CONVEGNO NAZIONALE

Let's stop HIV

Nuove prospettive
e popolazioni speciali

Quanto siamo vicini a un vaccino preventivo?

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HIV vaccines

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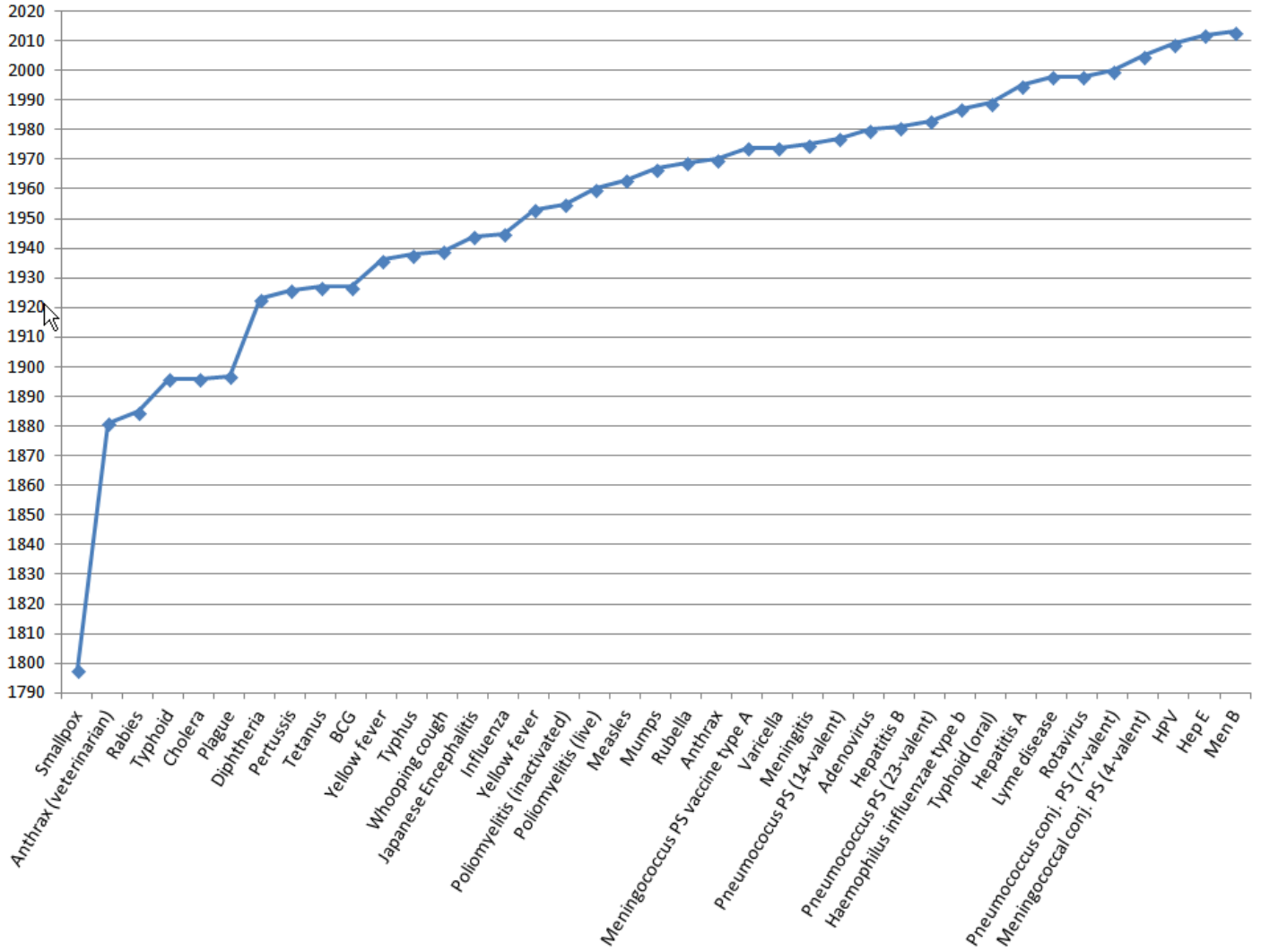
Current Status HIV Epidemic: 2017 (I)

- 36.9 millions people living with HIV globally
- 1.8 million of new infections
- There were 69% of people living with HIV in Africa, 14% in Asia and Pacific and 6% in Europe and North America
- 75% of people living with HIV globally were aware of their status
- 59% of people living with HIV were accessing ART
- AIDS-related deaths reduced by 51% since the peak in 2004

Current Status HIV Epidemic: 2017 (II)

- 940’000 people have died of AIDS-related illnesses in 2017
- New HIV infections have declined by 47% since the peak in 1996
- 77.3 million people have become infected with HIV since the start of the epidemic
- 35.4 million people have died of AIDS-related illnesses since the start of the epidemic

Continuous Generation of Novel Vaccins



Registered Vaccines – Vaccines Under Development

Available vaccines

Bacterial	Viral
Cholera	Adenovirus-based Diseases
Diphtheria	Hepatitis A
Haemophilus influenza	Hepatitis B
Meningococcal meningitis	Human papillomavirus
Plague	Influenza
Pneumococcal pneumonia	Japanese encephalitis
Tetanus	Measles
Tuberculosis	Mumps
Typhoid fever	Polio
	Rabies
	Rotavirus diarrhea
	Rubella
	Smallpox
	Tick-borne encephalitis
	Varicella zoster
	Yellow fever

No vaccines available

Disease
Campylobacter
Chlamydia
Cytomegalovirus
Dengue
Epstein-Barr (mononucleosis)
Helicobacter pylori: Gastrointestinal ulcers
Hepatitis C
Herpes Simplex
HIV
Influenza (universal flu vaccine to replace need for annual flu vaccine)
Leishmaniasis
Malaria
Respiratory syncytial virus
Rhinovirus
Schistosomiasis
Shigella
Streptococcus groups A and B
Tuberculosis
Urinary tract infections
Other: Allergies, Autoimmune diseases, Cancers*

Koff et al., Science 2013

Types of Vaccines (in red those for HIV)

- Live attenuated
- Inactivated
- Toxines
- **Sub-unit**
- **Peptide-based**
- **Combinations**
- Polysaccharides and conjugated
- **Recombinant viruses**
- **Nucleic acids**

General Concepts

- **Vaccine and acute infection**
  - If the disease follows the infection, the cure is associated with the elimination of the infection and of the pathogen
  - The immune response induced by the disease is generally protective against the same disease over time
  - The vaccine must induce an immune response similar to that caused by the natural infection

- **Vaccine and chronic infection**
  - Persistence of a pathogen capable of evading the host immune response
  - The immune response induced by the infection is not sufficient to prevent super-infection
  - The vaccine must induce an immune response different from that generated during the natural infection

General Concepts

- **Ratio benefit/risk of the vaccination**
  - A vaccine is an immunologic active substance
  - Side effects are expected but must be minimized
  - The side effects should be compared to the benefits expected by the vaccination

- **All the components of the vaccine may contribute to the side effects**
  - Substance active
  - Adjuvant
  - Formulation

General Concepts

- **Preventative Vaccine**
  - Product administered to an healthy person to induce an immune response specific and persistent over time in order to prevent the occurrence of a certain disease
  - Almost all the available vaccines have the above properties
- **Therapeutic Vaccine**
  - Product administered to an ill person with the objective of
    - To reduce the symptoms of the disease
    - To block the progression of the disease
  - It induces a novel immune response or modulates the existing immune response
  - Only one therapeutic vaccine in the market (immunotherapy for prostate cancer)
    - Sipileucel-T (PROVENGE™)

Dendreon
Targeting Cancer, Transforming Lives®

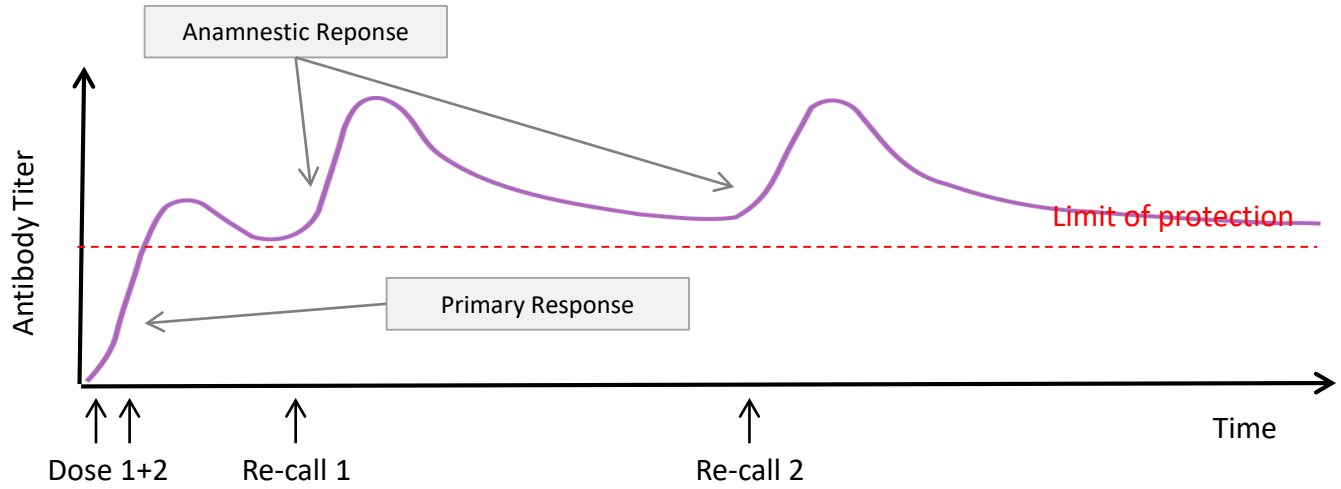
  - Le BCG is used in the case of bladder cancer but the effect is non-specific (immunostimulation)

General Concepts

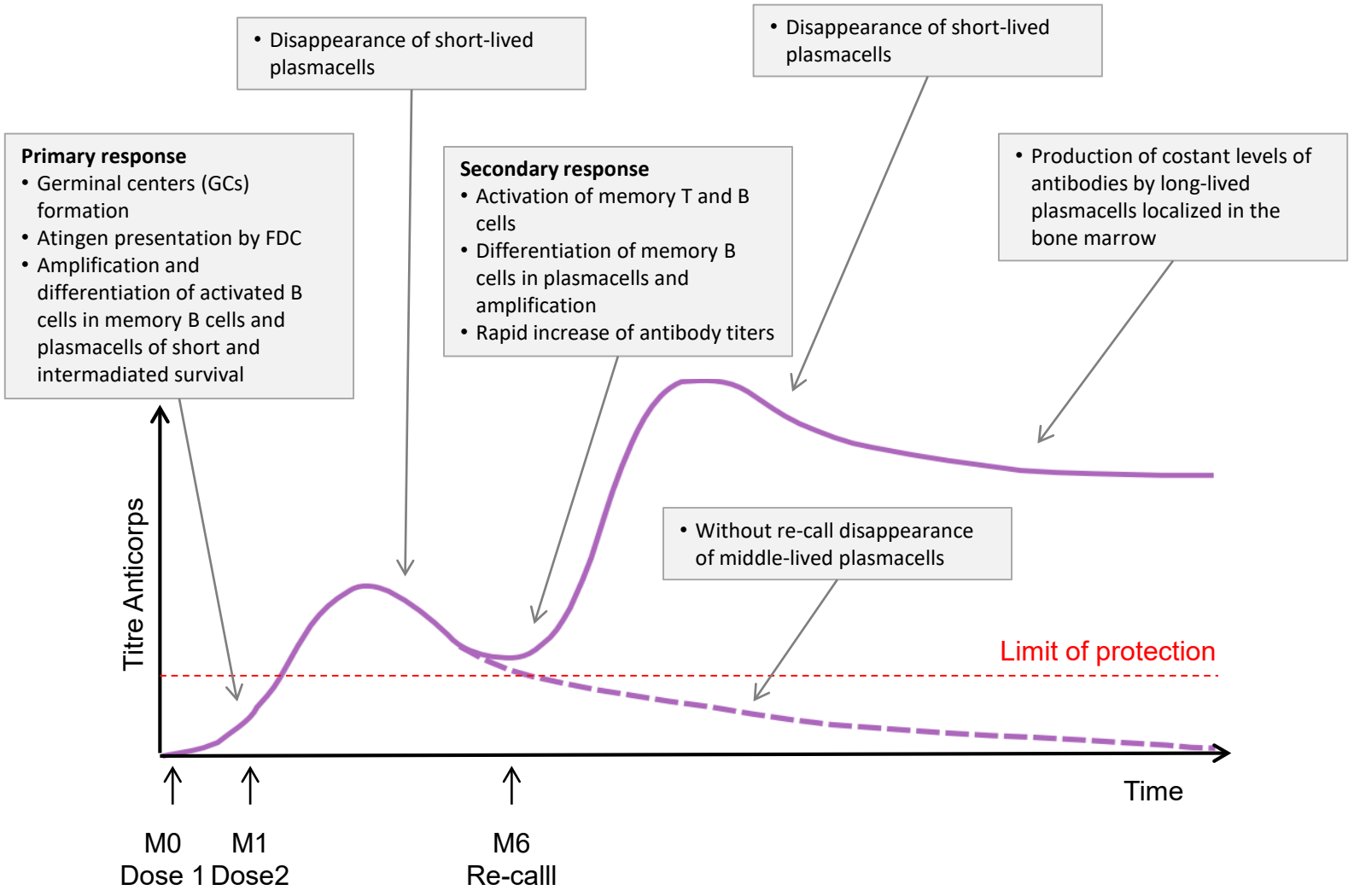
- **Active Immunization**
  - Induction of specific immune reponse(s) to
    - One or multiple antigen(s) administered) (killed vaccine) or
    - Produced by the pathogen itself (live vaccine)
  - Achievement of a durable effect, induction of immunological memory
- **Passive Immunization**
  - Transfert of the effectors components of the immune system specific to an antigen from one person to another person
    - Antibodies
    - Cells
  - Effect waining over time, no immunological memory
- **Immunostimulation/Immunomodulation**
  - For example by agonists of Toll receptors
  - Non-specific enhancement of the immune responses
  - Effect limited over time

Protein Antigen

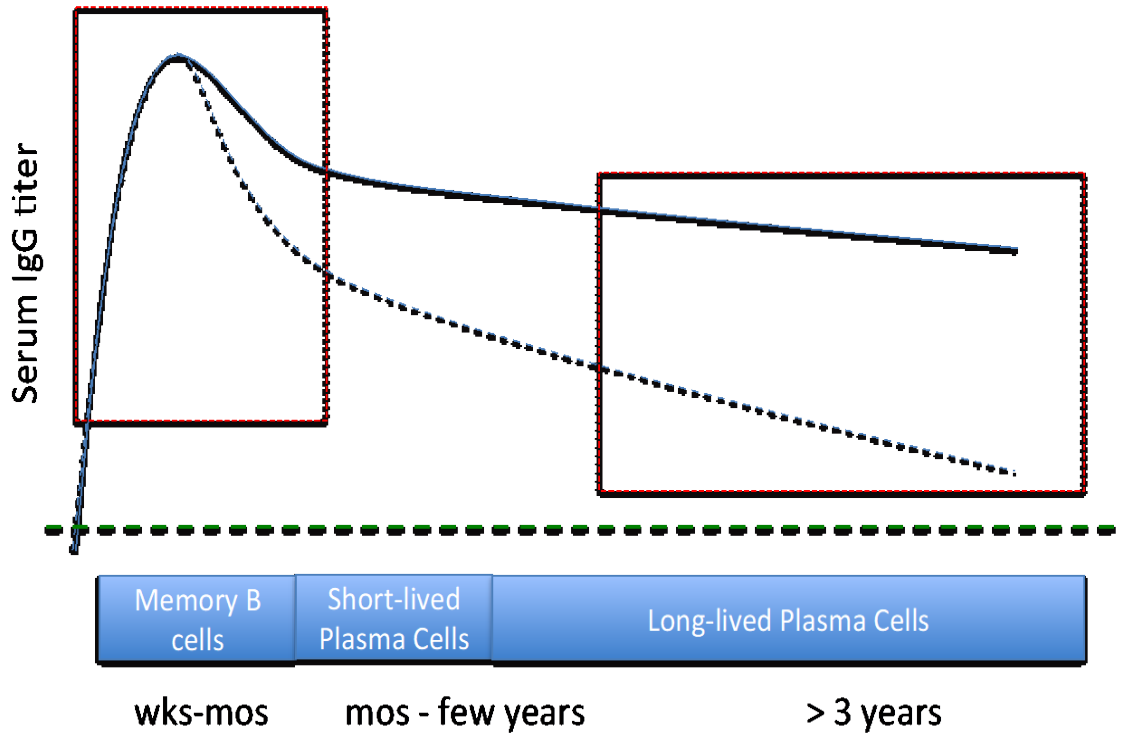
- **Stimulation of B cells**
- **Engagement of T cells and**
  - Formation of germinal centers in lymph nodes or spleen
  - Induction of responses IgM et IgG with affinity maturation
- **Response of variable duration, several months to years**
- **Generally two injections spaced of 1 month to maximise the primary response**
- **The antibody response decreases in time and reaches a plateau within 2-3 years**
- **The need of re-calls depends upon the level of protection, the plateau and the antigen**
- **Examples**
  - Protection of short duration: pertussis vaccine acelluar (*PT, FHA, PRN, FIM-2, FIM-3*)
  - Protection of intermediate duration: tetanus toxoide or diphterique
  - Protection of long duration: hepatite vaccines A and B and human papillomavirus



How To Interpret the Kinetics of Antibody Response ?



The Problem of Eliciting Durable Antibody Response with the Current HIV Vaccine Candidates

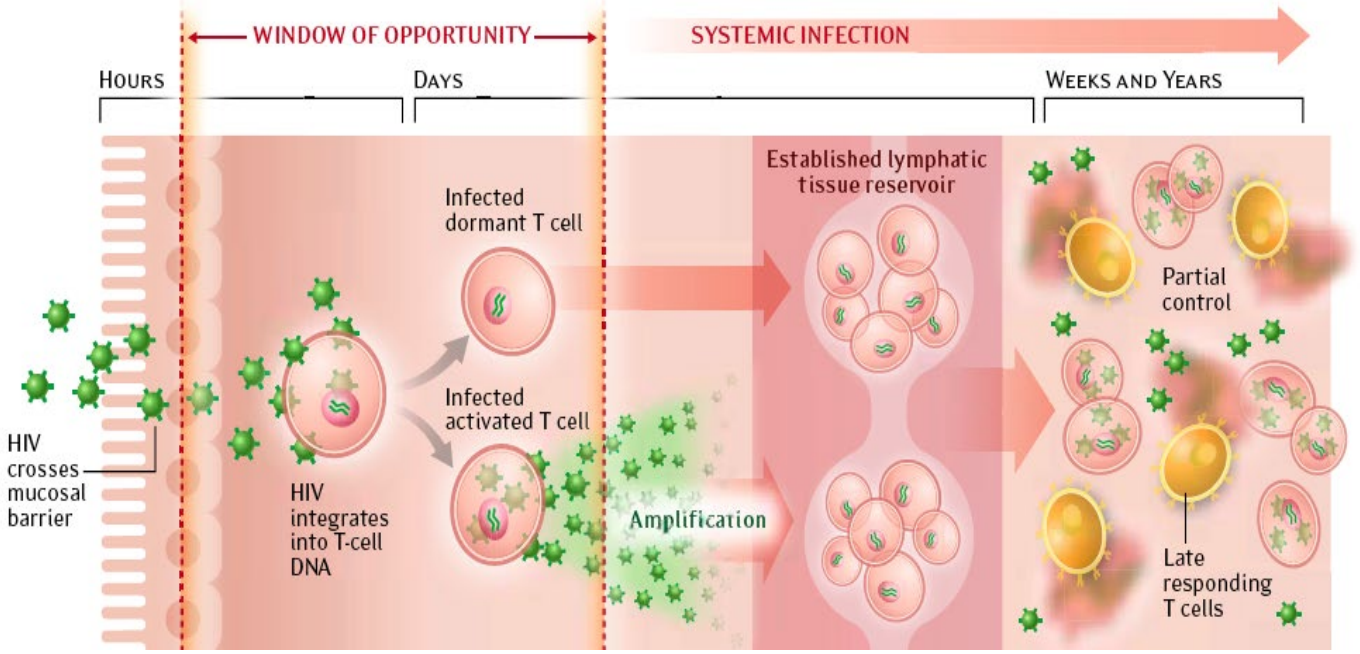


- Better antigens (envelope)
- Better adjuvants
- Replicating viral vectors (?)

Challenges in the Development of an HIV Vaccine

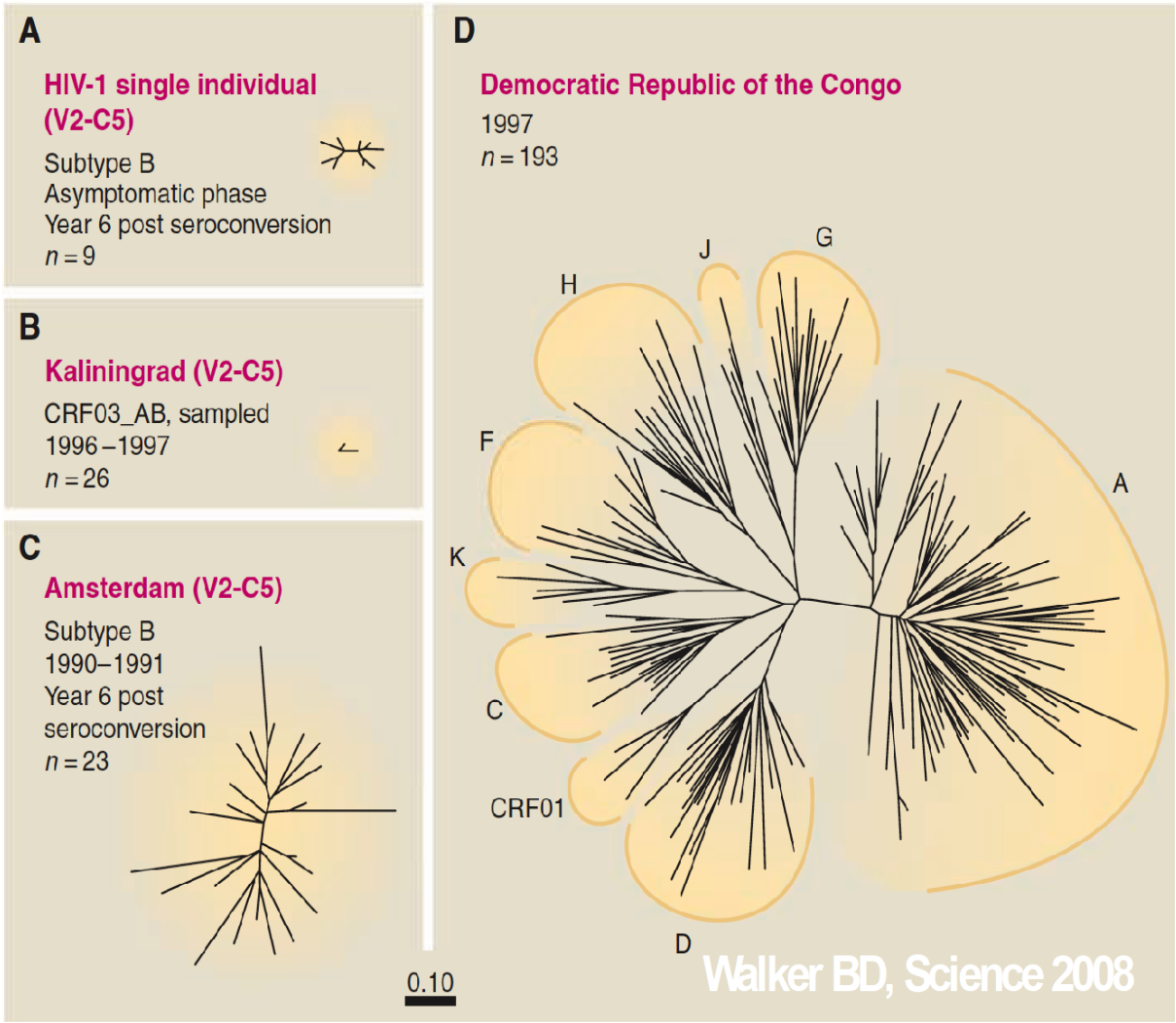
- Narrow window to prevent infection
- Extreme strain variation even in the same individual
- Glycan shield
- Immune escape, class I downregulation, immunosuppression
- Neutralizing antibodies develop late
- No natural recovery from chronic infection
- Undefined biomarkers of protection
- Lack of an ideal animal model

A Narrow Window To Prevent Infection

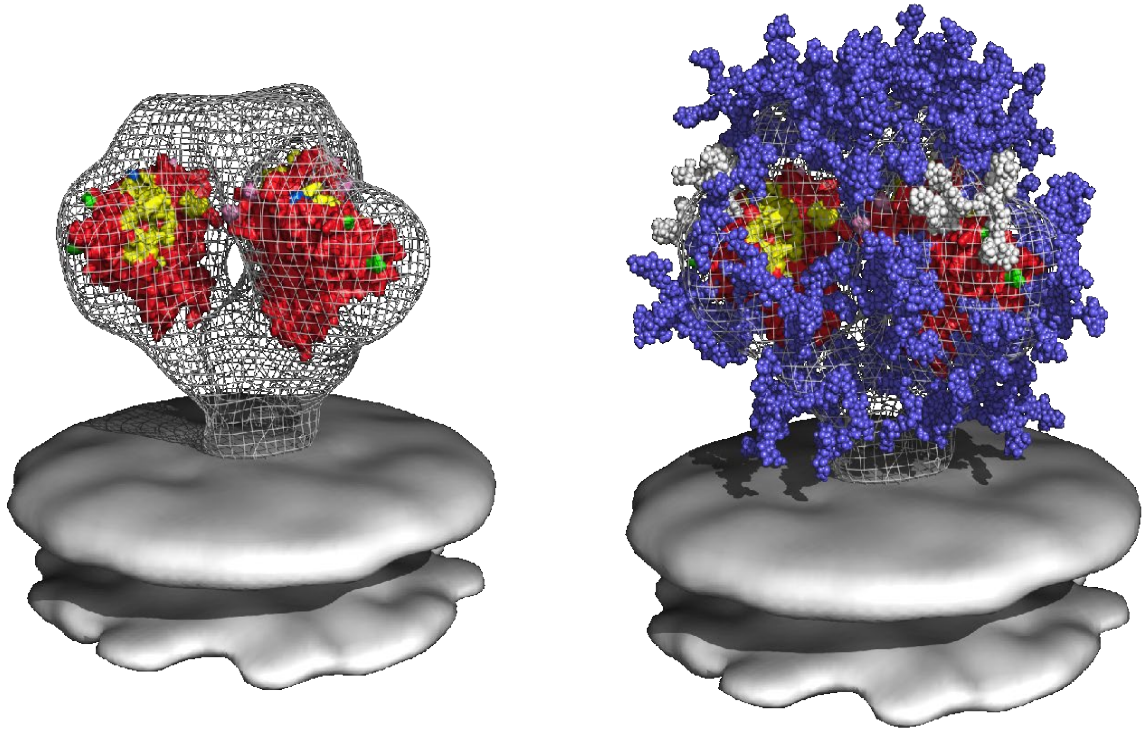


Rapid spreading from mucosal sites and latency

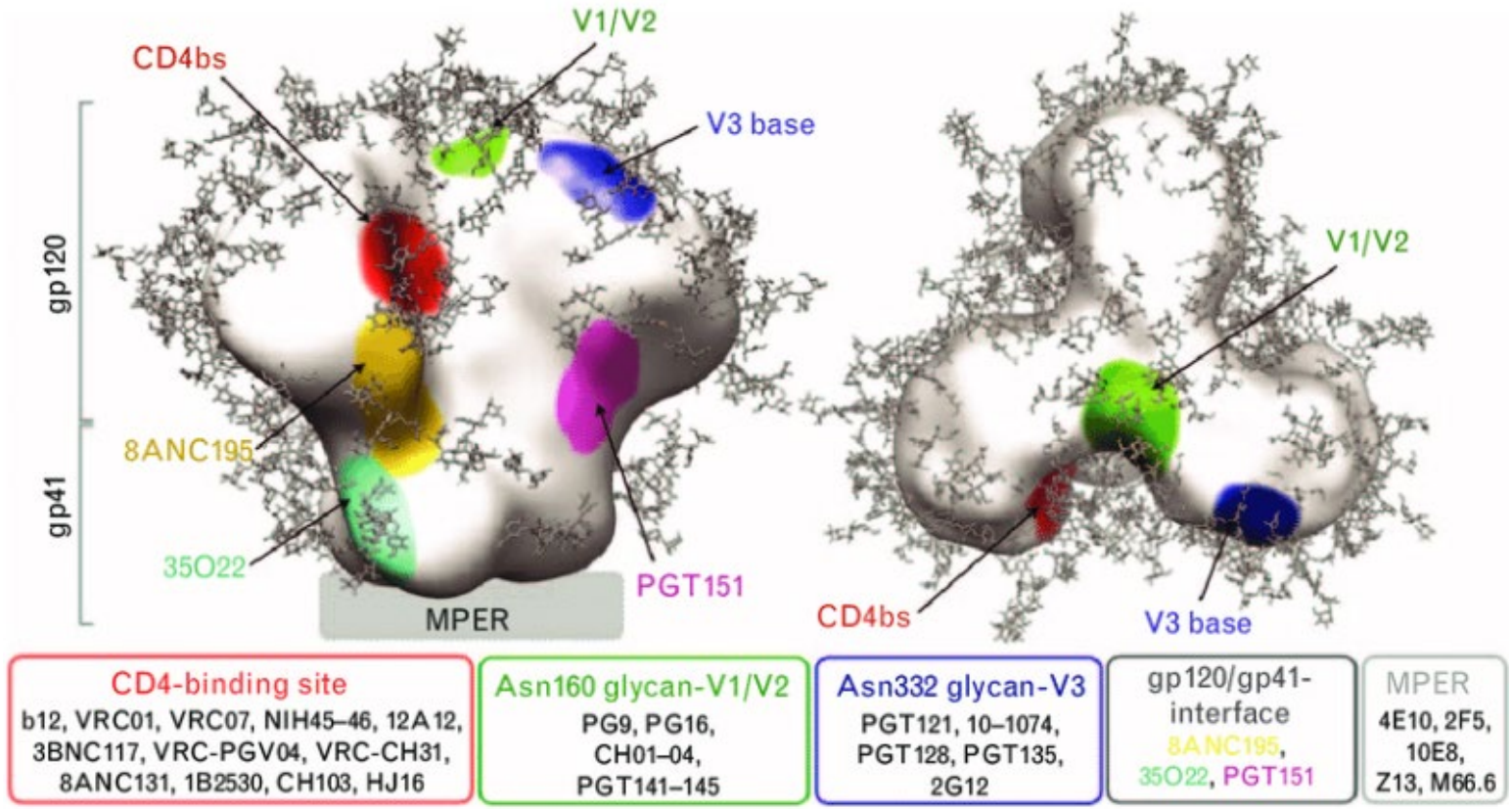
The Extraordinary Diversity of the HIV Envelope



The Glycan Shield



The HIV-1 spike is heavily glycosylated where conserved surfaces (i.e. CD4bs) are difficult for antibodies to access or only formed upon binding to host cell receptors

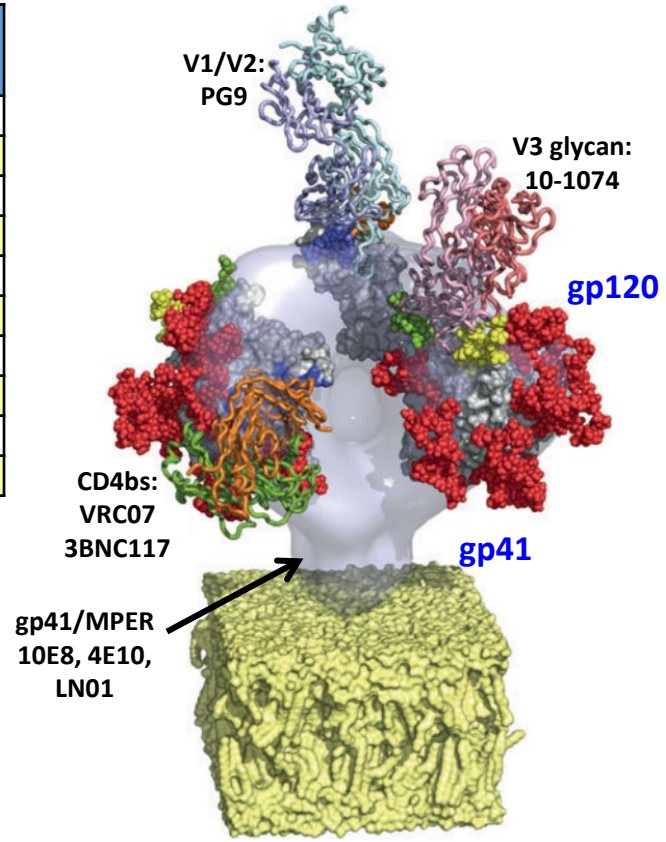


Stuart A Sievers, Louise Scharf, Anthony P West, Pamela J Bjorkman, Antibody engineering for increased potency, breadth and half-life, Current Opinion in HIV and AIDS 10(3) · March 2015

Panel of anti-Env Monoclonal Antibodies

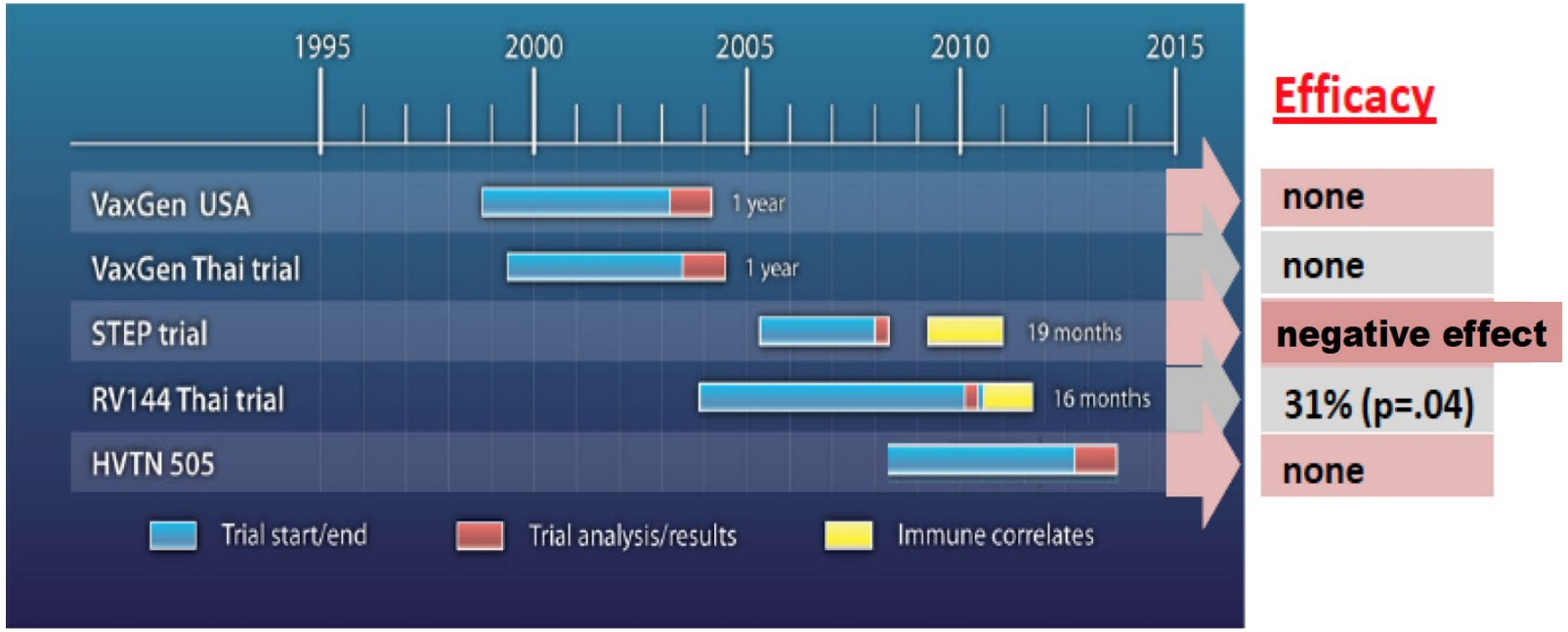
Antibody	Env binding site	Neutralization breadth * IC50 < 50 µg/ml	Neutralization breadth * IC80 < 50 µg/ml	Potency µg/ml *
VRC01	CD4bs	93%	89%	0.32
VRC07	CD4bs	97%	NA	NA
3BNC117	CD4bs	100%	95%	0.06
PG9	V1/V2	79%	51%	0.23
PGT145	V1/V2	78%	53%	0.29
10-1074	V3 glycan	57%	56%	NA
PG121	V3 glycan	70%	55%	0.03
10E8	gp41	98%	NA	0.25
4E10	gp41	98%	36%	3.41
LN01	gp41	97%	NA	NA

* As sited by Broadly Neutralizing Antibodies Electronic Resource
Eroshkin AM et al *Nucleic Acids Res*. 2014; 42:1133



Adapted from Corti D, Lanzavecchia A, *Annu. Rev. Immunol.* 2013; 31:705

HIV Vaccine Efficacy Trials - Duration



Corey L et al. Sci Transl Med 2011;3:79ps13-79ps13

- Vaxgen: HIV gp120
- Merck/NIAID **STEP** trial: Adenovirus 5 (gag T cells)
- Sanofi/MHRP/NIAID/Thai **RV-144** trial: canarypox vector + gp120
- HVTN 505: NIAID-VRC: DNA + Adenovirus type 5

Correlates of Reduced Risk to Infection in RV-144

No association:

- Neutralizing Abs
- Cellular immune responses

Decreased risk associated with:

- Binding IgG Env Ab responses to the V1/V2
- Low binding IgA Env Ab responses
- ADCC activity mostly to the C1 region of Env

Increased risk:

- Systemic IgA against HIV-1 Env
- Env-specific plasma IgAs may diminish the effects of protective IgGs

Durability of the efficacy:

- Limited and waned with time

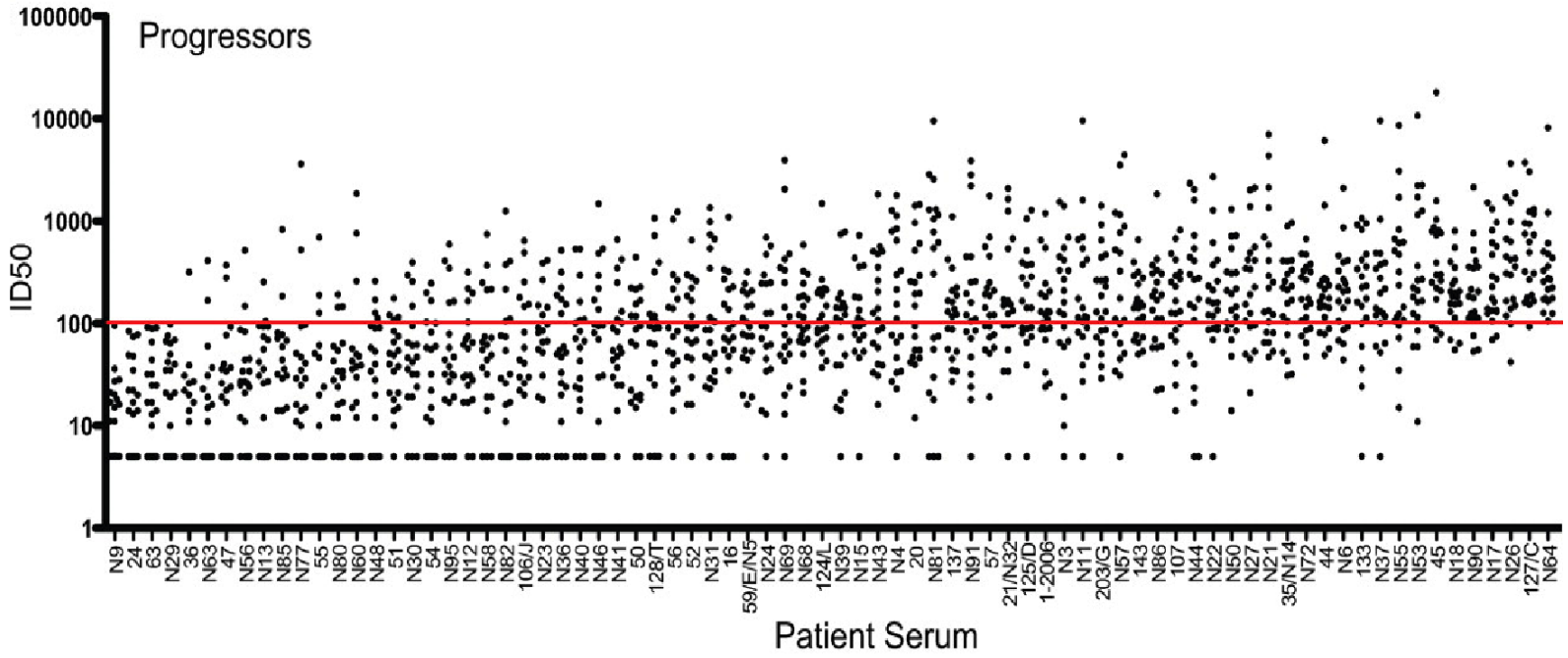
[1]Rerks-Ngarm et al. *New Engl J Med* 2009, 361:2209-2220.
[2]Haynes et al. *New Engl J Med 2*012;366(14):1275-86.
[3]Bonsignori et al. *J Virol* 2012; 86(21):11521-32.

Serum Neutralizing Antibodies Can Prevent Mucosal Infection in Macaques

But none of the vaccines tested so far elicited neutralizing antibodies

Neutralizing Antibody Responses Are Common

110 HIV+ sera tested against panel of 20 viruses



…but are produced only after years of chronic HIV-1 infection

Proof of Concept: Prophylaxis

bNAbs provide protection:

- in the SHIV macaque model
- in the humanized mouse HIV-1 model

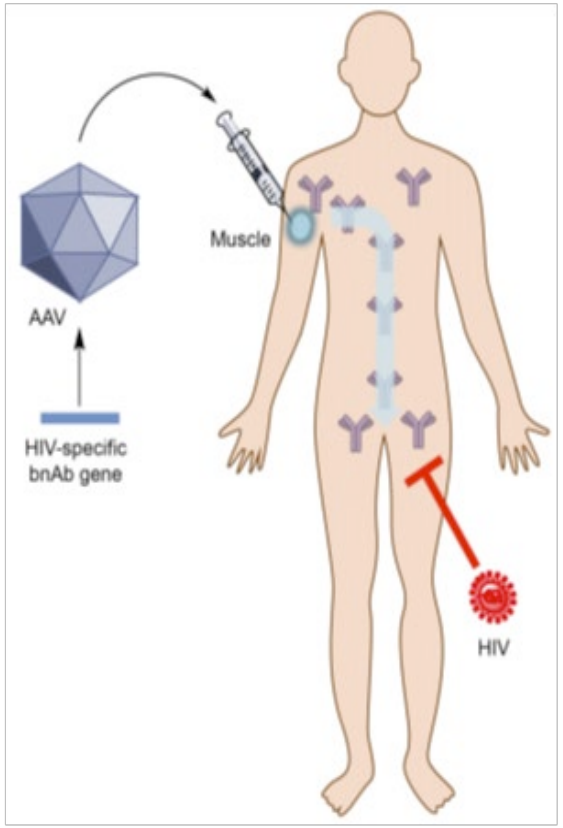
Current improvements:

- Protein engineering to extend half life and increase ADCC
- Vectored immunoprophylaxis using AAV vectors

Vectored Immunoprophylaxis: Alternative Approach of Administering bNAbs

Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys
Johnson et al. Nature Medicine 2009

Vectored immunoprophylaxis protects humanized mice from mucosal HIV transmission
Balazs et al. Nature Medicine 2014



Progress Towards an HIV Vaccine

- We have a detailed structural understanding of the viral spike and of the epitopes targeted by bNAbs
- We know that bNAbs can prevent and control infection
- We know what a vaccine should look like to elicit such bNAbs

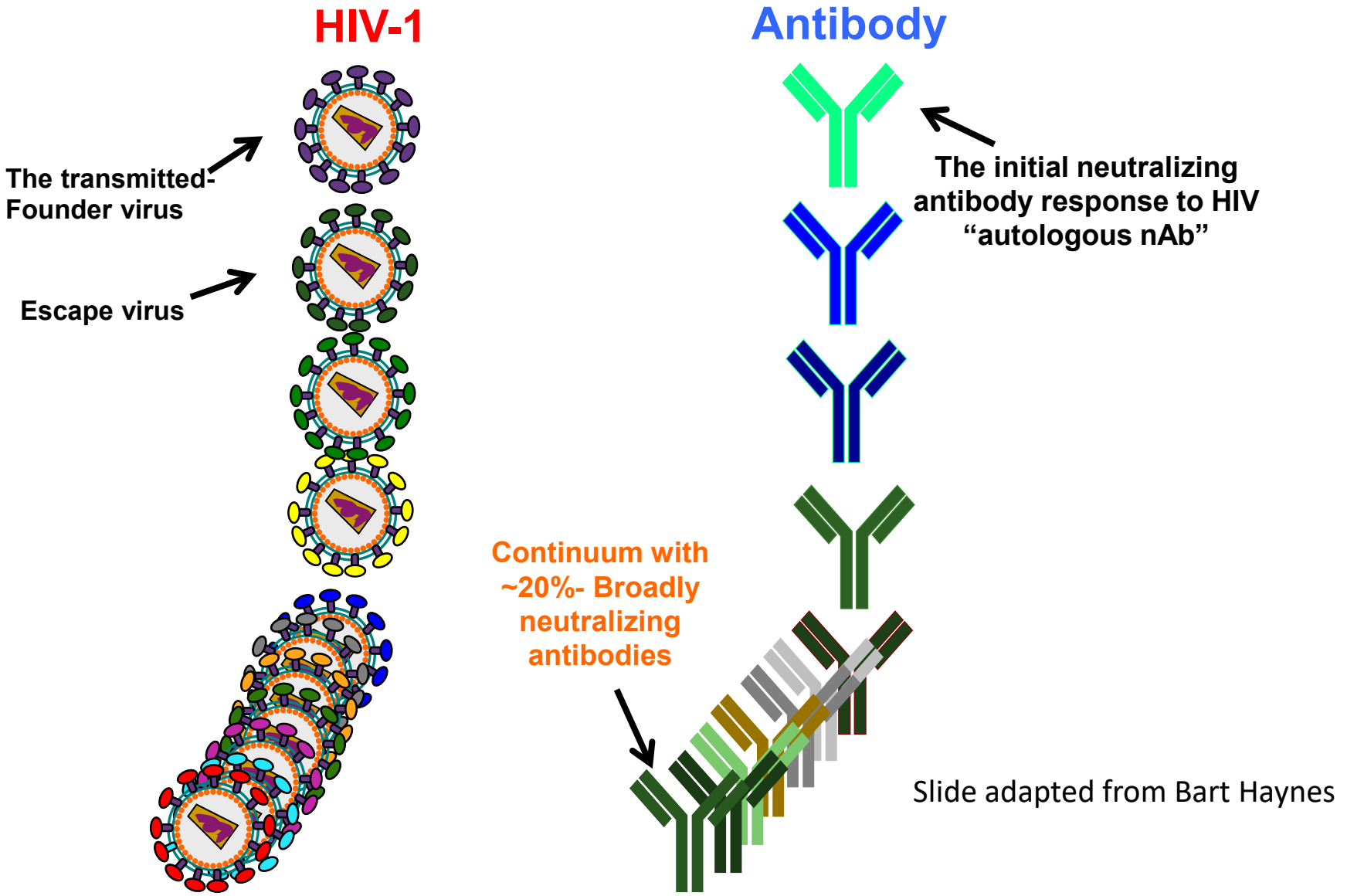
Outstanding questions:

- How do we stimulate the appropriate naive B-cells and promote affinity maturation leading to high affinity bNabs?
- How to immunize to induce durable bNAb responses?

Factors that Limit the Induction of bNAbs

- Diversion of B-cell responses from neutralizing determinants by immune-dominant, non-neutralizing epitopes of Env (decoys)
- The requirements for extensive somatic hypermutations and for complex maturation pathways
- The requirement for specific germline VH allelic variants for a bNAb response

The Evolution of Broadly Neutralizing Antibodies



Slide adapted from Bart Haynes

Challenges for An Antibody-Based Vaccine

- Antigenicity: antigen stabilized to display the “right” sites (manufacturability and developability)
- Immunogenicity: How to efficiently stimulate antibody responses to the specific sites (antigen-guided B cell development?)
- Sustained protective responses: breadth and protective antibody concentration
- Breadth: clade restricted vaccines? (clade C is prominent)
- Role of Adjuvants
- Stability of the trimer Env when mixed with adjuvants
- Role of T_{FH} and Long lived plasma cells

A CMV Vector for HIV Vaccine

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Hansen et al. Nature 2011

Immune clearance of highly pathogenic SIV infection

Hansen et al. Nature 2013

- Rhesus CMV carrying SIV genes induced effector T cell responses against SIV proteins
- 50% of monkeys were protected from challenge
- They were infected but controlled and aborted SIV so that it was undetectable

HIV Vaccines To Elicit a Broadly Reactive T Cell Response

Replicating viral vectors

- Mimic live attenuated and confer durable protective immunity
- Phase I: Sendai, measles, VSV, Pox, Ad4
- Preclinical: HCMV (controls SIV in monkeys; L. Picker)

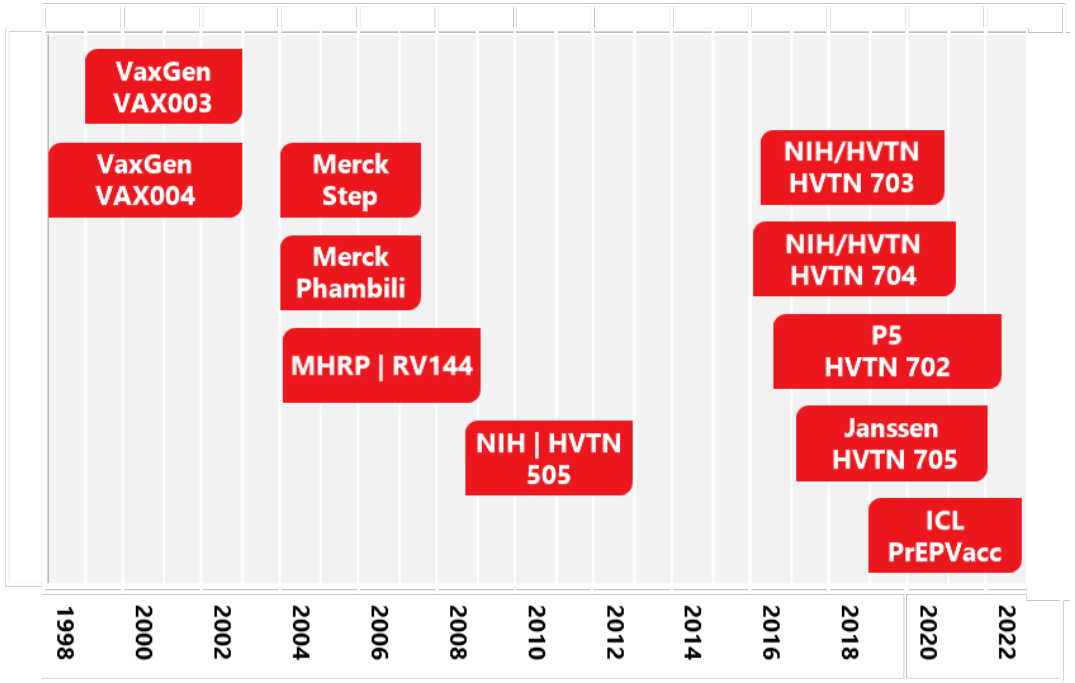
Conserved antigens

- Focus immune responses on conserved regions of HIV
- Genome required for viral fitness
- Phase I (Hanke-Oxford University)

Mosaic Antigens

- Provide optimal coverage of HIV epitopes (Korber)
- Phase I (Haynes-Duke; Barouch/Crucell/J&J- 2014)

HIV Vaccine and Biologic Efficacy Trials



Data Source: AVAC

Ongoing HIV Prevention Efficacy Trials

HVTN 702

- Phase IIb/III Randomized, Double blind
- 5400 people at high risk of infection
- Population: Women and Men
- Vaccines: ALVAC-HIV + subtype C gp120/MF59
- Regimen: 2700 participants will receive an IM injection of ALVAC-HIV (vCP2438) at months 0 and 1, and an IM injection of ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59 at months 3, 6, and 12
- Expected Results: Q4 2021

Ongoing HIV Prevention Efficacy Trials

HVTN 703/HPTN 081 (AMP Study)

- Phase IIb Randomized, Double blind
- 1900 people at high risk of infection
- Population: Women
- Product: VRC01 (human monoclonal antibody against CD4 binding site)
- Regimen: Participants will receive an intravenous (IV) infusion of 10 mg/kg of VRC01 over about 30 to 60 minutes at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72
- Expected Results: Q4 2021

Ongoing HIV Prevention Efficacy Trials

HVTN 704/HPTN 085 (AMP Study)

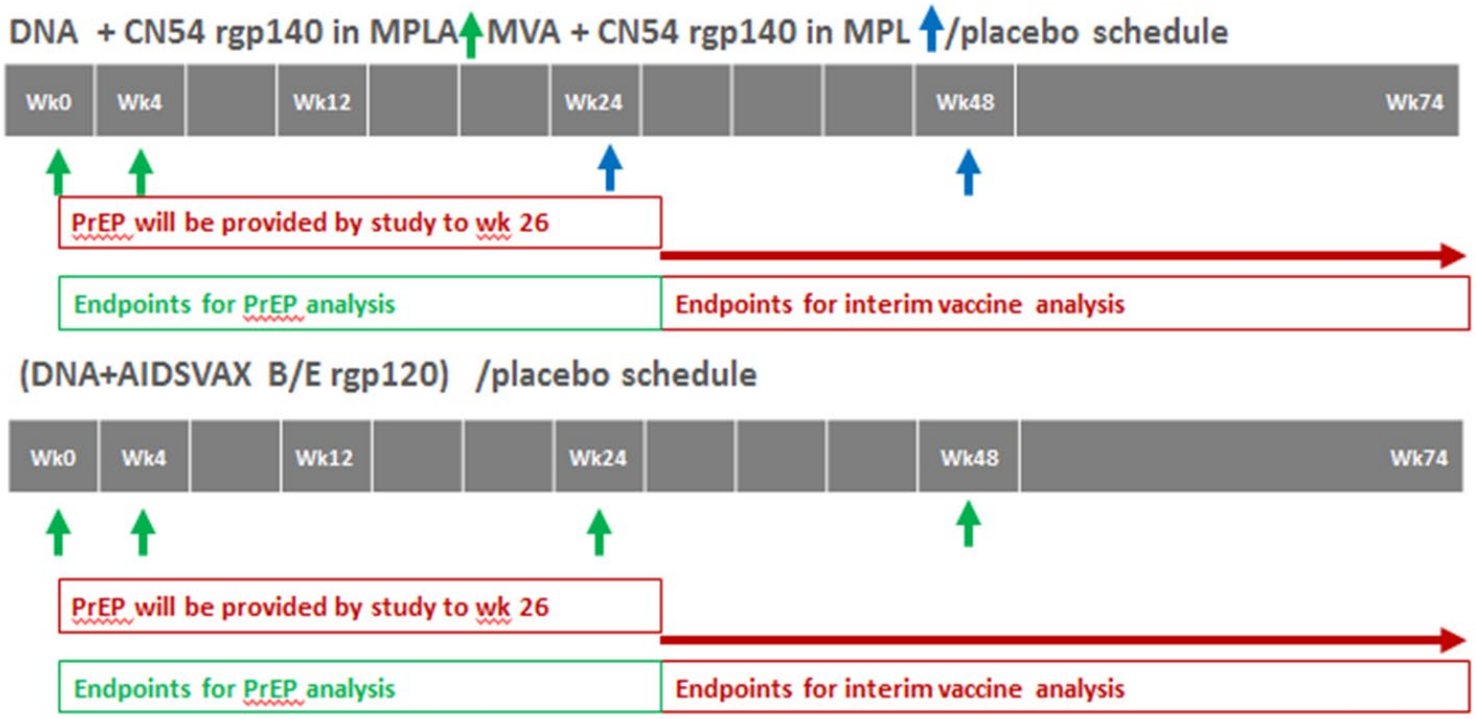
- Phase IIb Randomized, Double blind
- 1700 people at high risk of infection
- Population: Men, Transgender, MSM
- Product: VRC01 (human monoclonal antibody against CD4 binding site)
- Regimen: Participants will receive an intravenous (IV) infusion of 10 mg/kg of VRC01 over about 30 to 60 minutes at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72
- Expected Results: Q1 2022

Ongoing HIV Prevention Efficacy Trials

HVTN 705

- Phase IIb/III Randomized, Double blind
- 2600 people at high risk of infection
- Population: Women
- Vaccines: Ad26.Mos.HIV + Clade C gp140
- Regimen: Participants will receive Ad26.Mos4.HIV 5*10^10 virus particles (vp) as 0.5 milliliter (mL) via Intramuscular (IM) injection into the left deltoid on Months 0, 3, 6, and 12 and Clade C gp140 (250 [microgram] mcg) co-formulated with Aluminum phosphate adjuvant as 0.5 mL IM into the right deltoid on Months 6 and 12.
- Expected Results: Q1 2022

PrEPVacc



Up to 556 participants will be randomised to receive each of the vaccine combination or placebo at a 1:1:1 ratio

PrEPVacc Trial

Schedule	Week 0 Visit 2	Week 4 Visit 4	Week 16 Visit 7	Week 24 Visit 8	Week 48 Visit 12
Arm A **Vaccine combination**	DNA-HIV-PT123 AIDSVAX® B/E	DNA-HIV-PT123 AIDSVAX® B/E		DNA-HIV-PT123 AIDSVAX® B/E	DNA-HIV-PT123 AIDSVAX® B/E
Arm B **Vaccine combination**	DNA-HIV-PT123 CN54gp140 +MPLA-L	DNA-HIV-PT123 CN54gp140 +MPLA-L		MVA CN54gp140 +MPLA-L	MVA CN54gp140 +MPLA-L
Arm C **Placebo control**	N/saline	N/saline		N/saline	N/saline
PrEP Candidate **TAF/FTC**	60 tablets	90 tablets	+/-30 tablets		
PrEP Control **TDF/FTC**	60 tablets	90 tablets	+/-30 tablets		

The Target Product Profile for an HIV Vaccine

Variable	Minimum	Best Case
Indication	Prevention of acquisition OR control of HIV infection	**Prevention of acquisition AND control of HIV infection**
Efficacy	**≥60% reduction in HIV incidence OR ≥ 2 log reduction of viral load**	**≥ 90% reduction in HIV incidence AND ≥ 3 log reduction in viral load**
Product Platform	Prime-Boost (Two) platforms	**Single product platform e.g. replicating vector or VLP**
Target Population	At risk for HIV infection	**Pre-teen girls and boys (similar to HPV vaccine)**
Target Countries	Sub-Saharan Africa (SSA)	**Global, including SSA**
Immunizations	3 or less + annual booster	**3 or less**
Formulation	TBD	**TBD**
Stability	TBD	**TBD**
Cost	<$40 per regimen in LIC	**<$20 per regimen**

The Persistence of Scientific Challenges

Lack of understanding of how to drive specific, broad, potent, and durable protective immune responses against HIV in humans

Problem	Issue(s) to Address
Specificity and Breadth	- Identification of immunogens(s) required in the vaccine - Somatic hypermutation and affinity maturation of HIV-specific bnAbs - Overcoming immunodominance of "decoy" epitopes for effective Ab and CMI responses
Potency and Durability	- Adjuvants and vectors capable of providing long-lived, potent immune responses for HIV antigens
Limitations of Animal Models for predicting human vaccine immunogenicity and efficacy	- Lack of enabling environment for cost effective development and small batch manufacturing of large numbers of immunogens for conducting iterative, exploratory clinical trials

Koff, Gust, Plotkin et al, Nature Immunology, 2014

Challenges Other Than Scientific

- Development and implementation of Pre-exposure prophylaxis (Pr-EP) with antiviral drugs
- Pr-EP has been proposed as a tool to curtail HIV epidemic
- Pr-EP is being proposed as a tool to be used in prevention
- The world wide implementation of prevention interventions such as Pr-EP (antivirals) and bNabs may render impossible the evaluation of HIV vaccine candidates in efficacy trials