



# Broadly Neutralizing Antibodies for HIV Prevention

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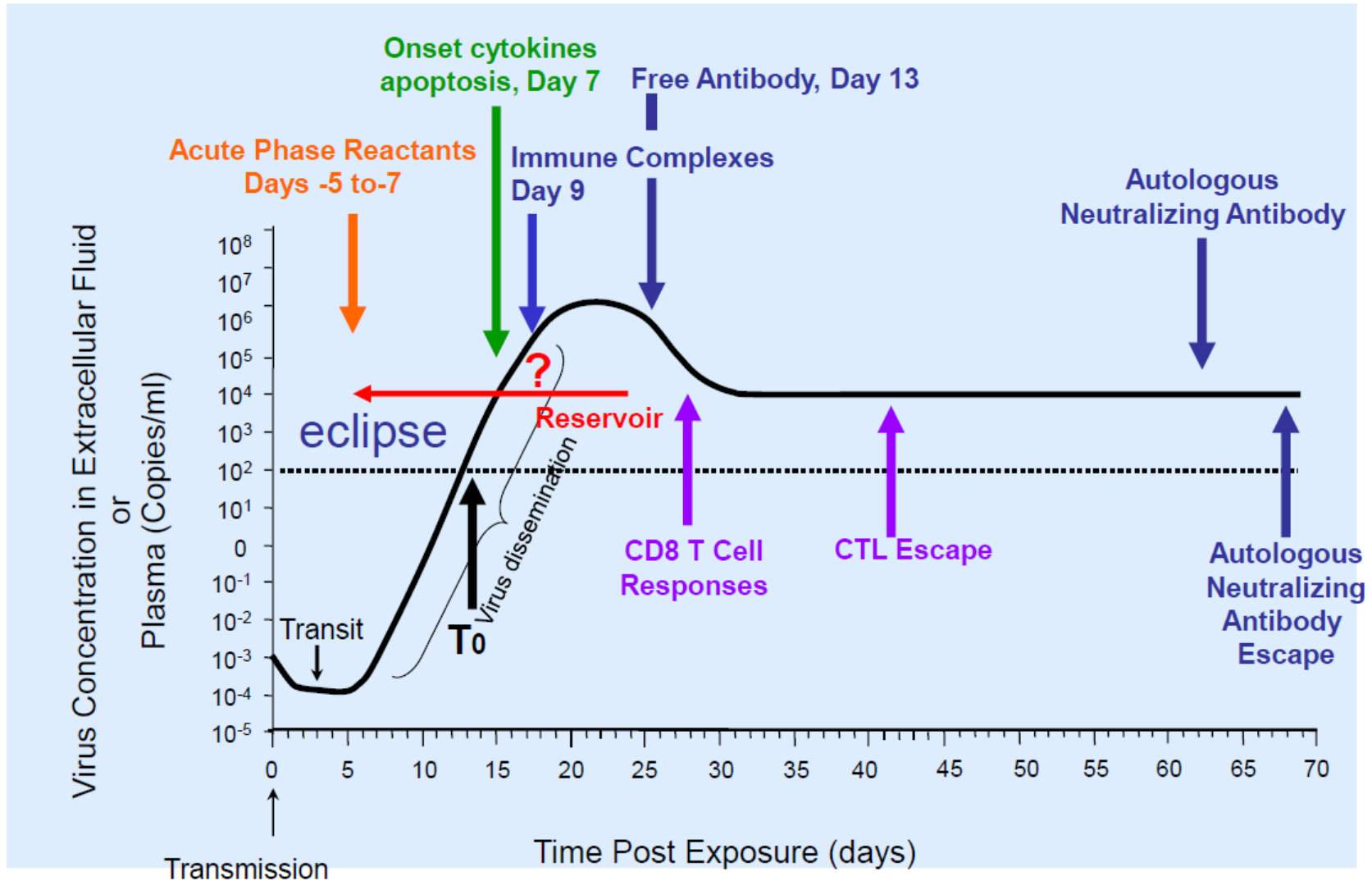
# Conflict of interest declaration

I have no conflicts of interest to declare

# Presentation outline

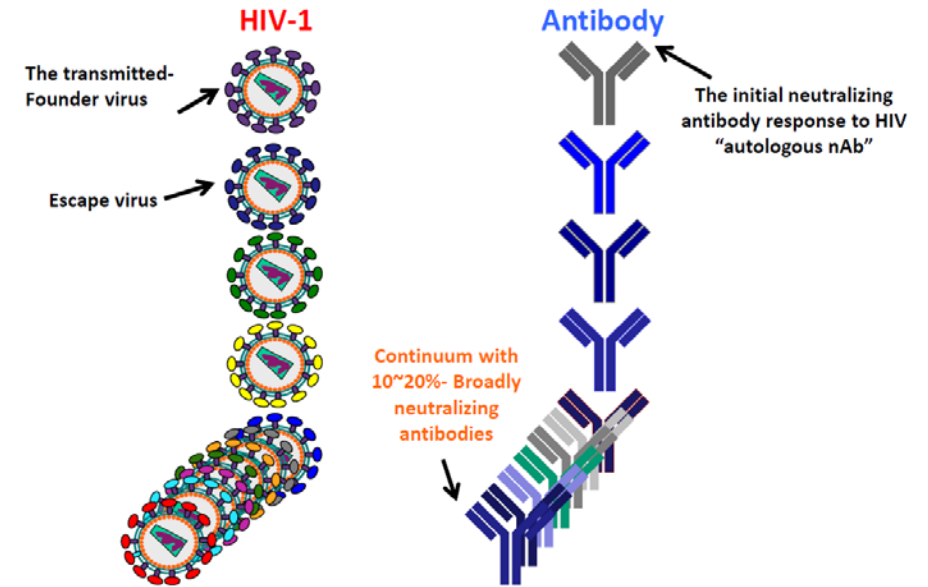
- The biology of HIV infection
  - transmission, eclipse, peak viraemia, viral set point
- Immune response to HIV infection
- Broadly neutralising antibodies (bnAbs)
- The AMP studies
- Next generation bnAbs
  - Combination/tri-specific antibodies
- Summary

# The biology of HIV infection



# Immune response to HIV

- 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
- bnAbs against the infecting strain appear months later in ~20% of infected people, are not able to neutralise more divergent viruses
- Autologous bnAbs drive immune escape - contemporaneous viruses are less sensitive to autologous bnAbs than earlier strains
- *“Today’s antibodies can neutralize yesterday’s virus.” - AVAC*



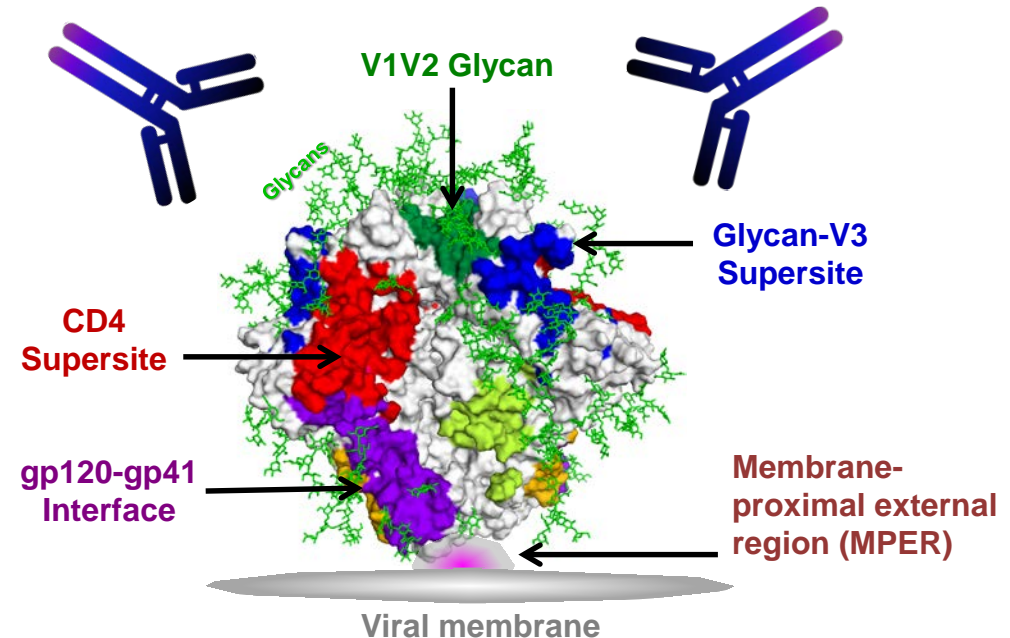
# Broadly neutralising antibodies

Many isolated 2009 - present

## Broadly neutralizing bnAbs to 5 major regions of Env

- V1V2-Glycan – binds to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

**Antibodies (VRC01, 3BNC117) and others in early phase clinical trials**



*Image by Stewart-Jones, Doria-Rose, Stuckey  
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014*

AMP = Antibody Mediated Prevention



**Can a passively infused monoclonal antibody (VRC01) prevent HIV-1 infection in high risk adults?**



**Two harmonized protocols:**

The AMP Studies:

**HVTN 704/HPTN 085**

**( 2700 MSM and TG in the Americas, Europe)**

**HVTN 703/HPTN 081**

**( 1900 Women in sub-Saharan Africa)**

Chairs – L Corey, M Cohen

Co-Chairs – S Edupuganti, N M Mgodu



**HIV VACCINE  
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# AMP Study design

HVTN 704/  
HPTN 085

HVTN 703/  
HPTN 081

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	634	1534	<p>10 infusions total &amp; Infusions every 8 weeks</p> <p>Study duration: ~22 months</p>
VRC01 30 mg/kg	900	634	1534	
Control	900	634	1534	
<b>Total</b>	<b>2700</b>	<b>1900</b>	<b>4600</b>	

- All subjects provided an HIV prevention package
- Two different infusion doses: important to know if lower dose of 10 mg/kg can protect
  - Powered to associate mAb serum level with protection



# AMP Study: Objectives and endpoints

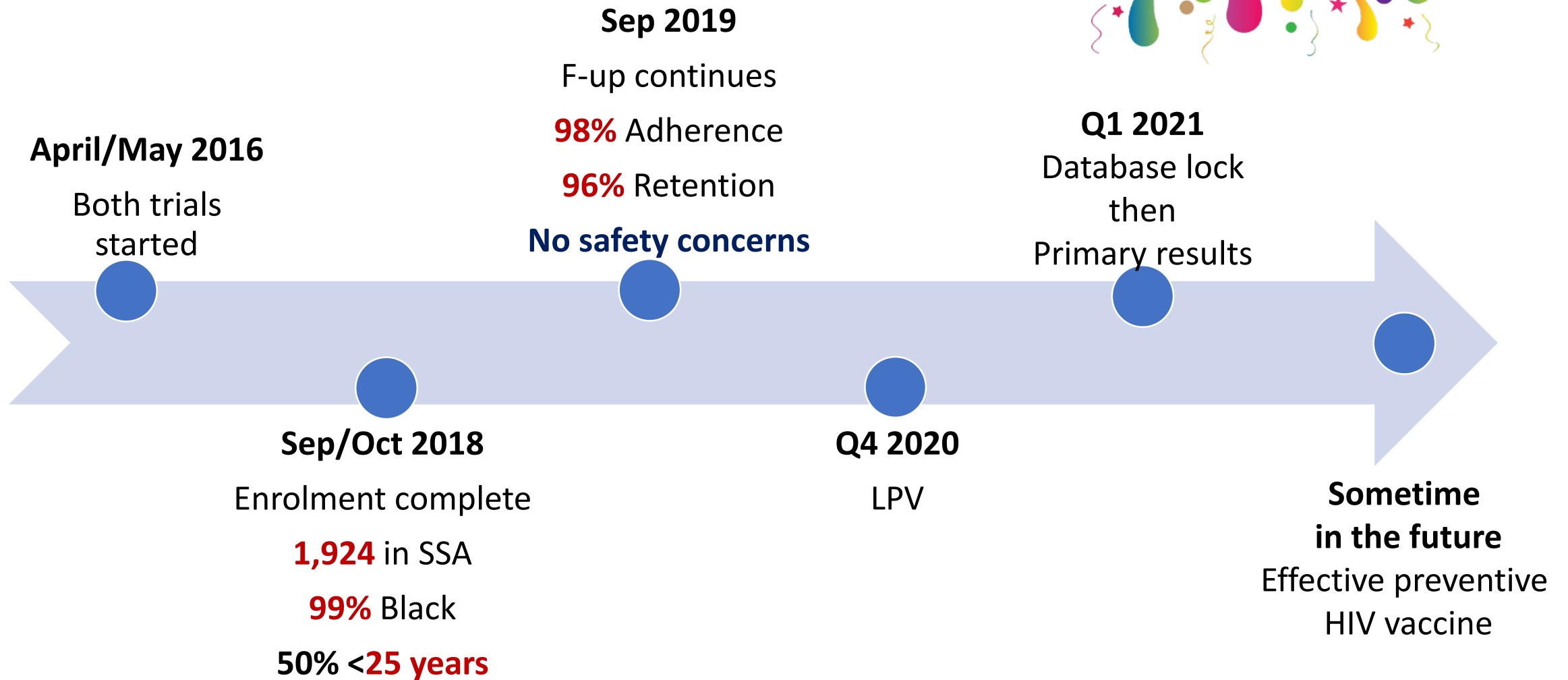
## PRIMARY

- 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
- 

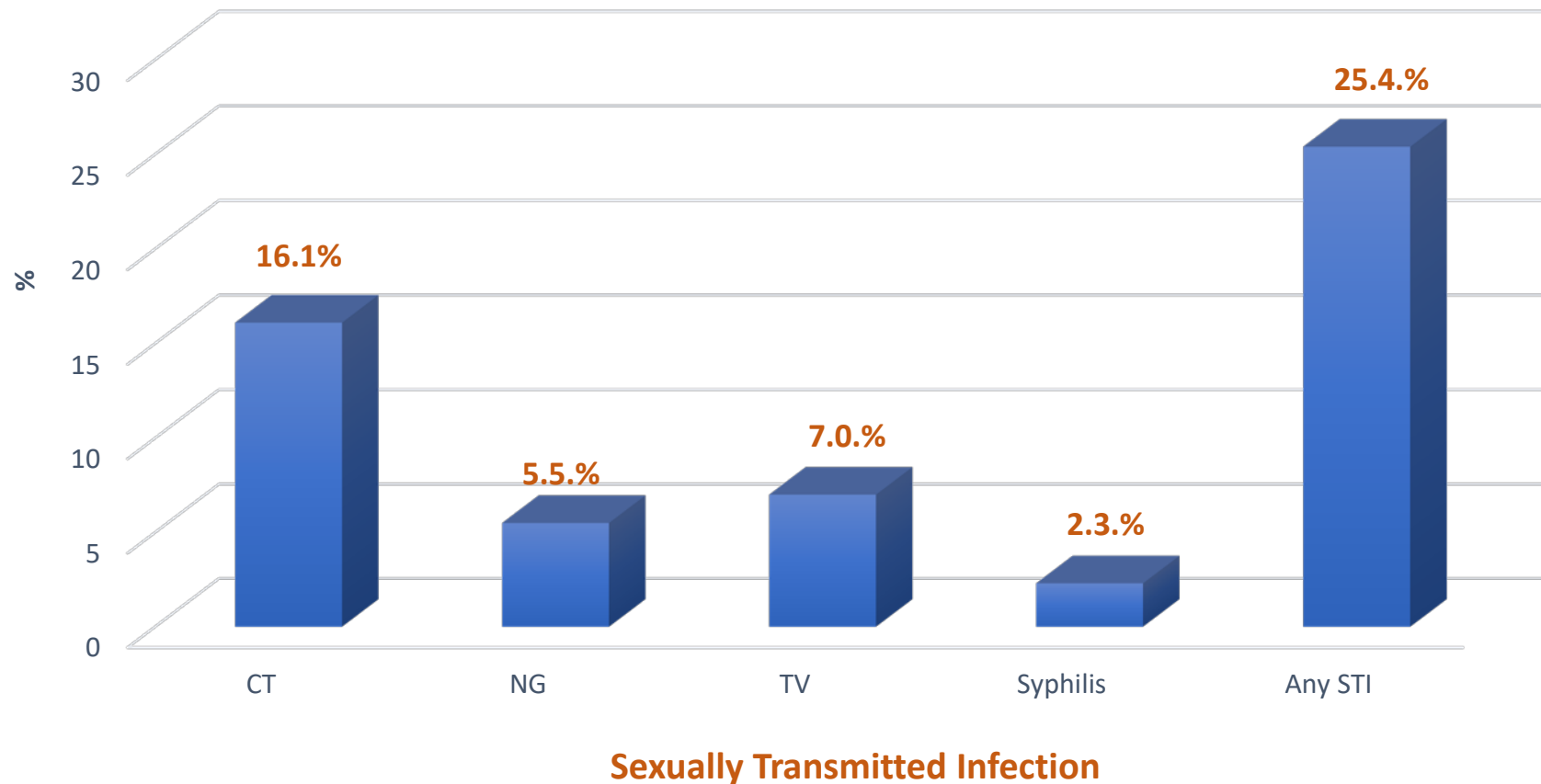
## SECONDARY

- 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

# AMP timelines and successes

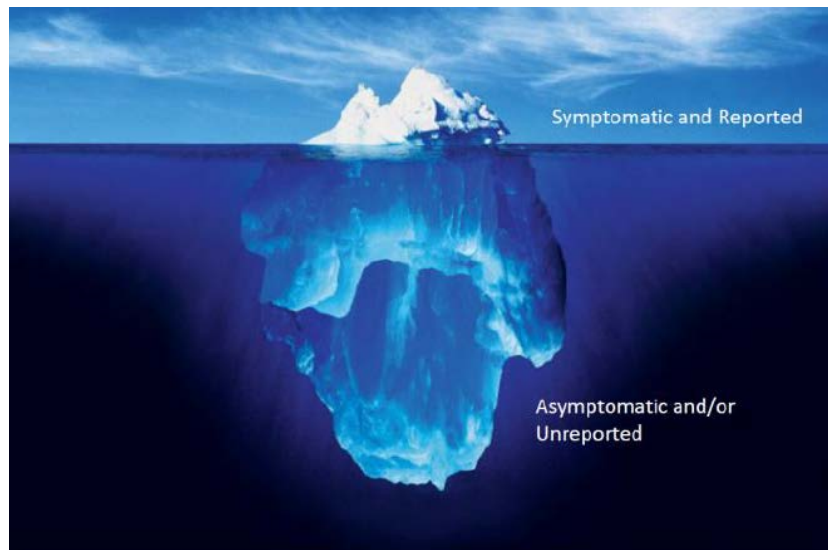


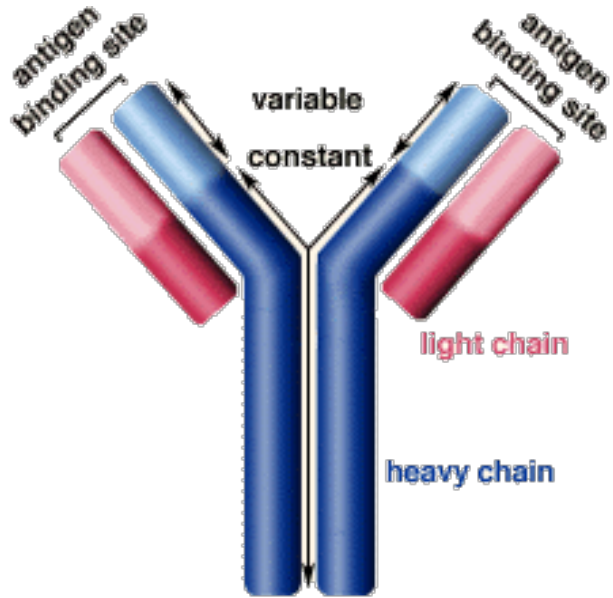
# AMP SSA Baseline Sexually Transmitted Infections



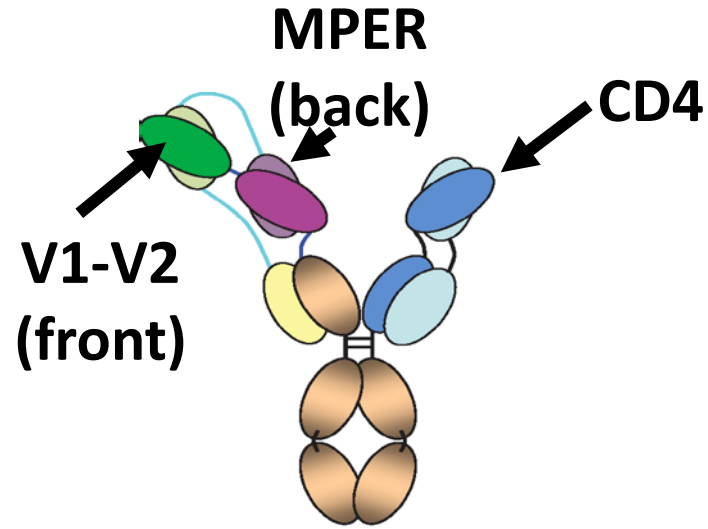
# Lessons learnt - STIs

- Prevalence of treatable STIs high among African women at substantial risk for HIV infection
- Majority are asymptomatic
- The prevention and control of STIs should be an integral part of comprehensive sexual and reproductive health services and HIV prevention services.

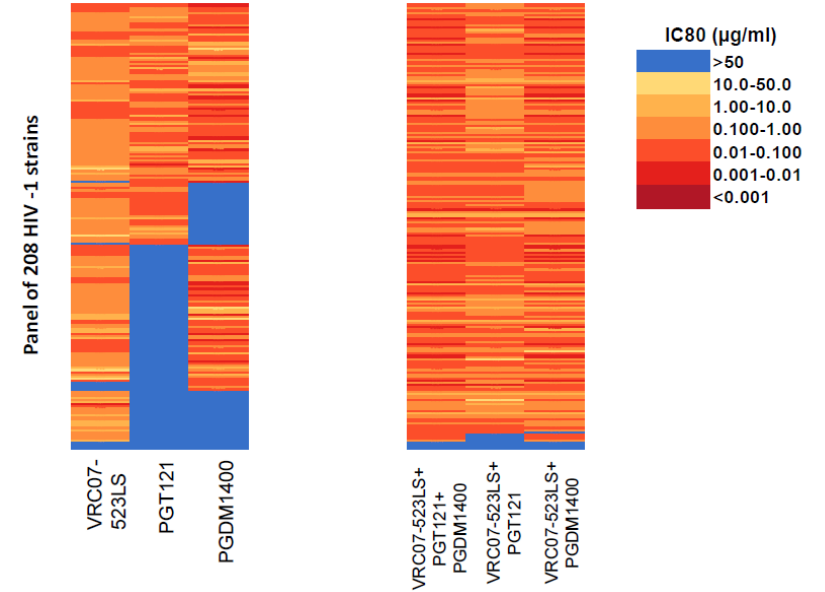




Basic antibody

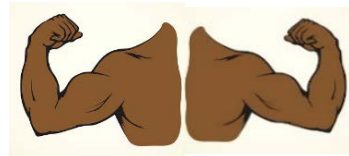


Tri-specific antibody



Combination antibodies

# Next generation broadly neutralising antibodies



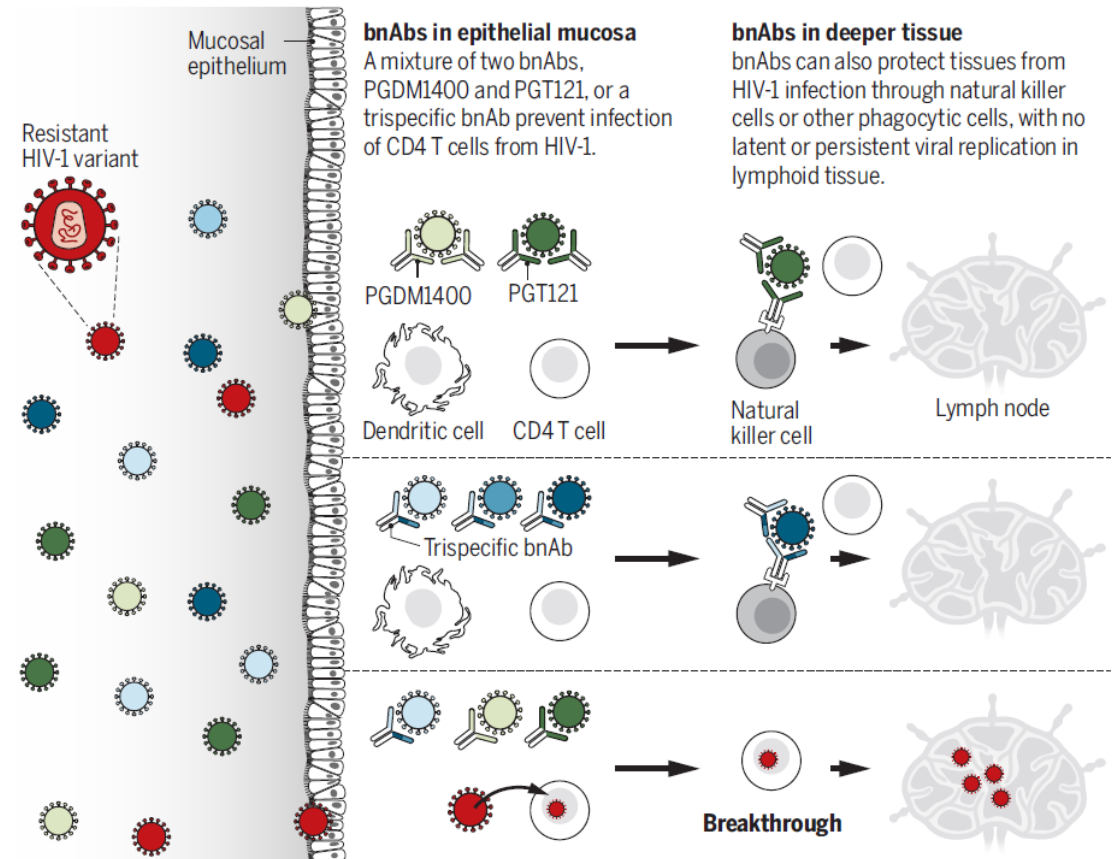
More potent, wider breadth

# Lessons learnt from ART – combination bnAbs

- HIV-1 exhibits genetic diversity and viral escape mechanisms
- Prudent to consider using a combination approach
- Like antiretroviral therapy, combinations of mAbs may reduce the likelihood of viral escape, and increase neutralization breadth
- Combining multiple bnAbs with specificities against different epitopes into a single molecule has the potential to:
  - improve efficacy
  - simplify prevention and treatment regimens
  - streamline the regulatory pathway to a licensed drug
- Trispecific mAbs derived from bnAbs with CD4bs, MPER, and V1V2 glycan specificities demonstrate remarkable breadth and potency *in vitro* and *in vivo*










## bnAbs prevent HIV-1



Combinations of bnAbs and a trispecific antibody can bind to virions and prevent HIV-1 mucosal infection and elicit antiviral responses in deeper tissue. It is hoped this multitarget approach will prevent resistant breakthrough.



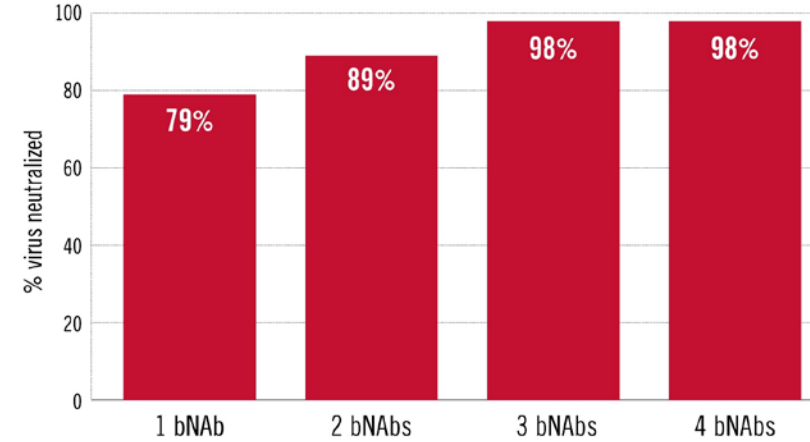
# BROADLY NEUTRALIZING ANTIBODY COMBINATIONS

As with antiretroviral combinations used in treatment to control the virus, passive immunization of broadly neutralizing antibodies to protect against HIV will likely require two or more bNAbs that target different parts of the virus. There are many factors to consider when selecting bNAb combinations, including how many bNAbs and which ones work best together. Here we outline the bNAb combinations being explored in early clinical studies.

bNAb Cocktails: Two or more antibodies in a regimen		
Regimen	Status	Research Institution
	Phase I, Ongoing	Rockefeller University
	Phase I, Planned	NIAID
	Phase I, Suspended	NIAID
	Phase I, Planned	CAPRISA, NIAID
	Phase I, Ongoing	BIDMC, IAVI, NIAID
	Phase I, Planned	CAPRISA, BIDMC, NIAID
	Phase I, Ongoing	BIDMC, IAVI
	Phase I, Ongoing	BIDMC, IAVI, NIAID
	Phase I, Planned	Columbia University











Multispecific: Parts of two or more antibodies on a single antibody		
Regimen	Status	Research Institution
	Phase I, Planned	Sanofi, NIAID
	Phase I, Ongoing	Aaron Diamond AIDS Research Center (ADARC)

Combining bNAbs to broaden neutralization\*

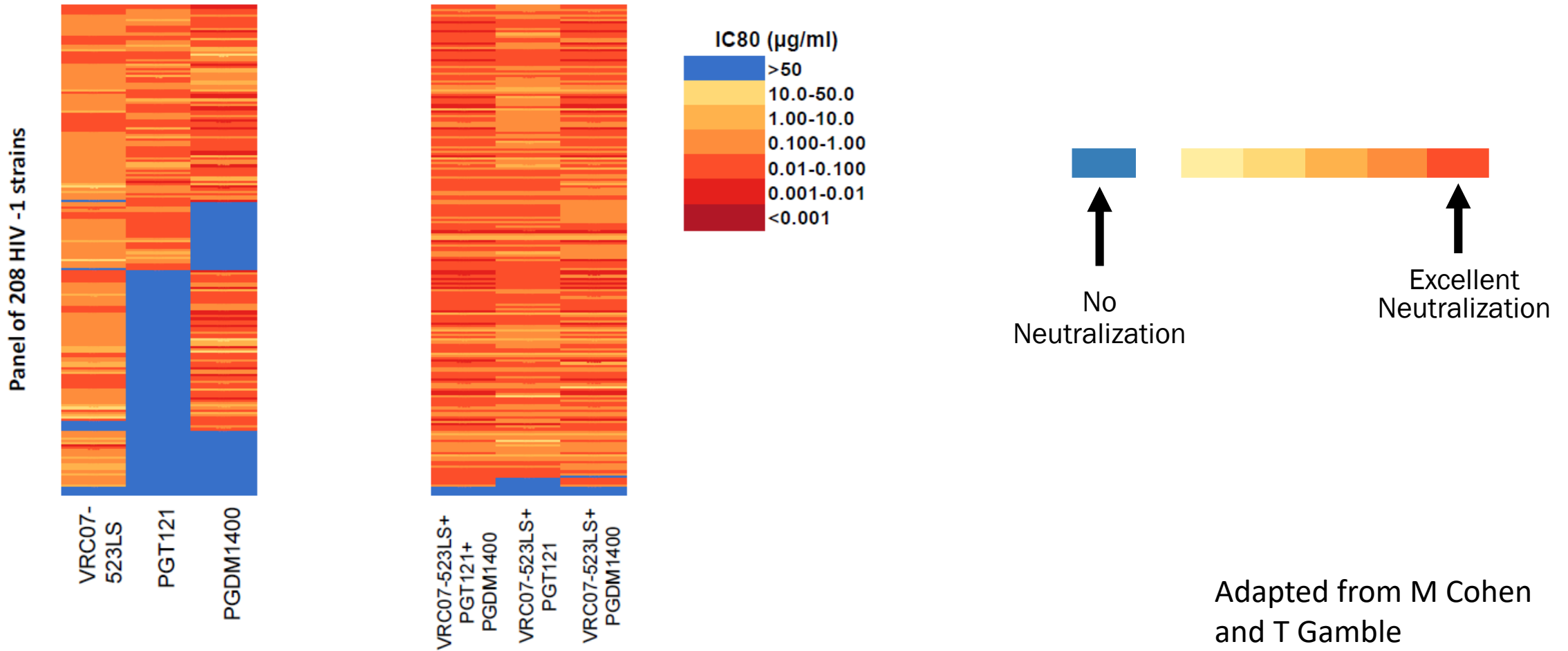


Different antibodies have different neutralizing activities. Modeling and preclinical studies suggest that combining bNAbs may lead to broader neutralization compared to giving bNAbs alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these differences are seen in humans, and guide selection of best antibodies and combinations types.

\*Data: Kong et al., 2015

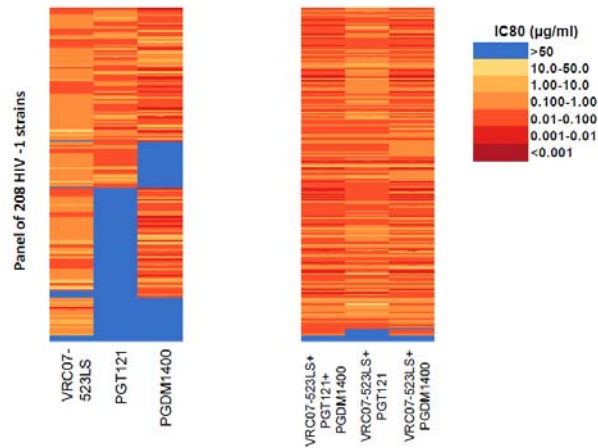
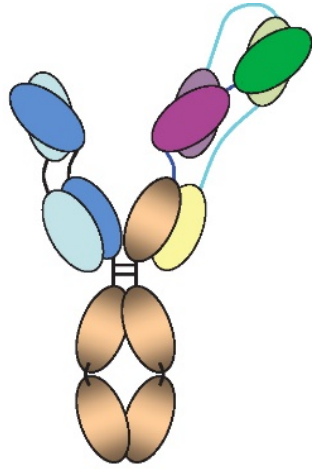
KEY				
 10-1074	 10E8VLS	 3BNC117	 CAP256LS- VRC26.25	 PGDM1400
 VRC07-523L	 PGT121	 VRC01	 Ibalizumab (IMab)	 10E8.4

# Theoretical combinations of bnAbs





# Next generation bnAbs Summary



- If virus is targeted by multiple or tri-specific bnAbs, then escape is difficult.
- Use of trispecific bnAbs or combinations of bnAbs anticipated to improve efficacy through both better coverage and higher potency.
- Unlike AMP, a **proof-of-concept** study,
- The goal of these studies is to identify the best regimens for moving to a **licensure trial**.

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**And the many participants,  
research communities and  
researchers who have  
helped develop studies  
that will end the HIV  
epidemic!**



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