MRC | MRC/UVRI Uganda Research Unit on AIDS

Uganda Virus Research Institute

HIV vaccine portfolio and research opportunities

Medical Research Council (MRC UK)
Uganda Virus Research Institute (UVRI)

Pontiano Kaleebu
UVRI

Summary

- Challenges and successes
- Pipeline
- Possible research questions and other potential areas for EDCTP

How different is HIV

Classical Vaccinology

The response to natural infection provides the proof of concept

HIV Vaccinology

No proof of concept

HIV is different

HIV integrates into the host cell genome, short window of opportunity before integration

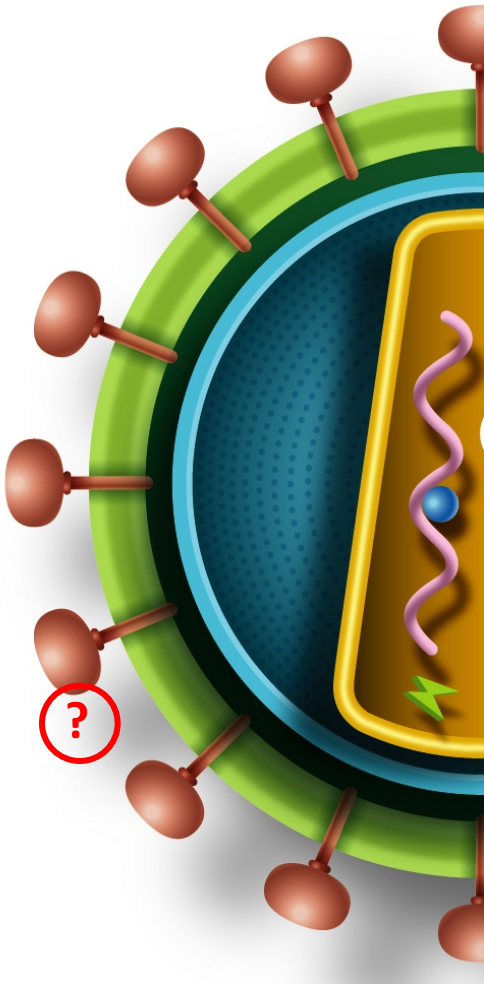
Correlates of protective immunity remain undefined

Protective immunity against subsequent infection does not appear to occur-documented super infection

HIV antigens required for protection remain undefined

Variability of HIV and escape from immune pressure

Limitations in the animal models for HIV/AIDS



AIDS vaccine efficacy trial results

Year Completed	Product/ Clade/ Trial Name	Countries	Number Of Participants	Result
2003	AIDSVAX B/B VAX003	Canada, Netherlands, Puerto Rico, US	5,417	No effect
2003	AIDSVAX B/E VAX004	Thailand	2,546	No effect
2007	MRK-Ad5 B Step	Australia, Brazil, Canada, Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico, US	3,000	Immunizations halted early for futility; subsequent data analysis found potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men.
2007	MRK-Ad5 B Phambili	South Africa	801	Immunizations halted based on Step result; additional data presented in May 2013.
2009	ALVAC-HIV (vCP1521) and AIDSVAX B/E Thai Prime-Boost/RV 144	Thailand	16,402	Modest effect (31.2%)
2013	DNA and Ad5 A/B/C HVTN 505	US	2,500	Immunizations halted early for futility; vaccine regimen did not prevent HIV infection nor reduce viral load among vaccine recipients who became infected with HIV; follow-up continues.

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Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitraporn Karnasuta, Ph.D., Ruengpueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.

RV 144 has shown that planned efficacy trials are important and can complement basic research in our efforts to understand protective immune responses

Broadly neutralizing HmAb

1. Bonsignori M, Hwang KK et al. J Virol 2011;85:9998–10009.
2. Walker LM, Phogat SK, et al. Science 2009;326:285–9.
3. Corti D, Langedijk JP et al. PLoS One 2010;5:e8805.
4. Scheid JF, Mouquet H et al. Science 2011;333:1633–7.
5. Wu X, Yang ZY, et al. Science 2010;329:856–61.
6. Walker LM, Huber M. et al. Nature 2011;477:466–70.

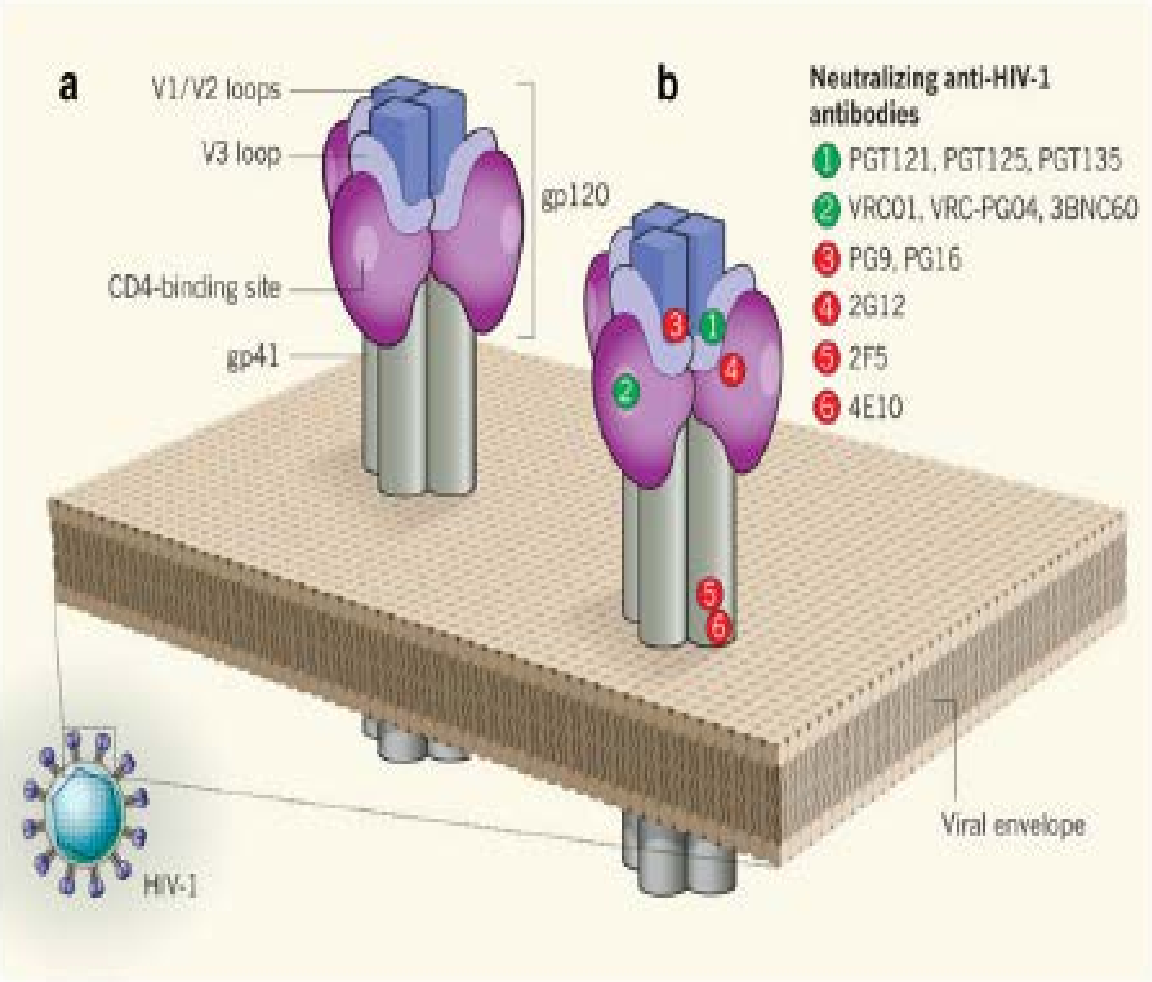
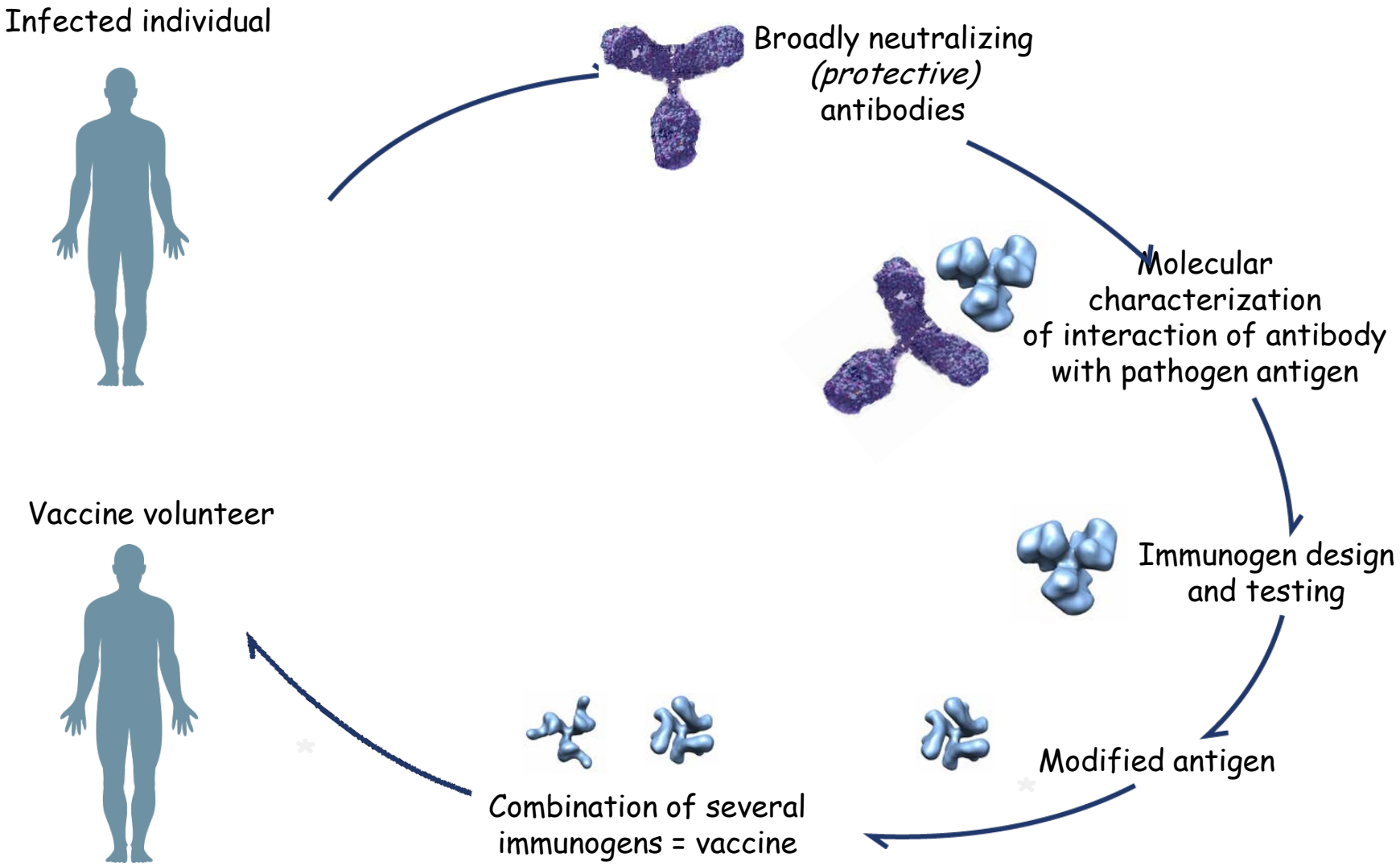


Fig. 1. The envelope of HIV-1 carries spikes. (a) Each spike is made of three molecules of the surface glycoprotein gp120 and three molecules of the transmembrane glycoprotein gp41. Glycoprotein gp120 contains variable V1/V2 and V3 loops, as well as the binding site for CD4. (b) The binding sites of broadly acting and potent HIV-1-specific neutralizing antibodies are shown as colored circles.

Retrovaccinology: From antibody to antigen



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

Other vaccines providing high levels of protection in SHIV model

1. Adeno/pox and Adeno/adeno vector
2. DNA + Ad5
3. Electroporated DNA + IL2 + Ad5
4. CMV-based vaccines

Human clinical trials

Vaccines with high immunogenicity include:

- DNA-MVA
- DNA-NYVAC
- Chip Adeno-MVA

Other research developments

- B cell maturation
- Importance of CD4 T cells
- Transmitted virus
- Elite controllers
- Viral suppression assays

Pipeline

Current to next 3 years in clinic

On-going trials-IAVI database August 2013

Globally:

36 phase I/IIa and one IIb efficacy trial

- IIb halted but participant follow up continues
- 20 prime-boost - DNA + Viral vector (Pox and Adeno)

  DNA: Multiclade, Multigene

  Pox mostly MVA; various adeno, 5,26, 35 etc
- Improved DNA delivery e.g electroporation

On-going trials in Africa IAVI report by August 26 2013

Title	Phase	Strategy	Product	Country
Extension HVTN 037/SAAVI 102	I	Protein	Sub C gp140	South Africa
HVTN 073	I	DNA/Viral Vector-Pox	SAAVI DNA-C2/SAAVI MVA-C	South Africa, USA
HVTN 086, SAAVI 103	I	Viral Vector-Pox/DNA protein	SAAVI MVA-C/SAAVI DNA-C2/Oligomeric gp140/MF59	South Africa
IAVI S001	I	Viral Vector-Replicating/Viral Vector-Adeno	SeV-G/Ad35-GRIN	Kenya, Tanzania, Uganda, Rwanda
RV262	I	DNA/Viral Vector Pox	Pennvax-G/MVA-CMDR	Kenya, Tanzania, Uganda, USA
TaMovac II	II	DNA/Viral Vector-Pox	HIVIS-DNA/MVA-CMDR	Tanzania, Mozambique

The Global HIV Vaccine Landscape - 2013

Basic research → Applied research → Preclinical development → Phase I / II → Large-scale Efficacy trials

Improving RV-144: CMI + non-neutralizing Ab

- ALVAC + gp120 Licensure Trial in Thailand (planned 2015)
- ALVAC + gp120/MF59 Licensure RSA (planned 2015)
- DNA + NYVAC + gp120 Test of Concept Trial
  NYVAC + gp120 (planned 2015)

Prime Boost Candidates- improve the breadth of vaccine

- Ad26 + MVA (mosaic antigens)
- Chimp Ad 63 + MVA HIVconsv (conserved antigens)
- epDNA + IL12+ Ad35 or chAd63
- DNA + MVA (Multiple)
- DNA + Tiantian-VV
- Electroporated DNA
- MVA (multiple)

Replicating Vectors- for durable responses to mimic live attenuated

- CMV
- CDV
- VSV
- Pox
- Adeno

→

- Measles virus
- Attenuated VSV
- Vaccinia virus Tiantan
- Sendai

Candidates to Elicit bnAbs

- HIV ENV trimers
- Designed Immunogens
- AAV –bnAb delivery

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Follow-on Trials Based on RV144: Strategy includes development and research tracks

RV144 FOLLOW-UP: Thailand

Research Studies:

- **RV305** protein boost in volunteer-subset from RV144
- **RV306** expanded immunogenicity of RV144 regimen
- **RV328** AIDSVAX B/E study

Partners/Funders:

US Army, Thai government, NIH, Sanofi Pasteur, BMGF

LICENSURE TRIAL: Thailand

Population: MSM, high-risk

Products: ALVAC (Sanofi Pasteur) + gp120/adjuvant (such as MF59)

Partners/Funders: US Army, Thai government, NIH, Sanofi Pasteur, BMGF, Novartis

LICENSURE TRIAL: South Africa

Population: Heterosexual, high-risk

Products: ALVAC (Sanofi Pasteur) + gp120/MF59 (Novartis)

Partners/Funders: NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

RESEARCH TRIAL

Population: Heterosexual, high-risk

Products: DNA + NYVAC (Sanofi Pasteur) + protein/adjuvant (such as MF59) vs. NYVAC (Sanofi Pasteur) +protein/adjuvant

Partners/Funders: NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

Source: This schematic comes from the Pox-Protein Public Private Partnership (P5), a collaboration spanning four continents established in 2010 to build on the results of RV144. P5 partners include the US NIAID, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the US Military HIV Research Program, Sanofi Pasteur and Novartis Vaccines and Diagnostics.

MHRP clinical vaccine development

ALVAC prime and gp 120 boost

- gag/pol/env

- env B/E

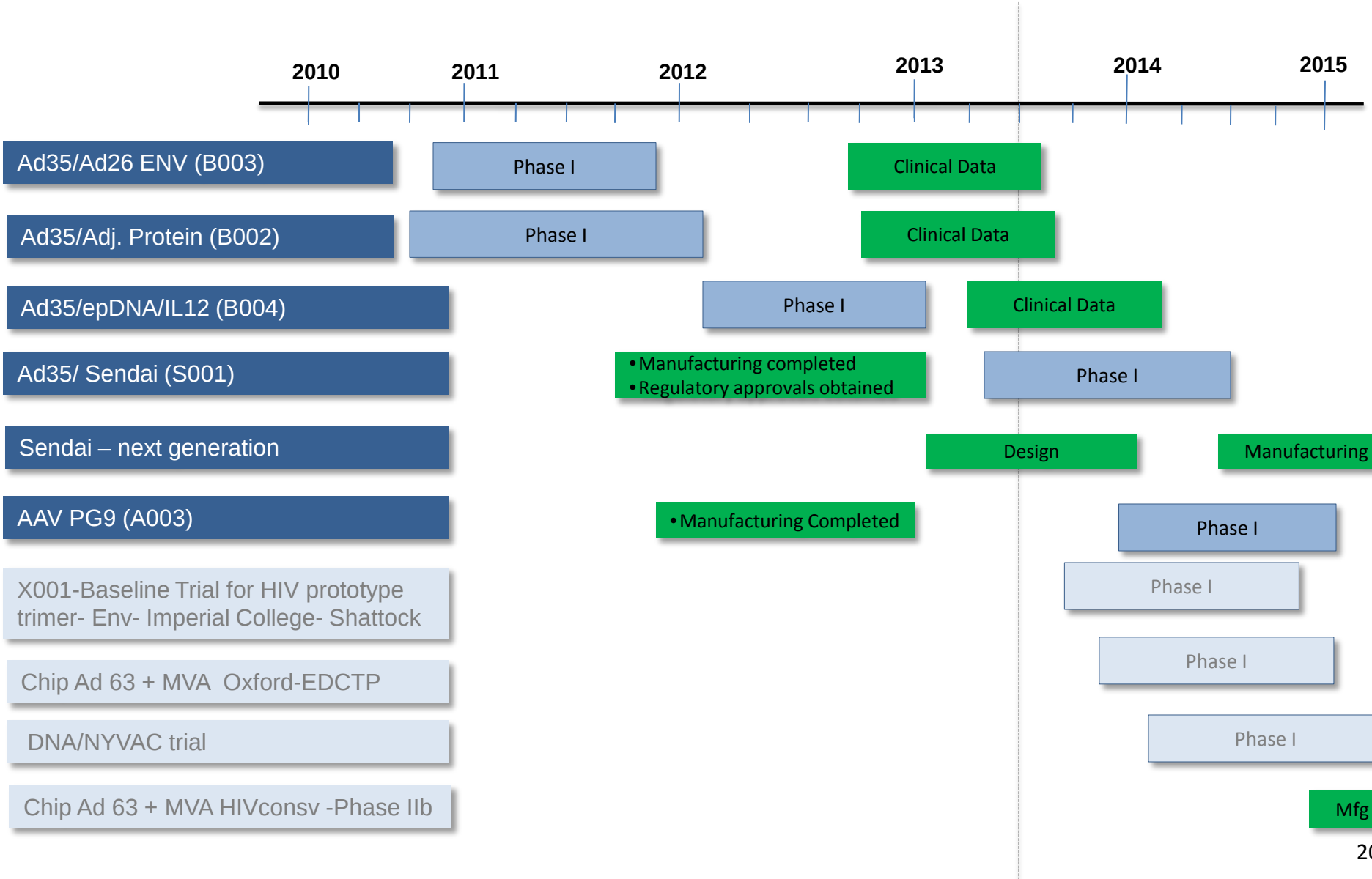
Ad26 prime and MVA boost

gag/pol/env with mosaic inserts

DNA prime and MVA boost

1) ***Inovio DNA prime***
2) ***HIVIS/TaMoVac DNA EDCTP funded***

IAVI Clinical Trials Program
2013 Plans for Data and New Trials



NIAID Pipeline Summary

- **T cell vaccines**
  - DNA with electroporation + adjuvant
  - Viral-vector approaches
    - VSV, novel serotype Ads, Chimp Ad, repAd4, NYVac, MVA, AAV1
  - HIV inserts
    - Native, codon optimized, or mosaic, Gag, Pol, and Envs multiclade

Pipeline Summary

- **B cell vaccines**
- **Protein-based immunogens in the following classes:**
  - Native trimers or molecules engineered to resemble native trimers
  - Intermediate immunogens: gp120s, gp41, etc.
  - Minimal immunogens: immunogens designed to selectively express subdominant BnAb epitopes (through scaffold displays, etc.)

UK HVC Clinical Strategy

- Core support for GMP material, data management and laboratory
  - ❖ Clinical trial costs through grants (EDCTP, MRC)

- D.A.M.P – DNA, Adenovirus, MVA, protein
  - ❖ **D> DNA-C**: ZM96 gag-pol-nef and CN54 env (Geneart)
  - ❖ **A> Chimp Adenovirus** ChAdC63 + SAd30/39 – on hold pending conclusion regarding adenovirus vectors
  - ❖ **M> MVA-C CN54** gag-pol-nef & env (M. Esteban)
  - ❖ **P> Protein**: recombinant **CN54 GP140**. (Polymun)
  - ❖ **Adjuvant**: **GLA** (IDRI)
- Exploratory trials
  - ❖ Adding UKHVC adjuvanted protein to DNA/MVA prime (following HIVIS/TaMoVac DNA/MVA as well as the UK HVC DNA MVA); specimens from 40 TM01 ppts being analysed now
  - ❖ To assess accelerated schedule after DNA priming giving the MVA/protein at the same time, compared to consecutively in Phase I (spoke 3), or compared to MVA alone in Phase IIa (TaMoVac II)
  - ❖ Other combinations – DNA/protein and possibly with Adeno in future

A comprehensive and integrated approach toward an HIV/HCV vaccine

Candidate vaccine

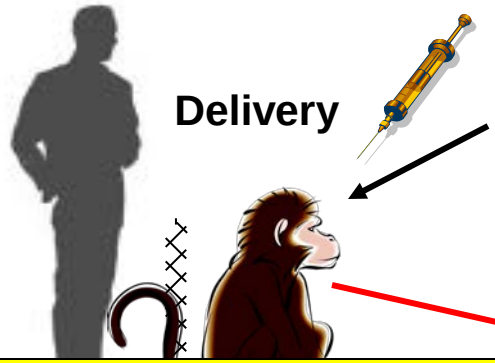
Development & in vitro validation

NH2-IRIQRGPGRAFVTIG-CO-NH-CH-CO-NH2

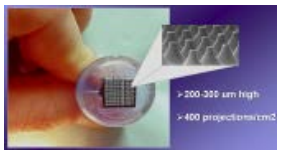
Lipopeptides

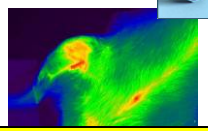
DNA

DC targeting Ex vivo pulsed DC



Delivery

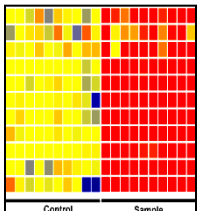




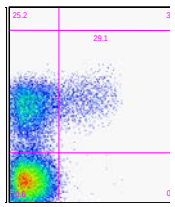
Vaccine biodistribution

Developement of an epitope-based vaccine approache that could be employed in prime-boost strategy combined with recombinant viruses aimed to elicit strong, long lasting, polyepitopic T and B-cell responses focused on highly conserved epitopes

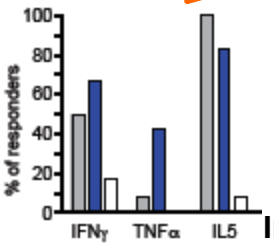
Viral changes/ adaptation



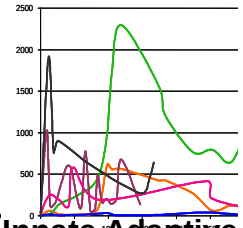
Gene profiling



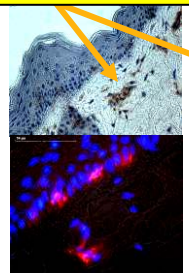
Cell responses

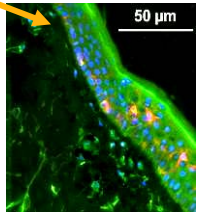


Cytokines



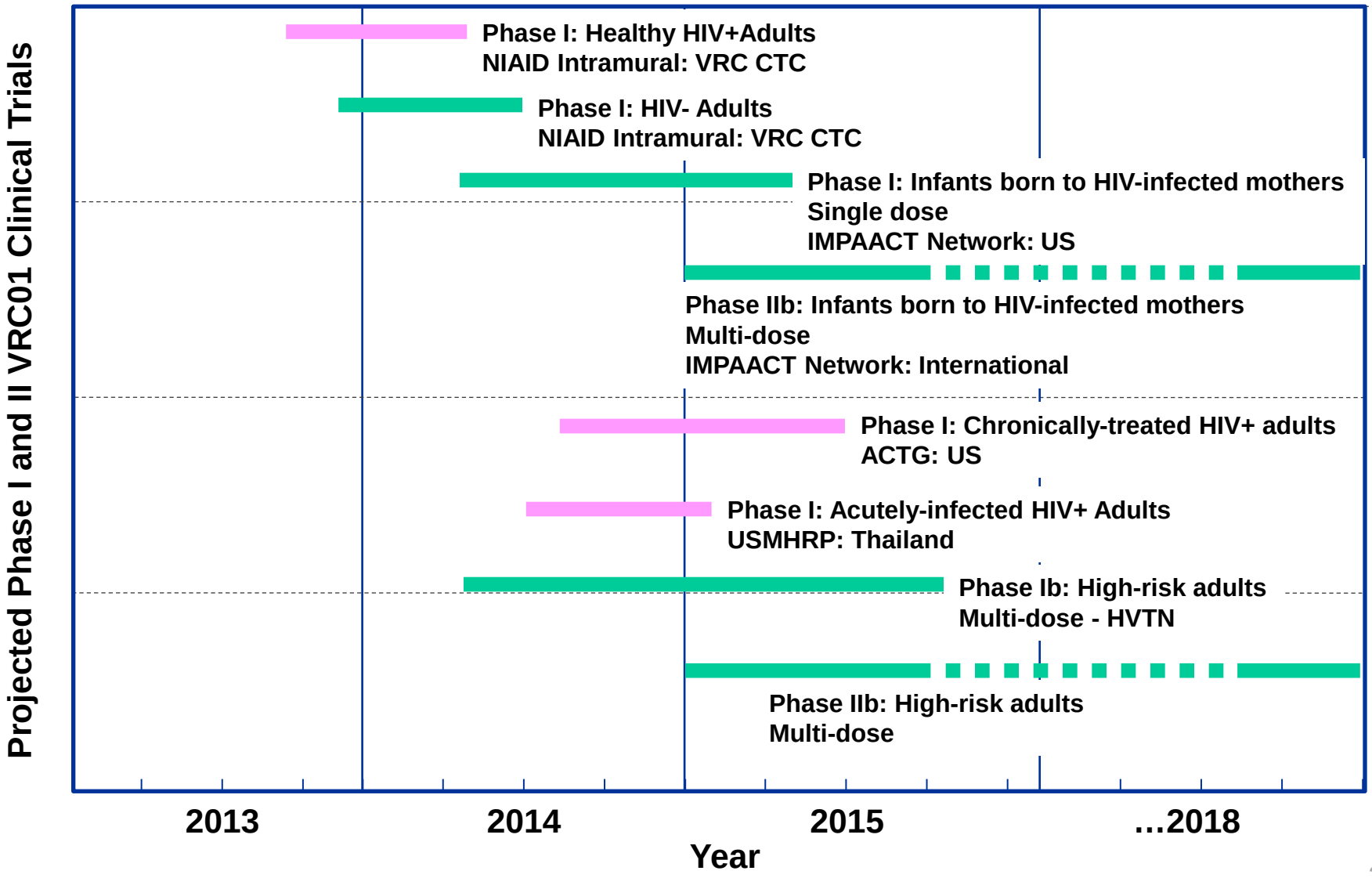
Innate Adaptive immunity



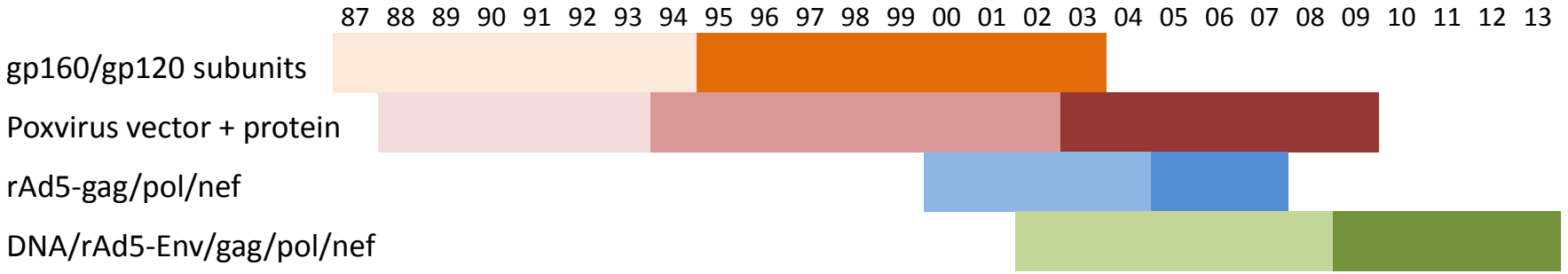


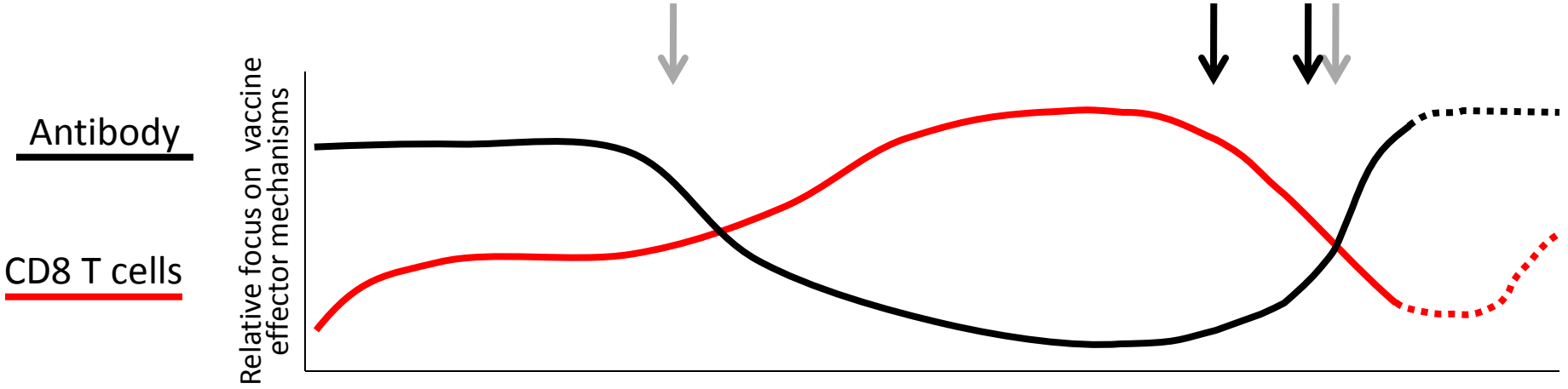
Tissue changes

VRC mAb VRC01 Clinical Trials
Projected Activity 2012-2018



Future of CD8 cell based vaccines ??





Therapeutic vaccines

Aim is to help restore CD4 T cells in cases of therapeutic failures

Better control of HIV and disease progression during treatment interruptions

More recently with the aim of achieving HIV cure

In HIV functional cure the aim is to boost HIV-specific immunity in a shock and kill strategy of the HIV reservoirs

Pipeline

- Multi-Antigen DNA Vaccine Prime Delivered by In Vivo Electroporation + IL12
- Synthetic peptides
- p24-RT-Nef-p17 fusion protein in proprietar adjuvant AS01B
- Tat protein vaccine
- Autologous dendritic cells pulsed with autologous, inactivated HIV–
- DNA/MVA
- MVA.HIVconsv
- DNA + lipopeptide vaccine (LIPO-5)
- NYVAC

Research priorities

Vaccine design

- Does EDCTP support vaccine design
- Should EDCTP partner to move forward products designed to prevent against a broad spectrum of strains (e.g conserved epitopes, mosaic, multi-clade, multi-gene)
- Should priority be products that will induce broad NAb,
- How about CD4 and CD8 responses
- Should EDCTP partner to advance passive delivery of Ab e.g gene transfer

Epidemiology

- Should priority be support and identification of suitable populations with high incidence e.g special groups such as fishing communities, sexworkers, MSM, etc
- Should we pioneer newer methods of following populations e.g virtual cohorts using biometric identifications
- How about evaluate cost effective methods for measuring incidence
- The need for social/behavioural studies for risk assessment, retention etc

Clinical trials

Phase I and II

- What products to move forward- go/no go criteria
- How should trials be designed to answer relevant basic science questions e.g bNAb generation, assays development, effect of co-infection and immune activation on immune responses
- Small trials in high risk groups to conduct sieve analyses
- Should we support cross laboratory standardization
- Should EDCTP support advancing potent broadly Nab into clinical studies of passive immunotherapy
- How about prophylactic vaccines in infants born to HIV positive mothers

Clinical trials

Phase IIB/III

- What is the go/no go criteria
- If there are no vaccines to test should EDCTP support mock vaccine trials and diversification to conduct other clinical trials
- Should EDCTP partner to advance pox-protein under P5 in East Africa
- Can EDCTP partners with others to enlarge trials and to have enough power

Basic sciences

Within existing or new cohorts and planned trials

- Should EDCTP support studies to better understand protective immune responses e.g acute/early infection events, development of broadly Nab. etc

Therapeutic vaccines

Recent interest as part of functional cure

- Should EDCTP support these studies
- There are unknowns such as viral reservoirs in African patients

Other

- Regulatory support including issues of vaccine manufacture and production relevant for some countries
- Capacity development including support to young investigators
- Networking/Advocacy including supporting the new AAVP

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  VRC (Barney Graham)

  Karolinska (Eric Sandstrom)

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