

State of HIV prevention clinical research: Latest on HIV Vaccines

Future of HIV Prevention Clinical Trials Summit
Johannesburg, 11 June 2025



Prof Nigel Garrett
Chief Scientific Officer
Desmond Tutu Health Foundation
























USAID-funded Brilliant Consortium suspended on 27 January 2025

- Project turmoil
- Infrastructure collapse
- Individual pains



Trials & Projects Halted by USAID Funding Suspension

Project	Product(s)	Type	Country(ries)	# of participants
	 TAF/EVG Fast-dissolving insert	MATRIX-001 Phase 1 safety and acceptability	Kenya, South Africa, USA	60
	 One month dapivirine vaginal film	MATRIX-002 Safety, acceptability, usability of placebo	Kenya, South Africa, USA, Zimbabwe	100
	 Non-ARV nonhormonal contraceptive multipurpose vaginal ring	MATRIX-003 Safety, acceptability, usability of placebo	South Africa, USA, Zimbabwe	100
	 Injectable CAB, Dapivirine Vaginal Ring, Oral TDF/FTC	Cohort study of safety in mothers and babies exposed to ARV-based prevention	Kenya, Lesotho, Zimbabwe	500-800
	 One-month dapivirine vaginal film plus levonorgestrel (LNG)	Preclinical study	USA	Preclinical
	 BG505 GT1.1 and 426c.Mod. Core-C4b	B-001 Phase 1 clinical trial	Kenya, South Africa, Uganda	48
	 Polyvalent HIV-SET saMRNA vaccine clinical program	Pre-clinical and clinical trials	Multiple African countries	Exploratory
	 CAP 256 based mRNA vaccine candidates incl Africa-based mRNA manufacturing	Development program	Multiple African countries	Exploratory
	 Multiple founder virus-based vaccines	Exploratory program	Multiple African countries	Exploratory
	 Tech-transfer activities in Uganda with SOSIP trimers	Technology transfer	Uganda	Exploratory
	 Mosaic Trimers: MOS1SIP, MOS2SIP, M3SIP8 and MPLA	Vaccine	Rwanda, Zambia	40
	 Multisite Adolescent Girls and Young Women study	MAGY Epidemiological study	Uganda, Zambia, Kenya, South Africa	1,210
	 Injectable CAB, Dapivirine Vaginal Ring, Oral TDF/FTC	CATALYST Implementation Science Study	Kenya, Lesotho, South Africa, Uganda, Zimbabwe	7,500
	 Injectable CAB, Dapivirine Vaginal Ring	Policy and programmatic support, including user-centered research and technical assistance	Botswana, Eswatini, Kenya, Lesotho, Namibia, South Africa, Uganda, Zambia, Zimbabwe	Community-based
	 Dapivirine Vaginal Ring, Oral TDF/FTC	Increasing PrEP Options for Women in Eswatini	Eswatini	400
	 PrEP, vaccines and multipurpose technologies	Research translation and preparedness, policy support and advocacy to support prevention research	Kenya, Lesotho, Malawi, Nigeria, South Africa, Uganda, Zambia, Zimbabwe	Community-based

The big question: Do we still need an HIV vaccine in the era of long-acting PrEP?

Perspective
APRIL 24, 2025

An HIV Vaccine in the Era of Twice-Yearly Lenacapavir for PrEP — Essential or Irrelevant?

Lauren P. Jatt, M.D.,¹ Nyaradzo M. Mgodzi, M.B., Ch.B., M.Med.,² Susan P. Buchbinder, M.D.,³ Glenda E. Gray, M.B., Ch.B.,⁴
and James G. Kublin, M.D., M.P.H.⁵

‘We...believe that the development of an HIV vaccine is still an essential component of the global, multipronged strategy that is needed for ending the HIV epidemic.’

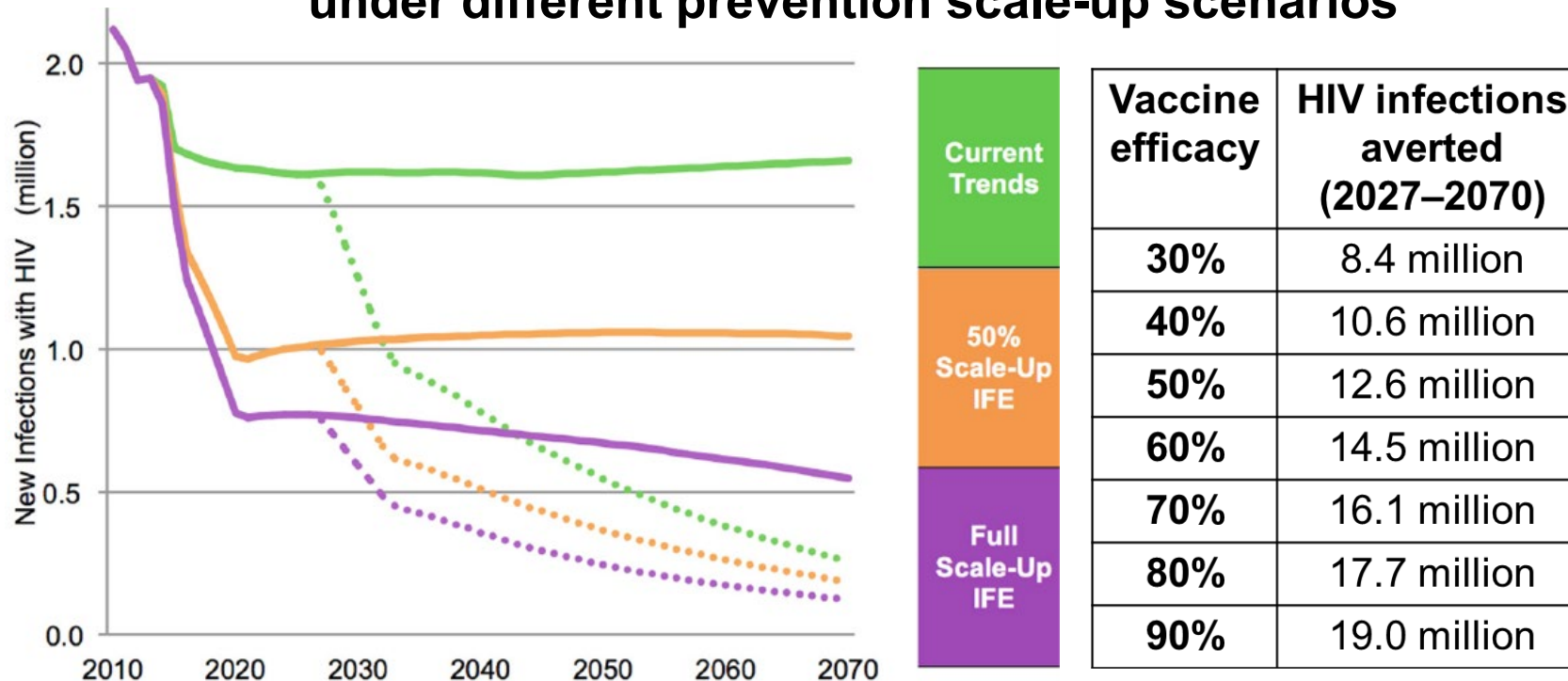
Reasons for a combination prevention approach with an HIV vaccine:

- PrEP non-adherence
- Need for 6-monthly injections
- Self-identification as low-risk
- Need to access health care consistently
- PrEP usually focused on specific populations
- Need for prevention choices
- Drug-drug interactions
- Possible future drug resistance
- Cost and access

Potential impact of an HIV vaccine

1.3 million people became newly infected with HIV in 2024

Reduction of new HIV infections with & without a vaccine under different prevention scale-up scenarios



- **Assumptions:** Vaccine introduction in 2027, 50% coverage, 70% efficacy
- **IFE** = UNAIDS' Investment Framework Enhanced includes scale-up of PrEP, TasP, and other prevention methods

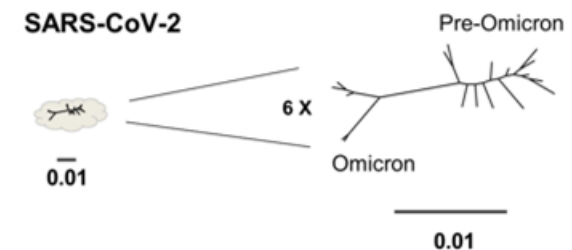
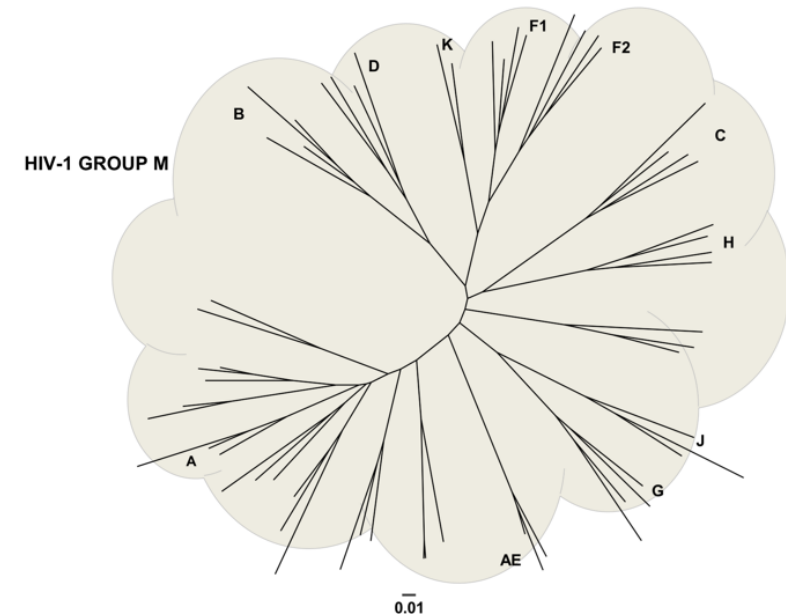
HIV Vaccine and Antibody Efficacy Trials to Date

Over 20 years and 12 trials, only two positive signals have been observed.

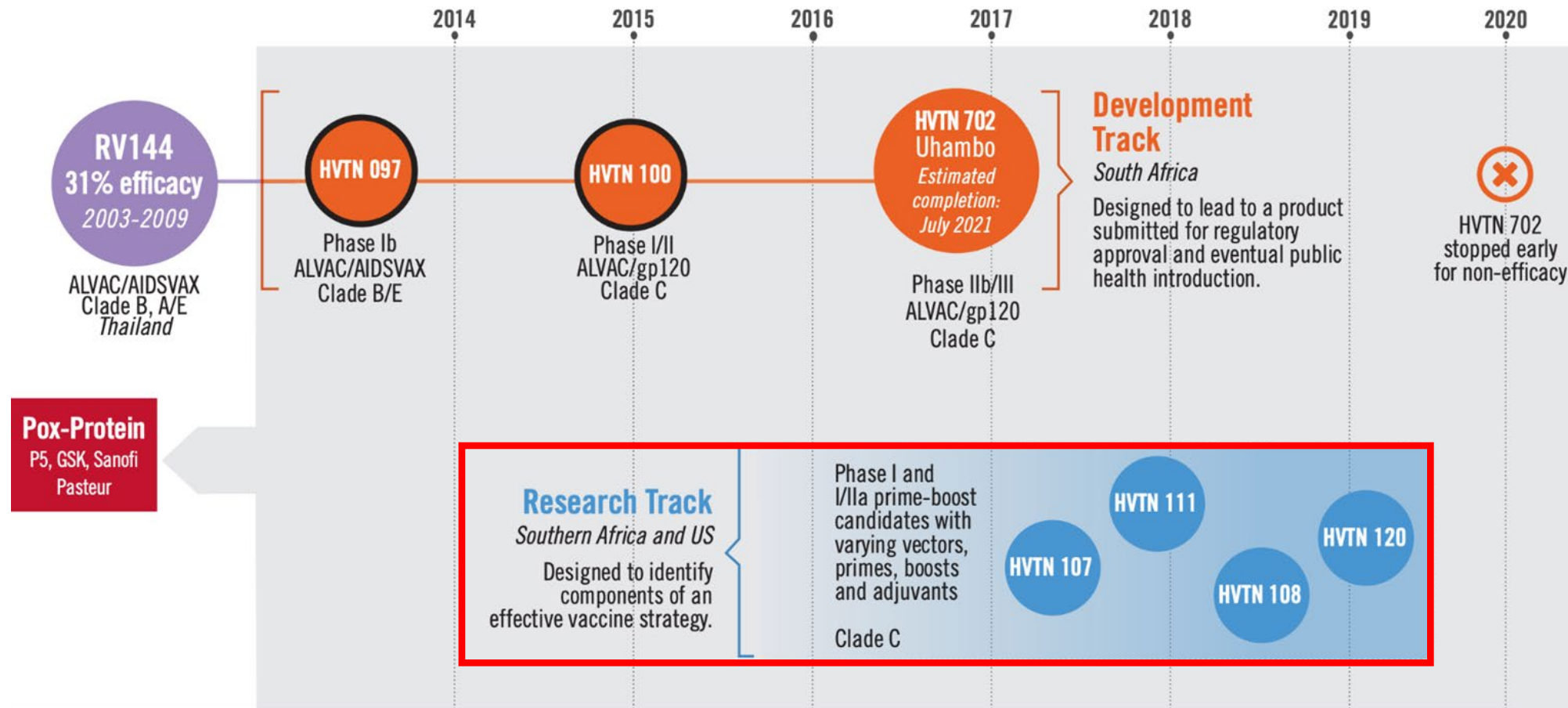
Year End	2003	2003	2007	2007	2009	2013	2020	2021	2021	2023	2024
Trial, Product/Clade	VAX004, AIDSVAX B/B	VAX003, AIDSVAX, B/E	STEP, MRK-Ad5, B	Phambili, MRK-Ad5, B	Thai Prime-Boost/RV 144, ALVAC-AIDSVAX, B/E	HVTN 505, DNA+Ad5, A/B/C	Uhambo/HVTN 702, ALVAC/gp120 MF59 boost	Imbokodo/HVTN705, Ad26 Mosaic/gp140 clade C boost	AMP Studies, VRC01 monoclonal antibody	Mosaico/HVTN706, Ad26 Mosaic/gp140 mosaic boost	PrEPVacc, DNA-HIV-PT123 (clade C) with AIDSVAX, B/E or with MVA A/E, CN54gp140
Location	Canada, Netherlands, Puerto Rico, US	Thailand	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	South Africa	Thailand	US	South Africa	Malawi, Mozambique, South Africa, Zambia, Zimbabwe	Botswana, Brazil, Kenya, Malawi, Mozambique, Peru, South Africa, Switzerland, Tanzania, US, Zimbabwe	Argentina, Brazil, Italy, Mexico, Peru, Poland, Puerto Rico, Spain, United States	South Africa, Tanzania, Uganda
Number of Trial Participants	5,417	2,546	3,000	801	16,402	2,500	5,400	2,600	1,924 2,699	3,900	1,512
Result		No effect	Stopped early for futility; potential increased HIV risk among Ad5-seropositive, uncircumcised men	Immunizations halted based on STEP result	Modest effect (31.2%)	Stopped early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load	Stopped early for futility	No efficacy	Did not reduce risk overall, but VRC01 did reduce risk of acquisition in small subset of HIV strains classified as "highly sensitive" to VRC01	No efficacy	Stopped early for futility

Challenges to HIV Vaccine development

- Most HIV vaccine trial concepts were assessed in NHP models and **passed strict Go/no-Go criteria** in Phase 1/2a studies.
- Concepts elicited strong binding antibody and T cell responses, but **none so far have induced broadly neutralizing antibodies (bnAbs)**.
- **No good models of natural HIV cure** hinders discovery of **correlates of protection**.
- **HIV attacks CD4+ T-cells** thereby weakening the immune system in clearing the infection
- HIV-1 continuously mutates and recombines resulting in incredible **diversity of the HIV-1 envelope** compared to, e.g. SARS-CoV-2



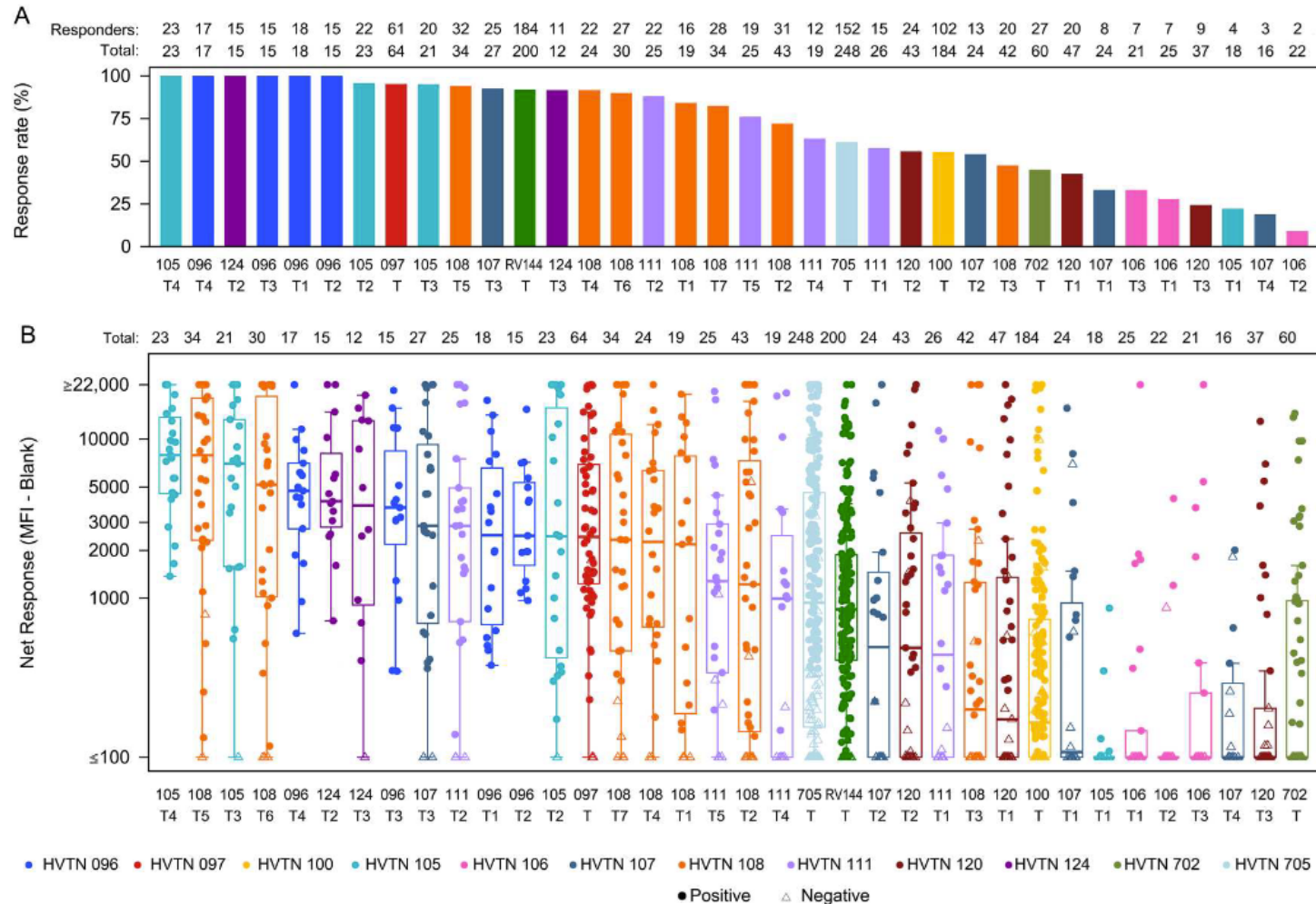
Pox-Protein Public Private Partnership (P5) Studies



Designed to investigate different:

- prime-boost regimens (DNA or ALVAC prime +/- protein co-administration)
- protein doses
- adjuvants (MF59, AS01_B and alum) or no adjuvant
- delivery methods (needle & syringe versus Biojector®)

Cross-Protocol Analyses of HVTN trial data



Polyvalent DNA prime with matched polyvalent protein/GLA-SE boost regimen (HVTN 124) elicited best combination of neutralizing antibody, non-neutralizing antibody, and cellular responses.

➤ **Potential Phase 2a trial planned in South Africa**

Potential Correlates of Protection

Caveat: Correlate studies in trials with low or no effectiveness

RV144/Thai Trial (ALVAC+AIDSVAX B/E):

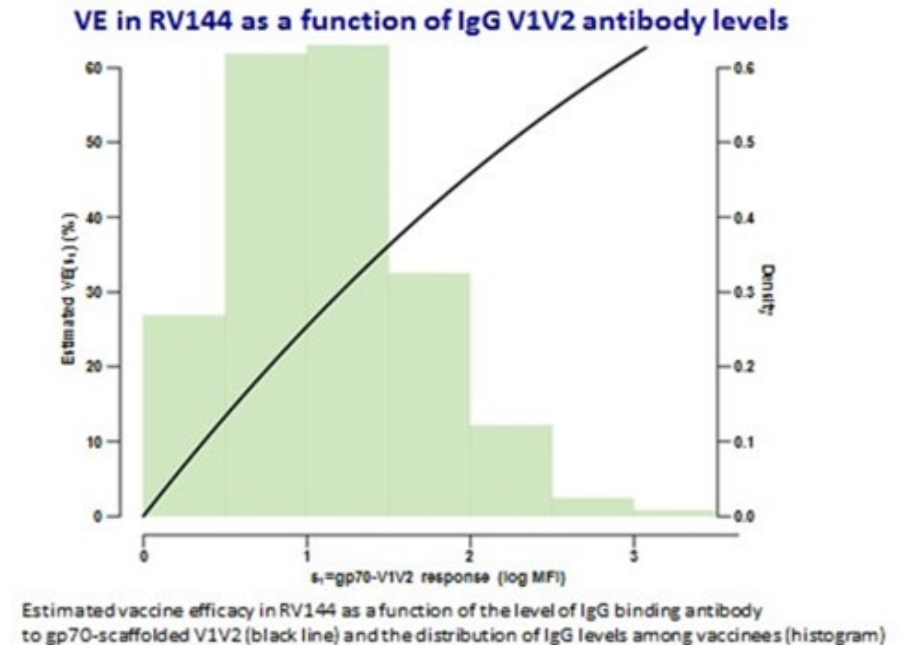
- IgG Ab responses against V1V2 tags.AE(A244)-V1V2.LL

HVTN 505 (DNA/Ad5):

- Combinations of high CD8+ T cell polyfunctionality and antibody responses

HVTN 702/Uhambo (ALVAC + bivalent subtype C gp120/MF59 boost):

- Role of V1V2 loop & CD4 T cell polyfunctionality



AMP trials: bnAbs may prevent infection with sensitive virus



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. Mgodhi, 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*

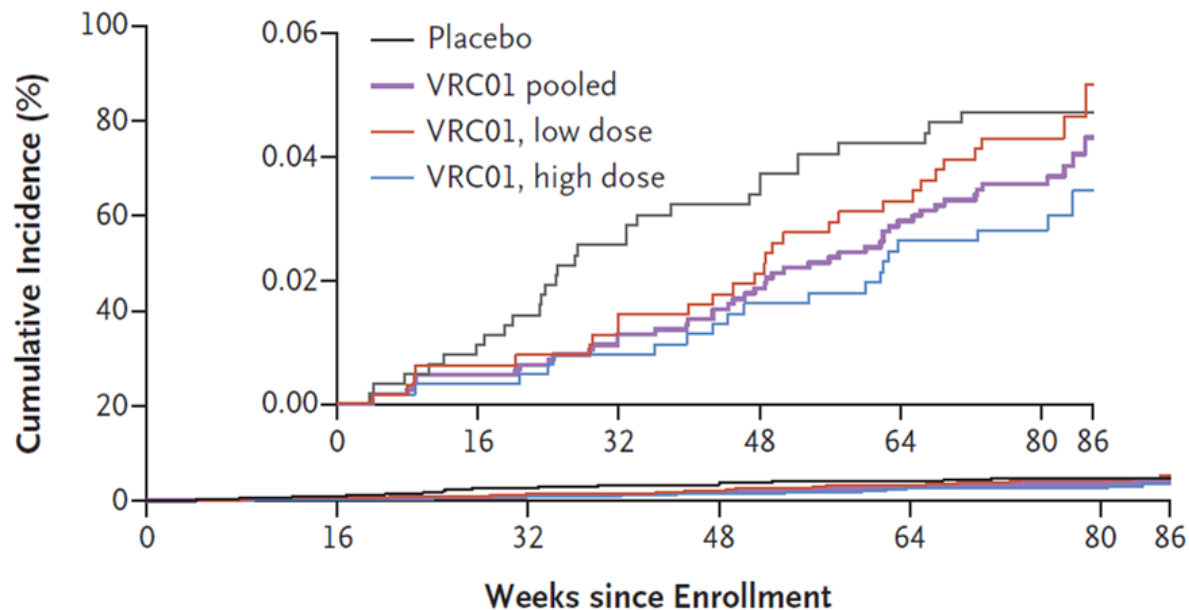


Figure. Overall Cumulative Incidence of HIV-1 Acquisition and Prevention Efficacy in HVTN 703/HPTN 081

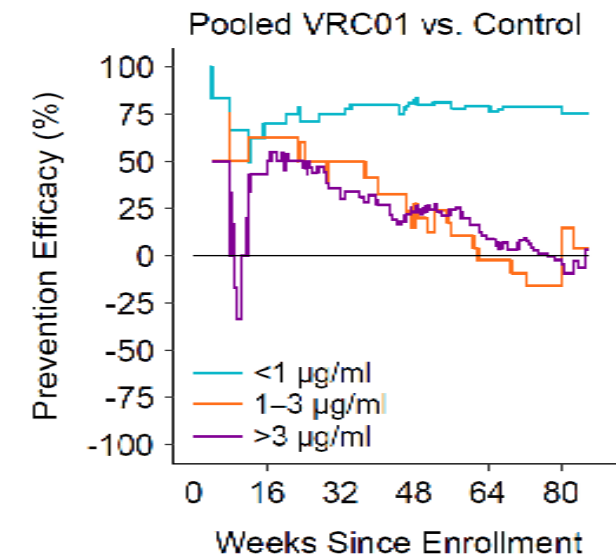


Figure. Prevention efficacy of VRC01, combined over both trials in both the 10 mg/kg and 30 mg/kg dose groups.



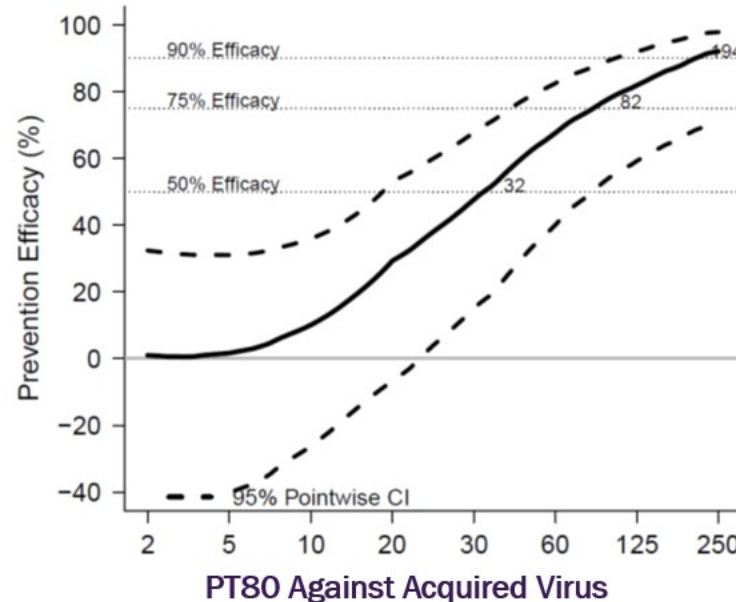
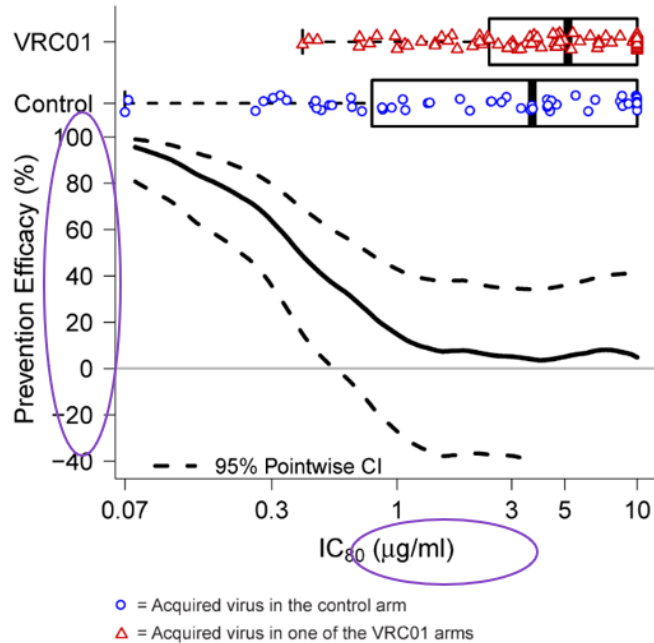
HIV VACCINE
TRIALS NETWORK

Prevention Efficacy Smoothly Increases with Predicted ID80 Titer (PT80) in AMP

nature
medicine

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

Gilbert, Huang, et al. *Nat Med.* 2022 Sep;28(9):1924-1932



- Predicted serum neutralization 80% inhibitory dilution titer (**PT80**) acts as **biomarker**
- Quantifies **Ab neutralization potency** in individual's serum against HIV isolate & can predict HIV **prevention efficacy**
- Modeling predicts available **triple HIV bnAbs cocktail**, administered every 4 – 6 months can reach **90% PE**

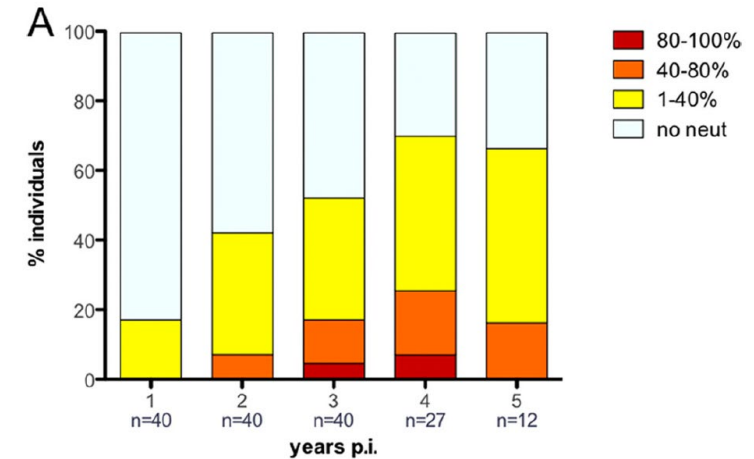
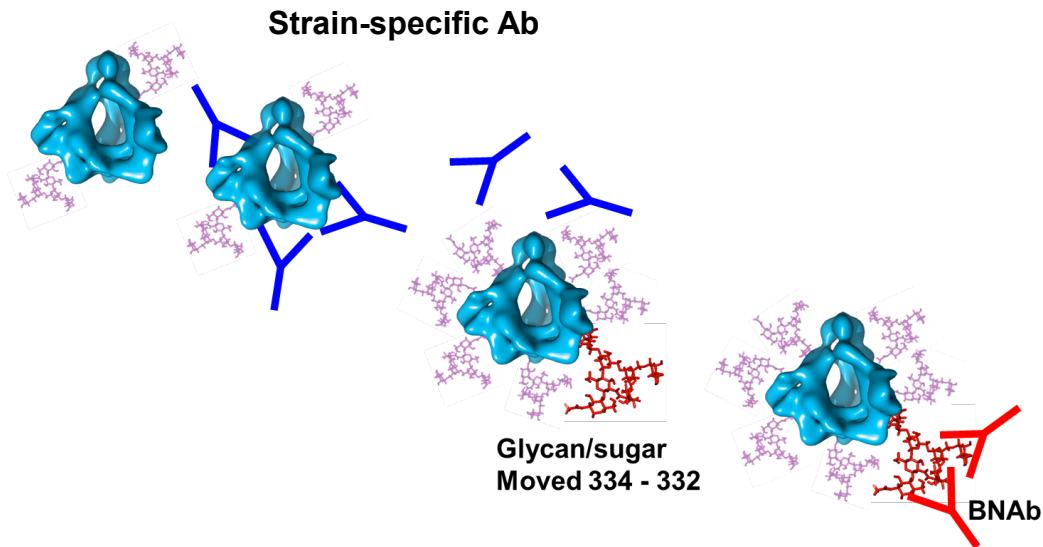
Serum PT80 = serum bnAb concentration / IC80

Evolution of BnAbs in people with HIV



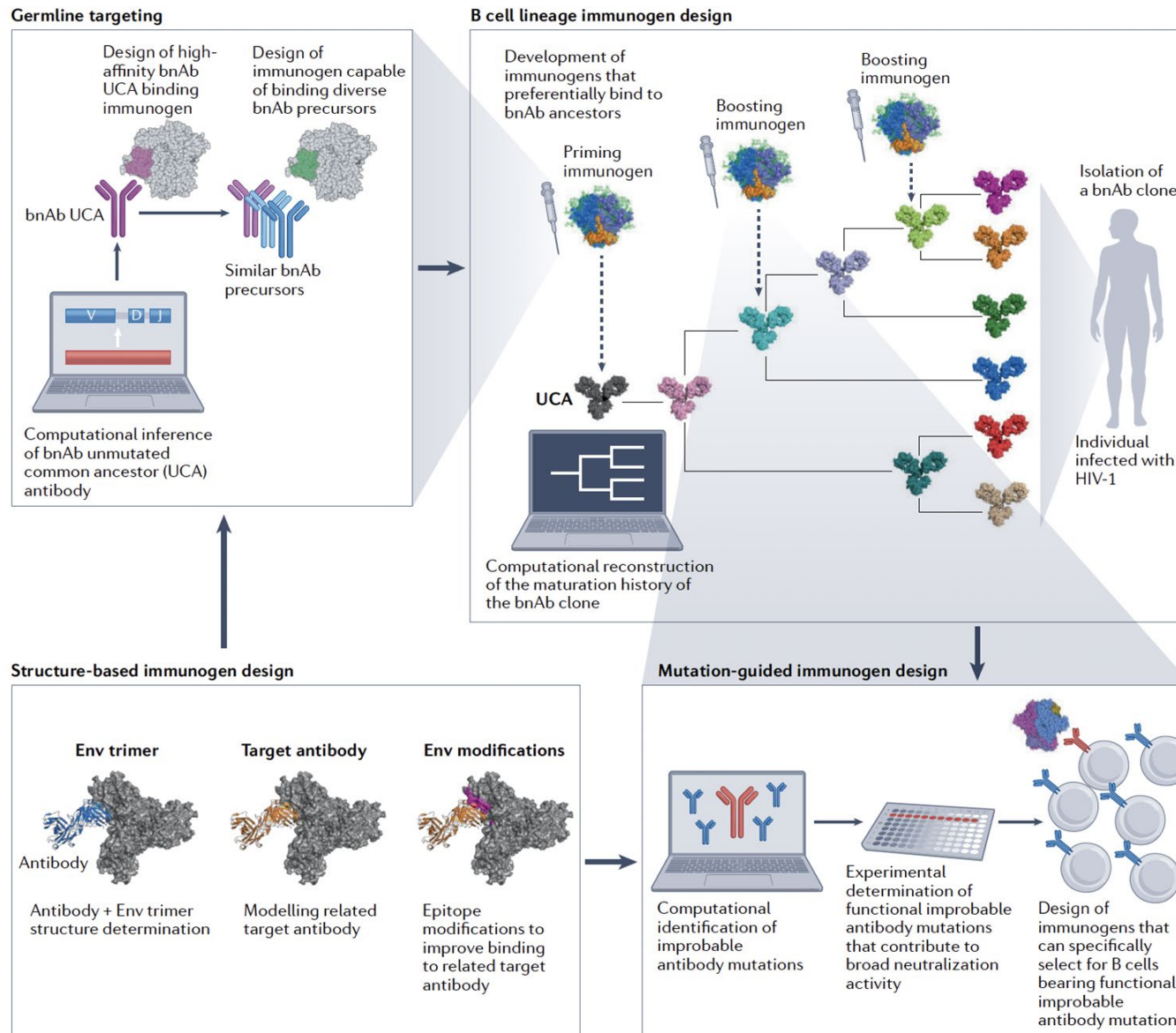
Evolution of an HIV glycan-dependent broadly neutralizing antibody epitope through immune escape

Penny L Moore^{1,2}, Elin S Gray¹, C Kurt Wibmer^{1,2}, Jinal N Bhiman^{1,2}, Molati Nonyane¹, Daniel J Sheward³, Tandile Hermanus¹, Shringkhala Bajimaya⁴, Nancy L Tumba¹, Melissa-Rose Abrahams³, Bronwen E Lambson¹, Nthabeleng Ranchobe¹, Lihua Ping⁵, Nobubelo Ngandu³, Quarraisha Abdool Karim⁶, Salim S Abdool Karim⁶, Ronald I Swanstrom⁵, Michael S Seaman⁴, Carolyn Williamson³ & Lynn Morris^{1,2}



- In CAPRISA 002 study only about 20% of PLWH developed bnAbs
- Unfortunately, people with these antibodies don't do better clinically
- But if the antibodies were there **before** the virus, through vaccination, would that be different?

'Rational' vaccine design strategies

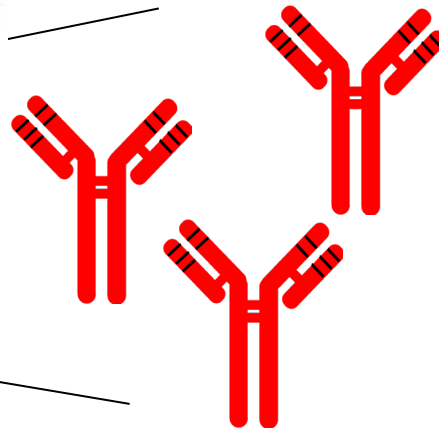
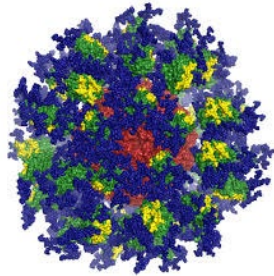
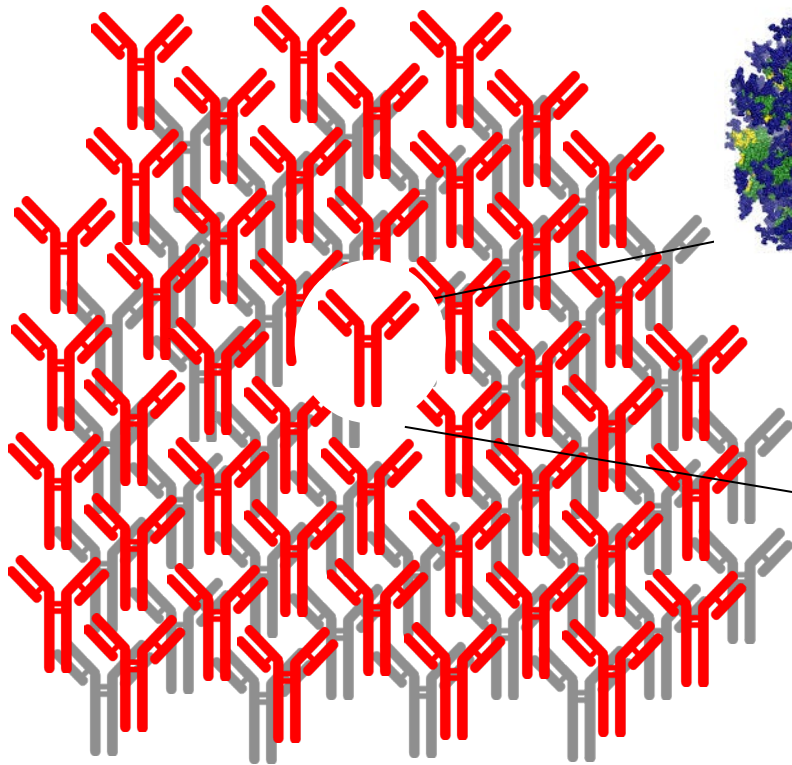


- **Sophisticated sequencing, structural biology and bioinformatics**
- **We now have the technology to rapidly assess these vaccine approaches!**

Triggering the precursors – finally a reality?

Rare **precursors** of broadly neutralizing antibodies (bNAbs)

eOD-GT8 Vaccine



Activated precursors with some mutations typical of bNAbs

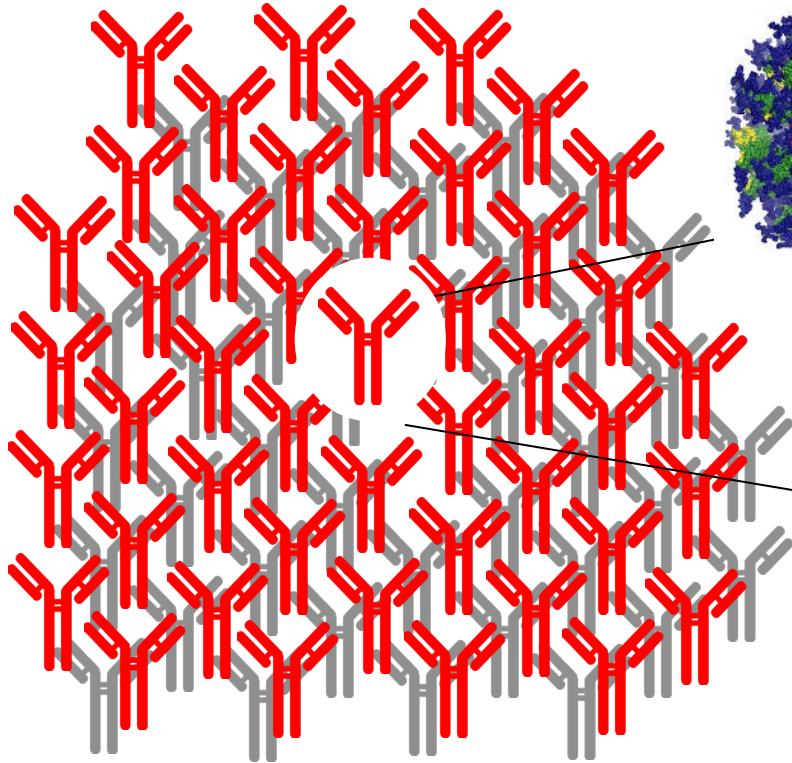
Leggat, Science, 2023

Achieved



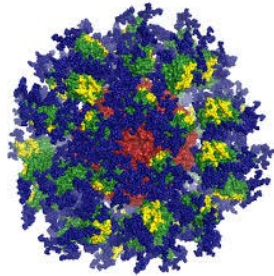
Triggering the precursors – finally a reality?

Rare **precursors** of broadly neutralizing antibodies (bNAbs)



Leggat, Science, 2023

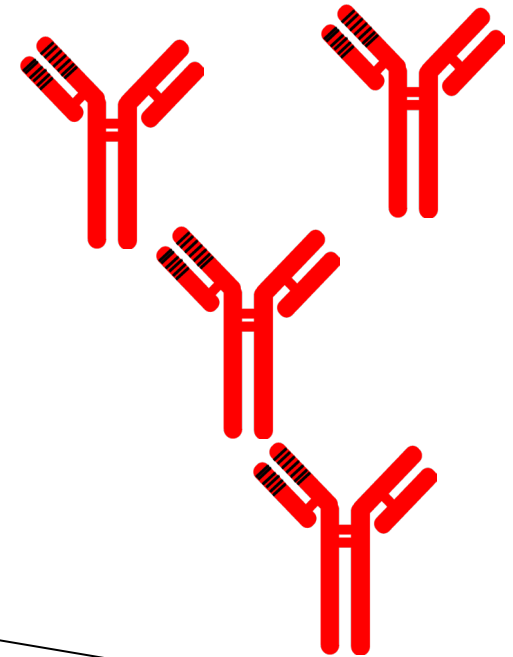
eOD-GT8 Vaccine



?
Vaccine(s)



Broadly neutralizing antibodies to HIV



Activated precursors with some mutations typical of bNAbs

Achieved

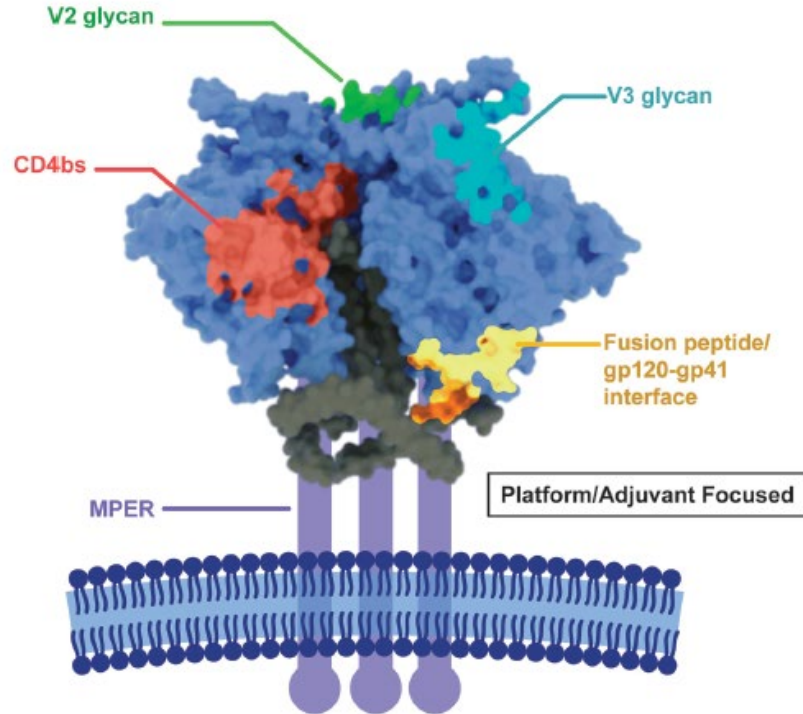
Not yet achieved



HVTN pipeline of trials to induce BnAbs

Will this research now be conducted in the US only?

DISCOVERY MEDICINE TRIAL PIPELINE



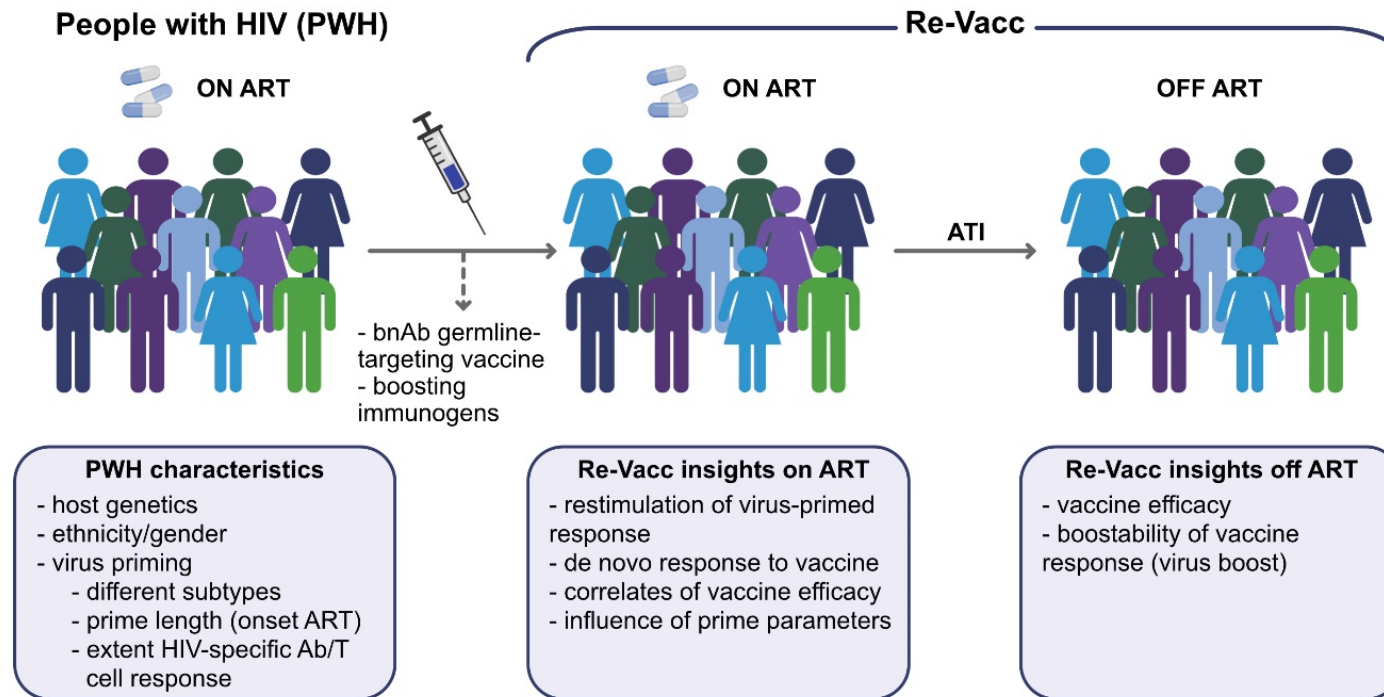
Adapted from Haynes et al. Nat Rev Immunol 2023

Expanding germline triggering to other Ab classes beyond CD4 binding site

22 Trials Launched/Anticipated in 2023-2024 (N = 1,064)

Envelope epitope	Key studies	Innovations	Preclinical data supporting approach
CD4bs	HVTN 301, 309	Escalating dose (ED) prime, mRNA prime-boost, ATI boost	Germline induction in mouse KI models & NHP, Heterologous neutralization
V2 Apex	HVTN 310	CD4bs-V2 chimera mRNA VLP	NHP SHIV challenge protection
V3 Glycan	HVTN 144	ED prime, SC vs. IM	Germline induction in KI mouse models
Fusion Peptide	HVTN 303	FP conjugate	NHP SHIV challenge protection
MPER region	HVTN 133	Peptide liposome	
Platform/Adjuvant Focused	HVTN 137, 135, 300, 302	Multi-adjuvant, infant gp120, mRNA trimer with CD4bs KO	Mouse KI models

Moving beyond germline targeting: Testing 'polishing' immunogens rapidly in PWH



Has the potential to accelerate vaccine design and if cleverly done, can provide essential biological insights

Trkola and Moore,
Lancet ID, 2024

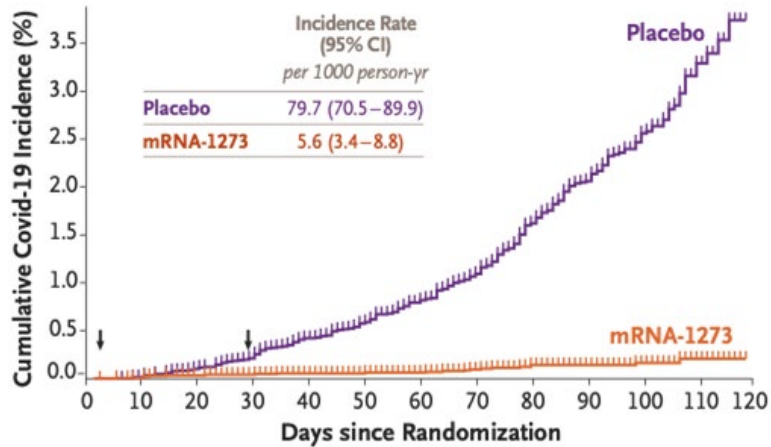
Is the mRNA platform the end of our HIV vaccine design woes?

THE NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Efficacy and Safety of mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

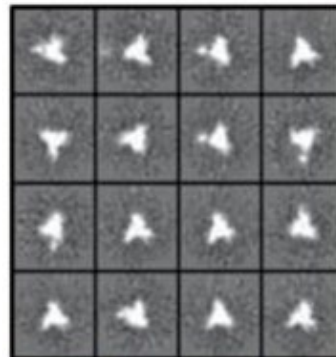
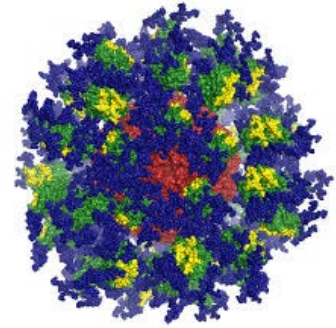


	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

mRNA platforms being used to express eOD-GT8 (G002 and G003) and trimers

Should enable rapid iteration... but...

Does not solve the intrinsic biological challenges that make HIV so difficult



losed/open/non-native: 57/43/0%

Cellular immune responses reduce the threshold of nAbs for protection

ARTICLES

<https://doi.org/10.1038/s41591-020-0858-8>

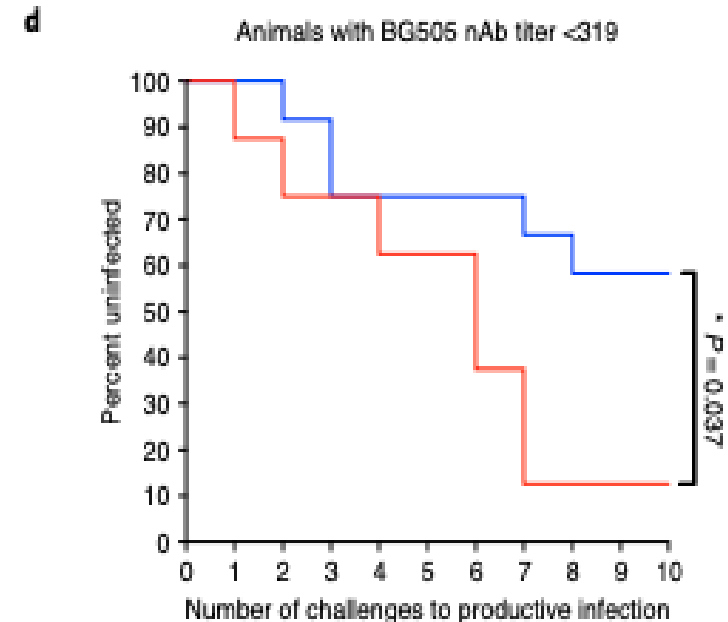
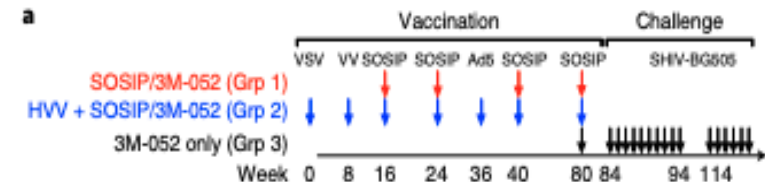
nature
medicine

Check for updates

OPEN

T cell-inducing vaccine durably prevents mucosal SHIV infection even with lower neutralizing antibody titers

Prabhu S. Arunachalam^{1,19}, Tysheena P. Charles^{2,19}, Vineet Joag^{3,19}, Venkata S. Bollimpelli^{4,19}, Madeleine K. D. Scott^{1,5}, Florian Wimmers¹, Samantha L. Burton², Celia C. Labranche⁶, Caroline Petitdemange^{4,17}, Sailaja Gangadhara⁴, Tiffany M. Styles⁴, Clare F. Quarnstrom³, Korey A. Walter⁷, Thomas J. Ketas⁸, Traci Legere⁴, Pradeep Babu Jagadeesh Reddy^{4,18}, Sudhir Pai Kasturi^{2,4}, Anthony Tsai⁹, Bertrand Z. Yeung⁹, Shakti Gupta¹⁰, Mark Tomai¹¹, John Vasilakos¹², George M. Shaw¹³, Chil-Yong Kang¹⁴, John P. Moore⁸, Shankar Subramaniam¹⁰, Purvesh Khatri^{1,5}, David Montefiori⁶, Pamela A. Kozlowski⁷, Cynthia A. Derdeyn², Eric Hunter², David Masopust³, Rama R. Amara⁴ and Bali Pulendran^{1,15,16}



Several other T-cell vaccine concepts currently in early phase trials.

Some Light at the End of the Tunnel

Brilliant-001

- Immunogen combination approach

Brilliant-002 (concept in development)

- mRNA expressed GT1.1 (GR2) mRNA immunogen

HVTN 317/DESIIGN001

- mRNAs encoding immunogens eOD-GT8 60mer, core-g28v2 60mer and N332-GT5 gp151

Table 1.1 BRILLIANT-001 Study Schema

No.	Prime 1 (Day 0)	Prime 2 (Week 8)	Boost 1 (Week 24)	Boost 2 (Week 40)
16/4 Active/Placebo	BG505 GT1.1 + 426c.Mod.Core-C4b + 3M-052-AF/ Alum	BG505 GT1.1 + 426c.Mod.Core-C4b + 3M-052-AF/ Alum	BG505 GT1.1 + 426c.Mod.Core-C4b + 3M-052-AF/ Alum	BG505 GT1.1 + 426c.Mod.Core-C4b + 3M-052-AF/ Alum

Table 1-1 Schema

Cohort	Group	N	Dose	Week 0	Week 8
Part A: 10 mcg dose level					
1A	1	16	10 mcg	mRNA-1645-eODGT8	mRNA-1645-CoreG28v2
	2	8	—	Placebo	Placebo
2A	3	16	10 mcg	mRNA-1645-N332GT5	mRNA-1645-N332GT5
	4	8	—	Placebo	Placebo
Part B: 30 mcg dose level					
1B	5	16	30 mcg	mRNA-1645-eODGT8	mRNA-1645-CoreG28v2
	6	8	—	Placebo	Placebo
2B	7	16	30 mcg	mRNA-1645-N332GT5	mRNA-1645-N332GT5
	8	8	—	Placebo	Placebo
Total ¹ : 96 (64 vaccinees, 32 placebo recipients)					

Conclusions

- Despite biological and technical challenges of making an HIV vaccine, we need to continue with our quest to develop it!
- Several unsuccessful trials, but all contributed to a journey of discovery and an advancement in vaccinology, immunology and science in general.
- Eliciting BnAbs, probably our best correlate of protection, is currently the main pathway to a vaccine.
- Technology, clinical trial infrastructure, scientists in place, but funding required to achieve this ultimate tool to eliminate HIV.

Acknowledgements

- **Penny Moore**, Wits University, NICD
- **Glenda Gray**, SAMRC
- **Betty Mwesigwa**, MUWRP
- **Nyaradzo Mgodzi**, UZ-CTRC
- **Linda-Gail Bekker**, DTHF
- **All collaborators, clinical teams and participants**

