HIV VACCINE
TRIALS NETWORK

The Road Less Traveled: Perspectives on an Effective HIV Vaccine

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Global estimates for adults and children | 2017

People living with HIV	36.9 million [31.1 million–43.9 million]
New HIV infections in 2017	1.8 million [1.4 million–2.4 million]
AIDS-related deaths in 2017	940 000 [670 000–1.3 million]

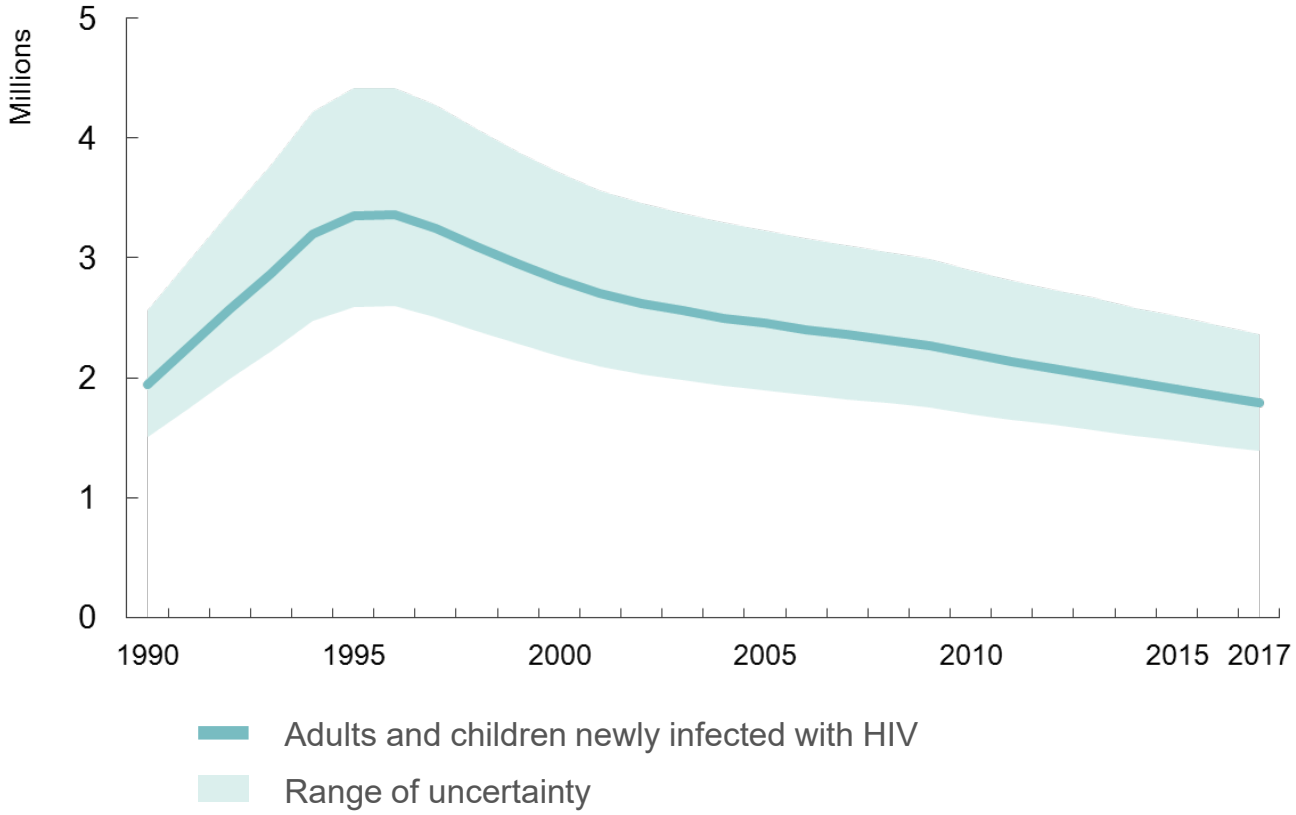
UNAIDS

About 5000 new HIV infections (adults and children) a day | 2017

- About 66% are in sub-Saharan Africa
- About 500 are among children under 15 years of age
- About 4400 are among adults aged 15 years and older, of whom:
  - almost 43% are among women
  - about 33% are among young people (15–24)
  - about 19% are among young women (15–24)

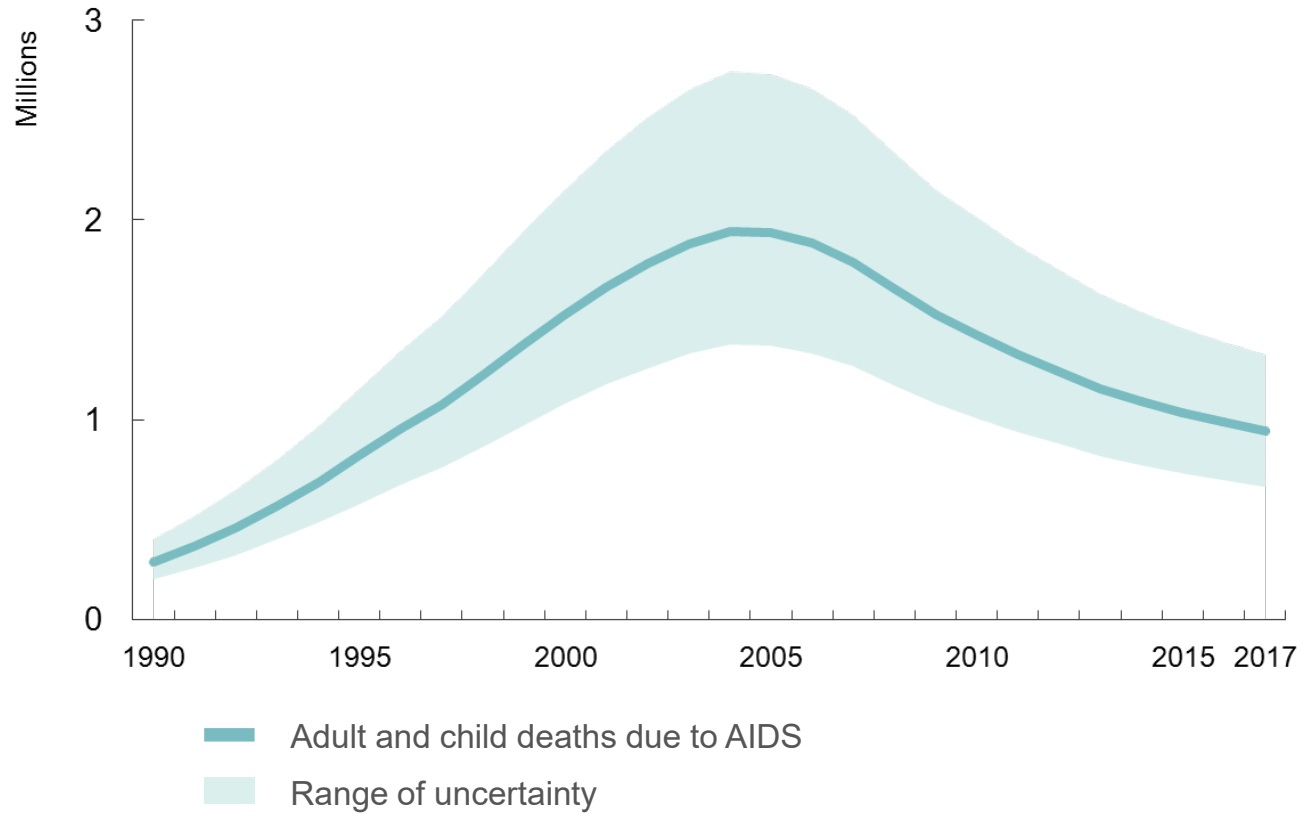
UNAIDS

Adults and children newly infected with HIV | 1990–2017



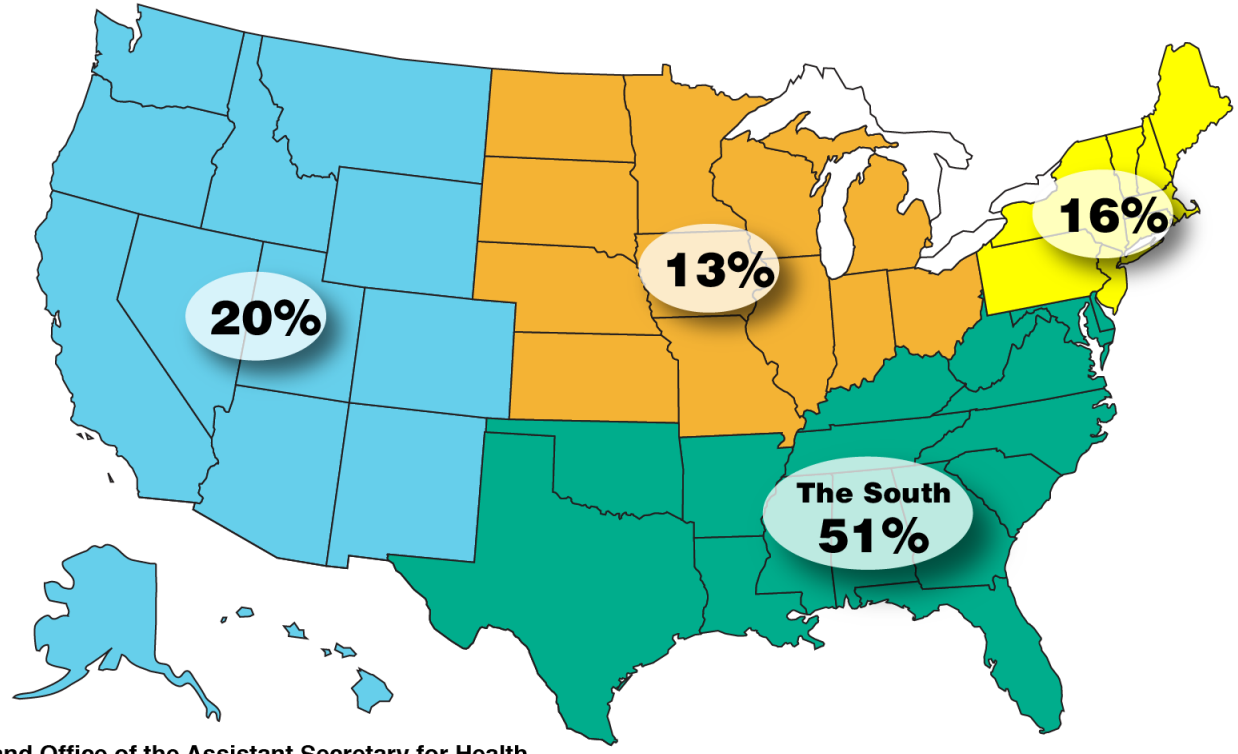
UNAIDS

Adult and child deaths due to AIDS | 1990–2017



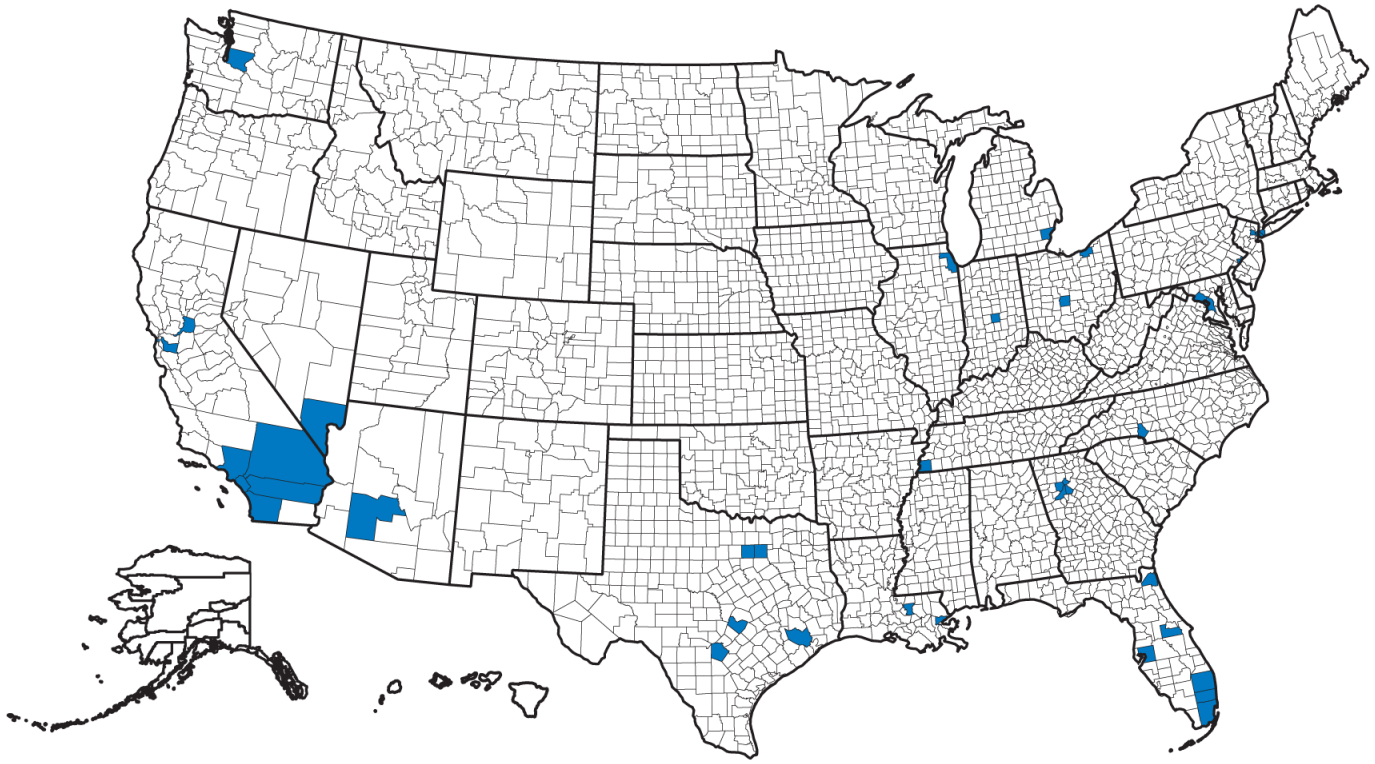
UNAIDS

Relative Percentage of New Diagnoses in the United States by Geographic Region, 2016



Source: CDC and Office of the Assistant Secretary for Health

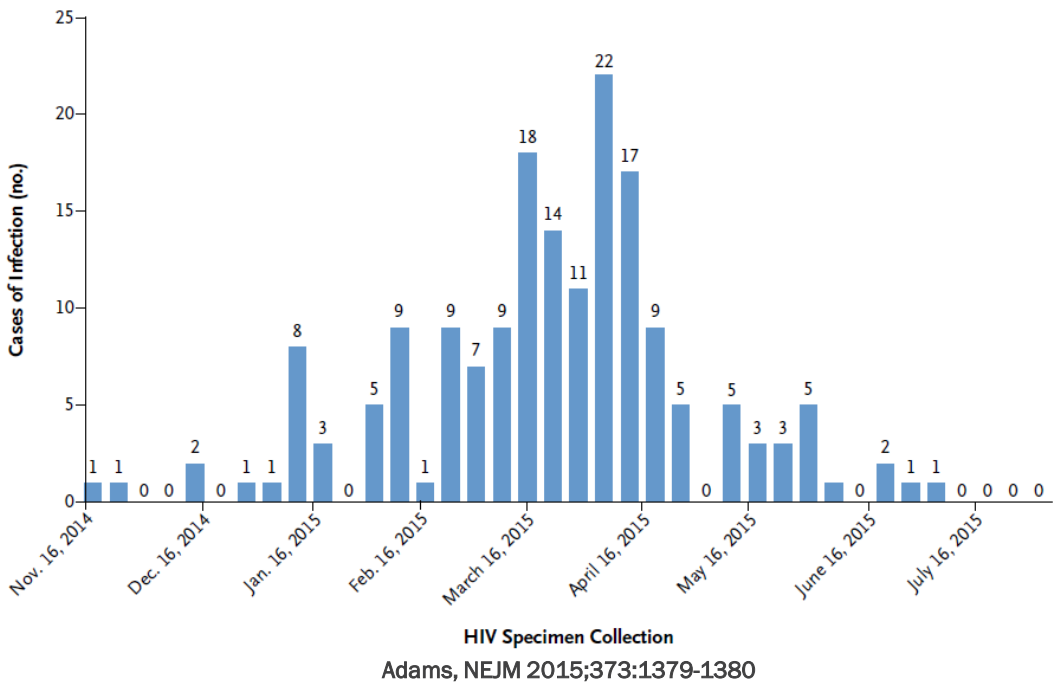
46 Counties Account for 50.3% of New HIV Diagnoses, 2016



Source: CDC and Office of the Assistant Secretary for Health

Indiana HIV Outbreak: Geographic Distribution

Scott County pop. 24,000; Austin, IN pop. 4,200



Adams, NEJM 2015;373:1379-1380

The Need for an HIV Vaccine

- With asymptomatic acquisition, prolonged subclinical infection, and sexual transmission, getting to an *AIDS Free Generation* will require a biologically based primary prevention modality with prolonged durability; preferably an effective HIV vaccine.

- Larry's definition of an *AIDS Free Generation*; 95% reduction in incident cases annually:
  - USA < 2,500 cases yearly
  - Globally < 100,000 cases yearly

Why Has It Been So Hard to Develop an HIV Vaccine?

- Science issues:
  - Genetic diversity of the virus is greater than any other pathogen
  - Envelope is less immunogenic than any other virus envelope protein; perhaps because of its' glycan shield
  - The gp160 envelope trimeric structure is unique, hard to simulate and there are fewer trimers on the surface than most viruses
  - Animal models are expensive and non-predictive of vaccine efficacy
  - There are no human cures of HIV and hence there are no models to mimic (0 of 65 million and counting)

Current Status of HIV Vaccines

- Robust pipeline of new concept immunogens dedicated to eliciting neutralizing antibodies to the virus.

- Major progress in prime boost regimens that elicit non-neutralizing antibodies that appear to be of enhanced magnitude as compared to the RV144 trial and/or equal the immune responses among NHP who are protected in mucosal challenge studies with SHIV.

Current Phase 2B/3 HIV Vaccine Efficacy Trials

AMP (POC)
HVTN 703/704

Uhambo
(Phase 2B/3)
HVTN 702

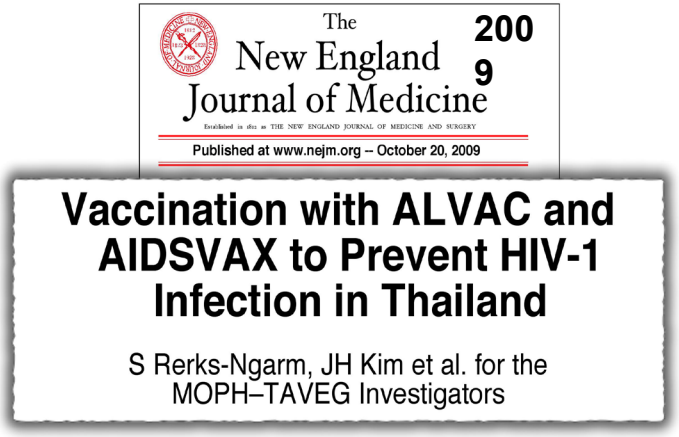
Imbokodo
(Phase 2B POC)
HVTN 705

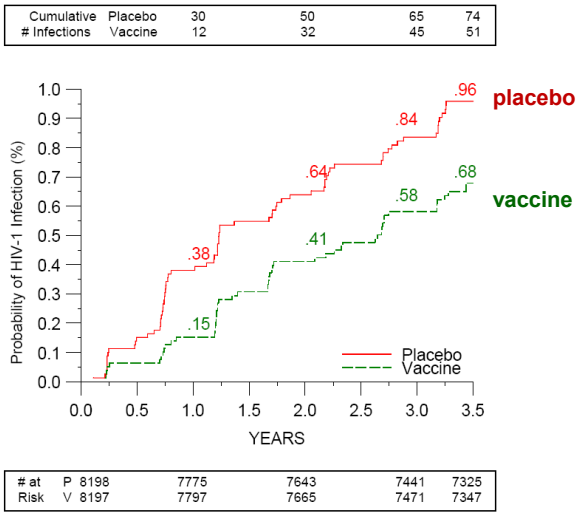
AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

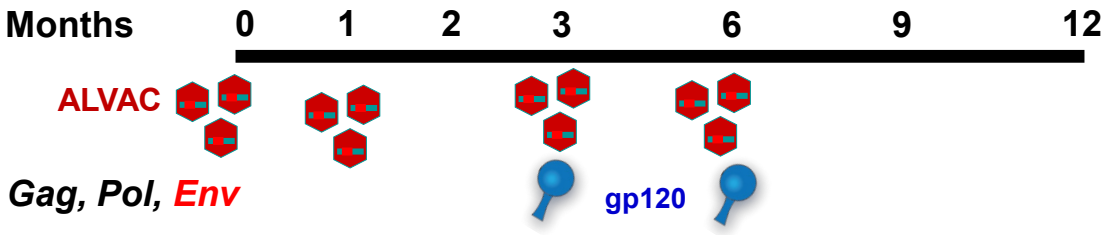
uhambo

IMBOKODO

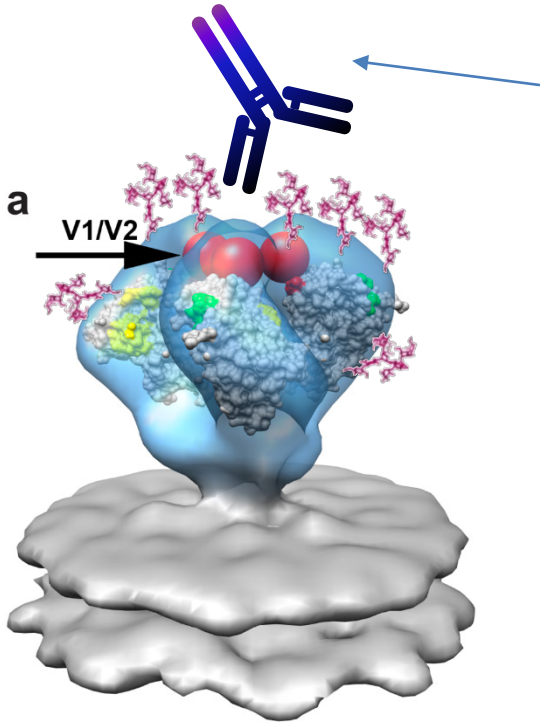
RV144: ALVAC prime, gp120 boost Vaccine Efficacy (31%)







RV144 – Immune Correlates



Subramaniam PloS Pathogens (2009)

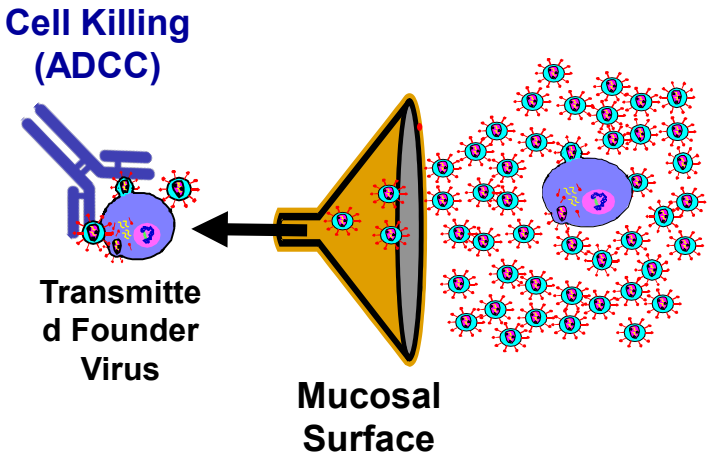
Antibodies to V1V2 region were associated with a reduced risk of infection

- Non-neutralizing antibodies
- How did the vaccine prevent infection?

Haynes, Kim et al. NEJM (2012)
Rolland, Kim at al. Nature (2012)
Liao, Haynes et al, Immunity (2013)

Transmission Bottleneck

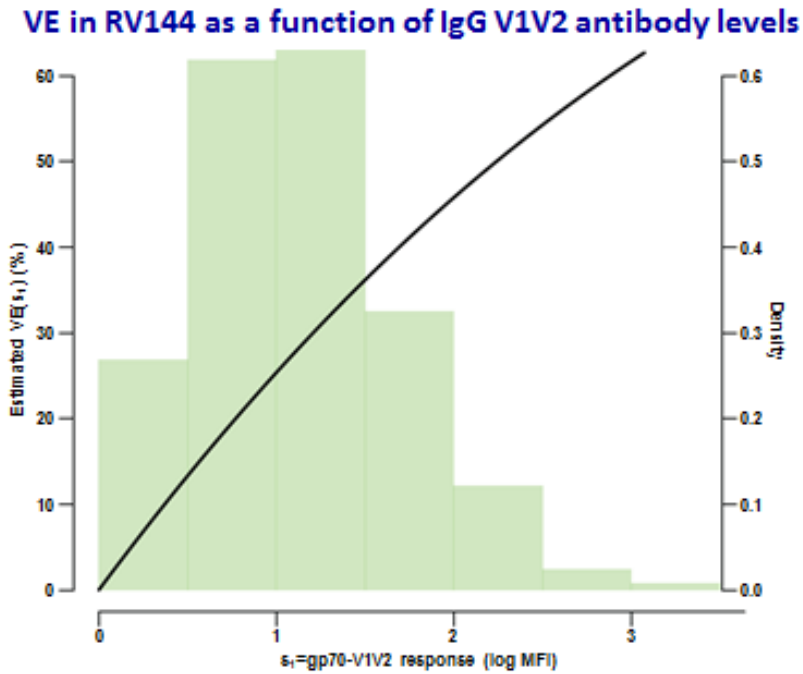
Vaccine Induced Antibodies (RV144)



- Non-neutralizing
- Kill infected cells
- Eradicate initial nidus of infection

Correlation Between Antibodies to the V1V2 Loop and Vaccine Efficacy in RV144

- Antibodies to the conserved region of V2, previously almost completely ignored by the HIV vaccine field, were highly correlated with efficacy.



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)

2010 Formation of the P5 Partnership

Purpose:

To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

Strategy:

- Developed a partnership to extend the RV144 concept to Clade C regions of the world.
- Use expert committees to select the strains and then use company expertise to manufacture these vaccines for immunogenicity, safety and efficacy.

NOVARTIS gsk

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

HIV VACCINE TRIALS NETWORK

BILL & MELINDA GATES foundation

National Institute of Allergy and Infectious Diseases

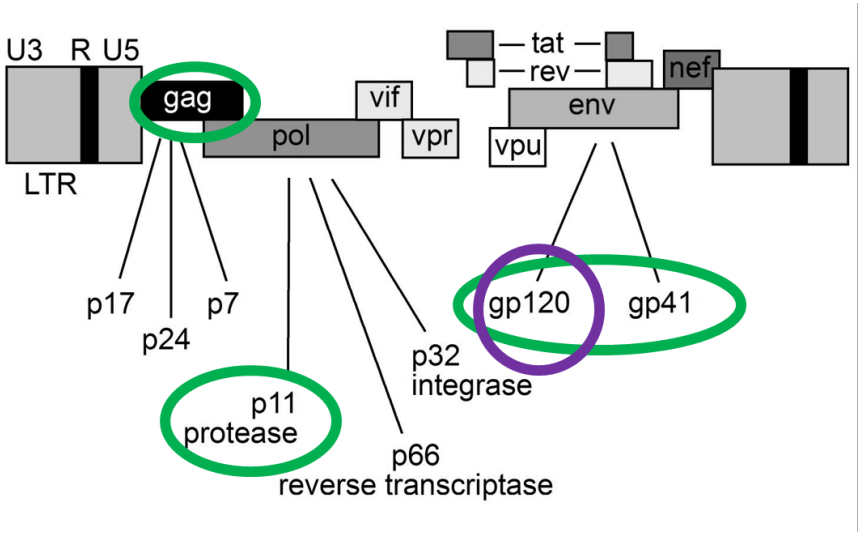
SANOFI PASTEUR

MRC SOUTH AFRICA SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

Build on RV144 design

Optimize regimen for regional relevance (C clade) and increased potency (MF59)

- ALVAC-HIV (vCP2438) expresses
  - env **gp120 of ZM96** strain (subtype C) + **gp41 transmembrane sequence** (subtype B LAI strain)
  - **gag + protease** (subtype B LAI strain)
- Bivalent Subtype C gp120/MF59:
  - env **gp120 of TV1.C** strain (subtype C)
  - env **gp120 of 1086.C** strain (subtype C)
  - mixed with MF59 adjuvant



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)

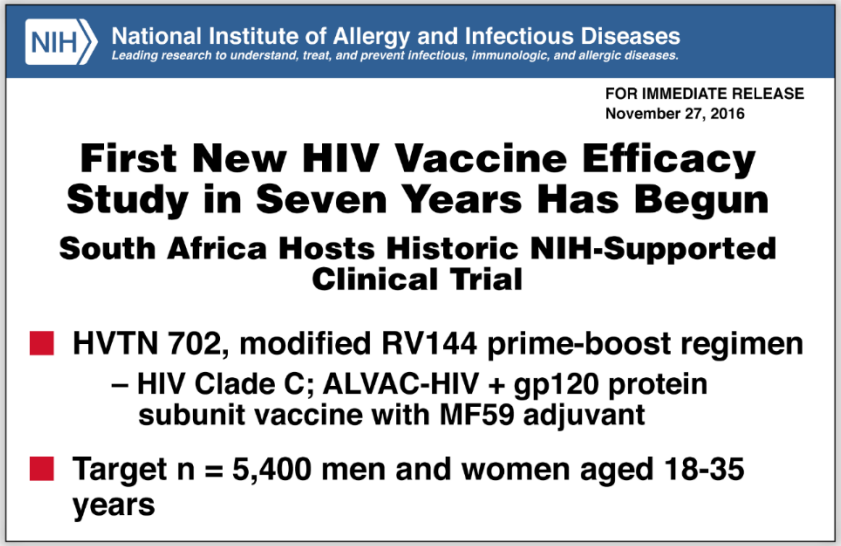
HVTN 702 Schema:
5400 South Africans (18-35 yrs)

Group	N*	Primary vaccine regimen				Boosters	
		Month 0	Month 1	Month 3	Month 6	Month 12	Month 18
1	2700	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438)	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438)+ Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59	ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120/MF59
2	2700	Placebo	Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo	Placebo + Placebo
Total	5400						

Immune Correlates – Phase 2b

HVTN 702: opened in Oct. 2016

ALVAC prime, gp120 boost



NIH National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

FOR IMMEDIATE RELEASE
November 27, 2016

First New HIV Vaccine Efficacy Study in Seven Years Has Begun

South Africa Hosts Historic NIH-Supported Clinical Trial

- HVTN 702, modified RV144 prime-boost regimen
  - HIV Clade C; ALVAC-HIV + gp120 protein subunit vaccine with MF59 adjuvant
- Target n = 5,400 men and women aged 18-35 years

HVTN 705: opened in Nov. 2017

rAd26 prime, gp140 boost

NIH National Institutes of Health
Turning Discovery Into Health

FOR IMMEDIATE RELEASE
November 30, 2017

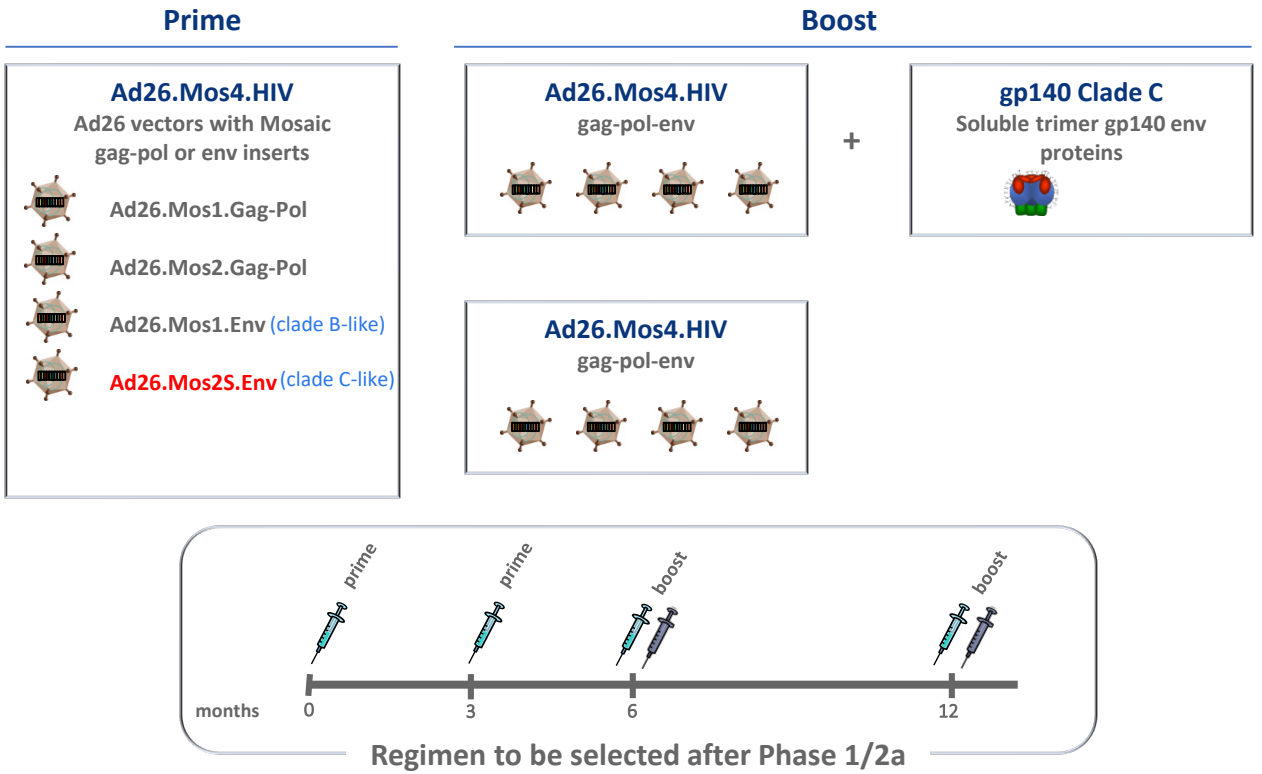
News Release

NIH and Partners Launch HIV Vaccine Efficacy Study

IMBOKODO
Imbokodo ("the rock" in Zulu)

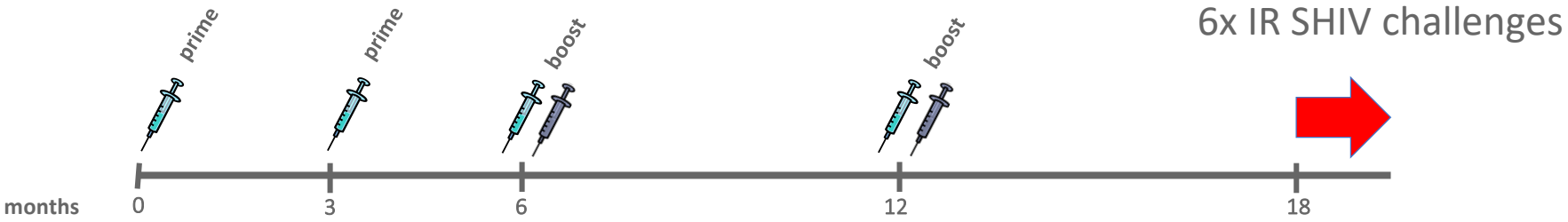
- Imbokodo trial (HVTN 705/HPX2008)
- Phase 2b; target n= 2,600 HIV-negative women in sub-Saharan Africa
- Quadrivalent, Ad26-vectored mosaic vaccine + recombinant clade C HIV gp140

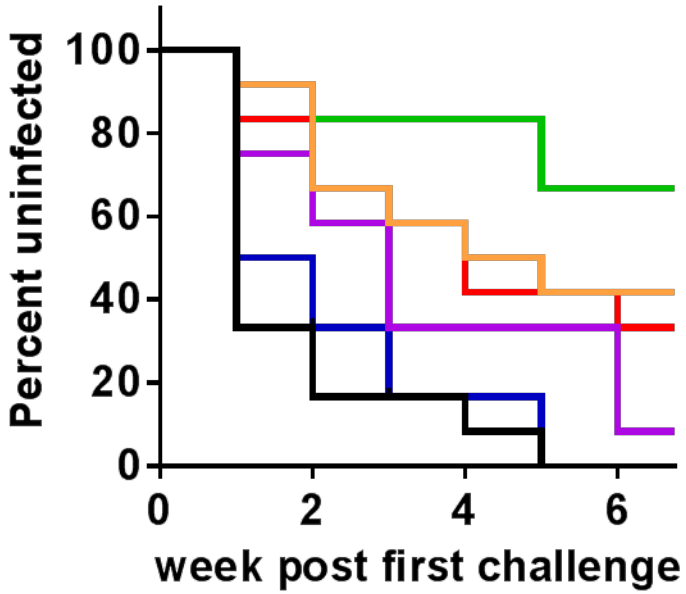
APPROACH (Ph 2):
Mixture of 4 mosaic Ad26 constructs + gp140 Clade C boost



The Ad26/Ad26+Env HIV vaccine regimen provides substantial protection against $SHIV_{SF162P3}$ challenges in non-human primates

[study designed to mimic APPROACH trial (HIV-V-A004)]



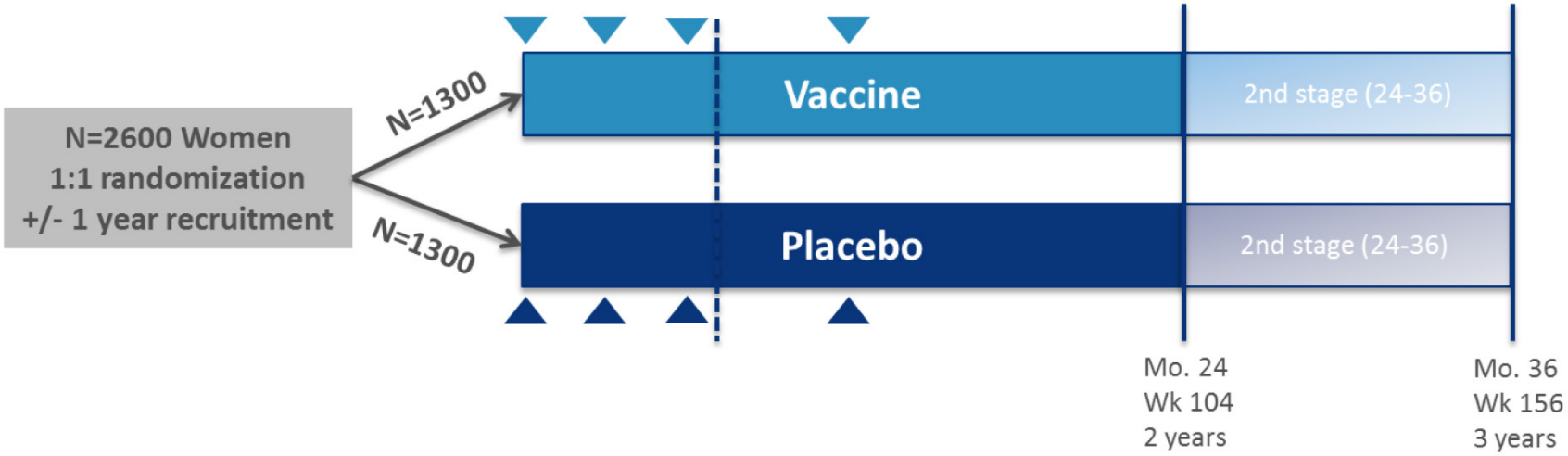


- Ad prime / Ad boost
- Ad prime / Env boost
- Ad prime / Ad+Env boost
- Ad prime / MVA boost
- Ad prime / MVA+Env boost
- Sham

N = 12 per group

	Per-Exposure Risk Reduction	Full Protection after 6 challenges
Ad26/Ad26+Env	94%	66%
Ad26/MVA+Env	87%	42%
Ad26/Env	84%	33%

Study Schema: HVTN 705/Imbokodo

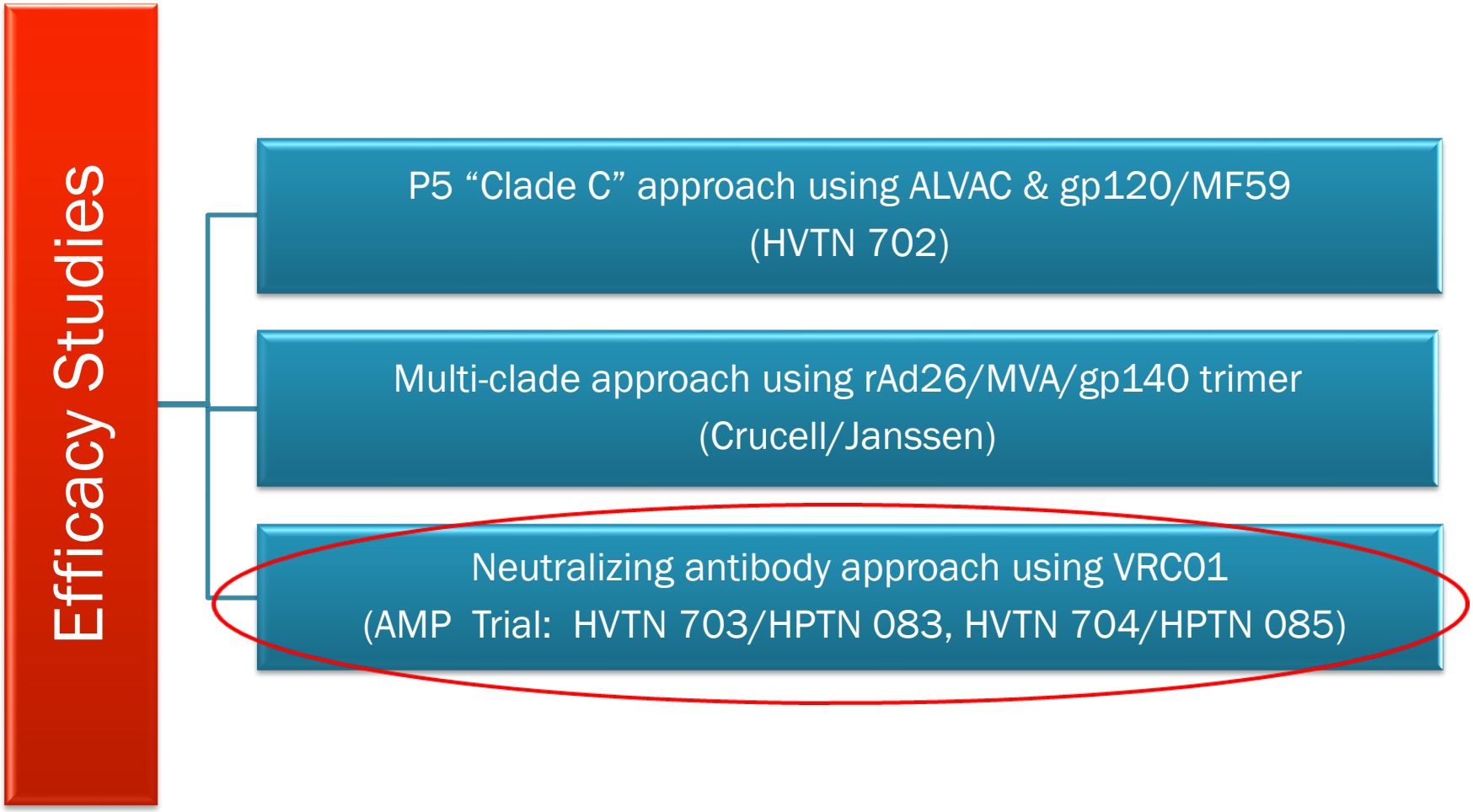


Chairs: Glenda Gray,
Co-chairs: Susan Buchbinder, Kathy Mngadi and Frank Tomaka

Non-neutralizing Approaches to HIV Vaccine Design

- Two non-neutralizing strategies are being undertaken:
  - 1 based upon RV144 correlates data and the other based upon correlates in NHP challenge experiments.
  - Both approaches suggest correlates relate to both binding/functional antibodies (ADCP and ADCC), as well as some T cell response (CD4 envelope and the other ELISPOT data).
  - We shall see whether these presumed correlates are shown to be consistent in human efficacy trials.
  - We shall see if any NHP challenge studies are predictive of vaccine efficacy.
  - In the end it may take both neutralizing and non-neutralizing antibodies to achieve success.

Neutralizing Antibodies for HIV Prevention



Broadly Reactive Neutralizing Antibodies Discovered since 2009

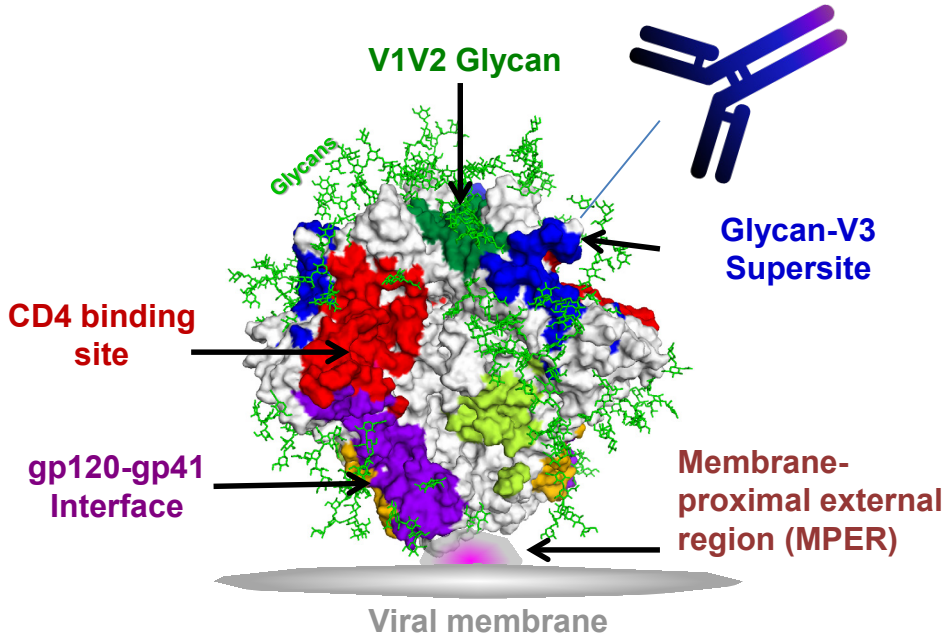


Image by Stewart-Jones, Doria-Rose, Stuckey
Adapted from Stewart-Jones et al Cell 2016 and Pancera et al Nature 2014

- Isolated from HIV-infected individuals
- Penetrate glycan shield
- Potently neutralize most strains of HIV-1

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.

Study Schema for the AMP studies

AMP
ANTIBODY · MEDIATED · PREVENTION
STUDY

INFUSION SCHEDULE (WEEKS)

[A = VRC01 infusion; C = Control infusion]

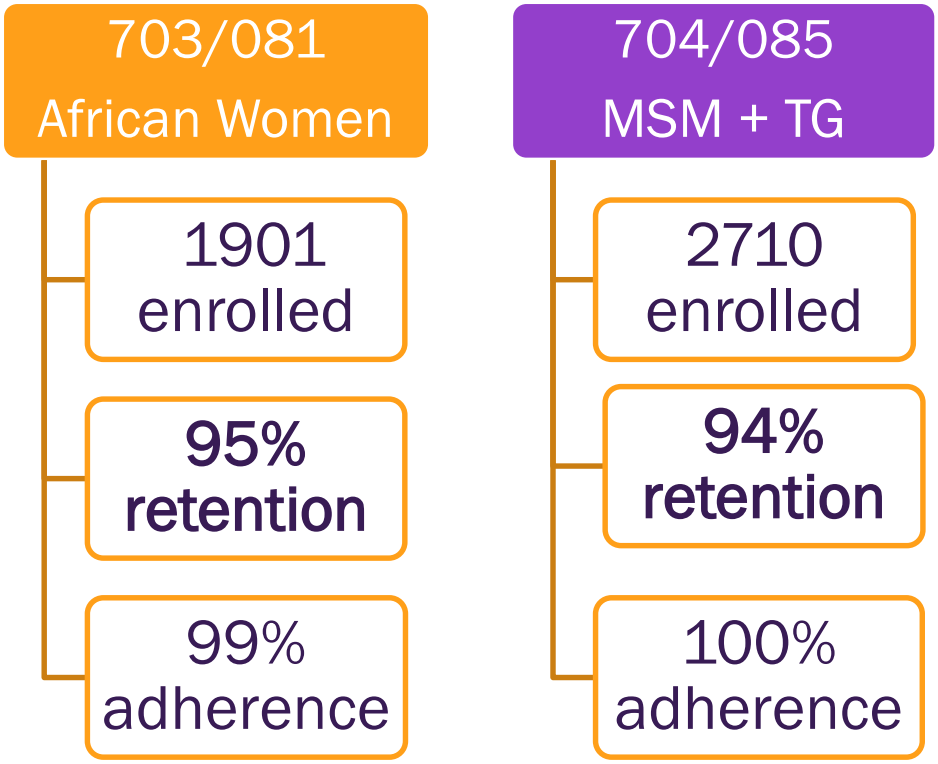
	Treatment: VRC01	N	0	8	16	24	32	40	48	56	64	72	80*	92**
Group 1	10 mg/kg	900 634	A	A	A	A	A	A	A	A	A	A		
Group 2	30 mg/kg	900 634	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900 634	C	C	C	C	C	C	C	C	C	C		

2700 (1900) for the MSM + TG (WSM) group; (1/3 VRC01 30 mg/kg; 1/3 VRC01 10 mg/kg; 1/3 control

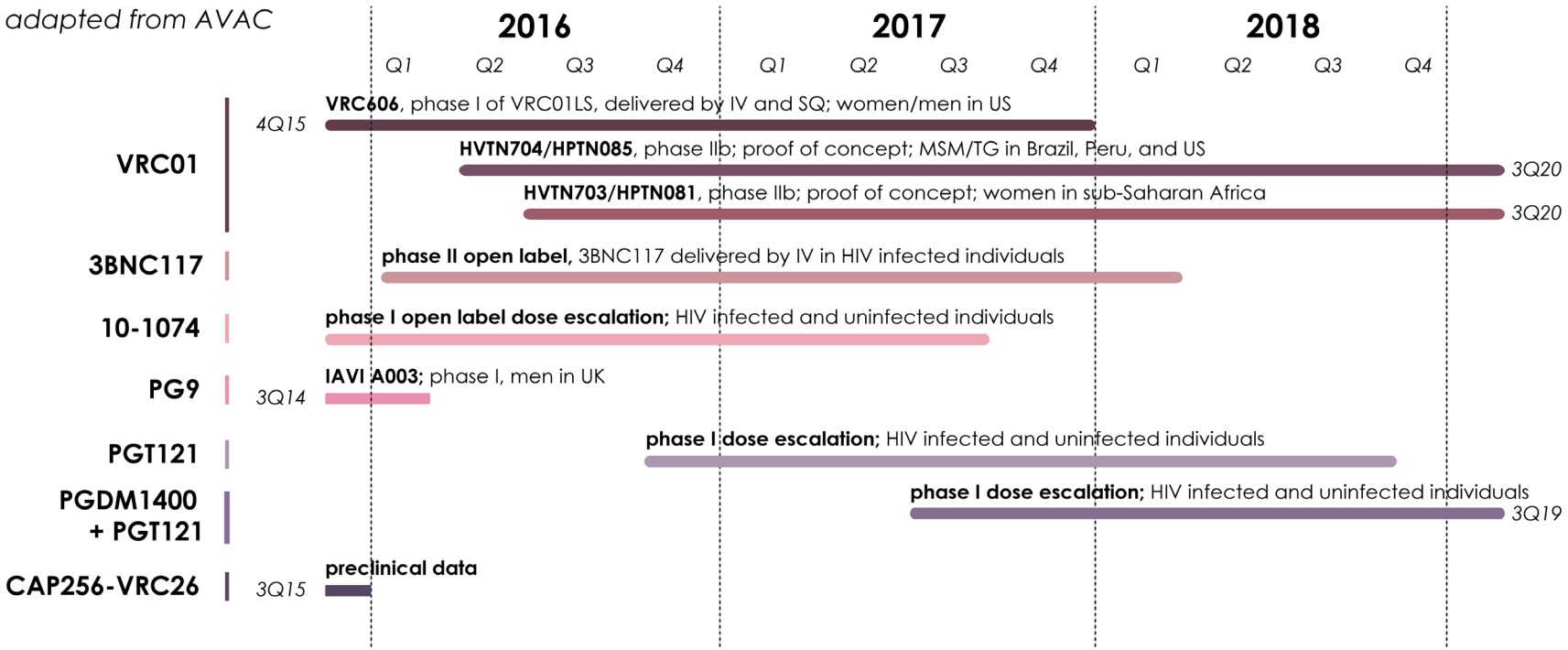
***Week 80: last study visit to evaluate efficacy – primary end point**

****Week 92: final study visit to evaluate safety and tolerability; co-primary end point**

Enrollment and Retention Updates



First Generation HIV mAbs in the Clinical Pipeline....



Note that first-generation bNAbs are not yet optimized for potency, breadth, half-life, or low-cost production.

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

Courtesy of John Mascola

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?

Acknowledgments

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- Modulakgotla Sebe

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- Ken Mayer
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