Current Status of HIV Vaccine Research

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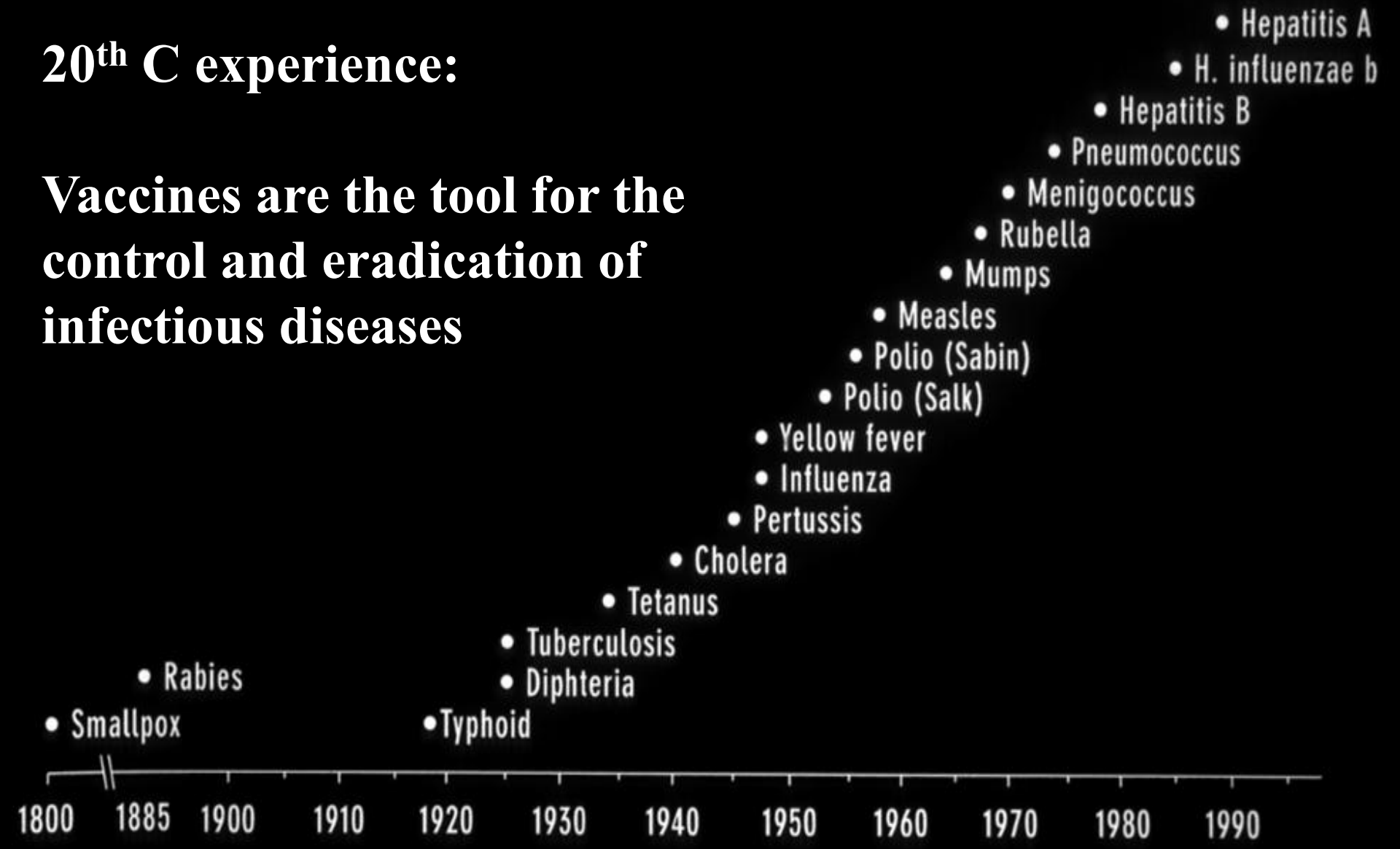
Medical miracles: The development of vaccines 1800-1996

20th C experience:

Vaccines are the tool for the control and eradication of infectious diseases



Vaccine research in perspective

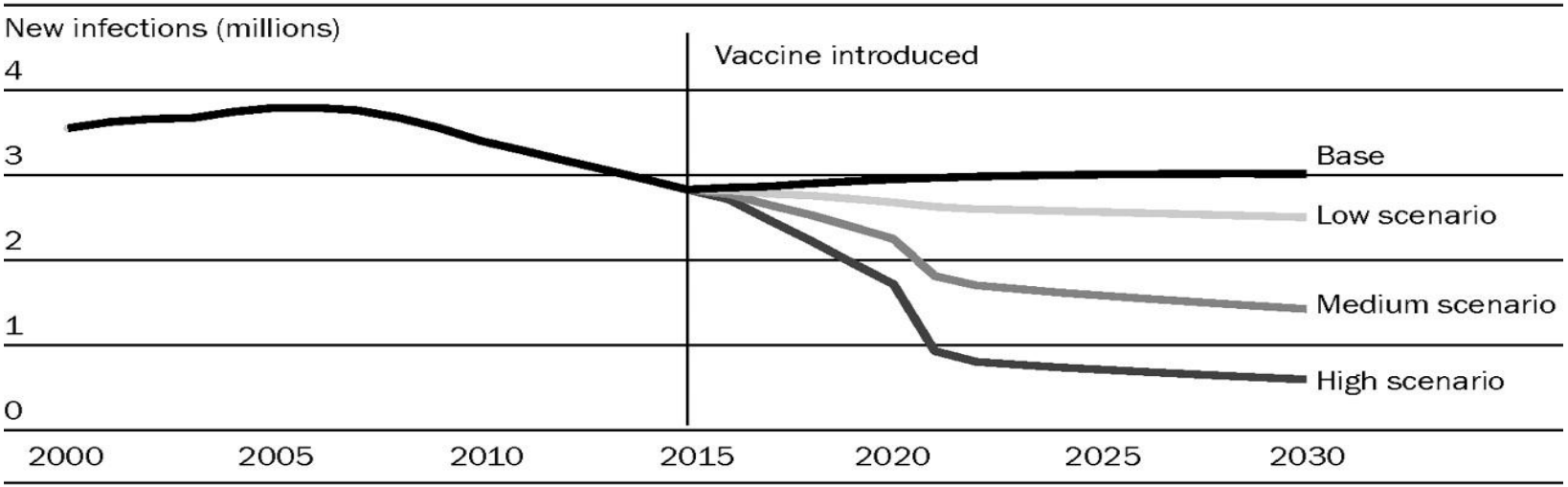
Duration between discovery of microbiologic cause of selected infectious diseases and development of a vaccine

Virus or bacteria	Year cause discovered	Year vaccine licensed	Years elapsed
Typhoid	1884	1989	105
Haemophilus Influenzae	1889	1981	92
Malaria	1893	None	–
Pertussis	1906	1995	89
Polio	1908	1955	47
Measles	1953	1995	42
Hepatitis B	1965	1981	16
Rotavirus	1973	1998	25
HPV	1974	2007	33
HIV	1983	None	–

Source: ***AIDS Vaccine Handbook***, AVAC, 2005

The Impact of an AIDS Vaccine in Developing Countries

EXHIBIT 4
Number Of New Adult HIV Infections In Low- And Middle-Income Countries, By Year And Vaccine Scenario, 2000–2030



SOURCE: Authors' calculations.
NOTE: For details about scenarios, see text.

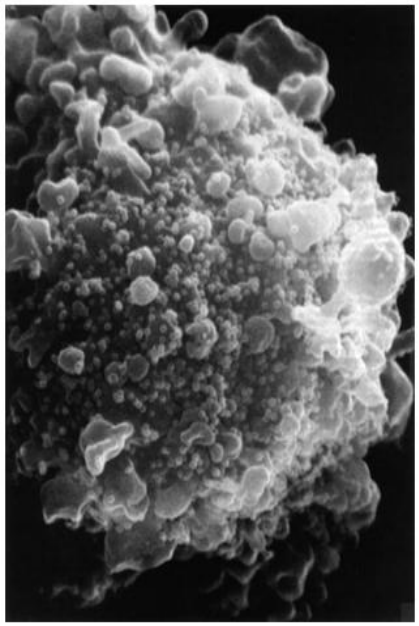
Low = 30% efficacy, 20% coverage
Medium = 50% efficacy, 30% coverage
High = 70% efficacy, 40% coverage

Stover J, Bollinger L, Hecht R, Williams C, Roca E: The impact of an AIDS Vaccine in Developing Countries: A New Model and Initial Results**. Health Affairs 26(4):1147-1158 (2007)**

Why don't we have a vaccine against HIV?

•Classic vaccines mimic natural immunity against re-infection : no one has recovered from HIV-1 infection.

•Most vaccines protect against disease, not against infection; HIV infection may remain latent for long periods before causing disease (provirus).



•Protection against HIV infection may require sterilizing immunity (preventing entry); no current vaccine is know to do this.

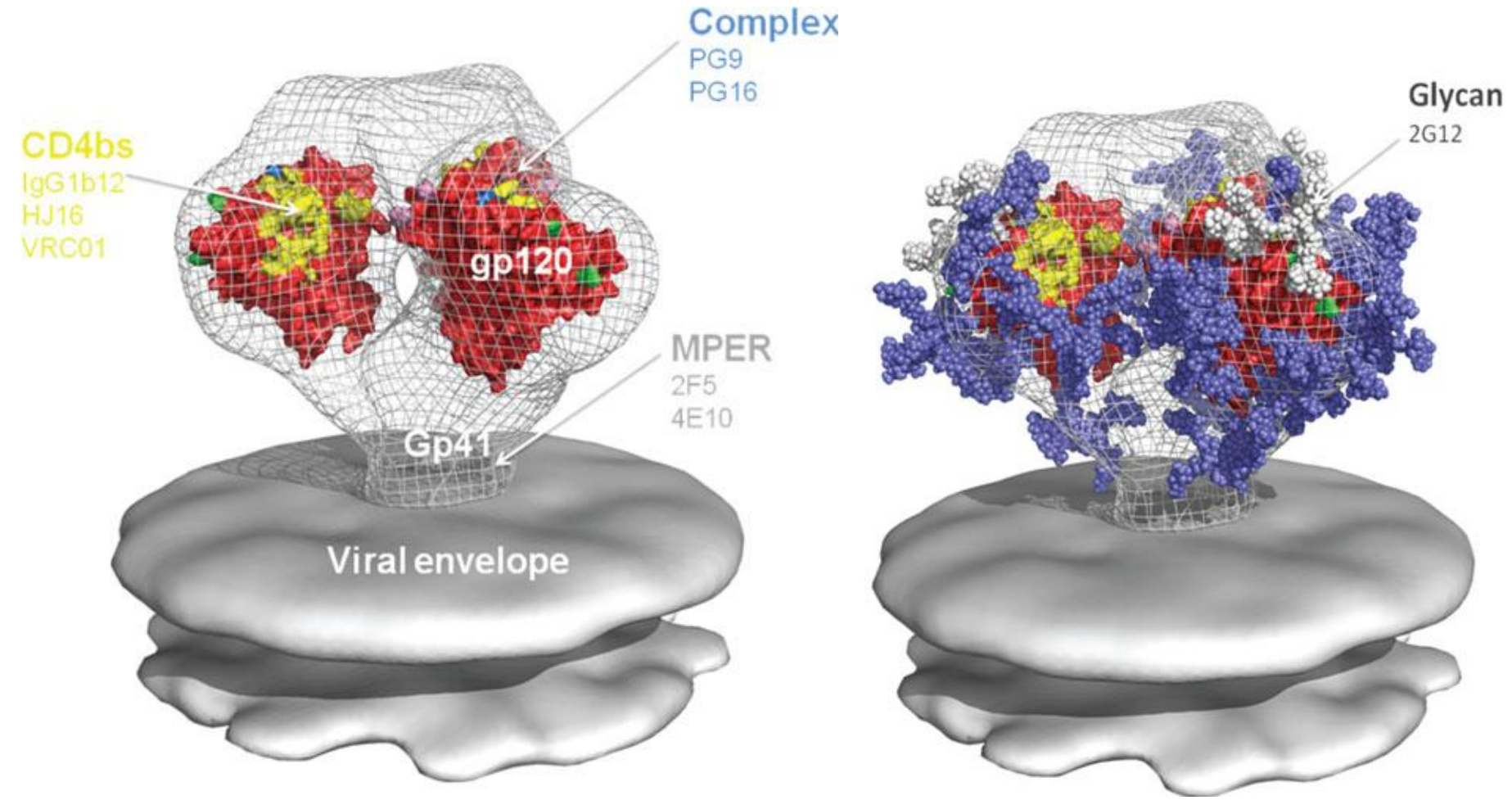
•Many vaccines use attenuated pathogens, this approach would not be appropriate for HIV due to inherent safety concerns.

•HIV has multiple mechanisms of immune evasion.

HIV-1 Mechanisms of immune evasion

- High levels of mutation (RT - 1 error per 10K nucleotides, 10^9 virus/day)
- Viral latency and infection of immuno-privileged sites
- Absence of neutralizing antibodies due to high levels of glycosylation, epitope masking by hypervariable loops, and shedding of monomeric gp120
- Promotion of Th1 to Th2 switch (misdirection)
- Destruction of immune response (CD4 cells role in coordinating immunity)

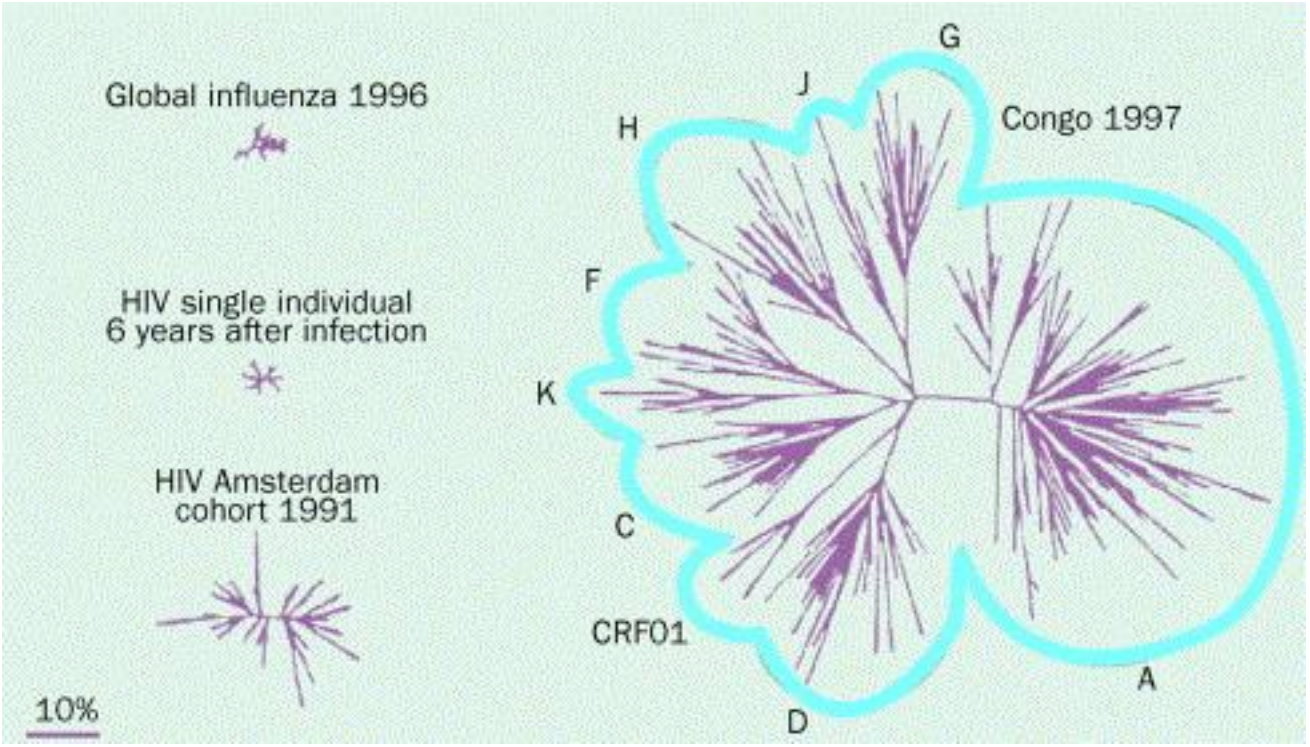
The HIV spike envelope protein is covered in sugars



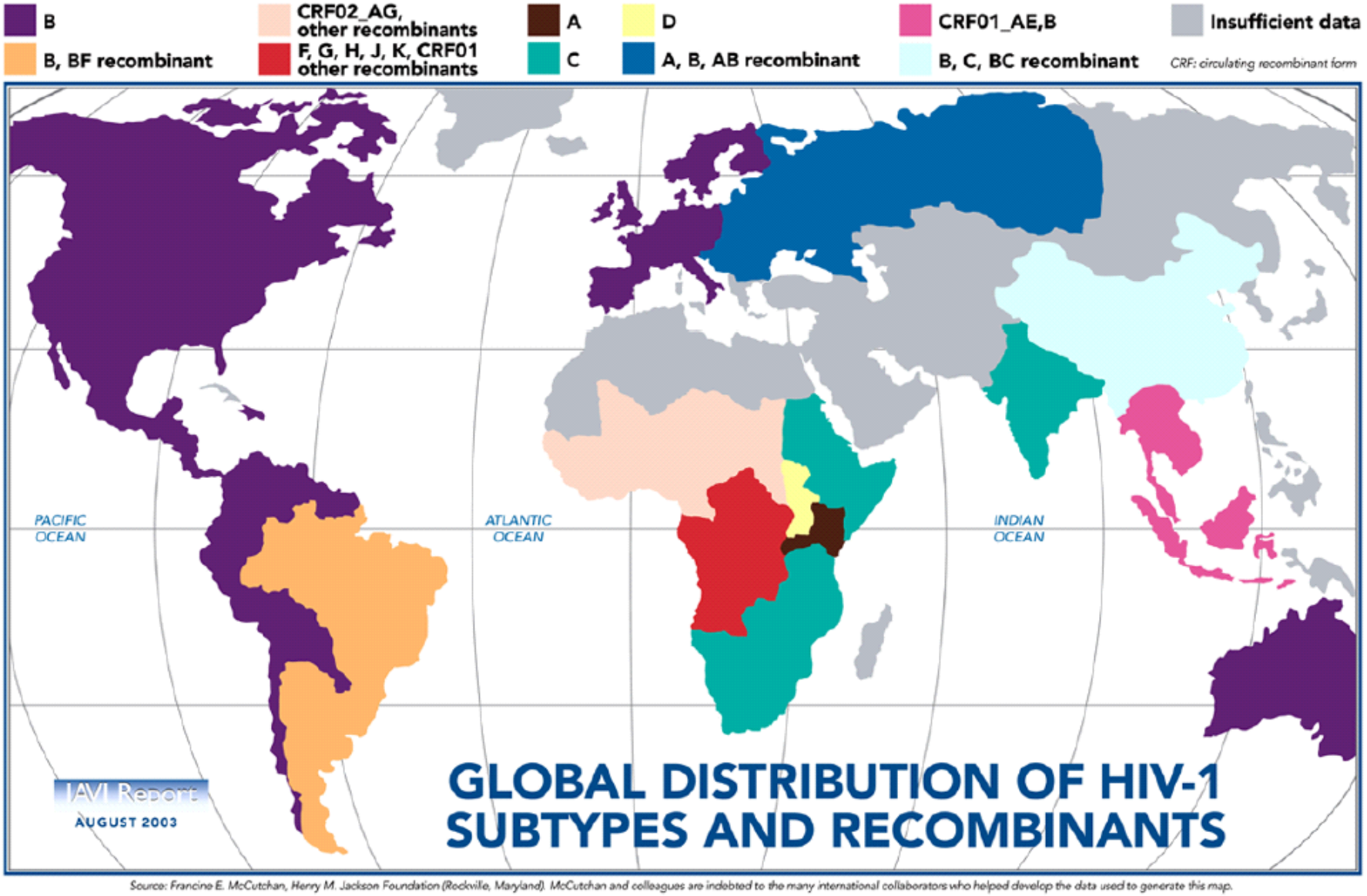
Global diversity

•HIV exists in multiple subtypes (clades) with different geographical distribution; generation of a single vaccine active a against multiple clades is a significant hurdle.

•Influenza strains are constantly changing, as a consequence a new influenza vaccine is produced each year; within a single HIV patient there is more viral diversity than there is for influenza across the entire globe.



B Korber, B Gaschen, K Yusim et al. Br Med Bull, 58 (2001), pp. 19–42



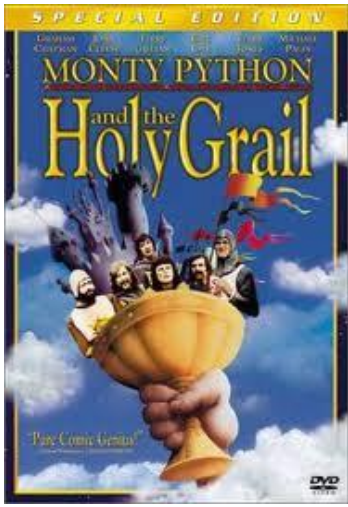
HIV-1 clades differ by >20% amino acid sequence. Differences within clades >5-10%: huge numbers (billions) of new variants accumulate during infection.

A simplified chronology of HIV Vaccine Research

- 1981: *AIDS identified*
- 1983/4: *HIV identified as the cause of AIDS*
- 1987: *First phase I HIV vaccine (gp160, MicroGeneSys)*
- 1989: *SIV vaccines protect monkeys* (R Desrosiers and others)
- 1991-1992*: role of host cell antigens in early NHP protection experiments (J Stott and others)*
- 1990s: *Intense effort to develop vaccines to induce antibodies*
- 1990: *Begin preparation of trial sites in developing countries*
- 1998: *Candidate vaccines failed to induce antibodies that neutralize primary (clinical) isolates*
- 2000s: Intense effort to develop vaccines to induce CMI (cell mediated Immunity)
- 1998-2003: *Phase III trials of VaxGen gp120 vaccine (Thailand, US)*
- *2004-2007: Phase IIb trials (STEP, Phambili) of Merck Ad5 vectored vaccine*
- *2003-2009: Phase IIb/III trial (RV144) of ALVAC + AIDSVAX in Thailand*

What Is Required of A Successful HIV-1 Vaccine?

- long-lived broadly neutralizing antibodies
- high levels of central and effector memory T cells
- present at the time of exposure,
- rapidly boosted by mucosal infection,
- augmented by innate responses
- able to rapidly eliminate infection before immune escape



What's new and how is it shaping research?

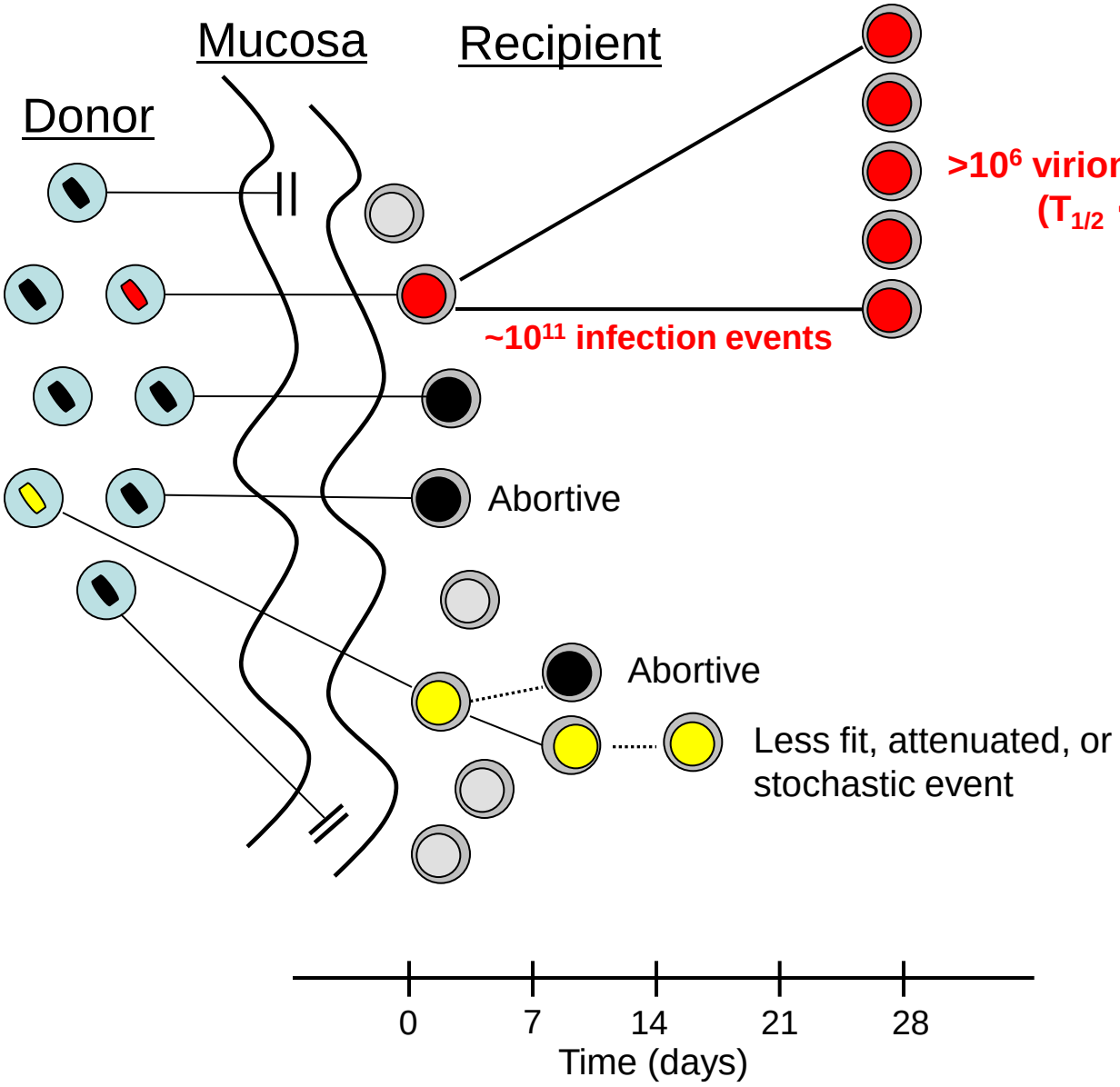
1. Transmitted/founder virus
2. Identification of broadly neutralizing antibodies
3. Levels of mucosal antibodies associated with protection – are they achievable?
4. The influence of clinical trials
5. Next steps

The Transmitted Virus

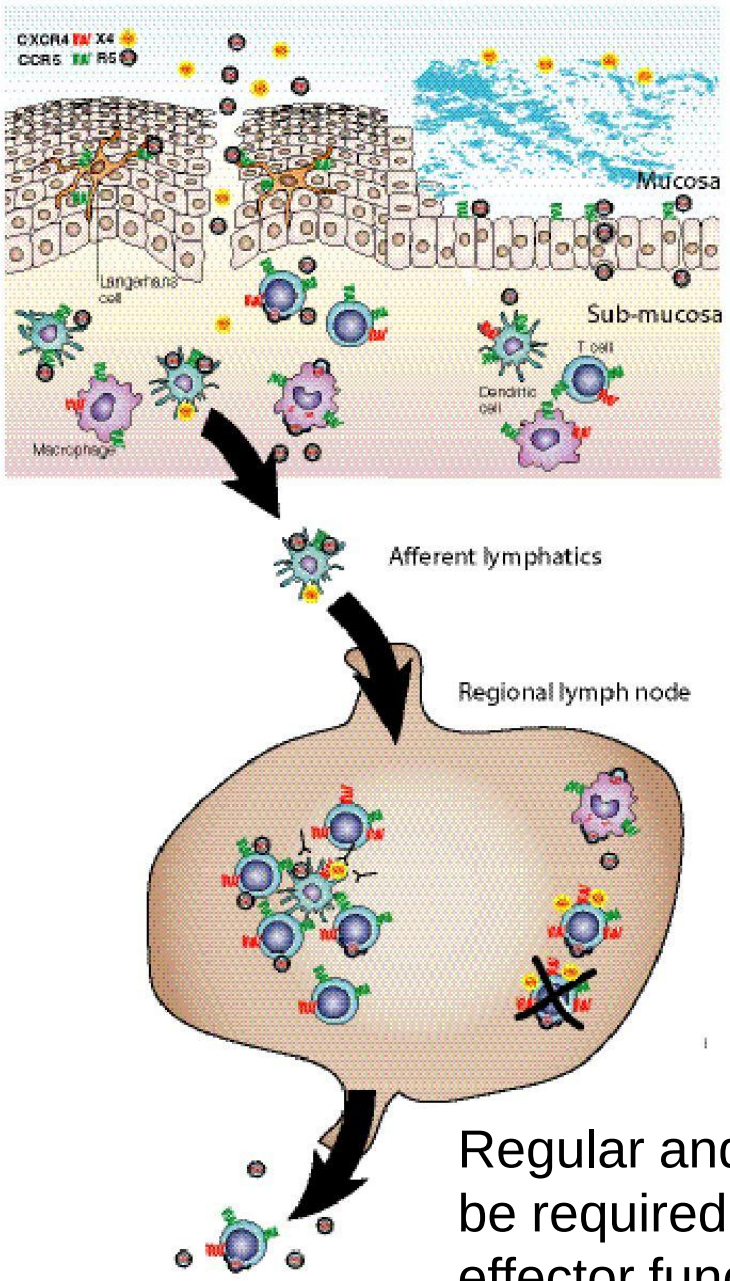
- 80% of HIV infected subjects are infected with a single virion/single quasispecies
- 20% are infected with a few HIV quasispecies
- The balance between infection and protection at mucosal surfaces my be small

PNAS 105: 7522-7, 2008 and others

Biological phenotype of transmitted virus



The time to act is short !



Exposure: 30-60 mins

DC-T cell transfer 1-4 hours
(virological synapse)

Localized infection: 16-72 hours

Dissemination to draining LN: 24-72 hours
(virological synapse)

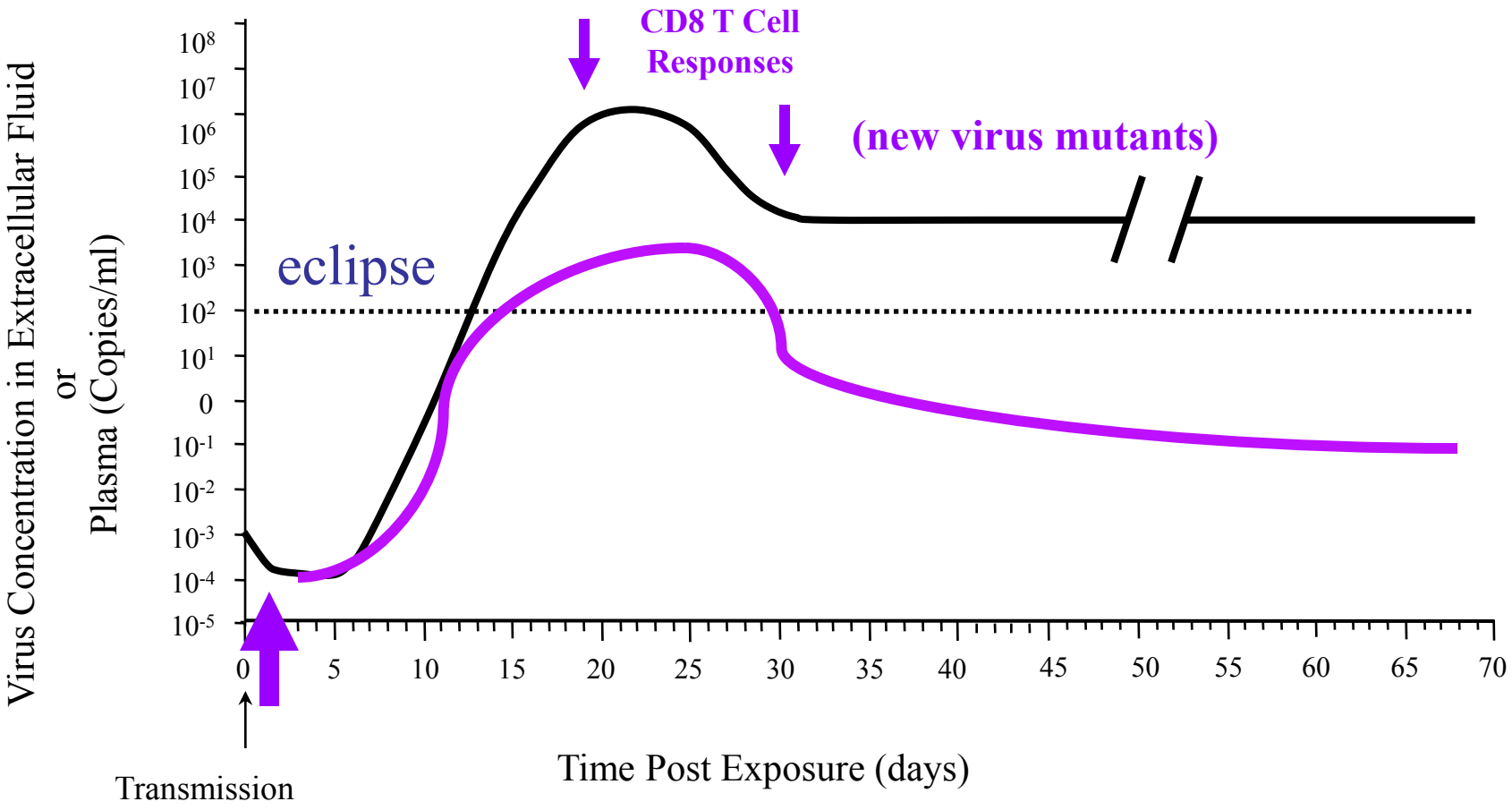
Induction of memory responses: 3-5 days

Regular and repeated intravaginal vaccination may be required to maintain local protective immune effector function

What Could A Vaccine Do To Prevent Infection?

- Block HIV from coming into contact with target cells and tissues
- Reduce the number of susceptible cells and overall susceptibility of target cells
- Controlling the spread of HIV from infected cells
- Eliminating any infected cells that occur within the vaccinated host or enter the host as part of the inoculum

Can cellular responses control infection?



Study of viral escape to inform cellular epitope design

Lessons learnt from the Step Trial: *2004-2007*

Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Lancet. 2008 Nov 29;372(9653):1881-93.

*Susan P Buchbinder, Devan V Mehrotra, Ann Duerr, Daniel W Fitzgerald, Robin Mogg, David Li, Peter B Gilbert, Javier R Lama, Michael Marmor, Carlos del Rio, M Juliana McElrath, Danilo R Casimiro, Keith M Gottesdiener, Jeffrey A Chodakewitz, Lawrence Corey, Michael N Robertson, and the Step Study Protocol Team**

- Merck Ad5 (vectored vaccine) gag/pol/nef vaccine provided no protection
- Draws the attention on the potential danger of pre-existing immunity
- It indicates that the magnitude and the quality (breadth) of the vaccine-induced T-cell responses (particularly CD8 T-cell responses) are not optimal.

The first trial (STEP) of a T cell based vaccine failed to work, so what do we need to know?

- How many epitopes are required to be effective?
- Is there a definable set that can prevent escape
- What functional characteristics are most important
- Can they be induce/maintained at mucosal sites of exposure
- How to define “enough” and “soon enough”

- Next generation epitope design
  - bioinformatics, consensus, mosaics to increase breadth
- Next generation vectors (heterologous, avoidance of anti-vector immunity, use of persisting or replicating vectors)
- Focus on mucosal responses
  - -where, when, how much

Barouch et al Nat Med. 2010 Mar;16(3):319-23

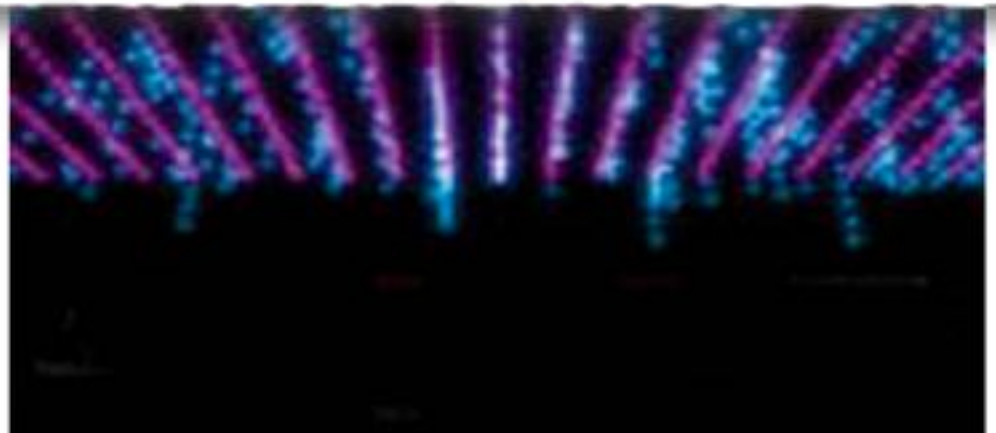
However….

- T-cell vaccines remain an important component of the overall HIV vaccine strategy
- Provide the critical priming component in combination regimens with env proteins
- May substantially impact the magnitude, quality and durability of the antibody response induced by env protein vaccines
- Are likely to augment partially protective antibody responses
- May control viremia if breadth and magnitude can be maintained…

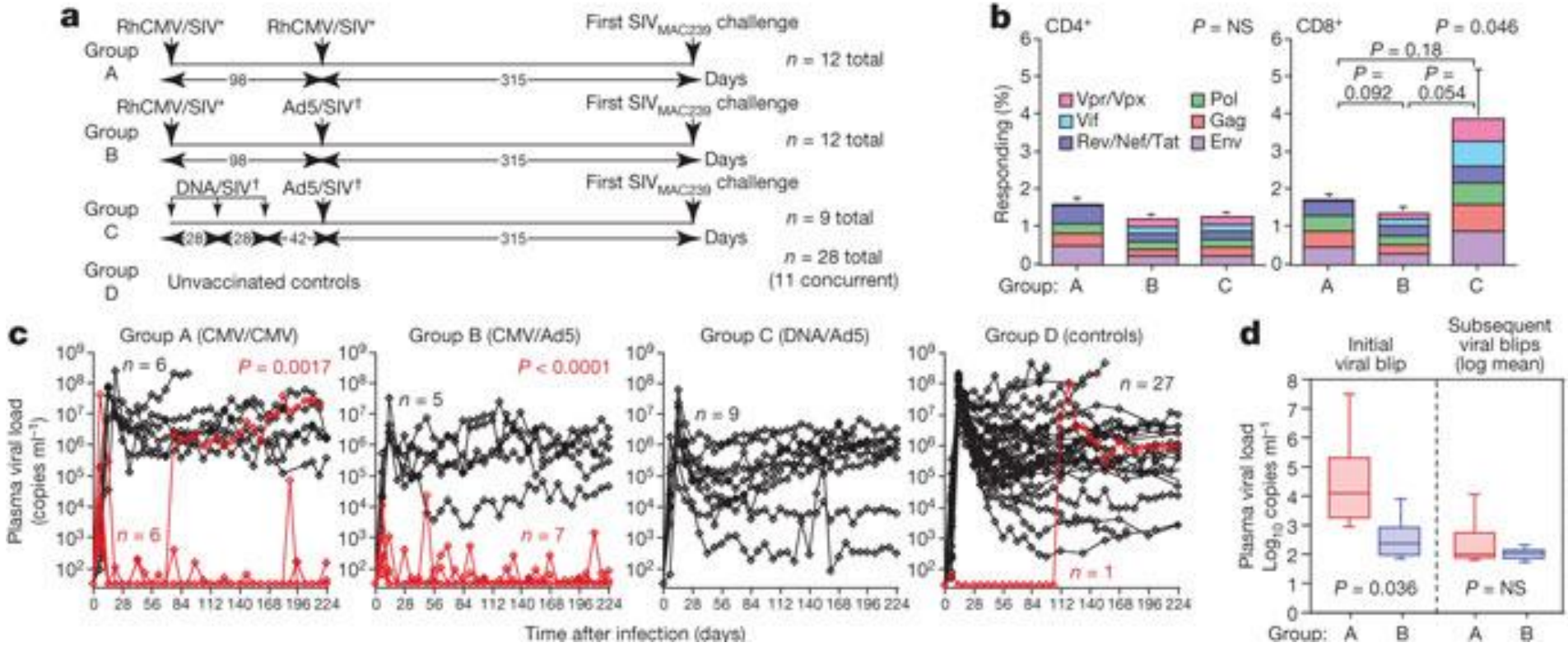
New Approaches in HIV Vaccinology
Persistent Vectors

Profound Early Control of Highly Pathogenic SIV by an Effector Memory T Cell Vaccine

Hansen S.G., Ford J.C., Lewis M.S., Ventura A.B., Hughes C.M., Coyne-Johnson L., Whizin N., Oswald K., Shoemaker R., Swanson T., Legasse A.W., Chiuchiolo M.J., Parks C.L., Axthelm M.K., Nelson J.A., Jarvis M.A., Piatak M., Lifson J.D., and Picker L.J.



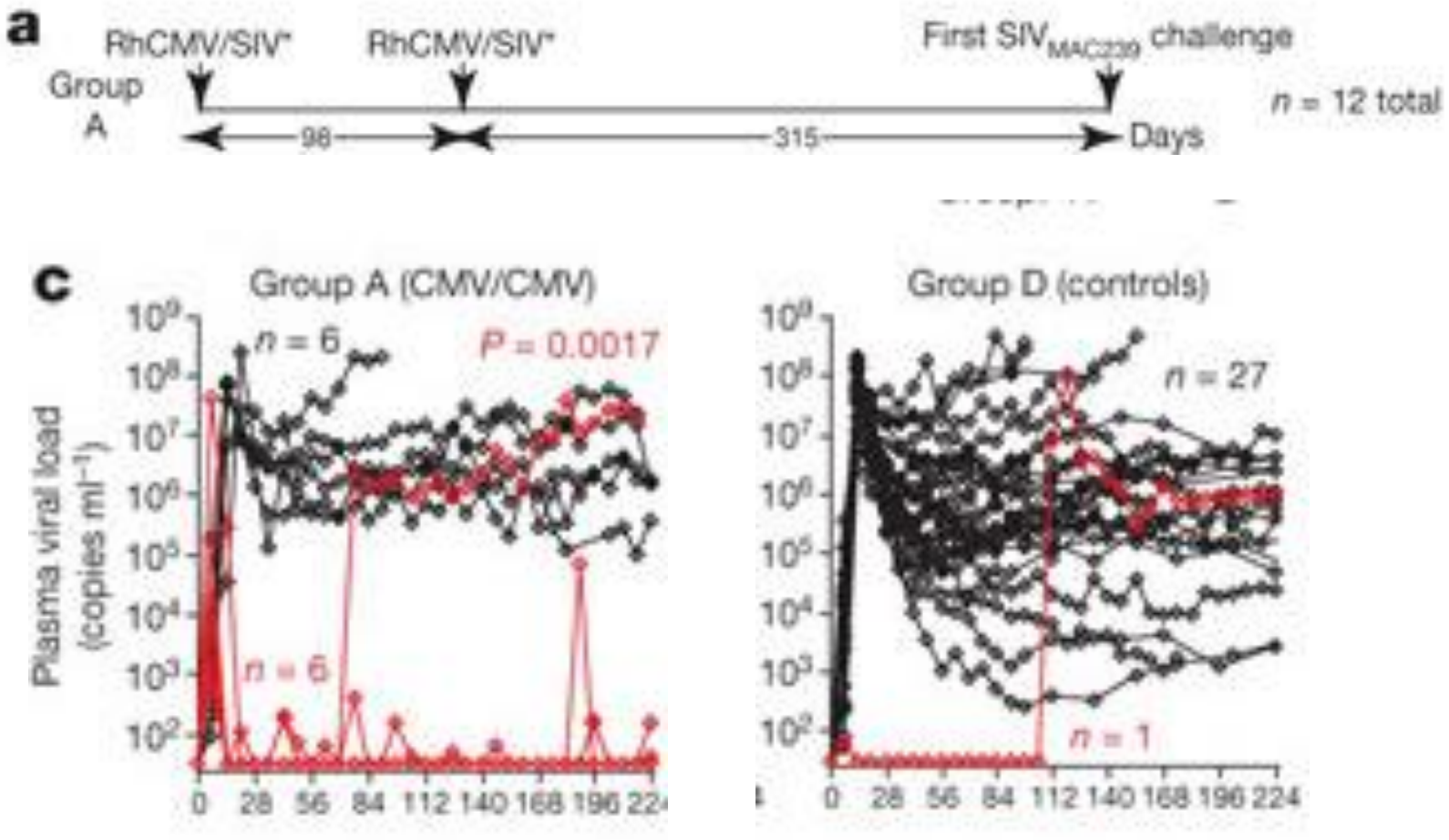
Immunogenicity and efficacy of RhCMV/SIV vectors.



nature

SG Hansen *et al. Nature* **000**, 1-5 (2011) doi:10.1038/nature10003

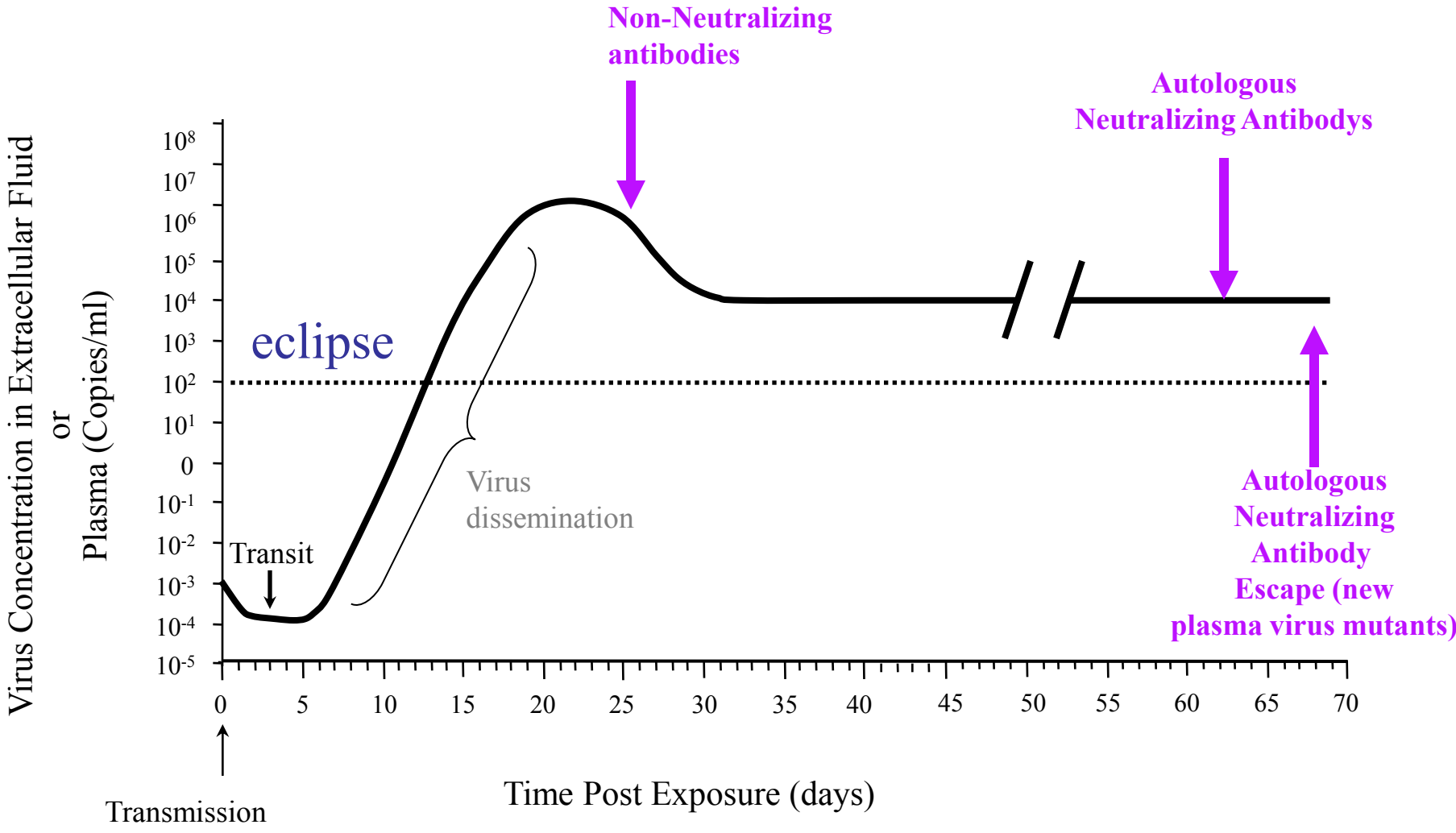
A persistent RhCMV/SIV vector protects 50% of animals from developing disease



13/24 macaques receiving either RhCMV vectors alone manifested early complete control of SIV (undetectable plasma virus), (≥1 year) protection

Nature. 2011 May 26;473(7348):523-7

Learning from naturally occurring neutralizing antibodies



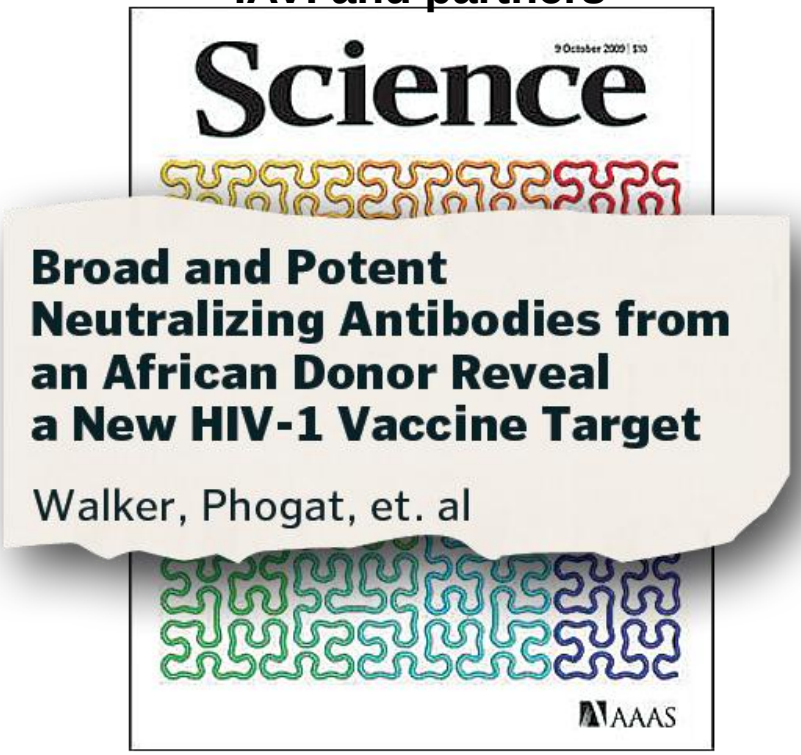
Learning from neutralizing antibodies generated in natural HIV infection

- Up to 25% of infected subjects found to have broadly neutralizing antibodies a year or more after infection
- 1% (elite controllers) have potent activity against a majority of strains
- Cross reactive antibodies arise over years – *maturation of response (? Implications for vaccines)*
- Maturation likely to focus on less immunogenic, more conserved regions of env
- Induction of responses to such regions could provide potent protection

Advances in quest for broadly neutralizing antibodies against HIV

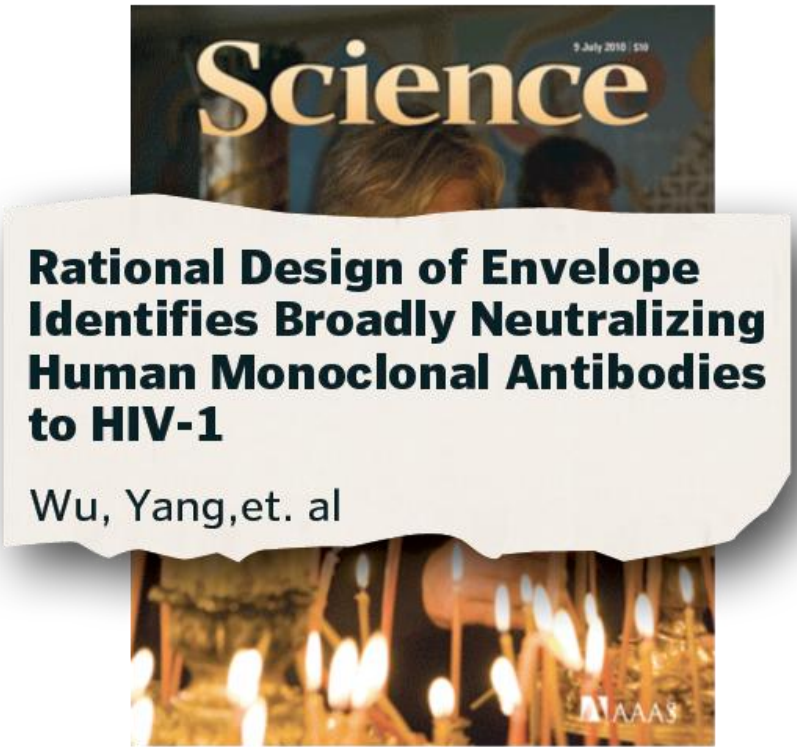
2009

IAVI and partners



2010

VRC



Screening the elite

Broad and potent neutralizing antibodies are found in about 1% of HIV-Infected subjects

			Clade A	Clade B		Clade C		CRF01-AE
Rank	Score	Country	94UG103	92BR020	JRCSF	IAVI C22	93IN905	92TH021
1	3.67	Ivory Coast	900	900	2700	2700	2700	2700
2	3.00	Zambia	300	300	2700	300	2700	2700
5	2.83	Ivory Coast	300	300	900	300	2700	2700
5	2.83	Ivory Coast	300	900	2700	900	2700	100
5	2.83	Kenya	300	900	900	900	2700	300
5	2.83	South Africa	300	900	900	2700	2700	100
5	2.83	Rwanda	300	2700	900	2700	2700	<100
8	2.69	Zambia	345	345	1190	1190	1190	345
10	2.67	U.K.	300	900	900	2700	900	100
10	2.67	Zambia	900	900	900	300	2700	100
10	2.67	Uganda	900	900	900	2700	900	<100
15	2.67	Ivory Coast	300	900	300	900	900	300
15	2.50	South Africa	100	300	300	2700	900	900
15	2.50	South Africa	300	300	300	2700	2700	100
15	2.50	U.K.	300	900	300	900	900	300
15	2.50	South Africa	2700	100	300	2700	2700	<100
15	2.50	Uganda	900	900	900	900	900	<100
15	2.50	Zambia	300	<100	900	300	2700	2700

Source: Simek et.al, *J Virology*. 2009; IAVI Protocol G

The **HIV antibody** challenge

- Because of difficulty of protection; lifetime infection and high fatality rate, an HIV vaccine should ideally produce **antibody** and **cell-mediated** protection

- However, if one could have only one arm of the immune system via a vaccine, **antibodies** can neutralize infecting virus and prevent initial infection of the host cell or limit early viral dissemination

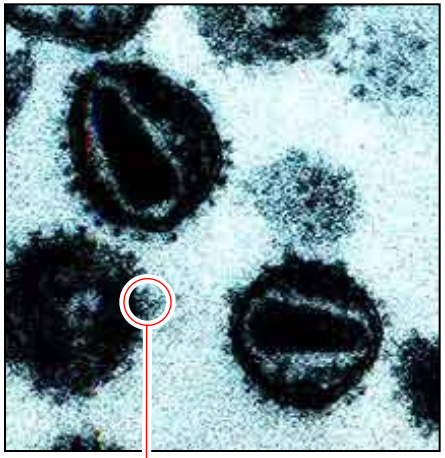
The story so far:

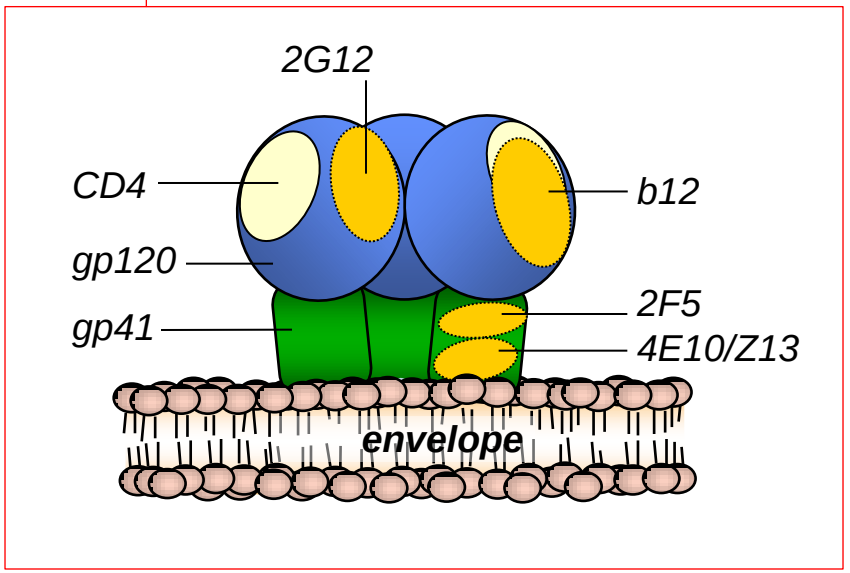
Initial approach, monomeric gp120 vaccine candidates

- Two efficacy trials of VaxGen product; results in 2003
  - Safe
  - 100% of persons develop antibodies
  - However, ***unable to neutralize circulating viruses***

The **neutralizing antibody** challenge, pre-2009

- Most licensed vaccines elicit neutralizing antibodies
- Four antibodies shown to be broadly neutralizing have been found, demonstrating that humans can produce them
- Neutralizing antibodies protect against SIV/HIV challenge in animal models
- The complex structures of the antibodies have been resolved, but the antibodies aren't particularly potent
- Despite a decade of work, no candidate vaccine in the pipeline elicits broadly neutralizing antibodies against HIV





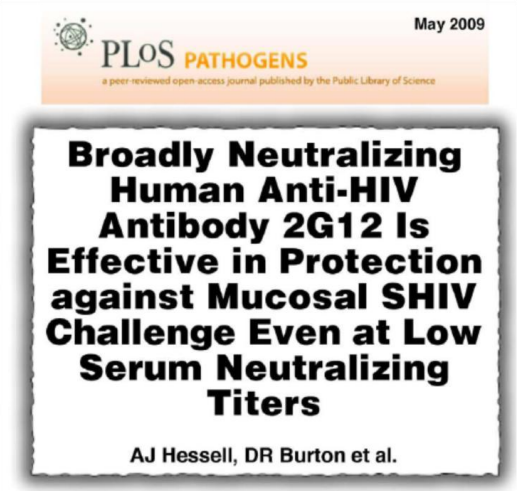
Reasons for optimism

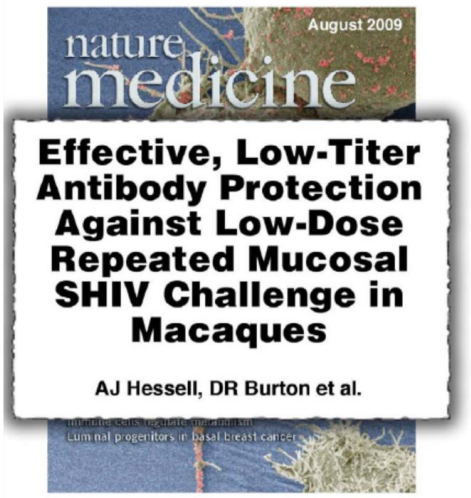
- The human immune system is capable: 10% to 30% of HIV-1 infected individuals produce moderate to broadly neutralizing antibodies against HIV-1

- Multiple new, highly potent antibodies and new, accessible targets have been identified. Combinations neutralize virtually all variants of HIV *in vitro*

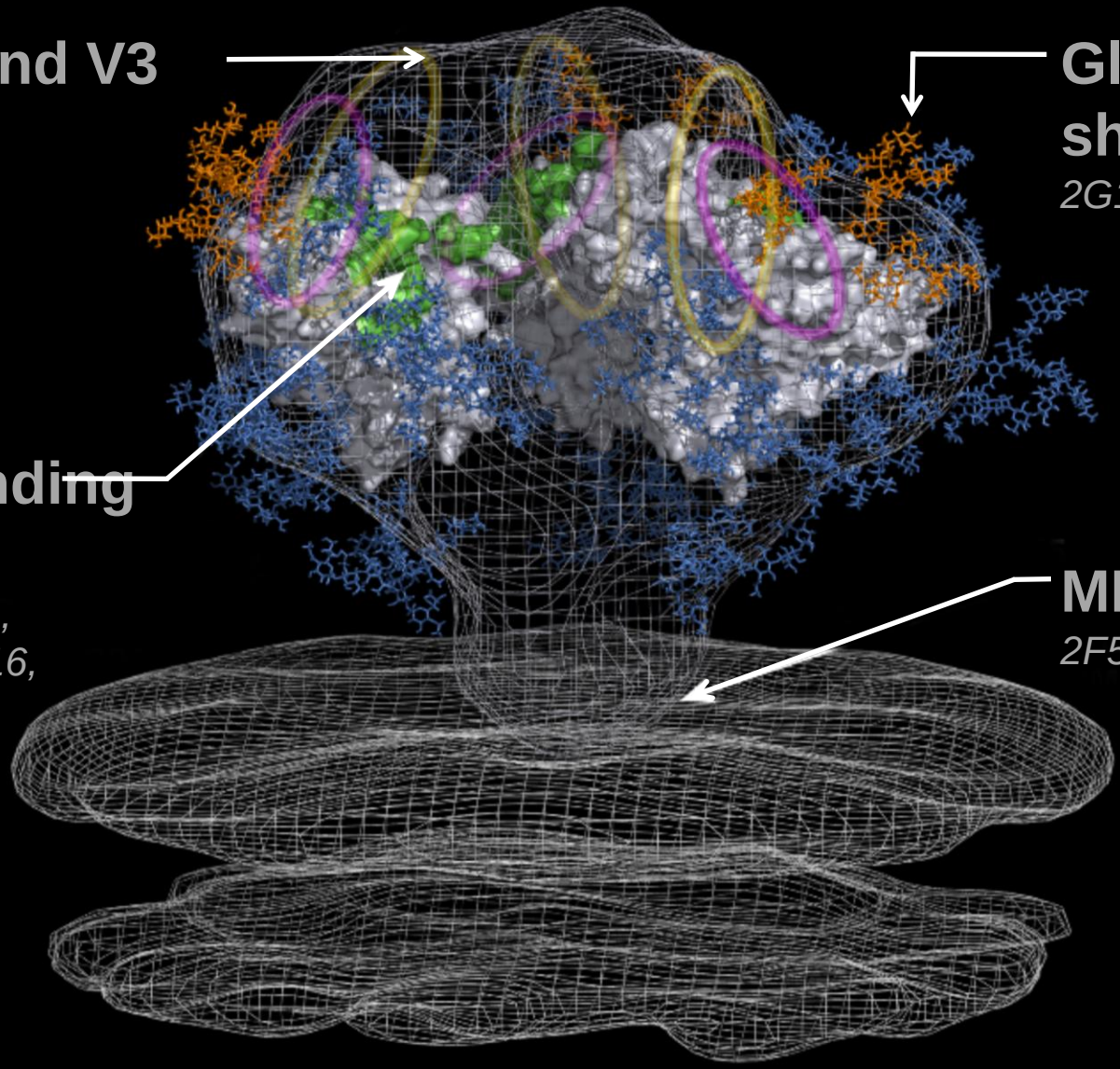
- Passive immunization with broadly neutralizing antibodies can protect against SHIV challenge and at much lower concentration than previously thought

- HIV infection in a heterosexually infected person is initiated by one or at most a few viruses, demonstrating vulnerability to early antibody neutralization





With new antibodies, **new targets**



V1/V2 and V3 Loops
PG9, PG16

Glycan shield
2G12

CD4 binding site
b12, VRC01, VRC03, HJ16, PGV04

MPER
2F5, 4E10, Z13e1

Source: Schief, W.R. et al.. Curr Opin HIV AIDS. 2009 Sep; 4(5):431-40.

Major challenges to eliciting broadly neutralizing antibodies against HIV

The HIV Envelope Trimer

- Highly variable
- Unstable
- Immune evasion
- gp140 trimer Mimics ≠ the native structure

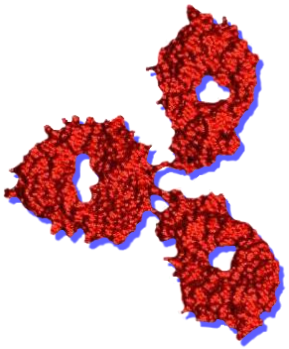
Progress will be accelerated by:

- Better understanding of antigenicity vs. immunogenicity
- Better understanding of how broadly neutralizing antibodies evolve in HIV infection
- Methods to stabilize the native Env trimer, to immunize as well as elucidate the crystal structure
- High throughput immunogen design and screening methods

An innovative approach: Passive Immunity

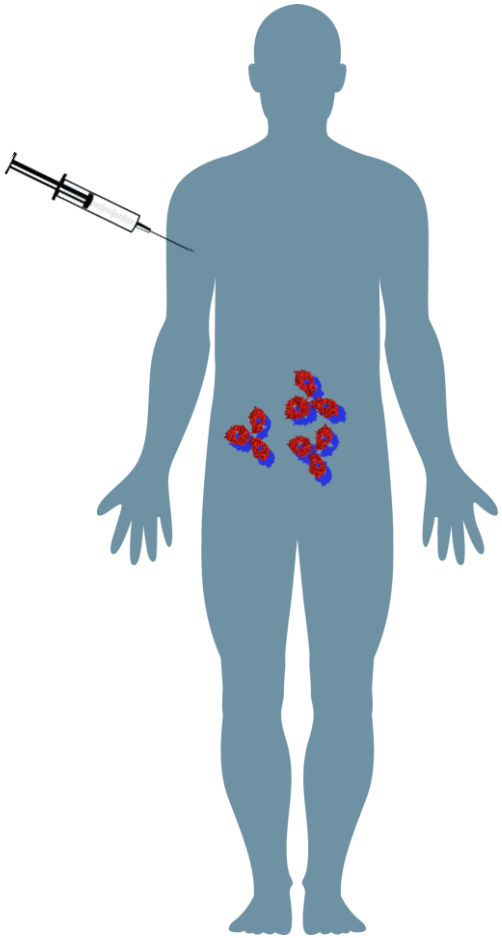
THE FIND

Multiple broadly neutralizing antibodies against HIV



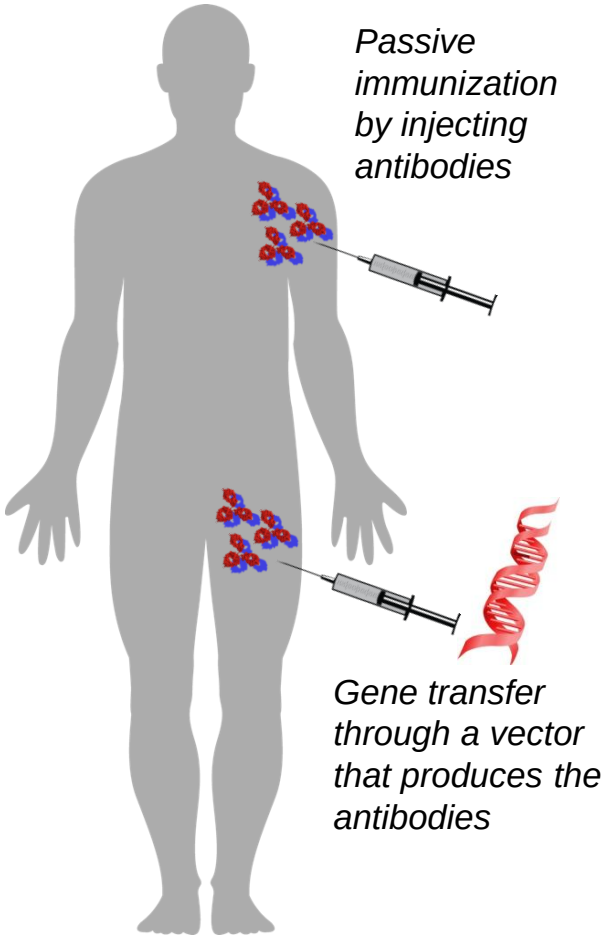
THE GOAL

Elicit those antibodies through vaccination



INTERIM STEPS

Prove concept through …

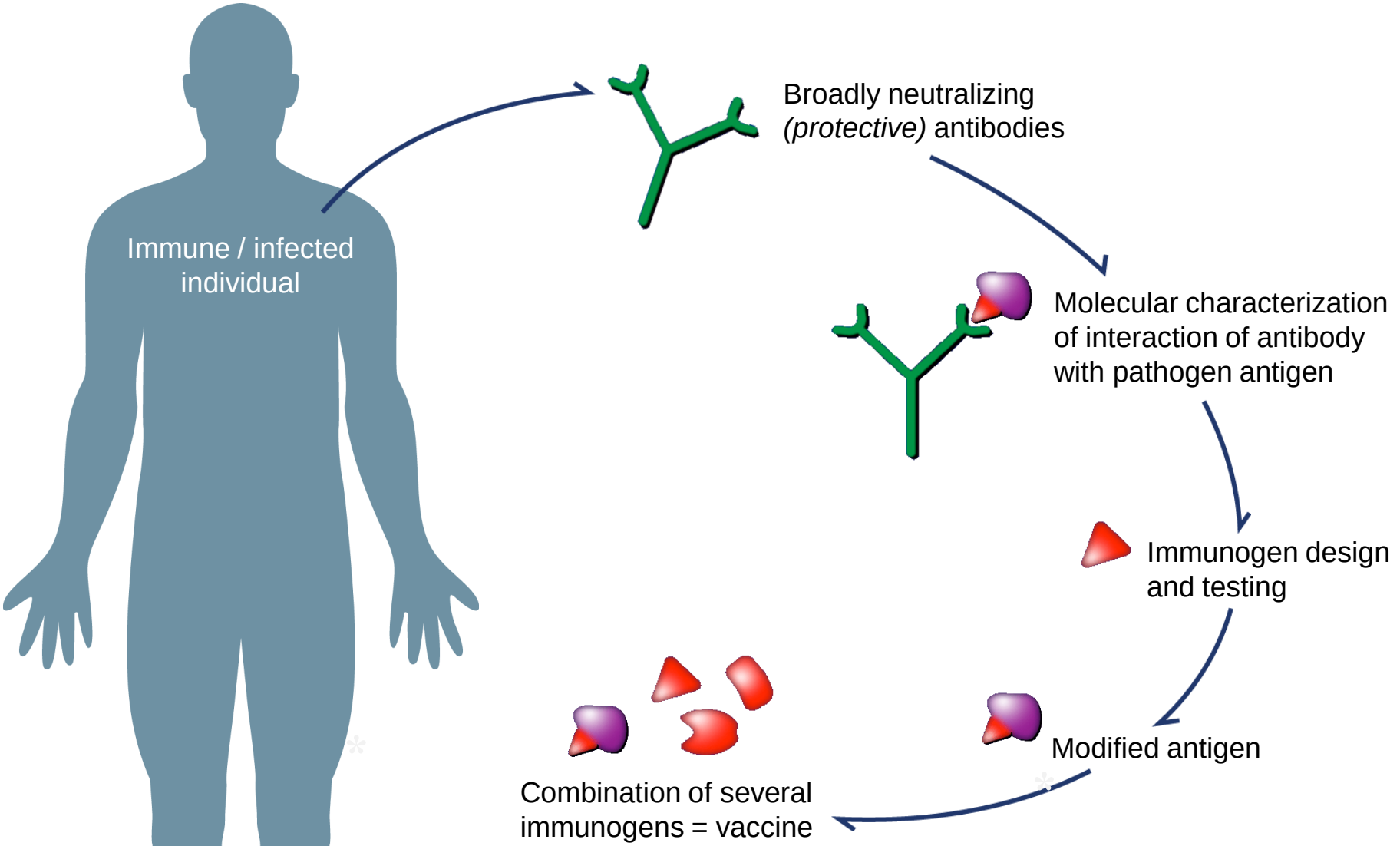


Using Nabs to generate potent vaccines

Identify broadly neutralizing serum	•Define targeted epitopes •Determine development and maintenance
Generate broadly neutralizing mAbs	•High throughput mAb generation •Confirm neutralization and viral epitopes
Structure based design	•Define structural basis for neutralization •Design vaccines to present desired epitopes
Antibody induction studies	•Identify immunological conditions to induce optimal neutralizing antibody responses
Optimization of immunization	•Determine No of epitopes required •Define levels of Nabs required for protection •Strategies for induction and maintenance

Stamatatos et al Nature Med 2009, 15, 866

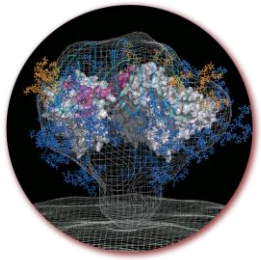
Retrovaccinology: From antibody to antigen



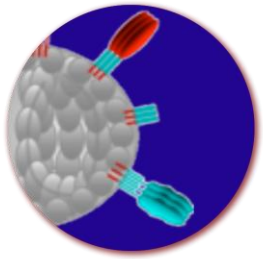
Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002

The road ahead: Three main strategies

Trimer mimics (native trimer)



Epitope mimics: Binding sites of broadly neutralizing antibodies



DNA and viral vectors platforms (surface expression of native trimers)

Likely a combination of elements – heterologous prime-boost
Need to short cut affinity maturation seen elite controllers

Comprehensive Approaches to Vaccination

Approaches		
Antigens	**Delivery**	**Route (prime/boost)**
Envelope -monomeric -trimeric	•Protein •DNA •Vector	•Trancutaneous •Intradermal •Subcutaneous •Intramuscular •Venus •Nasal •Rectal •Vaginal •Oral
nef, tat		
gag, vif, vpr, rev		

McElrath. Immunity Volume 33, 2010, Pages 542–554

But what of the Thai trial (RV144)?

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*

ABSTRACT

- 125 infections from17,115 participants
- 74 out of 8,198 volunteers who received placebo
- 51 out of 8,917 volunteers who received prime boost vaccine
- Protective efficacy a little over 31% p=0.039
- No affect on viral load or CD4 count in subjects infected with HIV

Vaccines components

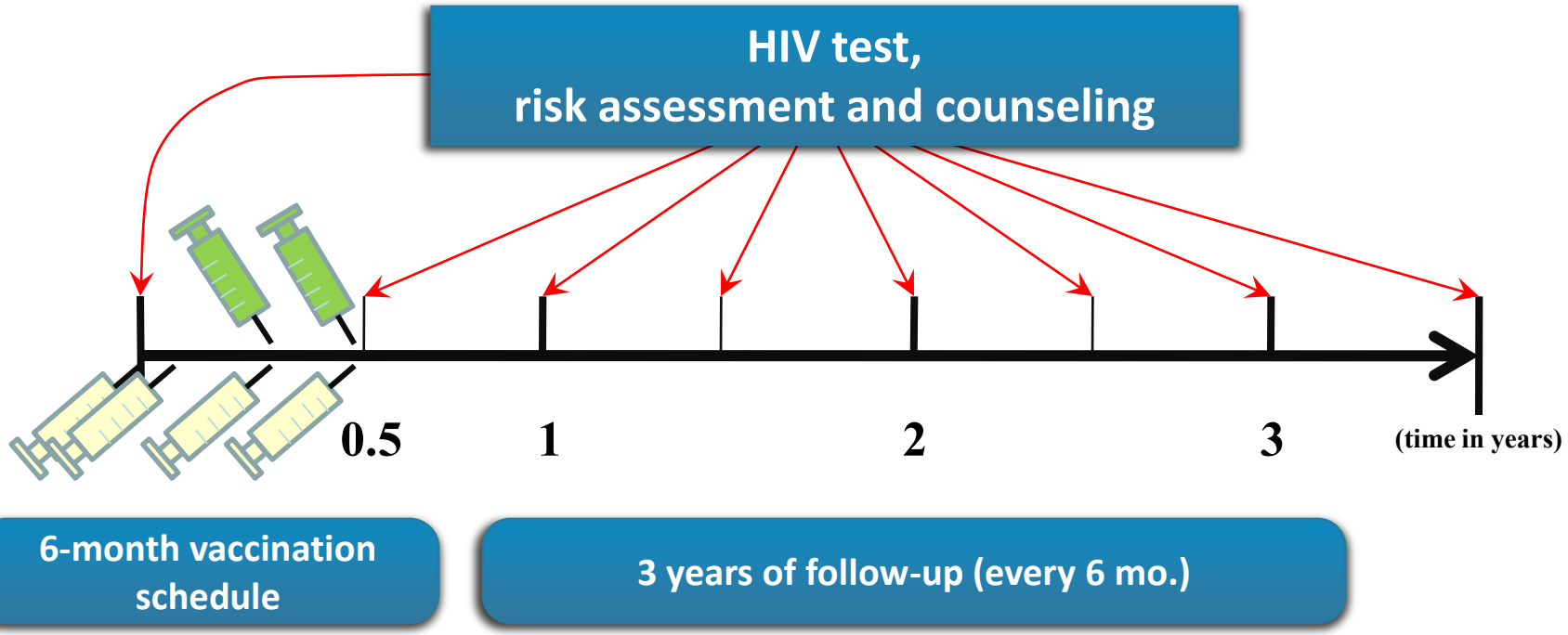
ALVAC®-HIV (vCP1521)

- Recombinant canarypox vector vaccine genetically engineered to express **HIV-1 gp120 (subtype E: 92TH023)** linked to the transmembrane anchoring portion of **gp41 (subtype B: LAI)**, and **HIV-1 gag and protease (subtype B: LAI)**.

AIDSVAX® B/E

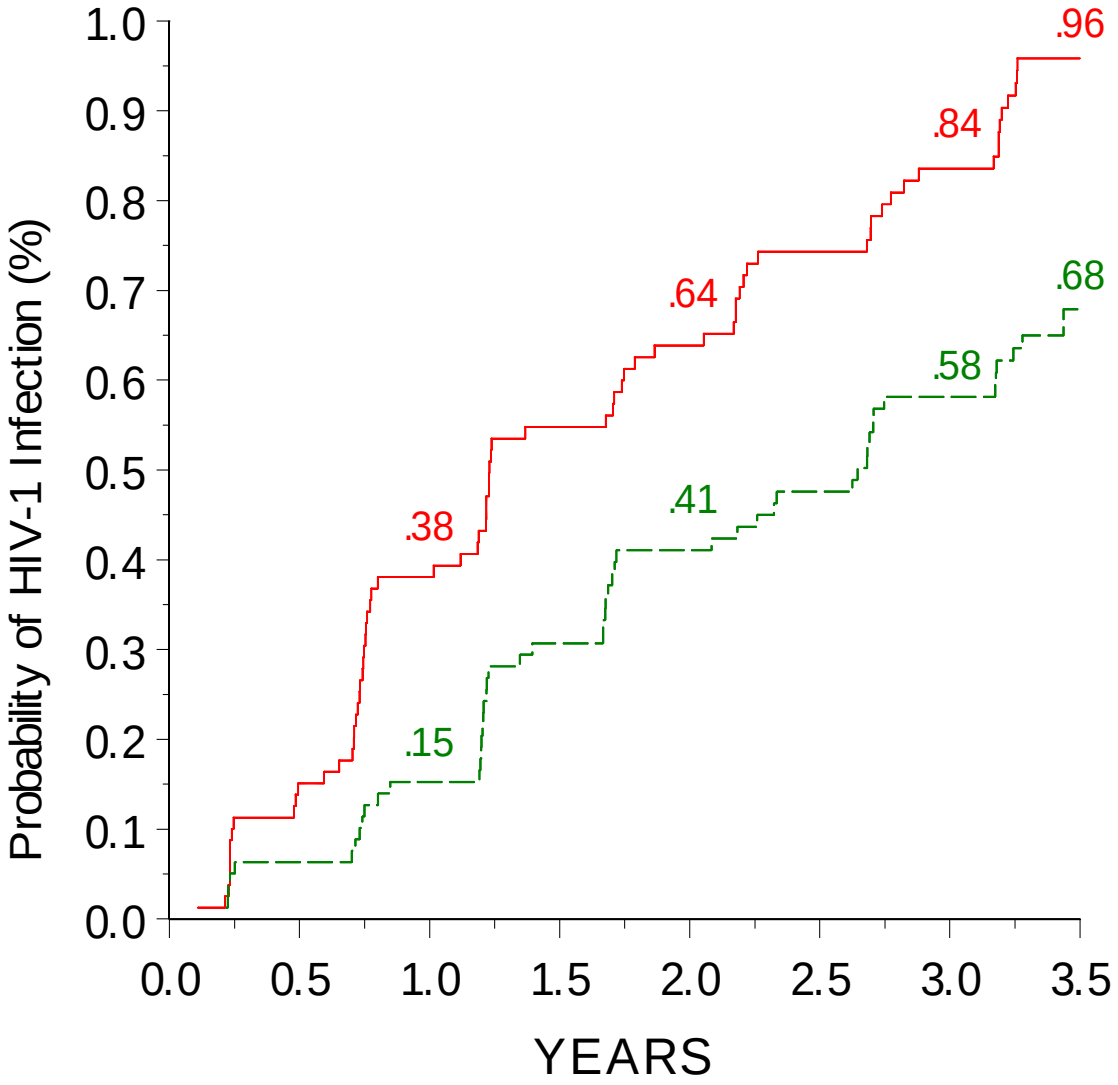
- Bivalent HIV gp120 envelope glycoprotein vaccine containing a **subtype E** envelope from the HIV-1 strain **CM244** and a **subtype B** envelope from the HIV-1 strain **MN**.

RV-144 Vaccination and Follow-up Schedule



ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24

AIDSVAX® B/E gp120 boosting at week 12, 24



Placebo

Vaccine

Vaccine infections: 51
Placebo infections: 74
p = 0.04
Efficacy: 31.2%
95% CI (OBF): 1.1, 51.2

RV144 Acquisition Endpoint: Modified Intent-to-Treat (mITT)

month	***6***	***12***	***18***	***24***	***30***
Events	**16**	**42**	**67**	**82**	**95**
Efficacy	**54%**	**60%**	**44%**	**36%**	**36%**

RV-144 lessons

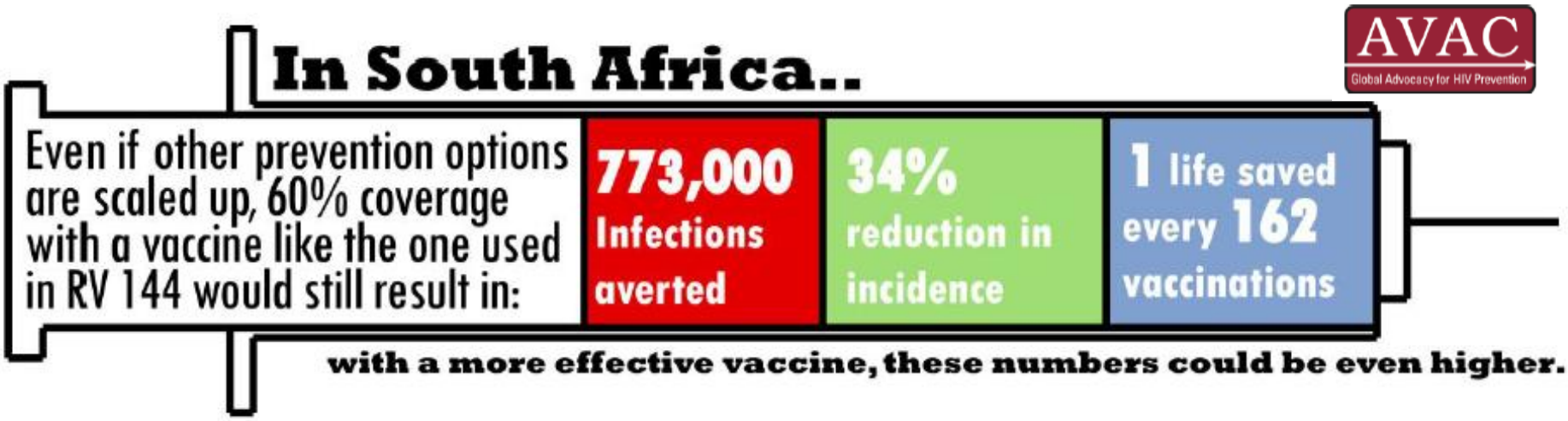
- Protection from infection is possible
  - Low levels of primary neutralizing antibody (Tier 1)
  - Limited CD8 T cell immunity
  - Other immune effectors likely to play a role
  - Highest protection in first 6-12 months
  - Antibody titers appear to wanes in line with protection
  - Follow up studies to determine if boosting can prolong protection

RV-144 setting the bar: room for improvement

- Augment (above the 61% efficacy observed at 1 year post-infection) the overall protection from infection
- Induce durable protection (boosting)
- Improve both components of the vaccine, i.e. the priming component (ALVAC (vector)) and the boosting component (the Env protein)

Lessons from RV144

– Protection from infection is possible
  - Highest protection in first 6-12 months (61%)
  - Antibody titers appear to wanes in line with protection
  - Follow up studies planned to determine if boosting can prolong protection
  - Ongoing work to improve both the priming (ALVAC) and boosting (AIDSVAX) components
  - Planned studies to assess similar approach in Sub-Saharan Africa

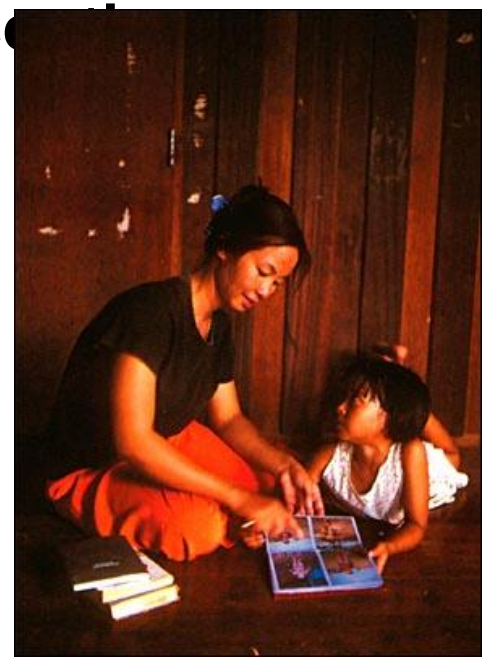


Conclusions

- An HIV vaccine will have to induce a protective antibody response with or without a cellular response.
- IgA or IgG antibody at the mucosae may help prevent acquisition
- Strong CD4+ and CD8+ cell responses will help control replication and increase duration of protection
- There is a good chance that a vaccine will give herd immunity by reducing viral load and transmission.
- Vaccine composition of envelope may have to change with time or region.
- Boosters probably will be necessary.
- Universal vaccination may be necessary.

Pathway to reversing the epidemic

Seeing prevention research/funding as a co



Circumcision

Treatment for prevention

Prophylaxis
(oral, topical, injectable)

Partially effective vaccine

highly effective vaccine

HIV incidence

Behavioral and structural interventions

Science. 2011;333:42-3

Thank you for your attention