The future of broadly neutralizing antibodies for HIV prevention: Road to combo AMP

Nyaradzo M Mgodi (MBChB, MMed)
University of Zimbabwe
September 30th, 2023

Presentation highlights

HPTN Regional Meeting

What is the future of broadly neutralizing antibodies (bnAbs) in prevention of HIV-infection?

- Antibodies are effective in preventing infections.
- bnAbs are safe, tolerable and can prevent HIV.
- Combination of bnAbs may be needed to increase prevention efficacy.
- Phase I trials utilizing (combinations of) more potent and/or broader bnAbs for HIV prevention are underway and/or planned.
- Trials will evaluate dose optimization and neutralization surrogates.
- The results from bnAb studies may help us understand what a successful anti-HIV antibody response might look like in an HIV vaccinated person.
- The results may help us develop future HIV prevention methods.

HIV pre-exposure prophylaxis landscape

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	Oral	Topical (ring, inserts, film)	Parenteral (IV, IM, SC, ID, implant)
Approved	TDF/FTC TAF/FTC TDF/3TC	Dapivirine vaginal ring*	Cabotegravir*
Investigational	TAF/FTC** Dual Prevention Pill (DPP)	Dapivirine/ levonorgestrel vaginal ring*	Lenacapavir* bnAbs* Vaccine*

*Long acting **Cisgender women

Long-term: A safe and efficacious vaccine

The availability of an HIV vaccine will be an essential component of a multi-pronged approach to a world without AIDS.

Short/medium-term:

- ARV-based and non-ARV interventions
- Broad and potent HIV neutralizing antibodies
- Structural and behavioral interventions

A single product or approach will not stop the HIV pandemic

We need a diversity of prevention options and programs to address the diverse needs of individuals at risk for HIV infection

> 100-year history of antibodies to prevent infections: Passive immunization

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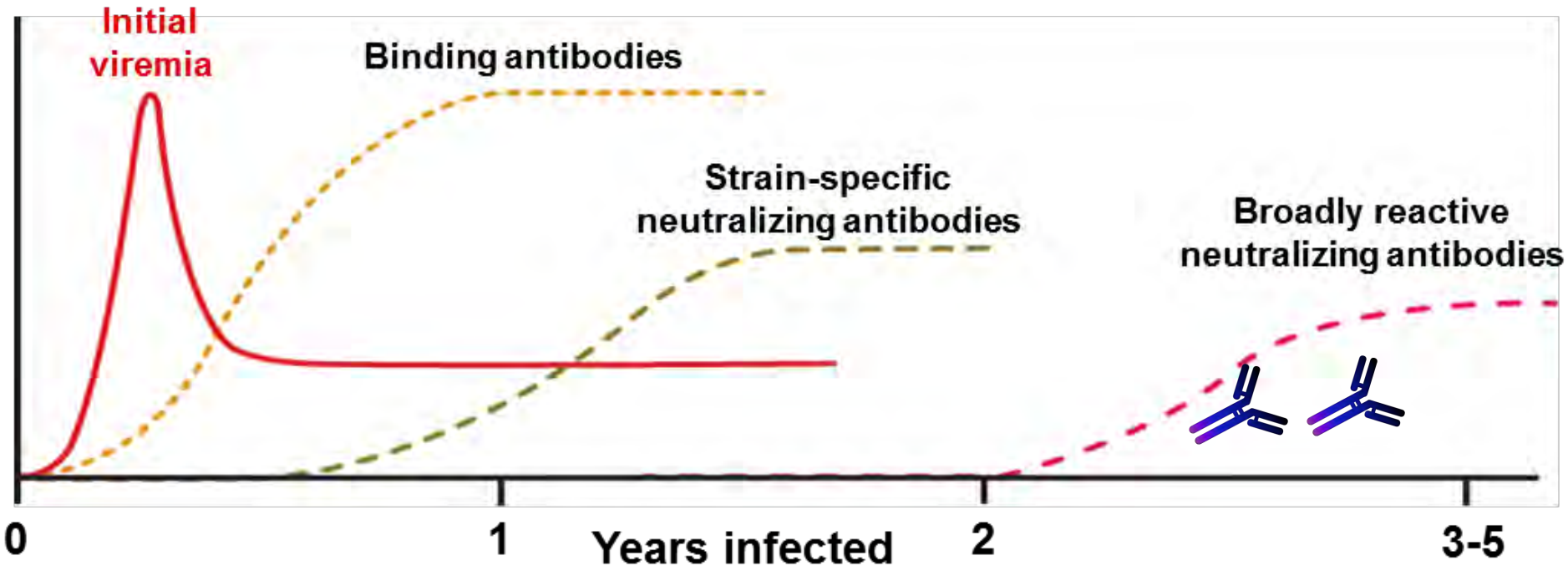
INFECTION	INDICATION	PRODUCT	YEAR
Tetanus	Prevention, treatment	Equine antitoxin	1890
		Human tetanus immune globulin (TIG)	1960
Measles	Prevention	Concentrated human gamma globulin	1944
Hepatitis A	Prevention (travel)	Immune serum globulin (ISG)	1945
Polio	Prevention	Concentrated human gamma globulin	1951
Rabies	Post Exposure	Rabies Immune Globulin	1954
VZ	Post Exposure	Varicella Zoster Immune Globulin	1978
Hepatitis B	Post Exposure	Hepatitis B Immune Globulin	1984
CMV	Prevention	Cytomegalovirus Immune Globulin	1987
RSV	Prevention (high-risk infants)	Pooled human Immune Globulin	1995
		Monoclonal antibody	2009
SARS-CoV-2	Prevention, Treatment	Monoclonal antibodies	2020
Malaria	Prevention	Monoclonal antibody	2022

This is not a complete list – Pre 2000 data modified from Keller & Stiehm https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88952/

Natural HIV infection: Development of broadly neutralizing antibodies



- **50% of those infected develop nAbs**
- Strain specific neutralizing Abs arise within 2-6 months
- Broad neutralization arises after 2-3 years, in 5-30% of patients
  - bnAbs develop faster, differently in infants

Mascola, Montefiori *Ann Rev Imm* 2010

Euler and Schuitemaker, *Frontiers in Immunology* 2012

bnAbs have several advantages over other PrEP products

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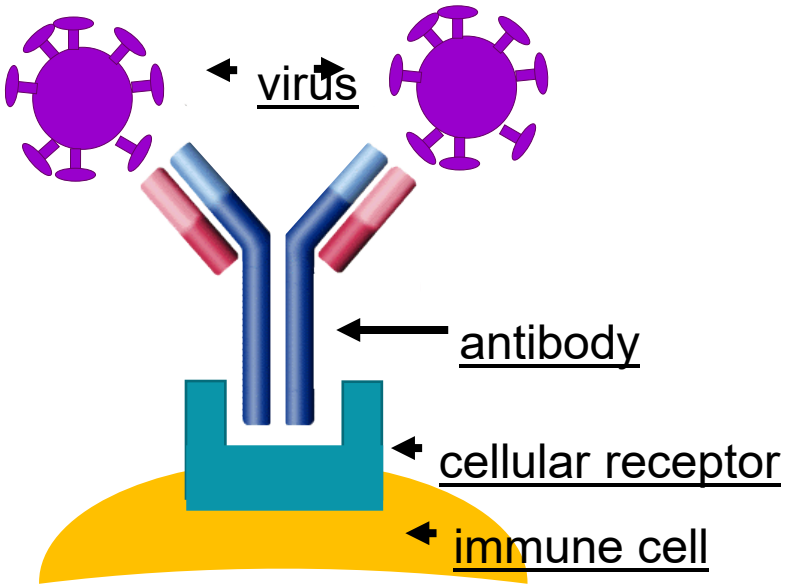
- Preclude antiretroviral therapy resistance
- Could be long acting
- No long pharmacokinetic tail
- Safe and non-toxic
- Potentially immunomodulatory
- bnAb PrEP provides another "choice"
- bnAb PrEP informs HIV vaccine development



AMP trials provide proof-of-concept that bnAbs can prevent HIV infection

HIV VACCINE TRIALS NETWORK

The NEW ENGLAND JOURNAL of MEDICINE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

Lawrence Corey, M.D., Peter B. Gilbert, Ph.D., Michal Juraska, Ph.D., David C. Montefiori, Ph.D., Lynn Morris, Ph.D., Shelly T. Karuna, M.D., Srilatha Edupuganti, M.D., Nyaradzo M. Mgodi, M.B., Ch.B., M.Med., Allan C. deCamp, Ph.D., Erika Rudnicki, M.S., Yunda Huang, Ph.D., Pedro Gonzales, M.D., et al., for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

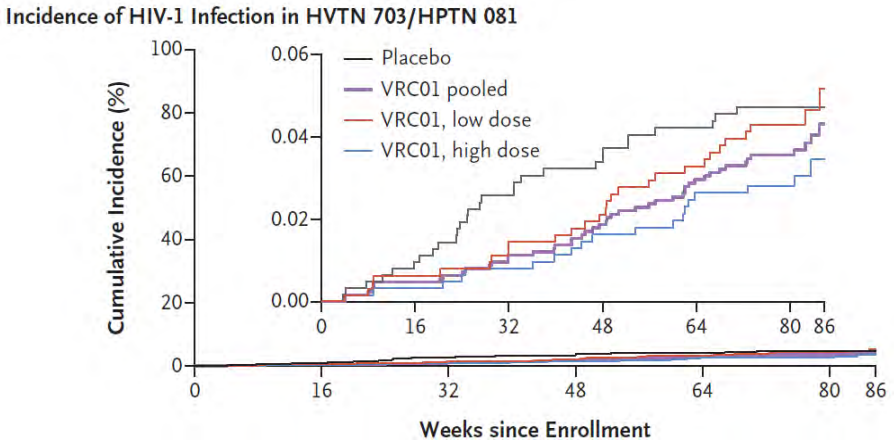
HPTN HIV Prevention Trials Network

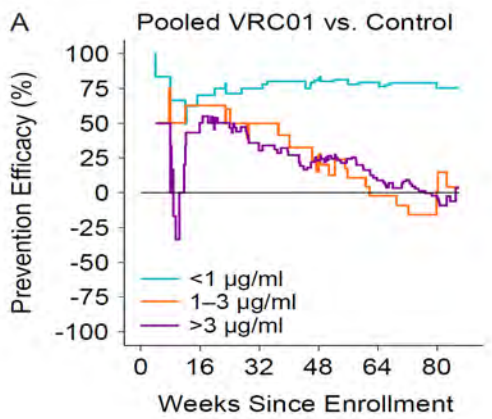
HVTN 704/HPTN 085 **HVTN 703/HPTN 081**

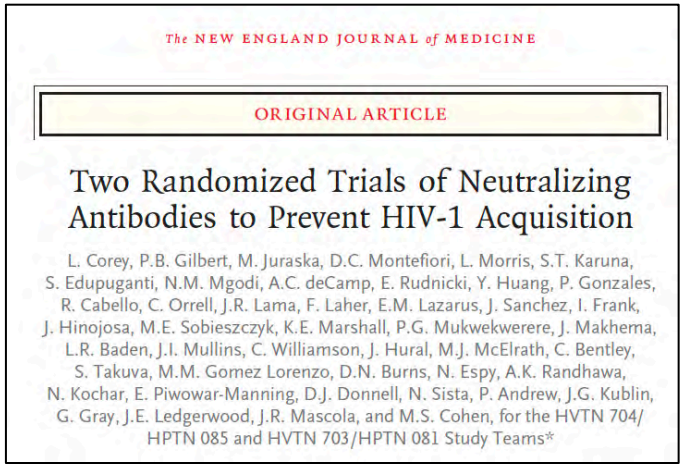
REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	633	1533	10 infusions total - given every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	900	633	1533	
Control	900	634	1534	
Total	2700	1900	4600	

Proof of concept

- HIV prevention with 1 bnAb is possible
- VRC01 protected only against acquisition of highly neutralization-sensitive viruses
  - Prevention efficacy of 75% (45 – 88%)
- Established putative marker of protection: PT80






The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition

L. Corey, P.B. Gilbert, M. Juraska, D.C. Montefiori, L. Morris, S.T. Karuna, S. Edupuganti, N.M. Mgodi, A.C. deCamp, E. Rudnicki, Y. Huang, P. Gonzales, R. Cabello, C. Orrell, J.R. Lama, F. Laher, E.M. Lazarus, J. Sanchez, I. Frank, J. Hinojosa, M.E. Sobieszczyk, K.E. Marshall, P.G. Mukwekwerere, J. Makhema, L.R. Baden, J.I. Mullins, C. Williamson, J. Hural, M.J. McElrath, C. Bentley, S. Takuva, M.M. Gomez Lorenzo, D.N. Burns, N. Espy, A.K. Randhawa, N. Kochar, E. Piwowar-Manning, D.J. Donnell, N. Sista, P. Andrew, J.G. Kublin, G. Gray, J.E. Ledgerwood, J.R. Mascola, and M.S. Cohen, for the HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams*

Corey L *et al.*, *NEJM* 2021; Gilbert *el al., Nat Med* 2022

IC80 → PT80

- **IC80:** in vitro neutralization property of the clinical lot of a given bnAb against a given HIV-1 pseudo virus
  - Not a sufficient correlate; has nothing to do with the bnAb concentration in a recipient's serum.
- **PT80:** in vivo neutralization property of the serum sample of a bnAb recipient at a given time against a given HIV-1 pseudo virus
  - Could be a sufficient correlate; a property of both bnAb serum concentration and virus.

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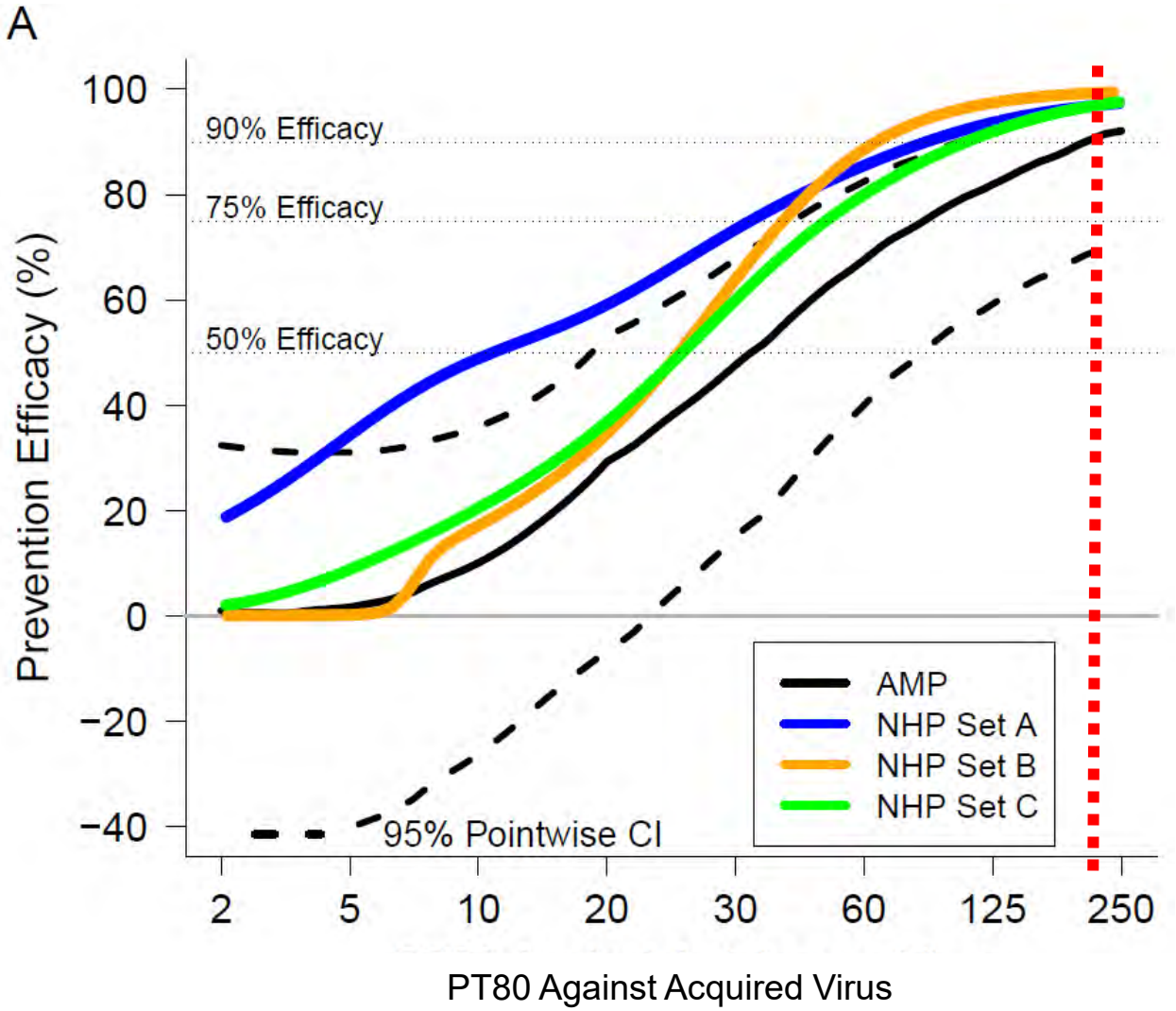
nature medicine

PT80

Neutralization titer biomarker for antibody-mediated prevention of HIV-1 acquisition

Peter B. Gilbert[1,2,26], Yunda Huang[1,3,26], Allan C. deCamp[1], Shelly Karuna[1], Yuanyuan Zhang[1], Craig A. Magaret[1], Elena E. Giorgi[4,24], Bette Korber[4], Paul T. Edlefsen[1], Raabya Rossenkhan[1], Michal Juraska[1], Erika Rudnicki[1], Nidhi Kochar[1], Ying Huang[1], Lindsay N. Carpp[1], Dan H. Barouch[5,6], Nonhlanhla N. Mkhize[7,8], Tandile Hermanus[7,8], Prudence Kgagudi[7,8], Valerie Bekker[7,8,25], Haajira Kaldine[7,8], Rutendo E. Mapengo[7,8], Amanda Eaton[9], Elize Domin[9], Carley West[9], Wenhong Feng[9], Haili Tang[9], Kelly E. Seaton[10], Jack Heptinstall[10], Caroline Brackett[10], Kelvin Chiong[10], Georgia D. Tomaras[10], Philip Andrew[11], Bryan T. Mayer[1], Daniel B. Reeves[1], Magdalena E. Sobieszczyk[12], Nigel Garrett[13,14], Jorge Sanchez[15], Cynthia Gay[16], Joseph Makhema[17,18], Carolyn Williamson[19], James I. Mullins[3,20,21], John Hural[1], Myron S. Cohen[22], Lawrence Corey[1,21,23], David C. Montefiori[9] and Lynn Morris[7,8,13]

Prevention efficacy smoothly increases with PT80 in AMP* and in NHP ** studies



PT80 of 80 → ~75% PE
PT80 of 200 → ~90% PE

NHP Set A: all 16 mAbs and 7 challenge viruses

NHP Set B: CD4-bs mAbs, excluding SF162P3

NHP Set C: excluding MPER mAbs and SF162P3

*Gilbert, Huang et al., 2022; **Pegu et al., 2019

The road to combo-AMP

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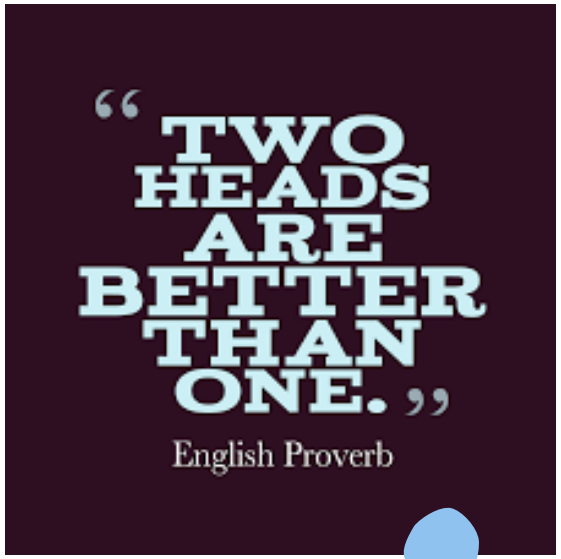
- HIV-1 exhibits genetic diversity and viral escape mechanisms.
- Resistance to neutralization has been attributed to amino acid changes, V1V2 loop length, and additions of glycans
- Next generation Abs are anticipated to improve efficacy through both better coverage and higher potency.
- Statistical modeling predicts that second-generation bnAbs, especially in combination, can neutralize close to 100% of global HIV-1 strains
- The goal of future studies is to identify the best regimens for moving to a **licensure trial.**



Kong et al., *J Virol*. 2015; Mkhize *et al., PLoS Pathog* 2023

Next generation broadly neutralising antibodies

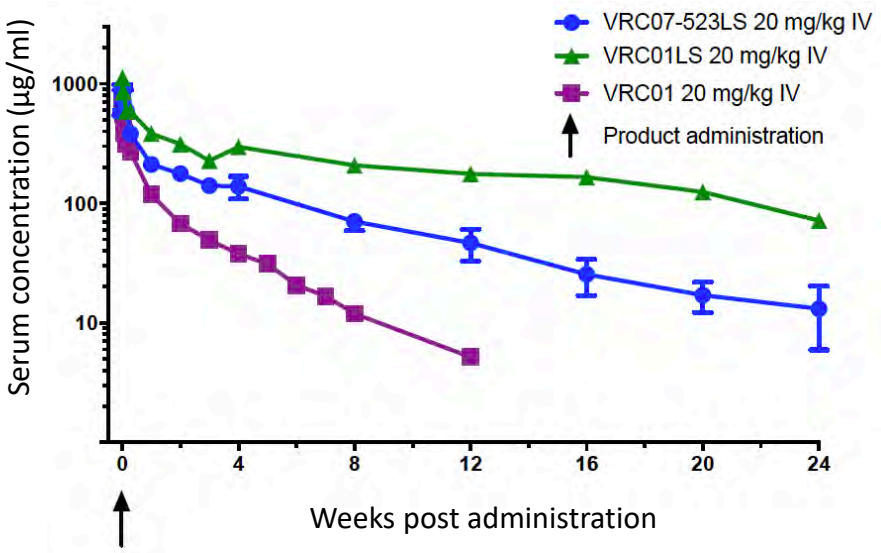
More potent, wider breadth

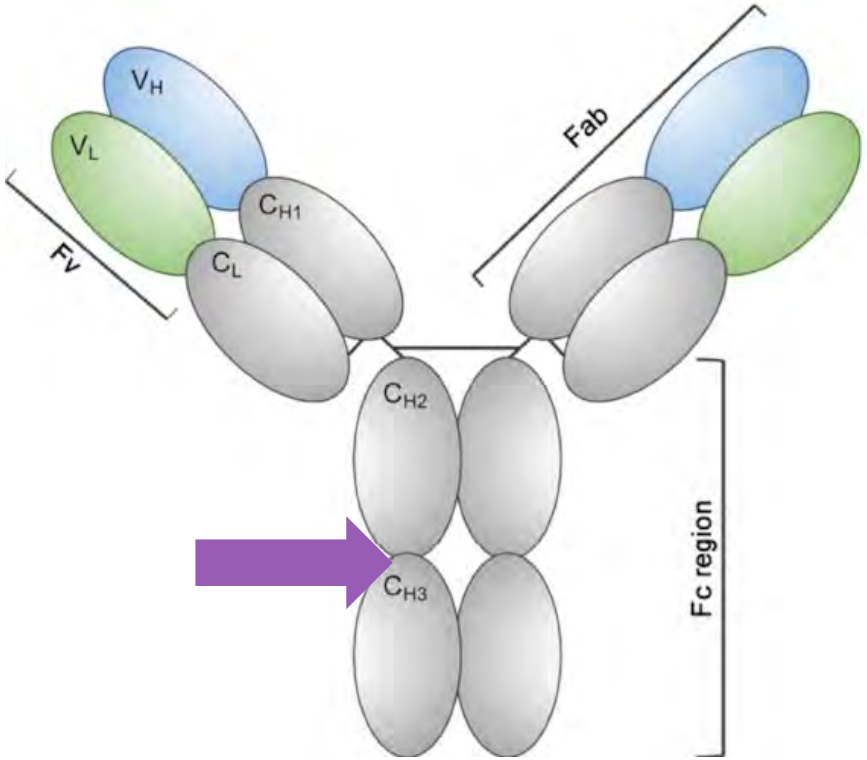
Antibody engineering can increase tissue levels and extend the half-life: May require administration only every 4 to 6 months.
Important implications for HIV vaccine development aimed at induction of bnAbs.

LS mutations

LS (M428L/N434S) amino acid mutation in Fc region of antibodies improves affinity for neonatal FC receptor (FcRn), increases concentration in mucosa, extends half-life from ~20 to ~60 days, allowing dosing every 6 months, minimized autoreactivity.

HIV bnAb pharmacokinetics





Gaudinski et al. 2019 Lancet HIV https://pubmed.ncbi.nlm.nih.gov/31473167/

From AMP to combo-AMP: Multiple bnAbs targeting different sites on the HIV-1 trimer may be needed for high prevention efficacy

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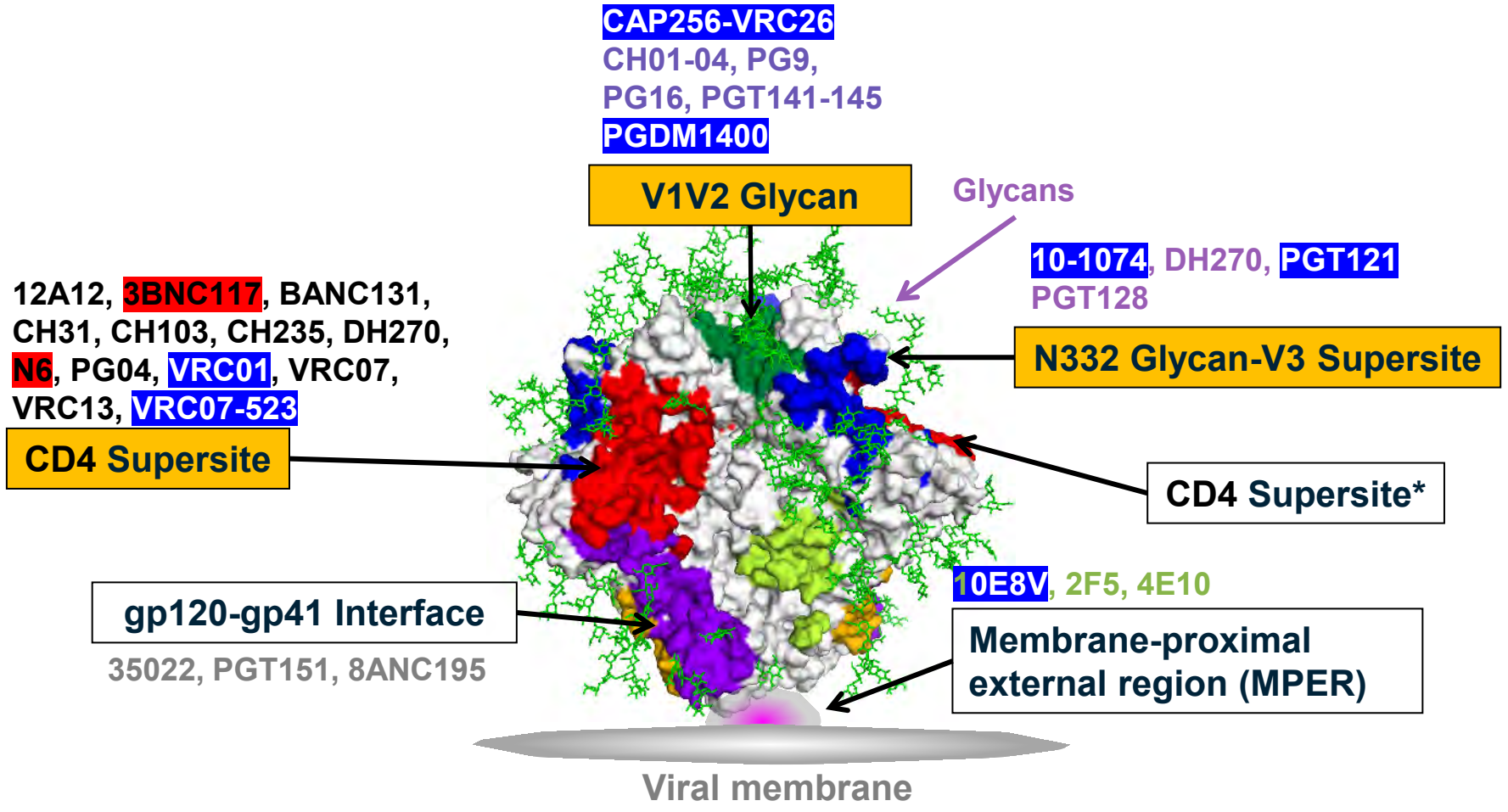

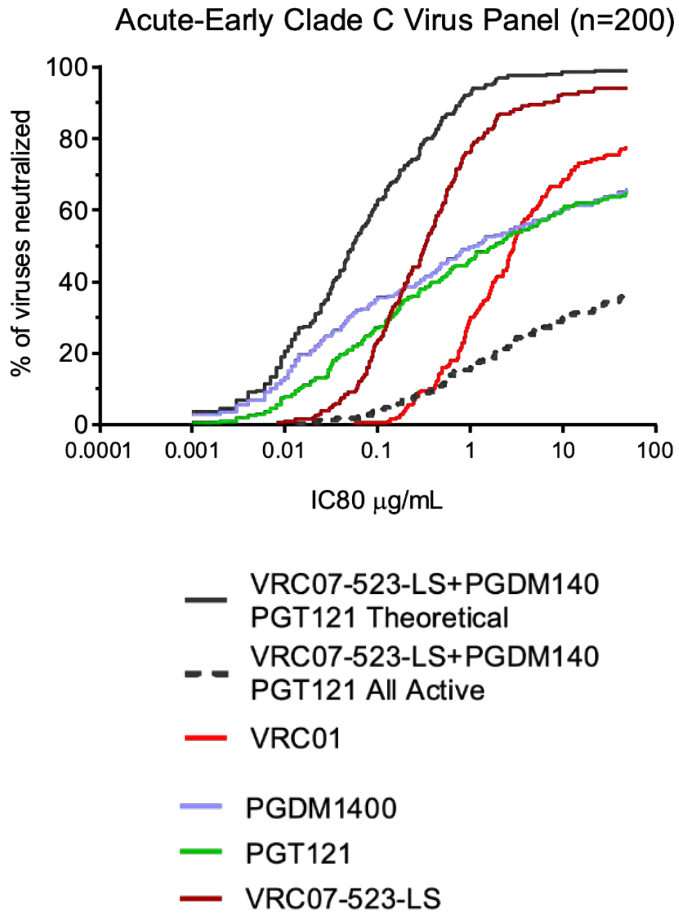

Blue background = mAb in Network Program

Adapted from Stewart-Jones et al, Cell 2016 & Pancera et al, Nature 2014, Klein, PLoS Pathogens, Scharf et al., 2015, Cell; Thanks to the NIAID Vaccine Research Center & Pamela Bjorkman's team

Theoretical antibody combinations for PrEP

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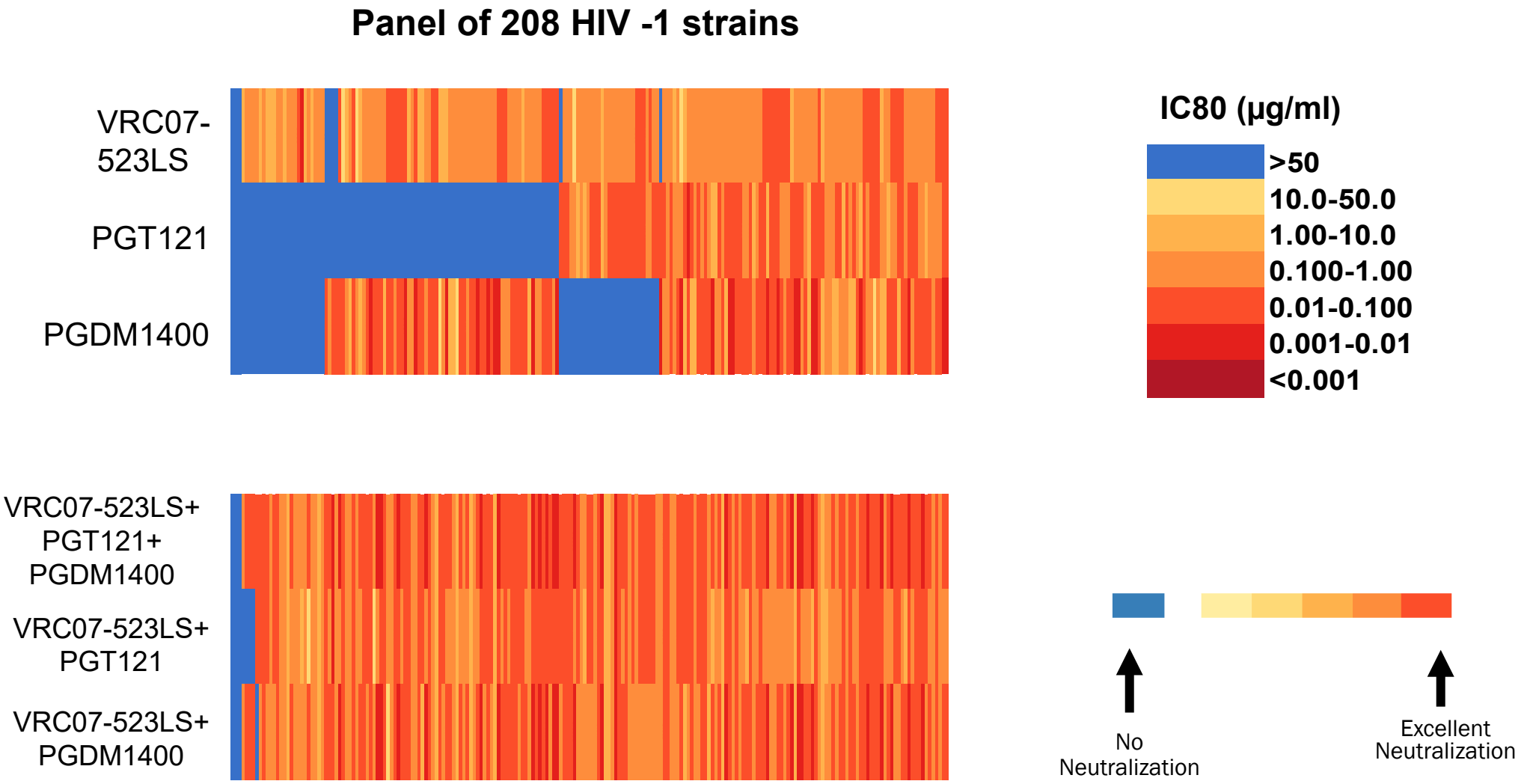
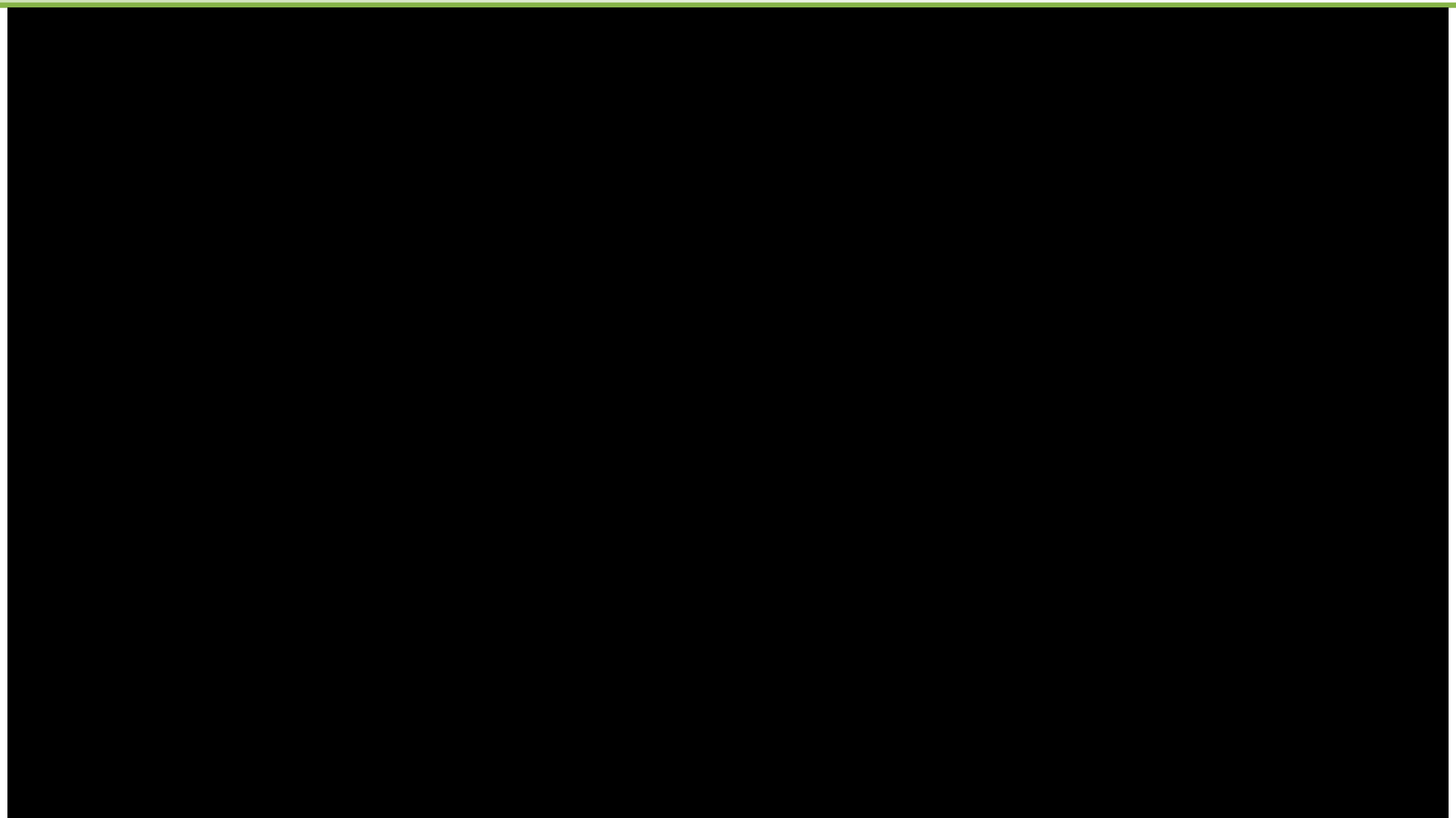


Adapted from M Cohen and T Gamble

Multiple antibody neutralization against HIV



Thanks to Lisa Donohue for this video.

HIV bnAb clinical trials in HIV-uninfected adults

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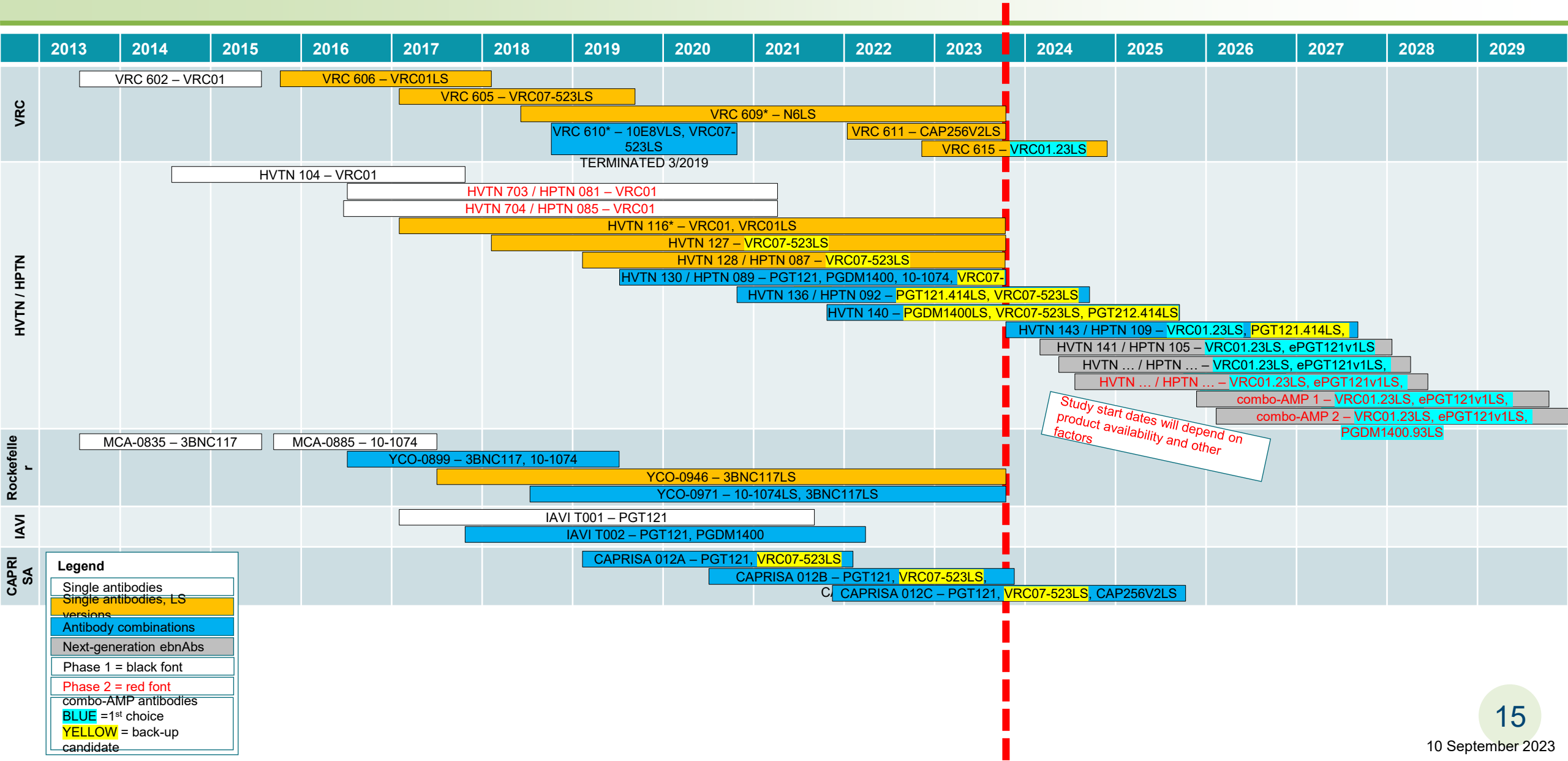

HVTN/HPTN HIV bnAb Clinical Trials in HIV-uninfected adults

> 4900 participants
> 50 sites
11 countries

Clinical Trial Participants	Start	bnAb	New concepts[1]	Key results – the road to combo-AMP	Countries
HVTN 104 N=88	2014	• VRC01 IV, SC	• Safety, PK, PD, neutralization • Repeat dosing up to 22 weeks	• Interim PK and neutralization data informed AMP protocol development	USA
HVTN 704/HPTN 085 N= 2699	2016	• VRC01 IV	• HIV prevention efficacy proof of concept • Correlate of protection	• HIV bnAb can prevent HIV acquisition • Correlate of protection – PT_{80} biomarker to predict protection • HIV bnAbs are safe – safety profile equal to placebo	Brazil, Peru, USA, Switzerland
HVTN 703/HPTN 081 N=1924	2016	• VRC01 IV	• HIV prevention efficacy proof of concept • Correlate of protection		Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe
HVTN 116 N=80	2017	• VRC01 IV • VRC01LS IV	• LS modification, longer half-life • Mucosa, tissue & secretions PK & activity	• VRC01LS ~3x longer half-life in serum, higher and prolonged levels in genital and rectal tissue	South Africa, USA
HVTN 127/HPTN 087 N=124	2018	• VRC07-523LS IV, IM, SC	• IM dosing	• VRC07-523LS ~2x longer half life • Neutralization consistent after 5 doses	Switzerland, USA
HVTN 128 N=28	2019	• VRC07-523LS IV	• Mucosa PK & activity		USA
HVTN 130/HPTN 089 N=27	2019	• VRC07-523LS IV • 10-1074 IV • PGT121 IV • PGDM1400 IV	• 2 bnAb combinations	• No PK interaction • No loss of complementary neutralization • Greater neutralization coverage in 3 bnAb arms compared to 2 bnAb arms	USA
HVTN 136/HPTN 092 N=32	2020	• VCR07-523LS IV, SC • PGT121.414.LS IV, SC	• 2 LS bnAb combination	• PGT121.414.LS ~3x longer half-life	USA
HVTN 140/HPTN 101 N=95	2021	• VRC07-523LS IV, SC • PGT121.414.LS IV, SC • PGDM1400LS IV, SC	• 3 LS bnAb combination • Fixed dose compared to weight-based dose	• PGDM1400LS ~2.5x longer half-life	Kenya, South Africa, USA, Zimbabwe
HVTN 143/HPTN 109 N=77	2023	• VRC01.23LS IV • PGT121.414.LS IV • PGDM1400LS IV	• 3 LS bnAb combination • 1st of 3 LS bnAbs to be used in 'combo AMP' in a 3 LS bnAb combination – 1 of 3		South Africa
HVTN 141/HPTN 105 N= 92	2024	• VRC01.23LS IV • ePGT121v1LS IV, SC	• 2nd (and 1st) of 3 LS bnAbs combination to be used in 'combo AMP' in a 2 LS bnAb combination – 2 of 3		South Africa, USA
HVTN TBD/HPTN TBD N= tbd ± 92	2024	• VRC01.23LS IV • ePGT121v1LS IV • PGDM1400.93LS IV, SC	• 3rd (and 2nd and 1st) of 3 LS bnAbs combination to be used in 'combo AMP' in a 3 LS bnAb combination – 3 of 3		TBD, South Africa, USA
HVTN TBD/HPTN TBD N=tbd ± 200	2024	• VRC01.23LS IV • ePGT121v1LS IV • PGDM1400.93LS IV	• Fixed 'combo-AMP' dose compared to weight-based dose • Safety run-in for combo-AMP		TBD, South Africa, USA

Combo-AMP studies
1. Women in SSA
2. MSM & transgender
N=tbd
	2025/ 2026	• VRC01.23LS IV
		• ePGT121v1LS IV
		• PGDM1400.93LS IV
			• 3 LS bnAbs combination
			  • HIV prevention efficacy proof of concept
			  • Correlate of protection
					AMP countries, TBD

[1]All trials evaluate safety, PK, & serum neutralization; additional protocol-specific evaluations noted here.

10 September 2023

Antibodies for HIV prevention: the path forward

Shelly Malhotra, Rachel Baggaley, Sharonann Lynch, Carmen Pérez-Casas, Yvette Raphael, Lynda Stranix-Chibanda

Reducing the complexity and cost of mAbs administration and supply chain.
Driving down the cost of goods sold (COGs) for mAbs.

JIAS, May 2023 Vol26 Issue5

Attributes of an optimal bnAb for HIV PrEP

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Safe, highly efficacious, durable and easily administered
Simple prevention and treatment regimens
Streamline supply chain management and administration
Streamline the regulatory pathway to a licensed drug
Affordable, scalable
High genetic barrier for viral resistance
Have a safety profile comparable to small molecule antiretroviral PrEP agents

JIAS, May 2023 Vol26 Issue5

The future of bnAbs for HIV prevention: Conclusion

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Future bnAb research:
A human rights-based approach

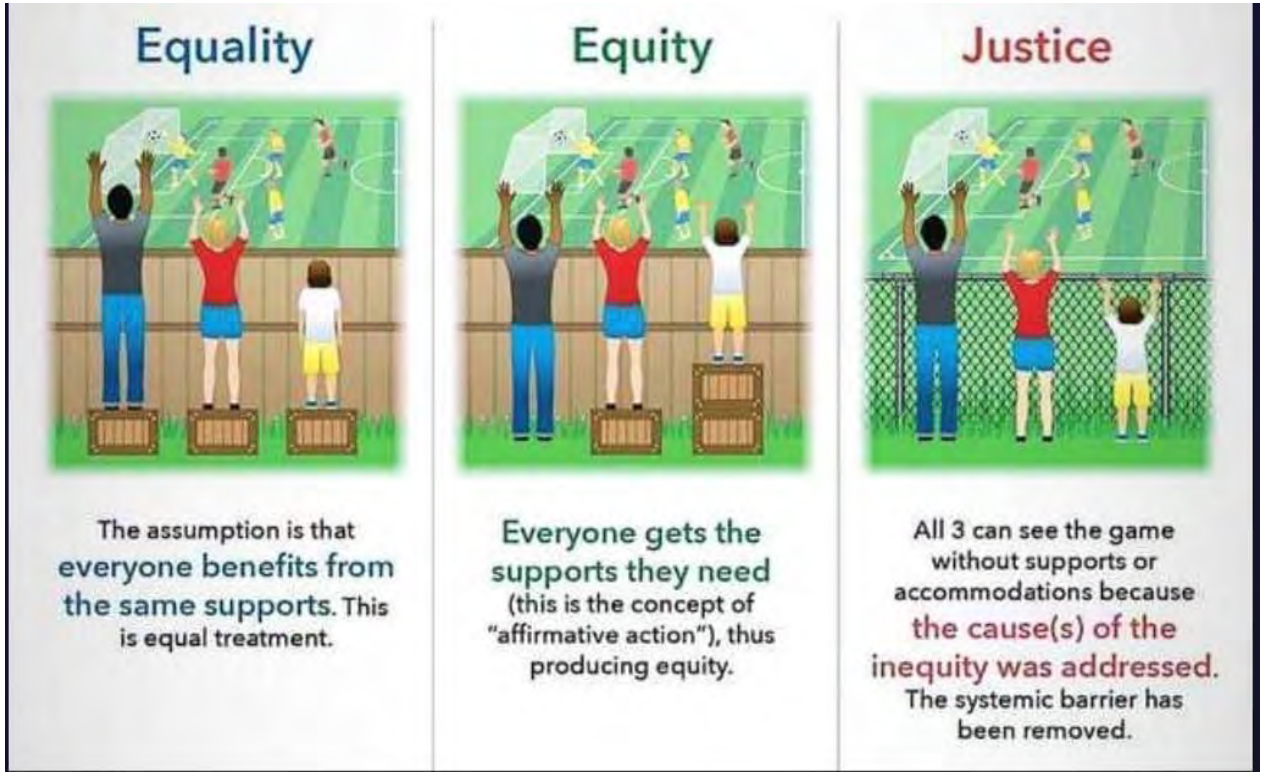

Image: Author unknown

The bnAb HIV prevention field is evolving faster than ever. Research must:

- Reflect diversity, equity, and inclusion.
- Uphold justice and beneficence.
- Target highest prevalence regions and special populations:
  - Pregnant and breast-feeding persons, infants, adolescents, women, KPs, PWID etc.
- Begin with the end in mind
  - Access, manufacturing, licensing, and delivery methods.
- Be framed by a human-rights-based approach.

Thank you

My sincere gratitude to colleagues who contributed to this presentation

- Myron S. Cohen, MD
- Nirupama Sista, PhD
- Huub Gelderblom, MD, PhD
- Linda Stranix-Chibanda, MD
- Sinead Delany-Moretlwe, MD
- Z. Mike Chirenje, MD

Thank you

Nyaradzo M Mgodi
nmgodi@uz-ctrc,org

@HIVptn

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- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.