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Celebrating 30 Years of HIV Research

Building on Excellence & Shaping the Future

The Future of HIV Prevention Clinical Trials Summit

HIV vaccine and bnAb R&D : Still relevant in the time of expanding prevention landscape

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Bixby Center for Global Reproductive Health

UCSF University of California San Francisco

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Key points

- Significant strides have been made in HIV prevention and treatment.
- PrEP began in 2012 with the approval of oral TDF/FTC taken once a day.
- Since then, PrEP options have expanded rapidly to suit different people.
- In the era of highly efficacious PrEP, passive and active immunisation strategies still have a role to play and could offer an additional HIV prevention choice.
- AMP trials provided proof-of-concept that bnAbs can prevent HIV infection.
- Two decades of HIV vaccine research – many challenges faced.
- Is there need to continue the pursuit of HIV vaccine/bnAb science?

HIV prevention options

	Barrier	Chemoprophylaxis (ARV-based)				Immunoprophylaxis	
	Condoms	**Oral ARV – Truvada, Descovy, Cimduo**	**Vaginal ARV ring – Dapivirine**	**Long acting injectable ARV – Cabotegravir**	**Long acting injectable ARV – Lenacapavir**	**Passive immunization – Long acting injectable HIV bnAbs**	**HIV Vaccine**
Class		Small molecule	Small molecule	Small molecule	Small molecule	Biologic	Biologic
Frequency of administration	On demand	Every day or as needed	Every month	Every 2 months	Every 6 months	Every 6 months	TBD shots, then protect for TBD years
Ease of administration	On demand	Oral	Vaginal	Intramuscular injection (IM)	Injection under the skin (SC)	Infusion in a vein (IV)*	Intramuscular injection (IM, most likely)
Important side effects		Reduced kidney function (Truvada)		IM injection can be painful	Nodules (drug depot) under skin	Very few	TBD
Compliance	Must be consistent	Many users stop using	TBD	TBD	TBD	TBD	TBD
Approved	Yes	Yes	Yes	Yes	No	No	No
Accessibility	Yes	Limited	Limited	Limited	Not yet	Not yet	Not yet

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We have all these chemo-prophylactic options for prevention.
What more do we want, and why?

Oral PrEP, dapivirine vaginal ring, cabotegravir and lenacapavir will not address the needs of all people who need HIV prevention.

People want options so they can make choices.

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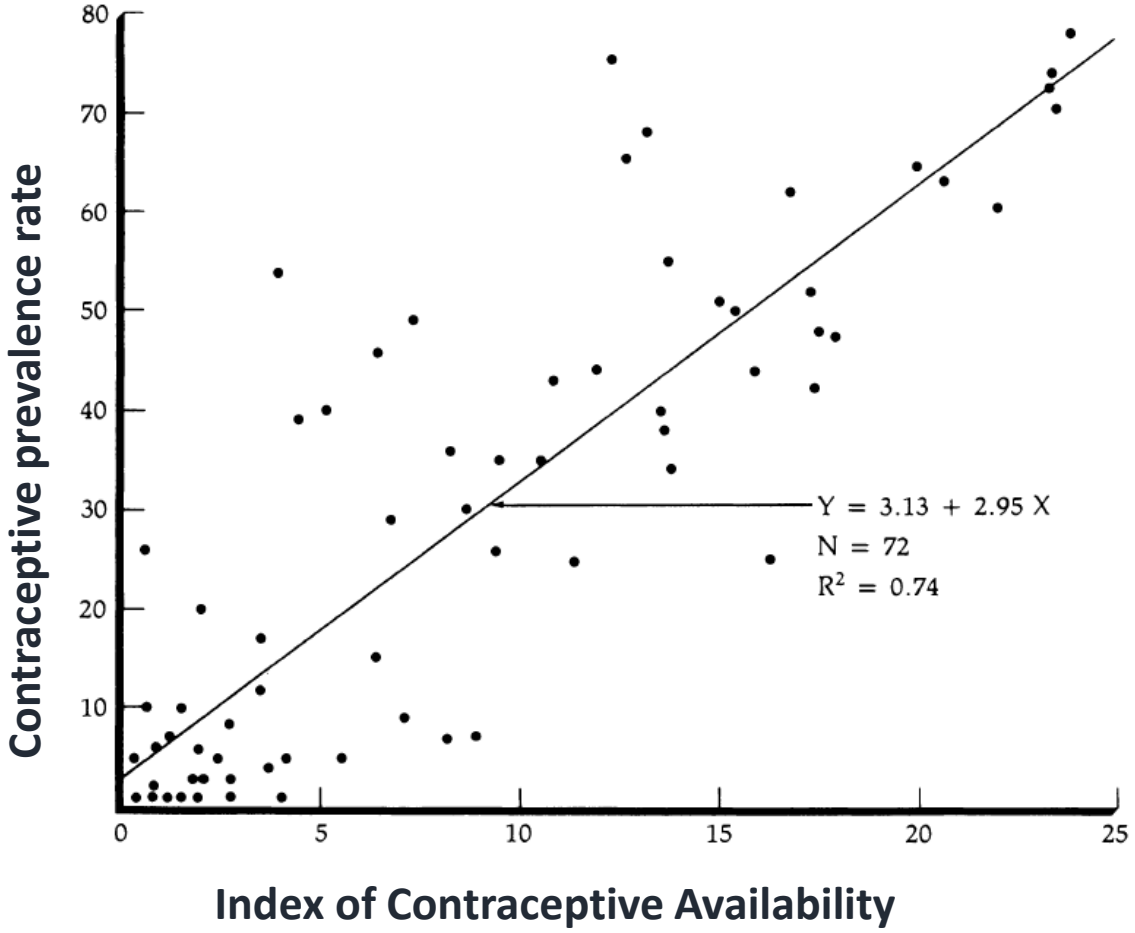
Choice matters in sexual reproductive health

- WHO systematic review (231 articles) showed increased choice associated with:
  - **Increased persistence** on chosen method
  - **Better health outcomes**
  - **12% increase in contraceptive prevalence for each additional method**
- Similar to contraceptive needs: different people have different HIV prevention needs at different times

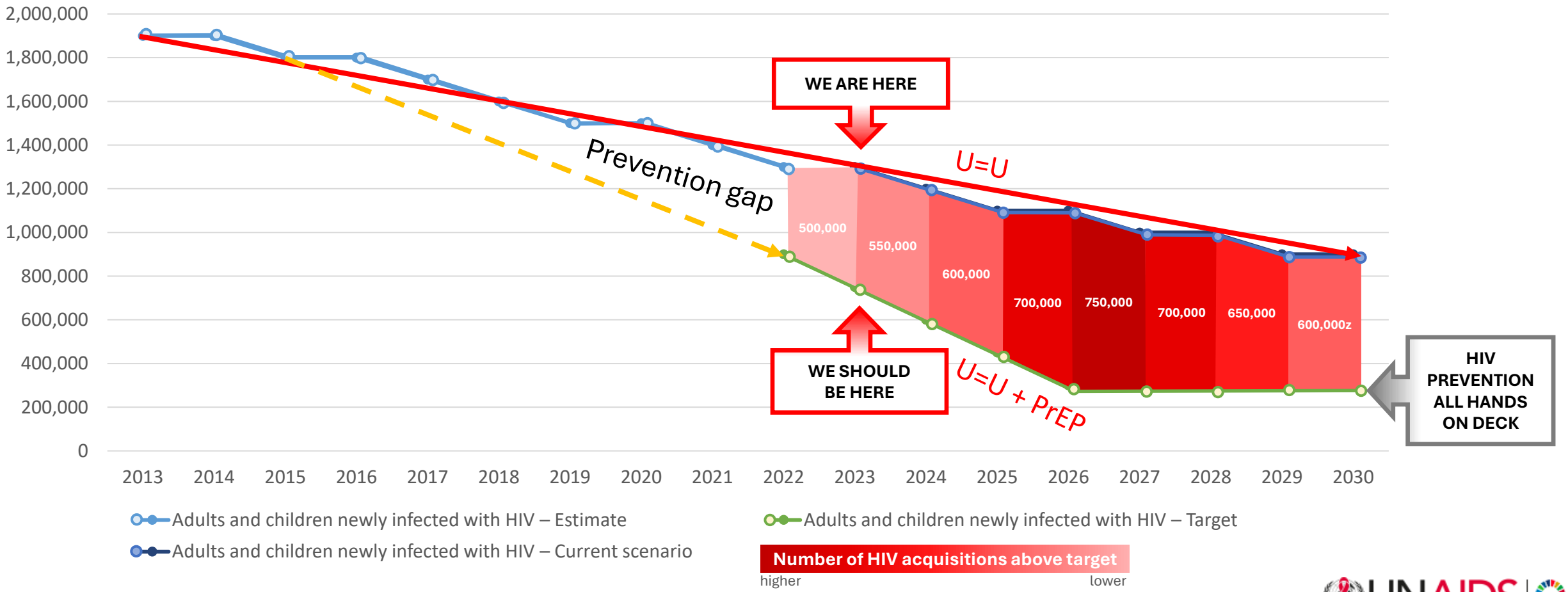


WHO Systematic review of contraceptive medicines "Does choice make a difference?" October 2006

Gray et al RHRU 2006; Jain AK Stud Fam Planning 1989

AVAC
Global Advocacy for HIV Prevention

HIV prevention not on track for 2030 UNAIDS targets



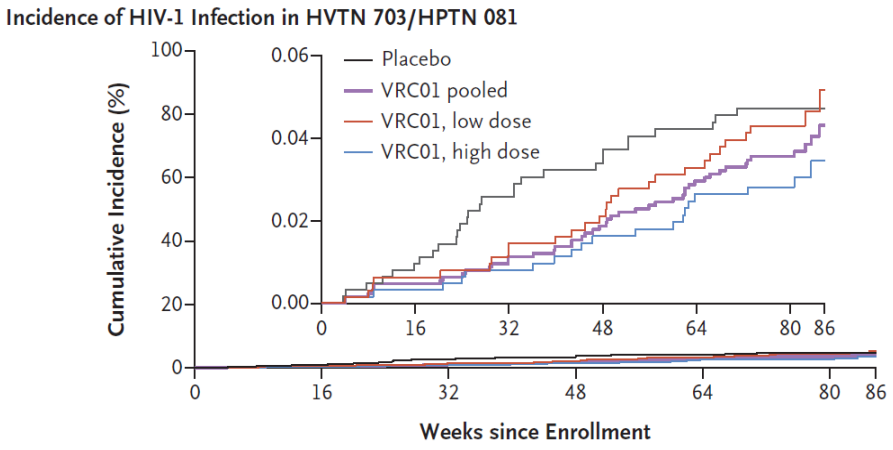
https://www.unaids.org/en/resources/fact-sheet

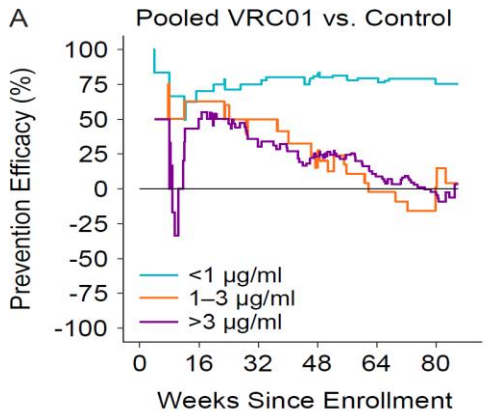
AMP trials provide proof-of-concept that bnAbs can prevent HIV infection

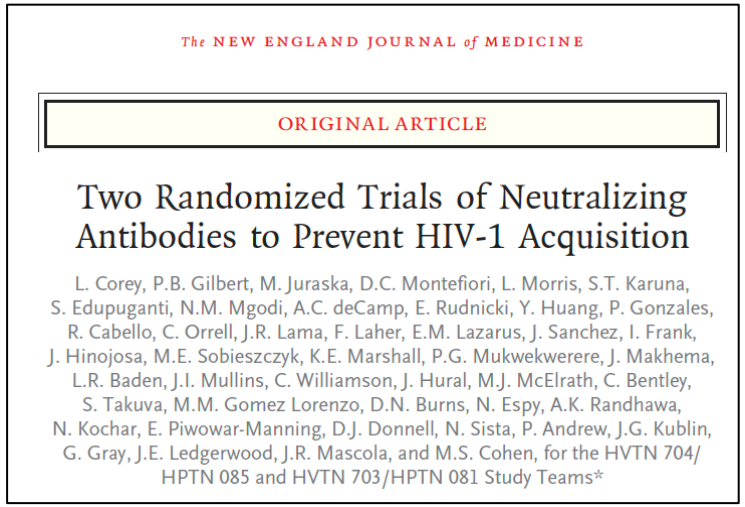
	HVTN 704/HPTN 085	HVTN 703/HPTN 081		
REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	633	1533	10 infusions total - given every 8 weeks Study duration: ~22 months
VRC01 30 mg/kg	900	633	1533	
Control	900	634	1534	
Total	2700	1900	4600	

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%)
- Correlate of protection
- 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*

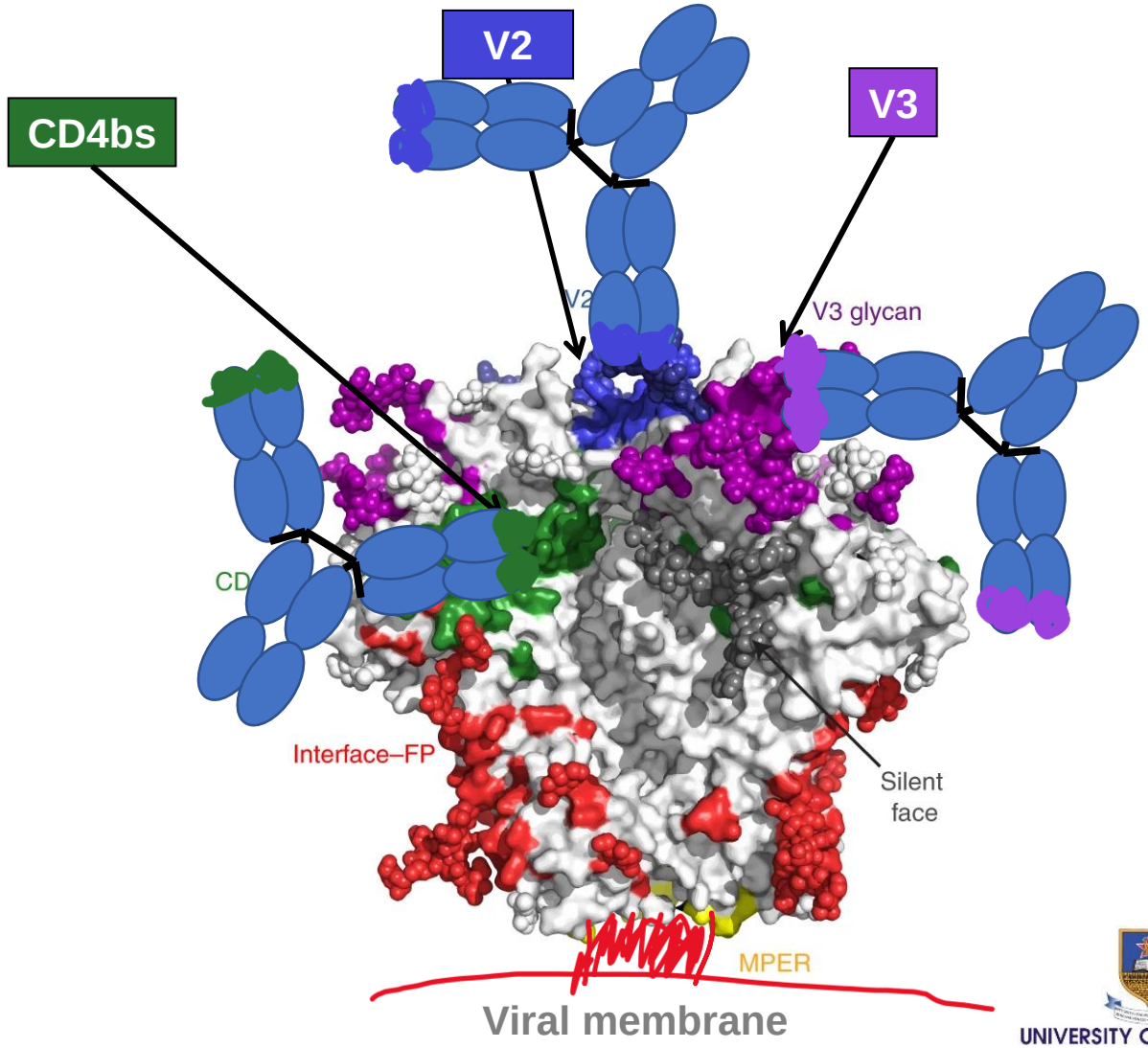
HPTN HIV Prevention Trials Network

HIV VACCINE TRIALS NETWORK

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

Next steps: Combo-AMP, combining three HIV bnAbs to increase prevention efficacy

- Each HIV bnAb targets a different part of the HIV envelope
- Potency & breadth greater than with single HIV bnAbs alone
- Double or triple coverage may limit early viral escape
- Reduced levels of incomplete neutralization
- CD4bs, V2, and V3 mix considered most promising



bnAbs have different coverage

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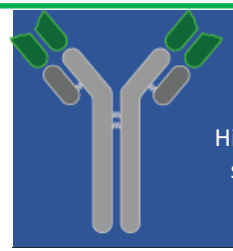
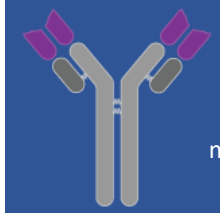
PGDM1400LS

Exceptionally broad and potent
~ 60% global coverage



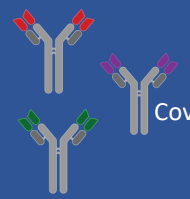
PGT121.414.LS

High potency against sensitive strains ~44% neutralization



VRC07-523LS

Works against 96% of the major circulating HIV-1 strains



Combo

Cover more possibilities for higher chance of neutralization

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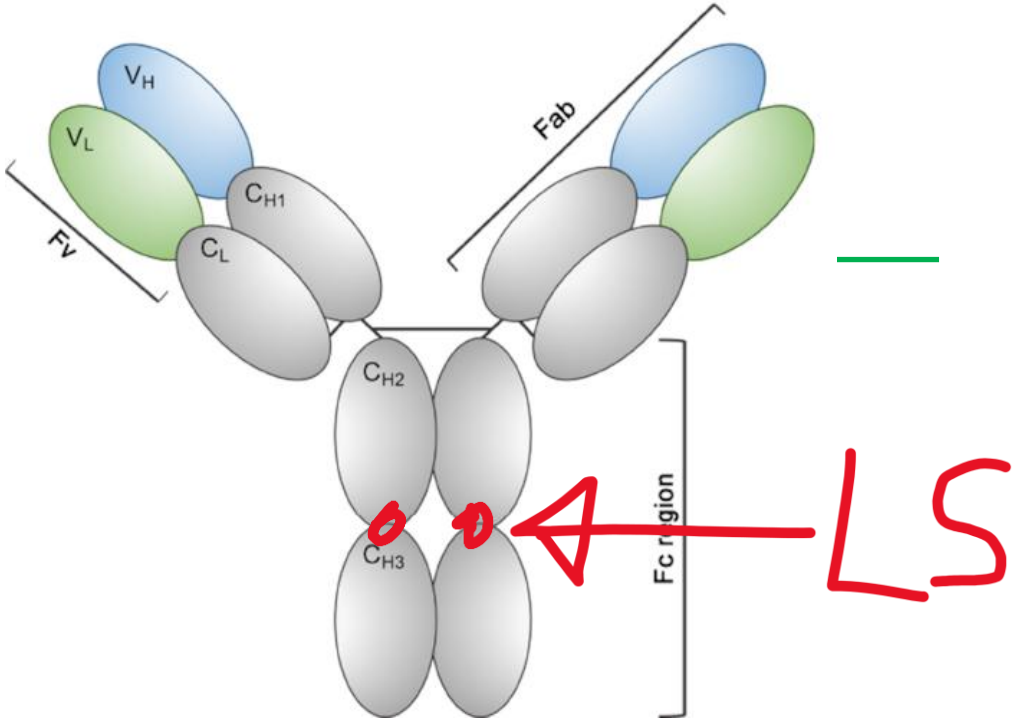
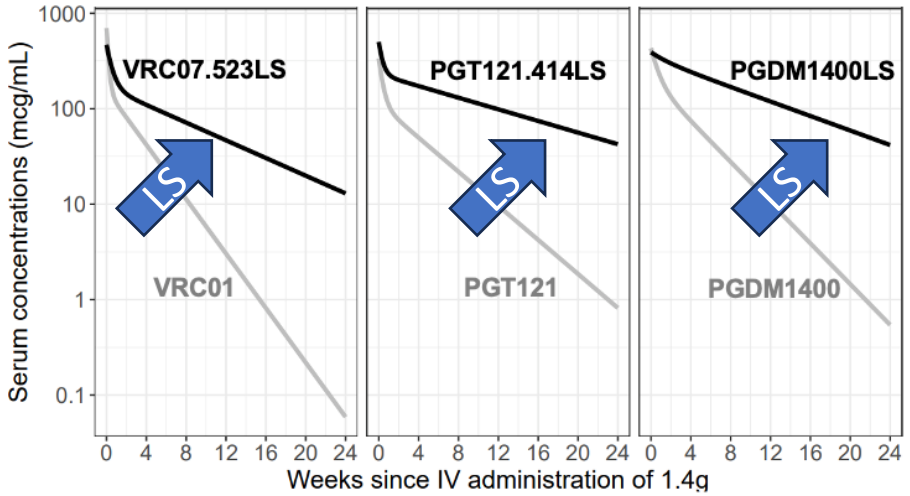
Next steps: LS mutation allows dosing every 6 month



- LS = 2 amino acid mutation in Fc part of antibodies
- Serum half-life extends ~3-fold from ~20 to ~70 days – allows dosing every 6 months
- Concentration in mucosa increases

The 'LS' effect on pharmacokinetics



HVTN 116 – Extended half-life of VRC01LS in rectum (IHC)

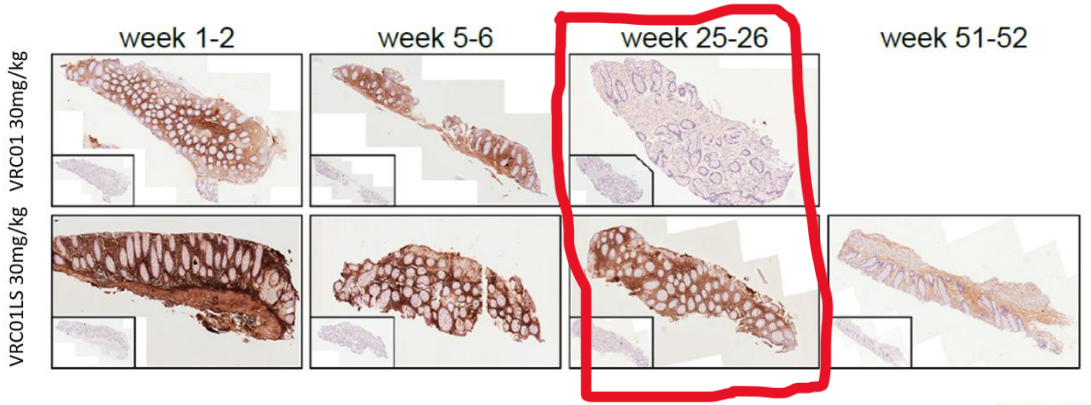


Image: M. Lemos, R. Astronomo, HVTN 116 Study Team.

Mayer et al 2024 Pharmaceutics

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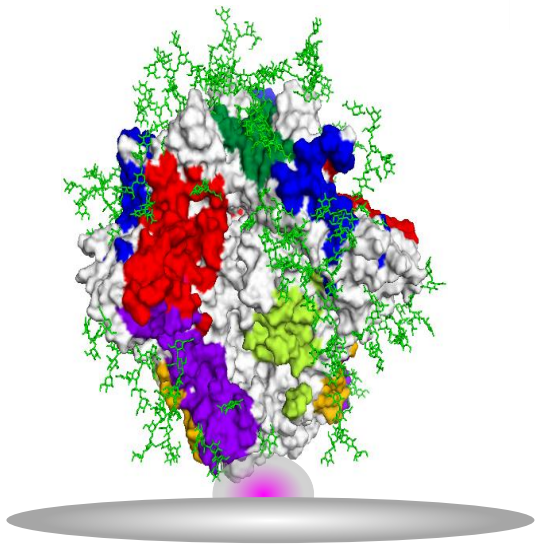
bnAbs have several advantages over ARV-based PrEP products

- bnAbs are derived from natural antibodies that can neutralize diverse HIV strains.



- Structural modifications improve breadth, potency, and half-life, enabling longer protection with fewer doses.

- bnAbs have:
  - No long pharmacokinetic tail (reducing risk of antiretroviral resistance)
  - High therapeutic index
  - Immunomodulatory potential
  - Favorable safety and pharmacokinetic (PK) profiles
  - Possibly fewer side effects than some antiretrovirals
  - Reliable PK in special populations (e.g., pregnant/breastfeeding individuals, infants, adolescents)

- bnAb-based PrEP offers a new prevention option and may also contribute to HIV cure strategies by targeting the viral reservoir.

- Supports and informs ongoing HIV vaccine development.

https://www.who.int/publications/i/item/9789240045729

The possibility of a preventive HIV vaccine

HIV vaccine development should prioritize factors such as the target population, efficacy, safety, durability, manufacturability, and affordability.

- The aim is to create a vaccine that serves people at risk of HIV, while being practical to produce and distribute.

- An ideal HIV vaccine would:
  - Offer long-lasting protection with few doses, timed before risk exposure.
  - Be widely accessible and allow for confidential administration.
  - Avoid reliance on behavior change or adherence.
  - Reach vulnerable populations not easily served by other methods.
  - Help achieve epidemic control.

- Even a vaccine that is 50% effective with 50% population coverage could prevent around **850,000 HIV-related deaths** over 30 years.

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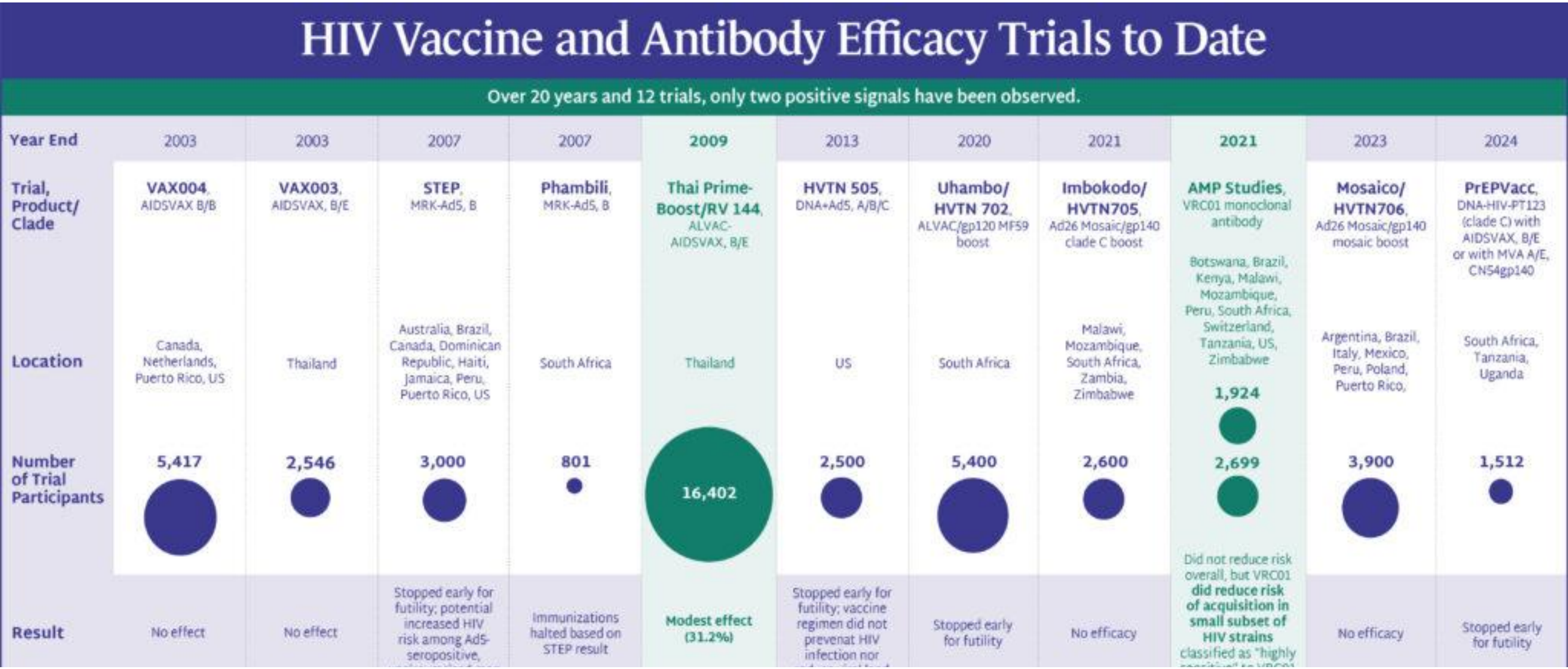
The HIV vaccine R&D pipeline



Infographic courtesy of AVAC

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Is the juice worth the squeeze?

Is the difficult HIV vaccine R&D still relevant in this era of efficacious and novel long/er antiretroviral based agents?

Let us use twice-yearly Lenacapavir as an example

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LEN has multiple advantages

- Twice-yearly lenacapavir shares important features with an ideal HIV vaccine:
  - it is safe and highly efficacious for preventing HIV.
- The efficacy observed in the PURPOSE trials is similar to, if not greater than, that of many conventionally available vaccines.
- LEN is also thermostable and can be shipped and stored at room temperature, an important advantage over most HIV vaccine candidates.
- But the most obvious advantage of lenacapavir for PrEP is that it is not hypothetical — it is available now!

But an ideal preventive HIV vaccine would offer several advantages over LEN

- Long-term immunity
- Cost-effective
- No drug resistance risk
- No drug-drug interactions
- Simplified implementation
- Broad immune response

When the peers of my age see a person taking PrEP, they will think that the person has AIDS or they are very unfaithful hanging out with many partners…I will be considered as a bad person in the community.

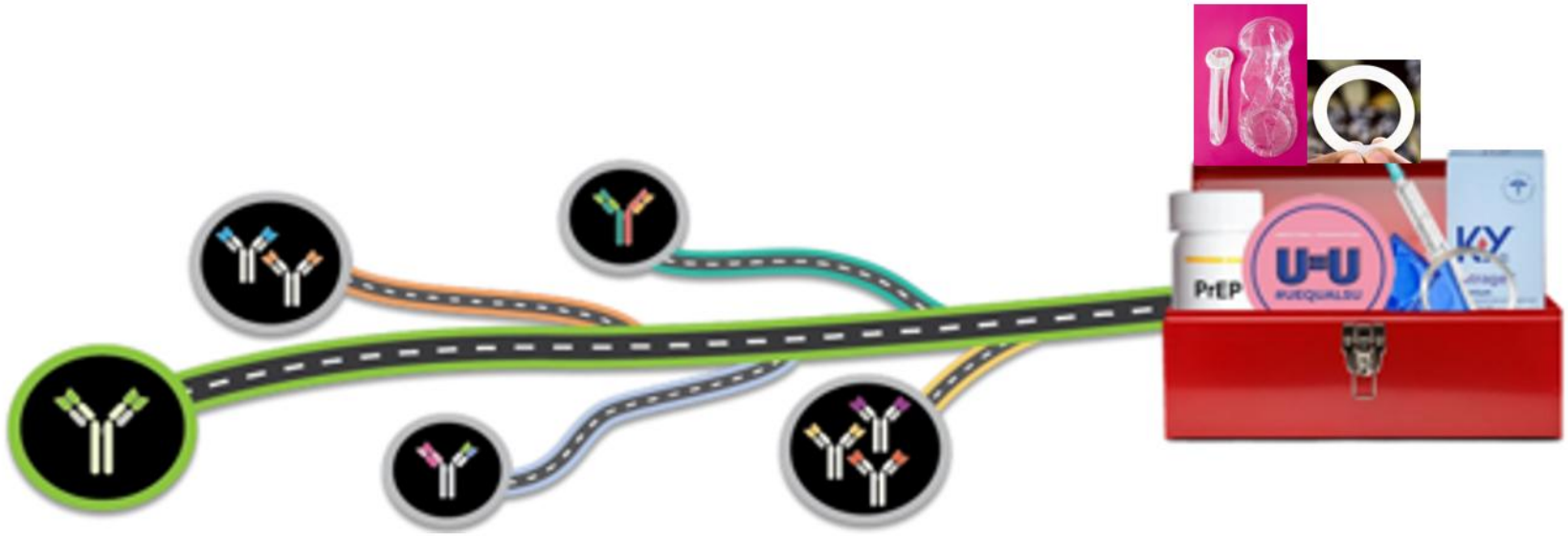
—Young woman, age 22, Tanzania

- Vaccines are typically given universally
- Around 40% of HIV infections in Eastern and Southern Africa (ESA) occurred in people who did not PrEP eligibility criteria beforehand.
- Even those who meet criteria may be missed due to clinician bias.
- Targeted (population-specific) interventions face more stigma-related barriers than universal ones like vaccines.
- Many individuals who contract HIV do not perceive themselves to be at risk.

bnAbs and vaccines are more difficult and costly than simple ARVs to develop and produce, but they remain relevant in this era

We found the potential of bNAbs is substantial, with the U.S. market alone presenting a billion-dollar opportunity. However, affordability and manufacturing costs pose significant challenges, especially in key lower-income regions where production costs far exceed market-viable prices

Blythe Adamson, PhD, MPH



A competitive landscape of PrEP prices in the US

In HICs, we recommend pricing bnAb PrEP **lower than long-acting injectable PrEP**. In the US, this is also expected to lower healthcare spending across PrEP products by ~1-2%

PrEP Product	Cost to US Healthcare Payer, Annual (USD)
Generic daily oral PrEP (TDF/FTC)	$8,300
bnAb twice-yearly infusions	**$14,000**
Branded daily oral PrEP (TAF/FTC)	$16,600
Injectable PrEP (CAB-LA) every other month	$25,800
Twice yearly LEN	$42,250

**Assumptions used in the base case for this economic evaluation*

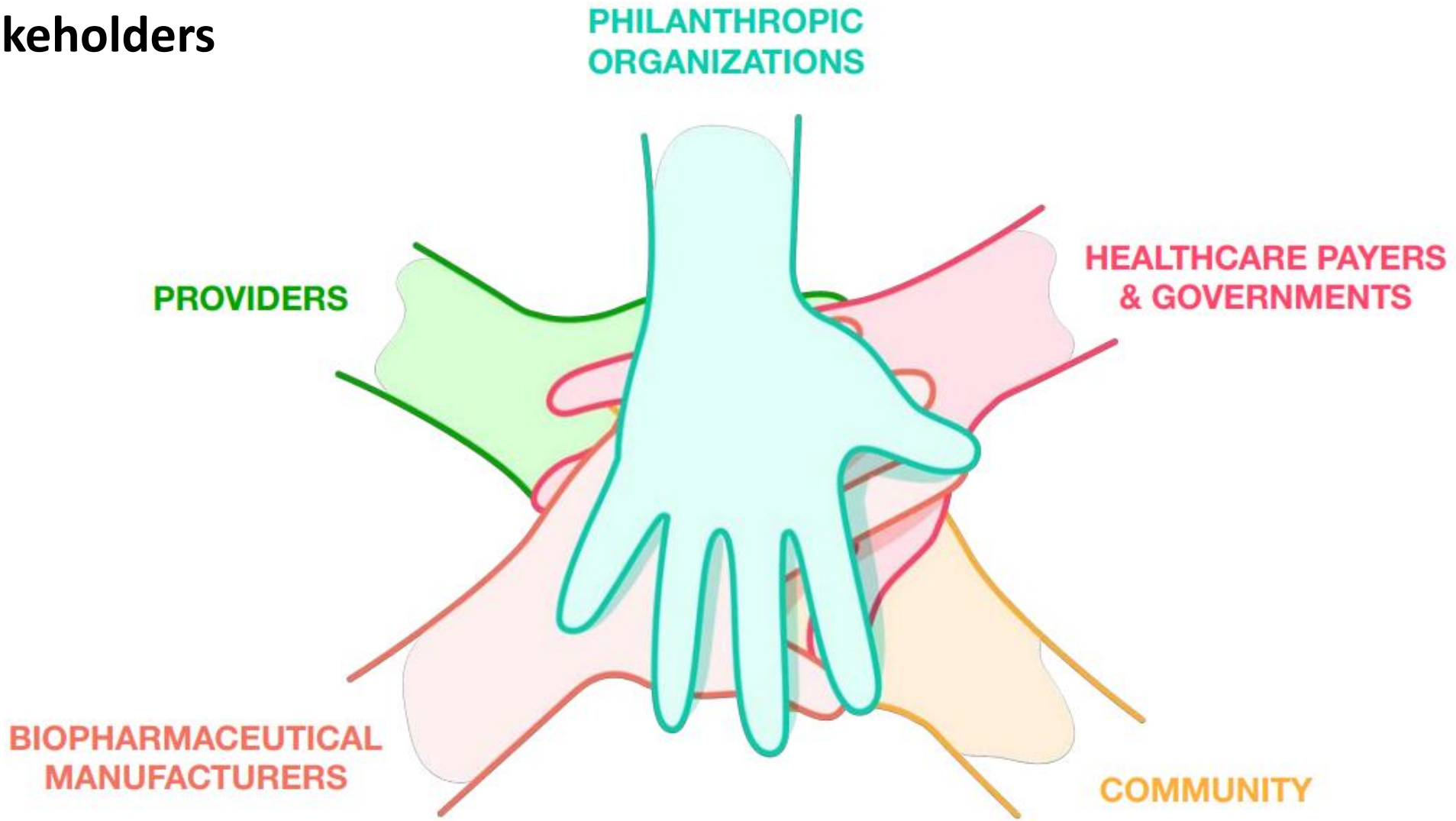
INFECTIOUS ECONOMICS

Key takeaway messages

Several **long-acting prevention technologies** are available or in the pipeline and can expand options for PrEP choice

- **Not a panacea**
  - Continue investigating **other PrEP options eg bnAbs and vaccines** (and MPTs, on-demand, other novel drug delivery systems etc)
  - Embrace current tools and increase access to current PrEP options
- Immune therapies have several advantages over ARV-based PrEP:
  - Provide privacy, avoid stigma toxicity aandssociated with ARVs
- Place communities at the core
  - A person-centred approach reflecting diversity, equity, and inclusion
  - Remove systemic barriers and address asymmetries in access to PrEP
- Begin with the end in mind
  - **Access, manufacturing, licensing, delivery methods.**

For bnAbs and vaccines to succeed, all stakeholders should benefit



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