HIV Vaccines in the Prevention Revolution.

Surita Roux
The Desmond Tutu HIV Centre
Institute of Infectious Disease and Molecular Medicine
Cape Town
November 2014

Desmond Tutu HIV Centre
Masibambane Ngezandla

RARE CANCER SEEN IN 41 HOMOSEXUALS

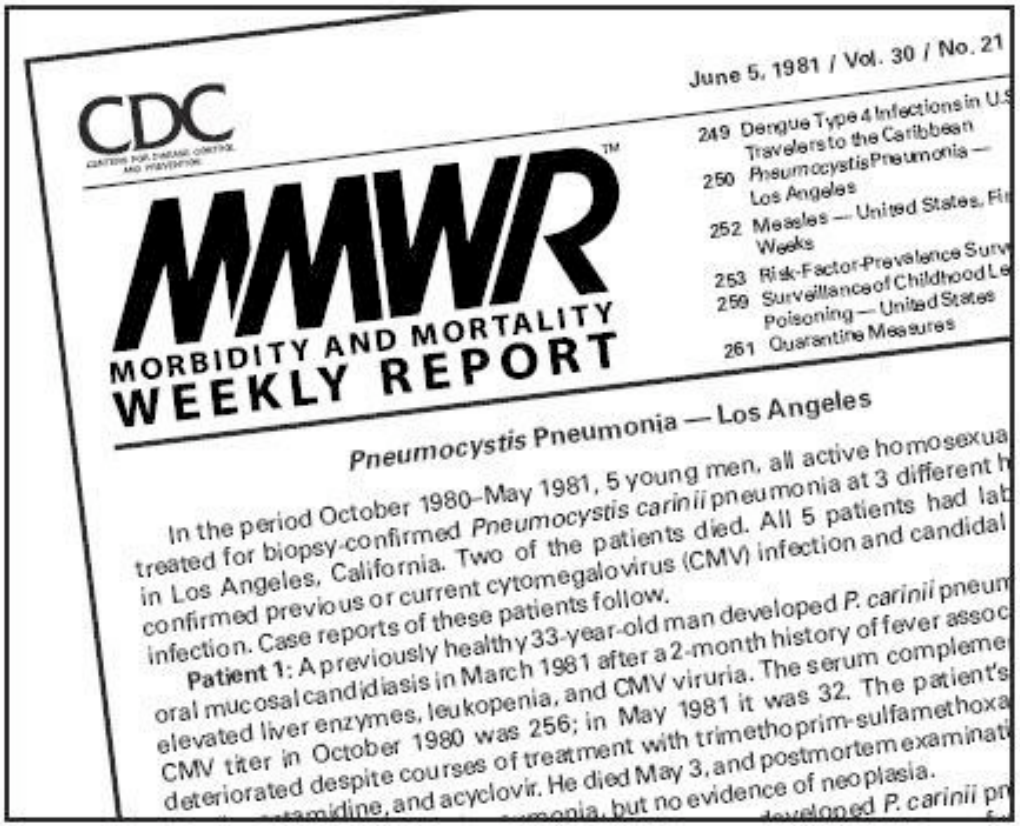
Outbreak Occurs Among Men in New York and California —8 Died Inside 2 Years

By LAWRENCE K. ALTMAN

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the

FIGURE. *MMWR* report on *Pneumocystis* pneumonia in five previously healthy young men in Los Angeles — June 5, 1981



CDC

June 5, 1981 / Vol. 30 / No. 21

MMWR™

MORBIDITY AND MORTALITY WEEKLY REPORT

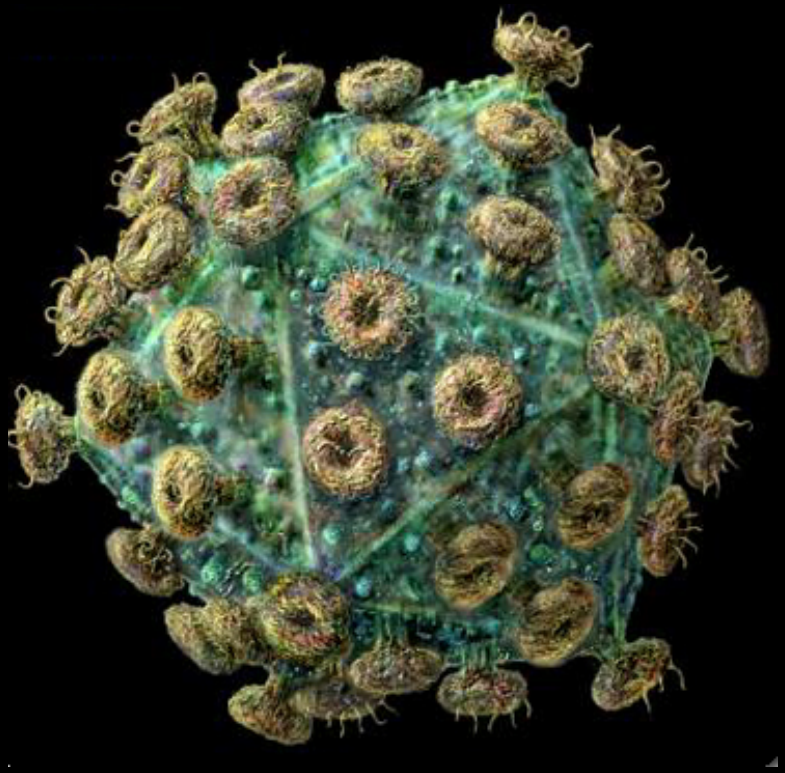
***Pneumocystis* Pneumonia — Los Angeles**

In the period October 1980–May 1981, 5 young men, all active homosexua treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different h in Los Angeles, California. Two of the patients died. All 5 patients had lab confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneum oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum compleme CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's deteriorated despite courses of treatment with trimethoprim-sulfamethoxa stamidine, and acyclovir. He died May 3, and postmortem examinati monia, but no evidence of neoplasia. developed *P. carinii* pn

1981…….a new epidemic-

In 30 years…..

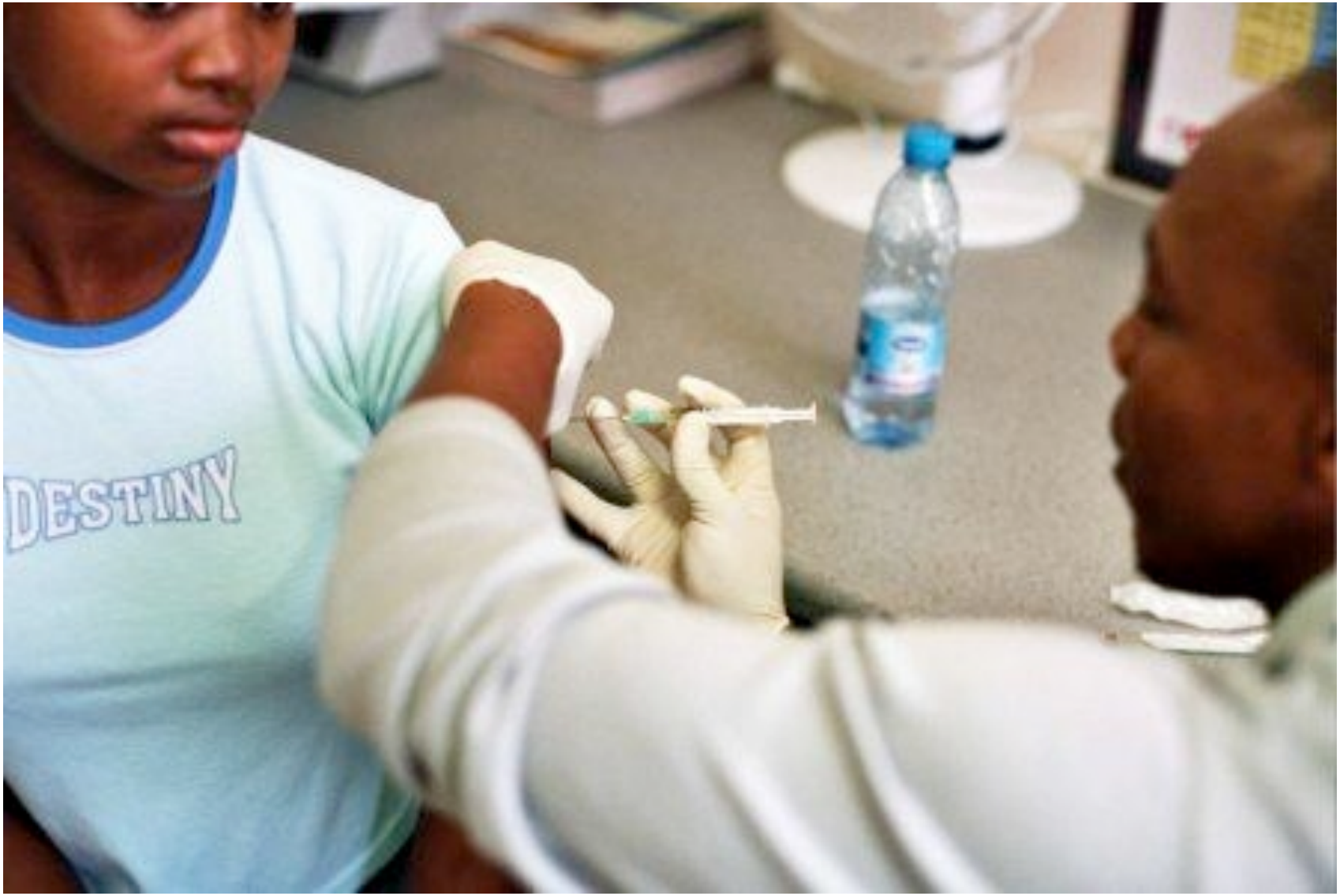


64 million infected, 24 million dead….


AVOIDING
AIDS
AS EASY AS...
ABSTAIN
BE FAITHFUL
CONDOMISE

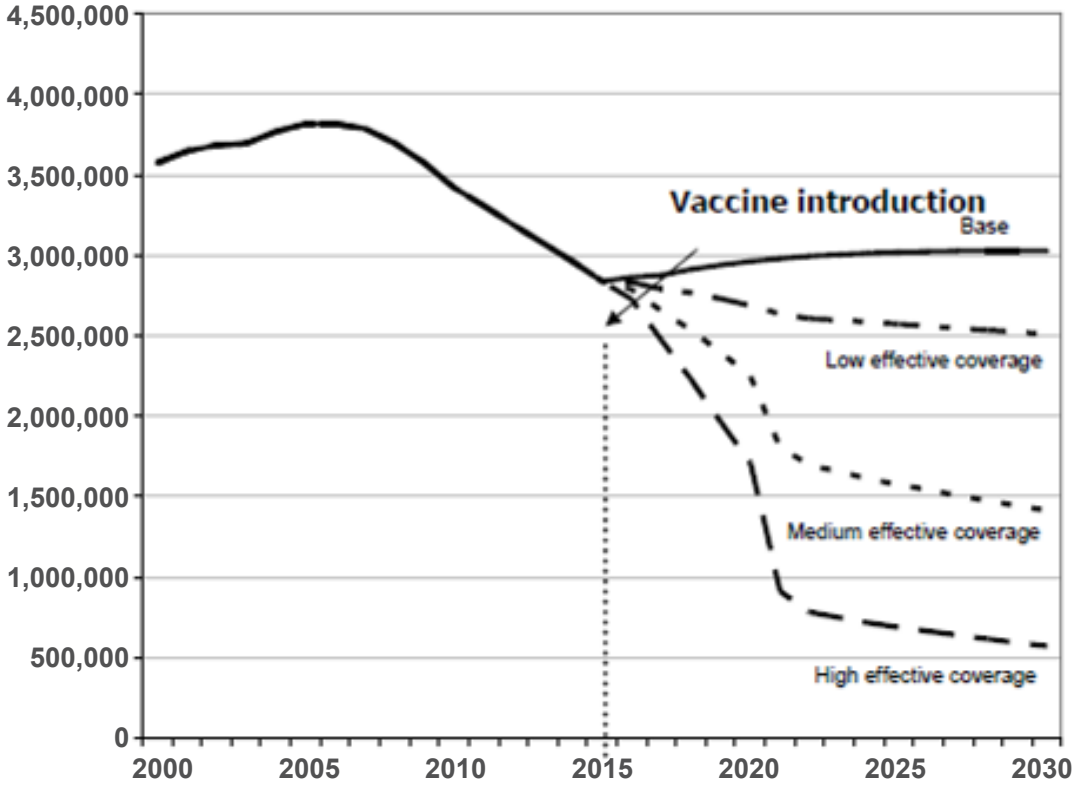

AS EA
AIN
ITHFUL
ONDOMISE

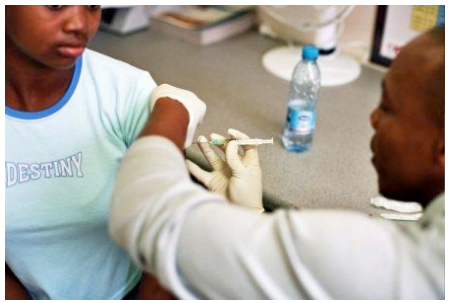
Hope of a preventive HIV vaccine remains real……



Potential Impact of a Vaccine

New Adult Infections in Low- and Middle-Income Countries by Year and Vaccine Scenario





Total new infections averted by an AIDS vaccine between 2015-2030

30% efficacy, 20% coverage	5.5 million
50% efficacy, 30% coverage	17 million
70% efficacy, 40% coverage	28 million

Even a vaccine with low efficacy and limited coverage can impact the epidemic and play a role in preventing future infections

Stover J, et al. The impact of an AIDS Vaccine in Developing Countries: A New Model and Initial Results**. Health Affairs 26(4):1147-1158 (2007)**

Obstacles to HIV Vaccine Development

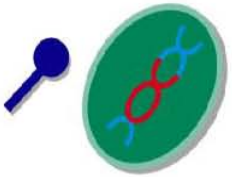
The window of opportunity for the immune system to clear the initial infection is narrow, since HIV integrates and establishes latent infection within days/weeks
Destruction of CD4+T cells begins early after infection
Enormous genetic diversity and mutations enable HIV to avoid immune surveillance
Conserved antibody targets on the outer envelope protein are “hidden” from immune recognition

Johnston, Fauci, NEJM 2008, 359;9

The Spectrum of HIV Vaccine Strategies

Viral surface proteins

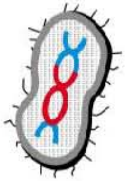
Live vector viruses



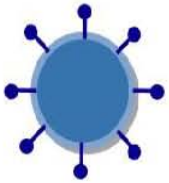
Combination of elements

Naked DNA

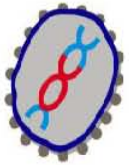
HIV peptides



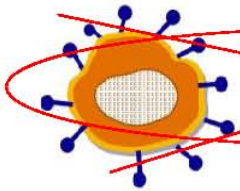
Live bacterial vectors



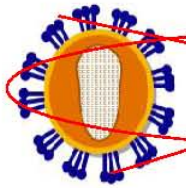
Pseudovirions



Replicons



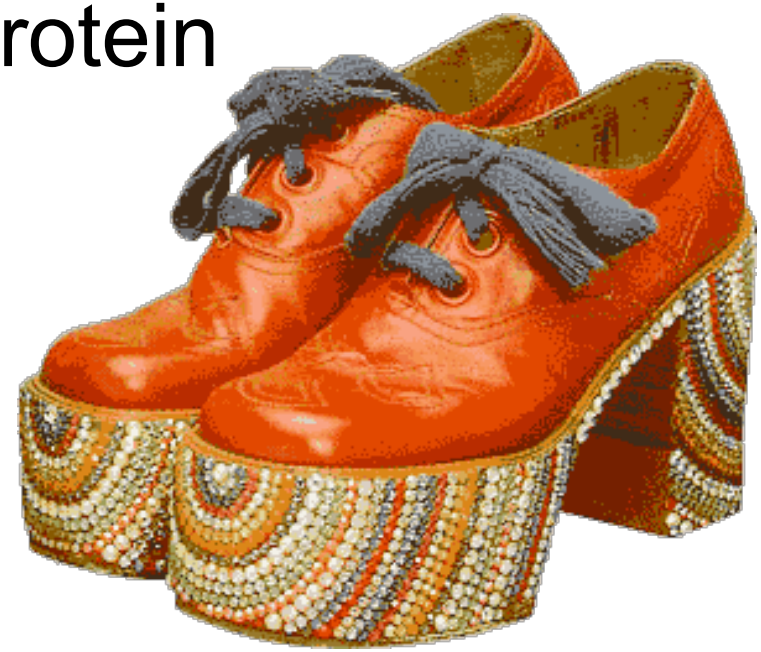
Whole, killed HIV



Live, attenuated HIV

Vaccine designs like fashion come and go…..

- 1991-1993 : protein
- 1997-1999 : pox vectors
- 2003-2005 : Adeno and DNA
- 2009-present : Pox, Protein



All about backing the right horse

HIV Vaccine Efficacy Trials

TRIAL	VACCINE	Antigen	Clade	Population	Vaccine Efficacy (VE)
Vax003	AIDSVAX B/E	A244, MN, gD	B/E	Thai IDU	0.1% (-31, 24%)
Vax004	AIDSVAX B/ B	MNE8, MN, gD	B/B	MSM	6% (-17, 24%)
Step	MRK rAd5	Gag, Pol, Nef	B	MSM	futility
Phambili	MRK rAd5	Gag, Pol, Nef	B	S. African High incidence heterosexual	halted
RV144	ALVAC-HIV + AIDSVAX B/E	92TH023 gp120; LAI gag/pro, A244, MN gD	E/B	Thai low risk community	31.2% (1, 52)
HVTN505	DNA + rAd5 (VRC)	Gag (D/A), Pol (D/A), Nef (D), Env (D/A)	Gag B, Pol B, Nef B, Env (A, B, C)	MSM	futility

STEP

(HVTN502)

PHAMBILI

(HVTN 503)

“CTL based approach”

HIV-vaccine trial to involve thousands in SA

South Africans of different races, sexual orientation and economic status are being recruited for $35m experiment

Tamar Kahn
Science and Health Editor

CAPE TOWN — Scientists have begun recruiting South African volunteers to test pharmaceutical giant Merck's candidate HIV vaccine in the largest and most advanced study of its kind to take place in SA to date.

It is being run in parallel with another trial in the US and Latin America, and will help determine whether the jab works against different strains of the virus, including the C-strain common to this region.

SA plays a pivotal role in global HIV research because it has strong scientific capacity and a high prevalence of the disease. At least 5,5-million South Africans, or 11% of the population, are infected with the virus.

“A vaccine would be the ultimate protection against HIV, hopefully for the duration of (one's) reproductive life,” said the trial's principal investigator, Glenda Gray, of the perinatal HIV Research Unit at the University of the Witwatersrand.

Merck's candidate vaccine, MRKAd5 HIV-1, is based on a modified version of the common cold virus combined with three HIV genes. It has already been tested for safety in phase I and IIa trials, and scientists are now assessing whether it stimulates the body to recognise and kill HIV that invades the body, and if so, whether it is equally effective against different strains of the virus.

The candidate vaccine was developed against the clade B virus, but scientists hope it will also help people defend themselves against clade C, the strain most common in sub-Saharan Africa.

The $35m trial, dubbed Phambili, is being run by the international HIV Trials Network and the South African AIDS Vaccine Initiative, with backing from Eskom and the South African government. It has been approved by the US Food and Drug Administration, the South African Medicines Control Council and the agriculture department, and will be overseen by an independent monitoring board.

News of the HIV vaccine trial comes barely a week after US-based health research group Conrad halted studies of Ushercell, a gel containing a cotton-based compound called cellulose sulphate, after interim analysis of trial data from more than 1 300 women in SA, Benin, Uganda and India showed more HIV infections among women using the microbicide than those given a dummy gel.

Independent monitors found that 22 of the 34 women who had used the gel and become infected were from SA.

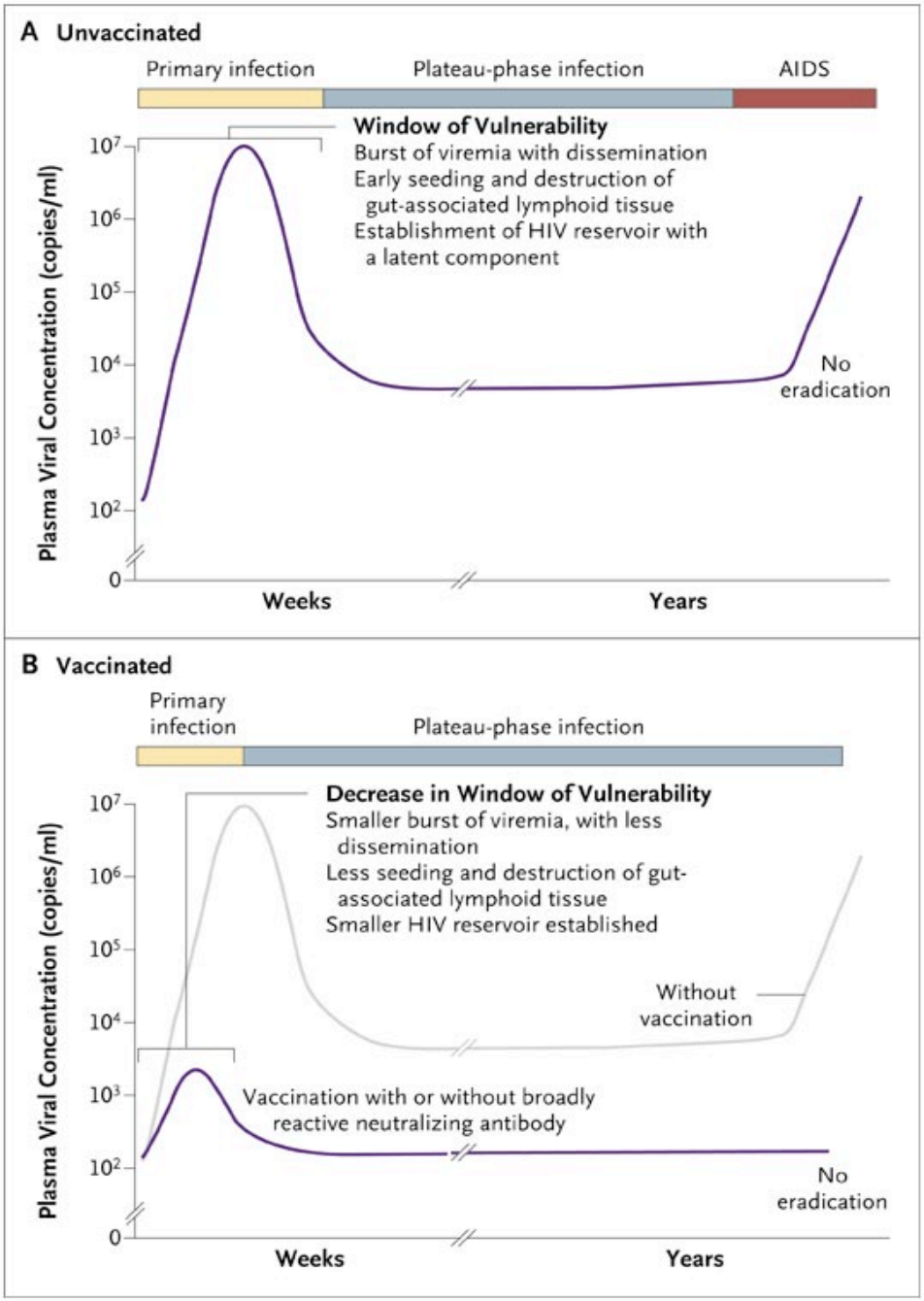
The South African arm of the Conrad HIV microbicide trial was headed by the Medical Research Council's (MRC's) Prof Gita Ramjee, and funded by the US Agency for International Development and the Bill and Melinda Gates Foundation. According to the MRC, 11 previous studies of the gel had not identified any problems.

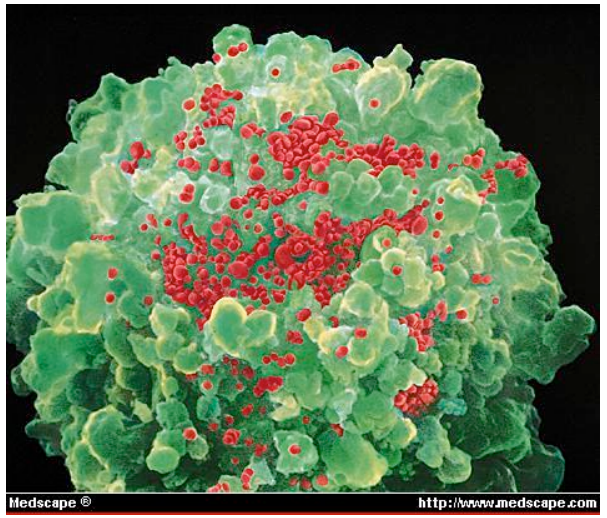
Gray said researchers had been worried about public perceptions of the risks involved in HIV research, but having alerted journalists to the launch several weeks ago, had decided to go ahead as planned.

“It's a terrible time to launch … but if we didn't announce it today, people might have thought we had something to hide,” she said. Gray said it was inevitable that some test products would fail, and so all the HIV vaccine trials under way in SA offered treatment to people who became infected.

Scientists have already recruited the first 16 volunteers for the HIV vaccine trial, which aims to enrol 3 000 people of different races, sexual orientation, and economic backgrounds in four provinces — Gauteng, North West, Western Cape and KwaZulu-Natal. Participants will be given free male and female condoms, and advice about safe sex. Men will also be offered circumcision, which research shows reduces the risk of HIV transmission.

PERINATAL HIV RESEARCH UNIT





A T cell vaccine might “reset” viral set point and modify disease and make vaccinees less infectious……

Johnston M, Fauci A. N Engl J Med 2007;356:2073-2081

The NEW ENGLAND JOURNAL of MEDICINE

What did this trial teach us

- This product didn’t work in MSM
- Especially didn’t work in MSM with foreskin and high background Ad5 immunity
- Combo of foreskin and vector immunity a problem but not sure how
- Some cause for pause around Ad5 as a vector
- T cell strategy on its own probably insufficient

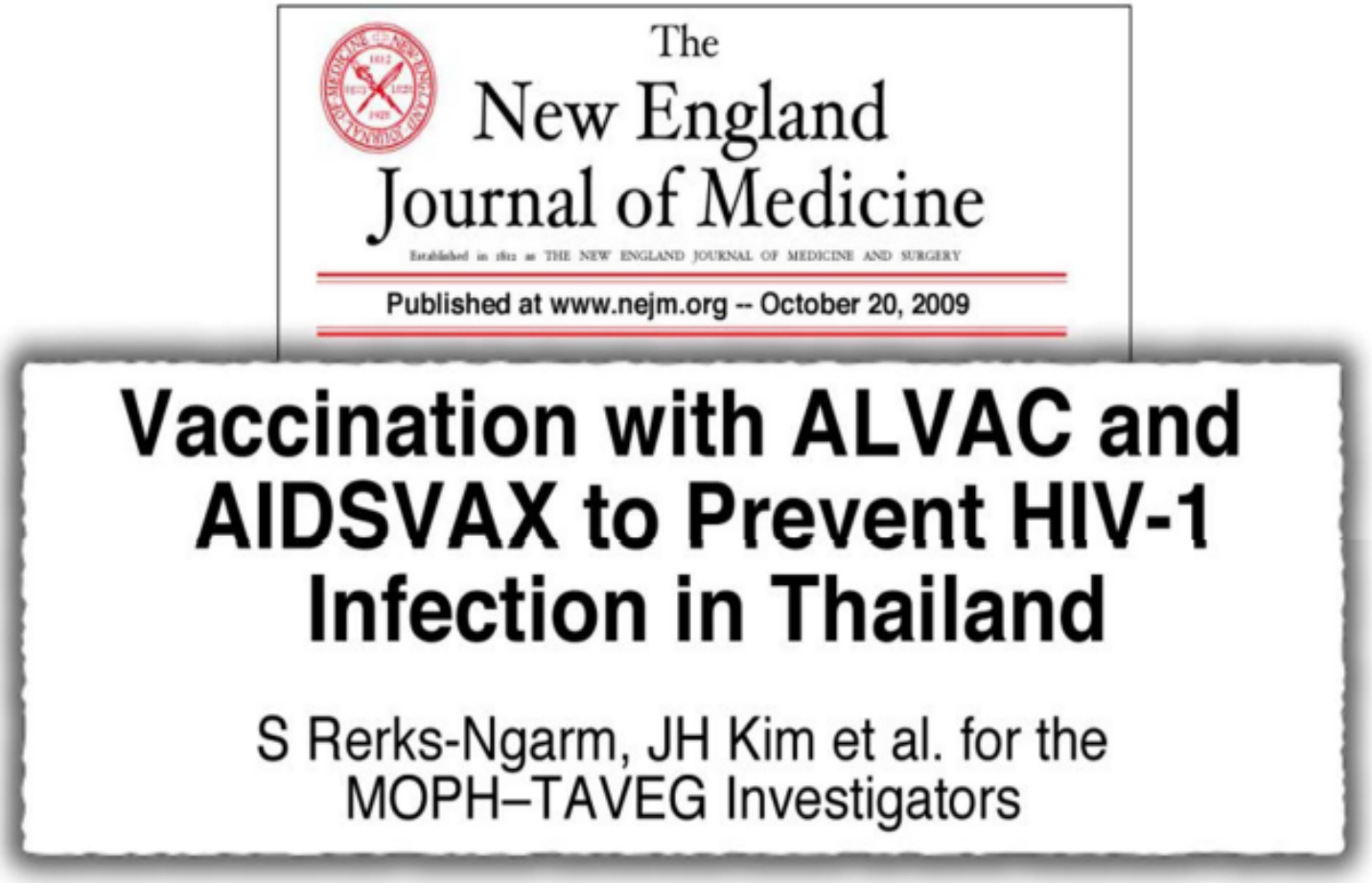
DSMB recommendation on HVTN 505

- Study of another Ad5 vector product in MSM in N America
- Circumcised men, with low background immunity to Ad5
- Enrollment stopped due to FUTILITY

- This vector is very unlikely to be ever used in an HIV vaccine-

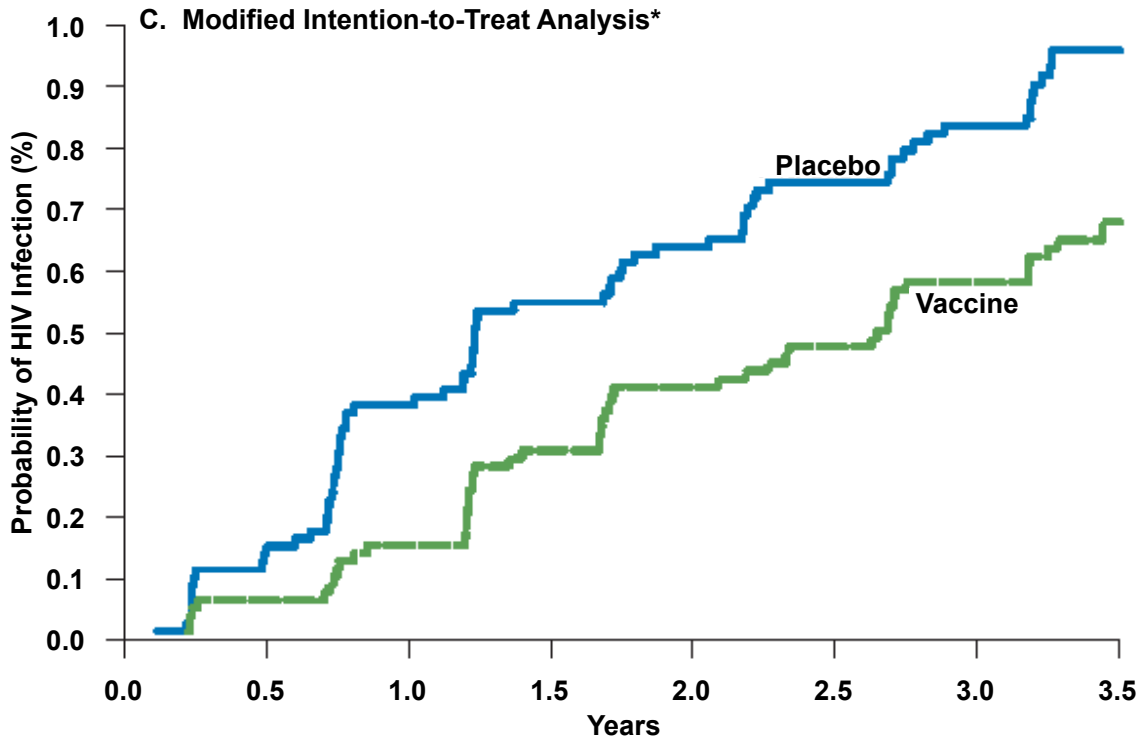
And then 2 important things happened……

First Signal of Efficacy in an HIV Vaccine Clinical Trial



RV144 ALVAC Prime, AIDSVAX B/E Trial

~~31.2% Estimated Vaccine Efficacy~~



Urgent "correlates analysis" to begin to identify how the vaccine might work…

New Broad Neutralizing Antibodies

- **CD4 binding site- VRC01, CH31, PG04**
- **V1/V2- PG9, PG16, CH01-04**
- **Glycan- PGT125, PGT128**
- **gp41 MPER-10E8**

Greater breadth of neutralization, more potent

Energised the field in 2 ways:

Design better products using new antibodies

Improve on the RV144 findings using the correlates of risk….

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.

Immune Correlates Case Control Study

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

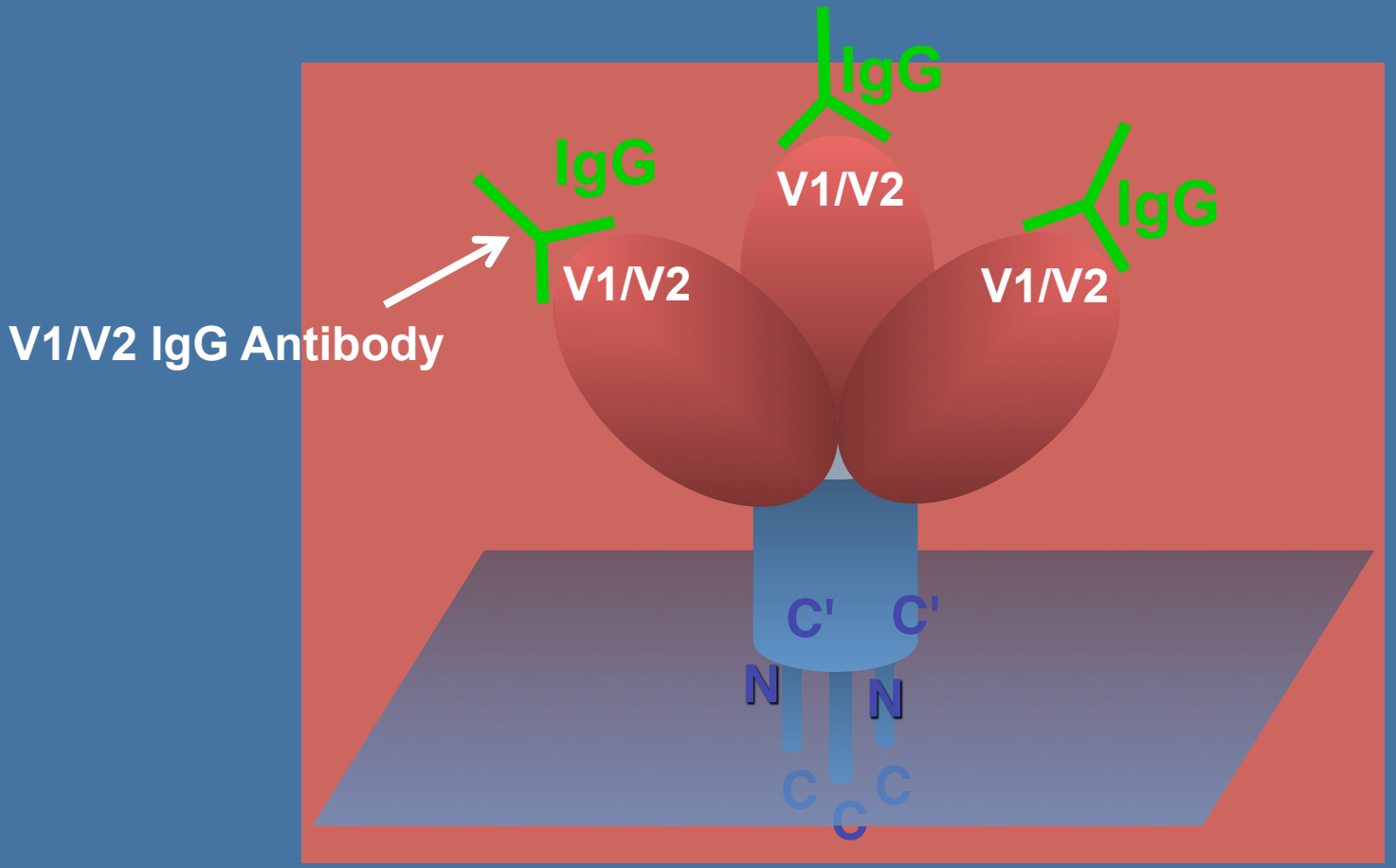
Question: What are the immunologic measurements in vaccinees that predict HIV-1 infection over 3 year follow-up?

NEJM 366: 1275, 2012

RV144 Trial Results: "Correlates Analysis"

- What is Correlates Analysis?
  - The identification of any **lab measures of immune system function correlated (linked) with study participants' HIV infection risk**
- Correlates are important: a lab measure that **can help predict if a vaccine is going to be effective**
- RV144 correlates analysis found 2 things:
  - V1-V2 antibody (Ab) – the higher the Ab level, the lower the risk of HIV infection
  - IgA levels – the higher the Ab level, the higher the risk of infection
    - Inverse did not result in more infection than placebo

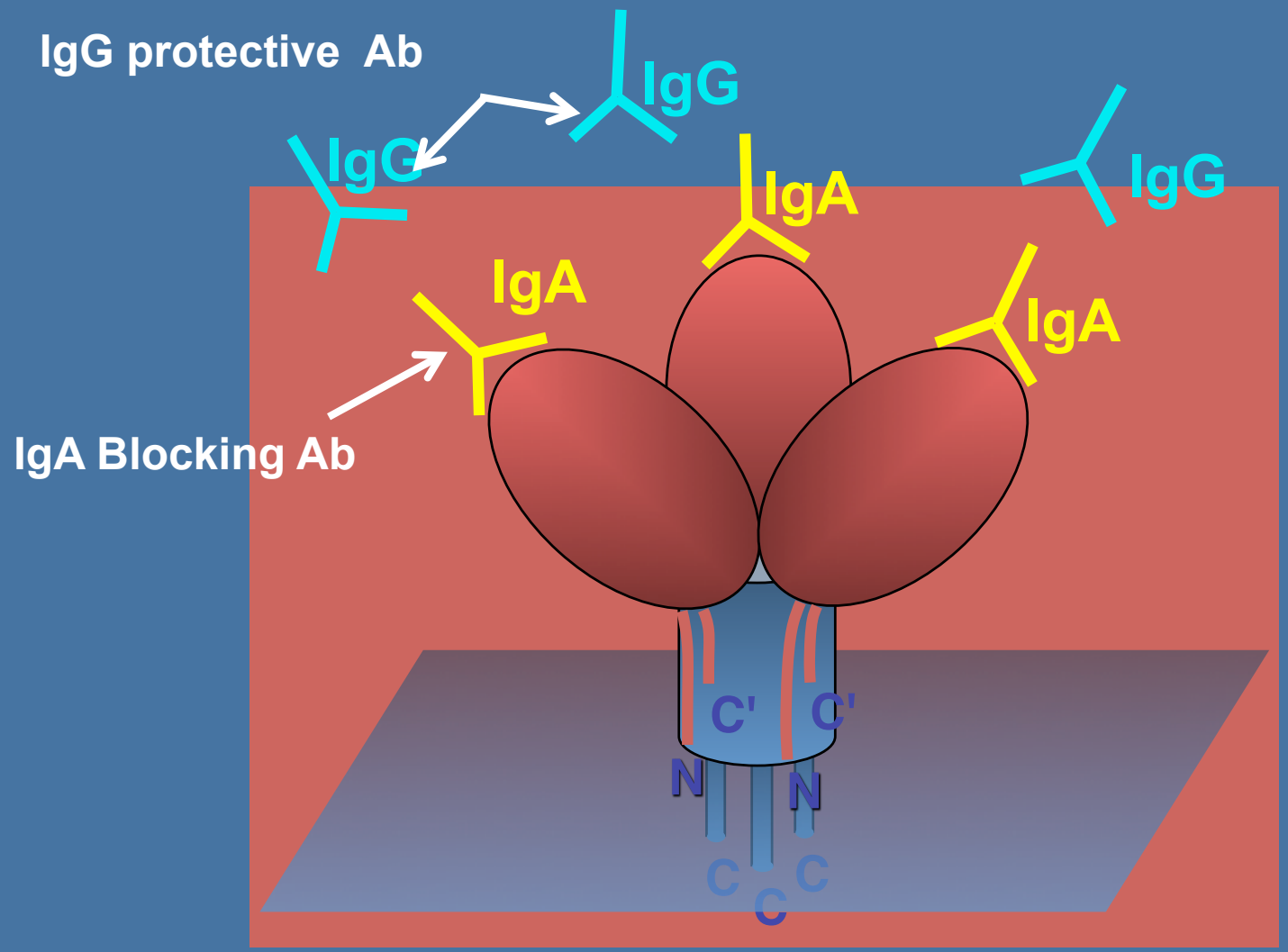
Hypothesis: IgG Antibodies to V1/V2 Can Protect Against HIV-1 Infection



Envelope on HIV-1 Infected Cell

NEJM 366: 1275, 2012

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



Envelope on HIV-1 Infected Cell

NEJM 366: 1275, 2012

Building on a Proof of Concept

The Quest for an HIV-1 Vaccine — Moving Forward

Dan H. Barouch, M.D., Ph.D.

There are clear reasons for optimism in the quest to develop an HIV-1 vaccine. The modest protection achieved in the RV144 study provides the proof of concept that an HIV-1 vaccine is in fact possible.

N ENGL J MED 369;22 NEJM.ORG NOVEMBER 28, 2013


uhambo
A JOURNEY OF HOPE TO BE HIV-FREE

Pox-Protein Public-Private Partnership (P5)

P5 is a partnership among Bill & Melinda Gates Foundation, HIV Vaccine Trials Network, NIAID, South African MRC, Novartis, Sanofi Pasteur, and U.S. Military HIV Research Program.

NOVARTIS

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

HIV VACCINE TRIALS NETWORK

BILL & MELINDA GATES foundation

National Institute of Allergy and Infectious Diseases

SANOFI PASTEUR

MRC SOUTH AFRICA SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

Purpose:

To build on the RV144 result and develop and ultimately license HIV pox-protein vaccines with the potential for broad and timely public health impact.

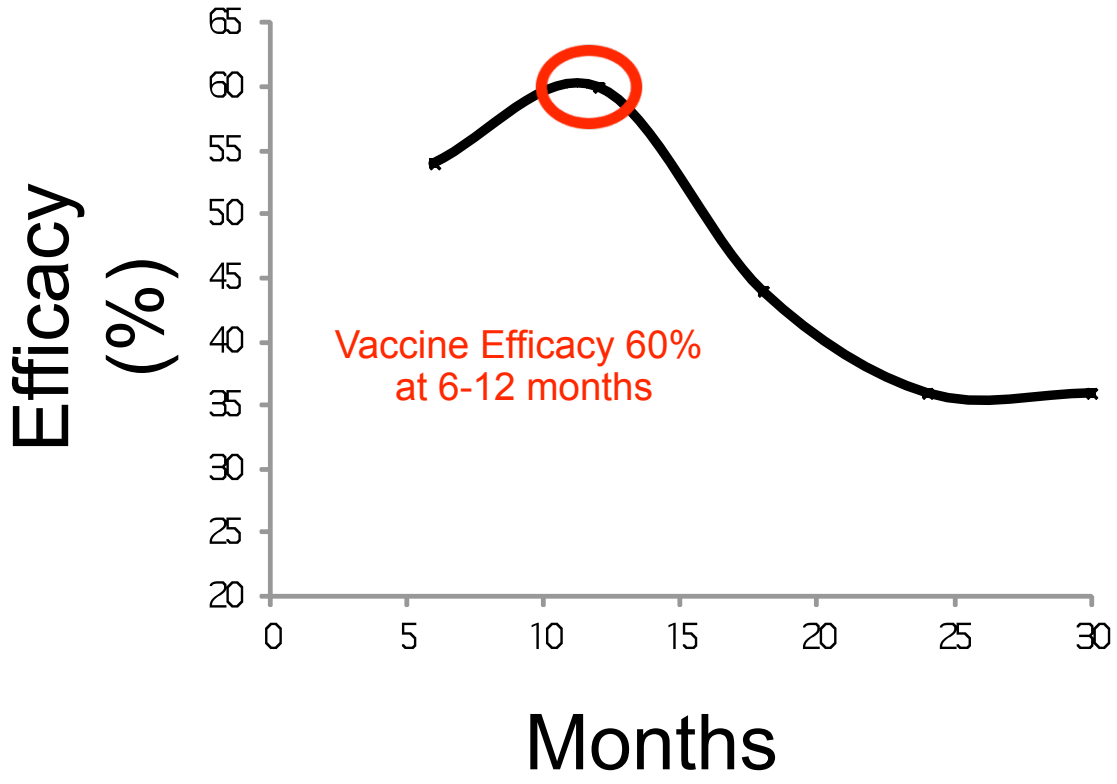
1. Continue to build public-private partnerships critical for success.
2. Work with host countries to support a flexible regulatory strategy in target populations and regions.
3. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.

Advancing the findings of RV144 in a clade C region of the world (P5 partnership)

Prime: ALVAC vCP1521

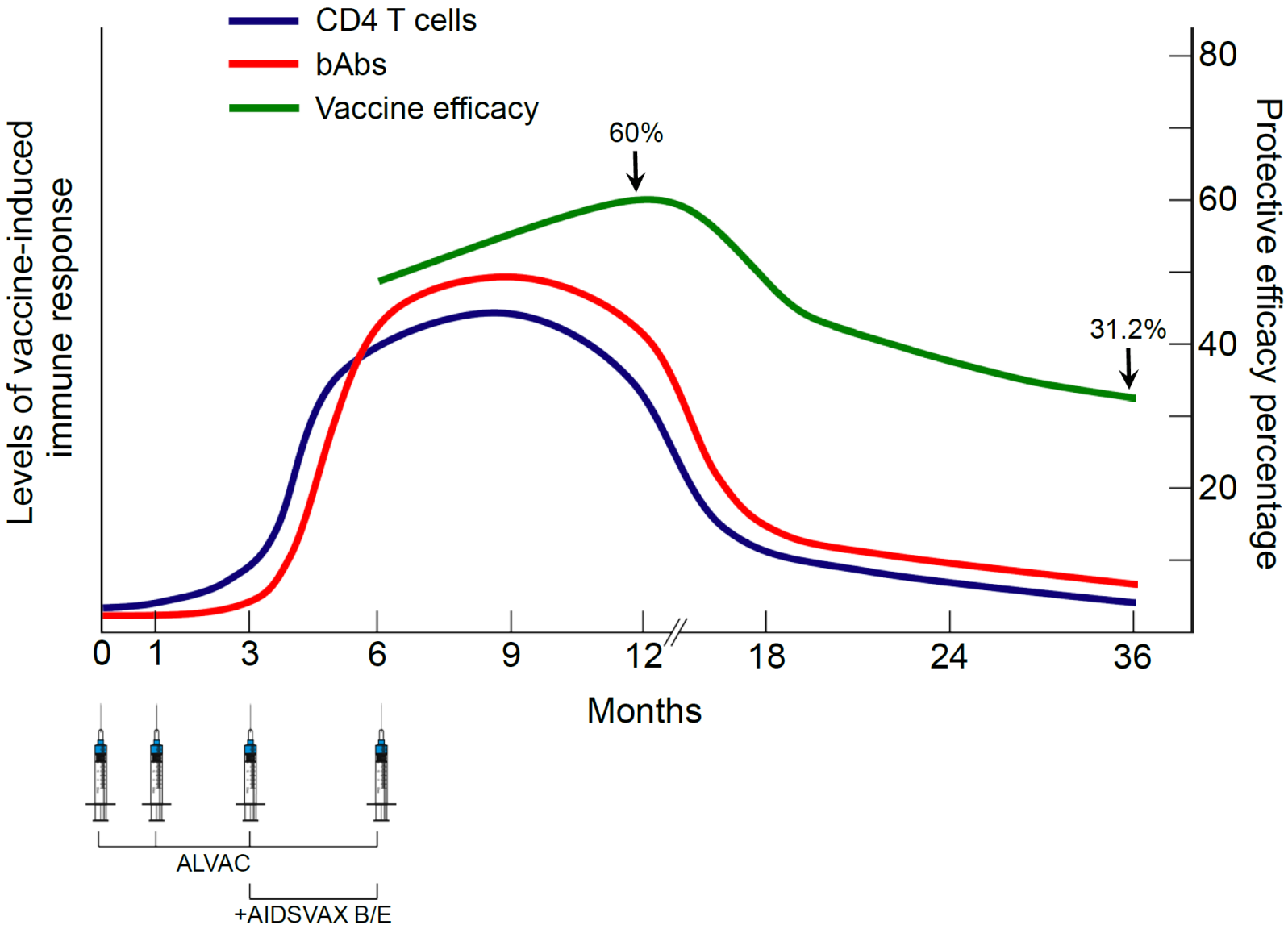
Boost: ALVAC vCP1521 plus VAXGEN env protein (B/E)

Schedule: 0,1,3,6 months; 16,000 volunteers; 1:1 vaccine: placebo; follow-up for 3 years



Although protective efficacy was 31.2% at the primary analysis, 42 months after first vaccination, the highest efficacy was observed at 6-12 months.

Efficacy and immune responses waned over time in RV144



Goals with the next generation of HIV vaccines

- Same if not better prevention of HIV infection in South Africa compared to the Thai trial
- Longer lasting protection – 2 or 3 years
- Correlates of risk consistent across both populations ……

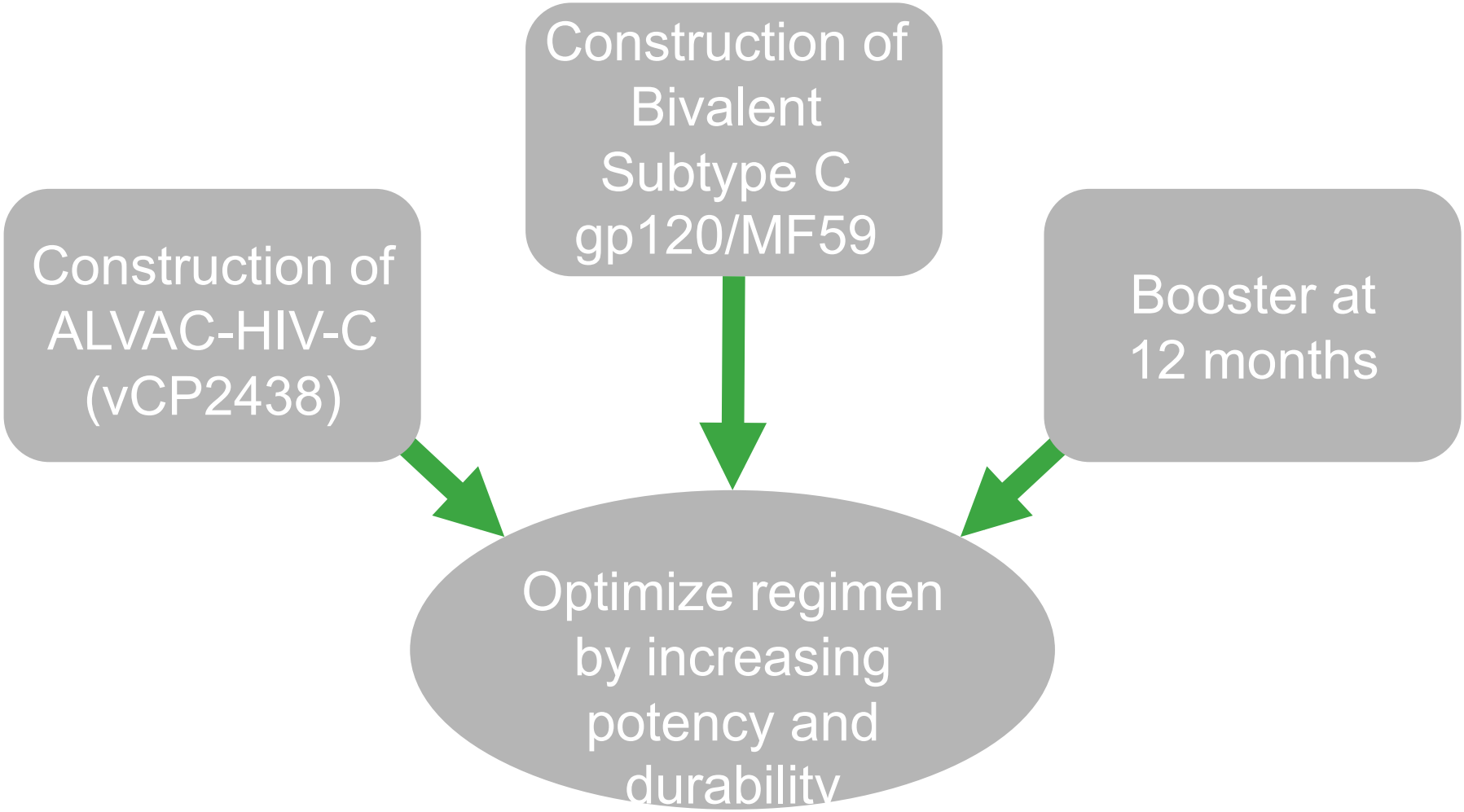
First step:

RV144 Vaccines
B/E

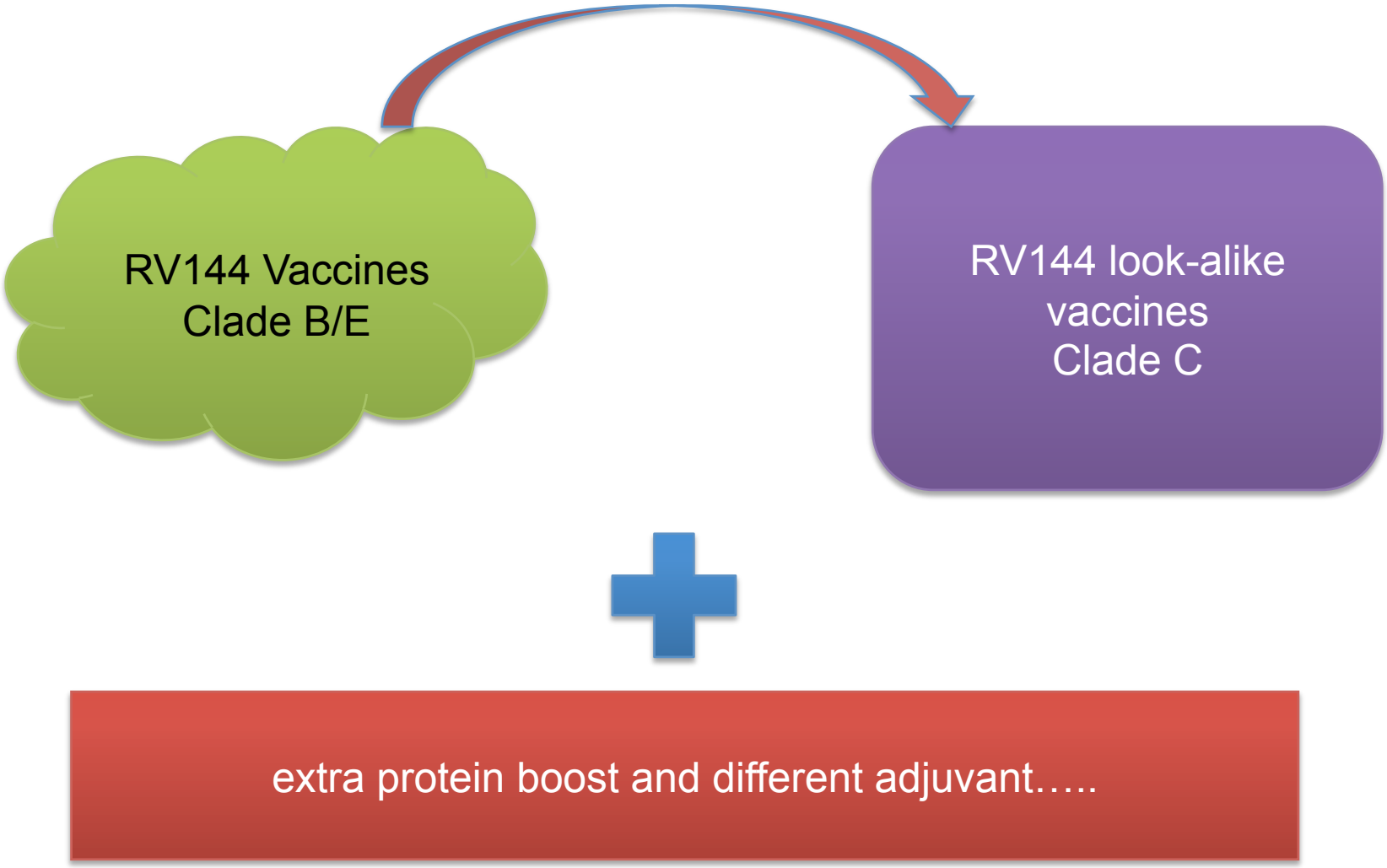
HVTN 097

- Exact same regimen as Thai Trial but in RSA
- Why?
  - **Will the population in RSA produce the same immune responses as the Thai population did?**
  - **Are there HOST issues involved?**
- **2013**
- 100 low risk participants

The Strategy for the ALVAC/Protein Phase 3 Program



Step 2: HVTN 100



Then test in RSA

RV144 look-alike vaccines
Clade C

HVTN 100
Cape Town

eThekwini
Isipingo

Klerksdorp
Soshanguve
Soweto

Study Schema: HVTN 100

N (total 252)	Primary Vaccine Regimen				Booster
	Month 0	Month 1	Month 3	Month 6	Month 12
210	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®	ALVAC-HIV+ Bivalent Subtype C gp120/MF59®
42	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo

Products:

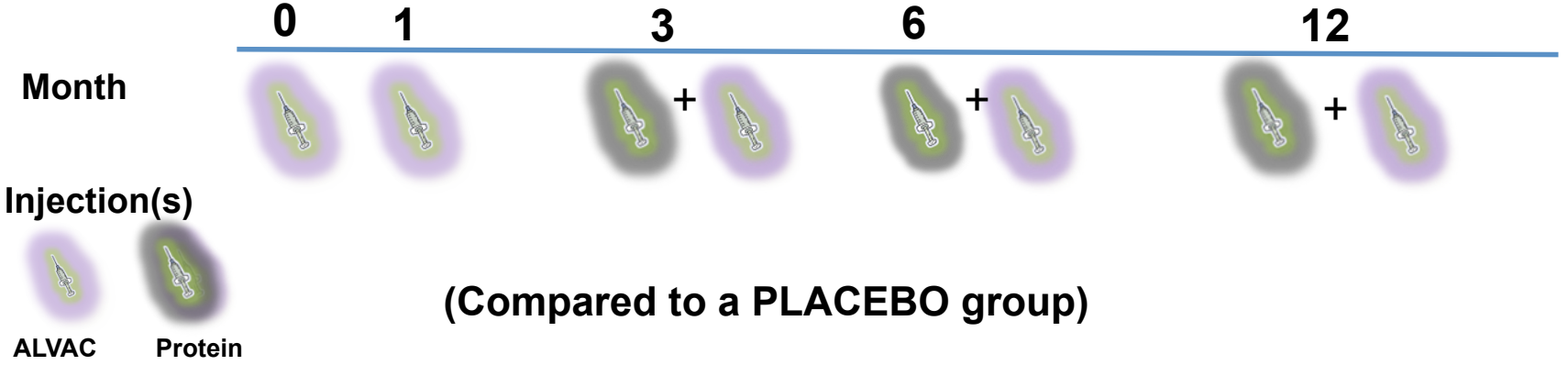
•ALVAC-HIV (vCP2438) expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >1 X 10^6 $CCID_{50}$)

•Bivalent subtype C gp120/MF59 containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

Immunogenicity evaluation to be applied to this study to inform advancement into phase 3

HVTN 100: Phase 1-2 Trial

- First clinical test of the new products
- Goals:
  - Ensure new products are safe
  - Ensure they show expected immune responses



Primary hypotheses

- 2 doses of ALVAC-HIV® (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + bivalent subtype C gp120 /MF59 will be safe and well tolerated
- 2 doses of ALVAC-HIV® (vCP2438) followed by 2 doses of ALVAC-HIV (vCP2438) + bivalent subtype C gp120 /MF59 will result in immune responses at least comparable to those induced by the RV144 vaccine regimen

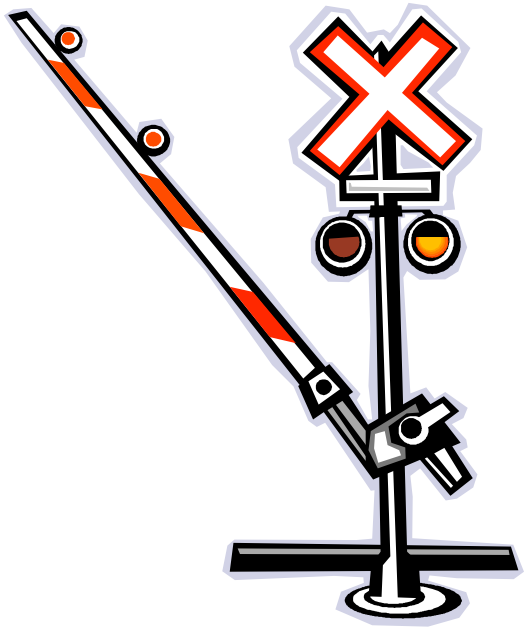
HVTN 100 Study rationale :

Build on the findings of the RV144 trial in South Africa.

- Phase 1-2 trial with a combination of 2 first-in -human vaccines, -extensive experience with ALVAC and gp120
- The two products reformulated to be as close to the structure of the RV144 products but with clade C inserts most relevant to the South African epidemic.
- The schedule of vaccinations mirrors that of RV144, but with the addition of a 12-month boost, to build on increased efficacy between the 6- and 12 -month visits in that trial.
- The adjuvant switched from alum to MF59 to

HIV VACCINE
TRIALS NETWORK

Immunogenicity Criteria to Advance a Clade C Vaccine Regimen for Phase 3 Testing in the RSA



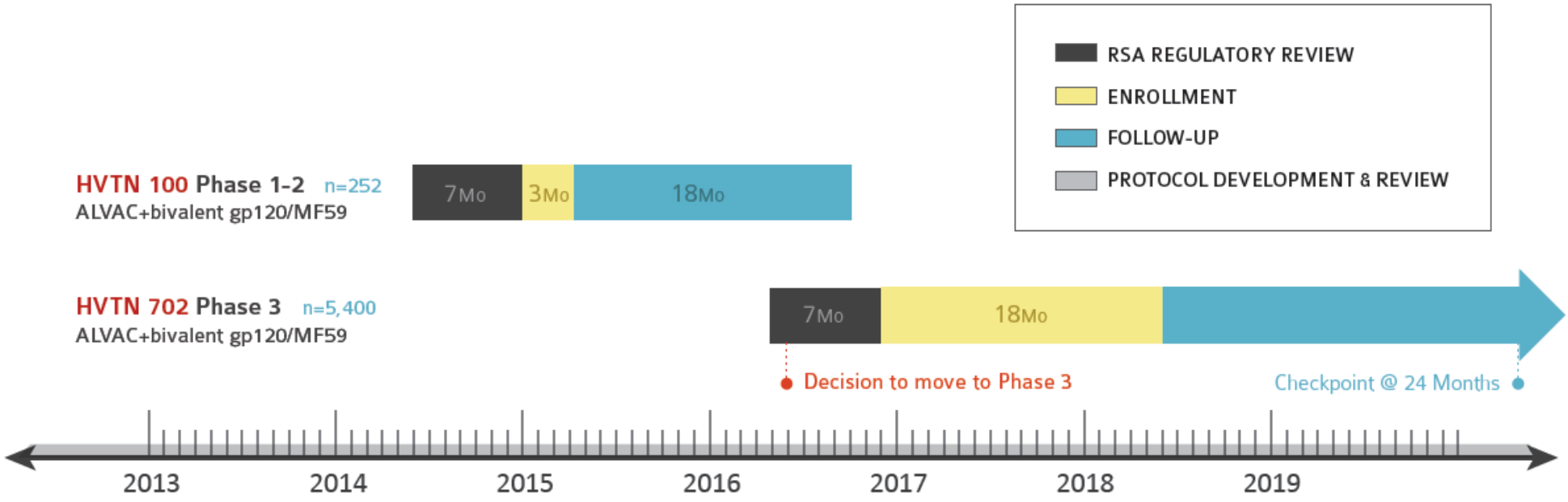
Phase 3 efficacy trial

- At-risk individuals in RSA
- >5000 participants, 1:1 vaccine: placebo
- Same vaccination schedule as phase 1-2
- RSA and Southern Africa
- 2015
- Plan ~18 months to enroll
- Plan Last Person Last Visit (LPLV) approximately Q1 2020

Goals of Phase 3 Trial

- Evaluate:
  - Efficacy of vaccine in preventing HIV infection at 24 months
  - Safety
  - Duration of efficacy to 36 months
  - Immunogenicity – lab measures
  - Determine correlates of risk/protection – can any labs predict vaccine protection?
  - Determine if people stay healthy longer if they received vaccine but still got infected, and if their HIV viral load is lower than those who got placebo

Timeline for Phase 3 Program



Ongoing research……

- To identify vaccine candidates that show improved magnitude and durability of vaccine efficacy compared to that seen in RV144

- DNA and NYVAC
  - Same vaccine products in HVTN 096, HVTN 092, and HVTN 095/MTN 022

- Gp120 protein + MF59 adjuvant
  - Same protein and adjuvant in the Development Track Trial

HIV vaccine field:

- Exciting time in the field……with RV144 follow on studies (ALVAC)
- Southern Africa – Clade C relevance
- Other similar strategies being honed (NYVAC)
- More excellent trial sites
- Interesting to watch other prevention modalities in this space…

Continued….

- Neutralizing antibody discovery holds the promise of tailor made vaccines….
- More work on correlates of risk and hopefully correlates of protection….

CANT BE DONE WITHOUT COMMUNITY….

- This will be a response for the REGION with SIGNIFICANT RSA contribution
- Will need strong civil society VACCINE ADVOCATES
- Will need well informed CABS
- Will need large numbers of informed, willing participants
- Will need excellent relationship between Communities, researchers, sponsors, regulators.

The Prevention Revolution

"Scientists have developed an array of effective tools which if implemented could reverse the AIDS epidemic"

- Professor Francoise Barré Sinoussi.

The Prevention Revolution

"Prevention activism is indispensible to overcome the epidemic"

– Archbishop Tutu.

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