HIV VACCINE
TRIALS NETWORK

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Immune Responses to Viruses and HIV Vaccine Trial Update

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Objectives:

- Overview of the immune response
- Understanding how the immune system fights viral infections
- Recent results, and Upcoming HIV 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

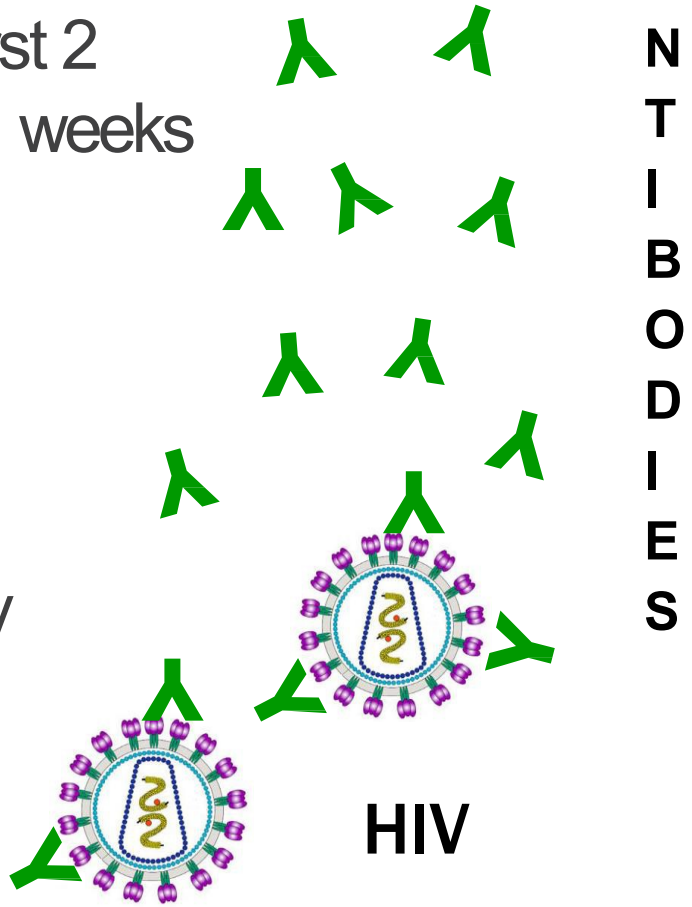
Adaptive = Acquired

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

Adaptive – Part 1

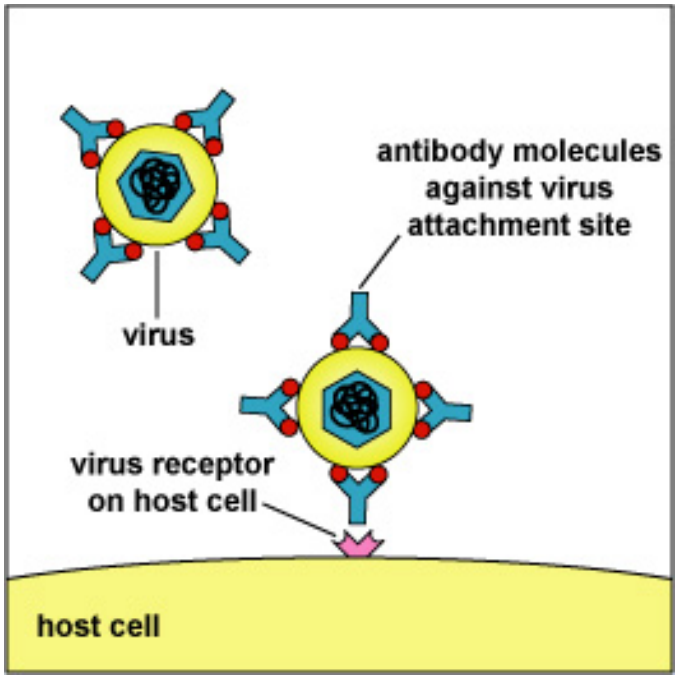
Humoral = Antibodies

- 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

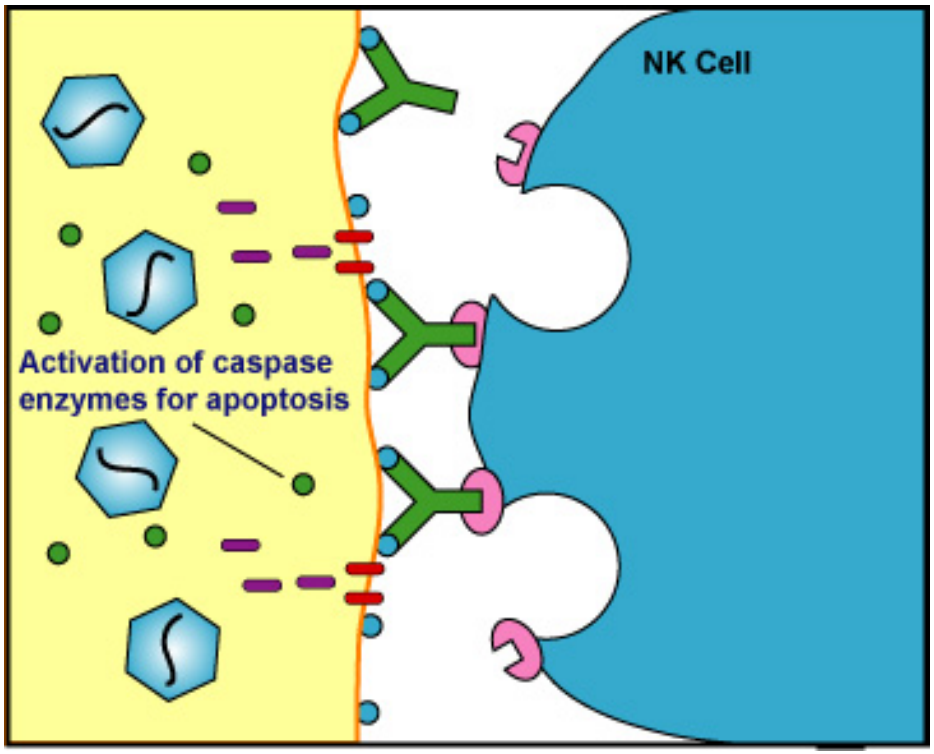
Tested in Antibody-mediated prevention trials (AMP)

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 probably 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

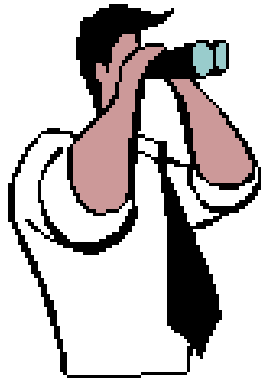
- Cellular response involves two types of cells:
  1) Helper T lymphocytes ($CD4^+$)
  2) Cytotoxic T lymphocytes (CTL or $CD8^+$)
- Have memory!
- Activated once infection occurs

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

HIV VACCINE
TRIALS NETWORK

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-1	2003	N/A	
SARS CoV-2	2019	2020	<1 (!)

The Impact of Vaccines in the United States

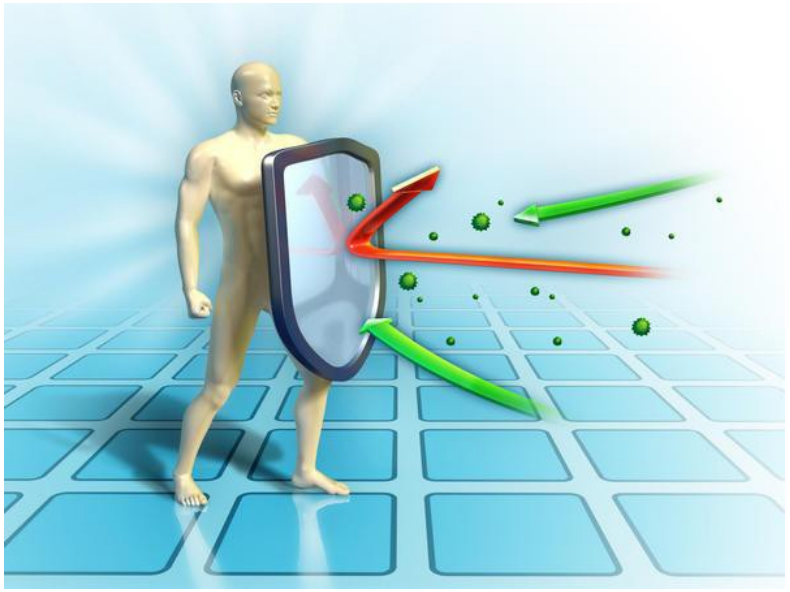
DISEASE	BASELINE 20TH CENTURY PRE-VACCINE ANNUAL CASES	2008 CASES*	PERCENT DECREASE
Measles	503,282	140	99.9%
Diphtheria	175,885	0	100.0%
Mumps	152,209	454	99.7%
Pertussis	147,271	10,735	92.7%
Smallpox	48,164	0	100.0%
Rubella	47,745	16	99.9%
Haemophilus influenzae type b, invasive <5 yrs.)	20,000	30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

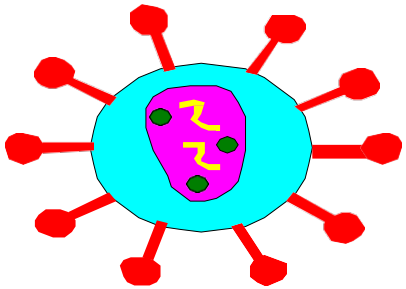


Vaccines Explained

- 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?

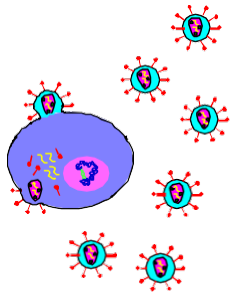
By teaching the body to recognize and fight invaders.



Body Recognizes HIV Virus

Body – Sounds Alarm

Fighter Cells Go Into Action

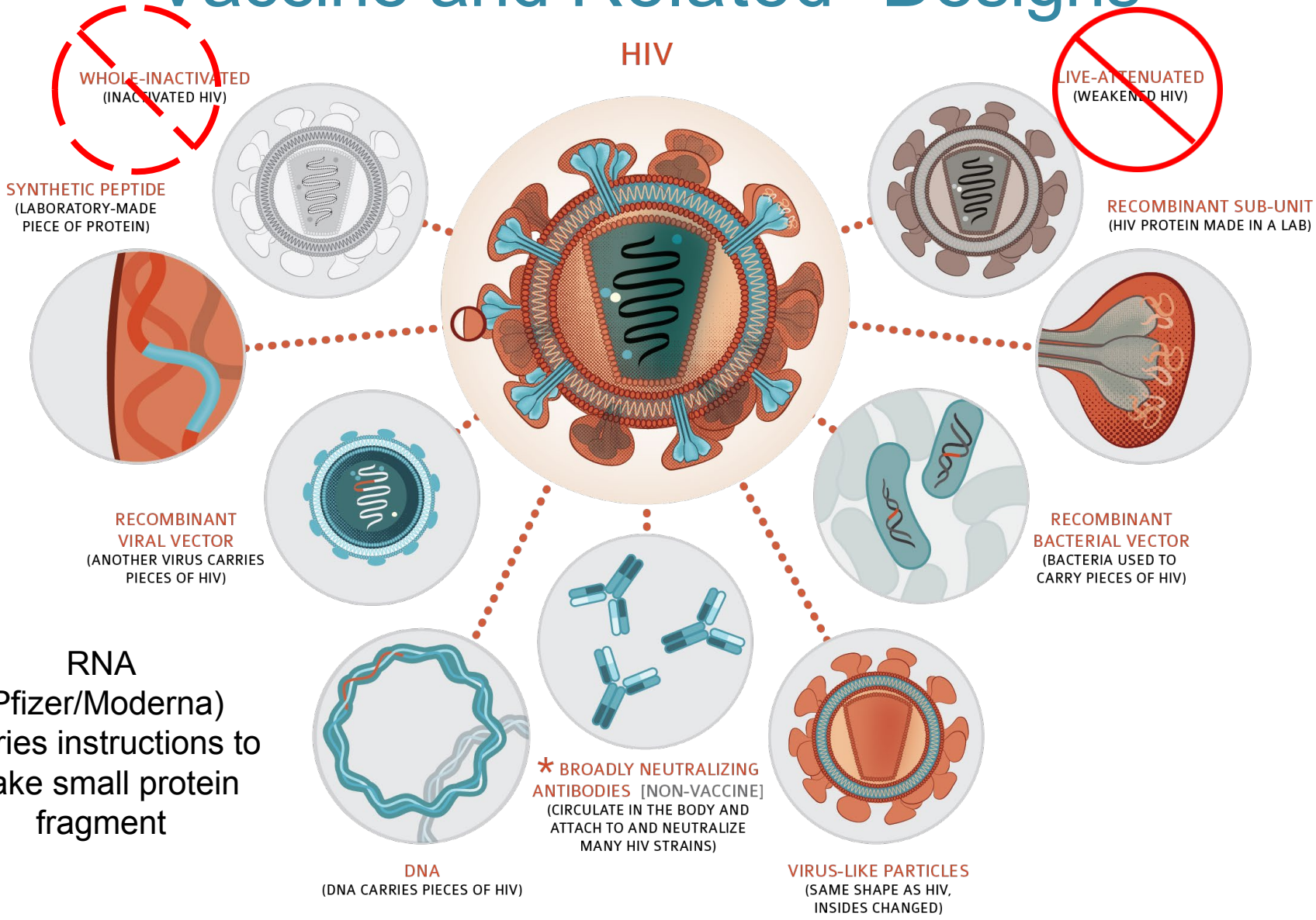


GOAL - HIV is controlled or killed

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



RNA
(Pfizer/Moderna)
Carries instructions to make small protein fragment

Vaccine Strategies

Prime-Boost vaccine strategy

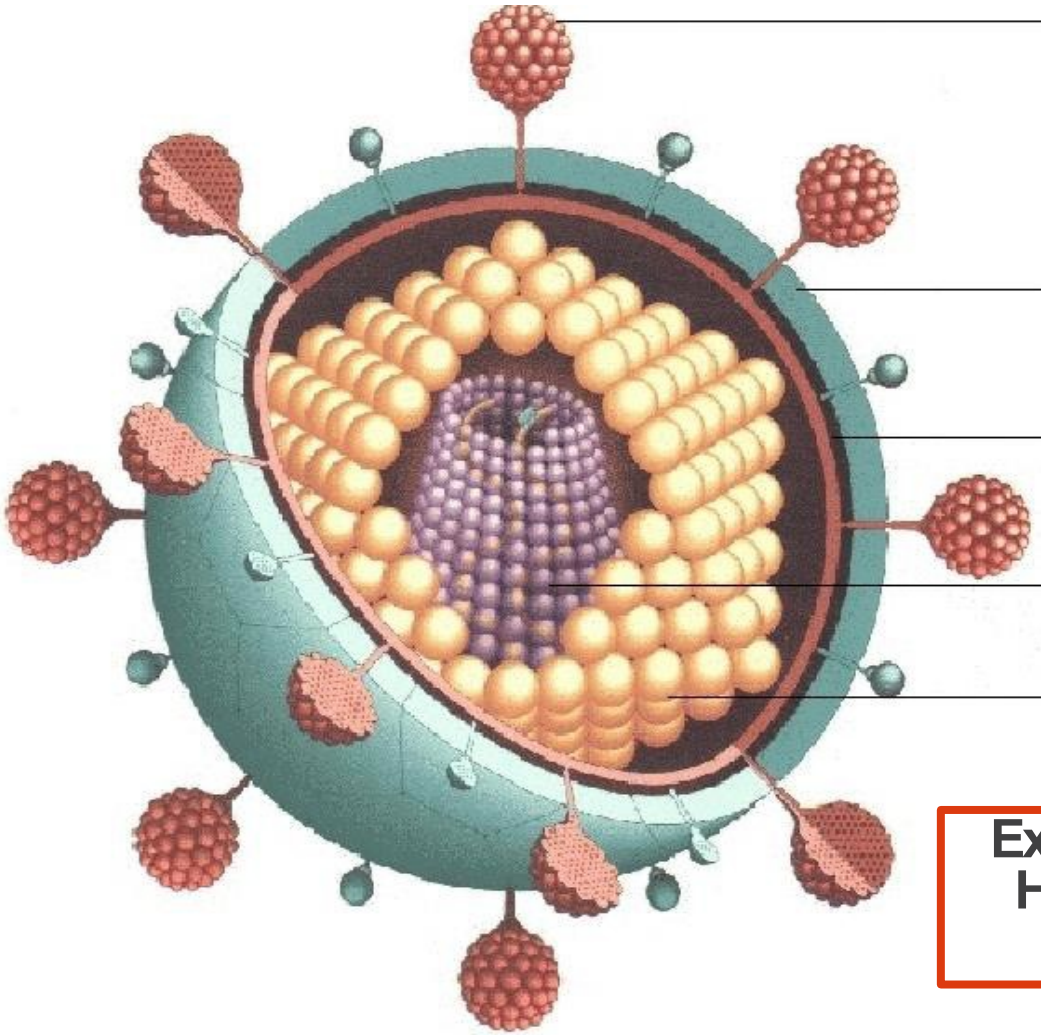
Prime	Boost
Viral vector	Subunit envelope protein
or	or
DNA	Viral vector

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

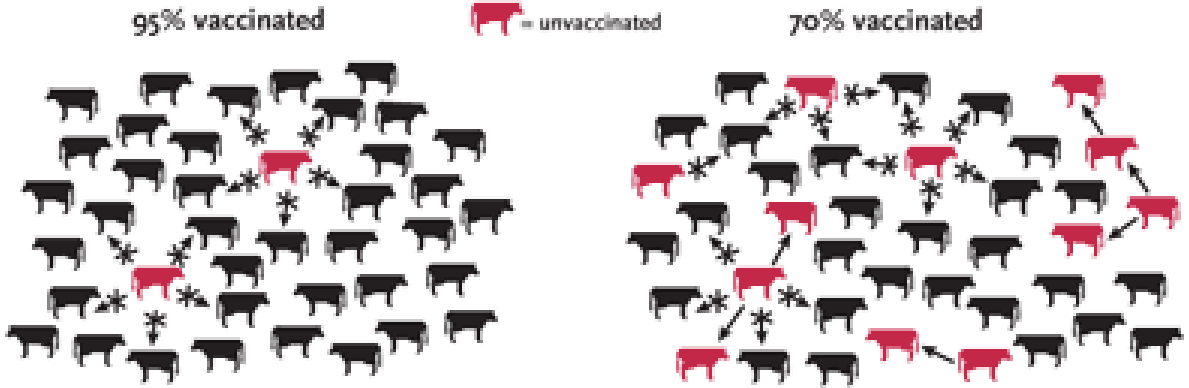
Nucleus (genes) (e.g., Gag, Pol, Nef, Tat)

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?



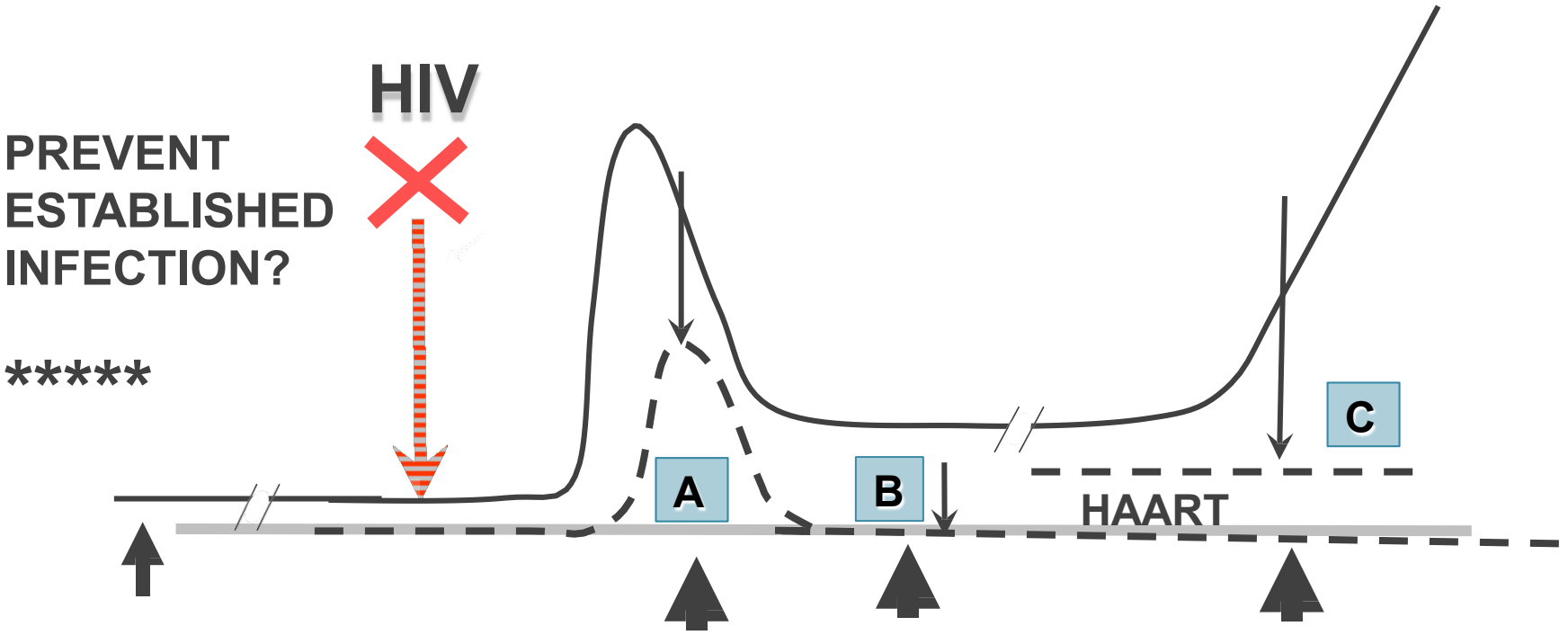
Benefits for the person who gets the vaccine:

- Prevent infection
- Prevent disease
- Delay disease progression

Benefits for the entire community:

- Prevent further transmission
- Create“herd” immunity

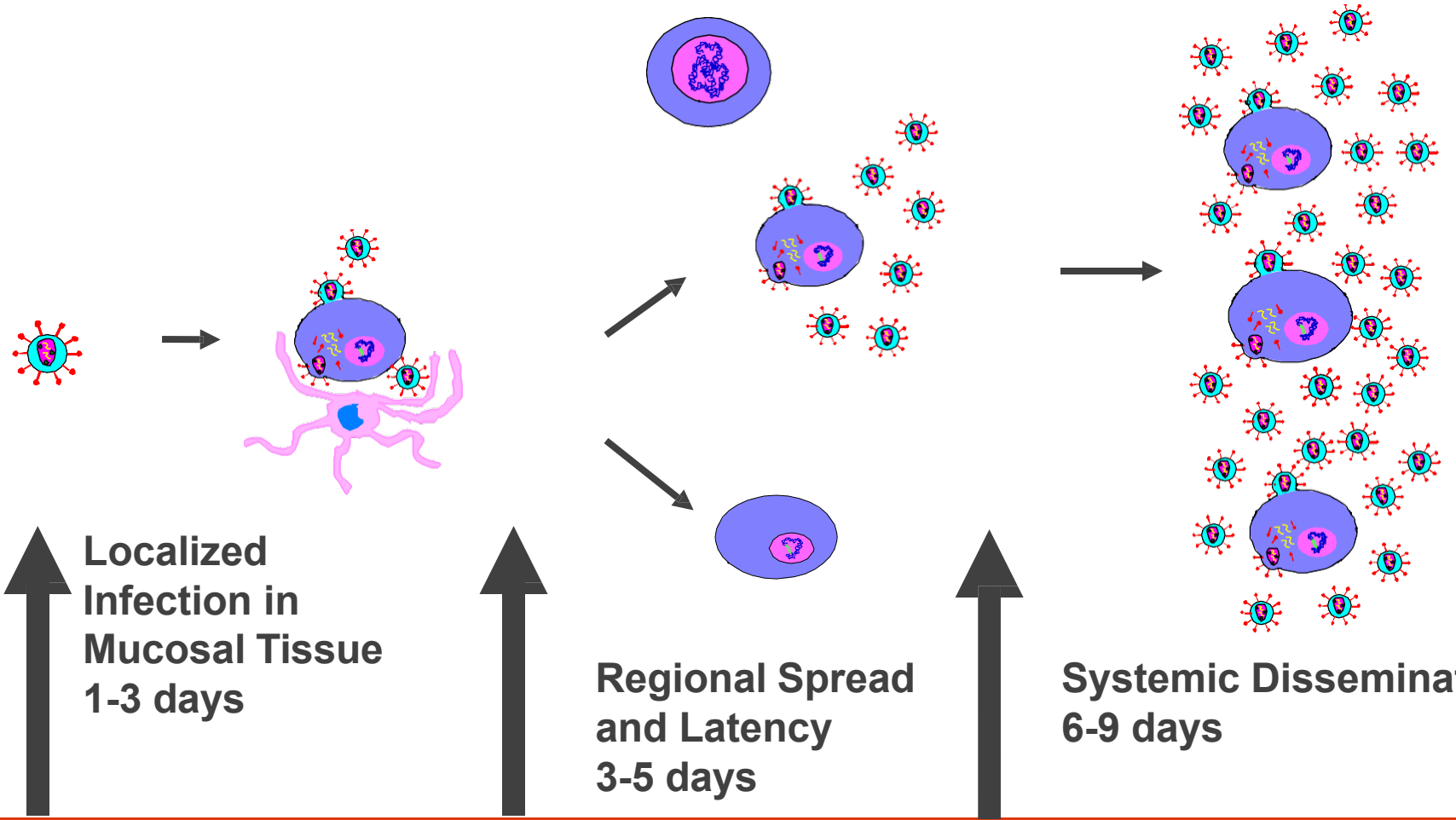
How an HIV Vaccine Might Work



- ***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

New Idea

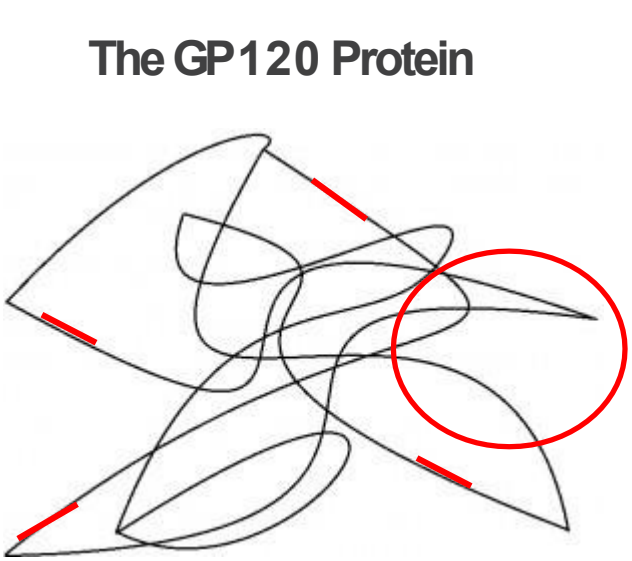
All infected people make neutralizing antibodies, but not all antibodies are created equal....

Strain-specific antibodies

Broadly Neutralizing antibodies

With thanks to Prof. Penny Moore

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

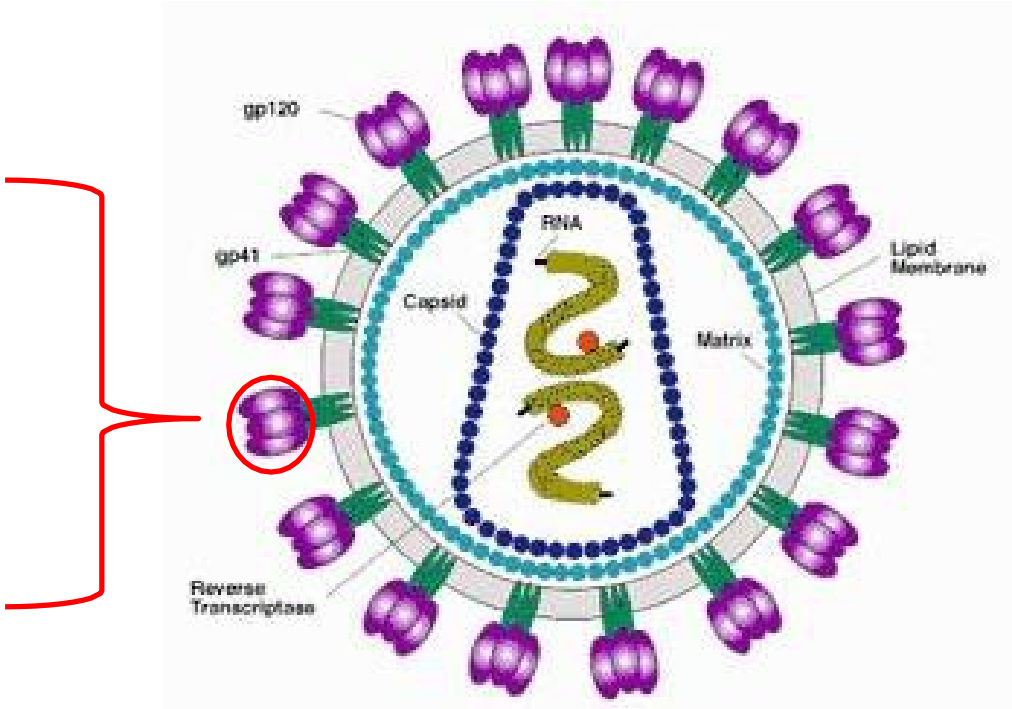
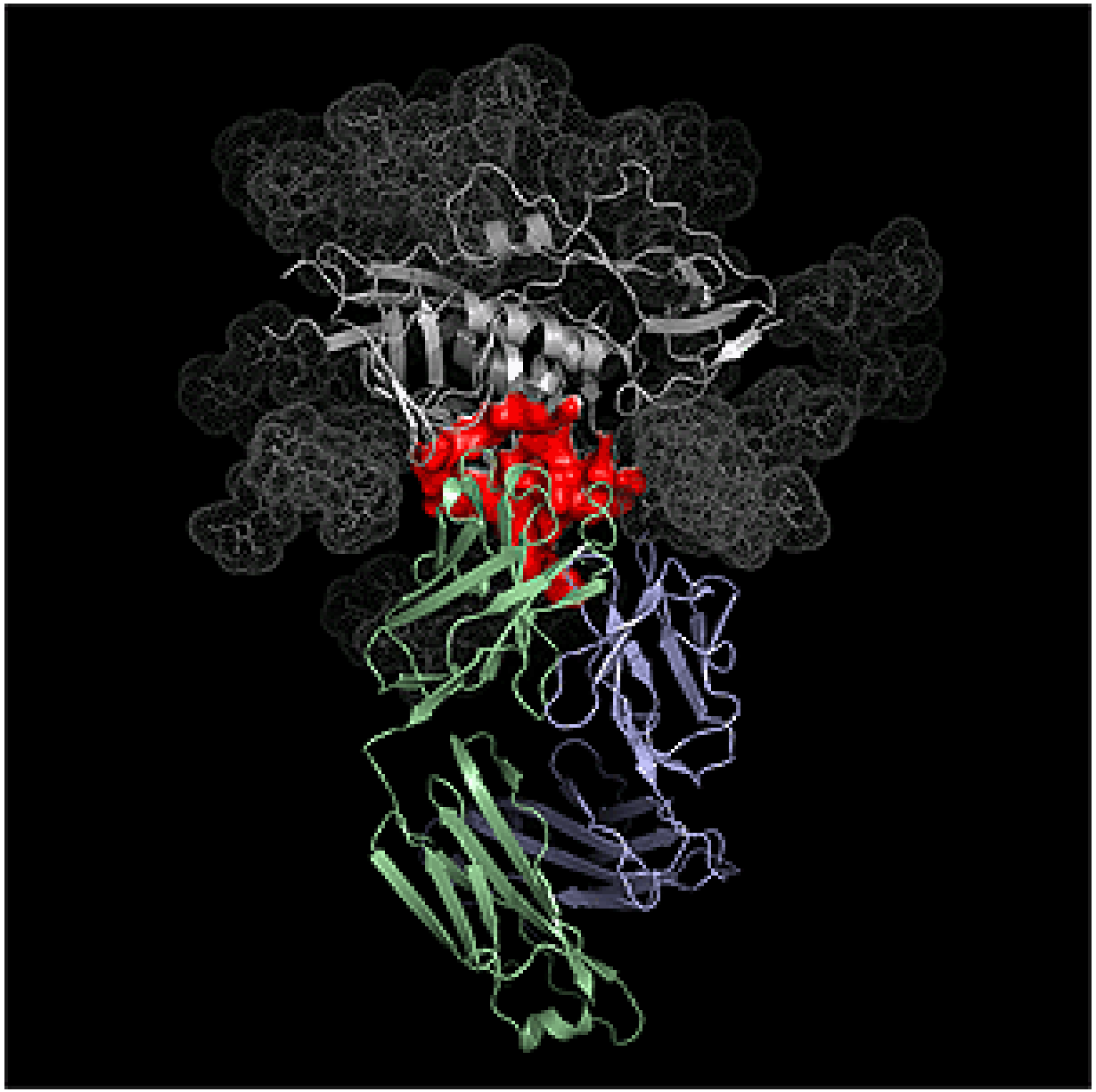


Image credit: NIAID

Gray-
Gp120

Red-
the CD4 binding site on gp120

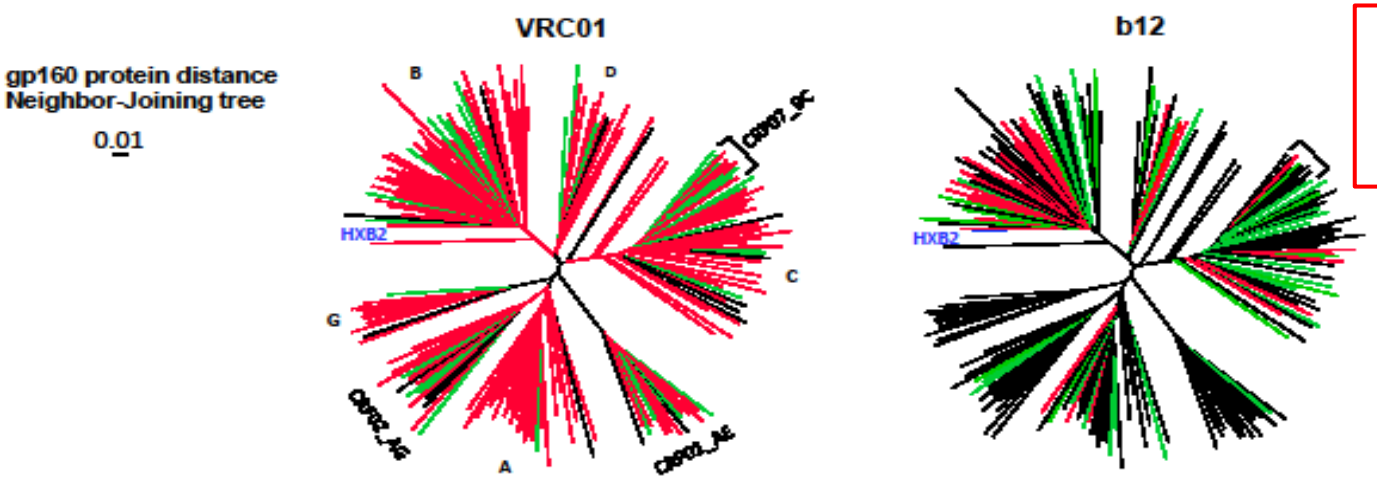


Green & Purple – the VRC01 antibody attached to the CD4 binding site

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%

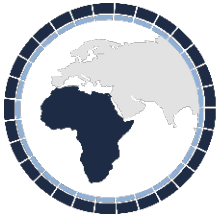
With thanks to
Dr. Barney Graham

HVTN 703/HPTN 081
HVTN 704/HPTN 085

The AMP Studies:
HVTN 703/HPTN 081 & HVTN 704/HPTN 085

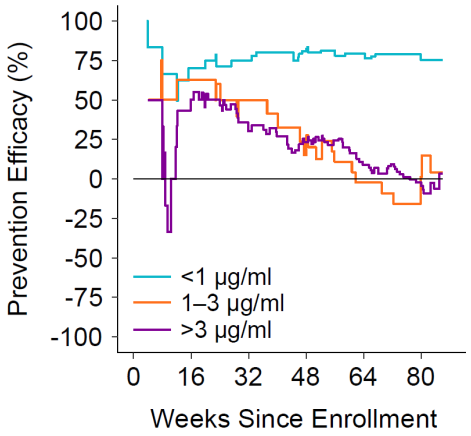
- AMP stands for Antibody Mediated Prevention
- These are the first studies testing whether a broadly neutralizing antibody can prevent HIV infection, and if it can, what dose is needed
- 703/081 enrolled1500 women in sub-Saharan Africa
- 704/085 enrolled 2700 men and transgender people who have sex with men in the Americas and Switzerland

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	

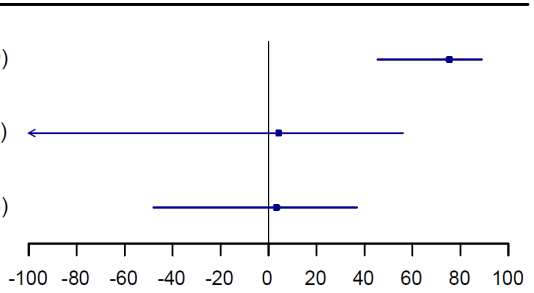
Estimated PE Over Time by IC80 Prevention Efficacy Declines with IC80 Category (Pooled Trials)

A



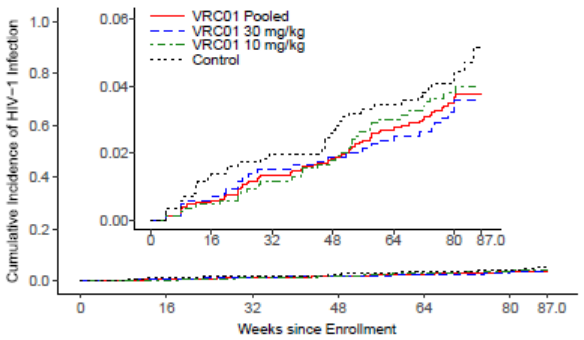
B

Pre-Specified IC_{80} Category	Treatment Arm	No. of HIV-1 Inf.	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)
<1 µg/ml	Control	19	2203	0.86	
	VRC01 Pooled	9	4427	0.20	75.4 (45.5, 88.9)
1-3 µg/ml	Control	10	2203	0.45	
	VRC01 Pooled	19	4427	0.43	4.2 (–108.7, 56.0)
>3 µg/ml	Control	35	2203	1.59	
	VRC01 Pooled	70	4427	1.58	3.3 (–48.0, 36.8)



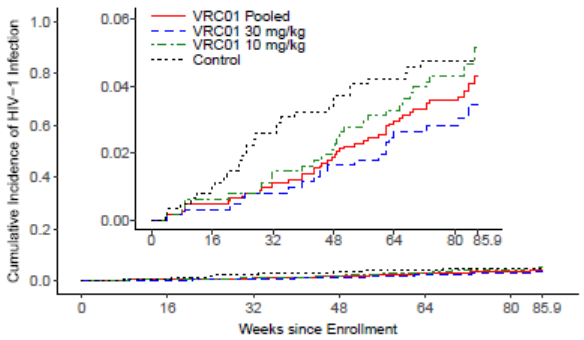
Cumulative incidence of overall HIV-1 acquisition in the two AMP trials.

A



No. at Risk							
VRC01 Pooled	1789	1711	1647	1600	1549	1072	340
VRC01 30 mg/kg	894	856	821	798	771	539	154
VRC01 10 mg/kg	895	855	826	802	778	533	186
Control	898	852	825	797	773	546	150
Cumulative No. of HIV−1 Infections							
VRC01 Pooled	0	10	23	31	45	59	60
VRC01 30 mg/kg	0	6	13	16	20	28	28
VRC01 10 mg/kg	0	4	10	15	25	31	32
Control	0	12	17	22	29	35	38

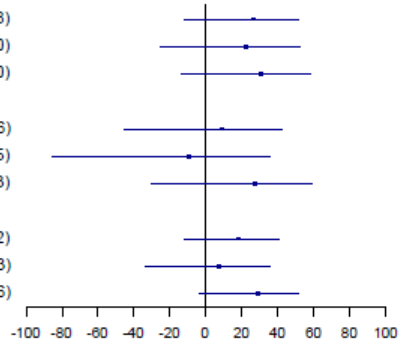
B



No. at Risk							
VRC01 Pooled	1287	1241	1211	1176	1146	938	312
VRC01 30 mg/kg	645	621	609	589	574	475	158
VRC01 10 mg/kg	642	620	602	587	572	463	154
Control	637	617	600	582	572	454	157
Cumulative No. of HIV−1 Infections							
VRC01 Pooled	0	6	14	23	36	43	47
VRC01 30 mg/kg	0	2	5	10	16	17	19
VRC01 10 mg/kg	0	4	9	13	20	26	28
Control	0	6	16	23	26	29	29

C

Study	Treatment arm	No. of HIV-1 Infections	No. of Person-Years	Rate per 100 Person-Years	PE (95% CI)	P-value
HVTN 704/HPTN 085	Control	38	1275	2.98		
	VRC01 Pooled	60	2555	2.35	26.6 (–11.7, 51.8)	0.15
	VRC01 10 mg/kg	32	1281	2.50	22.4 (–25.5, 52.0)	0.30
	VRC01 30 mg/kg	28	1274	2.20	30.9 (–13.9, 58.0)	0.15
HVTN 703/HPTN 081	Control	29	935	3.10		
	VRC01 Pooled	47	1889	2.49	8.8 (–45.1, 42.6)	0.70
	VRC01 10 mg/kg	28	941	2.98	–9.3 (–85.3, 35.5)	0.74
	VRC01 30 mg/kg	19	948	2.00	27.0 (–30.7, 59.3)	0.29
Pooled AMP Trials	Control	67	2207	3.04		
	VRC01 Pooled	107	4436	2.41	18.1 (–12.2, 40.2)	0.21
	VRC01 10 mg/kg	60	2217	2.71	7.2 (–33.3, 35.3)	0.69
	VRC01 30 mg/kg	47	2219	2.12	29.0 (–4.0, 51.6)	0.08



The AMP Trial Assumptions and the Eventual Reality

- Based upon the *in vitro* (test-tube) sensitivity assays from the global panel performed prior to initiation of the AMP trials, we assumed ~60-70% of strains would be sensitive to VRC01, at a cutoff of <10 ug/ml
- In the AMP trial itself 47 (73%) of the 64 isolates in the control group exhibited ID80 <10 ug/ml to VRC01, so the predictive panels were ok
- However, only 30% of viruses in the placebo group circulating in the regions were *in vivo* sensitive (i.e., those with an IC80 <1ug/ml)
- We were in effect a log off in estimating *in vivo* susceptibility to the antibody and this made 30% of the circulating strains susceptible, not 60%; affecting the overall power calculations
- Under these conditions the study had low power to detect overall efficacy

HVTN 704 status Conclusions:

- We can achieve preventive efficacy in humans in the high-risk populations globally with passive administration of a bnAb.
- It is a landmark asset that we have a neutralizing antibody assay that can be used to calibrate future studies and animal models.
- It is clear multiple potent antibodies will be needed to make a clinical product.
- The virus is formidable. It has shown that again.
- But it is transformative to have a tool to predict success and the target needed to achieve highly effective preventive efficacy.

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

HVTN 140

- Just announced
- 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

Current phase 3 vaccine trial

- Mosaic - a way of teaching your body to recognize common HIV proteins, used as an HIV insert

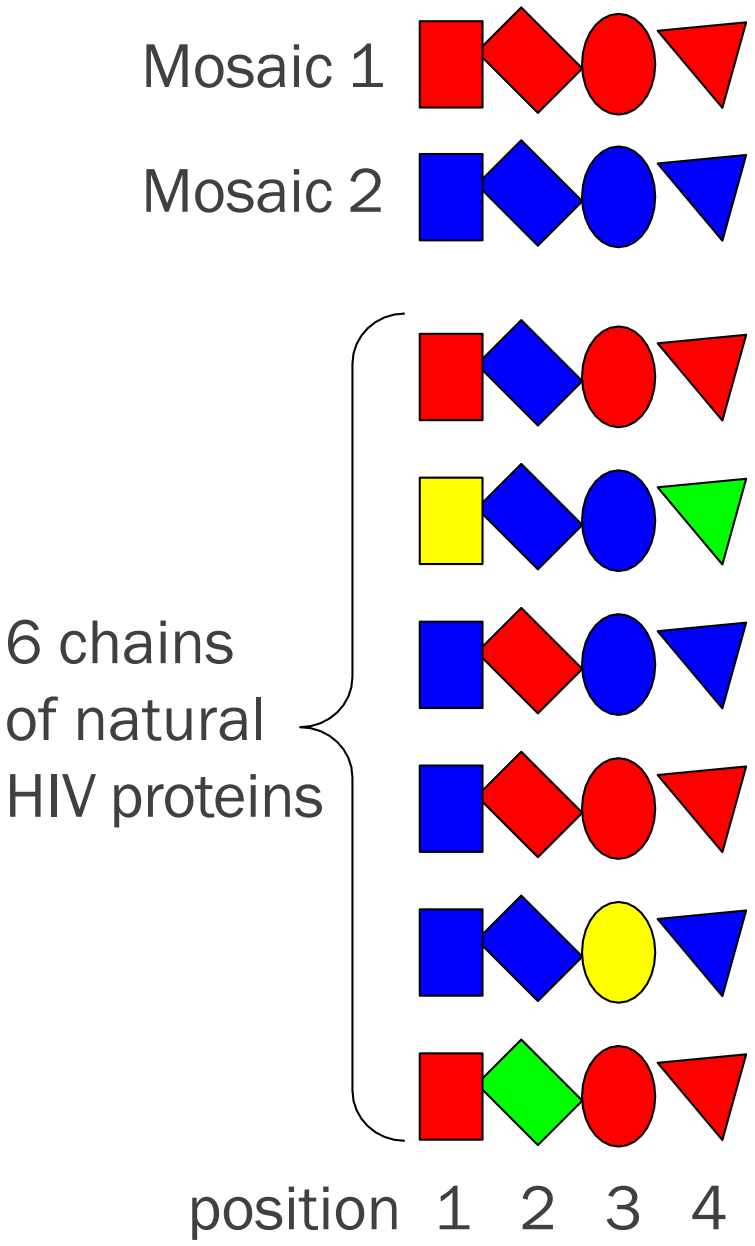
Mosaics Are Chains of Proteins

- 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)
- Enrolling now!

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

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)
- This is likely why the current generation of vaccines were so successful

Acknowledgements

HVTN

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