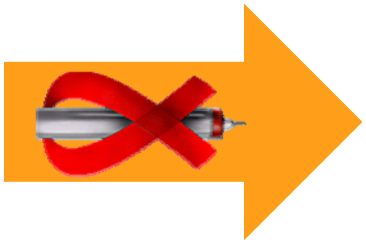
How Could VRC01 be a Prevention Tool?

- 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?

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 Study duration: ~22 months
VRC01 30 mg/kg	900	500	1400	
Control	900	500	1400	
Total	2700	1500	4200	

The AMP Study in SSA: Selected Eligibility Criteria

- 18-40 years of age
- HIV uninfected
- Risk behavior related criteria:
  - In Africa: 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.

Review: AMP Science

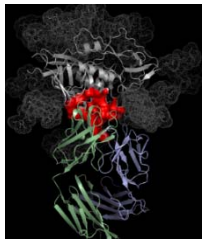
- HIV Prevention in sub-Saharan Africa
- The AMP Study: a brief introduction
- Antibodies: what they are & how they work
- Antibody Vocabulary: bnAbs, mAbs
- The AMP Study Antibody: VRC01
- And it all comes together: The AMP Study
  - What questions does the AMP Study help answer?
  - What does the AMP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

It is all about Choices!

Vaccine


Vaginal ring


Oral PrEP


bNAbs


Injectables

- Even the most effective product cannot protect against HIV if it is not used
- A product that best suits one's lifestyle and needs is more likely to be used
- Women's preferences are not all the same - just as women have choices in contraception, they should have choices for HIV prevention, too

And it all comes together…

It will take our combined effort to implement AMP successfully in SSA

HPTN HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK

THANK YOU

for your work on behalf of the AMP Study!

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
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- Community Educators/Recruiters: DaShawn Usher & Luciana Kamel
- Technical Editor: Erik Schwab


Thank You

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:

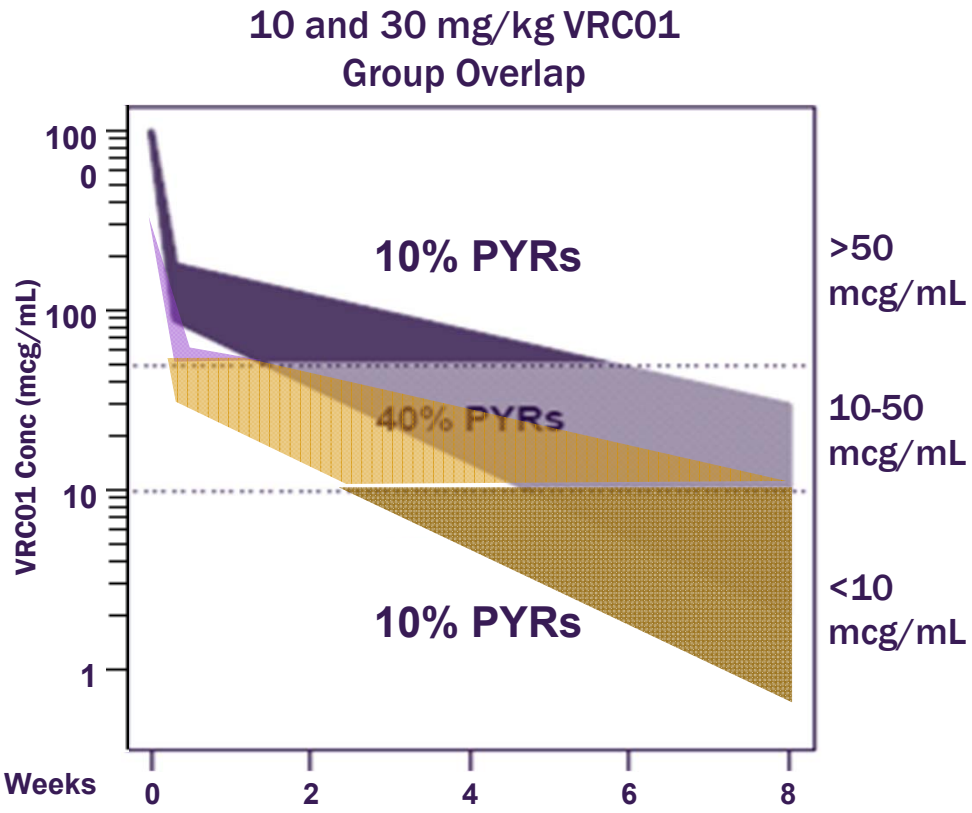
IV or SC in Healthy, HIV-Uninfected Adults

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/k 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/k 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			