HIV VACCINE
TRIALS NETWORK

TN CFAR
TENNESSEE CENTER FOR AIDS RESEARCH

Immune Responses to Viruses and upcoming HIV (and SARS CoV-2) Vaccine Trials

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Objectives:

- Overview of the immune response
- Understanding how the immune system fights viral infections
- Differences between SARS CoV-2 and HIV
- Ongoing and Upcoming HIV and CoV-2 vaccine trials

Innate Response

- First line of defense
- Prevents infection? No!
- NK cells activated when cells are infected
- Activation of innate response is required before the adaptive response can happen
- No immunological memory
- We don't think vaccination will help with immunological memory
- NK cells work by causing infected cells to burst, like a dart bursting a water balloon

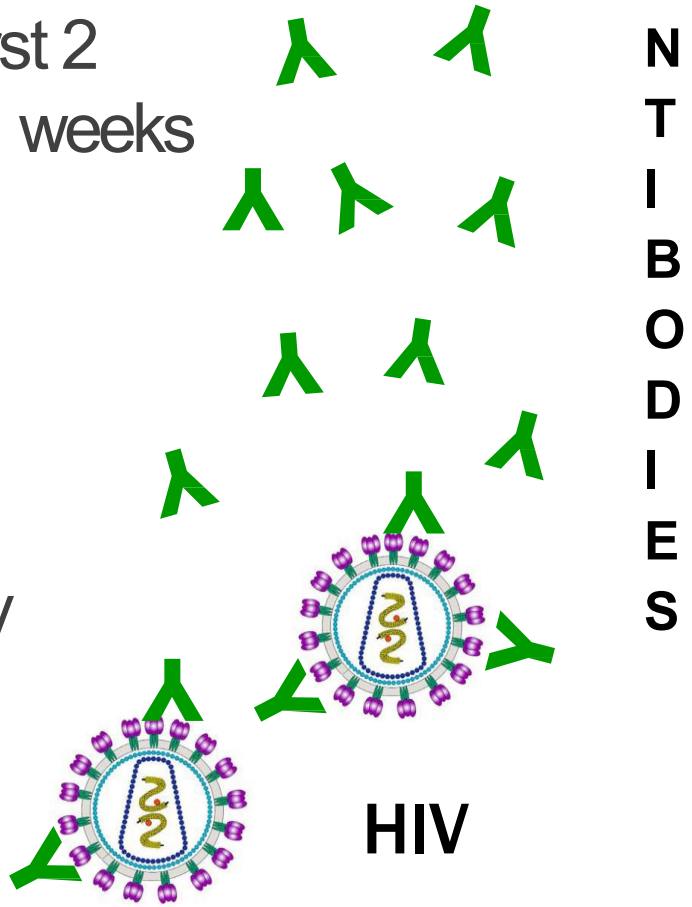
Adaptive = Acquired

- Antigen-specific defense mechanism
- Takes several days to become protective
- Develops throughout life

Adaptive – Part 1

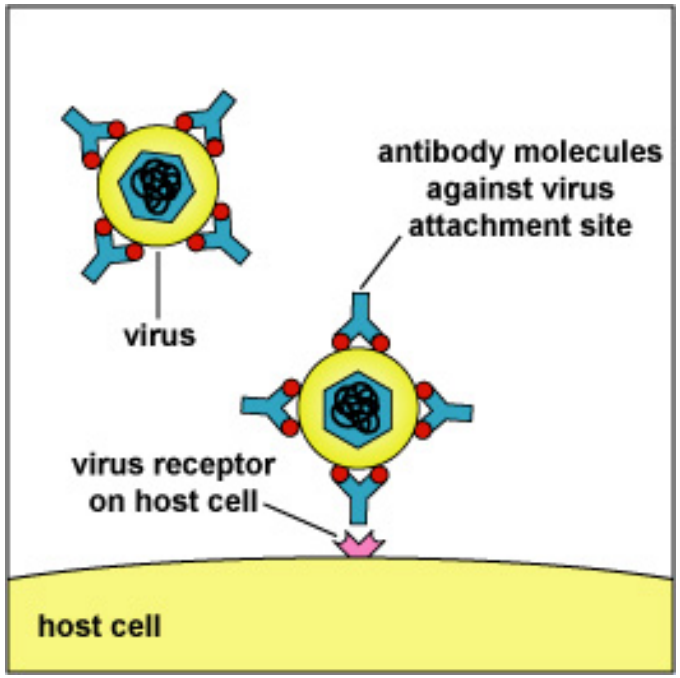
Humoral = Antibodies

- Antibodies are made by B cells in the first 2 days after infection, but usually takes 2 weeks for full effect
- Antibodies neutralize or stop the virus
- Antibodies help eliminate the virus
- Antibodies can prevent infection
- Antibodies have immunological memory



How Do Antibodies Prevent Infection?

1st way: Neutralization



Neutralization:

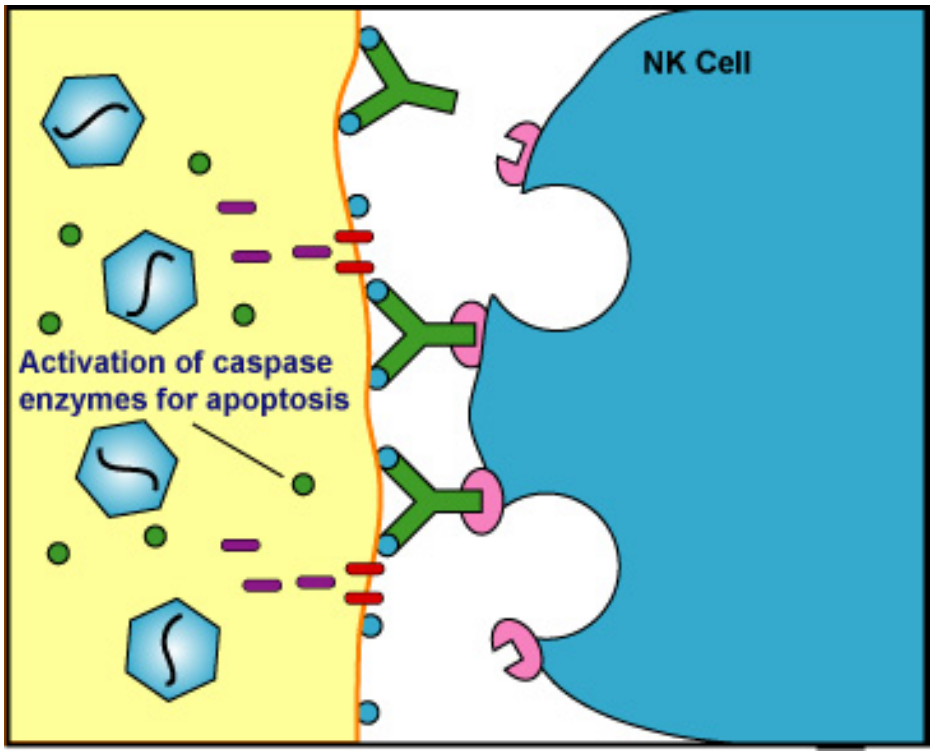
Antibody prevents the virus from attaching to the host cell

2nd Example: Binding Antibodies
Antibody Dependent Cellular Cytotoxicity (ADCC)

- Natural Killer (NK) cells may also be able to act like a CD8 killer Tcell ("a hitman")
- They need a binding antibody attached to the virus to act like a "lookout"
- With the lookout in place, the NK cell can identify the virus infected cell and kill it

How Do Antibodies Help Clear Infection?

Antibody Dependent Cellular Cytotoxicity (ADCC)



ADCC:

uses other cells of the immune system to destroy virus infected cells

Humoral Response – Summary

- Antibodies attach to the virus at sites that are used by the virus for entry into cells.
- Neutralizing antibodies can work alone to block a virus from entering cells.
- Vaccines designed to elicit neutralizing antibodies against HIV have not worked very well in trials so far, but work against other viruses such as influenza, and possibly (?) SARS CoV-2.
- Recent discoveries of several broadly neutralizing antibodies are very exciting, and designing a vaccine to produce these antibodies is underway!
- Binding antibodies can attach to HIV and call other parts of the immune system into action to help destroy it.

Adaptive Part Two - Cellular

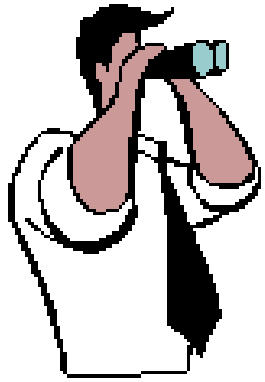
- Cellular response involves two types of cells:
  1) Helper T lymphocytes ($CD4^+$)
  2) Cytotoxic T lymphocytes (CTL or $CD8^+$)
- Have memory!
- Activated once infection occurs

The Two Types of Cells

- **$CD4^+$ cells recognize virus and help cells communicate with each other, calling the killers into action**

- **$CD8^+$ cells are the killers**

How Does the Adaptive Response Work?



- T-cell function: immunosurveillance
- Checks other cells of the body (are they infected or abnormal?)
- Destroys infected or abnormal cells

Adaptive Response – Summary

Cellular = Cytotoxic T lymphocytes (CTL or CD8+) and helper T lymphocytes (CD4+)

- Cannot prevent infection
- T cells are activated when cells become infected
- T cells can eradicate an established infection
- T cells have immunological memory
- T cells can be primed by vaccination

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Introduction to Vaccinology

Preventive Vaccines

- Used for decades around the world, most commonly in children
- Very safe when manufactured and used properly
- Very cost-effective compared to treatment
- Eliminated smallpox worldwide, soon polio
- 2008: 1st vaccine for girls and young women against a cancer-causing virus, human papilloma virus (HPV), and 2009-10 approval for boys and young men

Vaccine Research in Perspective

VACCINE	DISCOVERY OF VIRUS	VACCINE DEVELOPED FOR HUMAN USE	YEARS TO VACCINE
H. Influenzae-B	1892	1985	93
Herpes (HSV-1)	1919	Not available	>90
Pertussis	1906	1926	20
Polio	1909	1954	47
Yellow Fever	1900	1935	35
Influenza	1933	1945	12
Measles	1911	1957	46
Hepatitis A	1973	1995	22
Hepatitis B	1967	1984	17
HPV	1974	2007	33
HIV	1983	Not available	>30
SARS CoV-2	2019	Not available	???

The Impact of Vaccines in the United States

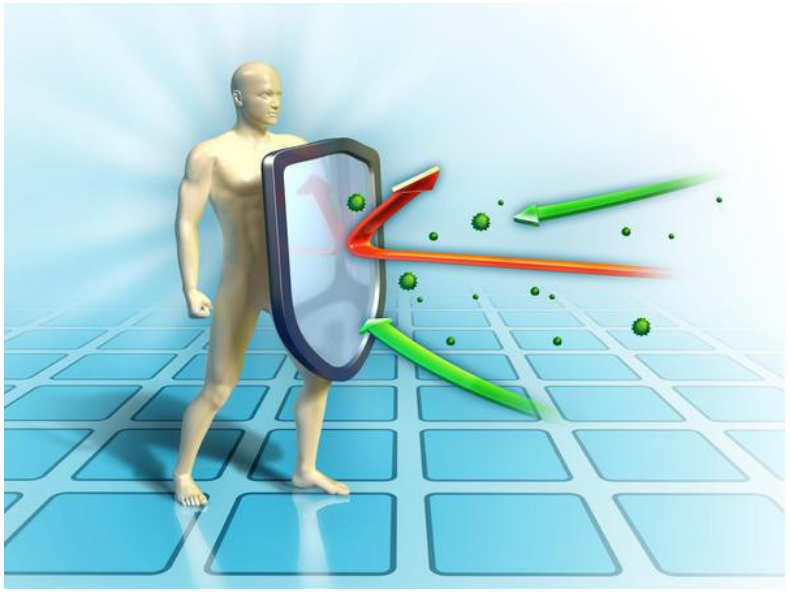
DISEASE	BASELINE 20TH CENTURY PRE-VACCINE ANNUAL CASES	2008 CASES*	PERCENT DECREASE
Measles	503,282	140	99.9%
Diphtheria	175,885	0	100.0%
Mumps	152,209	454	99.7%
Pertussis	147,271	10,735	92.7%
Smallpox	48,164	0	100.0%
Rubella	47,745	16	99.9%
Haemophilus influenzae type b, invasive <5 yrs.)	20,000	30	99.9%
Polio, paralytic	16,316	0	100%
Tetanus	1,314	19	98.6%

*Provisional

Source: *MMWR* 4/2/99, 12/25/09, 3/12/2010

An HIV Vaccine is More Challenging

- The only people who have a natural protective immunity to HIV are those with a genetic mutation to their CCR5 receptor (mostly of Western European ancestry).
- We have to do better than Mother Nature – need to induce "unnatural" protective immunity.
- This immunity needs to be a rapid response, and in all the right locations.

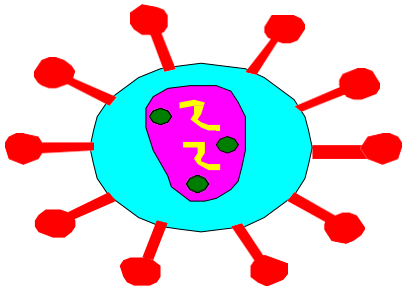


Vaccines Explained

- A vaccine can be **preventive**, **therapeutic**, or both
- **Preventive** HIV vaccines for HIV-negative populations are being developed to control the spread of HIV and are not a cure for AIDS
- Researchers are also evaluating **therapeutic** vaccines to treat people who are already HIV+ or living with AIDS

How Does a Vaccine Work?

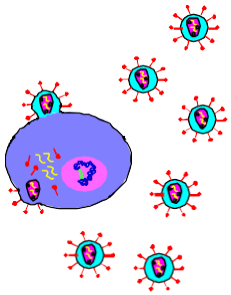
By teaching the body to recognize and fight invaders.



Body Recognizes HIV Virus

Body – Sounds Alarm

Fighter Cells Go Into Action

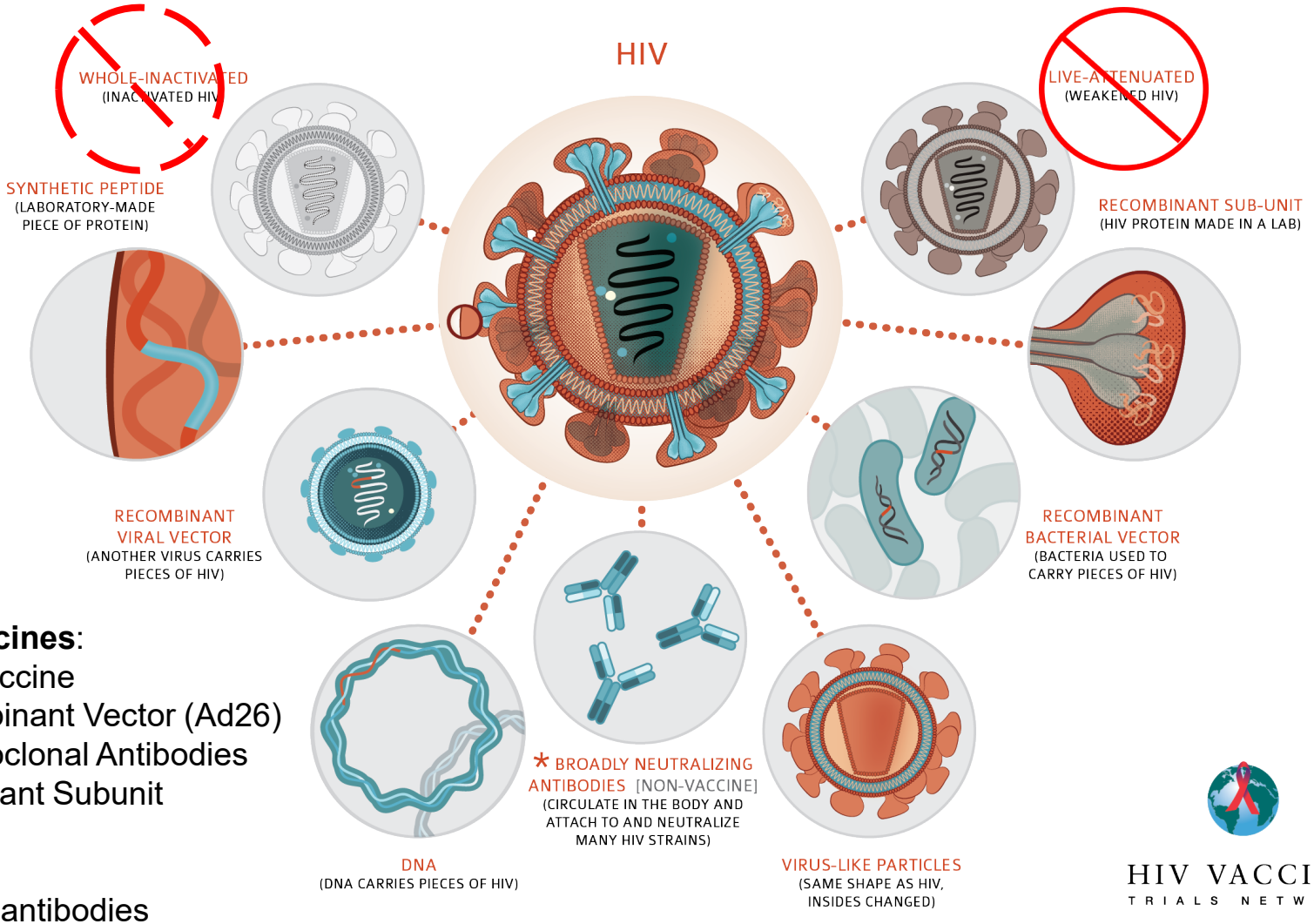


GOAL - HIV is controlled or killed

Traditional Approaches for Developing a Vaccine

- Live attenuated vaccines
- Whole virus inactivated vaccines
- Challenging for HIV - hard to manufacture, and have caused disease in animals

Vaccine and Related* Designs



SARS CoV-2 Vaccines:
Moderna: RNA vaccine
Janssen: Recombinant Vector (Ad26)
Regeneron: Monoclonal Antibodies
Sanofi: Recombinant Subunit

HIV Vaccines:
AMP: Monoclonal antibodies
Janssen: Ad26 prime protein boost

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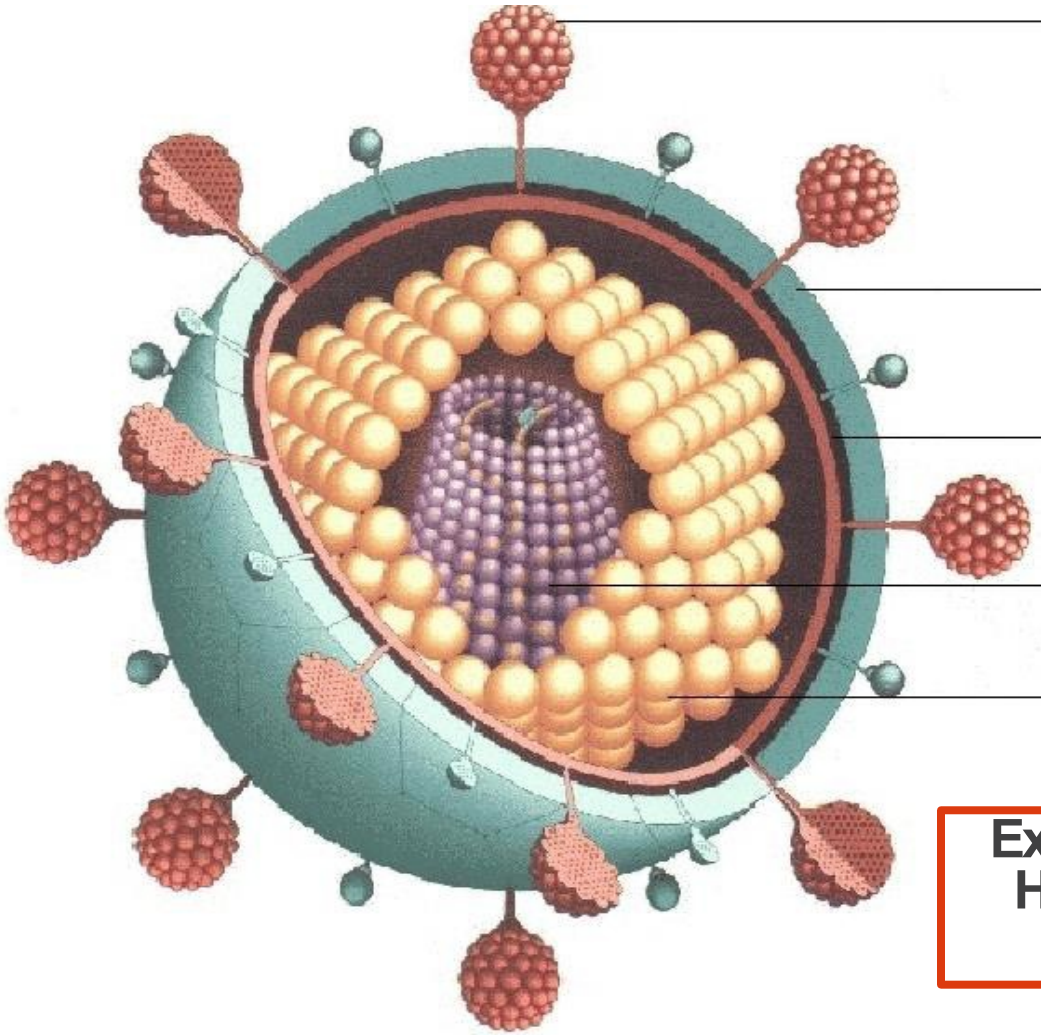
DESIGNING HIV VACCINES

Variables in HIV Vaccine Development

- **Vaccine modality:** whole killed, attenuated, DNA, peptide, recombinant proteins, VLPs, viral vectors (vaccinia, MVA, VSV, Ad, HSV, canarypox, etc.), chimeras
- **Gene(s):** *env, gag, tat, nef, rev, pol, vif, vpu, vpr,* mosaics
- **Adjuvant:** alum, cytokines, MF-59, GM-CSF, etc.
- **Dose**
- **Route:** intradermal, intramuscular, etc.
- **Timing:** how many injections, how far apart
- **Methods of administration:** needle and syringe, Biojector, using electroporation, etc.

HIV Viral Structure



Proteins on the viral envelope (e.g. gp120)

Membrane or envelope (env)

Matrix proteins

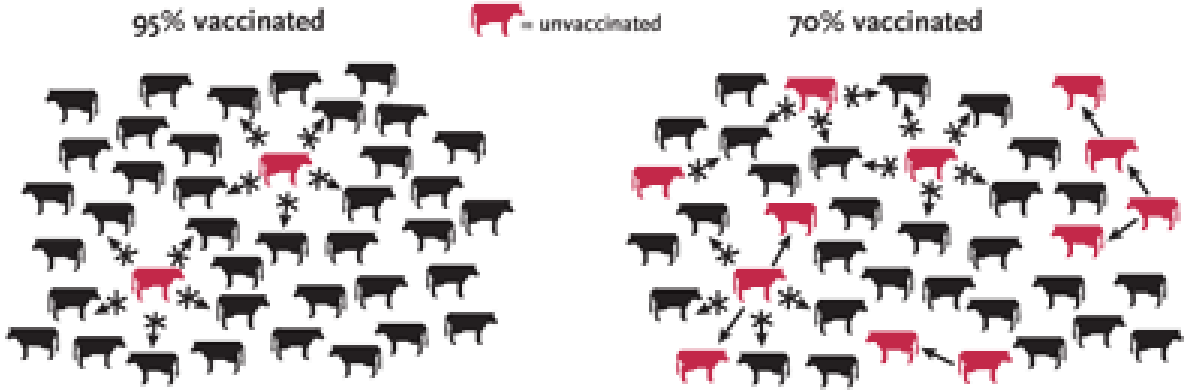
Nucleus (genes) (e.g., Gag, Pol, Nef, Tat)

Core proteins (e.g. p24, p17)

Experimental vaccines tested in the HVTN today do *not* include whole, killed or weakened HIV

HOW AN HIV VACCINE MIGHT WORK

What Might a Preventive HIV Vaccine Do?



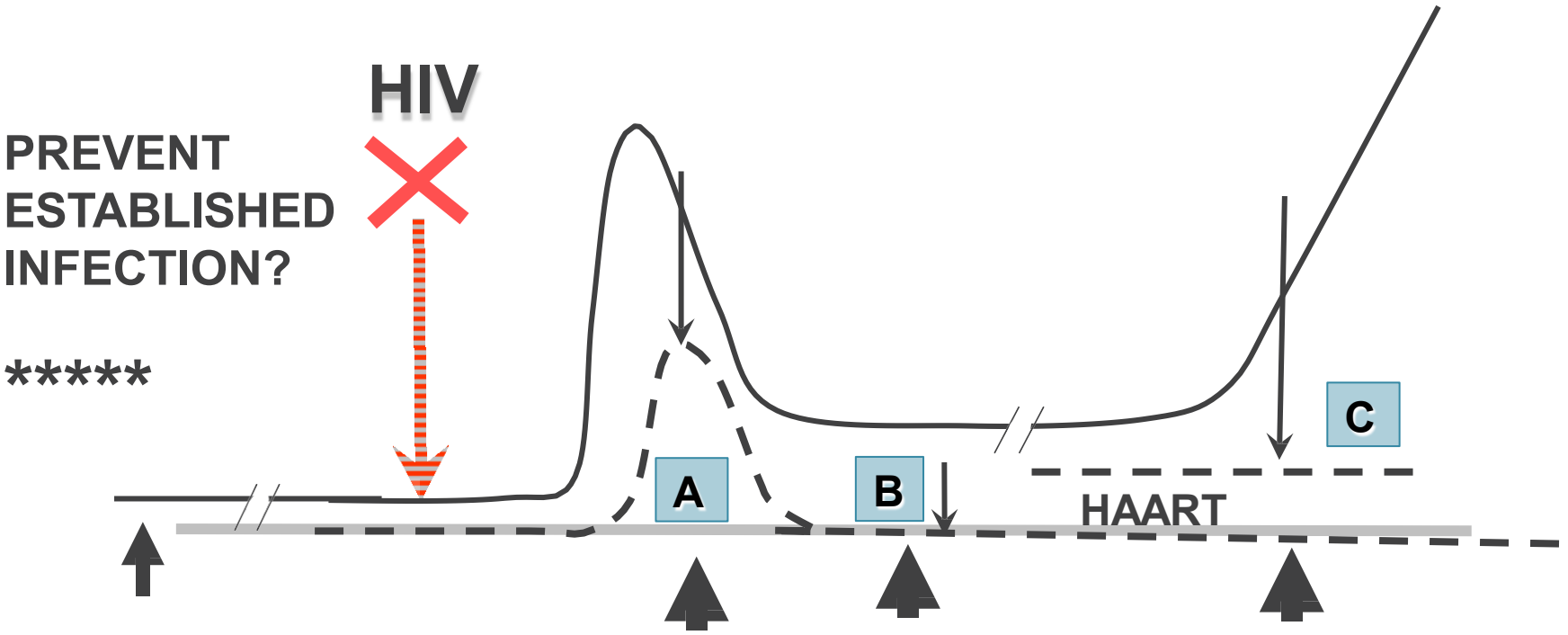
Benefits for the person who gets the vaccine:

- Prevent infection
- Prevent disease
- Delay disease progression

Benefits for the entire community:

- Prevent further transmission
- Create“herd” immunity

How an HIV Vaccine Might Work



A. Lower Initial Peak of Viremia

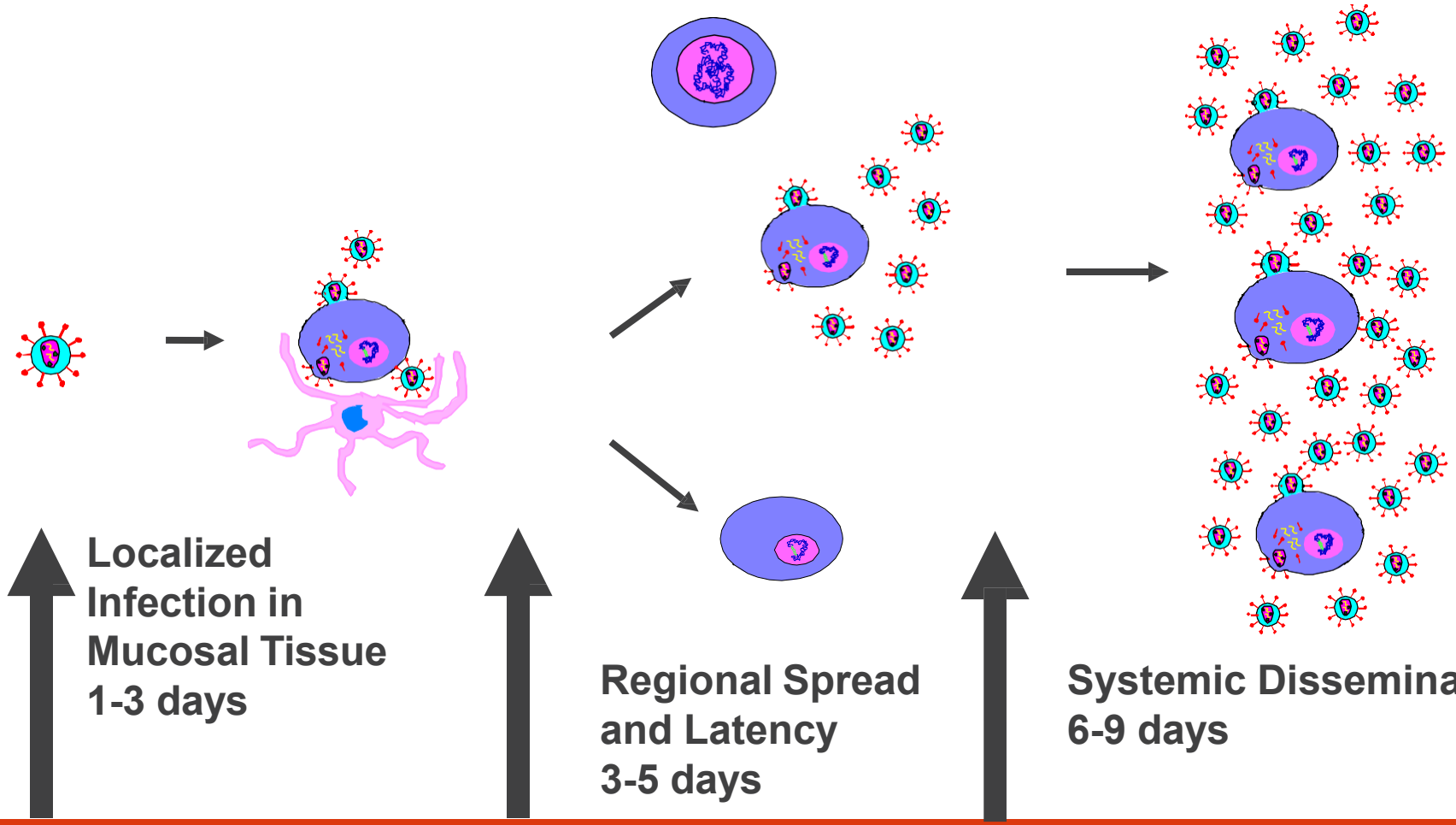
B. Lower Set Point

C. Stop Progression

- ***Effective in most people?***
- ***Effective in some people?***

Solid line – viral load in natural HIV infection
Dotted line – potential changes due to vaccination

What is the Time Frame for these Immune Responses?



TRYING NEW IDEAS

Antibody infusions

All infected people make neutralizing antibodies, but not all antibodies are created equal....

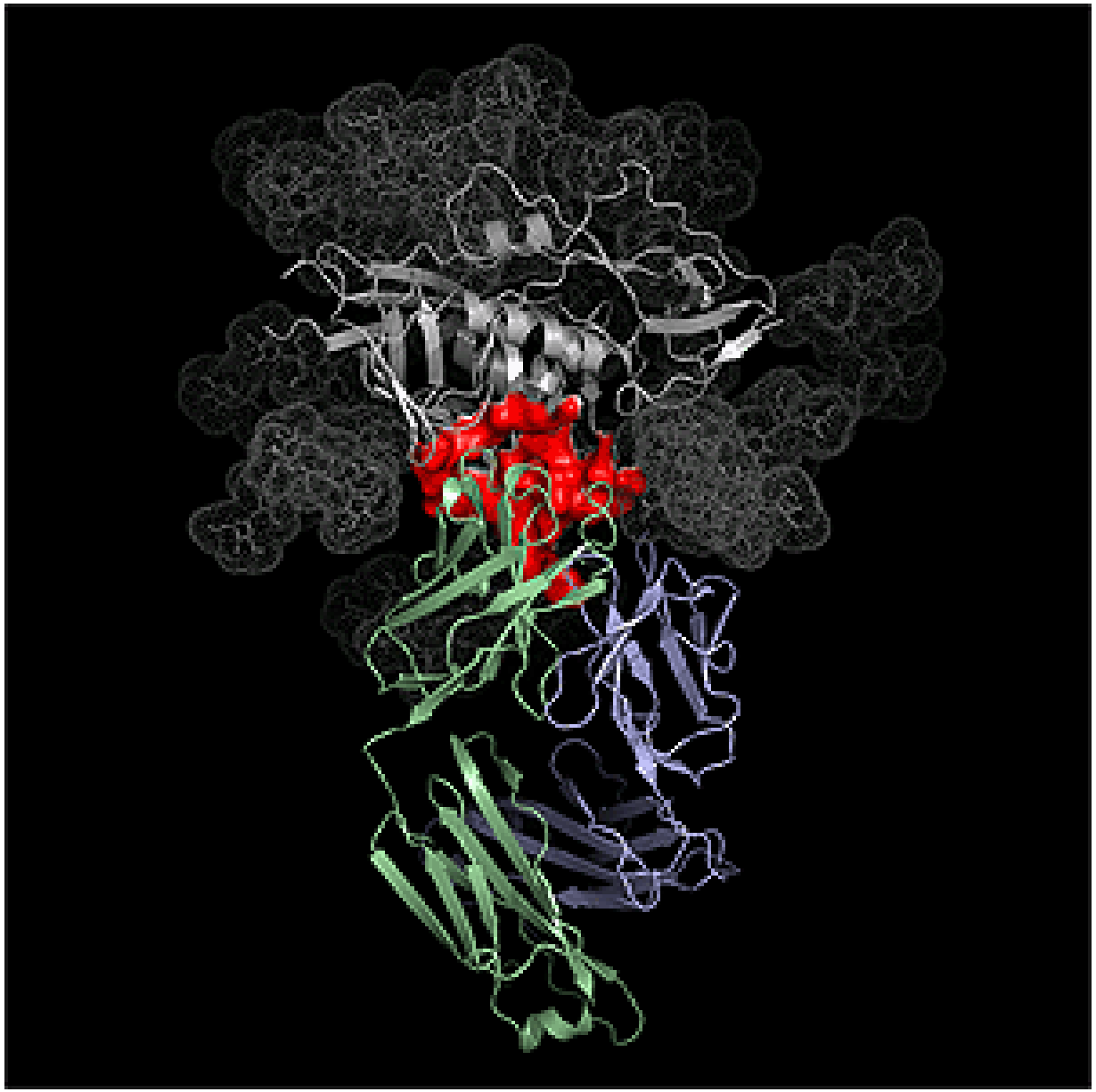
Strain-specific antibodies

Broadly Neutralizing antibodies

With thanks to Prof. Penny Moore

Gray-
Gp120

Red-
the CD4 binding site on gp120

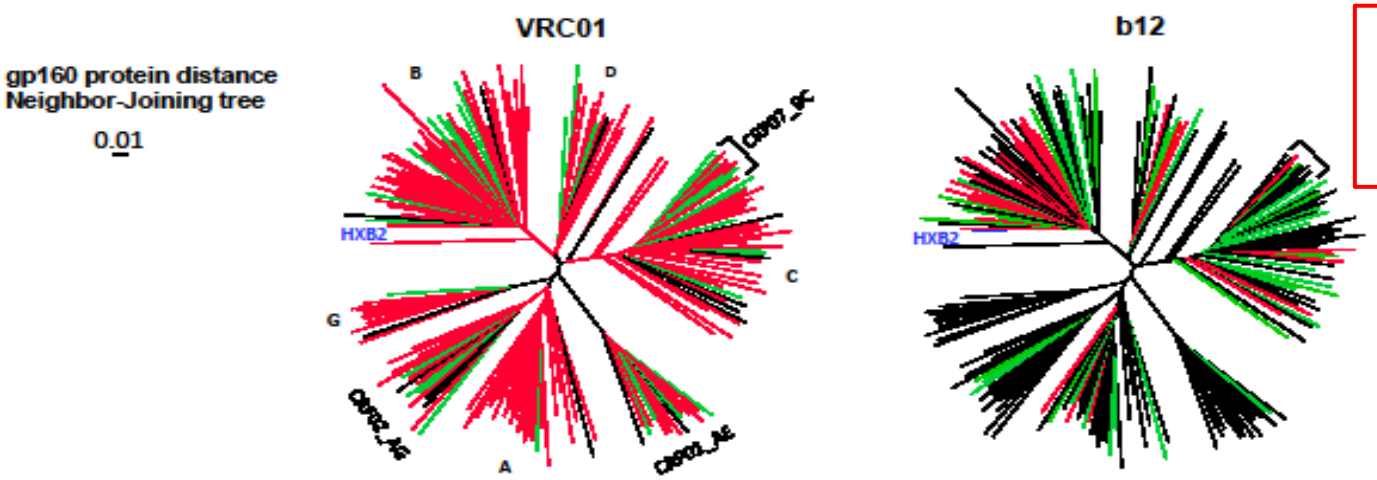


Green & Purple – the VRC01 antibody attached to the CD4 binding site

Image Credit:
NIAID Vaccine Research Center

Panel of 190 Diverse Viral Isolates

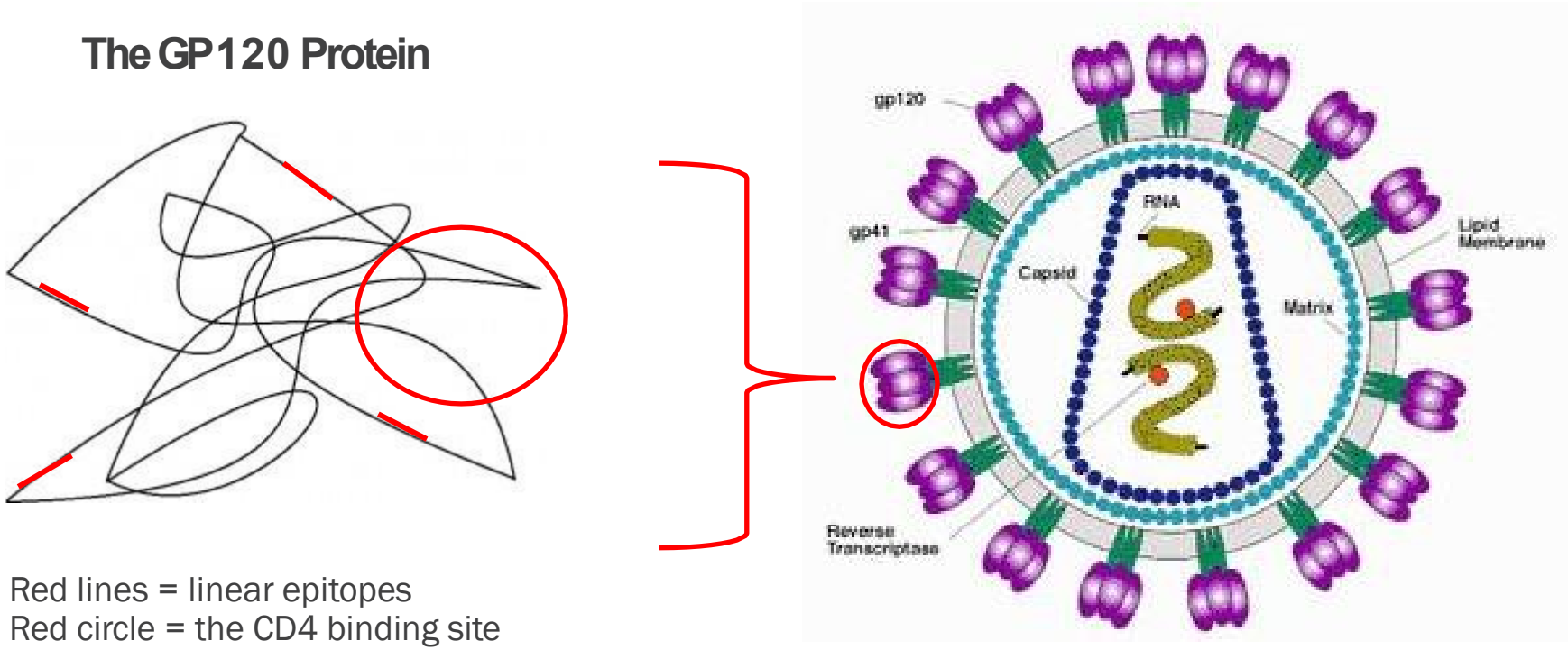
Mike Seaman



Virus clade	Number of viruses	IC_{50} < 50 µg/ml		IC_{50} < 1 µg/ml	
		VRC01	b12	VRC01	b12
A	22	100%	45%	95%	23%
B	49	96%	63%	80%	39%
C	38	87%	47%	66%	13%
D	8	88%	63%	50%	25%
CRF01_AE	18	89%	6%	61%	0%
CRF02_AG	16	81%	19%	56%	0%
G	10	90%	0%	90%	0%
CRF07_BC	11	100%	27%	45%	9%
Other	18	83%	33%	78%	6%
Total	190	91%	41%	72%	17%

With thanks to
Dr. Barney Graham

What do these antibodies do? Example: VRC01 attaches to the CD4 binding site on gp120



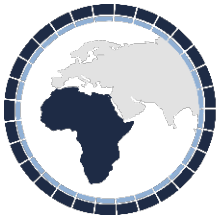
Red lines = linear epitopes
Red circle = the CD4 binding site

Image credit: NIAID

HVTN 703/HPTN 081
HVTN 704/HPTN 085

Study Schema for The AMP Studies

REGIMEN	HVTN 704/HPTN 085 MSM & TG in the Americas & Switzerland	HVTN 703/HPTN 081 Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	500	1300	10 infusions total; Infusions given every 8 weeks **Study duration: ~22 months**
VRC01 30 mg/kg	900	500	1300	
Control	900	500	1300	
Total	2700	1500	4200	



HVTN 130

- Antibody infusion trial with different combinations of antibodies:
- Antibodies can work with each other to increase coverage of circulating viruses
- Need to see how compatible they are with each other.
- Goal: could a ”cocktail” of antibodies provide lasting protection from infection

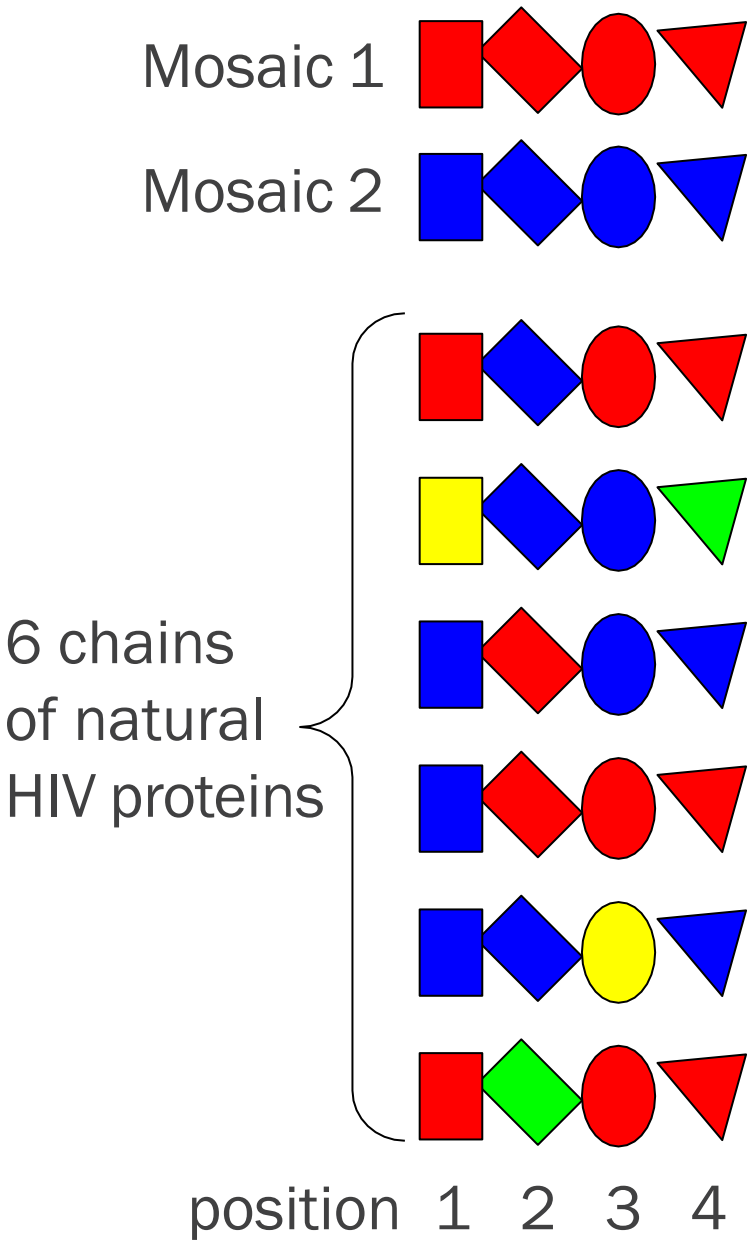
Mosaics Are Chains of Proteins

- A protein is a chain of amino acids, each one like a bead in a necklace. The mosaic sequence tells your cells which amino acid to include and where it goes in the chain.

- This mosaic chain is designed to look like the HIV proteins that are most likely to be seen if the body is exposed to HIV.

An Example

- Position 1 & 2: blue is most common, red is 2nd most common
- Position 3 & 4 are opposite
- The mosaics use the most common proteins and the 2nd most common
- The final 2 mosaics may not look anything like the natural chains
- Using several mosaics together in a vaccine gives you the broadest coverage of what might occur naturally



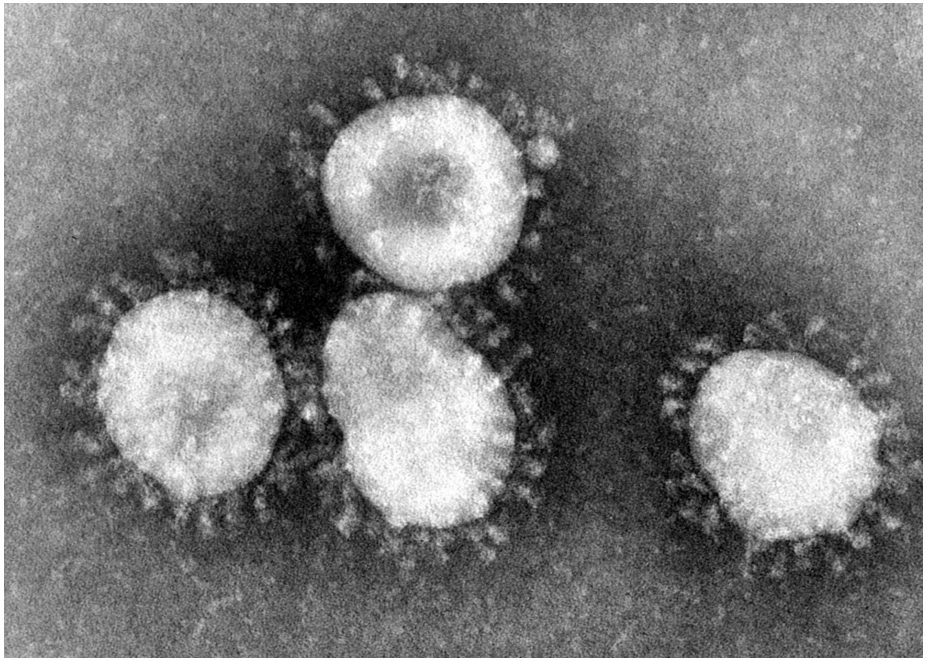
HVTN 706 “Mosaico”

- “Heterologous” prime boost
- AD26.Mos5.HIV (GagPol and ENV DNA insert)
  - Low incidence of pre-exposure to Adenovirus 26
- Gp140 protein boost (clade C and Mosaic)
- Efficacy trial: 1900 participants in each arm (vaccine vs placebo)
- M0 M3 (Ad26.Mos4.HIV)
- M6 M12 (Ad26.Mos4.HIV+gp140)

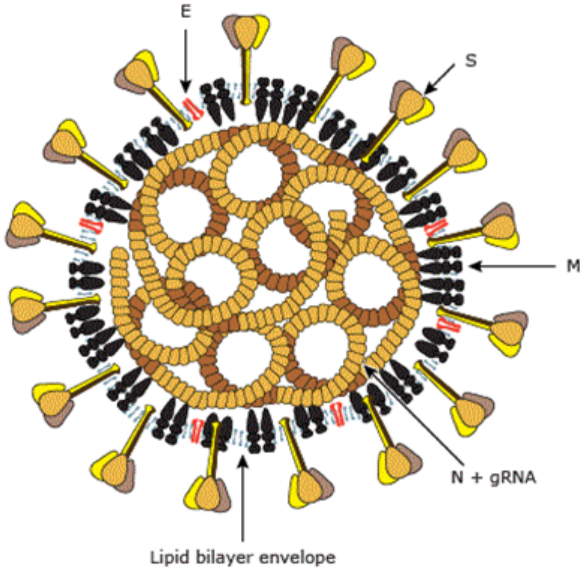
Take-Home Messages

- Antibody-mediated prevention (AMP) using broadly neutralizing antibodies could be another way to prevent HIV infection.
- Trials of AMP may also teach us more about vaccine design: which antibodies are protective, how much of them do we need, etc.
- Mosaic - a way of teaching your body to recognize common HIV proteins, used as an HIV insert, currently being tested in HVTN 106, HVTN 706 currently enrolling

Coronavirus structure



Model of coronavirus structure: A schematic diagram of virion structure



Schematic showing the major structural proteins of the coronavirus virion.

S: spike protein; M: membrane protein; E: envelope protein; N: nucleocapsid protein.

Compare and contrast HIV and SARS CoV-2

HIV-1 and SARS CoV-2 Similarities:

- RNA viruses: coronaviruses are the largest RNA viruses, genome 3x larger than HIV
- Enveloped viruses: lipid envelope, inactivated with detergent
- Each came from animal reservoirs: HIV from non-human primates, CoV-2 from bats or pangolins.

Compare and contrast HIV and SARS CoV-2

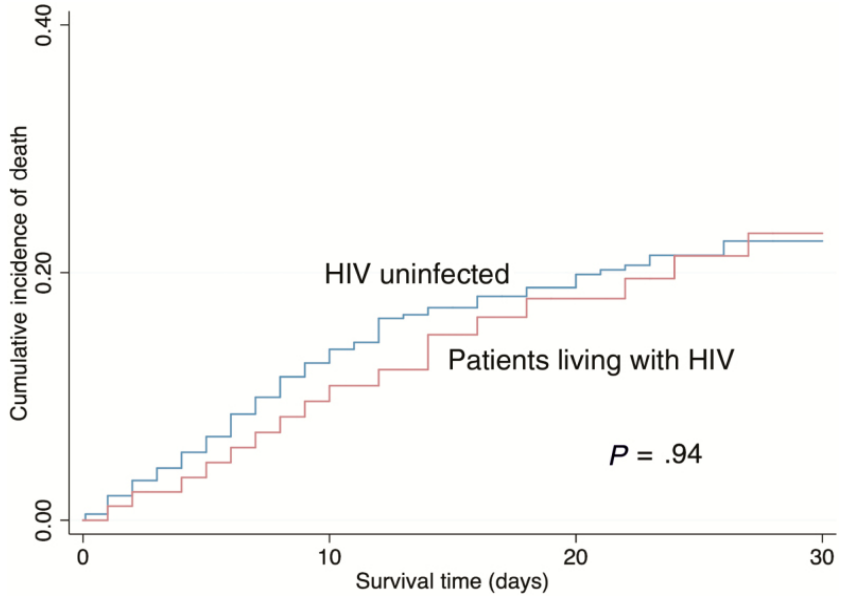
HIV-1 and SARS CoV-2 Differences:

- HIV-1 much more variable, multiple species in the host "quasispecies"
- HIV-1 is a retrovirus, integrates into the host genome and establishes chronic infection (no known instance of spontaneous clearance)
- HIV-1 blood transmission
- CoV-2: Respiratory spread
- CoV-2: an "acute" viral infection, cleared by the host (no integration, no latent reservoir)

Theoretically makes the path to a vaccine easier

SARS CoV-2 infection of HIV infected individuals:

- 88 PWH in NYC hospitalized with CoVID-19
- one PWH matched with up to five patients by age, sex, race/ethnicity and calendar week of infection
- no differences in adverse outcomes associated with HIV infection for hospitalized COVID-19 patients compared to a demographically similar patient group



Sigel et. al. CID 2020

Current SARS CoV-2 vaccines in testing or about to be tested at Vanderbilt:

Moderna:

- RNA vaccine (makes the Spike protein)
- 2 Doses (28 days apart)
- 30,000 participants, fully enrolled (about 500 at VUMC)
- Enrollment complete

Janssen:

- Ad26 vector (shell from Adenovirus, makes the spike protein)
- Single Dose
- About to start, 60,000 national participants, will be at Vanderbilt (Creech)

Current SARS CoV-2 vaccines in testing or about to be tested at Vanderbilt:

Regeneron

- Monoclonal antibody study
- Single dose
- Household contacts of individuals living with someone known to have CoVID-19 infection
- 2,000 participants (26 at VUMC)

Sanofi:

- Protein vaccine
- 2 Doses
- 30,000 participants
- 150 at VUMC (Kalams) Covidvaccine@vumc.org
- Anticipated in December 2020

Other SARS CoV-2 vaccines in testing:

Novavax (Meharry):

- Spike protein vaccine
- 2 Doses (21 days apart)
- Not open yet in US

Pfizer:

- mRNA Vaccine
- 2 doses (21 days apart)
- 40,000 national participants

Summary and ongoing questions (opinions)

- Several SARS CoV-2 phase 3 trials enrolled and/or ongoing
- Landscape/ability to do trials may change depending on interim analysis, or whether emergency use authorization granted (Pfizer and/or Moderna)
- No increased risk of death from CoVID among HIV infected individuals
- HIV infected individuals were enrolled in Moderna. Discussions regarding inclusion of HIV+ individuals in newer trials ongoing

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