IAS 2019

10TH IAS CONFERENCE ON HIV SCIENCE

Mexico City, Mexico 21-24 July 2019

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New prevention products in the pipeline: Advances in the field of broadly neutralising antibodies

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UZCHS-CTRC

Saving Lives Through Innovative Research Strategies

Conflict of interest declaration

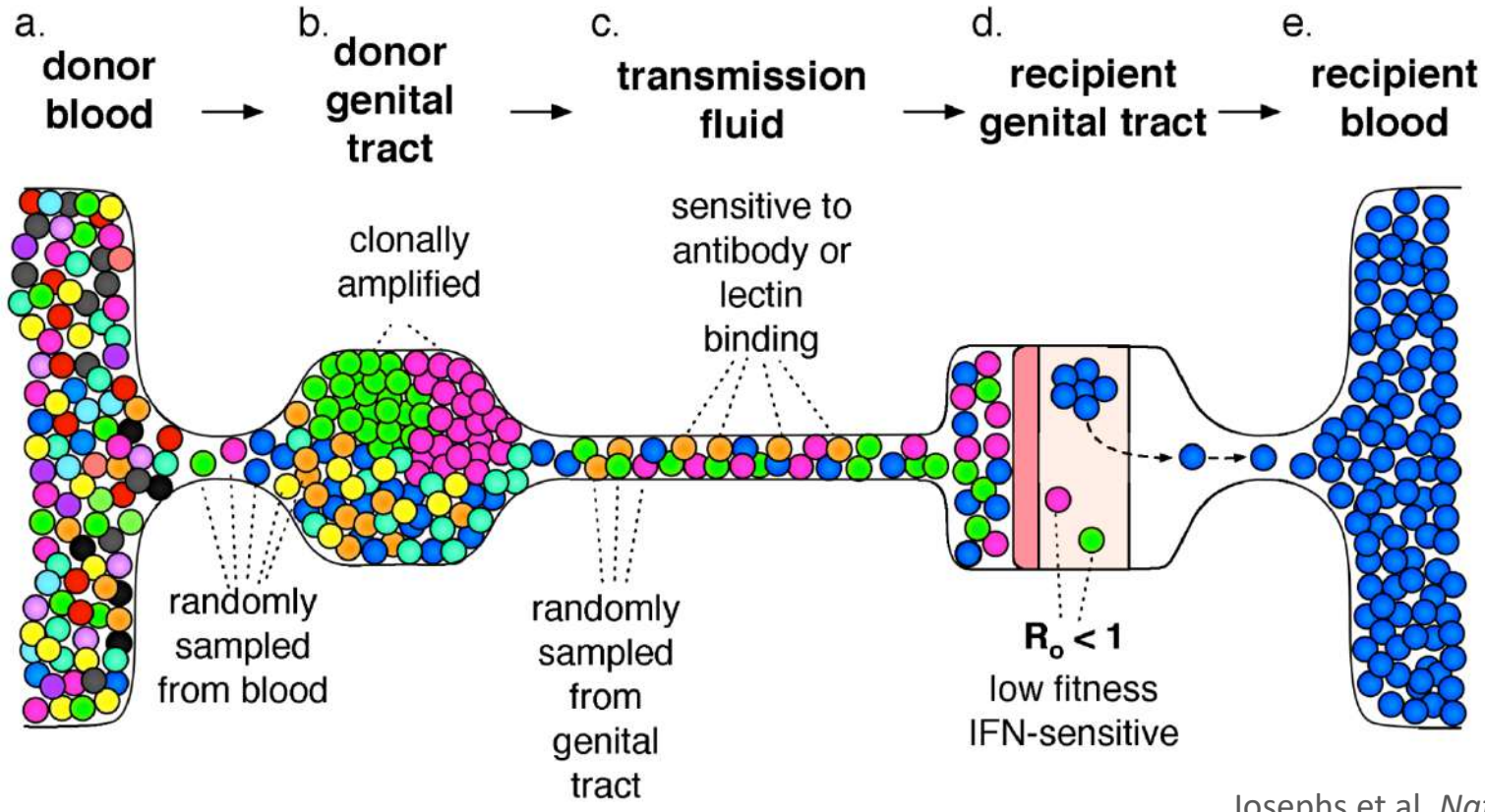
I have no conflicts of interest to declare

Presentation outline

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

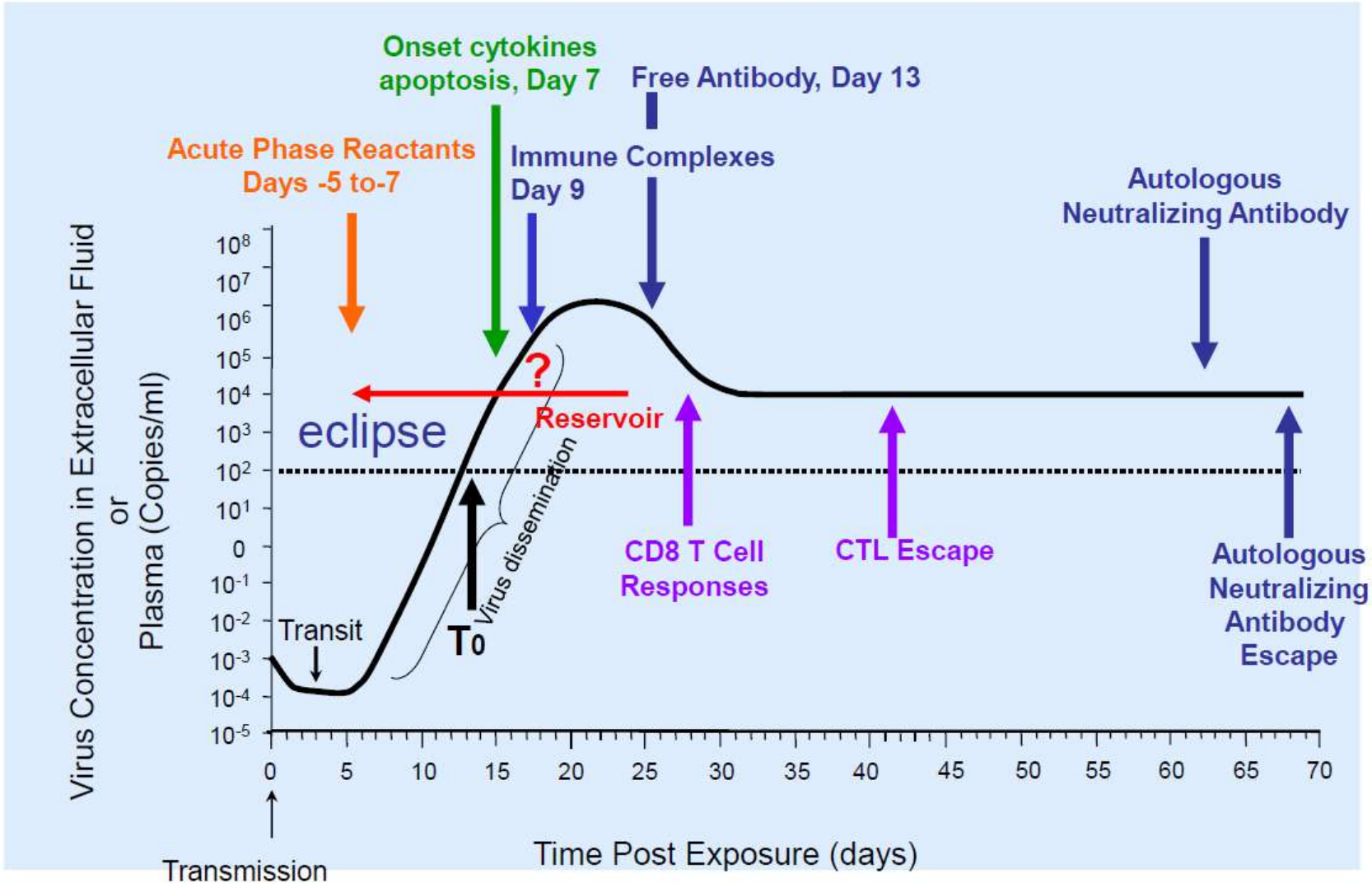
Biology of HIV infection

- HIV-1 encounters a genetic bottleneck during transmission
- Results in genetically homogenous population of initial plasma viremia



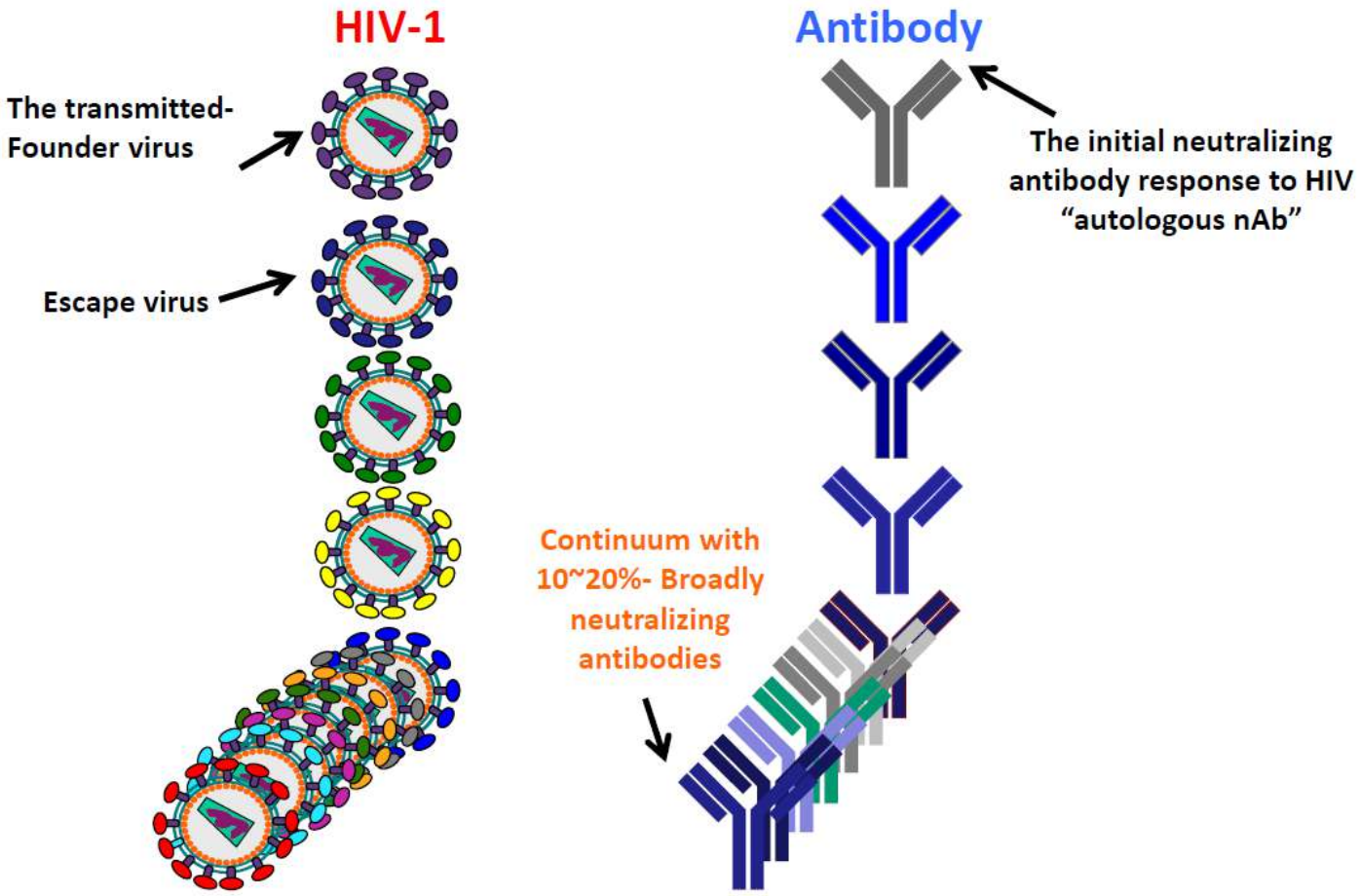
Josephs et al, *Nature Micro* (invited)

Acute HIV infection - immune response



McMichael. Nat. Immuno Rev; 2010,
Cohen NEJM 2011

Development of broadly neutralising antibodies



Broadly neutralising antibodies

Many Isolated 2009 - present

Broadly neutralizing mAb 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

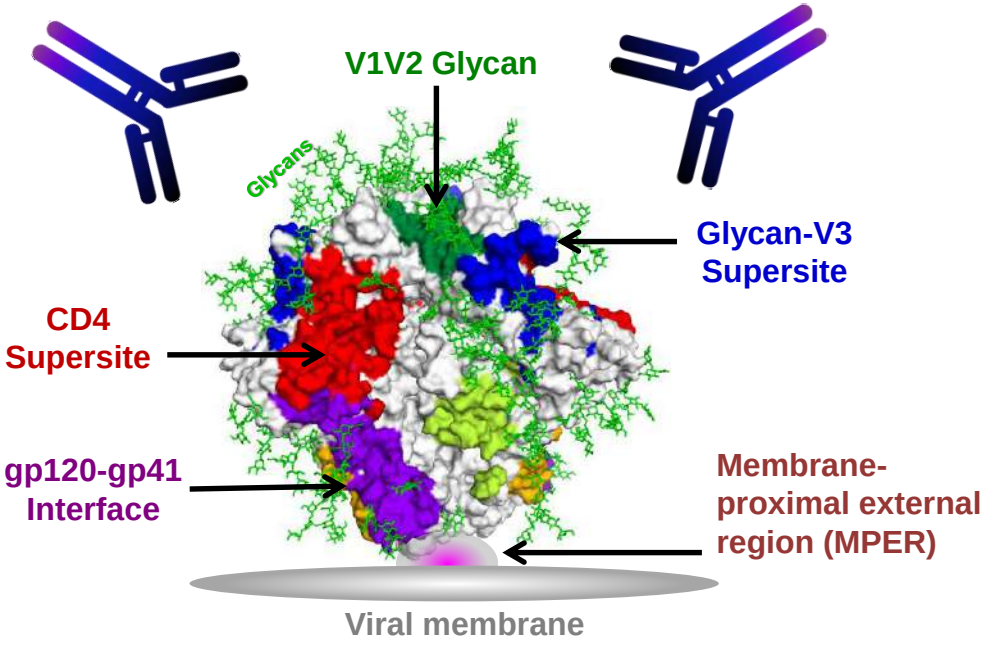


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

AMP = Antibody Mediated Prevention

Can a passively infused monoclonal antibody 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 Mgodi

AMP Study design

REGIMEN	HVTN 704 /HPTN 085 MSM & TG in the Americas	HVTN 703/ HPTN 081 Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	634	1534	10 infusions total & Infusions every 8 weeks
VRC01 30 mg/kg	900	634	1534	
Control	900	634	1534	
Total	2700	1900	4600	Study duration: ~22 months

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

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 SSA summary

Enrolment: 1924 (complete)

Retention: 96% - 34104/35591 visits

Adherence: 98% - 15673/16002 infusions

Data as of 20 July 2019

AMP MSM/TG summary

Enrolment: 2701 (complete)

Retention: 95% - 48937/51564 visits

Adherence: 100% - 22792/22844 infusions

Data as of 20 July 2019

Acceptability of bNAbs

AMP Behavioral Project

Six US Sites (HVTN 704/HPTN 085)

Mixed Methods - Exit Survey/Interview Focus

- Demographics, BnAbs, PrEP
- Perceptions of AMP community engagement efforts
- Perceptions of AMP participation
- Factors motivating participation in AMP
- Infusion Experience
- Recommendations to improve participant experience

AMP Success Story:

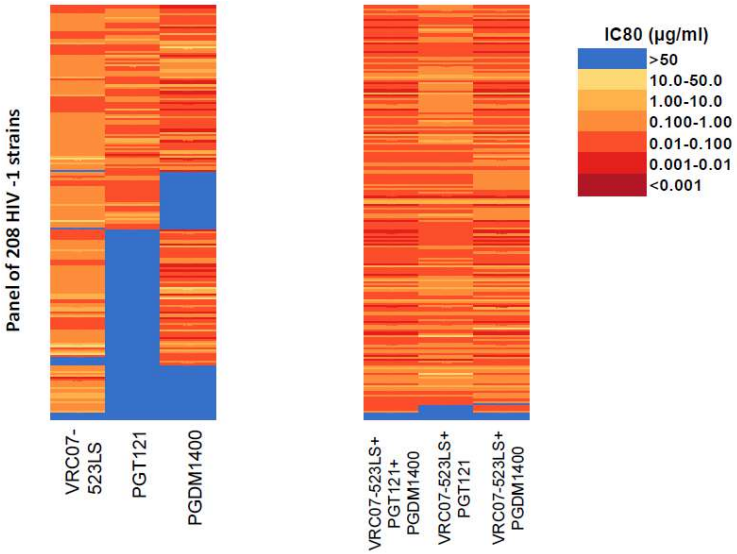
Strength of Relationships

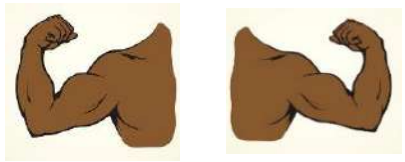
Altruism-Being Part of the solution

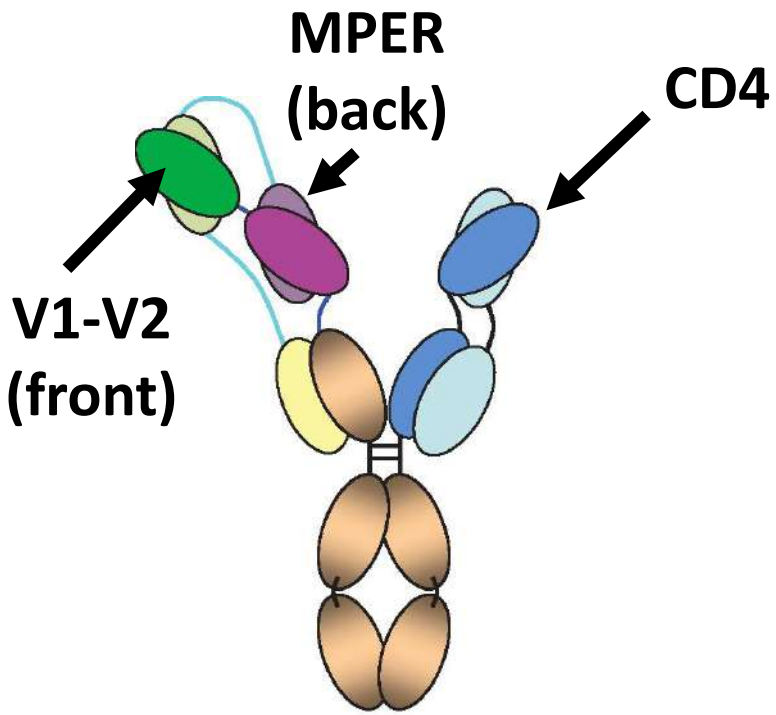
Community support – Andrasik TUAD0104

Responding to concerns

Michele Andrasik, PhD
Director Social and Behavioral Sciences and Community Engagement
HIV Vaccine Trials Network (HVTN)







NEXT GENERATION MONOCLONAL ANTIBODIES

VRC07-523LS

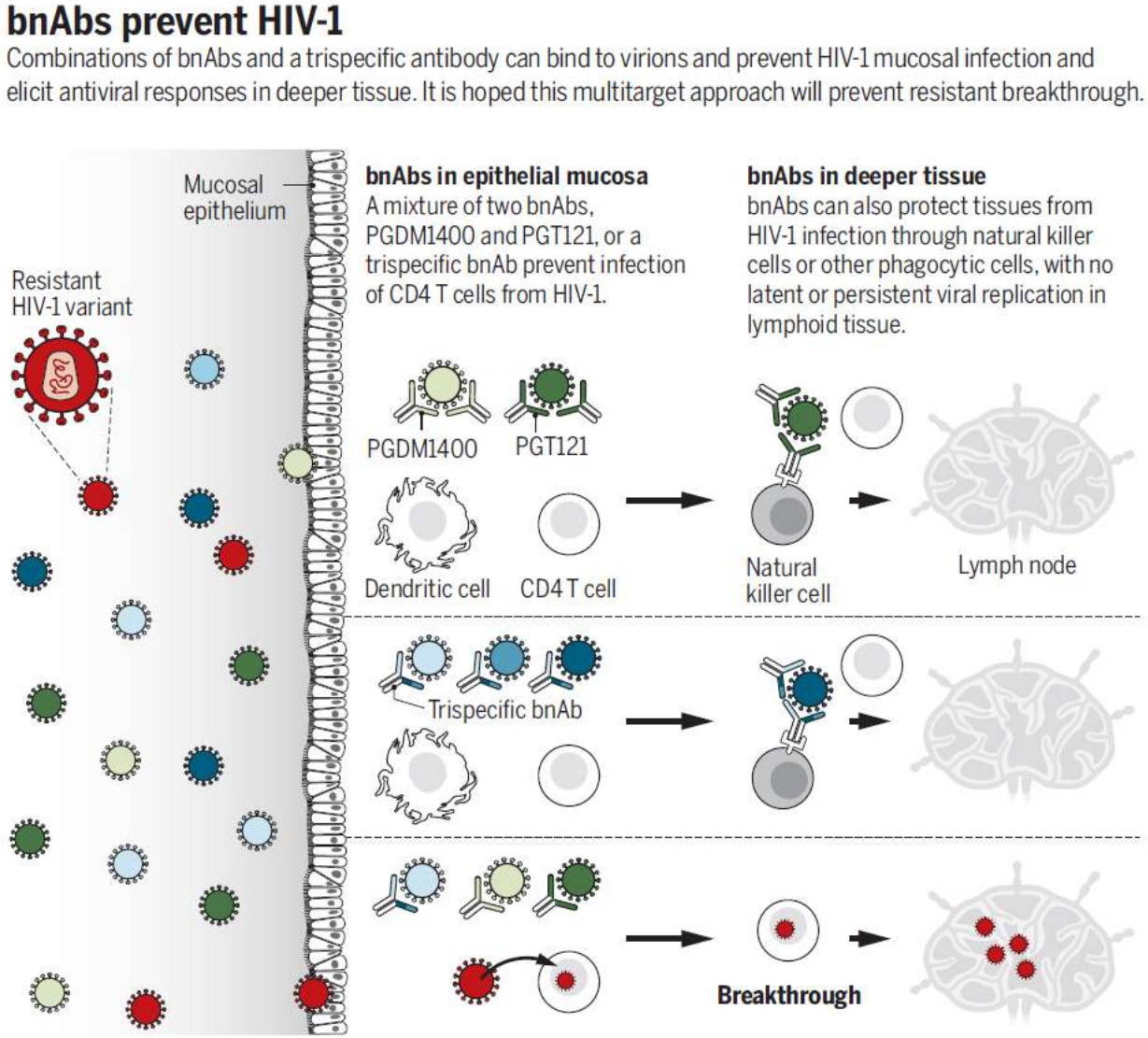
- Knowledge of the structure of VRC01 was used to engineer a next-generation antibody with 5- to 8-fold increased potency *in vitro*.
- A clonal relative of VRC01 has increased neutralization potency
- 07 denotes sequential numbering when discovered
- VRC07-523 ("523" denotes sequential numbering when engineered variant generated)
- VRC07-523LS ("LS" denotes 2 amino acid mutations)
- *Optimized VRC07 protects against infection at lower* ***plasma concentrations*** *and has minimal autoreactivity*

Rudicelli. J Virol; 2014

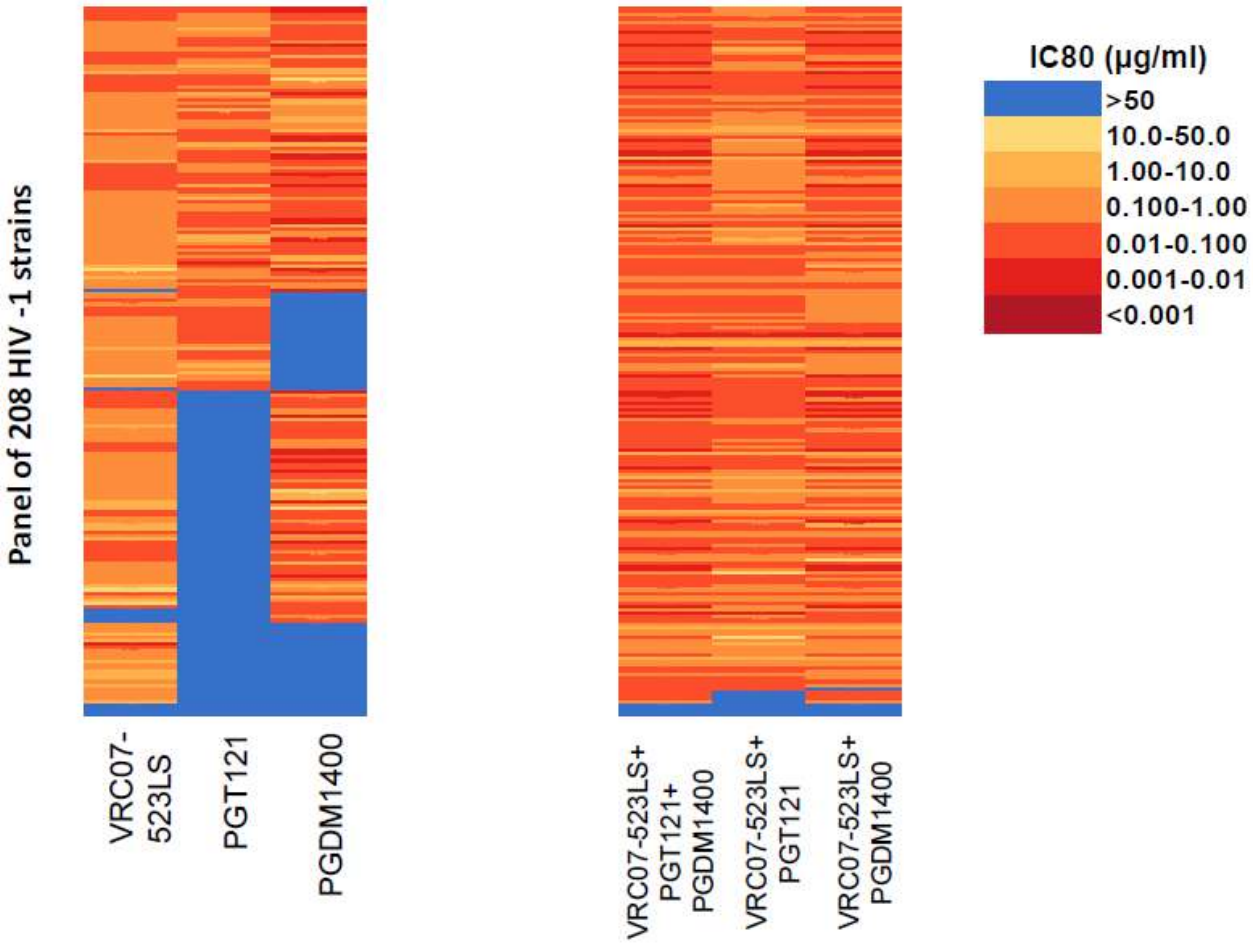
Lessons learnt from HIV treatment

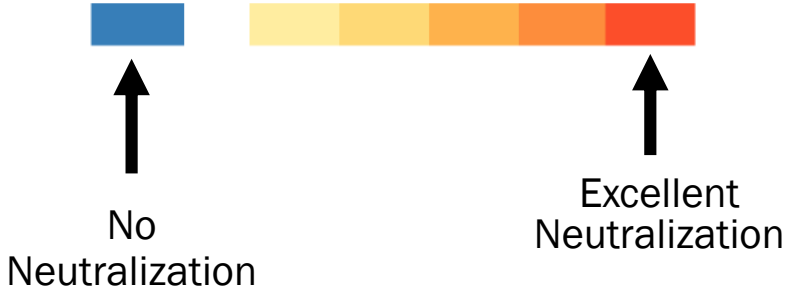
- HIV-1 exhibits genetic diversity and viral escape mechanisms
- Prudent to consider using a combination approach
- Like antiretroviral therapy, combinations of mAbs may reduce the likelihood of viral escape, and increase neutralization breadth
- Combining multiple bnAbs with specificities against different 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*

Xu, *Science*; 2017



Theoretical combinations of mAbs





Adapted from M Cohen and T Gamble

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.

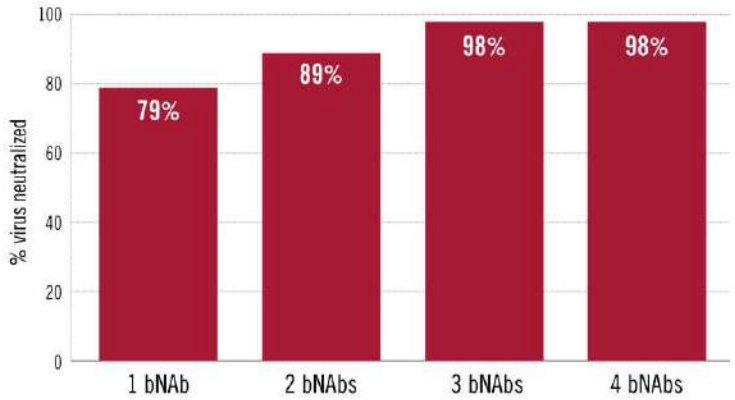
bNAb Cocktails: Two or more antibodies in a regimen

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)

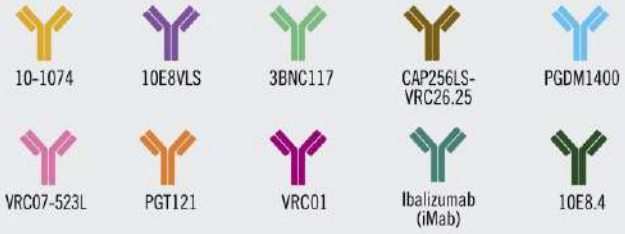
Combining bNAbs to broaden neutralization*



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



AVAC www.avac.org July 2019

Joint HVTN/HPTN mAb portfolio

HVTN 703/HPTN 081 HVTN 704/HPTN 085

AMP (VRC01)

HVTN 127/HPTN 087

VRC07-523LS (>VRC01)

HVTN 130/HPTN 089
HVTN 136/HPTN 092

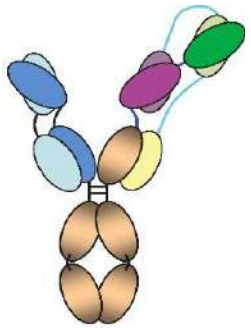
Iterative combinations of 2-3 antibodies

(multiple mAbs/targets)

HVTN 129/HPTN 088

Trispecific

(1 mAb, 3 targets)



Adapted from T Gamble

Next generation mAbs - Summary

- If virus is targeted by multiple or trispecific bNAbs, then escape is difficult.
- Studies are using/ will use trispecific bNAbs or combinations of mAbs to improve efficacy through both better coverage and higher potency
- The goal of these studies is to identify the best regimens for moving to a licensure trial

Acknowledgements

- Mike Cohen
- Wafaa el Sadr
- Larry Corey
- S Edupuganti
- Nirupama Sista
- Mike Chirenje
- Theresa Gamble
- Lisa Donohue

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

HIV VACCINE
TRIALS NETWORK

HPTN
HIV Prevention
Trials Network


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos