Broadly Neutralizing Antibodies (bnAbs): Where We've Been, and Where We're Going

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Review of bnAbs

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How do people fight illness and disease?

- One of the ways is by using antibodies.
- Antibodies are proteins produced naturally by the human body as a response to antigens (vaccines).
- They are part of the immune system, which protects us against illness and disease.
- They are specific for every different kinds of germs that cause illness that people get exposed to.
- They can also be made in a lab, to be used like a medication, known as “monoclonal antibodies”.

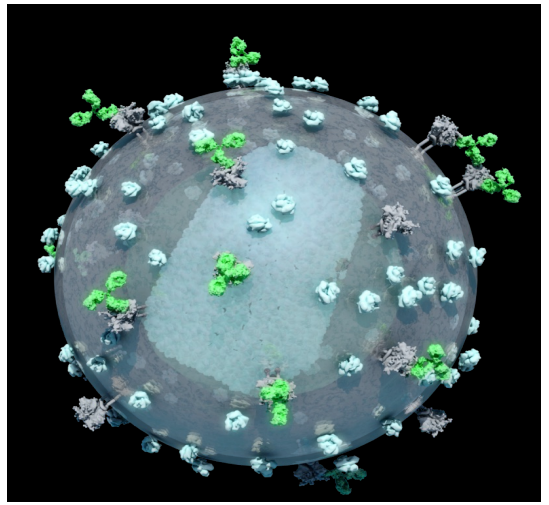
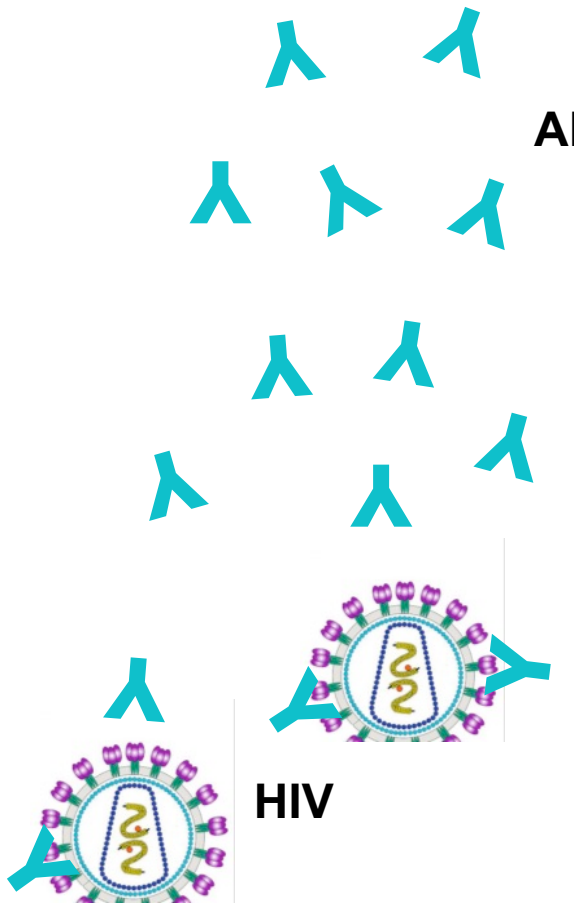


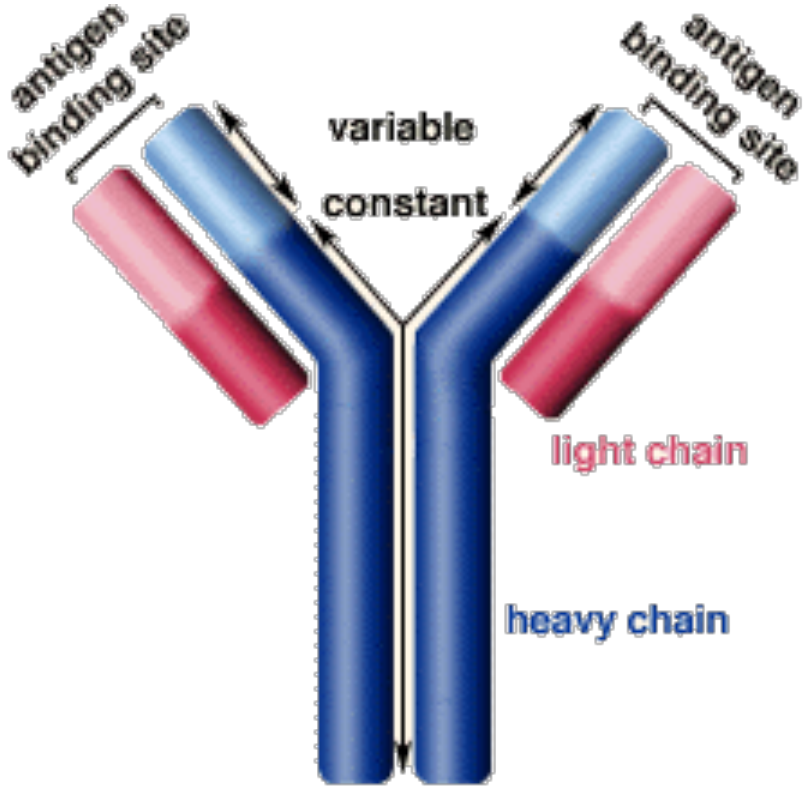
Image of HIV with antibodies (green) attached to surface proteins (credit: Lisa Donohue)

What are antibodies generally?



- Antibodies are proteins made in our white blood cells (B cells) in the first days after HIV enters the body, but can take weeks to get to full strength.
- Shaped like the letter Y, with 2 “arms” that bind to the invading germ, and a “foot” that binds to other cells that can clear it out of the body.
- Antibodies can prevent acquisition by blocking the virus from being able to attach to our cells.
- The immune system can make a stronger and faster antibody response against germs that you have been sick with before and/or have been vaccinated against.
- Antibodies don’t last very long naturally (typically <2 mos.); manufactured ones can be engineered to last longer.

Antibodies work 3 ways



NEUTRALIZATION

Binds to HIV & blocks it from attaching to host cells

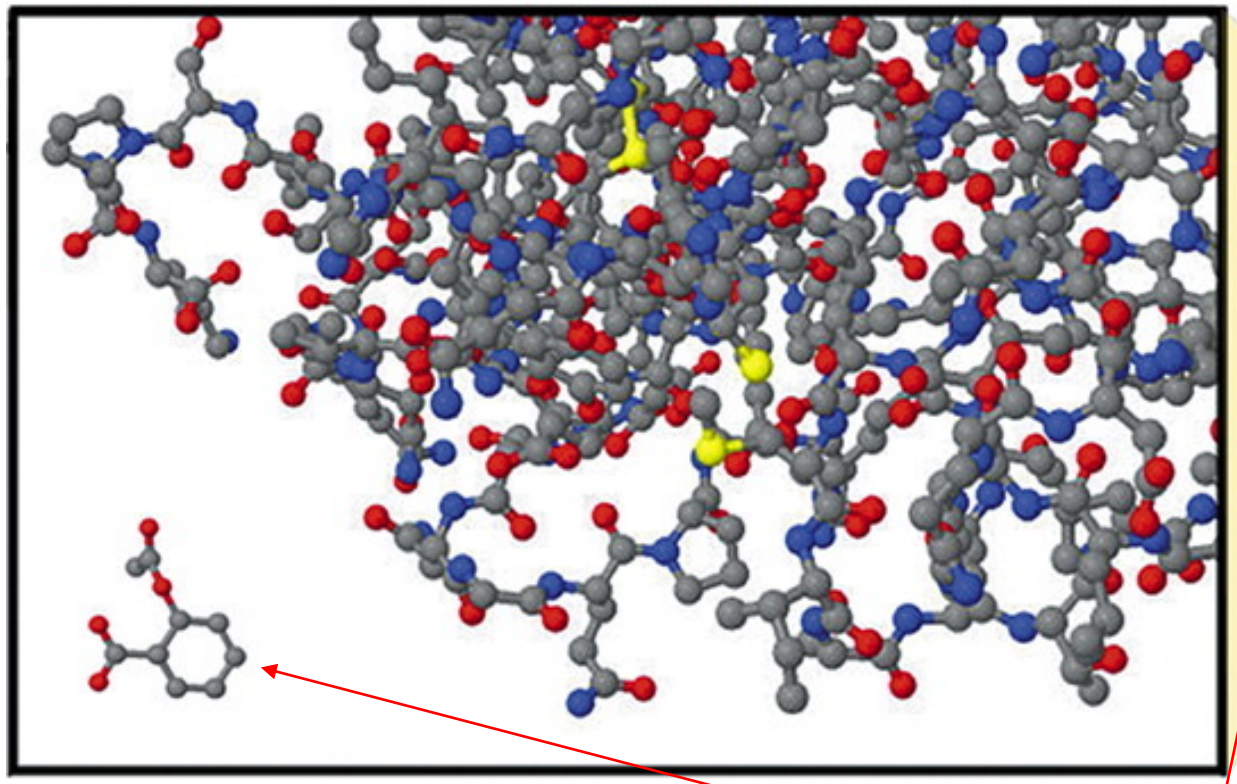
OPSONIZATION
("buttering the toast")

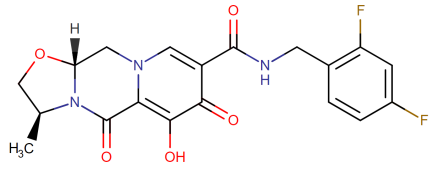
Binds to HIV, then uses the "foot" to bind to a macrophage; the macrophage then eats the HIV

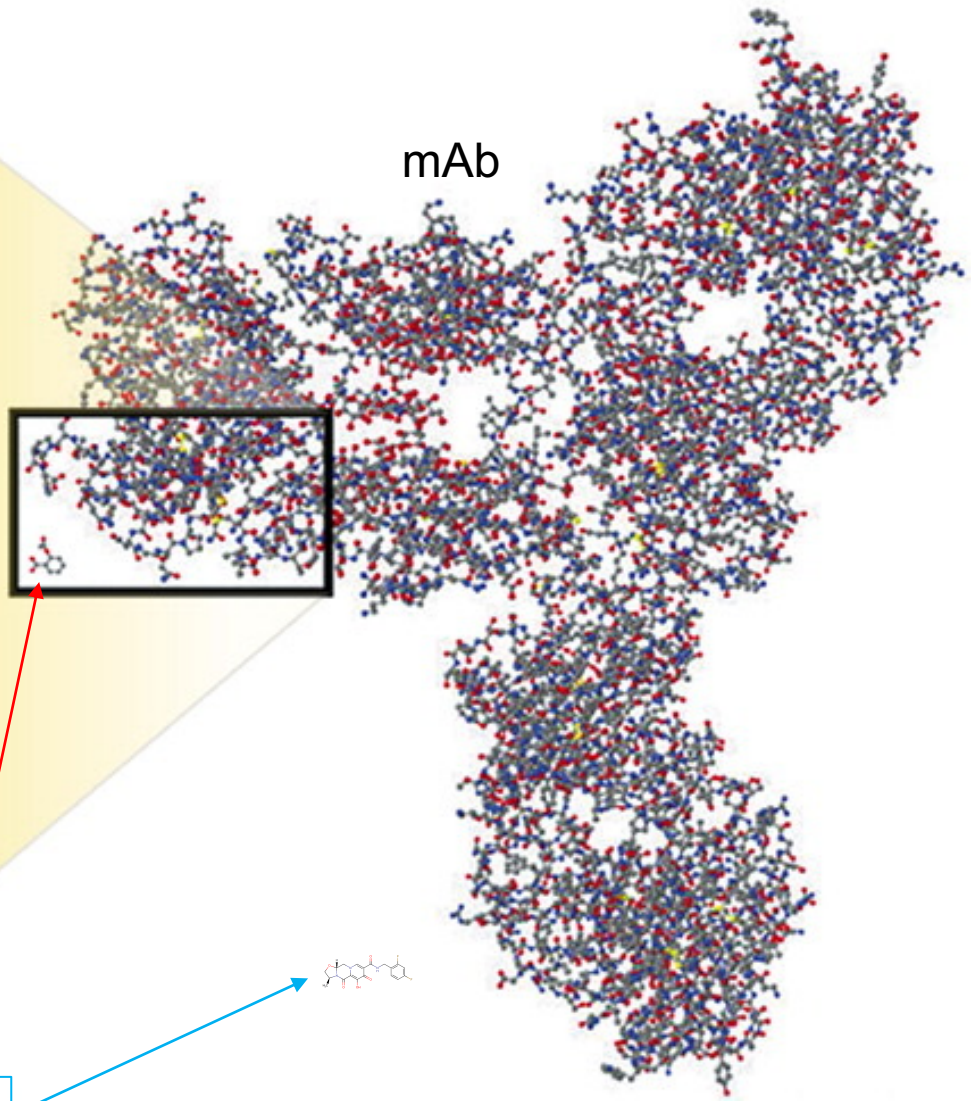
SENSITIZATION
("the lookout for the hitman")

Binds to HIV, allowing other killer cells and T cells to better respond, "seeing" HIV and killing it

Antibodies are large (800x bigger than an aspirin molecule)!







Aspirin

Cabotegravir

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The NEW ENGLAND JOURNAL of MEDICINE

Kozlowski S et al. N Engl J Med 2011;365:385-388, Drugbank

A new idea

All people with an infection make neutralizing antibodies, but not all antibodies are created equal…

Strain-specific antibodies

Broadly Neutralizing antibodies

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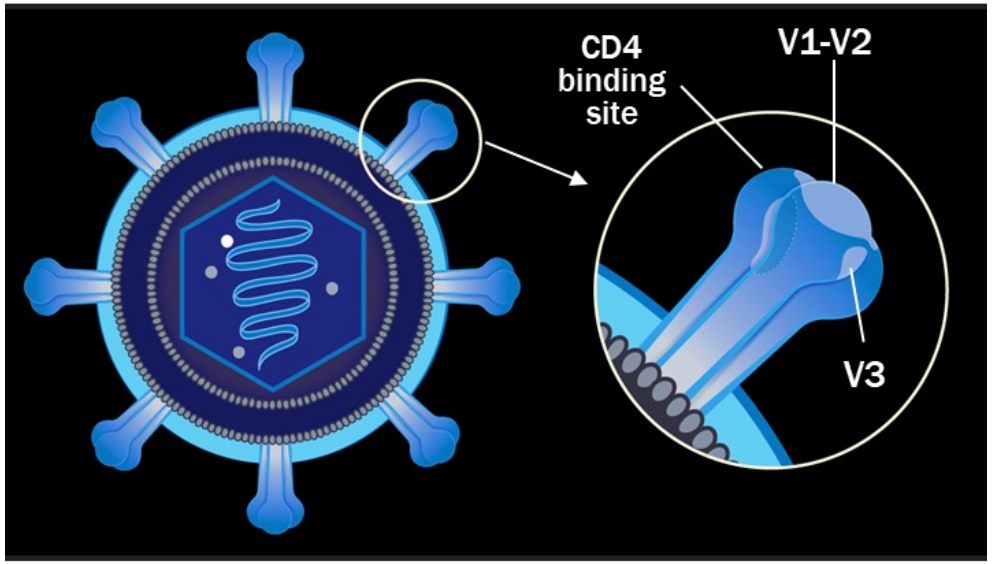
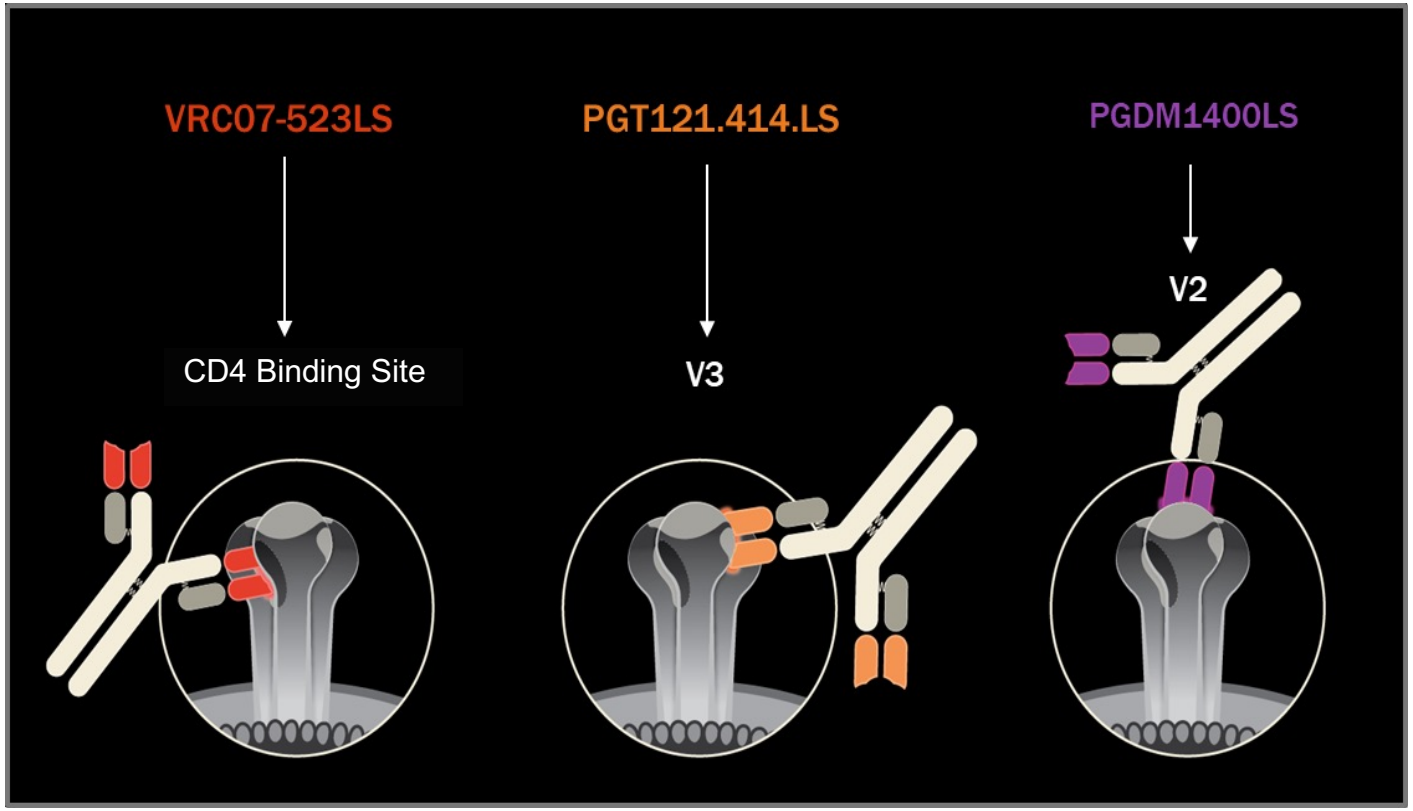
Slide credit: Penny Moore

bnAbs attach to different places on HIV



Each bnAb binds to different places on the spikes found on the surface of HIV, blocking HIV from attaching to human T-cells.



Example from current HVTN/HPTN studies

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What is a BROADLY neutralizing antibody?

The verb: “bnAb”

An antibody whose function is to neutralize (block) a lot of different global strains of HIV (broad/breadth).

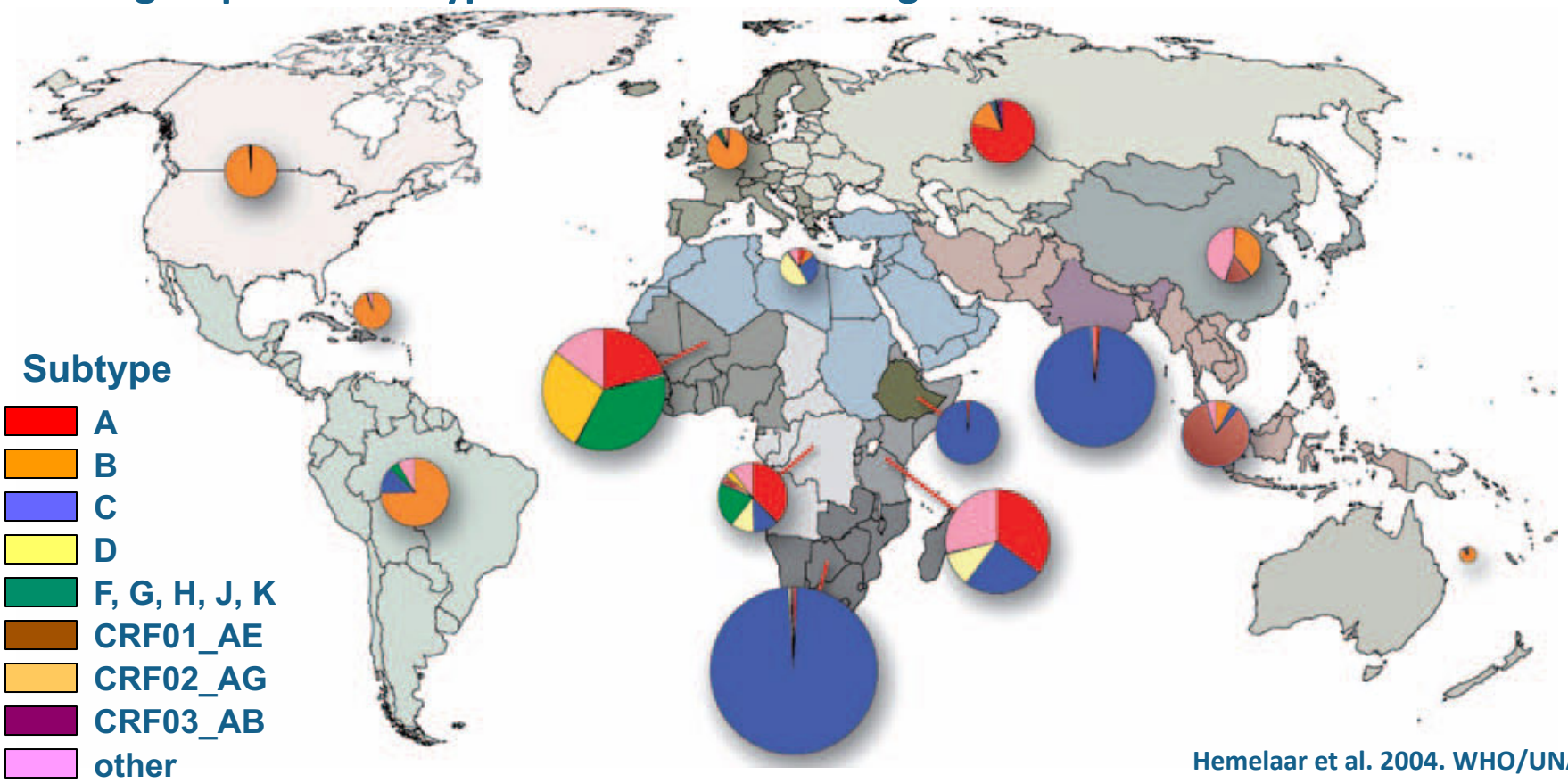
The noun: Monoclonal Antibodies

A copy (clone) of 1 (mono) single antibody that has been manufactured in a laboratory

And why is this important for HIV prevention?

HIV-1 Diversity Worldwide

HIV-1 group M: 9 subtypes & several circulating recombinant forms



Hemelaar et al. 2004. WHO/UNAIDS.

Human genomes differ by about 0.1%

HIV genomes differ by 10-30%

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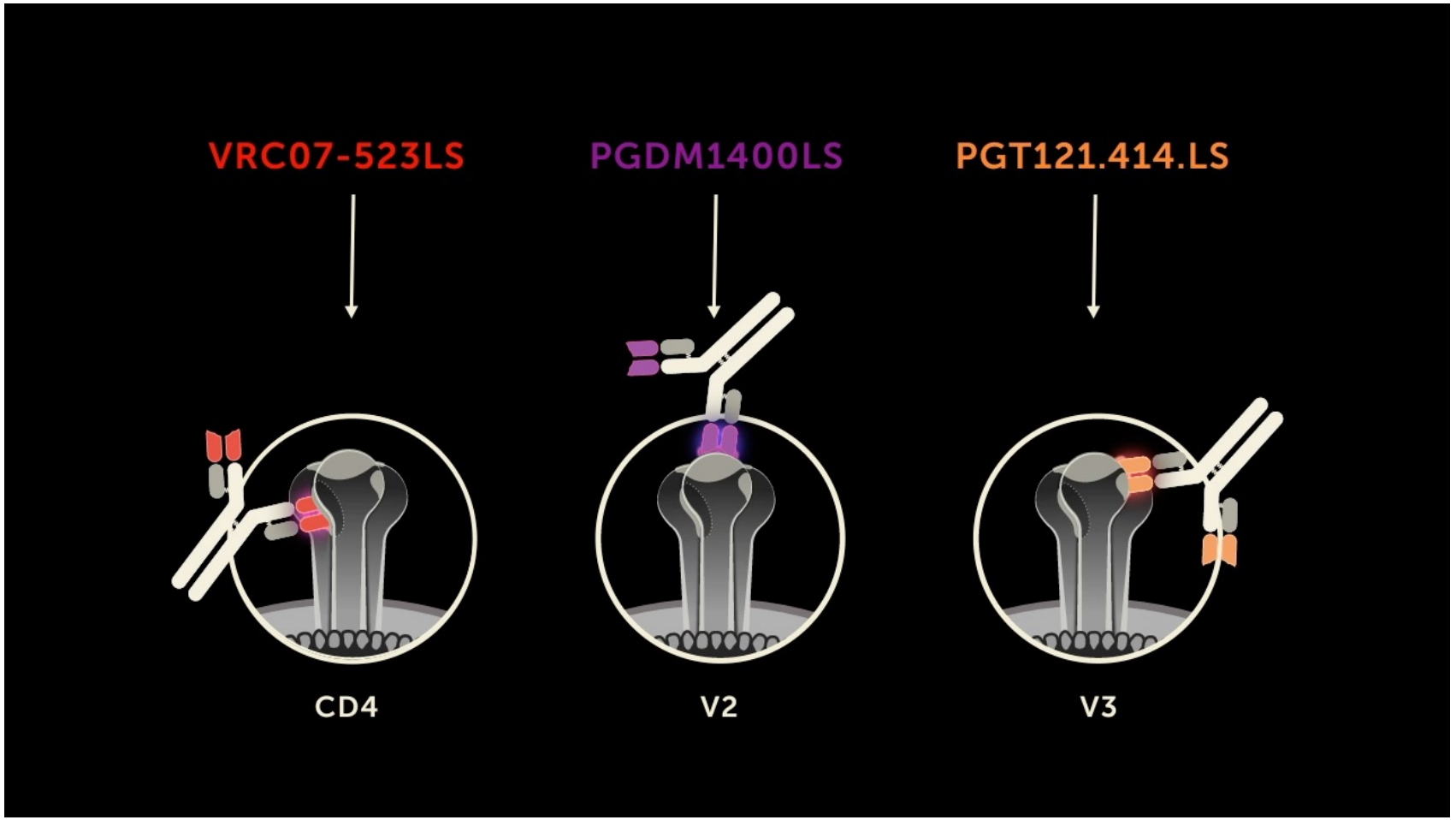
Difficult to vaccinate (and build immunity) against a moving target

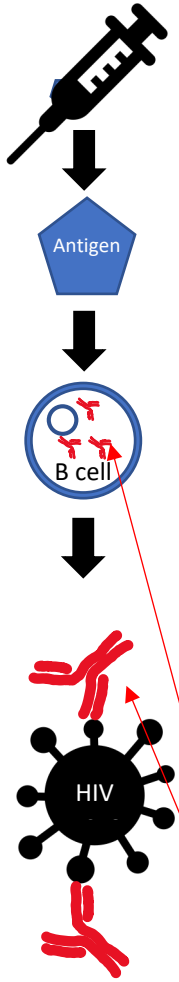
Slide credit: Lillian Cohen

Korber et al. BMJ, 2001.

Animation: combos of bnAbs can block more HIV



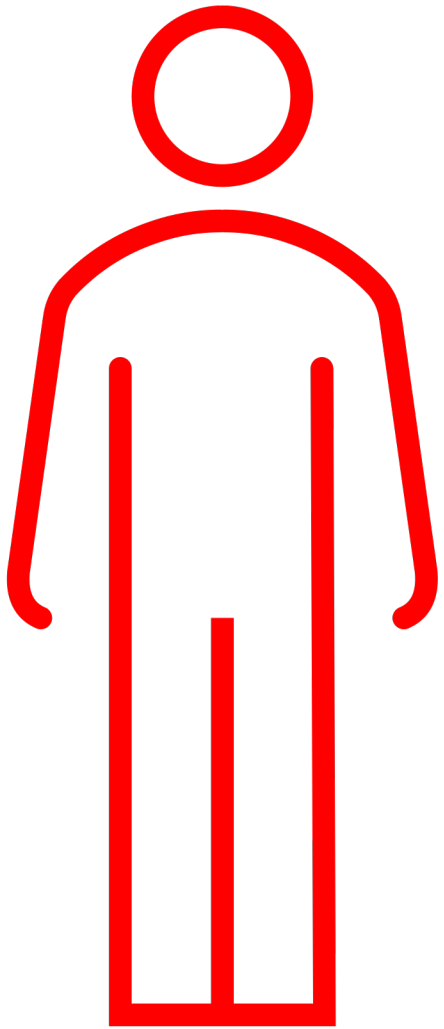
Active and Passive Immunization Compared



Active immunization

Potential HIV Vaccines

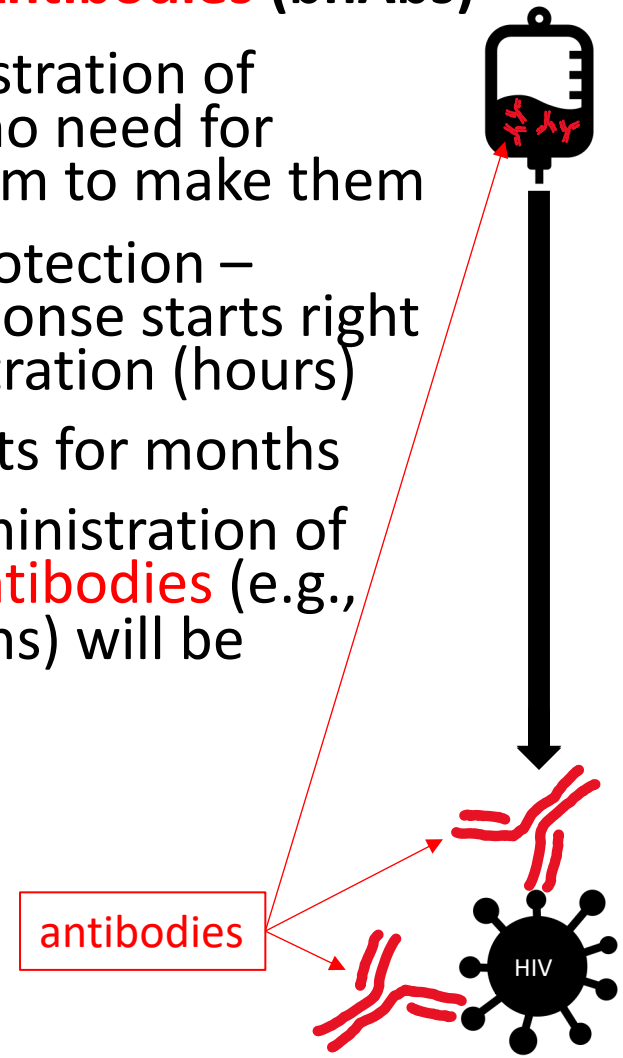
- Vaccines (antigens) stimulate the immune system to make antibodies
- No immediate protection – usually requires 2-3 immunizations with antigen to generate antibody response (weeks-months)
- Protection may last for years
- Vaccines may elicit broader immune responses



Passive immunization

Broadly Neutralizing Antibodies (bnAbs)

- Direct administration of antibodies – no need for immune system to make them
- Immediate protection – Antibody response starts right after administration (hours)
- Protection lasts for months
- Repeated administration of "potential" antibodies (e.g., every 6 months) will be required



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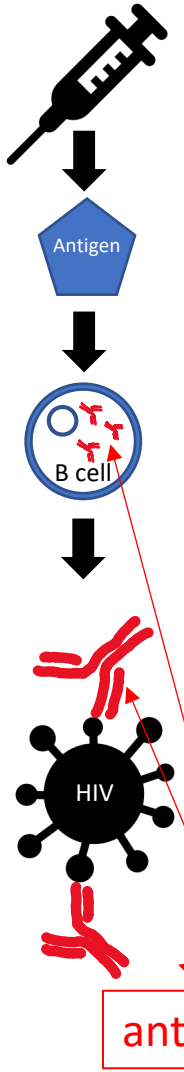
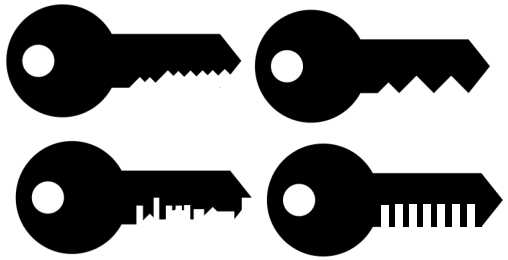
Active and Passive Immunization for HIV prevention

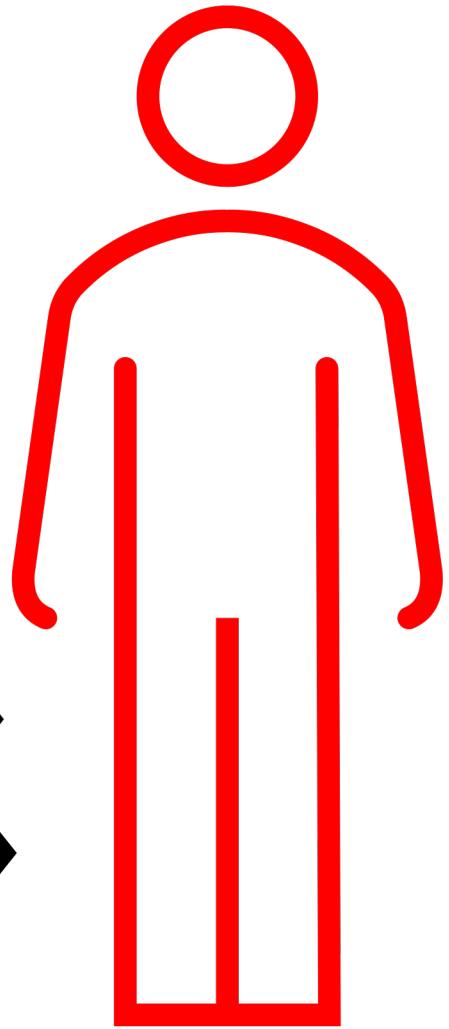


Active immunization

Vaccines

- HIV vaccine not yet available
- Relatively small (microgram) amounts of protein or mRNA (antigens) per dose
- HIV vaccine development informed by antibody research

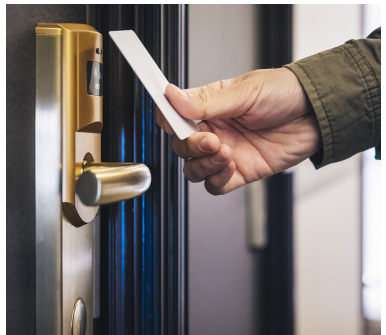


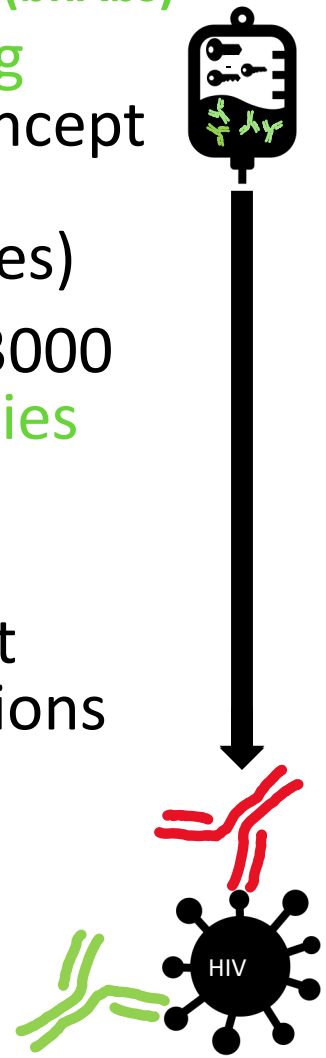


Passive immunization

Broadly Neutralizing Antibodies (bnAbs)

- HIV broadly neutralizing antibodies: proof of concept for HIV prevention is established (AMP studies)
- Relatively large (1000-3000 mg) amount of antibodies per dose
- bnAbs as pre-exposure prophylaxis can prevent millions of HIV acquisitions





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Where have we been with bnAbs?

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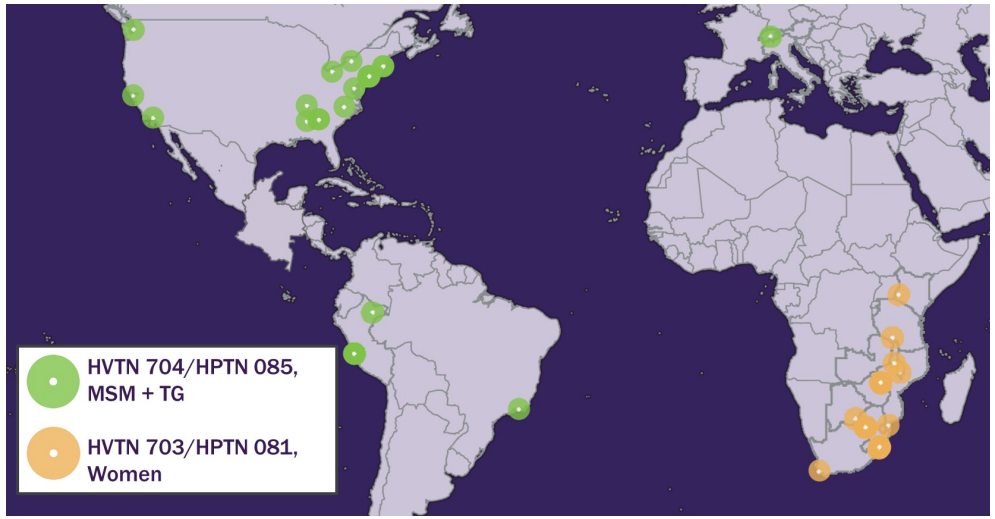
How do we know bnAbs work? The AMP Studies (Phase 2b)

- Proof of concept for HIV prevention (results in Oct. 2020)
  - HIV prevention with 1 bnAb is possible – however, VRC01 only protected against acquisition of viruses that were sensitive to this bnAb
- HIV bnAbs are safe and well tolerated
  - Most participants have no side effects
  - Side effects were the same for saline placebo & VRC01
- Large scale IV administration is possible globally
  - 11 countries
  - 46 sites (25 in Americas + 20 in Africa + 1 in Europe)
  - Delivered 82.5 KG (182 pounds) of VRC01 in 144,474 vials
    - Enrollment: 4,625 participants across 2 trials
    - **Retention: 95%** of 97,458 visits
    - **Adherence: 99%** of 41,116 infusions



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Corey L, Cohen M, et al, NEJM 2021;384:1003-14

bnAbs against HIV are safe and well tolerated

- Key safety results from the AMP studies
  - 41,116 IV infusions in 4,625 participants
  - Majority of participants have no side effects
  - Rates were about the same for VRC01 and placebo

Most common side effects	**Placebo**	**Dosage**	
		Low	**High**
Mild (grade 2) pain and/or tenderness at infusion site	22%	21%	20%
Mild (grade 2) systemic symptoms (e.g. headache, fever)	35%	33%	33%

- HIV bnAbs are human antibodies directed against a virus (non-self), which is a different mechanism of action compared to mAbs used for cancer and anti-inflammatory conditions like rheumatoid arthritis (anti-self)

What bnAb trials have taken place since AMP?

	LS versions with extended half-life for dosing every 6 Months			Combinations of 2 or 3 bnAbs for increased breadth and prevention efficacy		
Study	**HVTN 116**	**HVTN 127/ HPTN 087**	**HVTN 128**	**HVTN 130/ HPTN 089**	**HVTN 136/ HPTN 092**	**HVTN 140/ HPTN 101**
Products / **Study Questions**	**VRC01, VRC01LS**	**VRC07-523LS**	**VRC07-523LS**	**VRC07-523LS + PGT121 + PGDM1400**	**VRC07-523LS + PGT121.414.LS**	**VRC07-523LS + PGT121.414.LS + PGDM1400LS**
Is the bnAb(s) **safe**?	Yes	Yes	Yes	Yes	Yes	Yes
Can they be given **every 6 months**?	Yes	Yes	Yes	Yes	Yes	Yes
Was there **interference** between multiple bnAbs?	N/A	N/A	N/A	No	No	No
Were **predictions** about how long they last accurate?	Yes	Yes	Yes	Yes	Yes	Yes
Do bnAbs still have the same **neutralizing activity** 6 months after they are given?	Yes	Yes	Yes	Yes	Yes	Yes
Does the ability to **neutralize** correlate to the amount of bnAb in the body 6 months after they are given?	Yes	Yes	Yes	Yes	Yes	Yes
Were the neutralization **predictions** accurate?	Yes	Yes	Yes	Yes	Yes	Yes
Were there any clinically relevant **Anti-Drug Antibodies**?	No	No	No	No	No	No

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Where are we going with bnAbs?

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The next efficacy trials: Combo AMP

Tentative study plan:

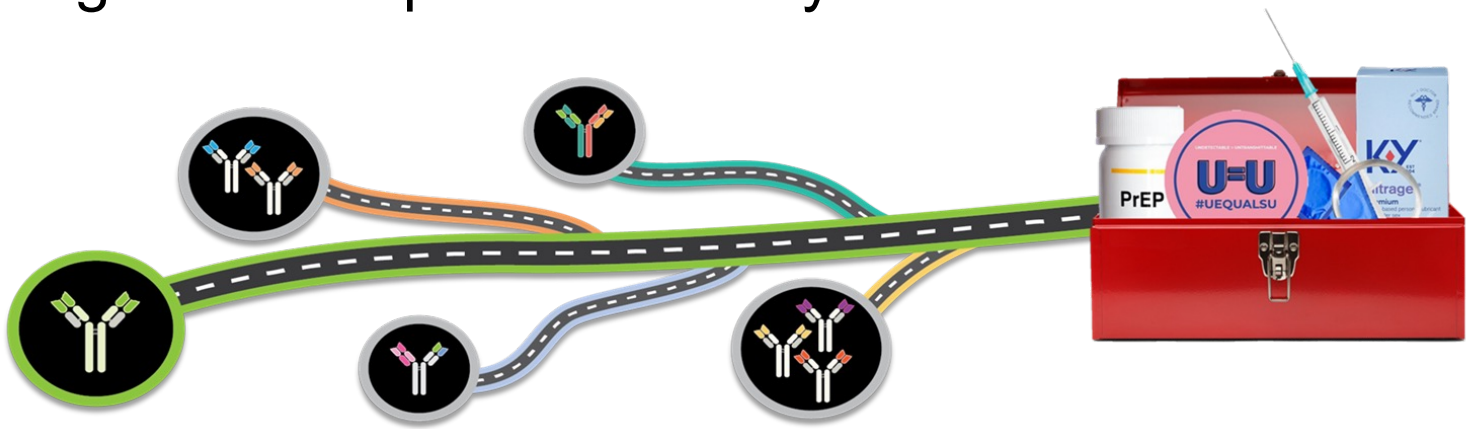
- 2 parallel trials in Africa (cis women) and the Americas (MSM/Trans/NB)
- 3 bnAb combo
- 3 doses of the bnAb combo – beginning of trial, 6 months, 1 year
- Overall study design is under consideration (number of participants, dose groups, control groups)

Phase 2b Combo AMP efficacy trials: VRC07-523LS + PGT121.414.LS + PGDM1400LS	**N = TBD**	**Week 0**	**Week 24**	**Week 48**
VRC07-523LS + PGT121.414.LS + PGDM1400LS Fixed dose IV	TBD	X	X	X

Quick Plug! Plenary on Monday, June 17, 10:00 am: Dr. Dan Barouch
"Broadly Neutralizing Antibodies (bnAbs) at the Crossroads: What Lies Ahead?"

How might bnAbs be used for HIV prevention?

- **Some <u>possible</u> uses of bnAbs for HIV prevention include:**
- Protecting newborn babies (during & right after birth, during breast/chest feeding)
- Cover the “tail” of long-acting PrEP injections, when the medication is waning
- Cover the ramp-up period of an HIV vaccine regimen that is given in multiple doses over several months to a year
- Combine bnAbs with other prevention methods as a prevention “cocktail,” similar to ART for treatment (e.g. combine bnAbs with a vaginal ring for improved efficacy)
- As an independent prevention tool given a couple of times a year



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  - Co-chairs: Dr. Sri Edupuganti, HVTN and Dr. Nyaradzo Mgodi, HPTN
  - Protocol Team leaders Dr. Shelly Karuna, HVTN and Phil Andrew, HPTN
- All 6 of the phase 1 bnAb protocol teams, sites, and study participants
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Questions?

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