MRC | MRC/UVRI Uganda Research Unit on AIDS

Uganda Virus Research Institute

New developments in the search for an HIV/AIDS vaccine and other prevention research

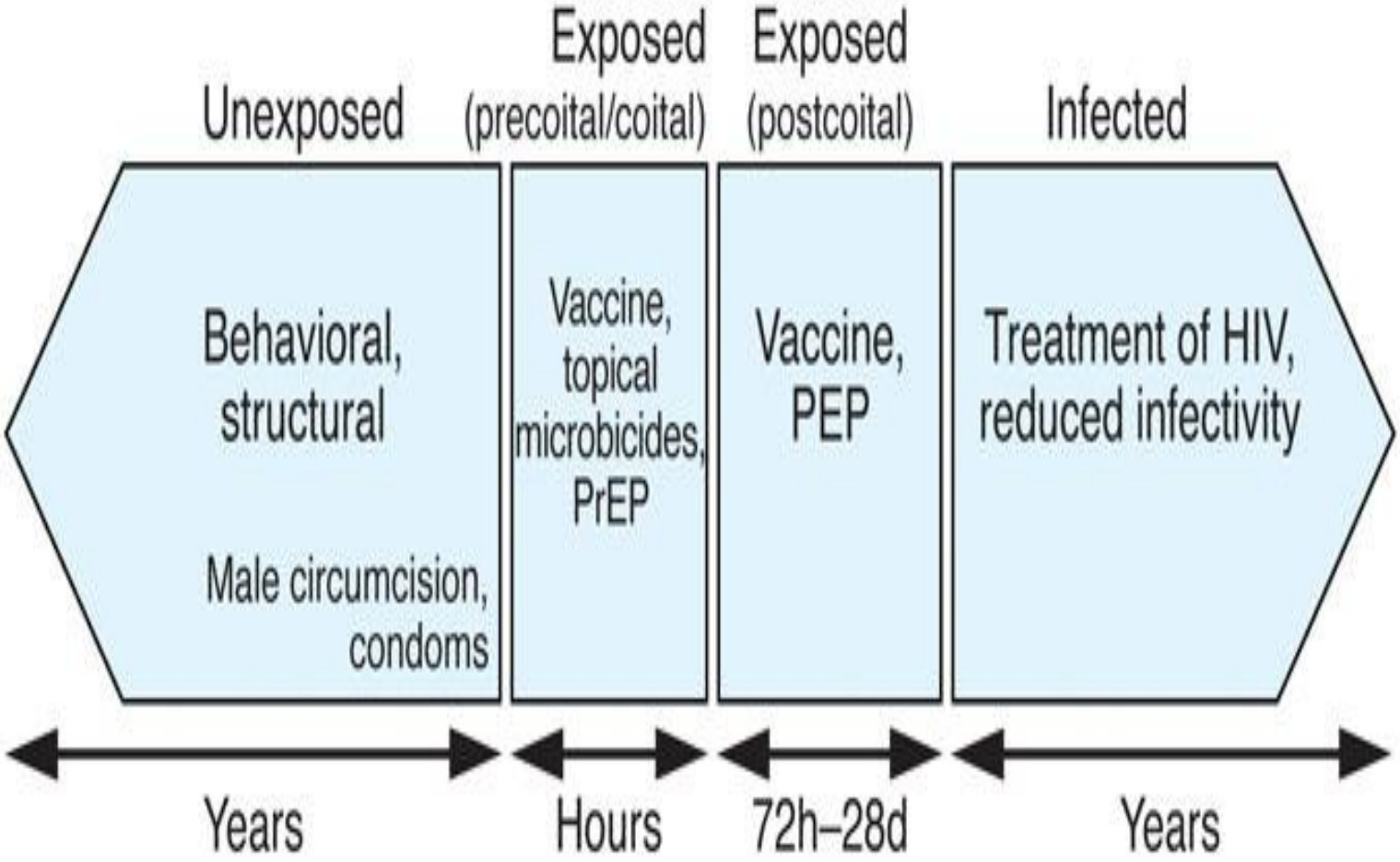
Medical Research Council (MRC UK)
Uganda Virus Research Institute (UVRI)

Pontiano Kaleebu
UVRI

HIV epidemic in Uganda

1. HIV prevalence between ages 15-49 has risen and now stands at 7.3% (higher in women at 8.3%) and up from 6.4% in the 2004-05 survey.

2. HIV prevalence in some high risk groups ~ 30% and incidence ~ 5/100 PYR

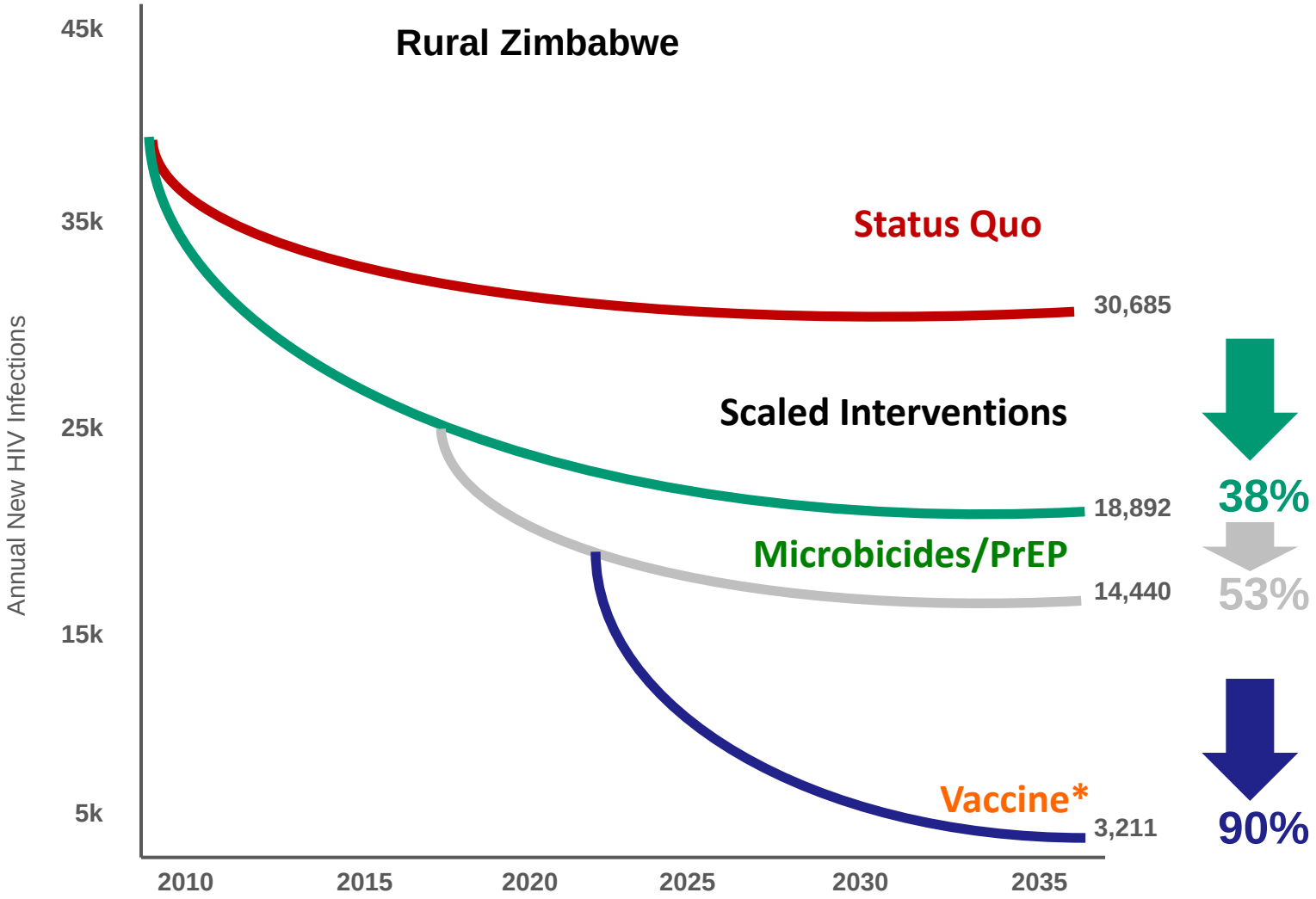


Cohen MS, Kaleebu P, Coates T.
J Int AIDS Soc. 2008 Oct 1;11-4

Summary of presentation

- Progress in HIV vaccine research
- Progress in other NPT: microbicides, PrEP
- Test and treat and other combination prevention trials
- Future trial design challenges
- Conclusion

New prevention technologies will reduce HIV incidence…
but only a vaccine will end the epidemic



Source: Imperial College and BMGF, 2010. *Assumed efficacy of 60% and uptake of 50%

On-going trials-IAVI report Oct 2012

Globally:

36 phase I/IIa and one IIb efficacy trial

- 19 of these USA
- Most prime-boost - DNA + Viral vector (Pox and Adeno)

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

On-going trials in Africa IAVI report by October 2012

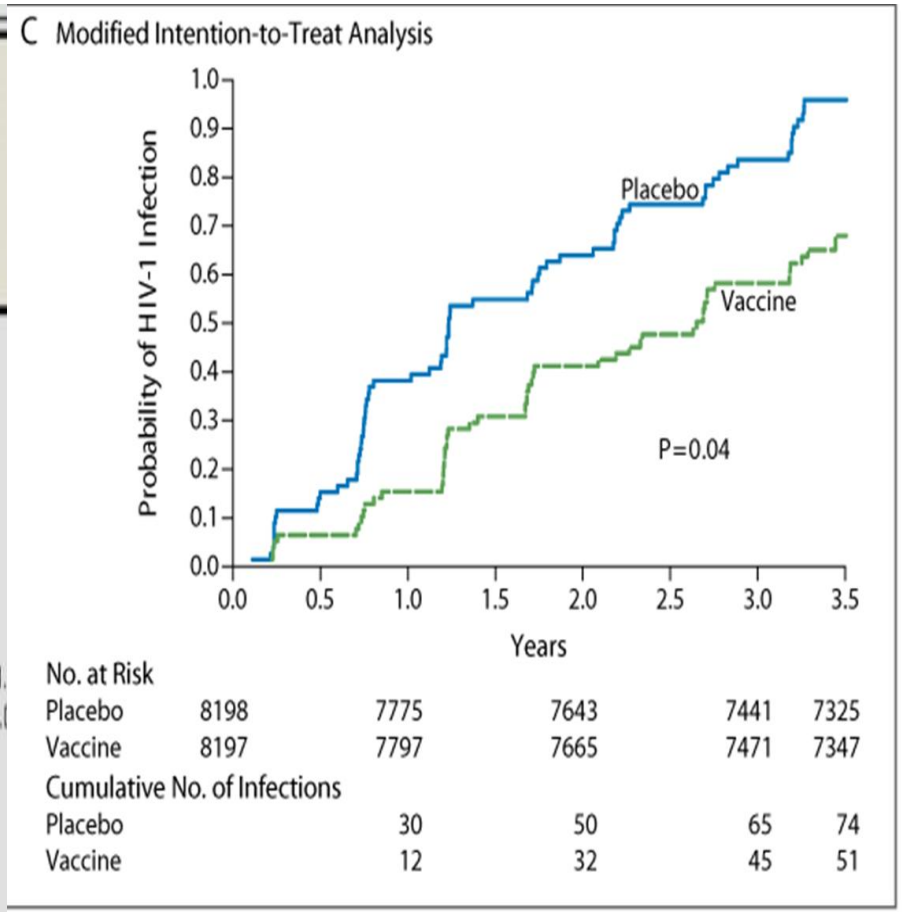
Title	Phase	Strategy	Product	Organizer/Developer	Country
073E/SAAVI 102	I	Protein	Sub C gp140	SAAVI, HVTN	South Africa
HVTN 073	I	DNA/Viral Vector-Pox	SAAVI DNA-C2/SAAVI MVA-C	HVTN	South Africa, USA
HVTN 086, SAAVI 103	I	Viral Vector Pox/DNA/Protein	SAAVI MVA-C/SAAVI DNA-C2/Oligomeric gp140/MF59	SAAVI, HVTN	South Africa
IAVI B002	I	Protein/Protein/Viral Vector-Adeno	Adjuvanted GSK products and Ad35-GRIN	IAVI	Kenya, Uganda, Zambia
IAVI B003	I	Viral Vector-Adeno/Viral-Adeno	Ad26, EnvA01-Ad35-ENV	IAVI	Kenya, Rwanda, South Africa, USA
IAVI B004	I	DNA/Viral Vector-Adeno	HIV-MAG/Ad35-GRIN/ENV	IAVI	Kenya, Rwanda, Uganda
PedVacc001 and PedVacc002	I	Viral Vector	Pox MVA.HIVA	Oxford University	Gambia, Kenya
RV262	I	DNA/Viral Vector-Pox	Pennvax-G/MVA-CMDR	USA DoD	Kenya, Tanzania, Uganda, USA
TAMOVAC-01MZ	I	DNA/Viral Vector-Pox	HIVIS-DNA/MVA-CMDR	Karolinska, USA DoD	Mozambique
HIVS06	I/II	DNA/Viral Vector-Pox	HIVIS-DNA/MVA-CMDR	Karolinska, USA DoD	Tanzania

RV144 Trial- Renewed hope

The NEW ENGLAND JOURNAL of MEDICINE

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. Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph. 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*



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 5, 2012 VOL. 366 NO. 14

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.

Definitions

Correlate of Risk- an immune response that predicts whether vaccinees become HIV-1 infected.

It may be causally related to protection from infection, or may be only a surrogate marker for another factor.

Case Control Study

1. Measured immune responses from:
   - 41 Infected Vaccinees
   - 205 Uninfected Vaccinees
   - 40 Placebo Recipients

Question: What are the immunologic measurements in vaccinees that predict HIV-1 infection over 3 year follow-up?

- Sample Time point: Peak Immunogenicity (2 weeks after final vaccination)
- Cryopreserved specimens

Two Correlates of Infection Risk Found

(Haynes, NEJM 366: 1275, 2012)

1. IgG antibodies that bind to a V1V2 recombinant fusion protein correlated *inversely* with infection rate. (Higher V1V2, *lower* infection rate)

2. Env binding plasma (monomeric) IgA correlated *directly* with infection rate. (Higher IgA to Env, *higher* infection rate).

LETTER

doi:10.1038/nature11519

Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2

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RV144 V1/V2 Antibodies (Mattia Bonsignori, Larry Liao)

1. **Isolated 4 human V2 mabs (3 vaccinees)-A244 gp120**

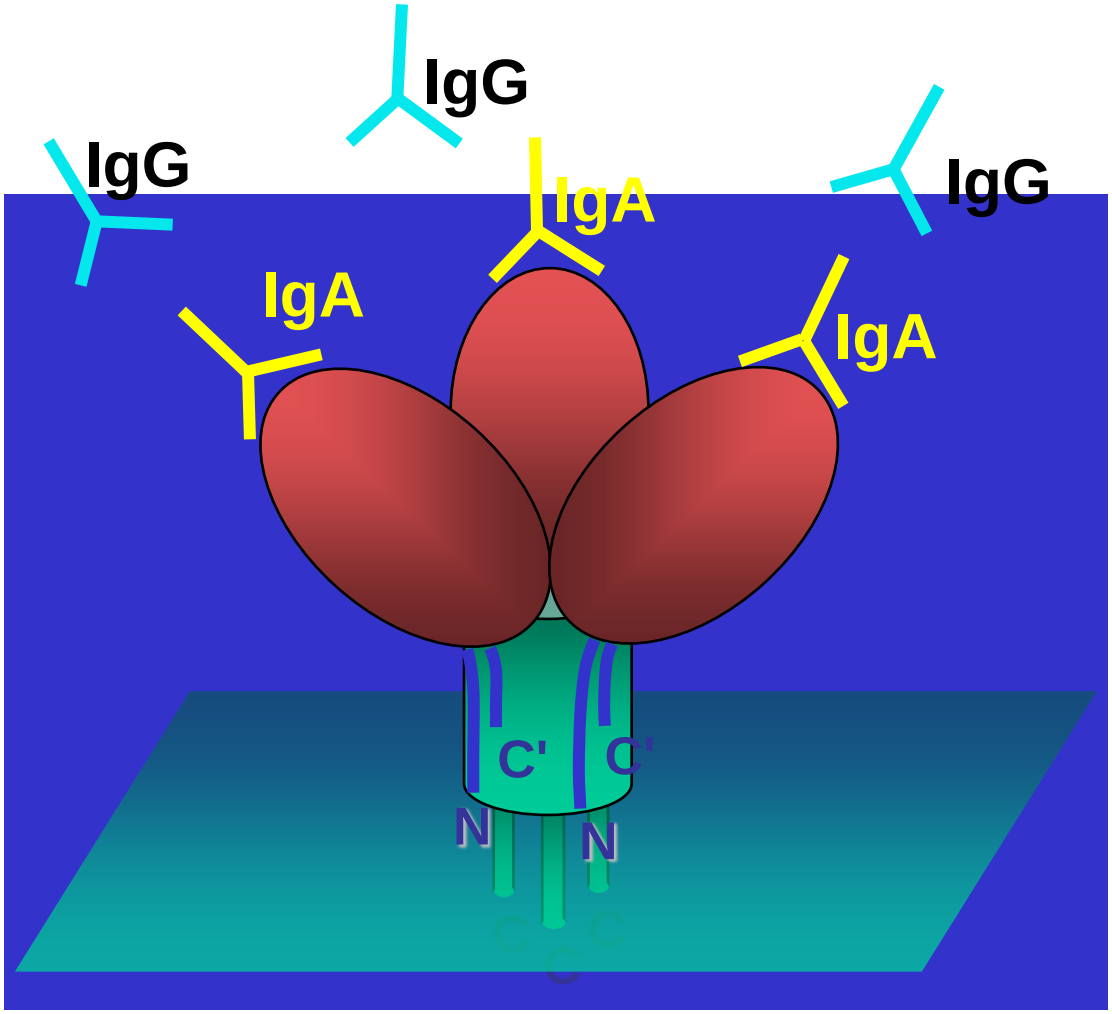
2. **Crystal structures of two CH58, CH59**

Hypothesis

Antibody dependent mediated cytotoxicity

Not by neutralization

Hypothesis: Monomeric IgA Can Block IgG Binding to HIV-1 Env on Infected Cells and Prevent IgG Effector Function



Envelope on HIV-1 Infected Cell

How To Move From a Correlate of Risk to a Causal Correlate of Protection?

To determine if the hypotheses generated from the RV144 case control study (the correlates of risk) are causal correlates, they must be directly demonstrated in new clinical trials, or antibodies tested in NHP passive protection studies, or tested in other ways.

NHP Passive Protection Trials

- CH58, CH90, CH58+CH90

Plans to move RV144 forward

On going

Thailand: RV 305 trial, phase II

- Safety and tolerability of late boost of AIDSVAX B/E alone, ALVAC alone or ALVAC/AIDSVAX B/E combination in 162 participants of RV 144

Planned

Thailand: RV 306 same vaccine in 460 high risk MSM

RV 328 additional AIDSVax

South Africa and Mozambique: Using subtype C prime and boost

Antibodies

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.

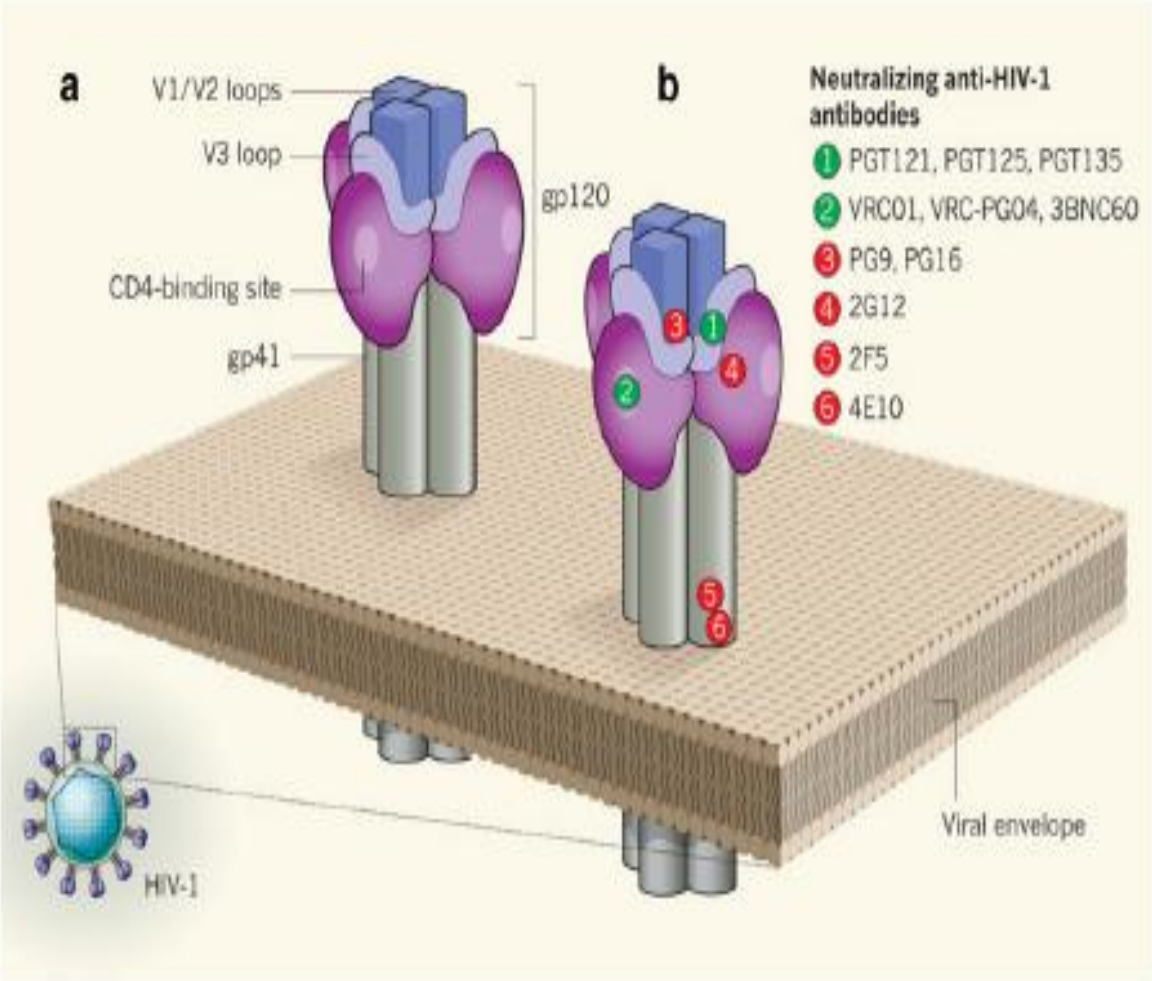
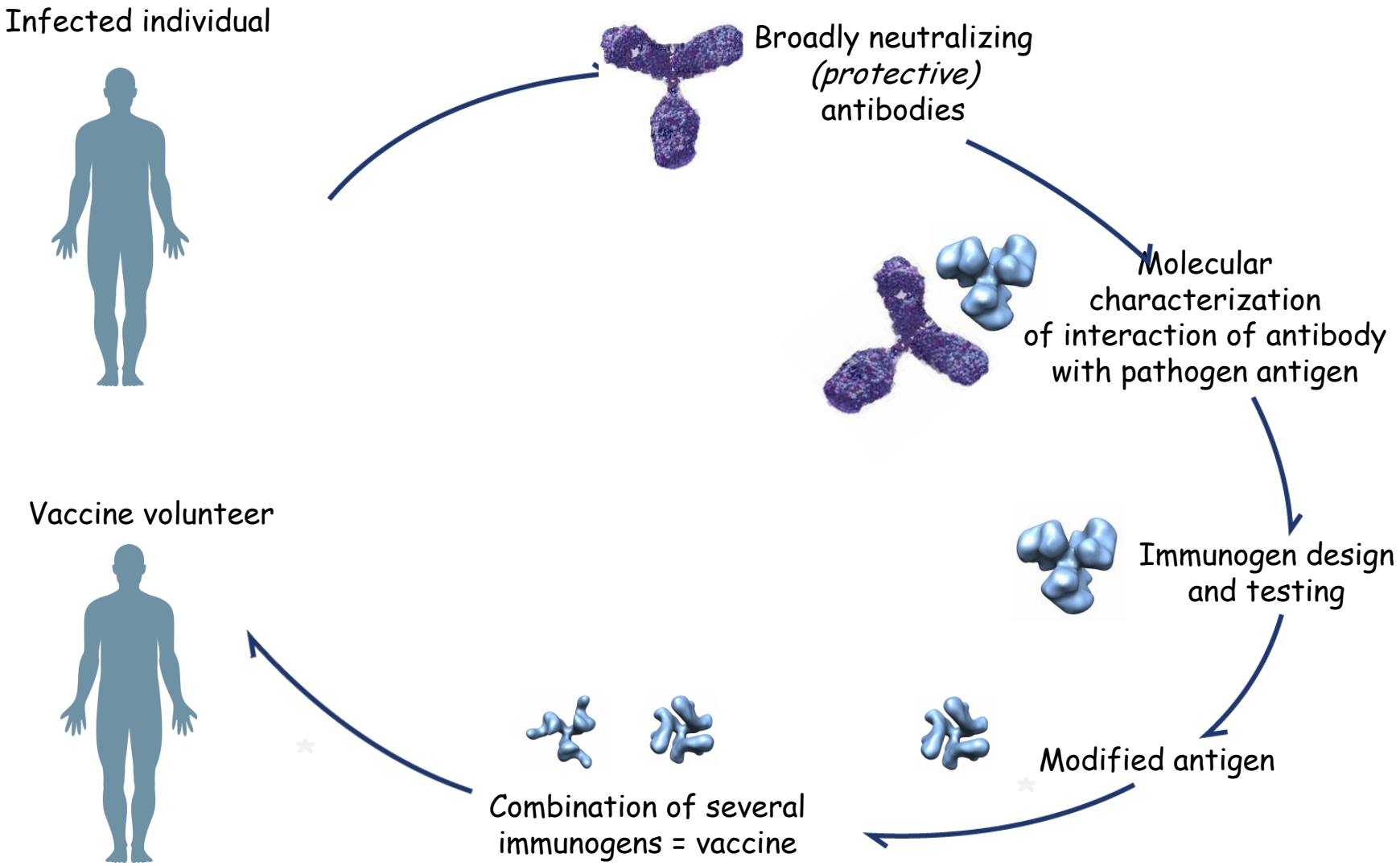


Fig. 1. The envelope of HIV-1 carries spikes. (a) Each spike is made of three molecules of the surface glycoprotein gp120 and three molecules of the transmembrane glycoprotein gp41. Glycoprotein gp120 contains variable V1/V2 and V3 loops, as well as the binding site for CD4. (b) The binding sites of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

Retrovaccinology: From antibody to antigen

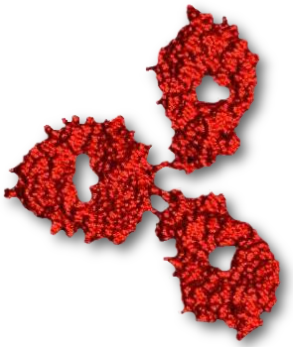


Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002

An innovative approach: Passive Immunity

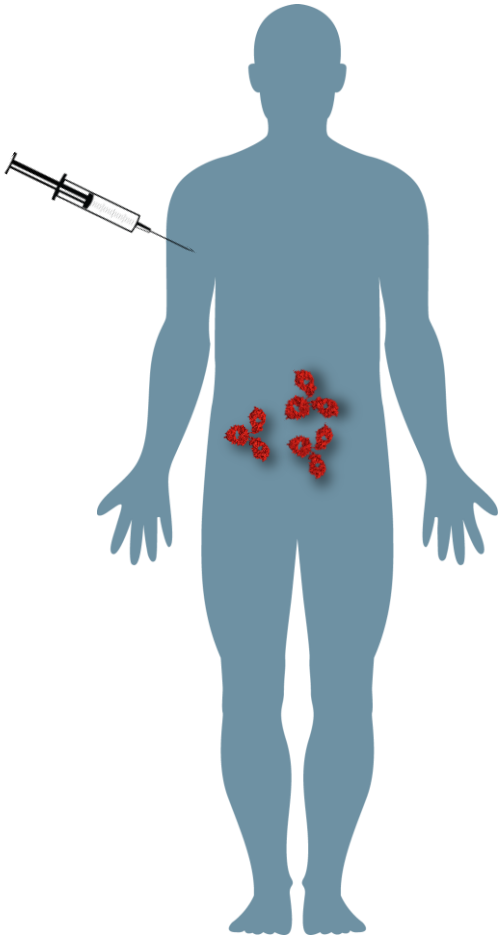
THE FIND

Multiple broadly neutralizing antibodies against HIV



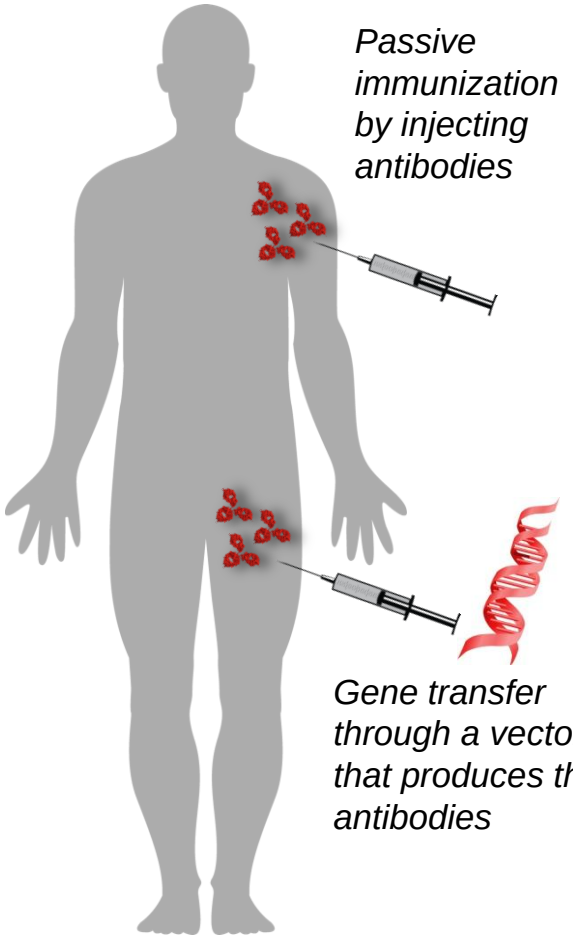
THE GOAL

Elicit those antibodies through vaccination



INTERIM STEPS

Prove concept through …



Progress

1. AAV 1 vector expressing gene for PG9 antibody has been developed (IAVI and NIAID) will be tested in phase 1 soon

2. Passive immunotherapy infants- GHVI consultative workshop using VRC01
   - Entebbe meeting

Other vaccines providing high levels of protection

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

LETTER

doi:10.1038/nature10766

Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys

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nature medicine

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H Barouch[1,2], Kara L O'Brien[1], Nathaniel L Simmons[1], Sharon L King[1], Peter Abbink[1], Lori F Maxfield[1], Ying-Hua Sun[1], Annalena La Porte[1], Ambryice M Riggs[1], Diana M Lynch[1], Sarah L Clark[1], Katherine Backus[1], James R Perry[1], Michael S Seaman[1], Angela Carville[3], Keith G Mansfield[3], James J Szinger[4], Will Fischer[4], Mark Muldoon[5,6] & Bette Korber[4,6]

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Conclusion

1. There is some progress in understanding correlates of risk and mechanisms in RV144 relevant for vaccine design
2. There is progress in moving bNab to vaccine design
3. Optimised HIV vaccines can block acquisition in heterologous neutralization resistant SHIV in NHP

CAPRISA 004 effectiveness by adherence

- 1% tenofovir gel – coitally dependent regimen (BAT24)
- **HIV: overall 39% reduction (6-61%, p=0.017**
- High adherers (>80% gel use): 54% lower, p=0.025
- Intermediate (50-80% gel use): 38% lower, p= 0.34
- Tenofovir vaginal concentrations:
  - Need to achieve high levels >1000 ng/ml

Post CAPRISA 004

- WHO/UNAIDS meeting – priority next steps
  - Additional safety studies e.g among young women
  - FACTS trial to confirm findings (same regimen)
  - Simplified dosing and less frequent HIV testing (MDP 302

FACTS 001, South Africa

1. Phase III testing 1% tenofovir gel, same regimen as CAPRISA 004
2. 2900 heterosexual women
3. Launched October 2011 and results expected 2014

Next generation microbicides

Formulations:

- Gel formulations been mainly evaluated as “coitally-dependent”
- Coitally –dissociated” formulations – offer sustained delivery (IVR, injectable, implants)
  - IVR most advanced of all

Why a ring?

- Long-acting: monthly or longer
  - Could potentially improve adherence
  - Better adherence → better effectiveness
- Easy to use, comfortable
  - Flexible ring, can be self-inserted
  - Rarely felt by women or their male partners
  - Little or no impact on sexual activity
- Suitable for developing world
  - Relatively low manufacturing cost
  - Good safety and acceptability data

IPM 027- Dapivirine ring

- Phase III safety and efficacy in 1650 women; results expected early 2015
  - Uganda (MRC to join)

ASPIRE (MTN 020)

- Phase III safety and efficacy study in 3,476 women, results expected early 2015
  - Uganda (MUJHU)

Treatment as prevention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D., Mina C. Hosseinipour, M.D., Nagalingeswaran Kumarasamy, M.B., B.S., James G. Hakim, M.D., Johnstone Kumwenda, F.R.C.P., Beatriz Grinsztejn, M.D., Jose H.S. Pilotto, M.D., Sheela V. Godbole, M.D., Sanjay Mehendale, M.D., Suwat Chariyalertsak, M.D., Breno R. Santos, M.D., Kenneth H. Mayer, M.D., Irving F. Hoffman, P.A., Susan H. Eshleman, M.D., Estelle Piwowar-Manning, M.T., Lei Wang, Ph.D., Joseph Makhema, F.R.C.P., Lisa A. Mills, M.D., Guy de Bruyn, M.B., B.Ch., Ian Sanne, M.B., B.Ch., Joseph Eron, M.D., Joel Gallant, M.D., Diane Havlir, M.D., Susan Swindells, M.B., B.S., Heather Ribaudo, Ph.D., Vanessa Elharrar, M.D., David Burns, M.D., Taha E. Taha, M.B., B.S., Karin Nielsen-Saines, M.D., David Celentano, Sc.D., Max Essex, D.V.M., and Thomas R. Fleming, Ph.D., for the HPTN 052 Study Team*

Test and treat

- Garnett et al Lancet 2009-mathematical modelling UTT may substantially reduce, even eliminate sexual transmission at population level

The PopART

- A 3-arm trial in Zambia and South Africa with 8 clusters in each arm and includes house-to-house universal voluntary HIV testing and immediate ART to all who test HIV-positive, VMMC for HIV negative men, counselling and condom promotion, strengthening PMTCT services and syndromic STI treatment.

PopART

- Arm A clusters receive the full intervention package,
- Arm B receive the full intervention but ART is only initiated to those with CD4<350 cells/μl or WHO stage 3/4, and arm
- C receives national standard of care

The Treatment as Prevention (TASP) trial in Kwazulu Natal

- A 2-arm trial with 16 clusters per arm.

Arm A clusters receive expanded testing, VMMC, immediate ART to all HIV positive, IEC and STI treatment are implemented.

Arm B receives same intervention package except that ART is provided at CD4 <350 cells/μl.

Other combination prevention studies

The Iringa Combination trial in Tanzania

- Is a 2-arm trial with 24 clusters per arm. Interventions include expanded testing and linkage to care, ART at CD4 <350 cells/μl, information education and communication (IEC), VMMC, conditional cash transfers and targeted outreach versus the national standard of care.

The Harvard School of Public Health-Botswana trial

- A 2-arm study with 10 clusters per arm, enrolling 18-49 year olds in rural communities.
- Arm A receives expanded testing and linkage to care, ART at CD4<350 cells/μl or viral load >10,000 copies/μl, and VMMC for HIV-uninfected adults.
- Arm B receives standard of care according to national guidelines. A key feature of this trial is that it focuses on individuals with high viral load who are most likely to be the main transmitters.

Preexposure Prophylaxis

- TDF2 and Partners PrEP efficacy 62-75%
- FEM-PrEP – discontinued due to lack of efficacy
- VOICE TDF alone stopped

- FDA approved TDF/FTC or Truvada for use as preexposure prophylaxis among sexually active adult men and women

Trial design challenges

- Future efficacy trials- large and expensive
  - Kublin J. et al It will require 5100 volunteers in S. Africa at 20 sites to observe a 50% efficacy with 4% incidence in a setting of male circumcision, increased ART uptake, possible PreP
  - Most cohorts have much lower incidence

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ESTABLISHED IN 1812 JANUARY 17, 2013 VOL. 368 NO. 3

Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*

ABSTRACT

Conclusion

- In the coming years we will have a number of additional prevention approaches
- This is causing excitement even talking about an end to the epidemic !!!
- But we think for longer term control of HIV we need a vaccine