# Current status and future prospects for HIV vaccines

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The Desmond Tutu HIV Centre, University of Cape Town

**GVIRF**

**Global Vaccine & Immunization Research Forum**

February 2021

# Benefits of a vaccine…..

Provision of long-lasting protection[1]

Delivery via existing infrastructure – with broad, confidential access[2]

Overcome social stigma, behaviour change and adherence[3]

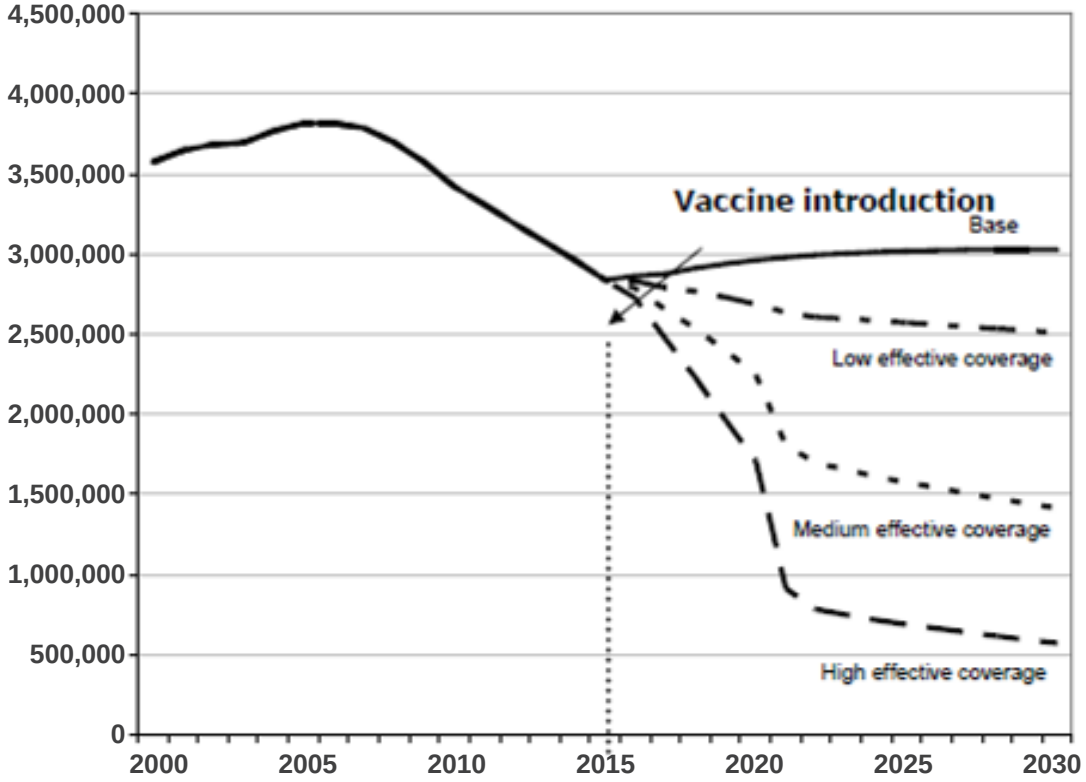
Protect all people at risk of HIV infection, including those most vulnerable[4]

Potential for herd immunity (as seen with other vaccines)[5]


1. U.S. Department of Health & Human Services. Online. Available at: https://www.vaccines.gov/basics/work/prevention. Accessed Sept 20.
2. GAVI Vaccine Alliance. Online. Available at: https://www.gavi.org/vaccineswork/now-time-pave-way-equitable-vaccine-distribution. Accessed Sept 20.
3. Vanable PA, et al. AIDS Behav. 2006; 10: 473–482.
4. de Montigny S, et al. Sci Rep. 2018;8:6066.
5. Kim TH, et al. Scand J Infect Dis. 2011; 43: 683–689.

# 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

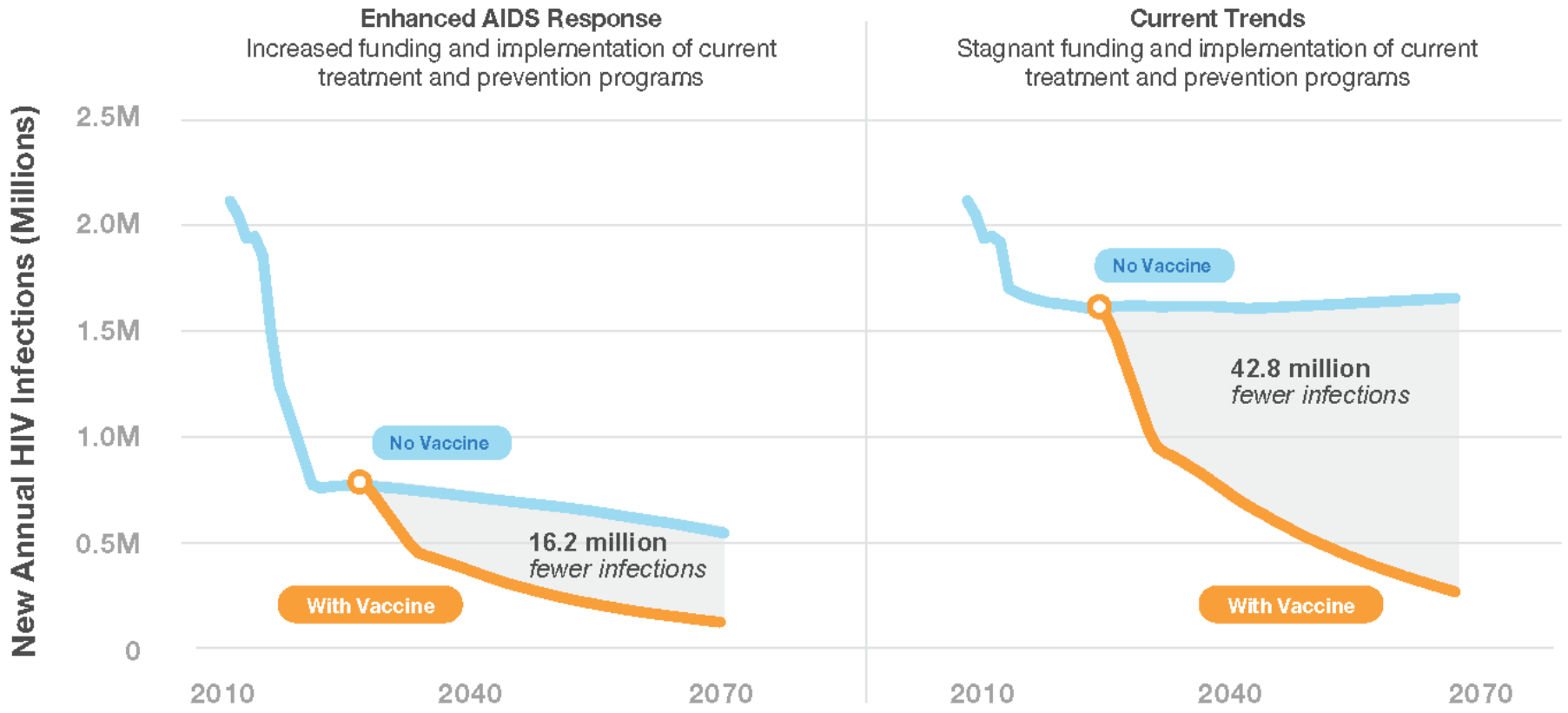
| | |
|---|---|
| 30% efficacy, 20% coverage | 5.5 million |
| 50% efficacy, 30% coverage | 17 million |
| 70% efficacy, 40% coverage | 28 million |

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)**

# Projected impact of vaccine in prevention

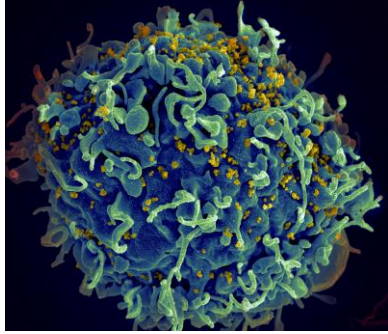
***Reduction of new annual HIV infections with and without an AIDS vaccine* between 2010 and 2070:***
***An effective "enhanced AIDS response" would require >$5b in new funding and major gains in access***




- **Assumptions**: Vaccine introduction in 2027, 50% coverage, 70% efficacy
- IFE = UNAIDS' Investment Framework Enhanced includes scale-up of PrEP, TasP, and other prevention methods

Ref: Harmon, *PloS One* 2016 doi:10.1371/journal.pone.0146387

# Why has HIV vaccine development been so challenging?



## Genetic diversity of virus greater than any other pathogen

- Envelope less immunogenic than other viruses (perhaps due to glycan shield)[1]
- The gp160 envelope trimeric structure is unique, hard to simulate and has fewer trimers on the surface[2]

## No natural immunity to HIV infection and no human challenge model[3,4] (latency, no cure)

## Imperfect animal model – different virus (SIV/SHIV)[4]

- Expensive, non-predictive of vaccine efficacy

## Limited return on investment to develop vaccines[5]

- Innovation comes from the public sector, less so from private sector
- Reluctance to do expensive efficacy trials of candidate vaccines
- Need for expanded capacity to manufacture complicated vaccine products

## Vaccine development is slow[6]

SIV, Simian immunodeficiency virus; SHIV, simian-human immunodeficiency virus


1. Klasse PJ, et al. Cell Host Microbe. 2020;27:507-518.
2. Ward AB and Wilson IA. Trends Biochem Sci. 2015; 40: 101–107.
3. Elsheikh MM, et al. EBioMedicine. 2019; 45: 624–629.
4. Sui Y, et al. Curr Protoc Immunol. 2013; 102: 12.14.1–12.14.30.
5. Serdobova I and Kieny M. Am J Public Health. 2006 September; 96(9): 1554–1559.
6. Struck MM. Nat Biotechnol. 1996;14:591–593.

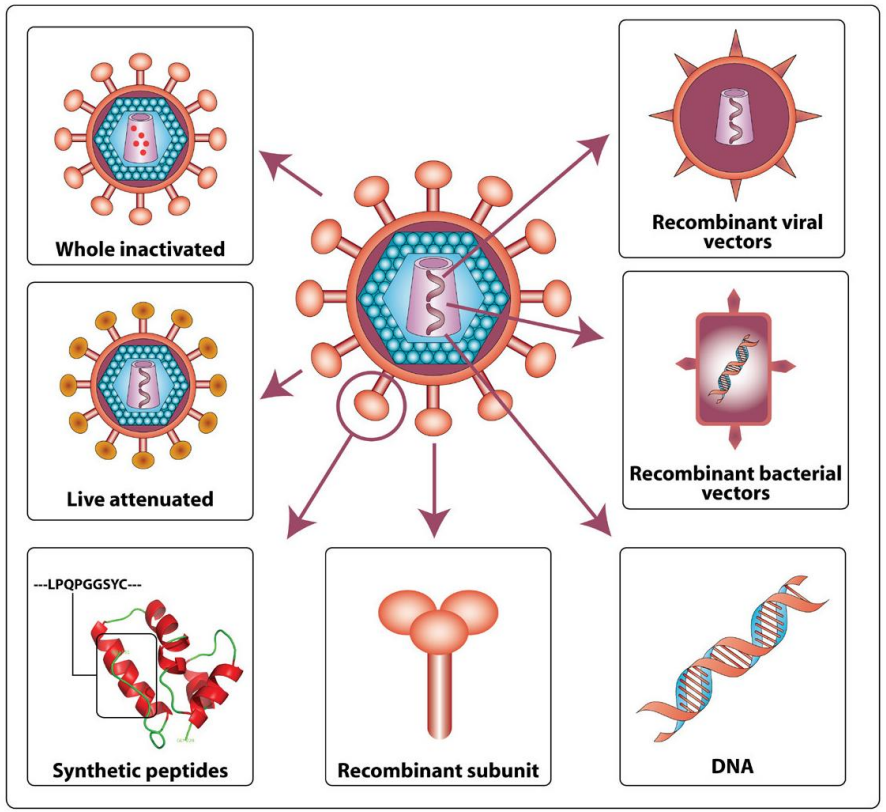
# What do we need this vaccine to look like?

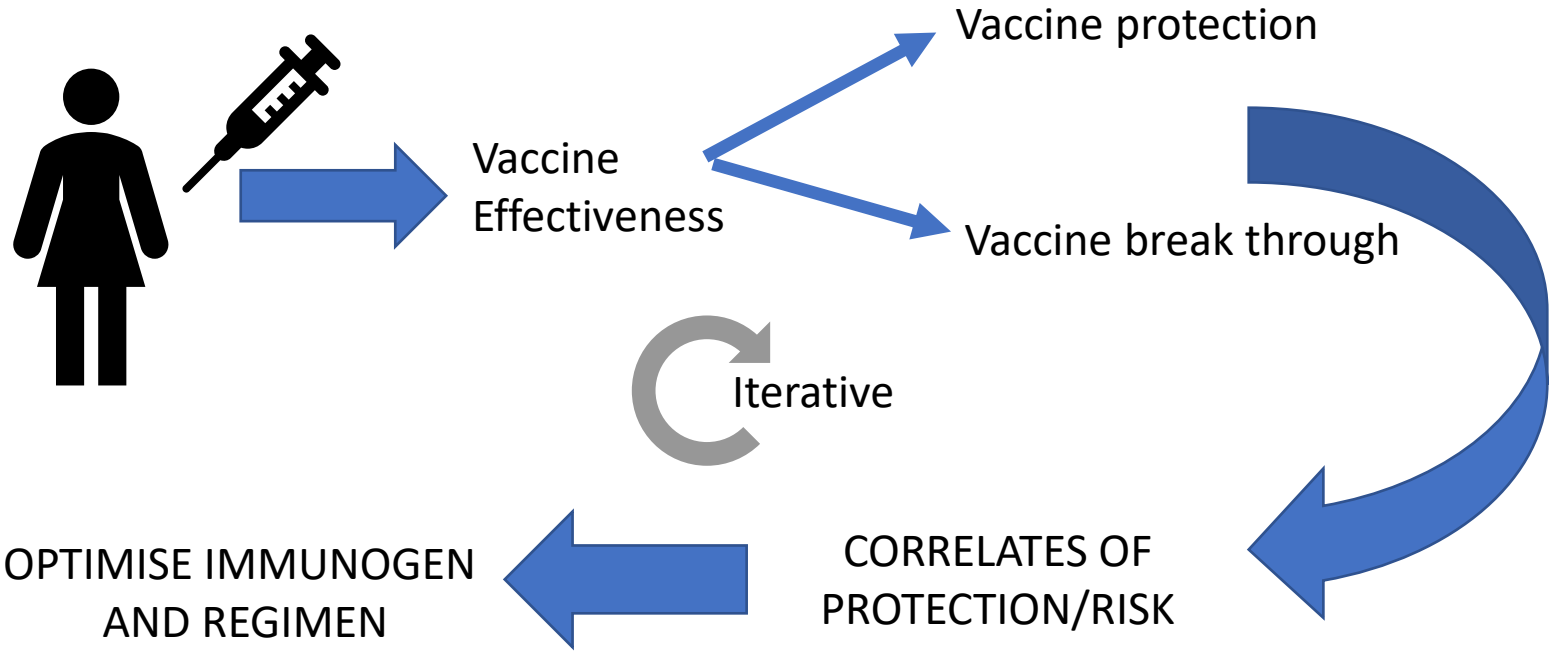
- ✓Effective in a single dose
- ✓Durable enough to provide life-time infection, or at least for several years
- ✓Minimal side effects
- ✓Cross-Clade Protection
- ✓Administered simply
- ✓Vaccine preparation that does not require special handling (cold chain, bed-side mixing)
- ✓Co-administered with other vaccines

# Vaccine Approaches

## Empirical or Inductive Approach

**Test promising candidates until Vaccine Efficacy achieved, identify correlates and optimize regimen.**



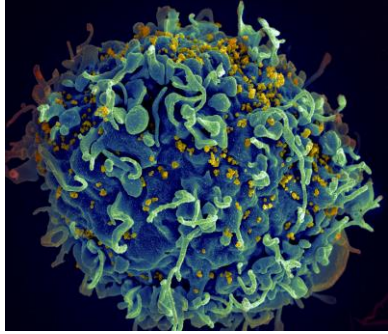




## Theoretical or Deductive Approach

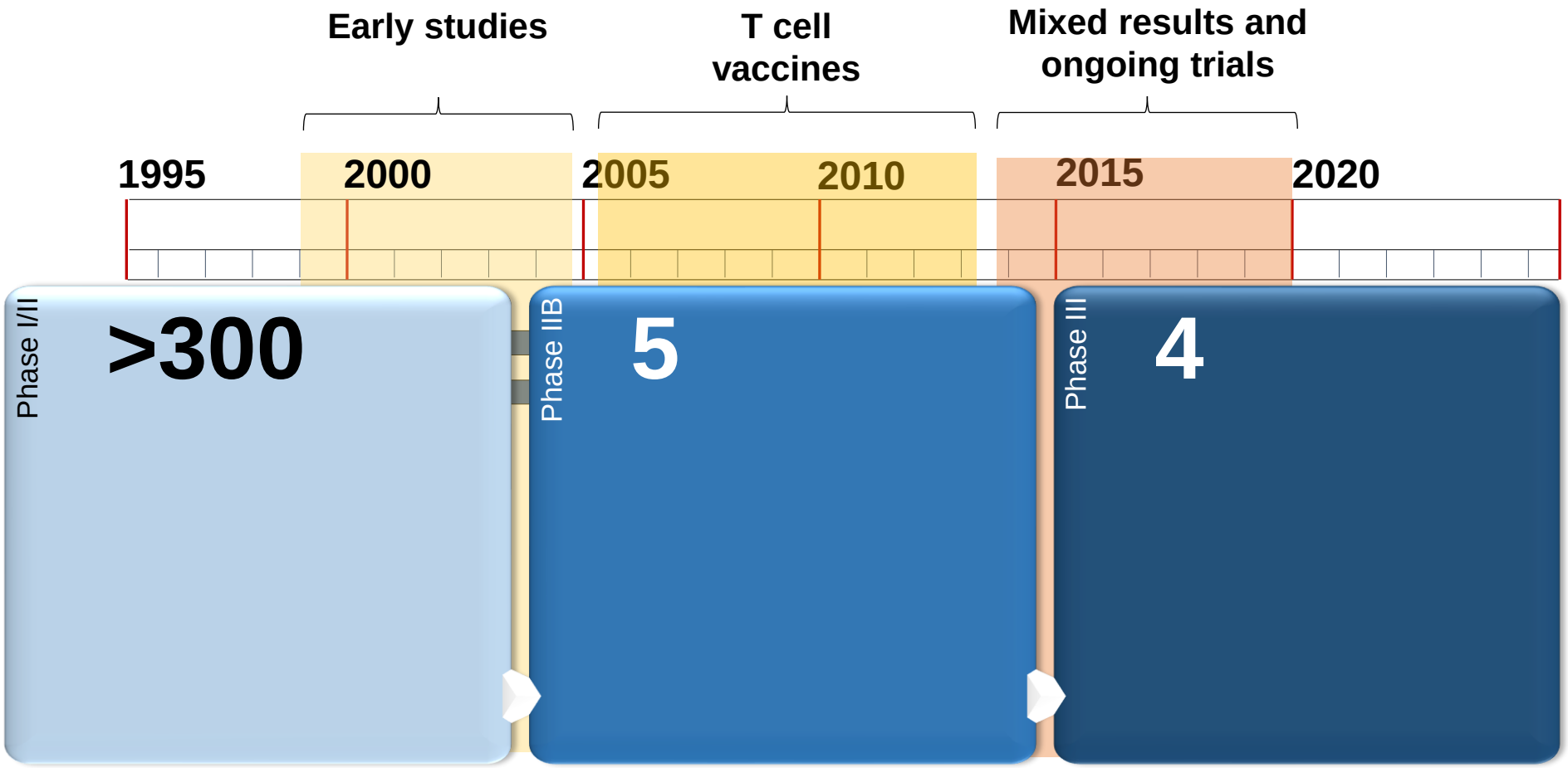
**Determine immune correlates of protection and design immunogen to induce those Immune correlates.**

Slide courtesy of M Marovich

# In the last 30 years….



Three eras of HIV-1 vaccine efficacy trials:



# Early Trials

## *(1) VaxGen USA (gp120) – 1998-2003*

- AIDSVAX, First HIV-vaccine to enter full-scale efficacy testing
- Based on 2 different isolates of subtype B virus
- Tested among 5400 participants in the US, Canada, Puerto Rico and the Netherlands
- No evidence of protection and did not elicit HIV antibodies

Graph: Kaplan-Meier curve showing time to HIV-1 infection, with adjusted *P*-values.

*rgp120 HIV Vaccine Study Group. J Infect Dis. 2005*

## *(2) VaxGen IDU Thai Trial (gp120) – 1999-2003*

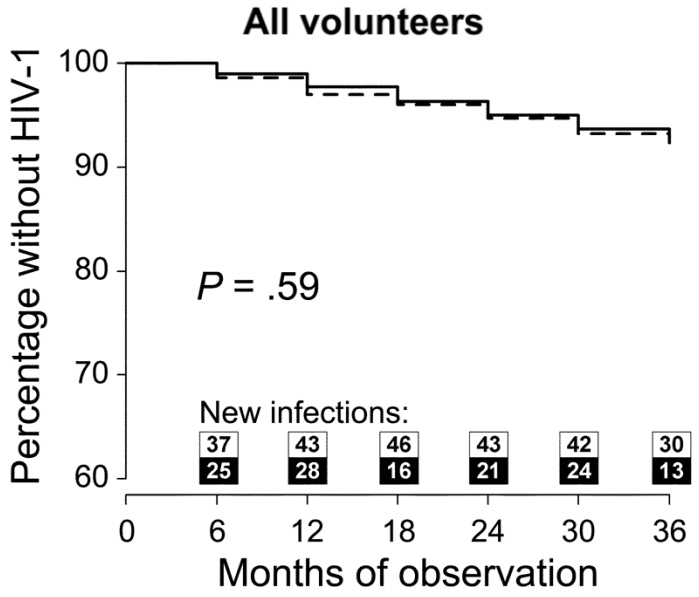
- 2nd AIDSVAX trial based on subtype B and E
- Thailand, tested among 2500 injecting drug users
- No evidence of protection.

Graph: Kaplan Meir curve for time to HIV-1 infection

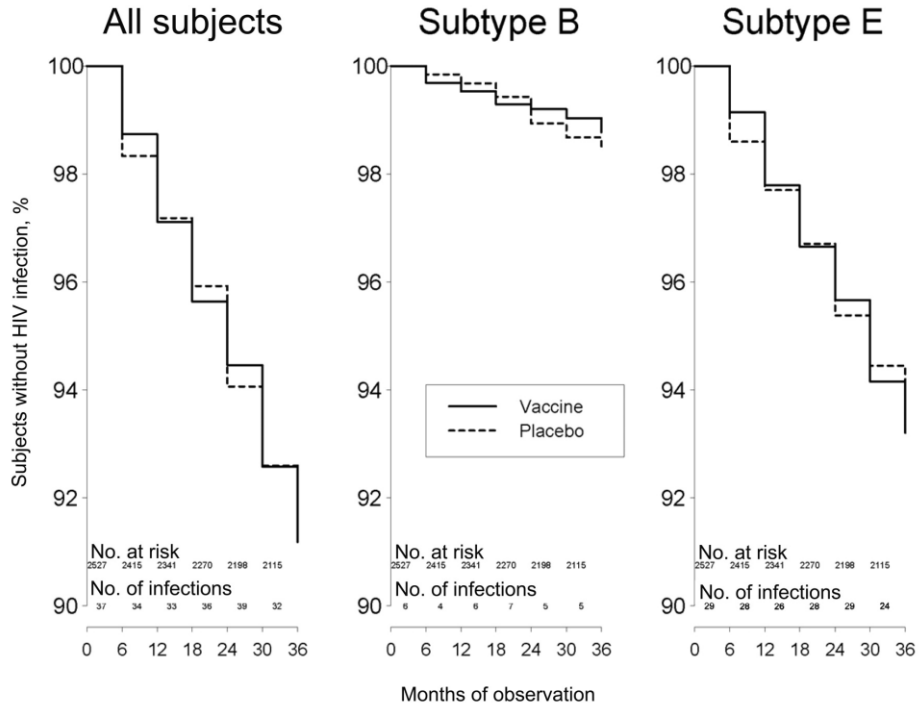
*Pitisutithum P, et al. J Infect Dis. 2006.*

Volunteer retention for the trial was higher than predicted in all settings, and higher in Thailand than the U.S.

**1**




**2**

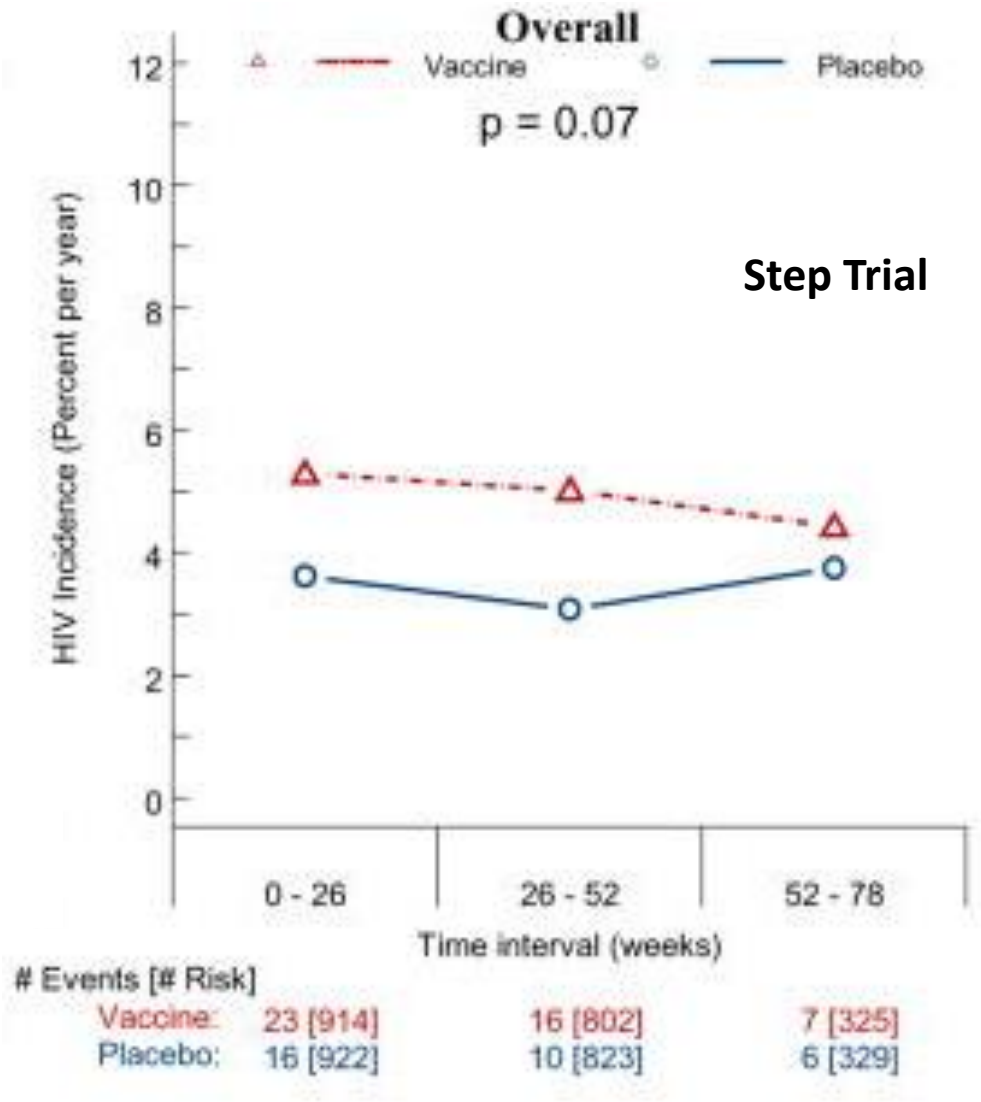


# Second Era Trials:

***(1) Step Trial (HVTN 502)/ Phambili Trials (Ad5 gag/pol/nef) – 2004-2007***

- Phase II test of concept trial enrolling 3000 participants
- Approach was stimulation of T-cell responses
  - CD8+ T cell responses appeared high (Hope!)
- Trial stopped by the DSMB after preliminary analysis as decided that the vaccine would not meet it's efficacy endpoints.
- Made some participants more vulnerable to infection
  - Adenopositivity, Male Circumcision status.
- Phambili, a companion trial for in southern African, was halted

Graph: HIV incidence during 6 month intervals for male vaccine and placebo groups.




***(2) HVTN 505 (DNA/Ad5 env/gag/pol) – 2009-2013***

- 2504 participants in the US
- Low Adenovirus seropositivity, circumcized men.
- Stopped in 2013 by the DSMB – no sign of effective HIV prevention or reduction in viral load

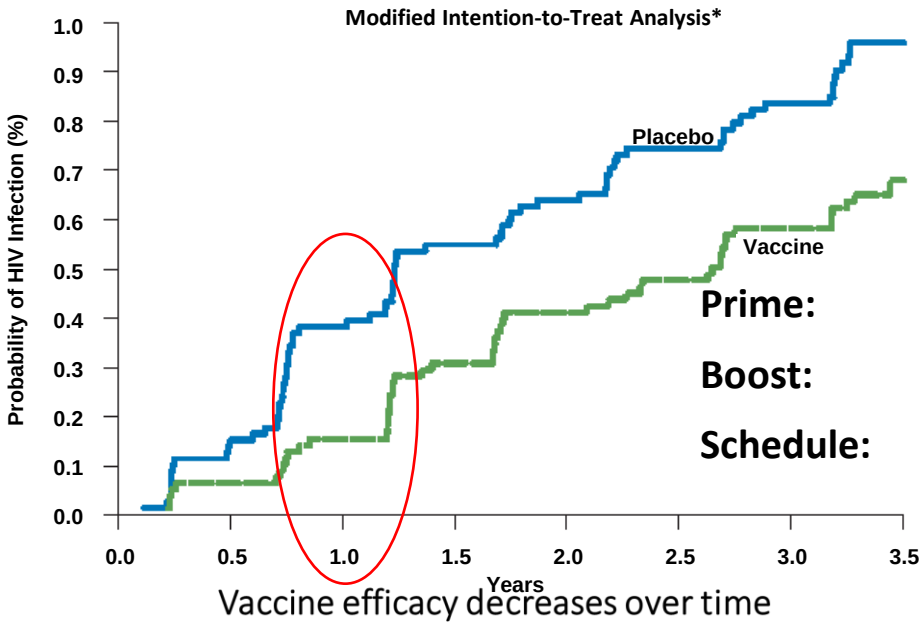
*Buchbinder SP et al. The Lancet. 2008*

# Thai Trial (RV144) Primary Results

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

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*




Vaccine efficacy decreases over time

**Prime:** ALVAC vCP1521

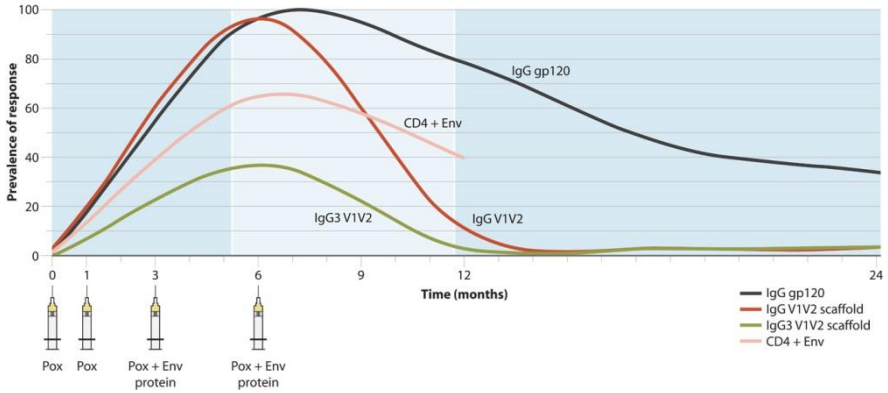
**Boost:** ALVAC vCP1521 plus AIDSVAX Env protein (B/E)

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

| | Vaccine | | Placebo | | |
|---|---|---|---|---|---|
| Time (mo) | Cumulative Infections | % HIV-1 infection rate (95% CI) | Cumulative Infections | % HIV-1 infection rate (95% CI) | Vaccine Efficacy (%) |
| 12 | 12 | 0.15 (0.07,0.24) | 30 | 0.38 (0.24,0.52) | 61 |
| 24 | 32 | 0.41 (0.27,0.55) | 50 | 0.64 (0.46,0.82) | 36 |
| 36 | 45 | 0.58 (0.41,0.75) | 65 | 0.84 (0.63,1.04) | 31 |
| 42 | 51 | 0.68 (0.49,0.87) | 74 | 0.96 (0.74,1.18) | 31 |

VE = 31% at study end (42 months)

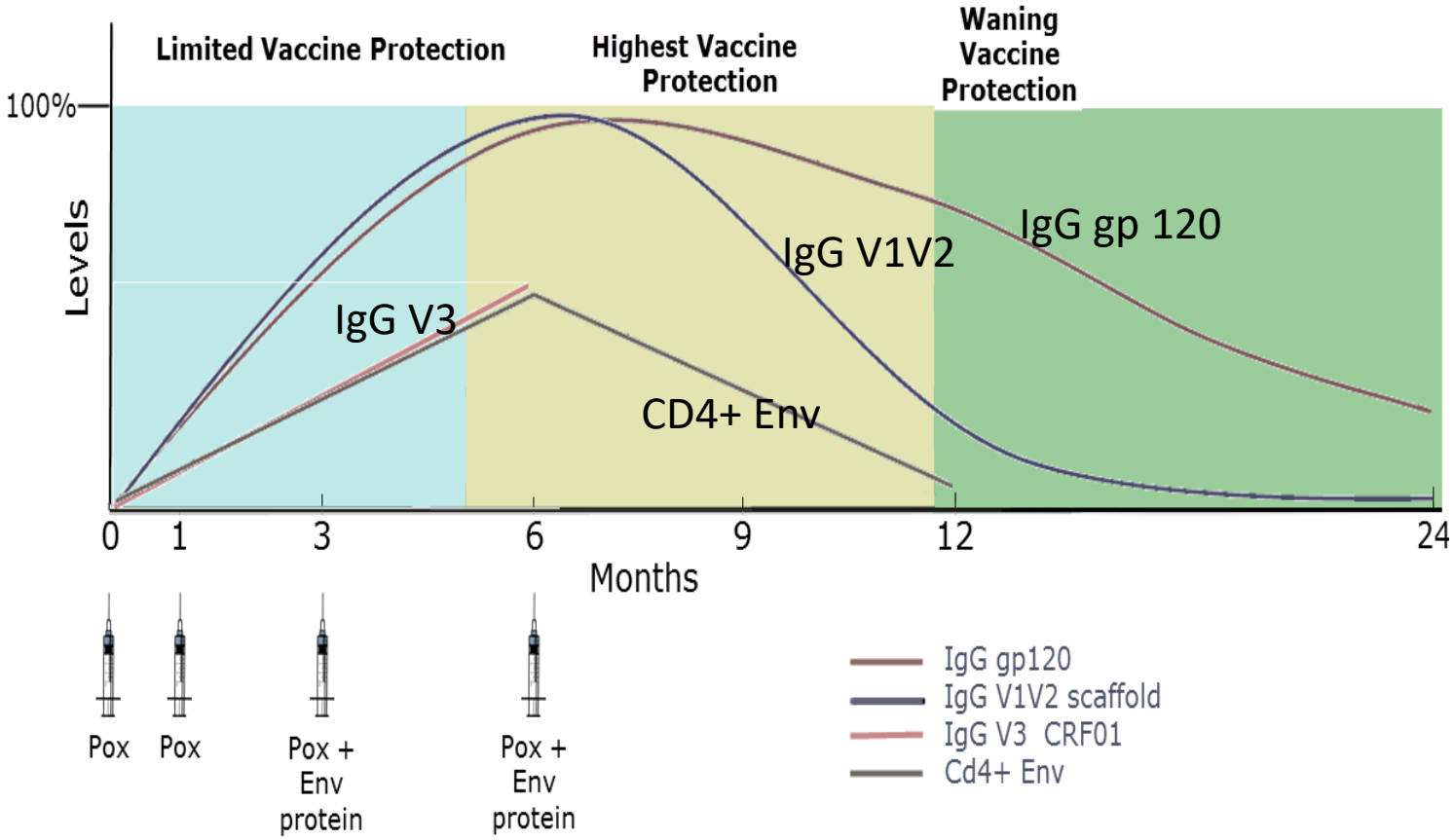
VE = 61% (12 Months)

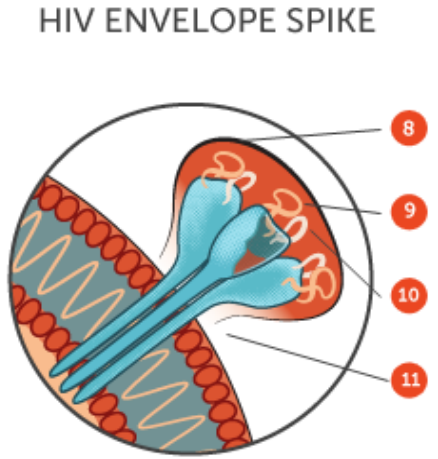


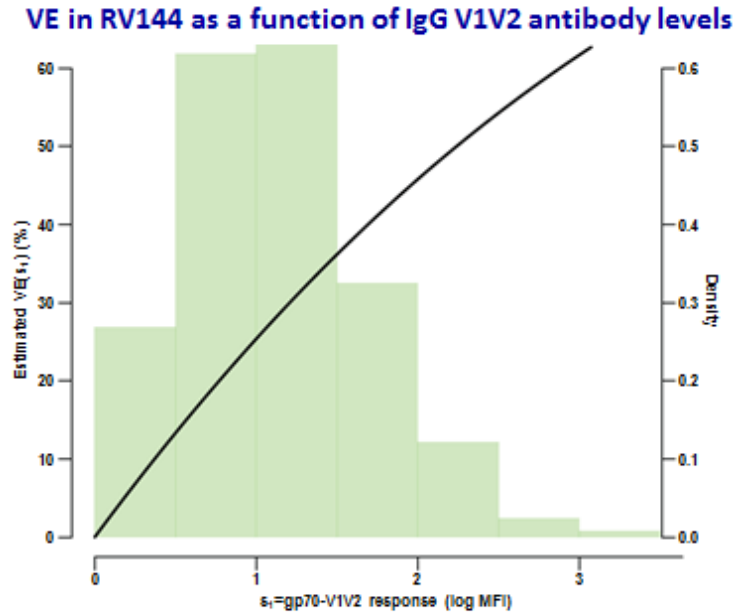

Robb M, et al

First indication of protection but rapid waning…..

# Lessons from RV144




Estimated vaccine efficacy in RV144 as a function of the level of IgG binding antibody to gp70-scaffolded V1V2 (black line) and the distribution of IgG levels among vaccinees (histogram)

- Antibodies to the conserved region of V2 were highly correlated with efficacy.
- No direct correlation between neutralizing antibodies and HIV-1 acquisition.
- Polyfunctionality scores of env-specific CD4+ T-cell responses also key

**Importance of the insert (HIV envelope gene) in the vector.**

# Strategy for the P5 Program- based on RV144

**HVTN 097**

**Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand**

Gray G, etal 2020

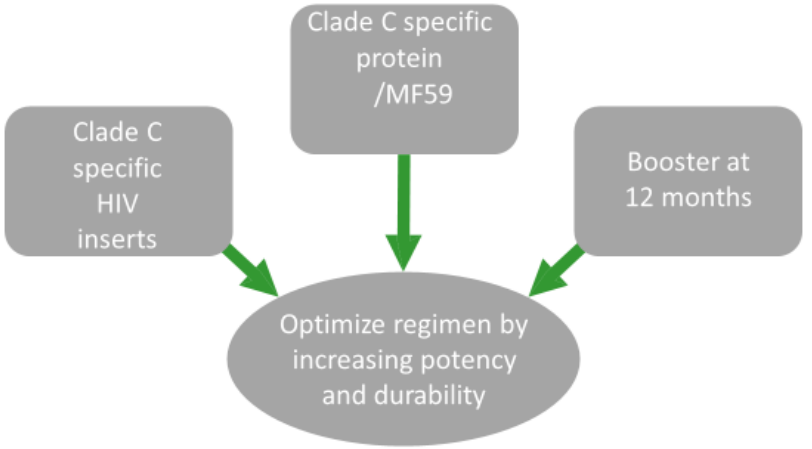
**HVTN 100**

**A standard phase 1/2A trial of the clade C products to decide whether to proceed to phase 3**

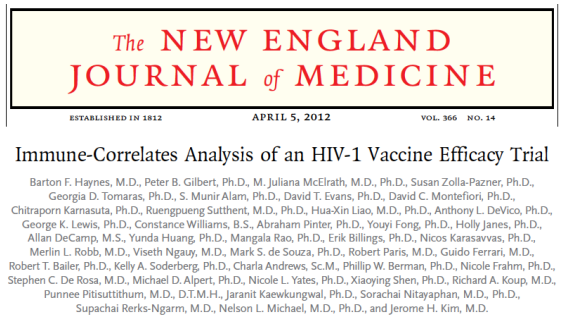
Bekker et al 2019

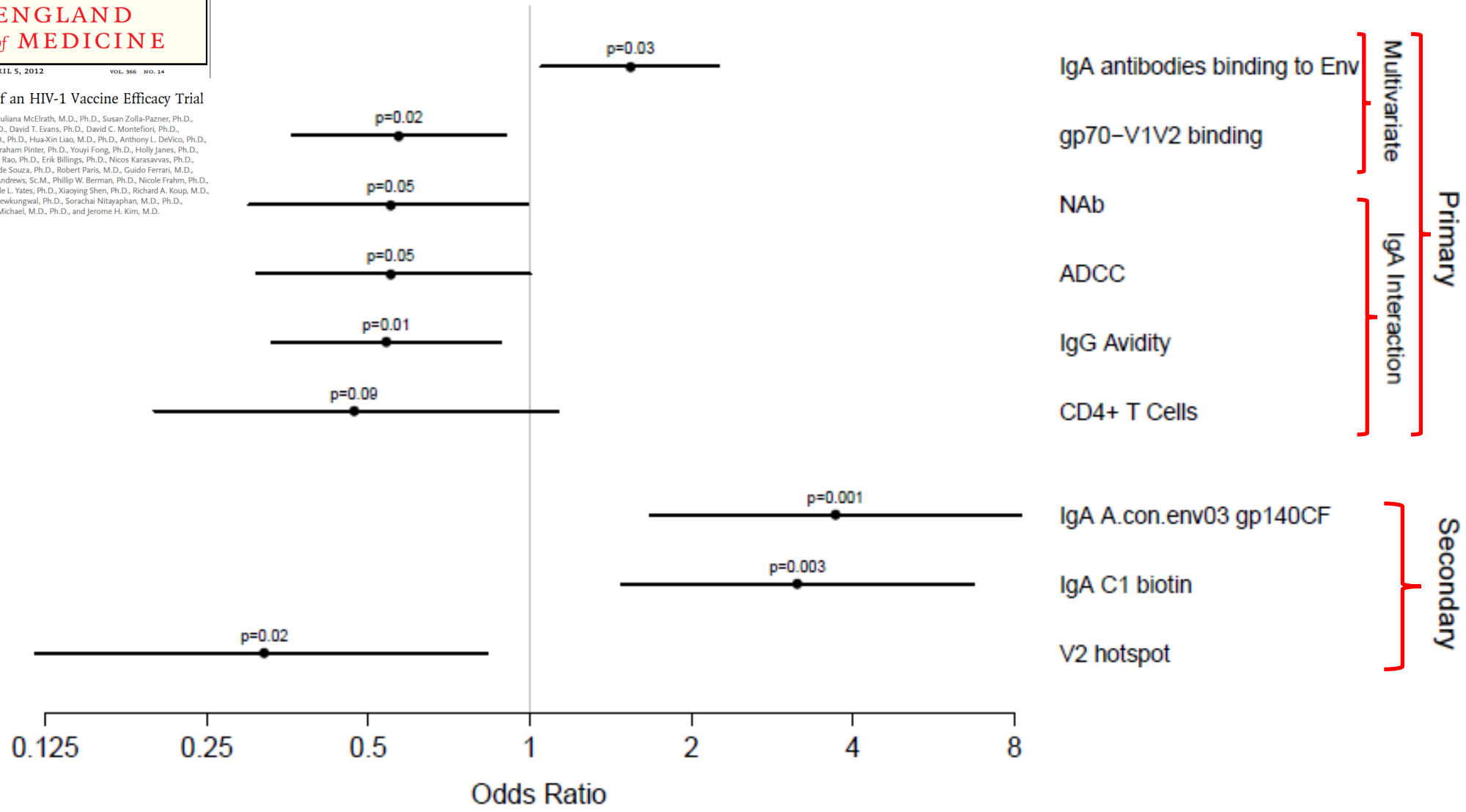
**HVTN 702**

**A Classic phase 3 RCT assessing efficacy and safety aimed at licensure**



# Correlates of Risk of HIV Infection Reported (2012, *NEJM*)




**Haynes *et al.* NEJM 2012; Gottardo *et al.* Plos One 2013; Zolla-Pazner *et al.* Plos One 2014; Yates, Tomaras *et al.* Sci. Trans. Med 2014; Chung *et al.* Cell 2015; Tomaras, Ferrari *et al.* PNAS 2013; Rolland *et al.* Nature 2012; Liao *et al.* Immunity 2012; Gilbert *et al.* Statistics in Biosciences 2016; Li *et al.* JCI 2014; Gartland *et al.* JV 2014; Prentice *et al*. Sci.Trans Med. 2015; Lin *et al.* Nature Biotechnology 2015)**

# HVTN 702

**A pivotal phase 2b/3 multi-site, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of ALVAC-HIV (vCP2438) and bivalent subtype C gp120/MF59 in preventing HIV-1 infection in adults in South Africa**

- Commenced: Nov. 1, 2016
- Chair: Glenda Gray
- Co-Chairs:

  Linda Gail Bekker, Fatima Laher,

  Mookho Malahlela


**First HVTN 702 Vaccination: Soweto-Bara (Oct 2016)**

# HVTN 702 RSA sites

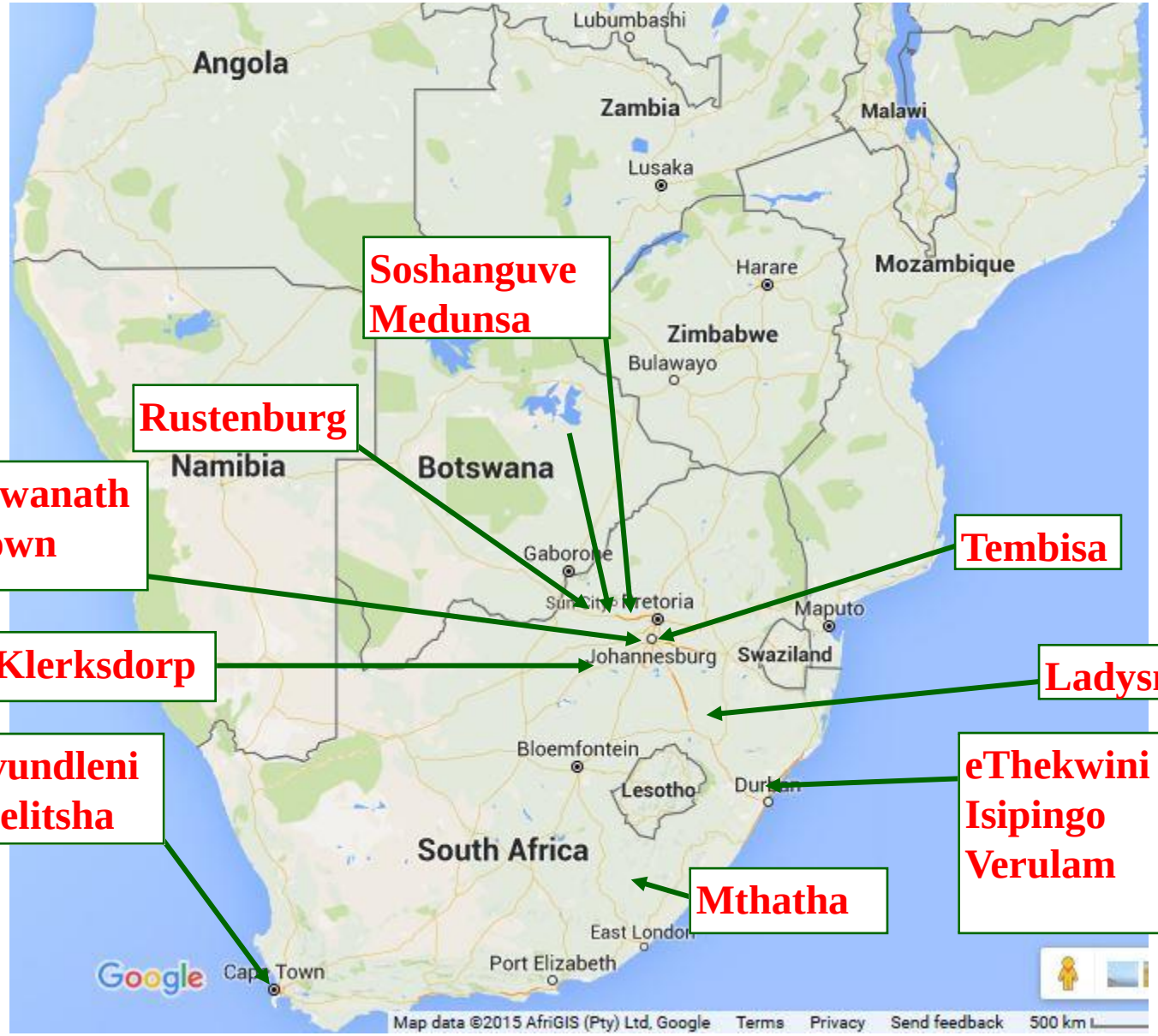
**Progress:**

**14 sites activated**

**Accrual : 80%**

**Gender: 65% in YW**

**Accrued: Feb 2019**
**End : Jan 2021**




Soshanguve
Medunsa

Rustenburg

Soweto – Baragwanath
Soweto – Kliptown

Tembisa

Klerksdorp

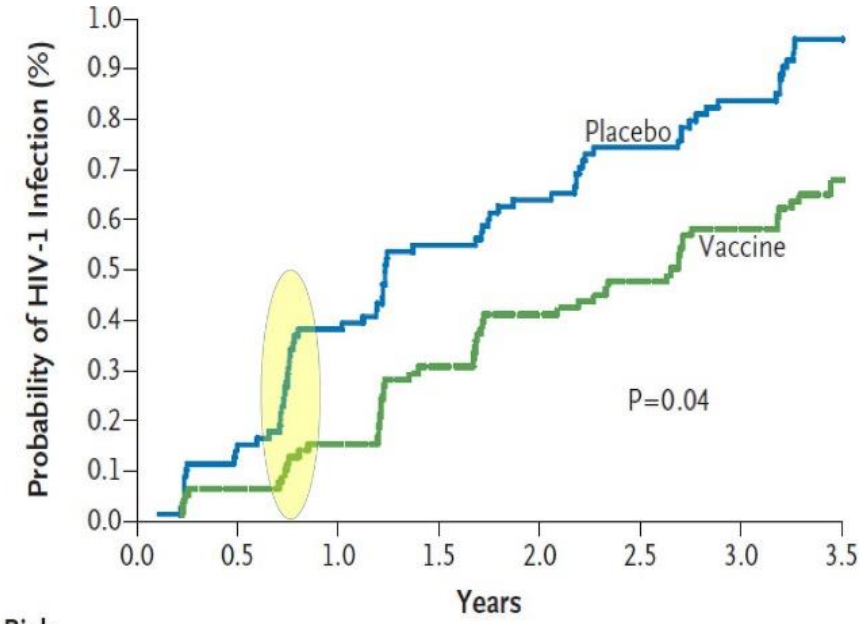
Ladysmith

Cape Town-Emavundleni
Cape Town-Khayelitsha

eThekwini
Isipingo
Verulam

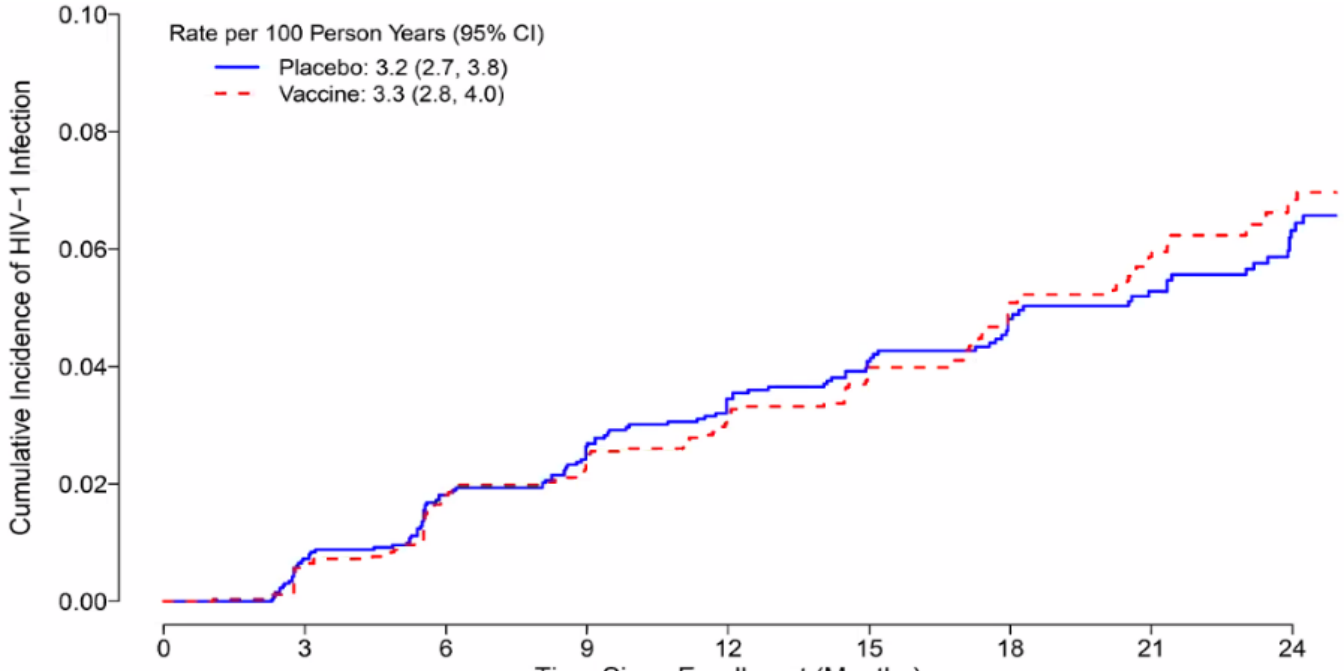
Mthatha

# RV144




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 8198 | 7775 | 7643 | 7441 | 7325 |
| Vaccine | 8197 | 7797 | 7665 | 7471 | 7347 |
| **Cumulative No. of Infections** | | | | | |
| Placebo | | 30 | 50 | 65 | 74 |
| Vaccine | | 12 | 32 | 45 | 51 |

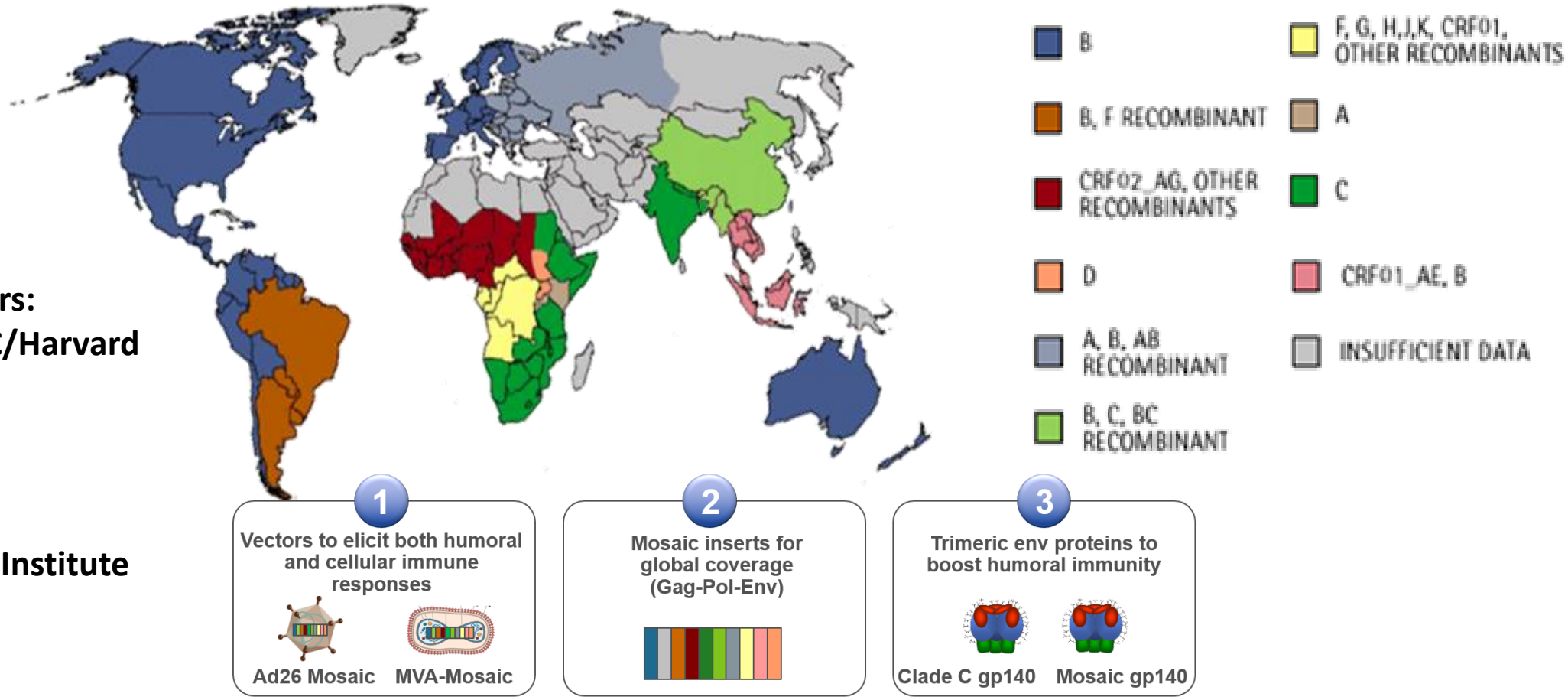
# HVTN702




| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2689 | 2573 | 2327 | 2128 | 1920 | 1596 | 1320 | 1038 | 764 |
| Vaccine | 2694 | 2586 | 2351 | 2160 | 1945 | 1621 | 1349 | 1045 | 754 |
| **Cumulative Events** | | | | | | | | | |
| Placebo | 0 | 19 | 46 | 65 | 82 | 94 | 105 | 111 | 121 |
| Vaccine | 0 | 16 | 46 | 60 | 77 | 91 | 108 | 118 | 128 |

# J and J Vaccine Research Program: Preventive HIV Vaccine aiming for Global Coverage

- **Partners:**
- **BIDMC/Harvard**
- **HVTN**
- **IAVI**
- **MHRP**
- **NIAID**
- **Ragon Institute**




Barouch, D.H., *et.al.* Nature 482, pp. 89–93 (02 February 2012) ; Barouch, D.H., *et.al.* Cell, Volume 155, Issue 3, pp. 495-497 (24 October 2013) ; Barouch, D.H., *et.al.* Science Vol. 349, Issue 6245, pp. 320-324 (17 Jul 2015)

**M. Pau/Janssen**

# HVTN 705/HPX2008: Vaccine Aiming at Protection Against all Clades of HIV-1

**1**

Potent Priming Vectors
Low seroprevalent Ad26

**2**

Mosaic inserts for global coverage
(Gag-Pol-Env)

**3**

Trimeric env proteins for improved humoral immunity
gp140 Clade C

| Group | N | Month 0 | Month 3 | Month 6 | Month 12 |
|---|---|---|---|---|---|
| 1 | 1300 | Ad26.Mos4.HIV | Ad26.Mos4.HIV | Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant) | Ad26.Mos4.HIV + Clade C gp140 (250 mcg + adjuvant) |
| 2 | 1300 | Placebo | Placebo | Placebo + Placebo | Placebo + Placebo |

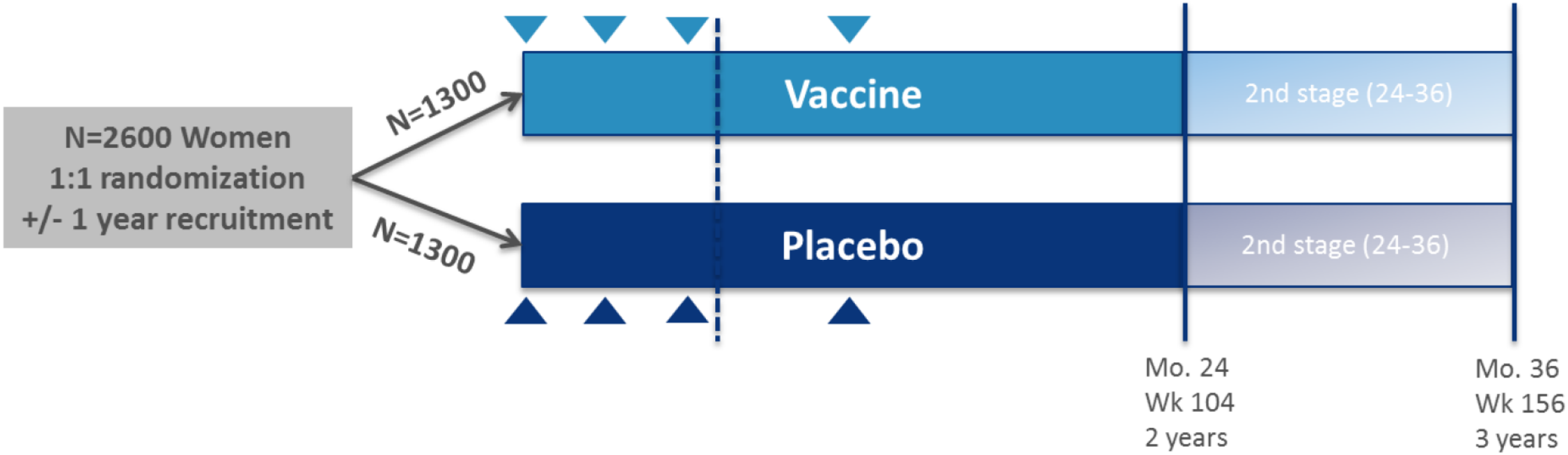
**Phase 2b Proof of Concept - Not a licensure trial**

Source: Maria Grazia Pau, © Janssen (Infectious diseases and Vaccines)

- **Protective Efficacy hypothesis:** 50% (lower bound >0%) reduction in HIV-1 acquisition,
- Preparatory work ongoing to move to Phase 3
- Ongoing planning around licensure and implementation (discussions with RA, pricing strategy, WHO prequalification)

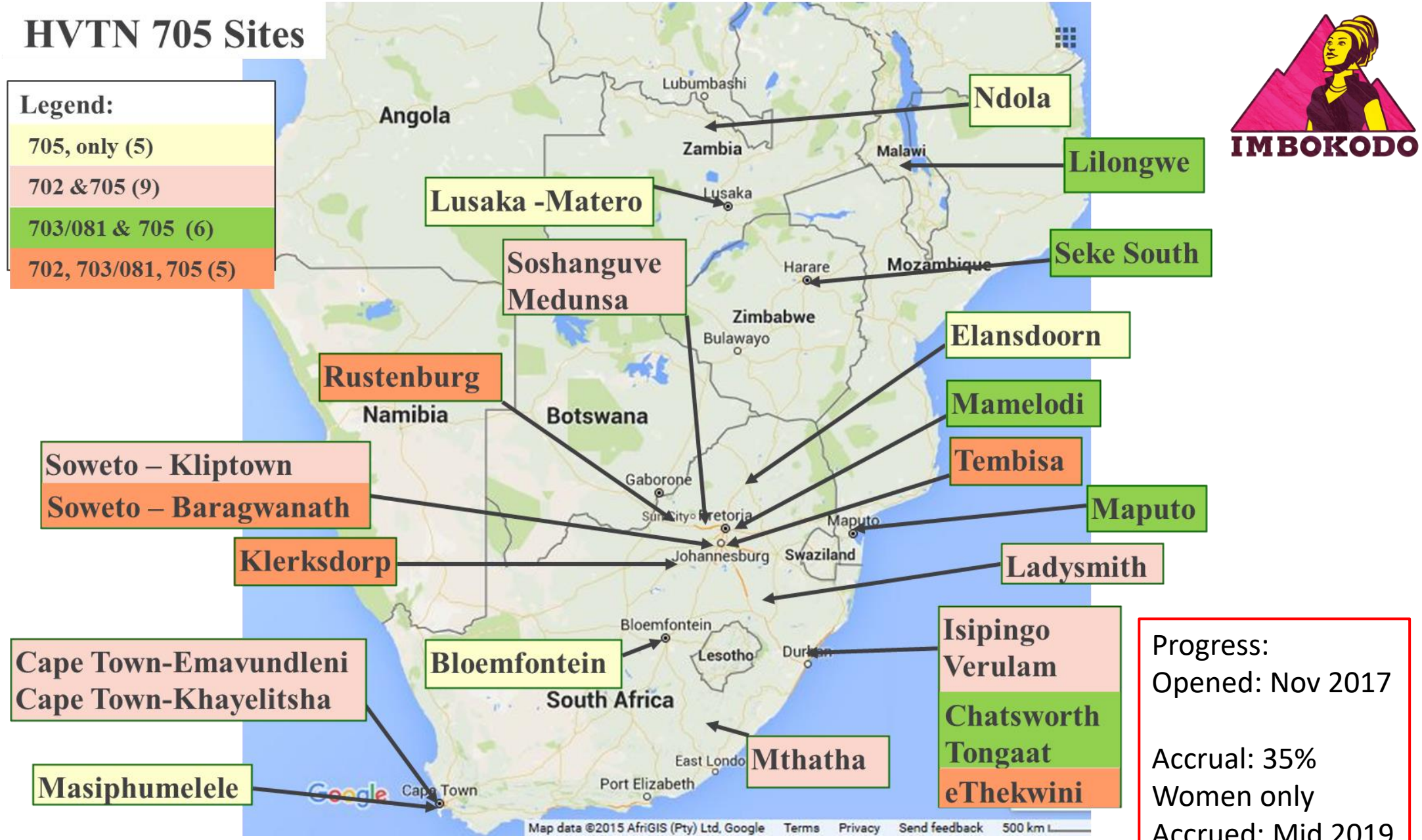
IMBOKODO

# Study Schema: HVTN 705/Imbokodo




**Chairs: Glenda Gray,**
**Co-chairs: Susan Buchbinder, Kathy Mngadi and Frank Tomaka**

# HVTN 705 Sites

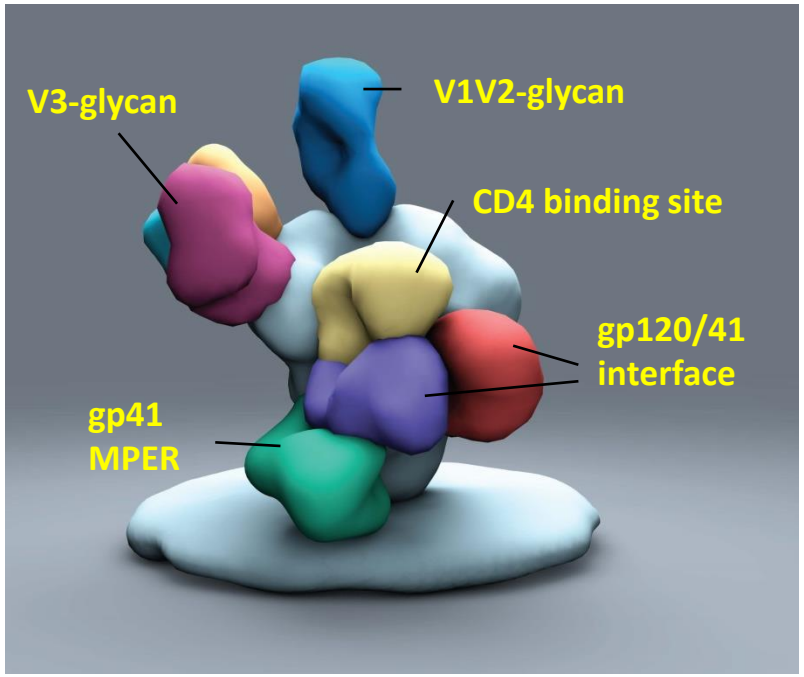



IMBOKODO

Progress:
Opened: Nov 2017

Accrual: 35%
Women only
Accrued: Mid 2019
End: Mar 2021

# Neutralizing Antibodies to HIV-1




Christina Corbaci, Andrew Ward,

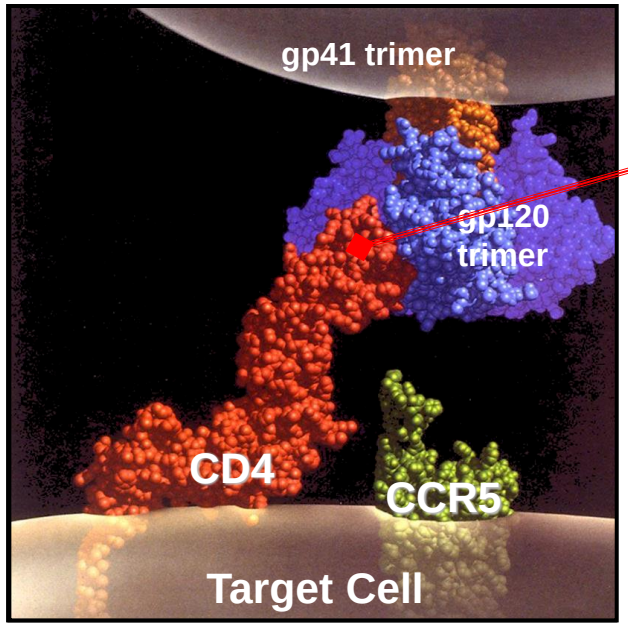
V1V2-GLYCAN – BIND TO TRIMER CAP

V3-GLYCAN, N332 SUPERSITE

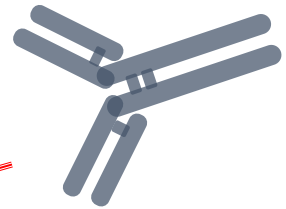
GP41 MPER – NEAR MEMBRANE

GP120/41 INTERFACE – BIND TO PARTS OF BOTH GP120 AND GP41

CD4 BINDING SITE OF GP120 – WHERE THE VIRUS ATTACHES TO CD4




VRC01 Blocks Attachment to CD4



**CD4 binding site on gp120 is functionally conserved: all viruses must bind CD4**

**VRC01 neutralizes ~ 90% of diverse viral isolates**

# Passive Antibody Prevention
## Phase IIB Efficacy Studies

**AMP = Antibody Mediated Prevention**

**Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & heterosexual women in sub-Saharan Africa**

- **Placebo controlled trial of VRC01 mAb (IV), given on 8 weekly schedule**
- **Two cohorts:**
  - **2,400 MSM + TG in North & South America (HVTN 704/HPTN 085)**
  - **1,900 Women in sub-Saharan Africa (HVTN 703/HPTN 081)**
- Both trials opened in April/May 2016
- 703/081 Accrued September 20, 2018 (End Jan 2021)
- 704/085 Accrued October 5, 2018 (End Oct 2020)

**Chairs:** **Lawrence Corey, HVTN**
**Mike Cohen, HPTN**
**Co-chairs:** **Srilatha Edupuganti**
**Nyaradzo Mgodi**

# Cohorts for the AMP Studies

| Cohorts | Antibody (VRC01) 10mg/kg | Antibody (VRC01) 30mg/kg | Placebo Saline | Total Population |
|---|---|---|---|---|
| **HVTN704/HPTN085:** MSM & TG persons (Clade B) United States, Peru, Brazil & Switzerland | 900 | 900 | 900 | 2,700 |
| **HVTN703/HPTN081:** Heterosexual women (Clade C) Sub-Saharan Africa – 7 countries | 634* | 634* | 634* | 1,900 |
| Total | 1,534 | 1,534 | 1,534 | 4,600 |

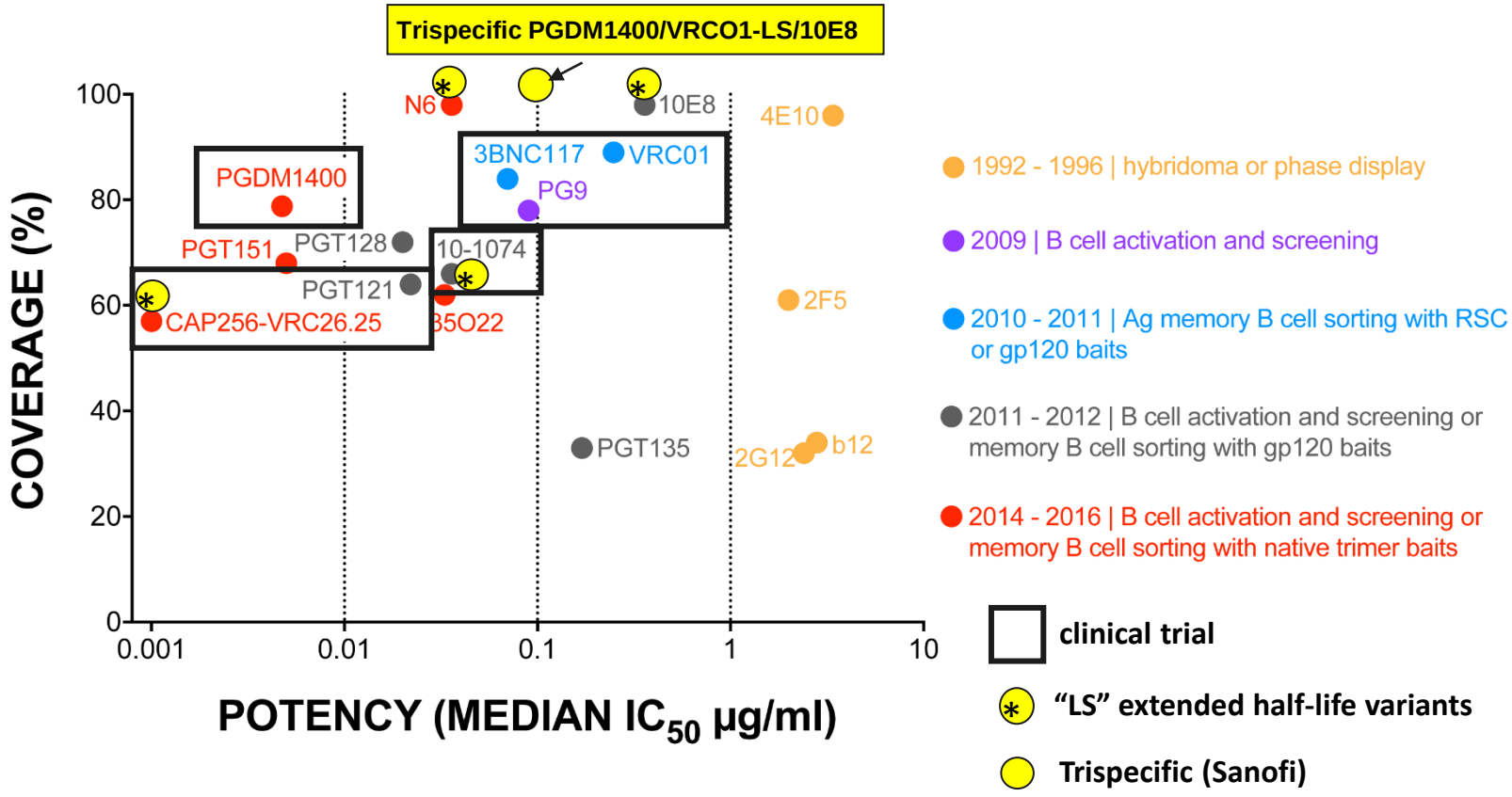
* Due to the randomization scheme, the numbers of vaccine and control recipients may differ slightly.

# VRC01 Efficacy in Preventing HIV-1 Infection: Dependent on Viral Neutralization Sensitivity

- In vitro viral susceptibility to VRC01 predicts prevention efficacy in vivo; only effective against viruses measured to be neutralization sensitive (< 1 mg/mL)
- In overall data, no significant difference seen in HIV-1 acquisition between treatment arms
- Only 30% of circulating strains in control group were susceptible in vivo to the antibody ($IC_{80}$ < 1 mg/mL), giving study low power to detect overall efficacy
- Among 107 individuals with HIV-1 infection, viruses in VRC01 recipients showed greater VRC01 resistance than those in placebo recipients[1]
  - Geometric mean $IC_{80}$ for viruses was 2.36-fold higher in VRC01 recipients vs placebo recipients (*P* = .003)
- Viral load of acquired strain influenced by treatment group only in susceptible isolates[1]
- Sequencing of viral genomes from individuals with breakthrough infection revealed evidence of selective pressure at sites associated with VRC01 resistance[2]

Corey. HIVR4P 2021. Abstr HY01.01LB.

# Innovation in antibody discovery has led to the development of increasingly potent bnAbs




Mark Feinberg

# bnAb combinations

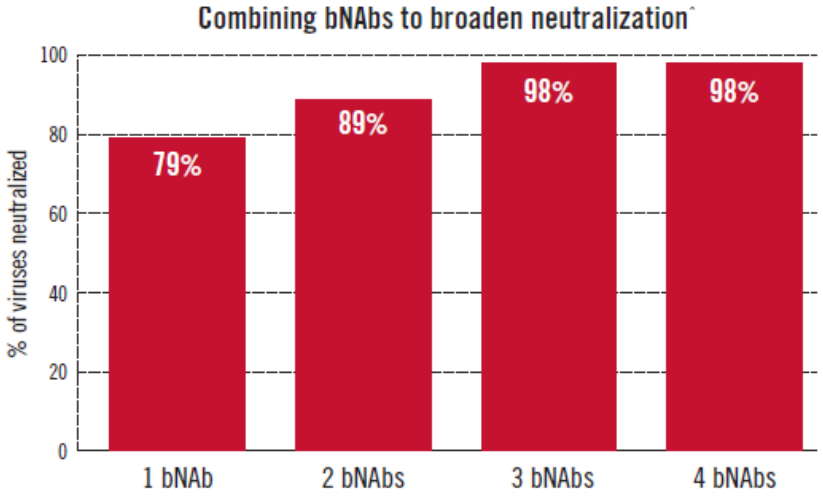
**bNAb Cocktails: Two or more antibodies in a regimen**

| Regimen | Status | Route | Research Institution | Trial Name |
|---|---|---|---|---|
| | Phase I, Completed | IV | Rockefeller University | YCO-0899 |
| | Phase I, Ongoing | IV, SC | Rockefeller University | YCO-0971 |
| | Phase I/2, Ongoing | IV, SC | IAVI, Rockefeller University, University of Washington | IAVI C100 |
| | Phase I, Completed Phase I/2a, Ongoing | IV | BIDMC, IAVI, NIAID | IAVI T002 IAVI T003 |
| | Phase I, Ongoing | IV | NIAID | HVTN 130/ HPTN 089 |
| | Phase I, Ongoing | IV, SC | NIAID | HVTN 136/ HPTN 092 |
| | Phase I, Ongoing | SC | NIAID | HVTN 138/ HPTN 098 |
| | Phase I, Ongoing | IV, SC | CAPRISA, NIAID | CAPRISA 012B |

• *Various combinations*

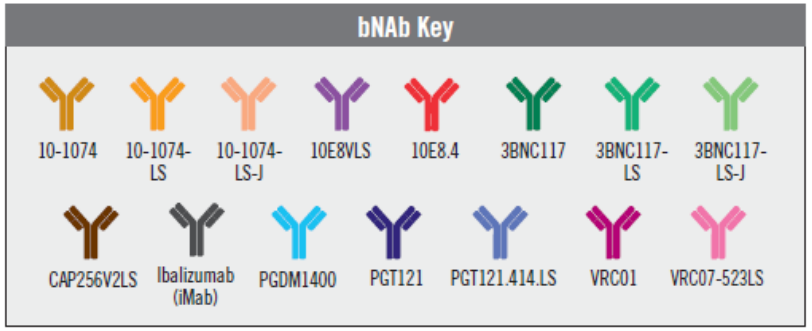
**Multispecific: Parts of two or more antibodies on a single antibody**

| Regimen | Status | Route | Research Institution | Trial Name |
|---|---|---|---|---|
| SAR441236 | Phase I, Planned | IV | Sanofi, NIAID | HVTN 129/ HPTN 088 |
| | Phase I, Ongoing | IV, SC | ADARC | AAAS1239 |




Different antibodies have different neutralizing activities. Modeling and preclinical studies suggest that combining bNAbs may lead to broader neutralization compared to giving bNAbs alone, and multispecific antibodies might perform better than combinations. Clinical trials will validate whether these differences are seen in humans, and guide selection of best antibodies and combinations types.

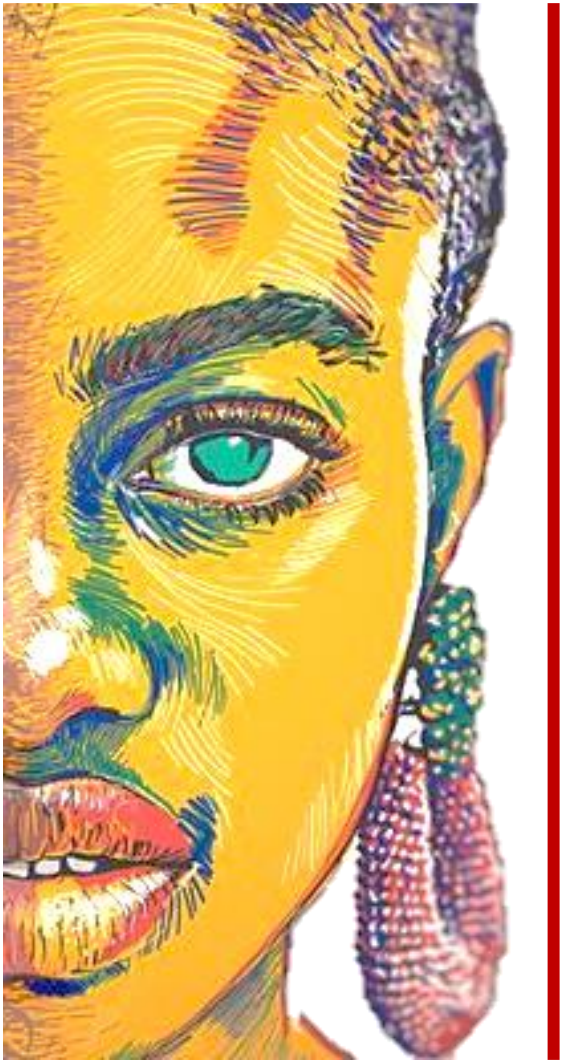
*Data: Kong et al., 2015

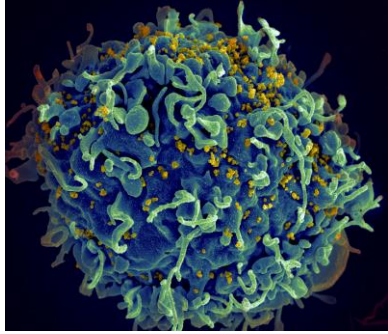



ADARC: Aaron Diamond AIDS Research Center; BIDMC: Beth Israel Deaconess Medical Center; CAPRISA: Centre for the AIDS Programme of Research in South Africa; IAVI: International AIDS Vaccine Initiative; NIAID: National Institute of Allergy and Infectious Diseases; VRC: Vaccine Research Center of NIAID; IV: Intravenous; SC: Subcutaneous

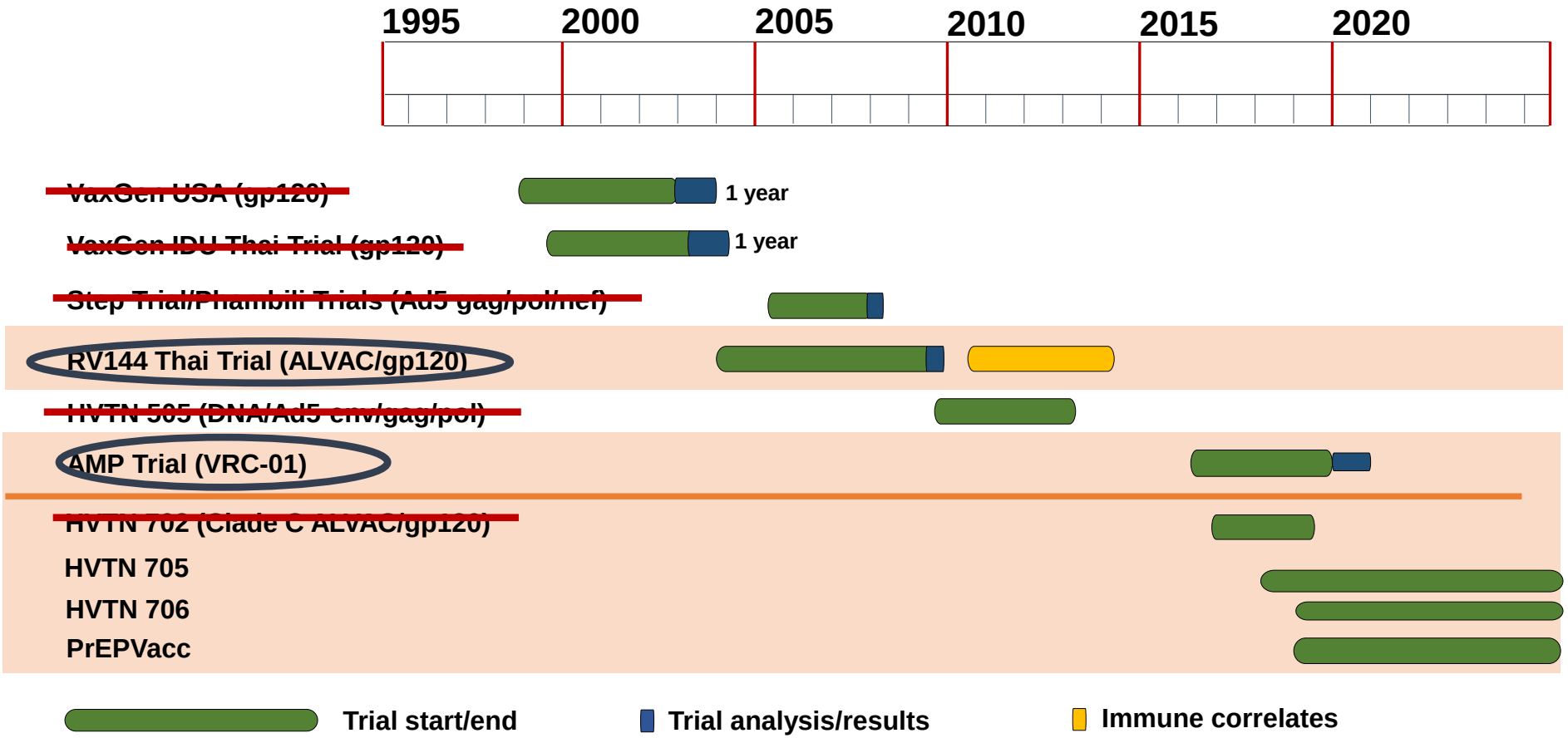
AVAC
25 Years and Counting

# The quest continues…..





## A history of HIV-1 vaccine efficacy trials[1–3]



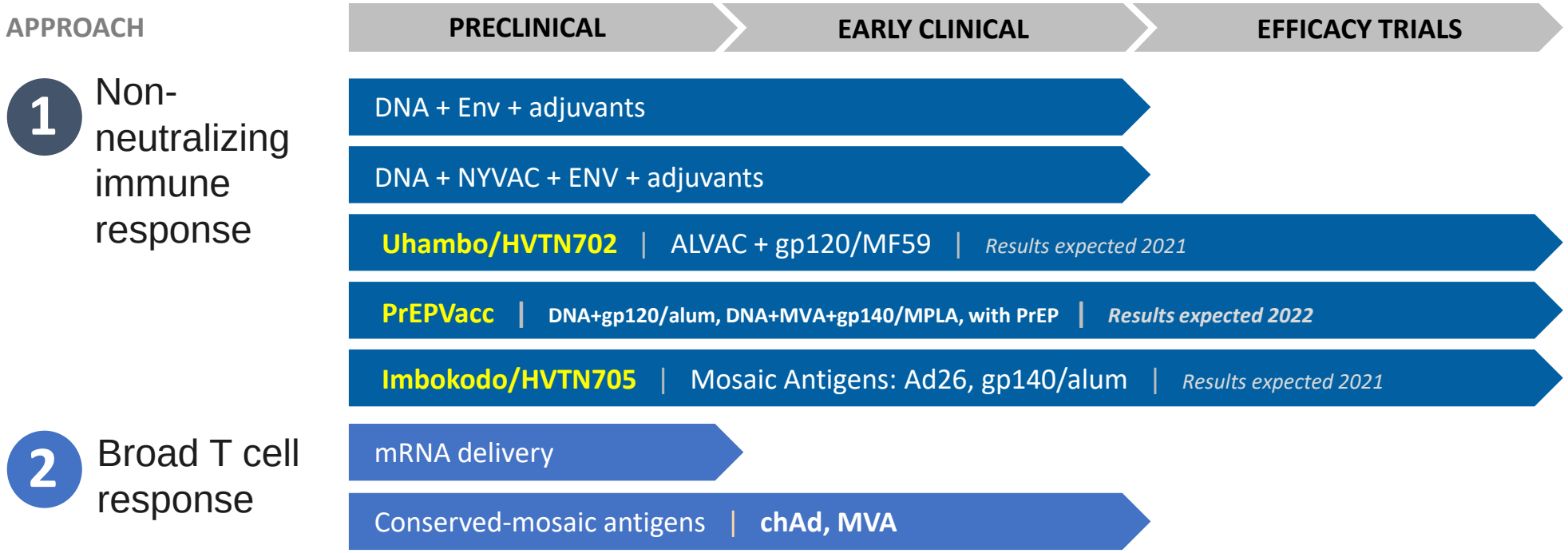


1. NIH. Online. Available at: https://www.niaid.nih.gov/diseases-conditions/hiv-vaccine-research-history. Accessed Sept 20.
2. NIH Press Release. Online. Available at: https://www.niaid.nih.gov/news-events/experimental-hiv-vaccine-regimen-ineffective-preventing-hiv.
3. ClinicalTrials.gov Identifier: NCT03060629.
4. ClinicalTrials.gov Identifier: NCT04066881.

# HIV vaccine pipeline 2018

Mark Feinberg

- Attenuated viral vectors +/- DNA with adjuvanted Env proteins
- Follow-up efficacy study on RV144 in South Africa
- Several early stage trials testing various DNA/protein/viral vector/adjuvant combinations

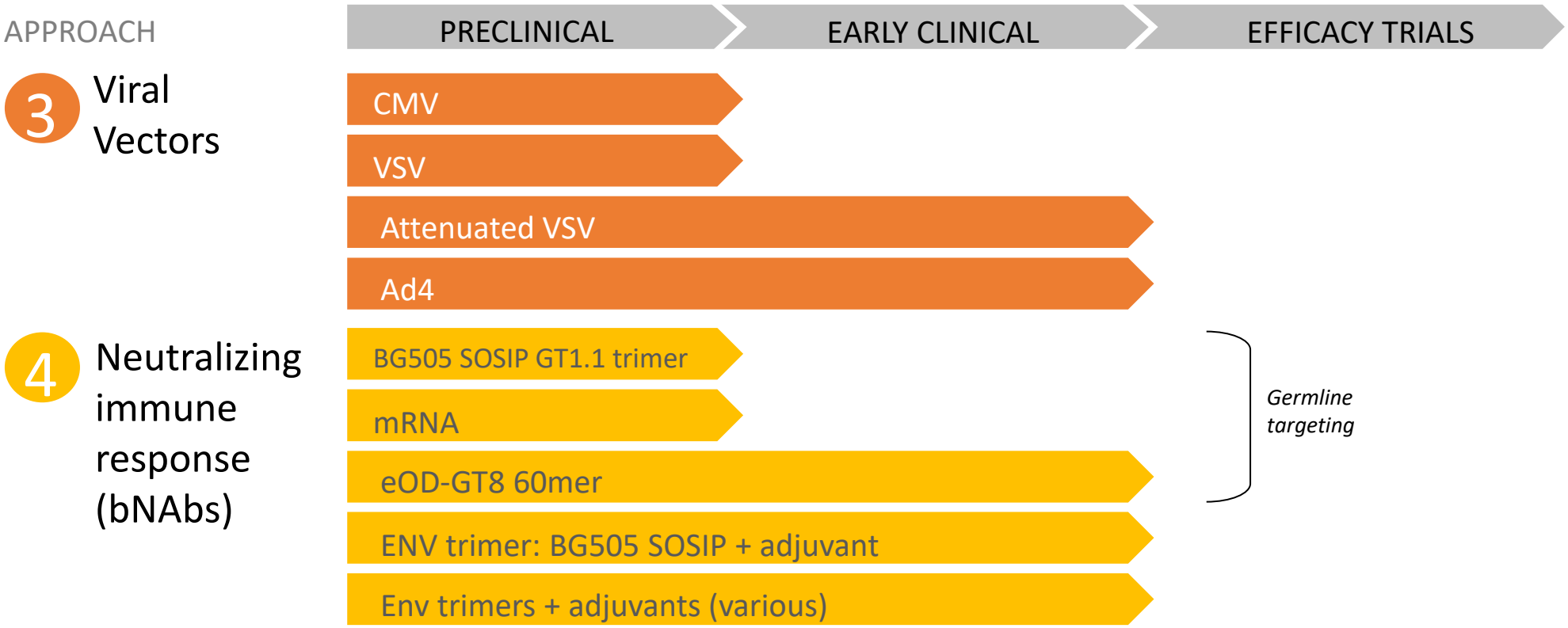



Mosaic antigens that are computationally derived to provide maximum coverage against all HIV strains in circulation

# HIV vaccine pipeline 2018

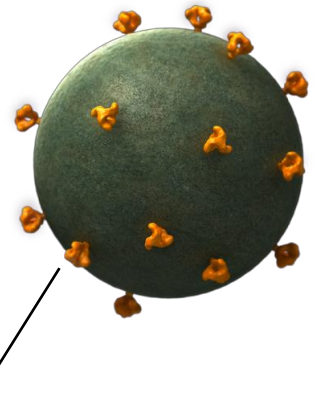
Mark Feinberg

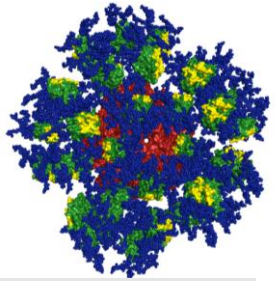
Replicating virus vectors that can express vaccine antigens over an extended period



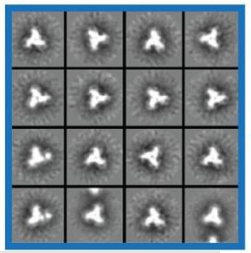

- Native-like HIV Envelope trimers administered alone, in combination, or sequentially
- Reverse engineered immunogens based on viral epitopes targeted by bNAbs

# Engineered vaccine design- Clinic debut

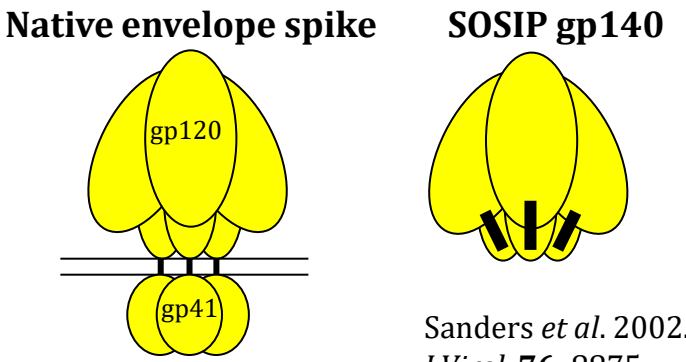




eOD-GT8 60mer



BG505 SOSIP trimer




Sanders *et al.* 2002. *J.Virol.* **76**: 8875

## IAVI G001

eOD-GT8 60mer/ $AS01_B$

Phase 1 trial
Germline targeting approach

***Partners***
TSRI
NIH CHAVI-ID
BMGF
GSK
University of Washington
George Washington University
NIH Vaccine Research Center

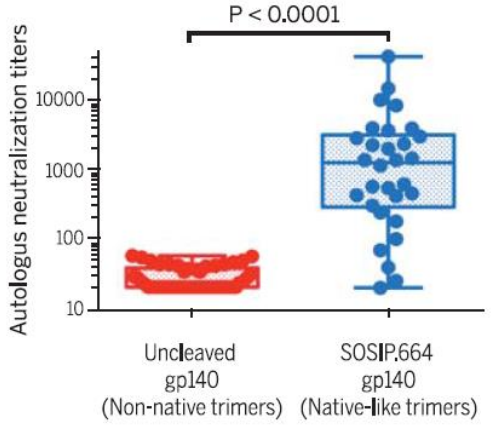
## IAVI W001

BG505 SOSIP / $AS01_B$

Phase 1 trial
Native like Env trimer

***Partners***
NIH
USAID
BMGF
GSK
University of Washington
Ragon Institute
KAVI-ICR
Weill Cornell Medical College
Academic Medical Center (AMC)

Native like Env immunogen in rabbits.




*"This trial is going to tell us how much control we can have over the immune responses induced by a targeted vaccine candidate."*

Mark Feinberg

Dennis Burton

Track A, Rapporteur Session, (Rogier Sanders, THSY04), AIDS2018

# An exciting time to be in vaccine discovery….

## The Science is advancing through clinical trials

- **Three pivotal** HIV vaccine related efficacy trials are underway (AMP/ Uhambo/ Imbokodo).
- These trials will define if **either or both neutralizing and/or non-neutralizing antibodies** can be tweaked to provide reasonable vaccine efficacy in high risk regions of the world.


## Scientific advances are fueling vaccine discovery.

- Antibody isolation and characterization has revolutionized our understanding of the immune response.
- Technologic advances allow researchers to understand where antibodies target the virus in unprecedented detail.
- Stabilization of the HIV Env trimer allows for engineering of trimeric mimics.
- Have shifted from empiric approaches to hypothesis-driven approaches.

## Next Generation Vaccines are entering the clinic

- Native-like trimers meant to resemble HIV's Env spike
- Germline-targeting approaches generated using structure-based vaccine design.

**Questions remain:**

Do bNabs protect?
Potency and durability?
HIV variability ?
bNab maturation?

# Acknowledgements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DAIDS, NIAID.