Translating **science** into
**global** health impact

# IAVI HIV ebnAb development

## HIV Treatment bnAbs: Clinical Research Considerations Workshop

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**Senior Scientific Advisor, IAVI**

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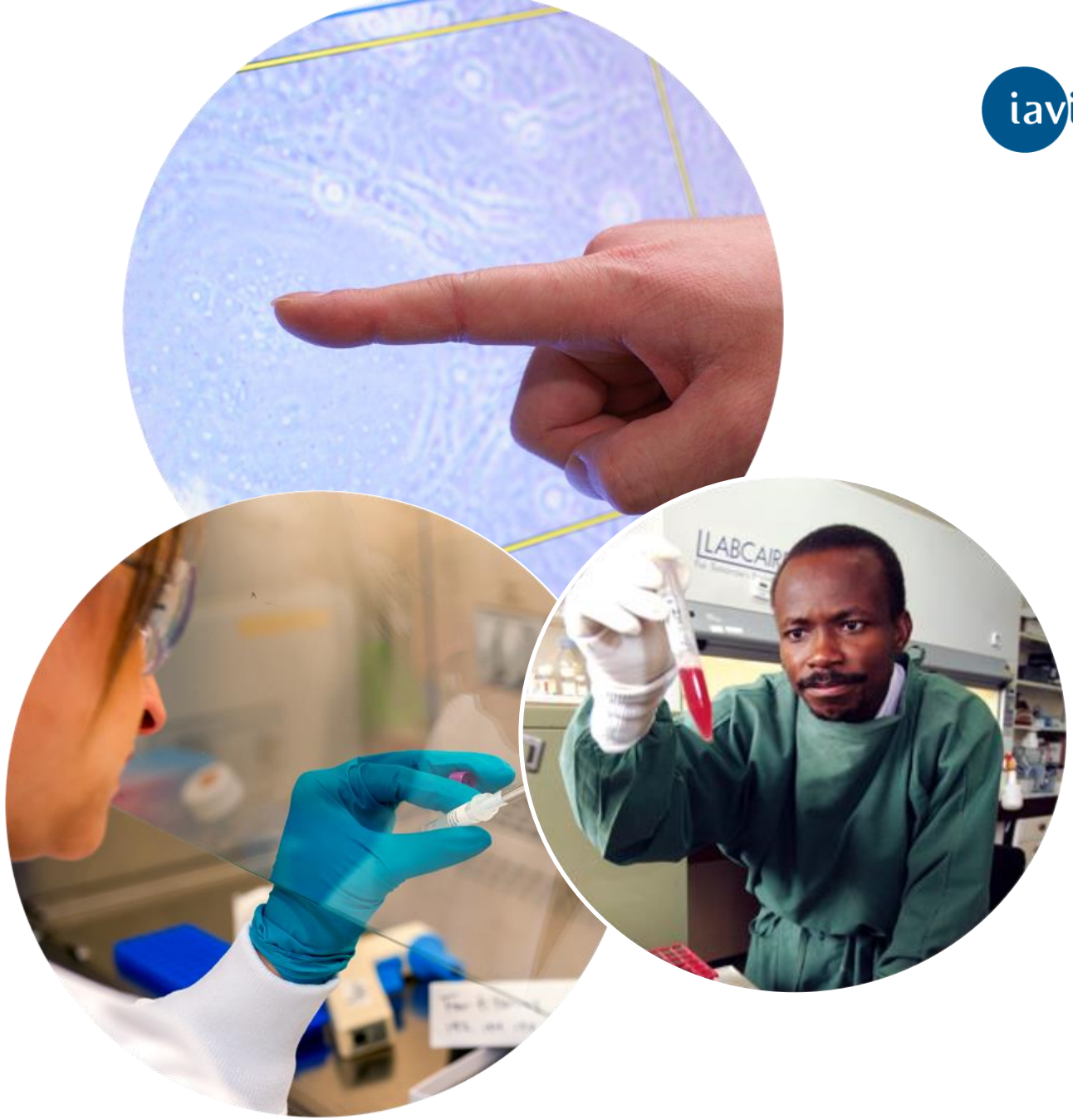
And many other generous individuals and partners around the world

As of July 2023

# IAVI's Mission and Vision

**Mission:** Our mission is to translate scientific discoveries into affordable, globally accessible public health solutions

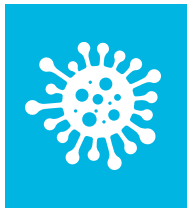
**Vision:** Our vision is a world where all people have equitable access to innovative vaccines and therapeutics



# IAVI today is advancing vaccines and antibodies for major global health challenges across poverty-related & neglected diseases, emerging epidemics and drug-resistant infections

## HIV Abs

*Long-acting antibody treatment and prevention product*

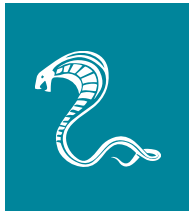


## Sarbecovirus Abs

*Neutralizing antibodies for therapy and prophylaxis*

## Enteric bacteria Abs

*Bactericidal antibodies for treatment and prevention of enteric bacterial infections*



## Snakebite Abs

*Antibody cocktail as universal therapy for snakebite envenoming*

## HIV Vaccine

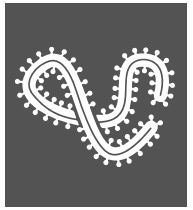
*Rational vaccine design to elicit broadly neutralizing antibodies*

## Tuberculosis

*H56:IC31, MTBVAC*

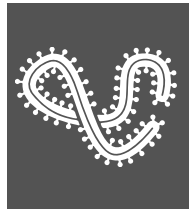
## Lassa Fever

*VSV vaccine expressing the Lassa glycoprotein*



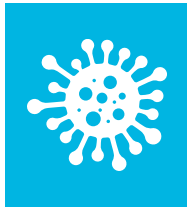
## Ebola Sudan

*VSV vaccine expressing the Ebola Sudan glycoprotein*



## Marburg

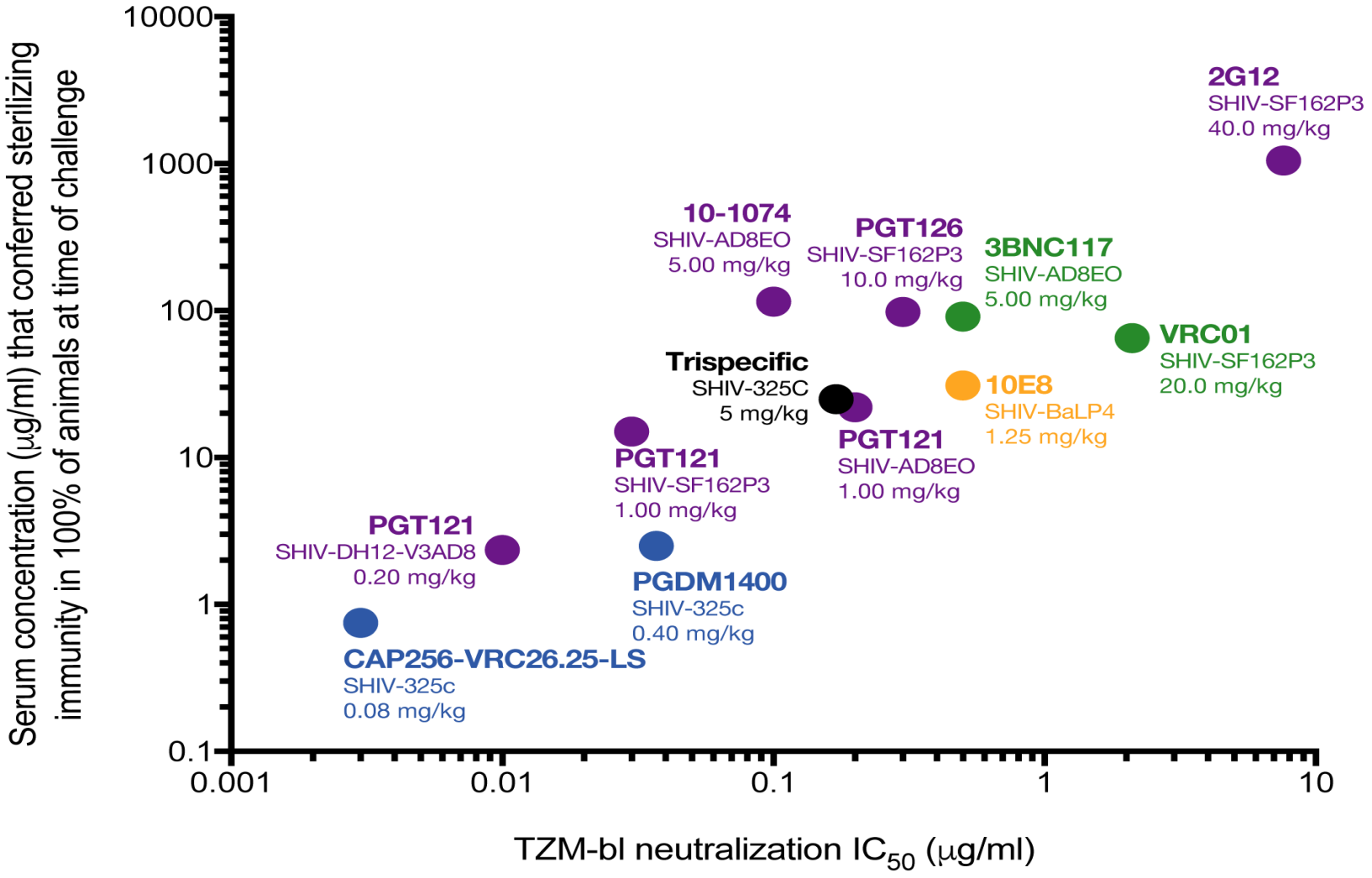
*VSV vaccine expressing the Marburg glycoprotein*



## SARS-CoV-2

*VSV vaccine expressing the SARS-CoV-2 spike protein*

# HIV bnAb in vitro neutralization titers correlate with serum titers required for complete protection against HIV challenge in NHP




*Sok & Burton, Nature Immunology, 2018*

# To select for bnAbs with enhanced neutralization activity, IAVI employed yeast display and directed evolution

**Parental Antibody**
*PGT121*

→

**Create mutagenesis library for heavy and light chain**

→

**Select for high-affinity variants using yeast display and target Ag**

→

**Characterize variants with mutations that enhance Ag affinity**
*ePGT121v1*
*ePGT121v2*

→

**Downselect lead based on neutralization, SEC, SDS, polyreactivity**
*ePGT121v1*

***Unpublished, similar strategy used for ePGDM1400v9***

**Joseph Jardine**

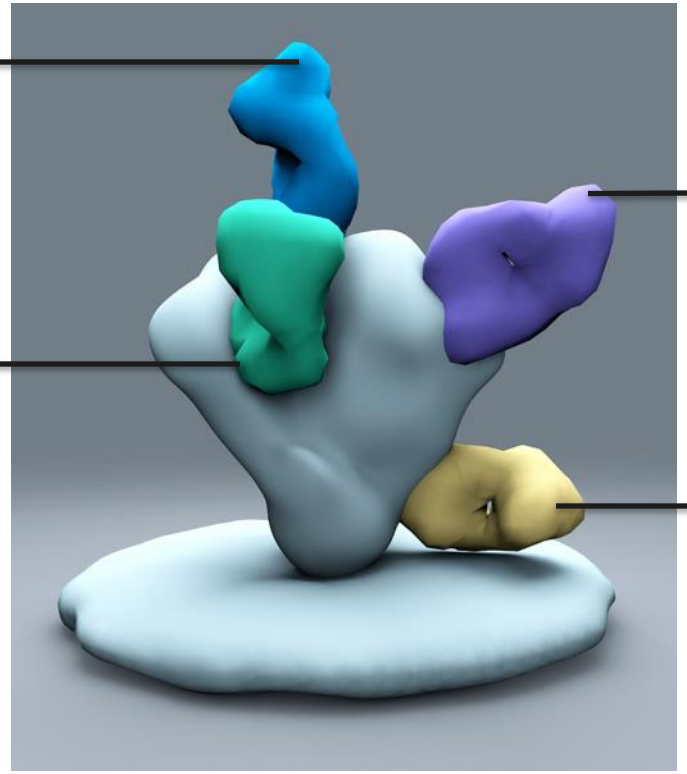
# HIV bnAbs targeting different epitopes should provide complementary neutralization coverage (titers and breadth) to increase the potential for high protective efficacy against global HIV isolates

V2 apex (ePGDM1400v9)

30-60% breadth
Avg neut potency: ~1-10 ng/ml

CD4bs (VRC01-class)

>90% breadth
Avg neut potency: ~100-1000 ng/ml



V3 glycan (ePGT121v1)

50-60% breadth
Avg neut potency: ~1-10 ng/ml

MPER (10E8 class)

>90% breadth
Avg neut potency: ~100-1000 ng/ml

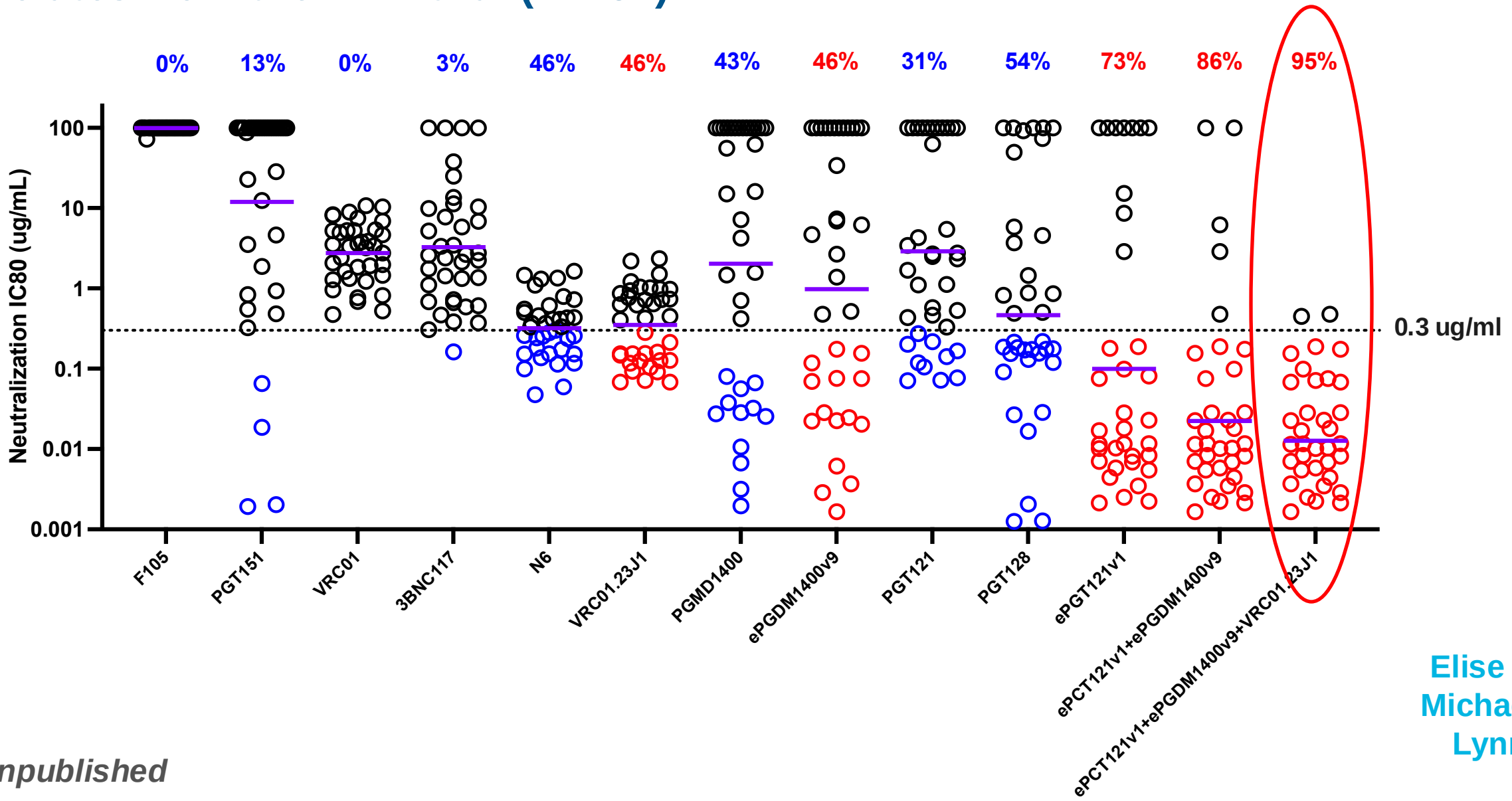
Models indicate that 90% protection should be be achievable if the serum bnAb concentration is at least 200X higher than the in vitro $IC_{80}$ (Gilbert et al., Nat Med 2022)

# HIV bnAb discovery and optimization

## Multiple generations of improved HIV bnAbs

| Epitope | Parental | 1st generation | 2nd generation |
|---|---|---|---|
| **V3 Glycan** | **PGT121** | **PGT121.414-LS** | **ePGT121v1** |
| | *Walker et al, Nature, 2011*<br>***IAVI/Scripps*** | *Unpublished*<br>***IAVI/Scripps/BIDMC*** | *unpublished*<br>***IAVI/Scripps*** |
| **V2 apex** | **PGDM1400** | **PGDM1400-LS** | **ePGDM1400v9** |
| | *Sok et al, PNAS, 2014*<br>***IAVI/Scripps*** | *Unpublished*<br>***IAVI/Scripps*** | *unpublished*<br>***IAVI/Scripps*** |
| **CD4bs** | **VRC01**<br>**VRC07** | **VRC01-LS**<br>**VRC07-523-LS** | **VRC01.23LS** |
| | *Wu et al, Science, 2010*<br>*Rudicell, JVI, 2014*<br>***NIH/VRC*** | *Ko et al, Nature, 2014*<br>*Gaudinski et al, Lancet HIV, 2019*<br>***NIH/VRC*** | *Kwon et al, mAbs, 2021*<br>***NIH/VRC*** |

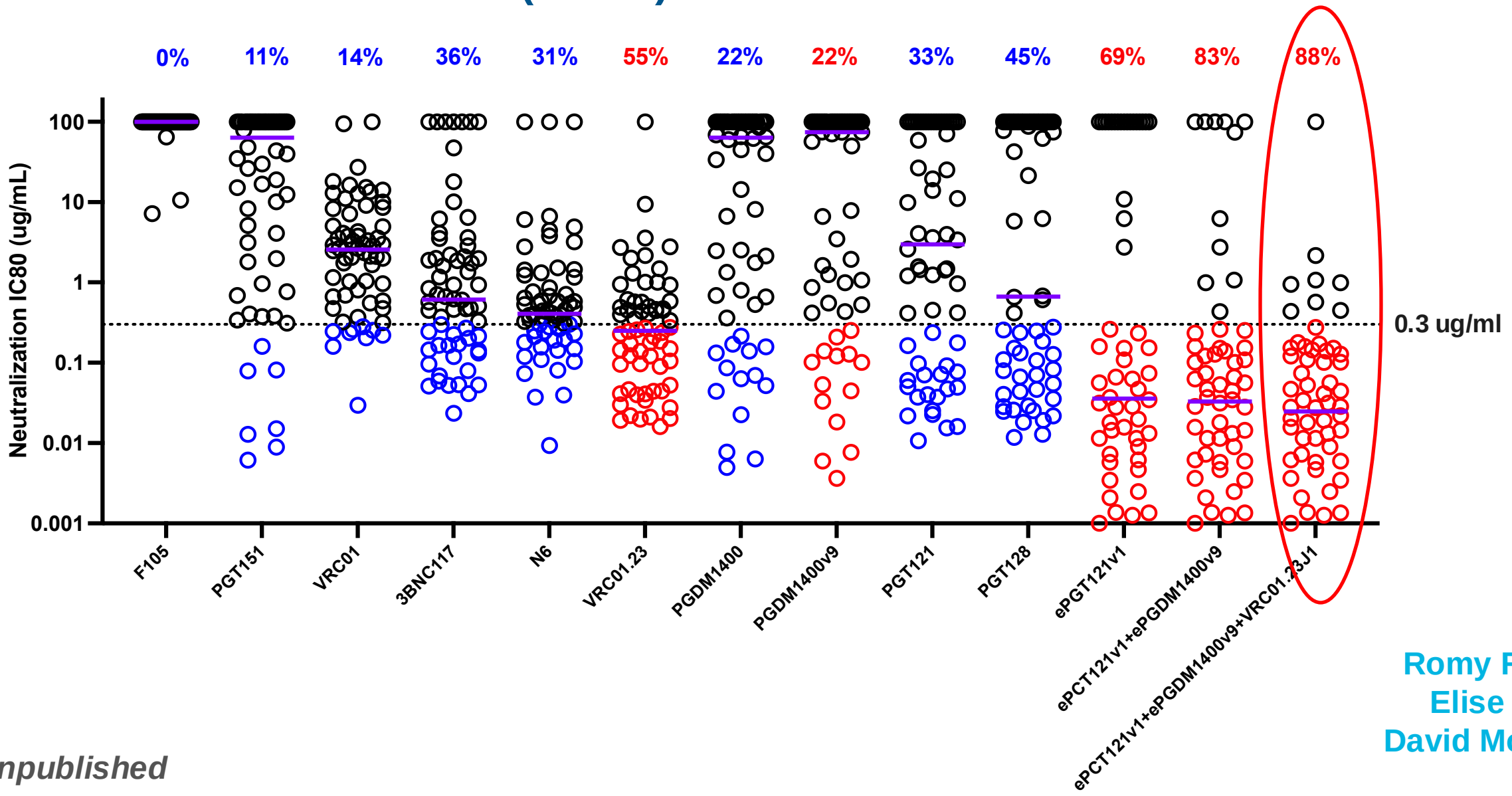
# Enhanced antibodies also show broad neutralization against Clade C virus isolates from the AMP trial (n = 37)




Elise Landais
Michael Appel
Lynn Morris

*Unpublished*

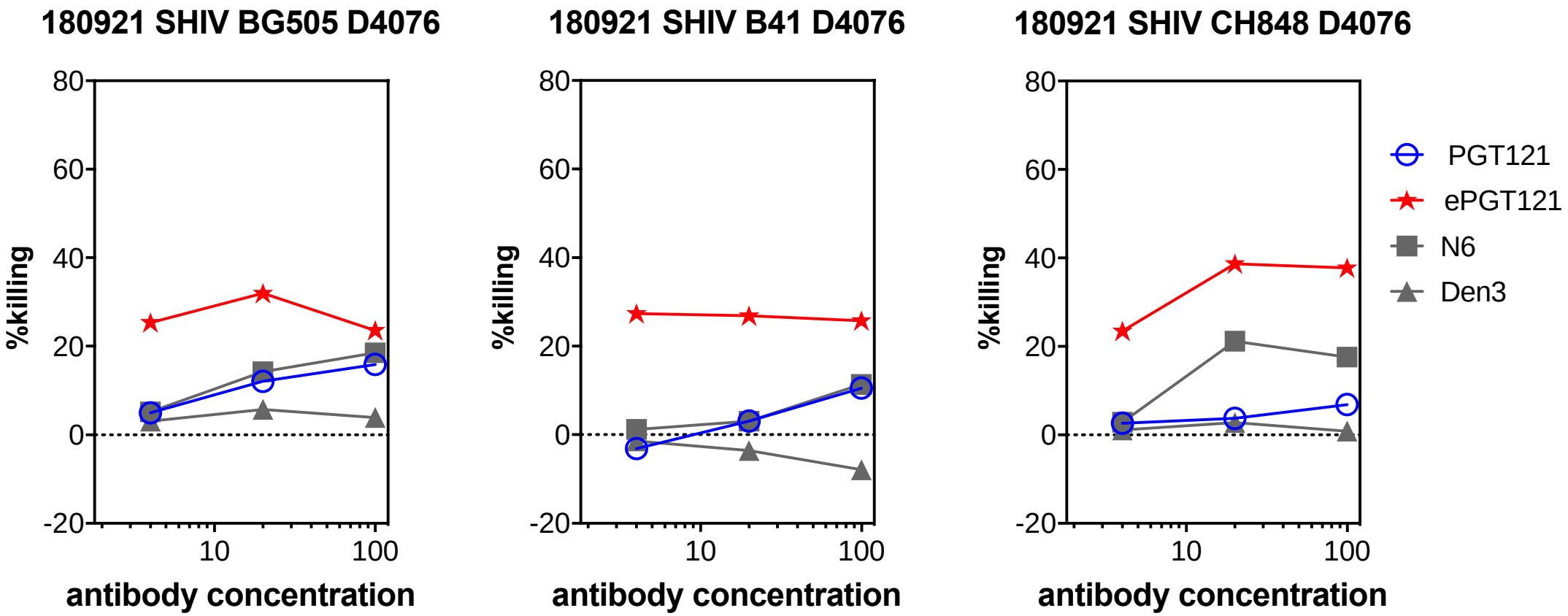
# Enhanced antibodies also show broad neutralization against Clade B virus isolates from the AMP trial (n = 62)




Romy Rouzeau
Elise Landais
David Montefiori

*Unpublished*

# ePGT121 shows improved ADCC activity compared to parental PGT121



# Topline Development Update – Pediatric Development Program (PNP prophylaxis)

- VRC01.23LS: Manufactured, FTIH underway, CTM available for HVTN141/HPTN105 (Concentration 100 mg/mL)
- ePGT121v1: GMP production (2KL) underway, CTM should be available for trial start Q2 2024 (Concentration 125 mg/mL)
- ePGD1400v9: Low productivity of cell line led to switch to PGDM1400.93LS (BIDMC/JustBio) which is slightly less potent but appears to have high productivity. DAIDS development contract in place for GMP production, CTM expected late 2024
- Clinical – Concept Protocol approved, full Phase I Protocol development waiting on CTM availability and COA
- Intent is to start adult FTIH with VRC01.23LS and ePGT121v1 and initiate pediatric program once initial safety and PK data available
- Addition of PGDM1400.93LS when CTM and adult safety PK data are available.

**IAVI believes its bnAbs could also play a role in treatment and cure indications**