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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

An overview of anti-HIV bnAbs

AVAC HIV Vaccine Awareness Day webinar, 7 June 2023

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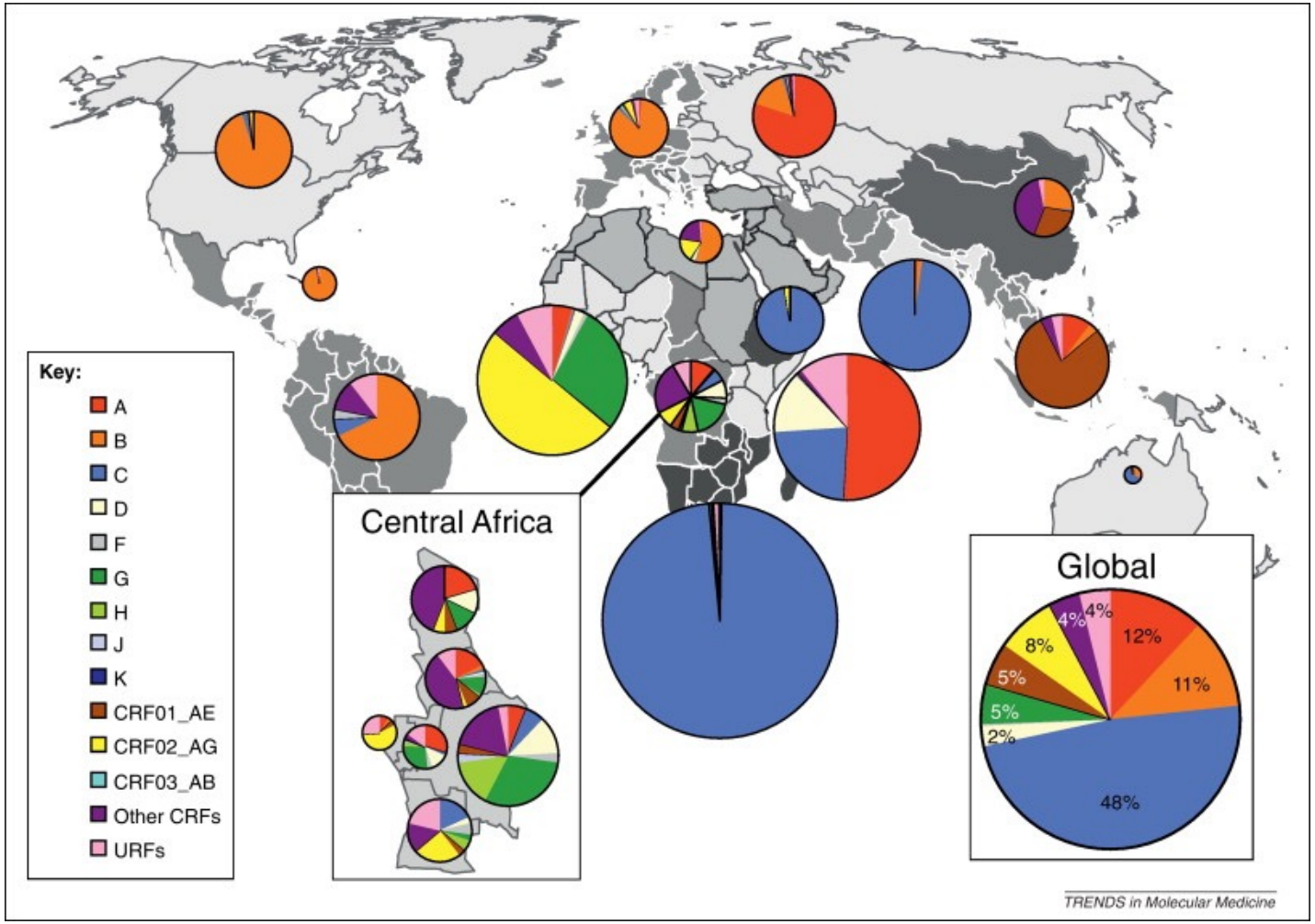
HIV has substantial genetic diversity: A major obstacle to vaccine development



HIV infection usually leads to strain-specific Abs

In rare instances, individuals develop bnAbs that can neutralise many strains

bnAbs from specific germlines and steps in Ab maturation

Source: *Hemelaar. Trends Mol Med. 2012*

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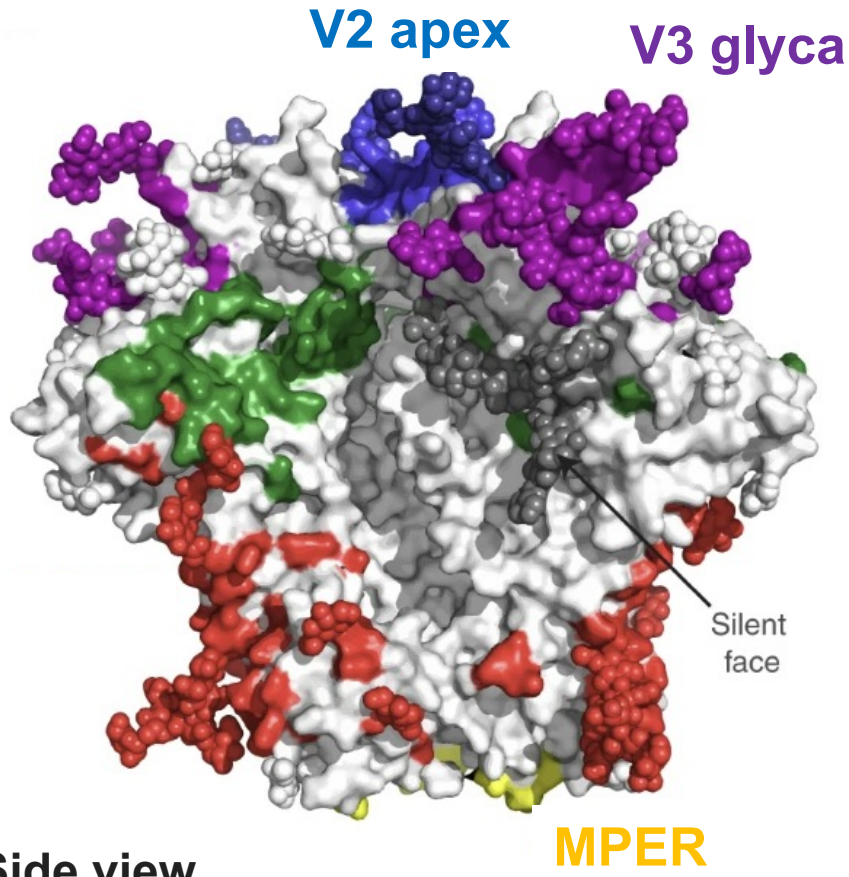
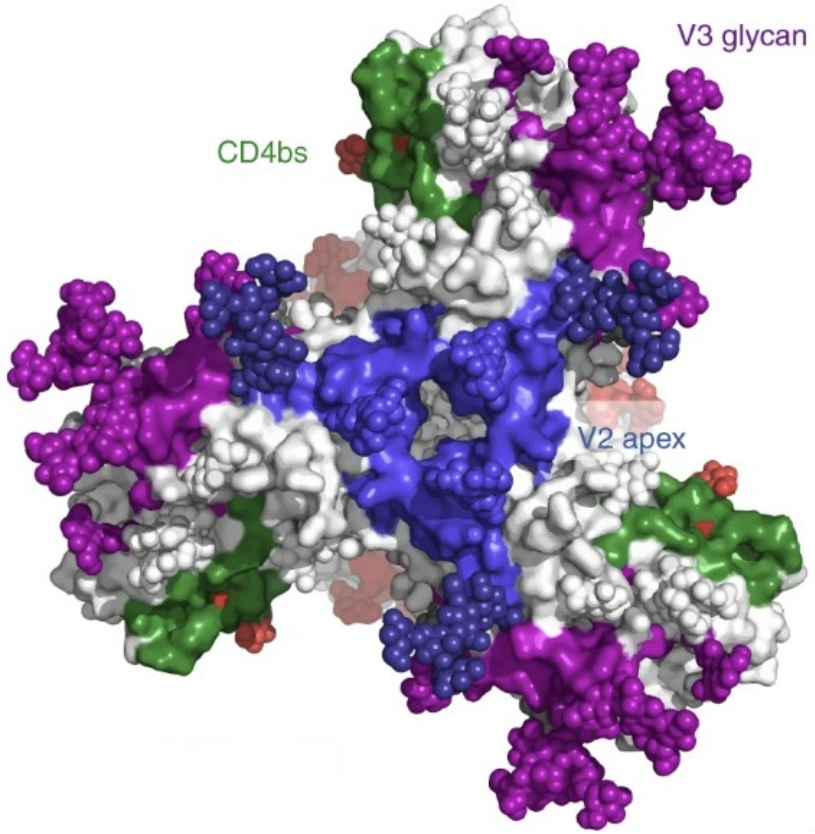
4 anti-HIV bnAb targets – CD4bs, V2, V3 & MPER



Side view



Top view

Source: *Sok and Burton, Nature Immunology 2018; 19(11):1179-88*

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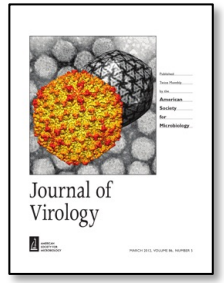
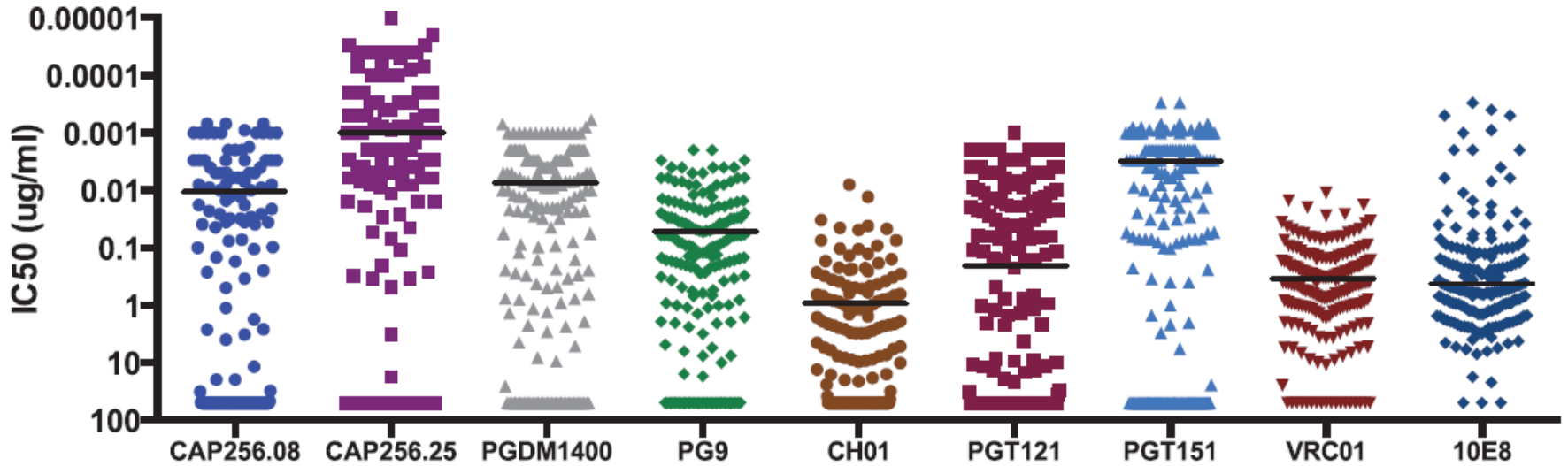
Potency & breadth of each anti-HIV bnAb

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Virology

New Member of the V1V2-Directed CAP256-VRC26 Lineage That Shows Increased Breadth and Exceptional Potency

Nicole A. Doria-Rose,[a] Jinal N. Bhiman,[b,c] Ryan S. Roark,[a] Chaim A. Schramm,[d] Jason Gorman,[a] Gwo-Yu Chuang,[a] Marie Pancera,[a] Evan M. Cale,[a] Michael J. Ernandes,[a] Mark K. Louder,[a] Mangaiarkarasi Asokan,[a] Robert T. Bailer,[a] Aliaksandr Druz,[a] Isabella R. Fraschilla,[a] Nigel J. Garrett,[e] Marissa Jarosinski,[a] Rebecca M. Lynch,[a] Krisha McKee,[a] Sijy O'Dell,[a] Amarendra Pegu,[a] Stephen D. Schmidt,[a] Ryan P. Staupe,[a] Matthew S. Sutton,[a] Keyun Wang,[a] Constantinos Kurt Wibmer,[b,c] Barton F. Haynes,[f] Salim Abdool-Karim,[e,g] Lawrence Shapiro,[d] Peter D. Kwong,[a] Penny L. Moore,[b,c,e] Lynn Morris,[b,c,e] John R. Mascola[a]





	CAP256.08	CAP256.25	PGDM1400	PG9	CH01	PGT121	PGT151	VRC01	10E8
% neutralized	46	57	78	80	51	66	68	90	98
Median IC50	0.01	0.001	0.008	0.06	0.99	0.023	0.003	0.393	0.54

Neutralization by bNAbs directed to diverse epitopes

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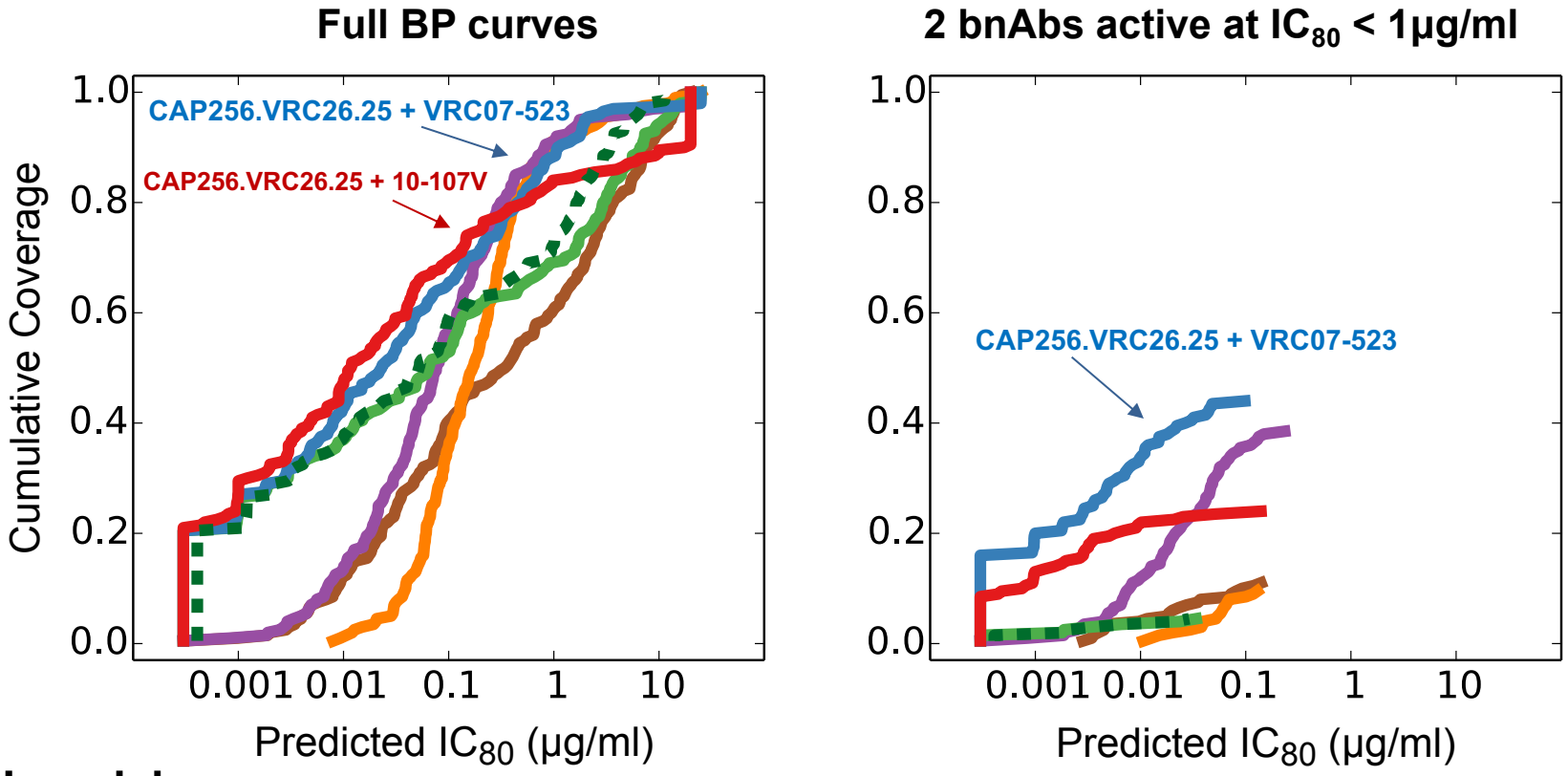
Coverage & potency of the 2 bnAb combinations



a = CD4bs Ab: VRC07-523.LS
b = V2g Ab: CAP256-VRC26.25
c = V3g Ab: 10-1074V
d = MPER Ab: 10E8

***Source**: Wagh et al., PLoS Pathogens 2016*

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Potential uses & limitations of bnAbs

bnAb uses

1. **Treatment: of multi-ARV resistant viruses**
2. **Prevention: of sexual HIV transmission**
3. **Prevention: of mother-to-child transmission**
4. **Cure: reduce size and diversity of viral reservoir**
5. **Vaccine: template pathway for active vaccination**

Limitations

1. ***Large doses by injection & durability (? >6 months)***
2. ***Can lead to auto-antibodies to the bnAb***
3. ***Viral escape by resistant strains :–***

   need bnAb combinations or bi-specific Abs
4. ***Manufacturability, cost & feasibility***

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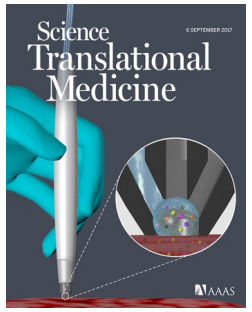
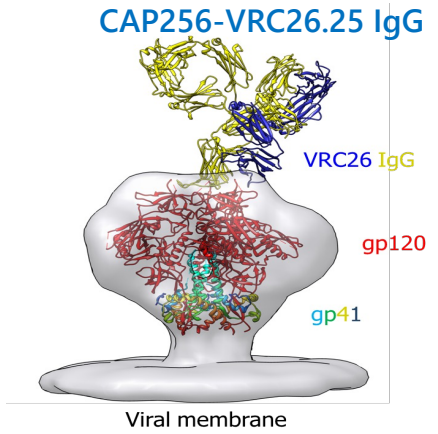
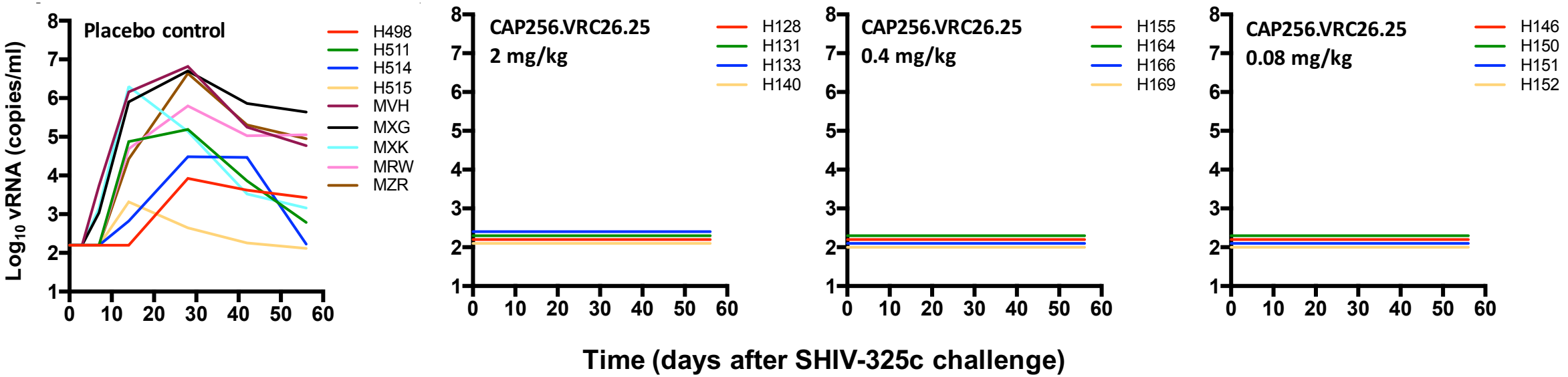
bnAbs - good protection in monkey challenge studies



Broadly neutralizing antibodies targeting the HIV-1 envelope V2 apex confer protection against a clade C SHIV challenge

Boris Julg,[1,2]* Lawrence J. Tartaglia,[2]* Brandon F. Keele,[3] Kshitij Wagh,[4] Amarendra Pegu,[5] Devin Sok,[6] Peter Abbink,[2] Stephen D. Schmidt,[5] Keyun Wang,[5] Xuejun Chen,[5] M. Gordon Joyce,[5] Ivelin S. Georgiev,[5] Misook Choe,[5] Peter D. Kwong,[5] Nicole A. Doria-Rose,[5] Khoa Le,[6] Mark K. Louder,[5] Robert T. Bailer,[5] Penny L. Moore,[7,8] Bette Korber,[4] Michael S. Seaman,[2] Salim S. Abdool Karim,[8,9] Lynn Morris,[7,8] Richard A. Koup,[5] John R. Mascola,[5] Dennis R. Burton,[1,6] Dan H. Barouch[1,2†]





Plasma viral loads in rhesus macaques pretreated with different doses of the bnAbs PGDM1400 and CAP256-VRC26.25 and challenged with SHIV325c.

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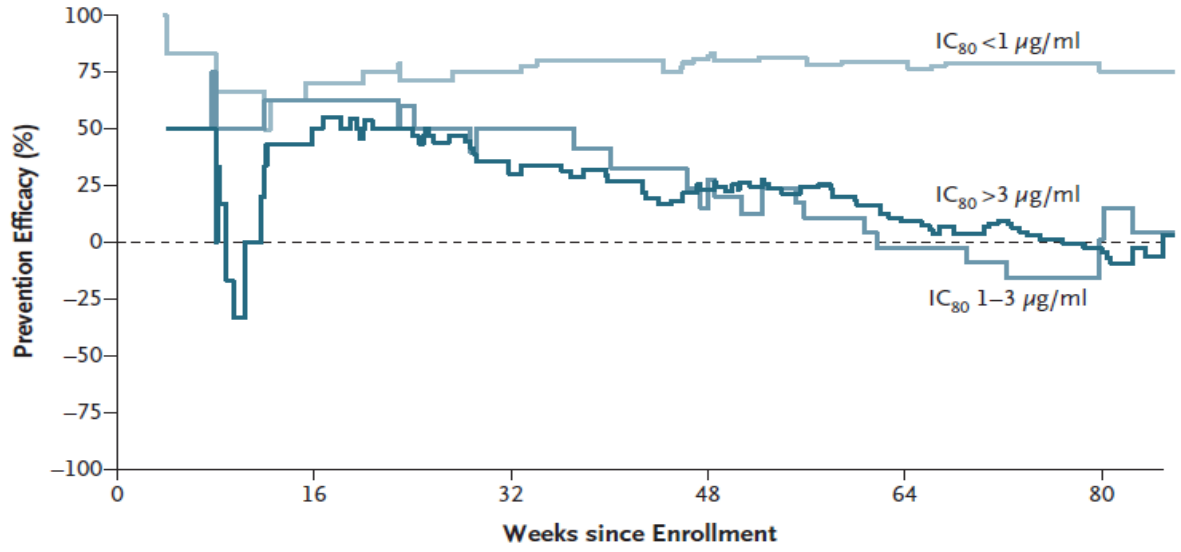
AMP: Clinical evidence of a promising approach

A



B

Prespecified IC_{80} Category and Treatment Group	No. of HIV-1 Infections	No. of Person-Yr	Rate per 100 Person-Yr	Prevention Efficacy (95% CI)
<1 μg/ml				
Placebo	19	2203	0.86	
VRC01 pooled	9	4427	0.20	75.4 (45.5 to 88.9)
1–3 μg/ml				
Placebo	10	2203	0.45	
VRC01 pooled	19	4427	0.43	4.2 (–108.7 to 56.0)
>3 μg/ml				
Placebo	35	2203	1.59	
VRC01 pooled	70	4427	1.58	3.3 (–48.0 to 36.8)

AMP trial did not show overall protection against HIV acquisition

but

75% prevention efficacy against HIV strains susceptible to VRC01

Source: *Corey et al., NEJM 2021;384:1003-14*

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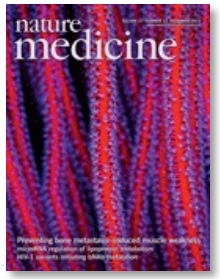
Big hope in bnAbs – can they provide a pathway to neutralization breadth ie. roadmap for vaccines



Viral variants that initiate and drive maturation of V1V2-directed HIV-1 broadly neutralizing antibodies

Jinal N Bhiman[1,2], Colin Anthony[3], Nicole A Doria-Rose[4], Owen Karimanzira[1], Chaim A Schramm[5], Thandeka Khoza[1], Dale Kitchin[1], Gordon Botha[3], Jason Gorman[4], Nigel J Garrett[6], Salim S Abdool Karim[6], Lawrence Shapiro[4,5], Carolyn Williamson[3,6,7], Peter D Kwong[4], John R Mascola[4], Lynn Morris[1,2,6] & Penny L Moore[1,2,6]

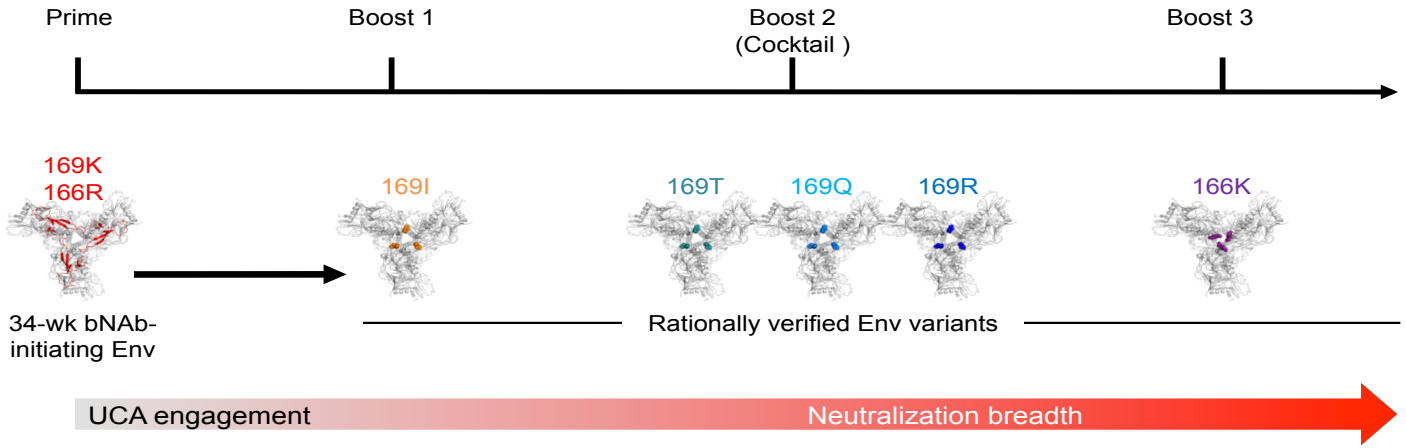
Possible vaccine strategy based on viral variants that drove breadth

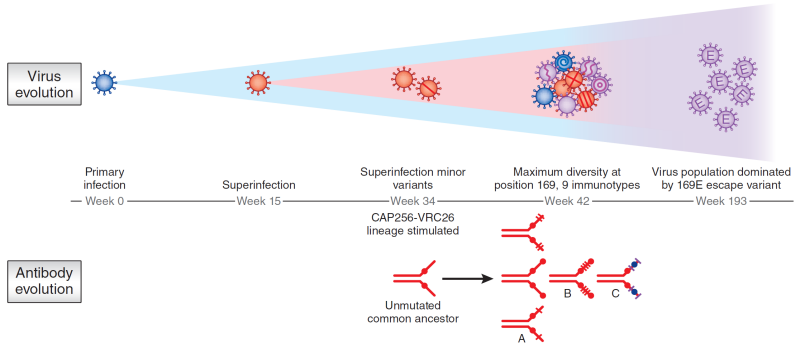
A pathway to HIV-1 neutralization breadth

S Abigail Smith & Cynthia A Derdeyn

nature medicine

Neutralization breadth is thought to be an important feature of an effective vaccine against HIV-1. A study in one individual has now identified the specific viral variant that engaged the necessary antibody precursor, as well as the viral immunotypes that drove neutralization breadth, improving understanding of how to mimic this process with a vaccine.





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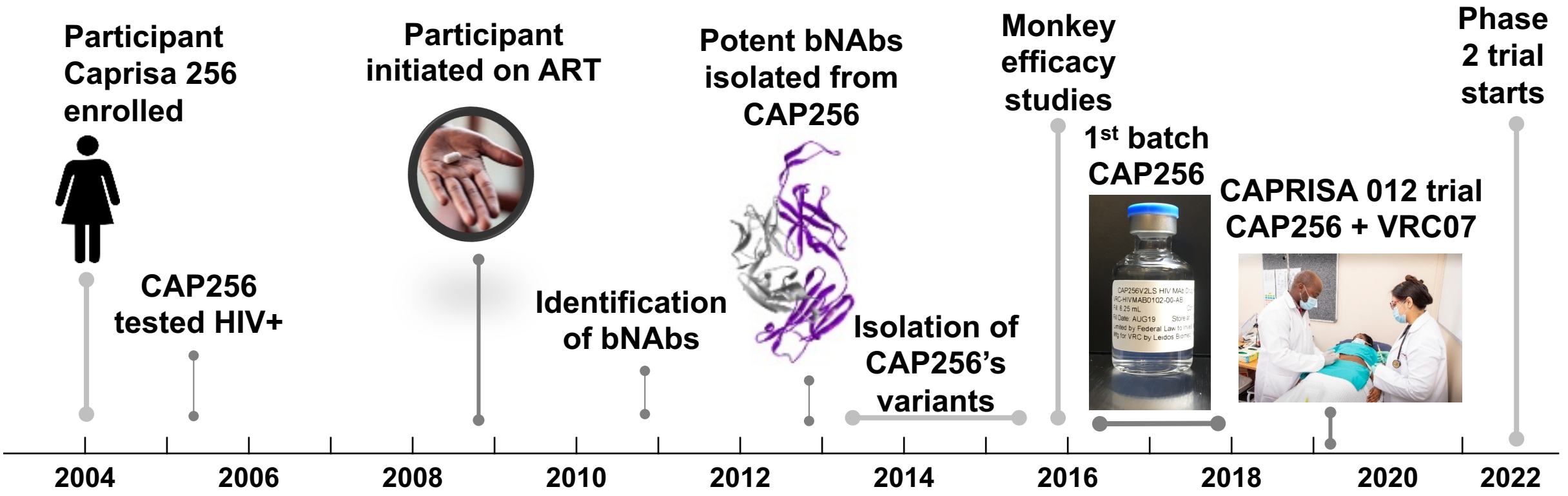
bnAb time from lab to clinic: e.g. 15 years for CAP256

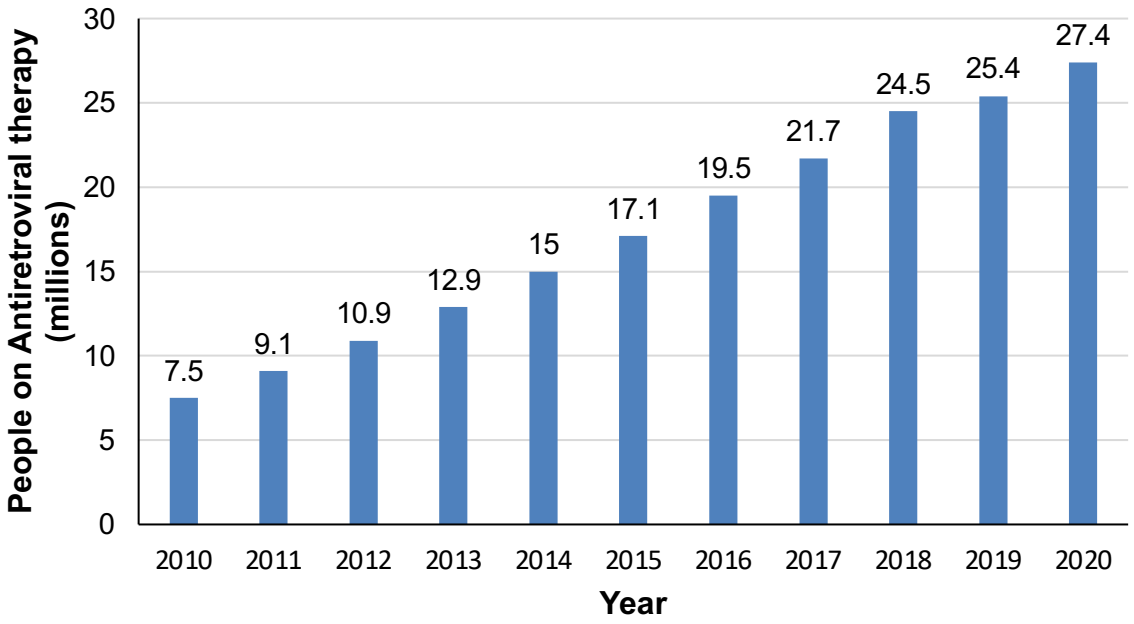


Clinic → laboratory → Clinic

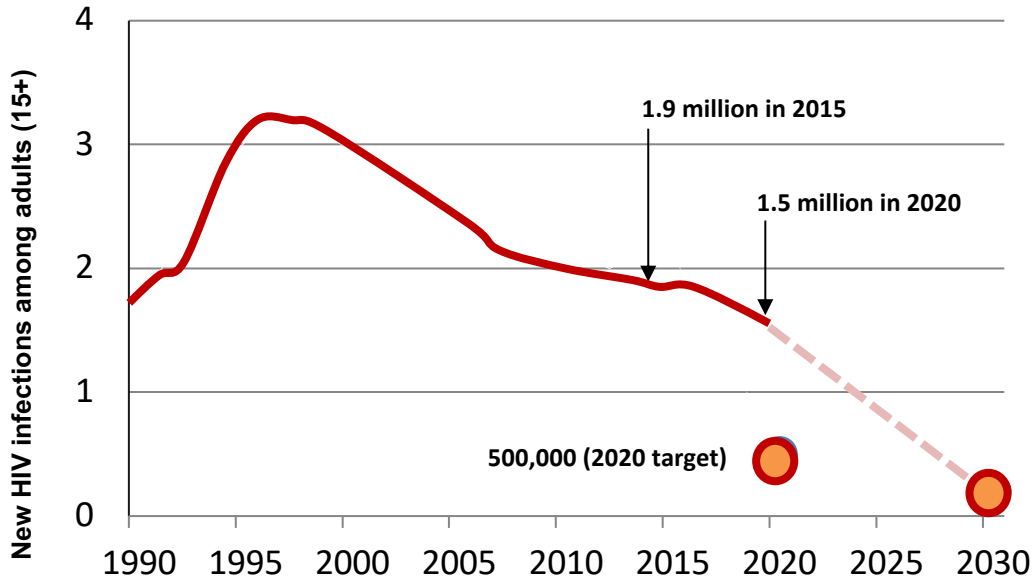
National Institute of Allergy and Infectious Diseases · aighd · Université Jean Monnet Saint-Étienne · CIDRZ · EDCTP · SAMRC · Department of Health Republic of South Africa · science & innovation Department: Science and Innovation Republic of South Africa · NRF · National Institute for Communicable Diseases · CAPRISA Centre for the AIDS Programme of Research in South Africa

Great progress on increasing HIV treatment but we are lagging in prevention

Number of people receiving antiretroviral therapy: 2010–2020



1.5 million new infections in 2020 but target was 500,000



Source: UNAIDS reports

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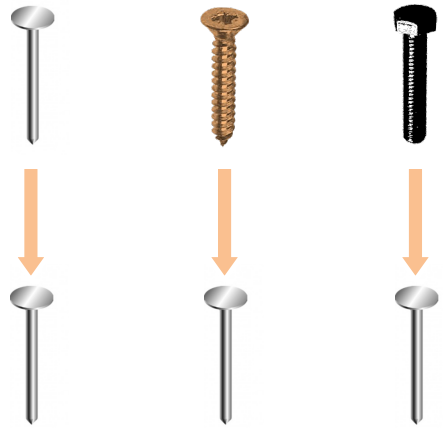
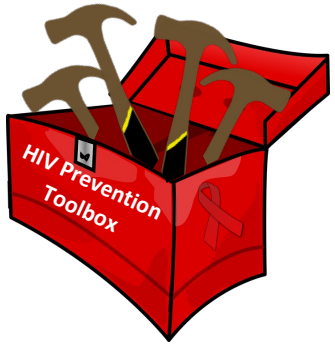
Ending AIDS as a public health threat needs more than a single solution to the many different problems

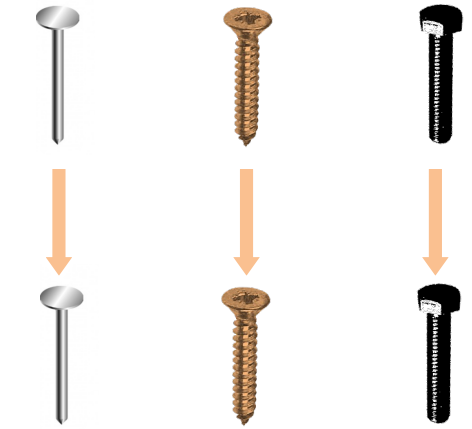
Challenges in AIDS pandemic

Solution



ARVs





High-risk young populations

Provider-initiated long-acting PrEP

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