HIV VACCINE
TRIALS NETWORK

Getting to an HIV Vaccine: Necessity and Frustration

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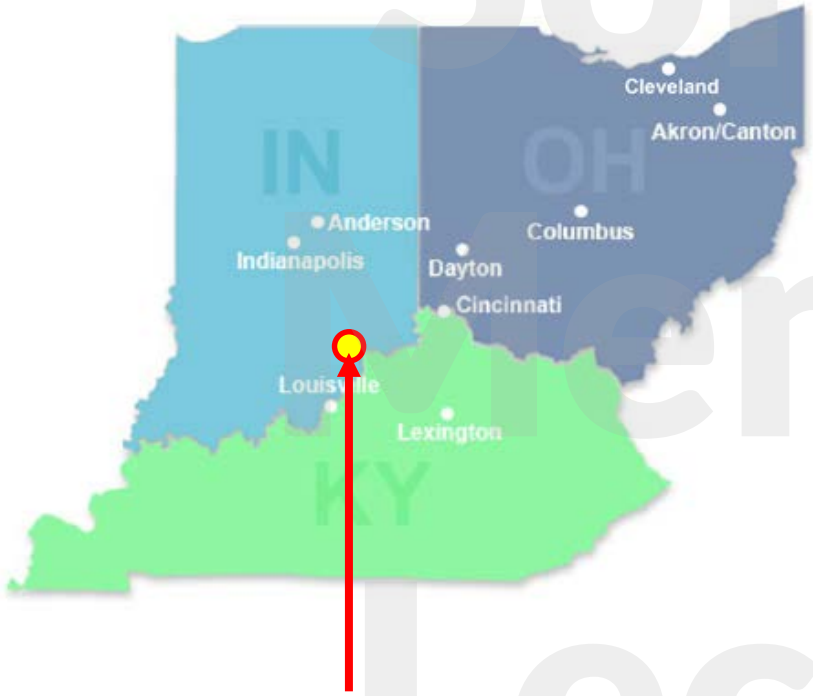
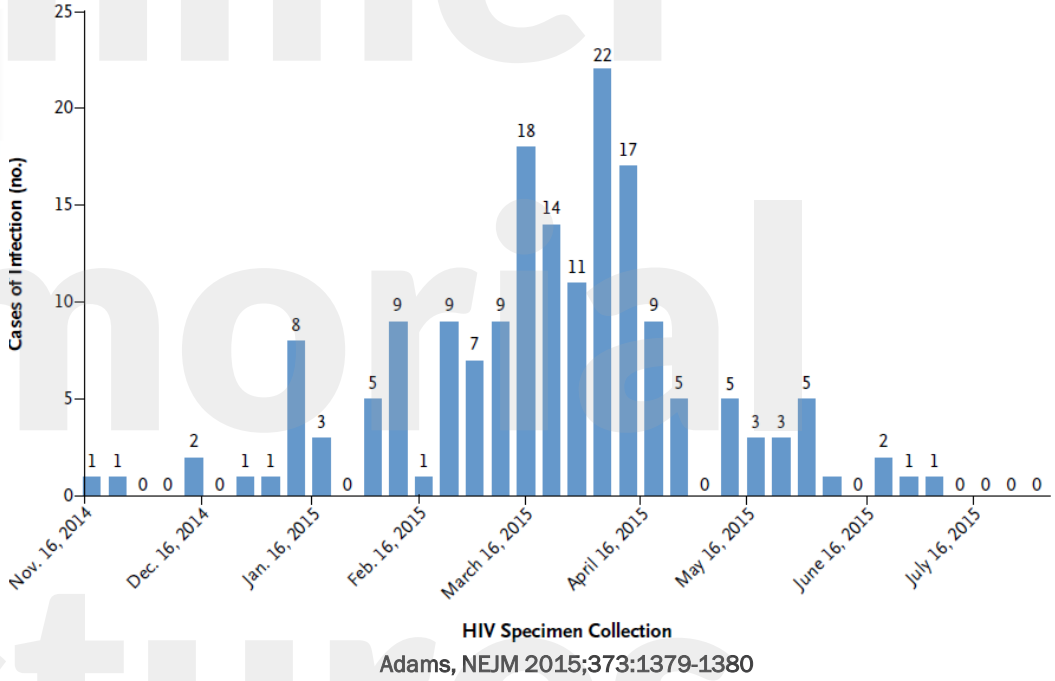
HIV: Still the World's Most Important Global Health Problem

- U.S. still over 45,000 new cases yearly
- Globally more than 1.5 million new infections occur per year
- Number of people living with HIV increasing yearly despite the marked increase in ART use worldwide
- Micro outbreaks still occurring; even in the U.S.

Indiana HIV Outbreak: Geographic Distribution

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





Adams, NEJM 2015;373:1379-1380

Global estimates for adults and children | 2016

People living with HIV	36.7 million [30.8 million–42.9 million]
New HIV infections in 2016	1.8 million [1.6 million–2.1 million]
AIDS-related deaths in 2016	1.0 million [830 000–1.2 million]

UNAIDS

About 5000 new HIV infections (adults and children) a day | 2016

- About 64% are in sub-Saharan Africa
- About 400 are among children under 15 years of age
- About 4500 are among adults aged 15 years and older, of whom:
  - almost 43% are among women
  - about 37% are among young people (15–24)
  - about 22% are among young women (15–24)

UNAIDS

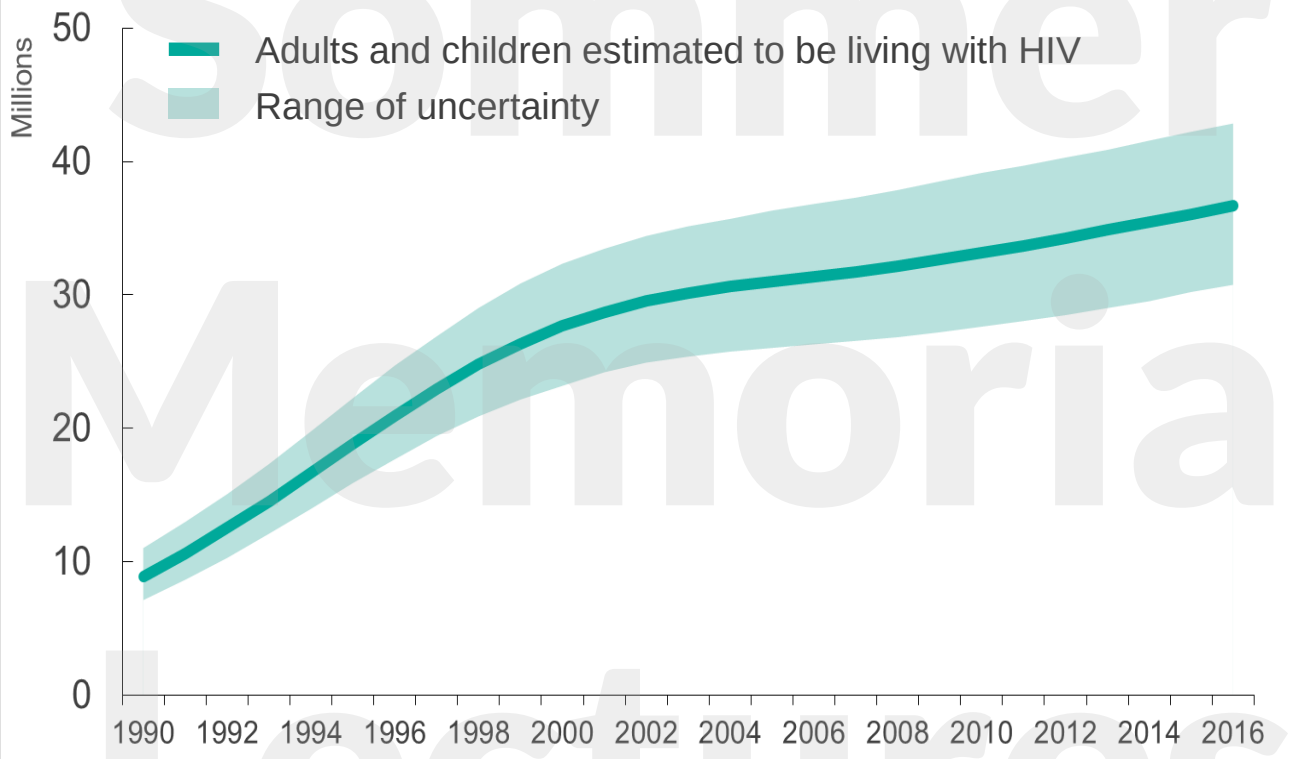
Regional HIV and AIDS statistics and features | 2016

	Adults and children living with HIV	Adults and children newly infected with HIV	Adult & child deaths due to AIDS
Eastern and southern Africa	19.4 million [17.8 million–21.1 million]	790 000 [710 000–870 000]	420 000 [350 000–510 000]
Western and central Africa	6.1 million [4.9 million–7.6 million]	370 000 [270 000–490 000]	310 000 [220 00–400 000]
Middle East and North Africa	230 000 [160 000–380 000]	18 000 [11 000–39 000]	11 000 [7700–19 000]
Asia and the Pacific	5.1 million [3.9 million–7.2 million]	270 000 [190 000–370 000]	170 000 [130 000–220 000]
Latin America	1.8 million [1.4 million–2.1 million]	97 000 [79 000–120 000]	36 000 [28 000–45 000]
Caribbean	310 000 [280 000–350 000]	18 000 [15 000–22 000]	9400 [7300–12 000]
Eastern Europe and central Asia	1.6 million [1.4 million–1.7 million]	190 000 [160 000–220 000]	40 000 [32 000–49 000]
Western and central Europe and North America	2.1 million [2.0 million–2.3 million]	73 000 [68 000–78 000]	18 000 [15 000–20 000]
TOTAL	36.7 million [30.8 million–42.9 million]	1.8 million [1.6 million–2.1 million]	1.0 million [830 000–1.2 million]

The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.

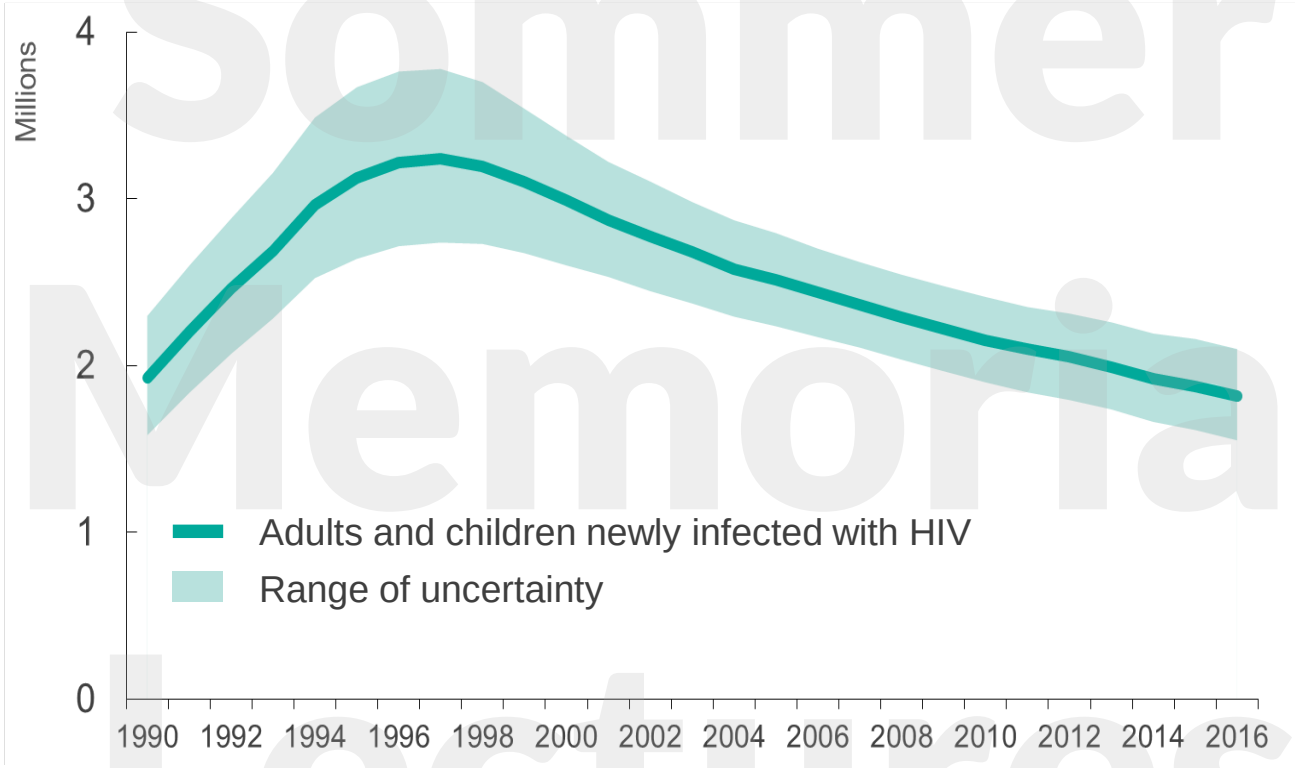
UNAIDS

Adults and children estimated to be living with HIV | 1990–2016



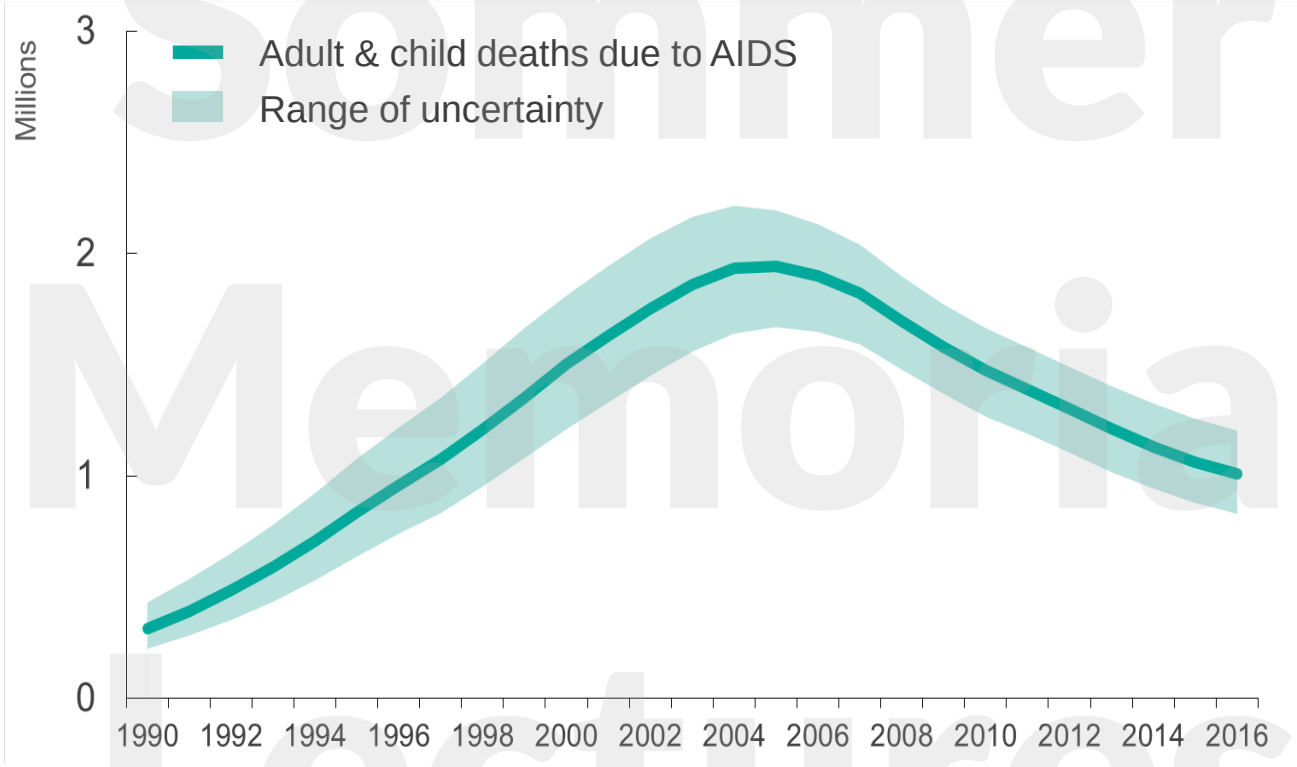
UNAIDS

Adults and children newly infected with HIV | 1990–2016



UNAIDS

Adult & child deaths due to AIDS | 1990–2016

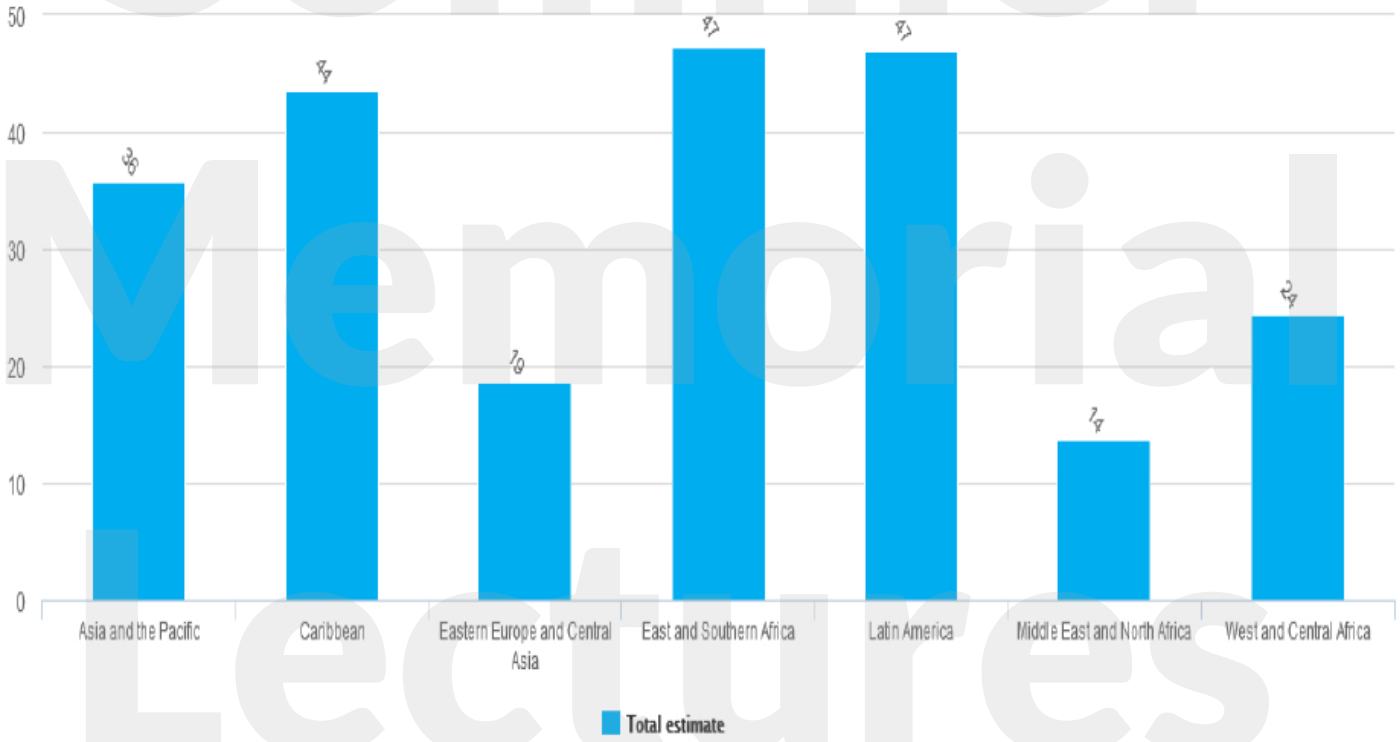


UNAIDS

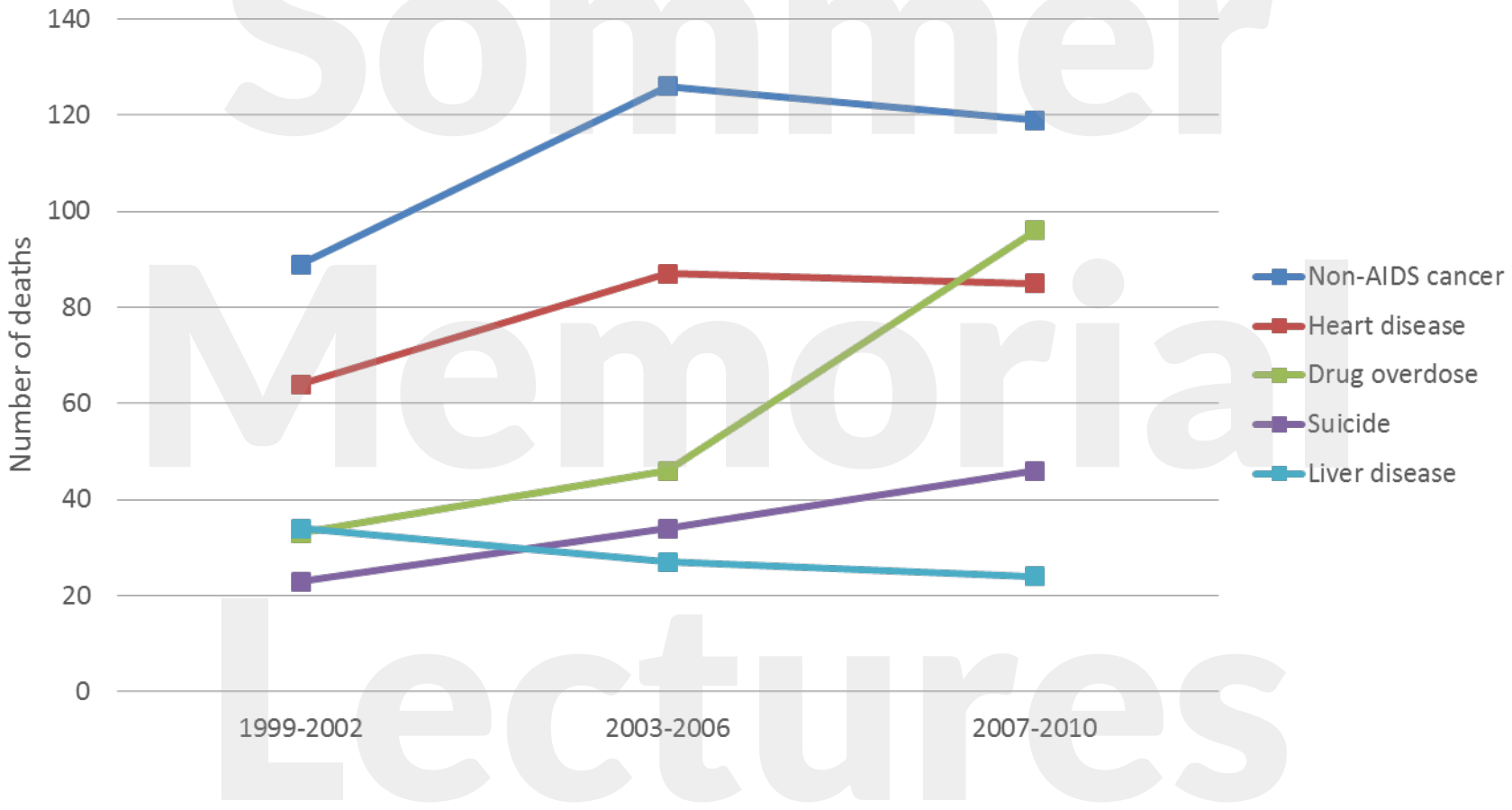
UNAIDS | AIDSinfo

Treatment

3. Coverage of people receiving ART (all ages)- by region



Non-HIV Causes of Death, SF



Why the Need for an Effective Biomedical Prevention

- Recent mathematical models demonstrate that secondary prevention (test and treat) will not reduce new acquisitions to what anyone could call "acceptable"

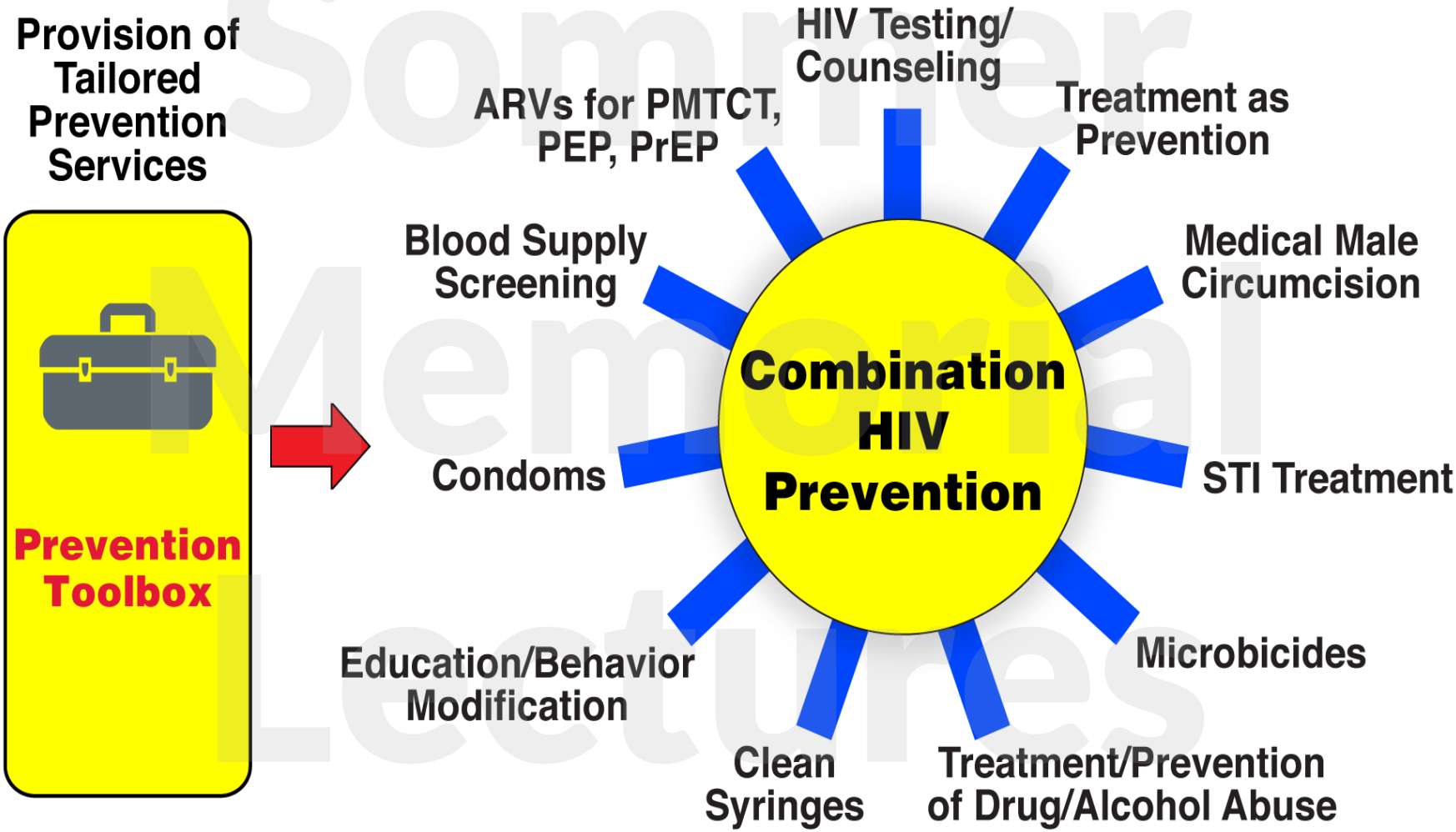
- UNAIDS Goal of 90-90-90 is a useful aspirational framework for optimizing therapy for people who acquire HIV

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

Tailored Prevention Using HIV Prevention Toolbox



AS Fauci/NIAID

Commentary on HIV Prevention Strategies

- While many prevention strategies have high efficacy in clinical trials, their extended effectiveness requires continuous adherence (circumcision excepted), which often results in decreased effectiveness over time.

- They also require high saturation in a community and hence their long term effects on population based incidence in country's with generalized epidemics is uncertain.
  - Condoms; PrEP; vaginal rings; PEP; circumcision, all deserve support and increased uptake
  - Vaccine efficacy trials are best available prevention +/- experimental vaccine

The Two Major Scientific Questions Facing the HIV Vaccine Field:

- Can non-neutralizing antibodies be potent enough to achieve desirable vaccine efficacy (VE >50%) for at least 2 years?
  - Can this be achieved by designing better recombinant proteins and adjuvants?
  - By eliciting better T helper responses to drive higher and more durable antibody production?

- Is neutralization, as we currently measure it, associated with vaccine protection and will this protection be of a sufficient magnitude to overshadow other vaccine design approaches?

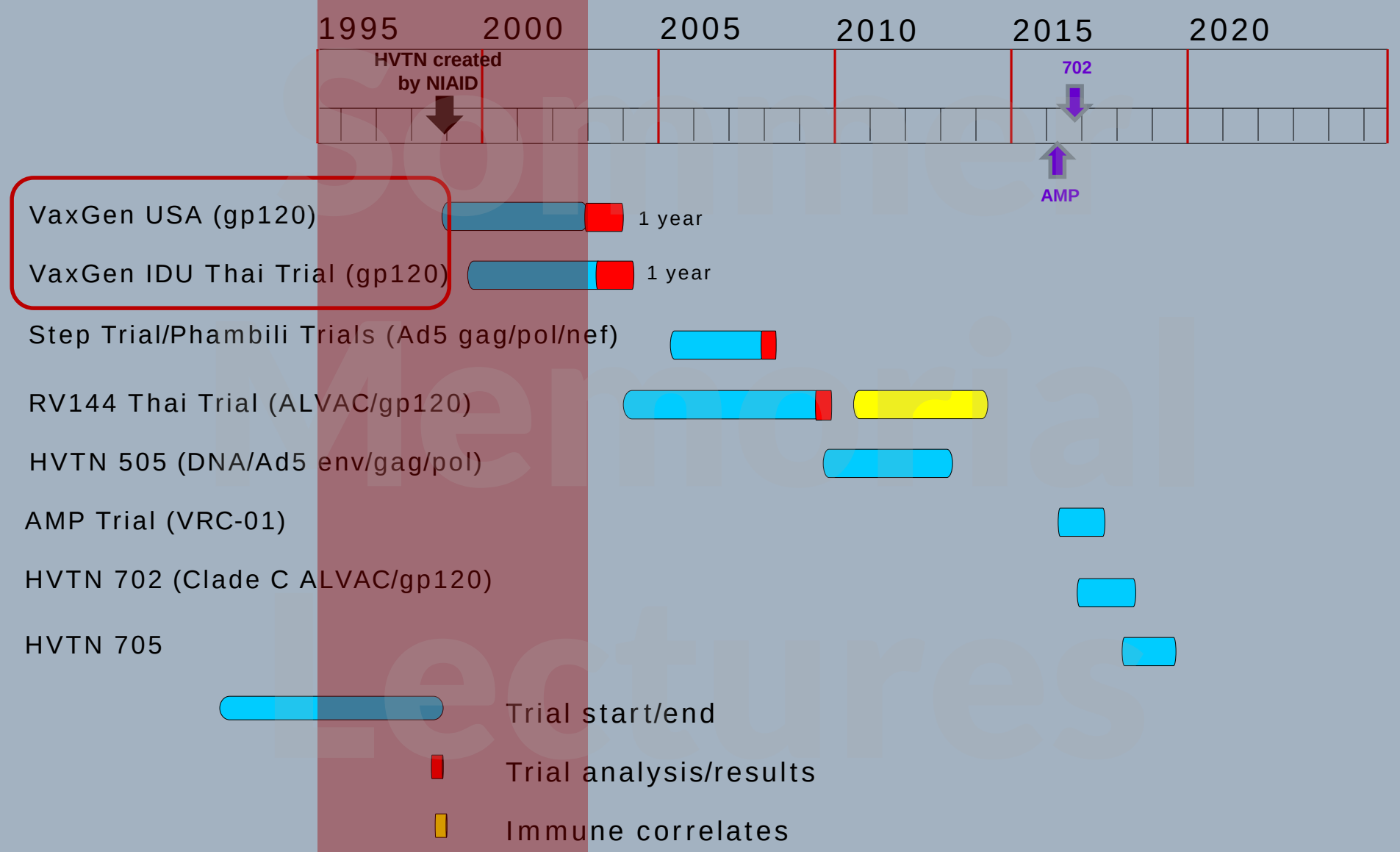
Why Has It Been So Hard to Develop an HIV Vaccine?

- 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)

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

- Policy/administrative issues
- Reluctance to do expensive efficacy trials of candidate vaccines
- Almost all vaccine innovations are in the public sector; pharmaceutical and biotechnology companies sitting on the sidelines
  - Need to develop the expertise in the non-commercial sector to do consistent manufacturing of complicated vaccine products

A Pictorial History of HIV-1 Vaccine Efficacy Trials

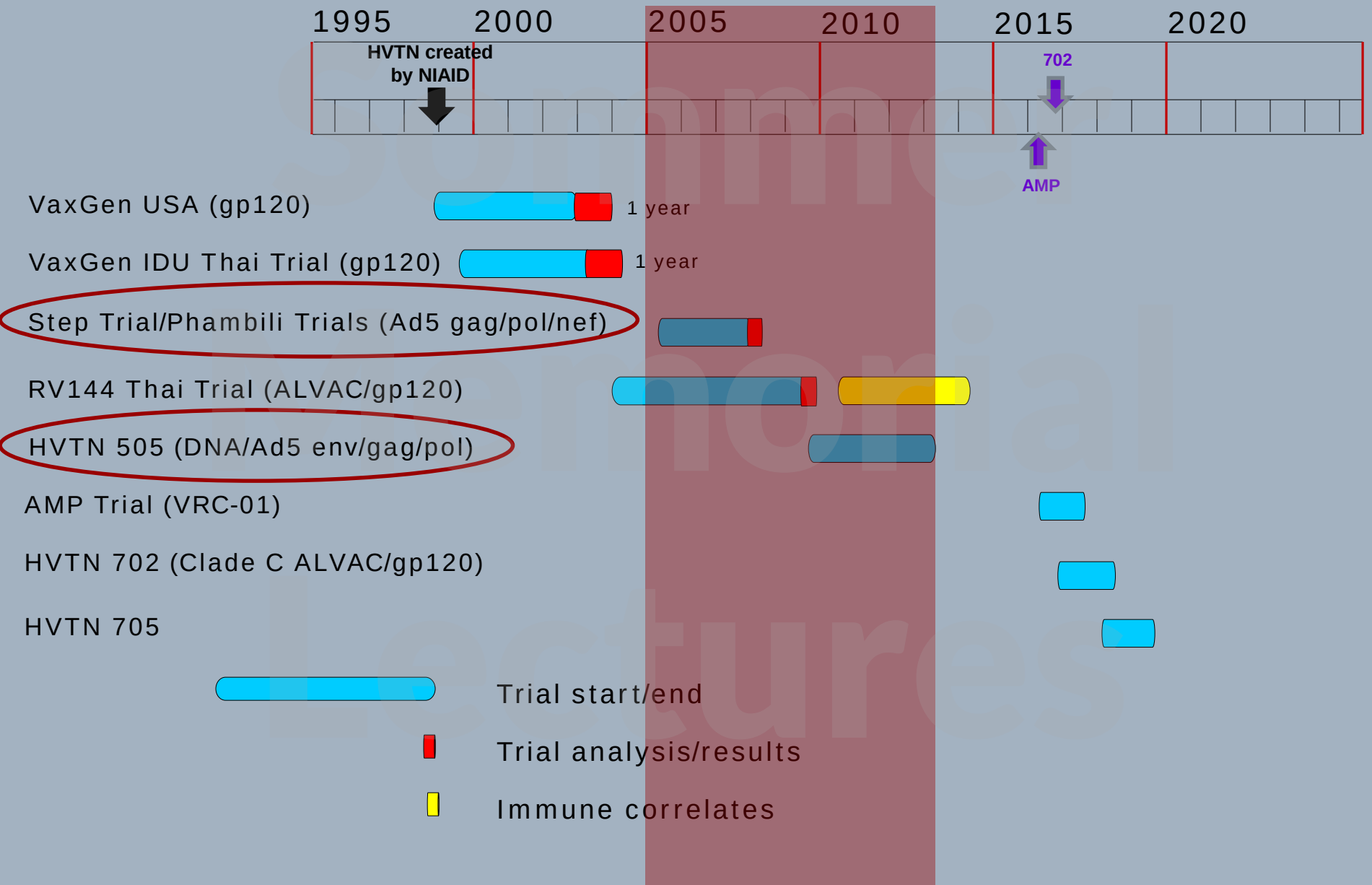


Second Generation Vaccines: T Cell Based Vaccines

- Post-VaxGen, HIV vaccine field turned to "T cell based" vaccines – CD8+ T cells were what differentiated elite controllers from progression and it was hoped that vaccines that would induce such responses would be effective in either reducing acquisition or post-acquisition viral load.

- Hypothesis: the more potent T cell responses, the better the vaccine:
  - Ad5 vector based vaccine much more effective in inducing CD8+ T cell responses than ALVAC

A Pictorial History of HIV-1 Vaccine Efficacy Trials



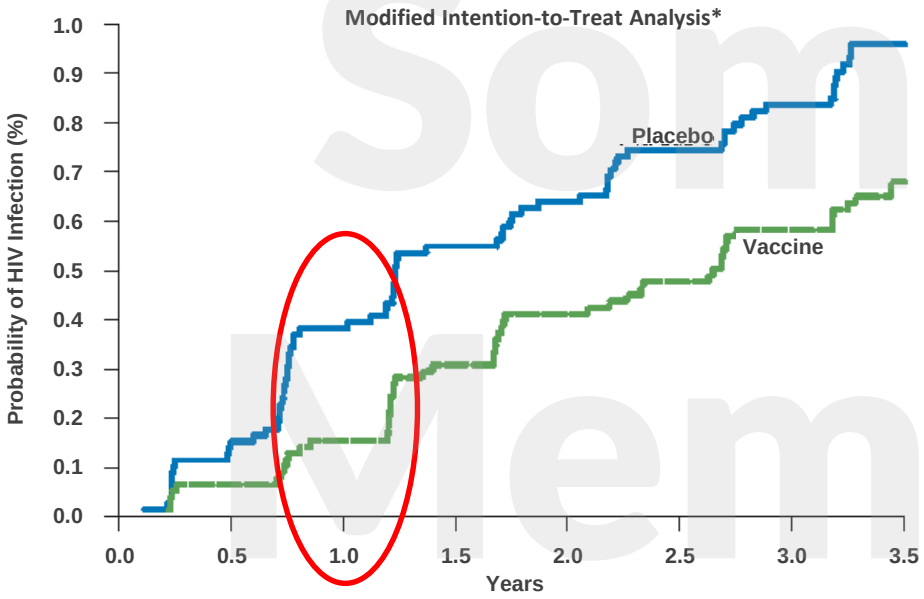
The Good News for HIV Vaccine Development – September 2009 and the RV144 Trial

- Regimen of ALVAC priming followed by gp120 results in efficacy in large trial in Thailand.

- Results met with surprise and skepticism:
  - ALVAC not as good as Ad vectors for T cell priming
  - gp120 used had failed in IDU trial

- How could these two together all of a sudden produce efficacy?

Thai Trial (RV144) Primary Results



Vaccine efficacy decreases over time

	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

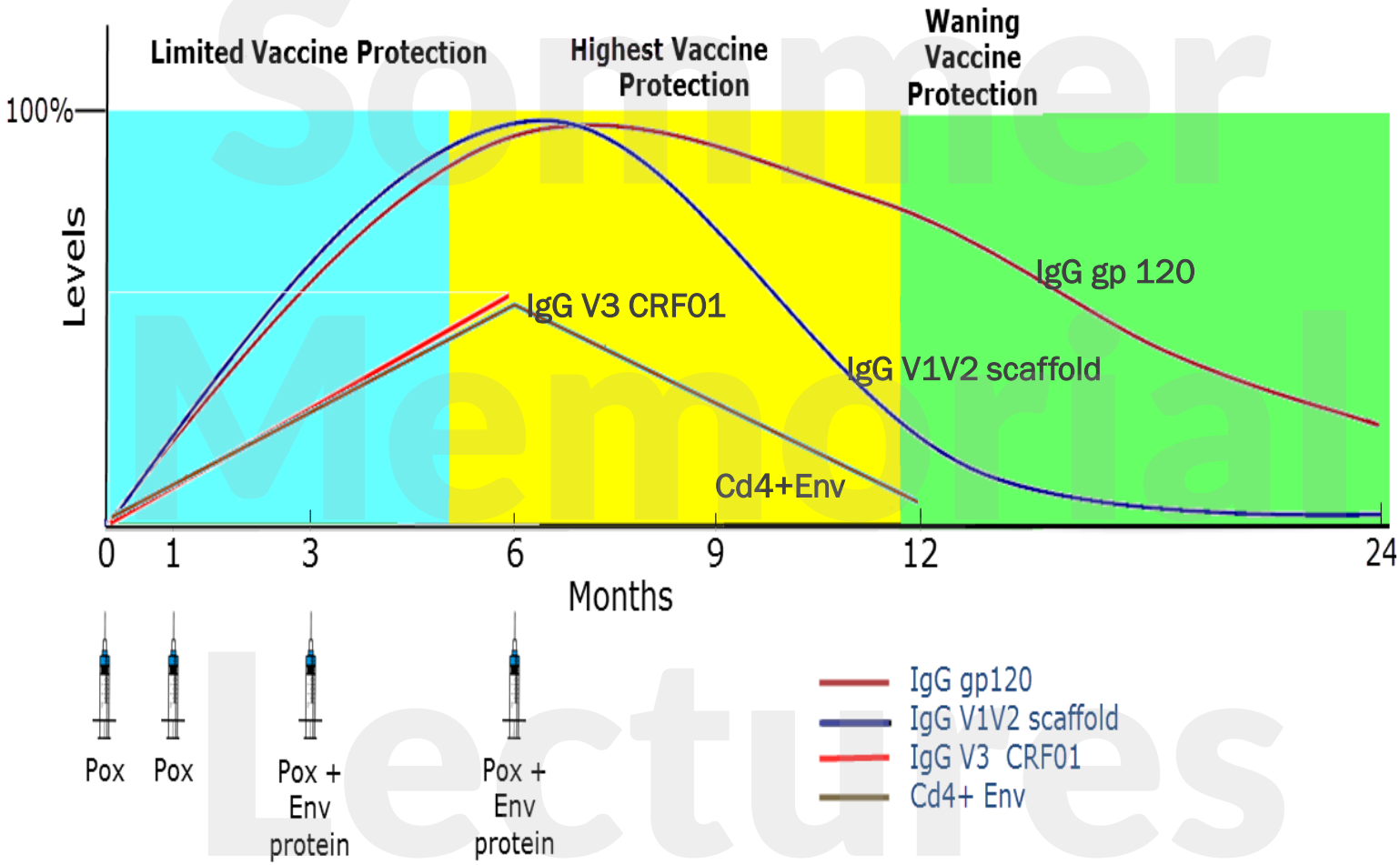
The NEW ENGLAND JOURNAL of MEDICINE

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*

Kinetics of Vaccine-Induced Immune Response and Vaccine Protection Based on RV144

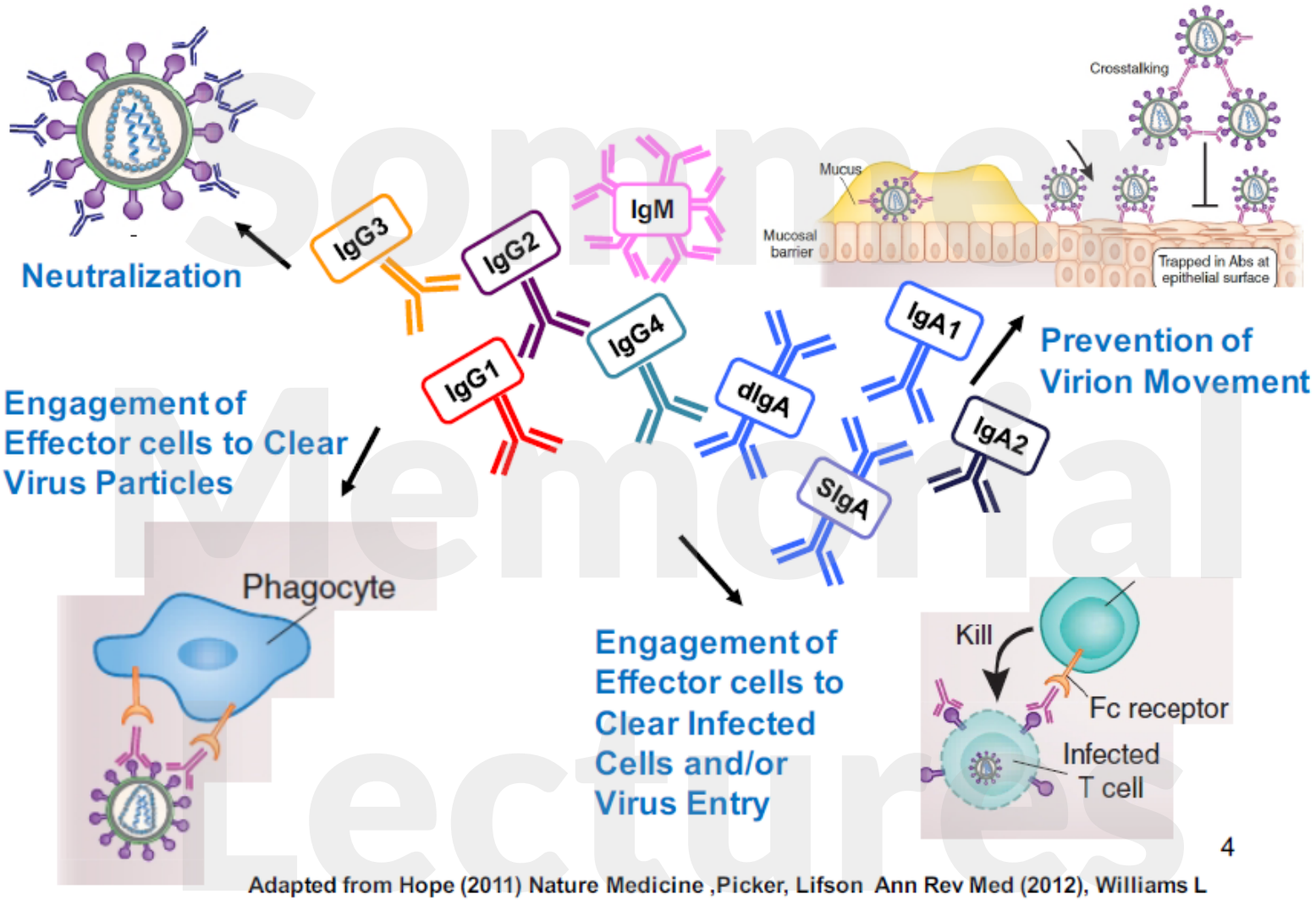


Post-RV144

- Massive scientific effort to understand how did RV144 work: correlates of risk/correlates of protection.

- Pivot in the field from concentrating on novel vectors to understanding that it is the insert (HIV envelope gene) and structure of the envelope antigen that one puts in the vector that is critical for vaccine design.

Multiple Ways for Antibodies to Stop HIV-1



Adapted from Hope (2011) Nature Medicine ,Picker, Lifson Ann Rev Med (2012), Williams L

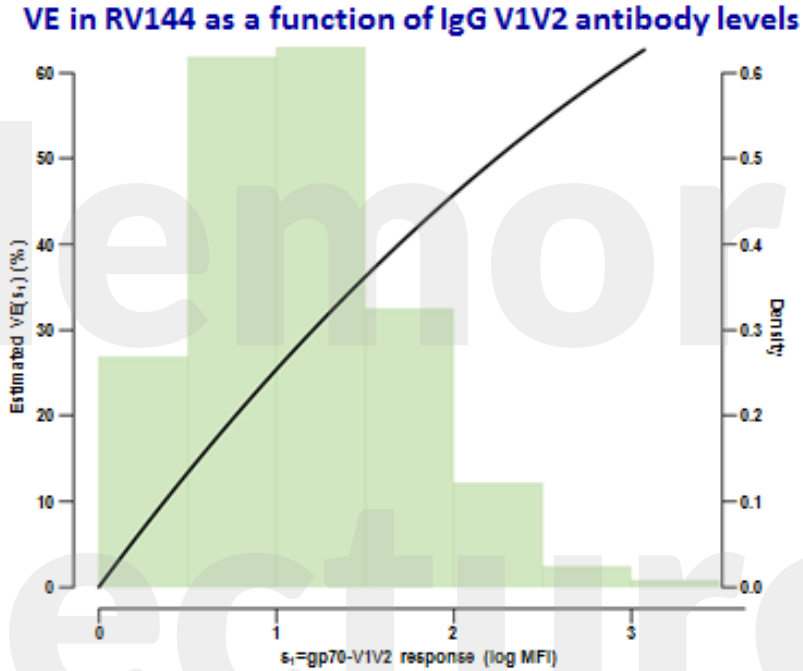
Concepts from the RV144 Correlates Program 2010 - 2014

- **No direct correlation between neutralizing antibodies and HIV-1 acquisition in RV144:**
  - *None of the sera from the RV144 vaccinees neutralized a panel of 20 contemporaneous isolates of HIV-1 circulating in Thailand during the course of the trial*

- **The antibody related correlations associated with vaccine efficacy in RV144 were in the magnitude and the epitope specificity of non-neutralizing antibodies which exhibited virion binding or infected cell associated functions.**

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.



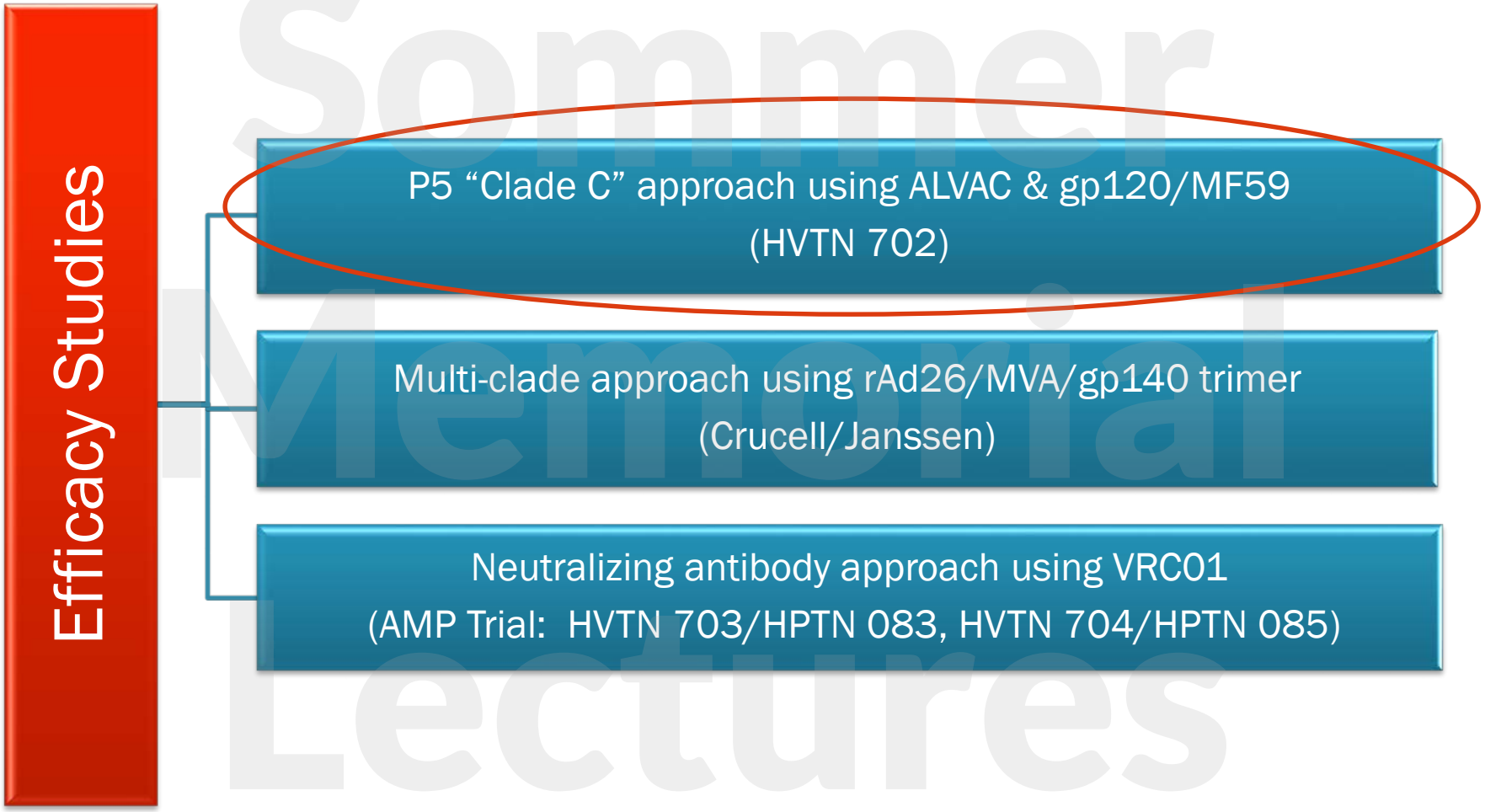
Estimated vaccine efficacy in RV144 as a function of the level of IgG binding antibody to gp70-scaffolded V1V2 (black line) and the distribution of IgG levels among vaccinees (histogram)

RV144 Correlates Observations

- Sequencing studies of the viral envelope from persons on the trial revealed that distinct immunological pressure was observed in the crown of the V2 loop where vaccine immune responses were directed.

- Distracting/inhibitory antibodies could be produced that reduced vaccine efficacy.

2016/2017: 3 Novel Strategies



2010 Formation of the P5 Partnership

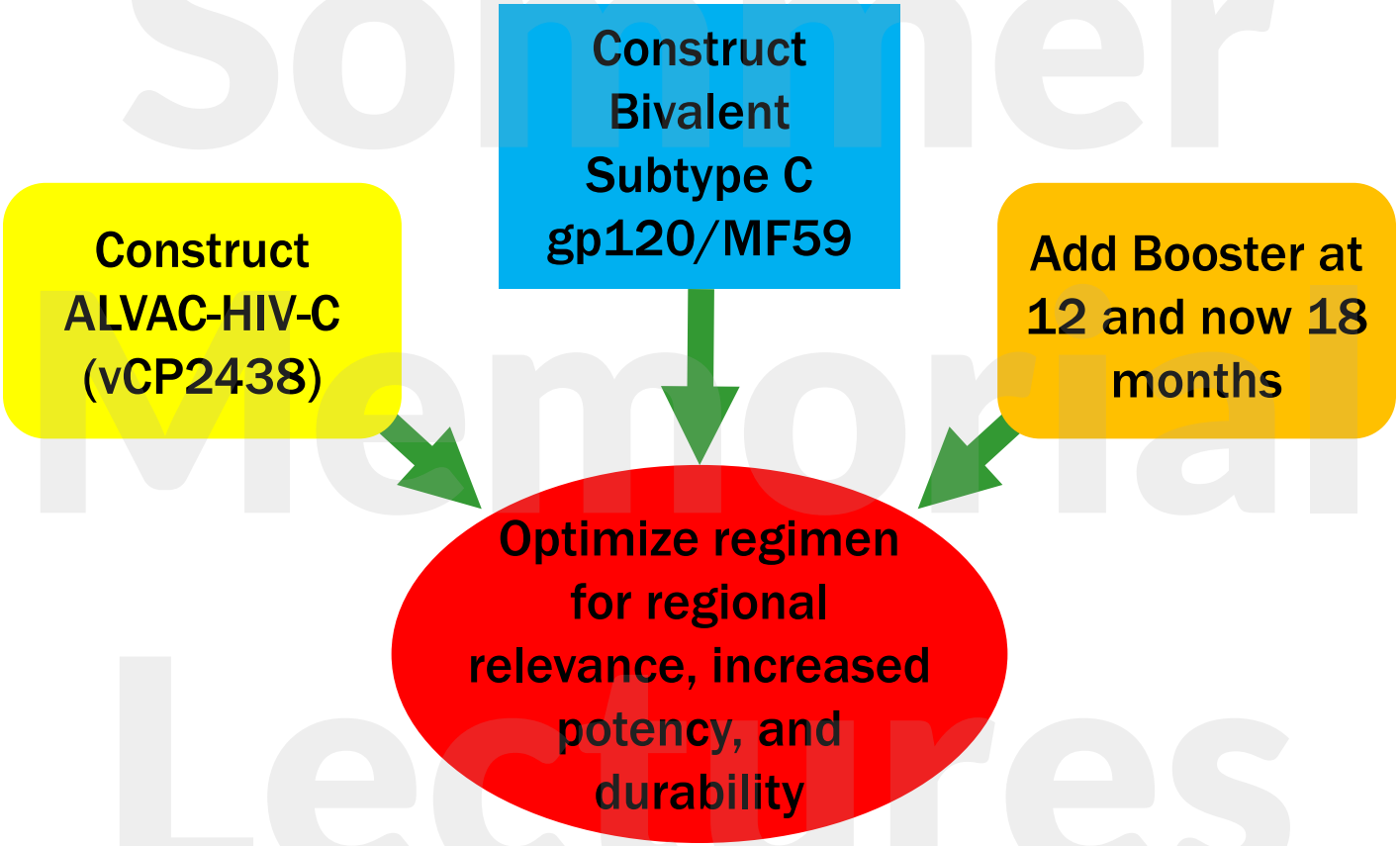
Purpose:

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.

Construction of the P5 Clade C Vaccine Regimen



HVTN 702

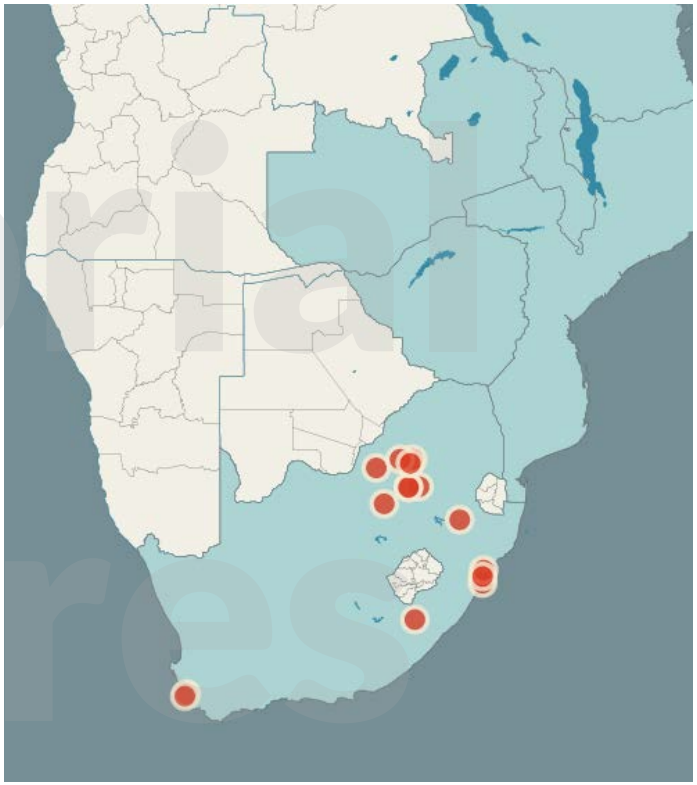
A pivotal phase 2b/3 multi-site, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of ALVAC-HIV (vCP2438) and bivalent subtype C gp120/MF59 in preventing HIV-1 infection in adults in South Africa

- Started Nov. 1, 2016 in RSA
- 3050 enrollees
- Glenda Gray, Chair
- Co-Chairs:

  Linda Gail Bekker, Fatima Laher,

  Mookho Malahlela

uhambo

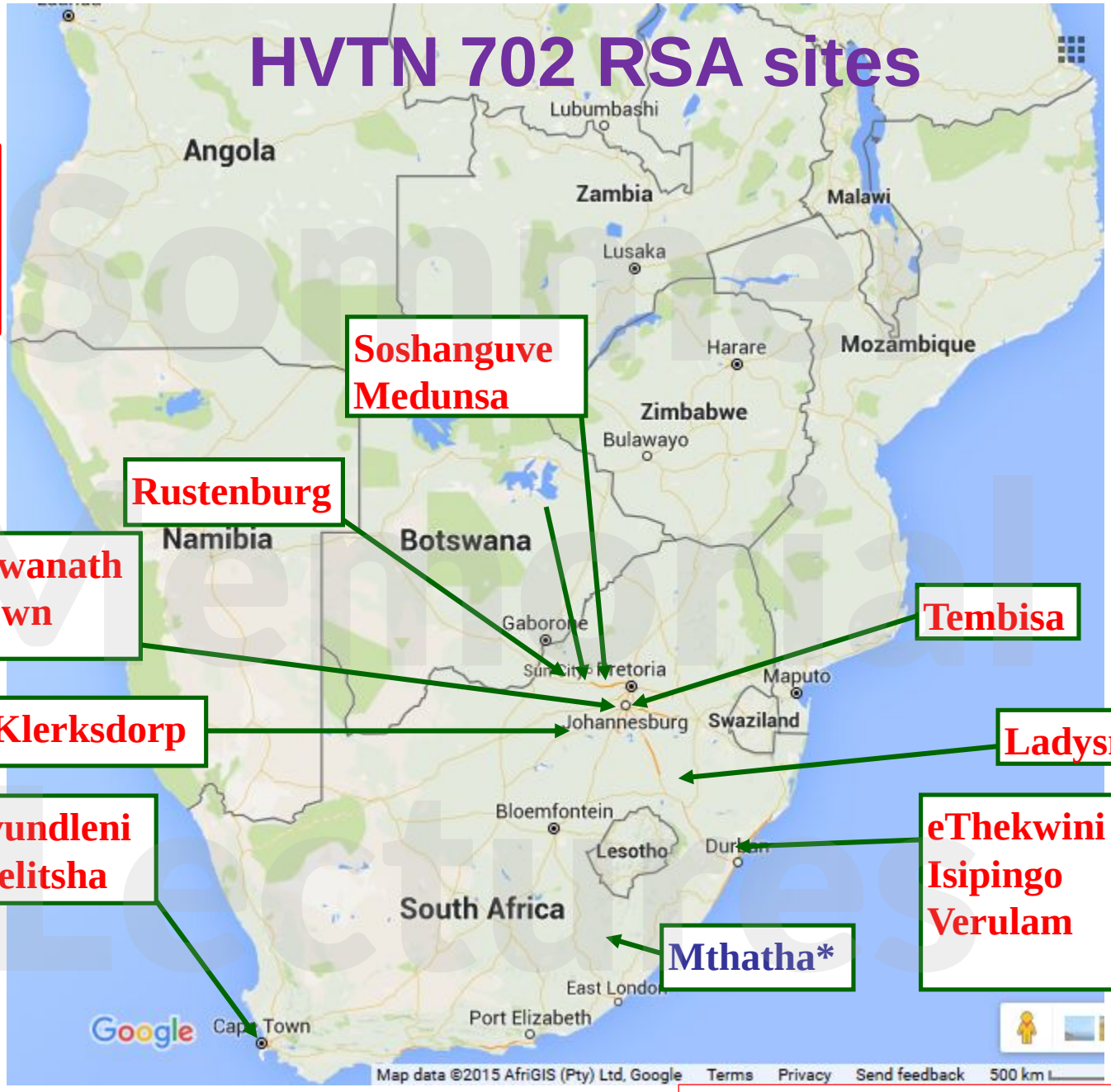


Study Schema: HVTN 702

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						

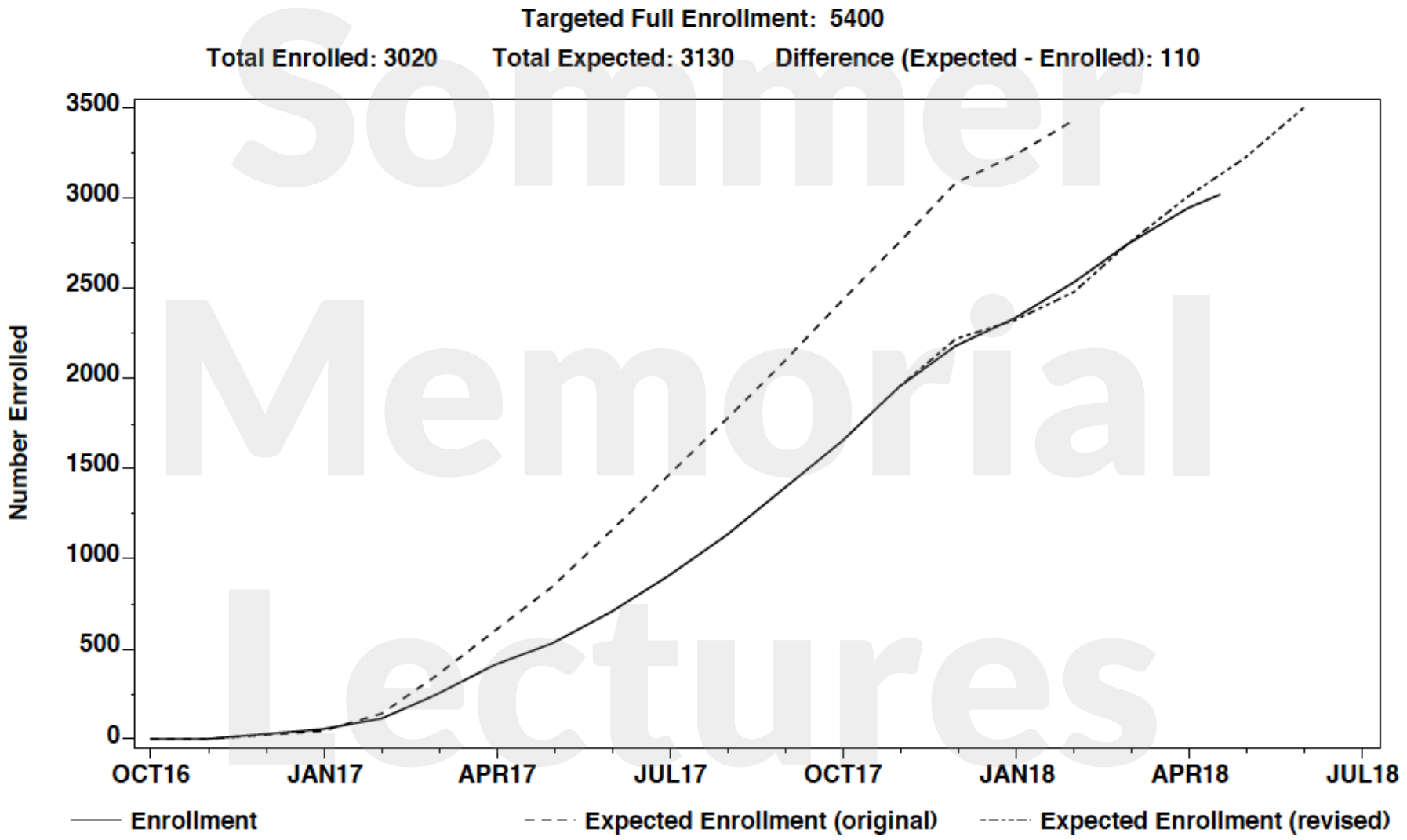
HVTN 702 RSA sites

13 sites activated (in red) as of March 2, 2018

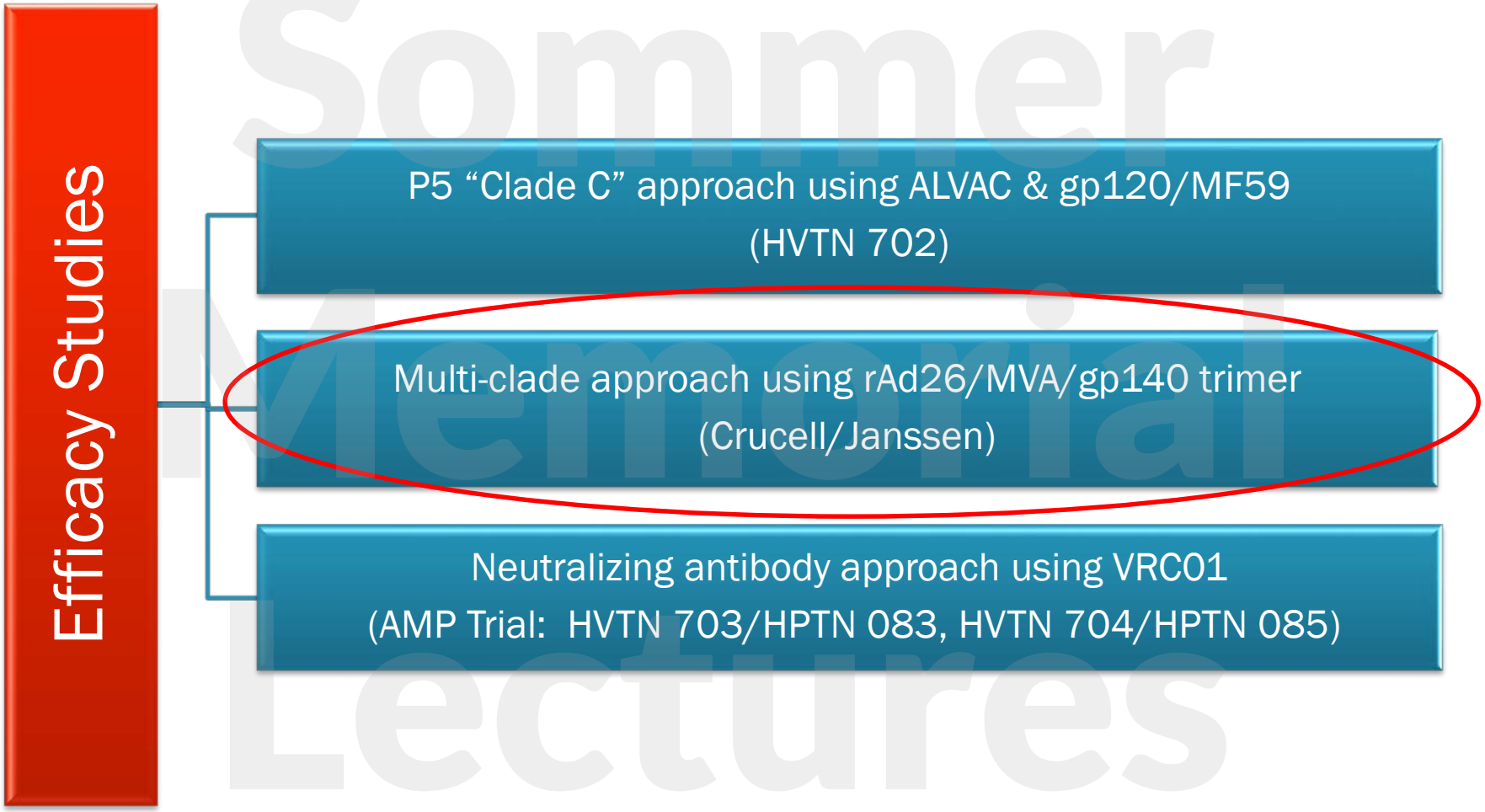


*Expected to open in April, 2018

Accrual Through April 17, 2018 (close-up of updated Figure 1)



2016/2017: 3 Novel Strategies



Mixture of 4 mosaic Ad26 constructs + gp140 Clade C boost

Prime

Ad26.Mos4.HIV
Ad26 vectors with Mosaic gag-pol or env inserts

- Ad26.Mos1.Gag-Pol
- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env (clade B-like)
- **Ad26.Mos2S.Env** (clade C-like)

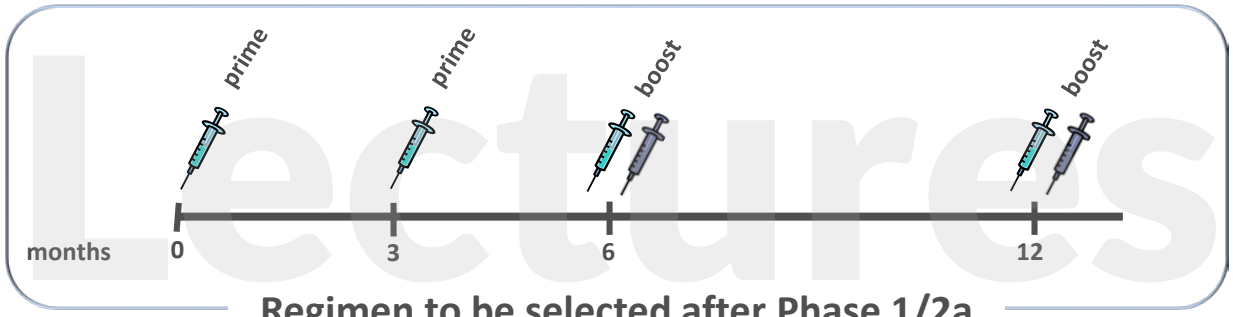
Boost

Ad26.Mos4.HIV
gag-pol-env

+

gp140 Clade C
Soluble trimer gp140 env proteins

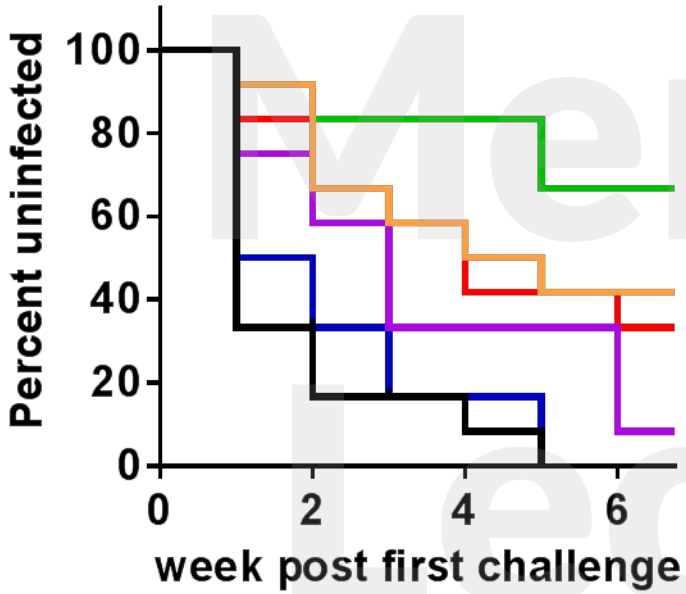
Ad26.Mos4.HIV
gag-pol-env



Regimen to be selected after Phase 1/2a

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)]

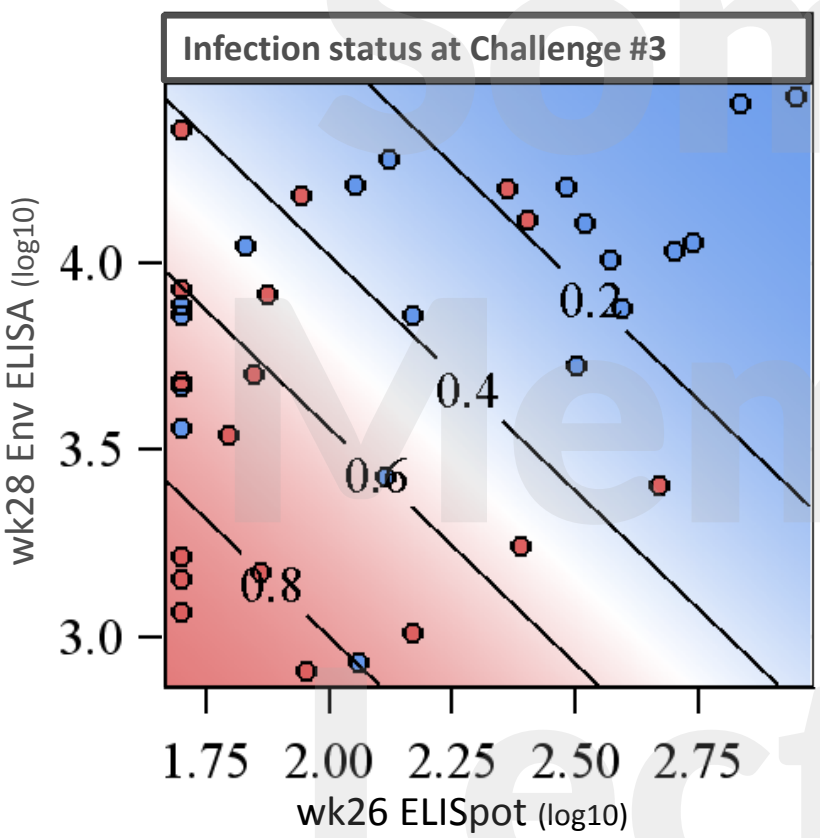


- Ad prime / Ad boost
- Ad prime / Env boost
- Ad prime / Ad+Env boost
- Ad prime / MVA boost
- Ad prime / MVA+Env boost
- Sham

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%

Binding antibodies to HIV Env together with HIV Env specific T cells correlate with protection in NHP $SHIV_{SF162P3}$ challenge study

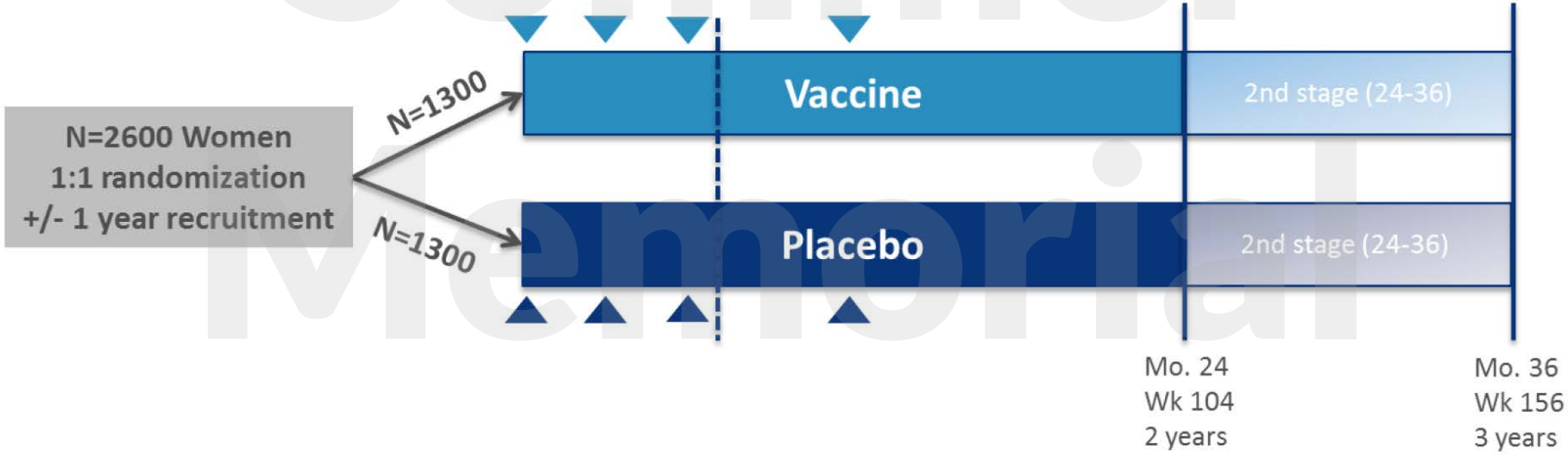


Shaded colors and diagonal lines indicate the prediction model of infection based on **ELISpot** and **ELISA** responses

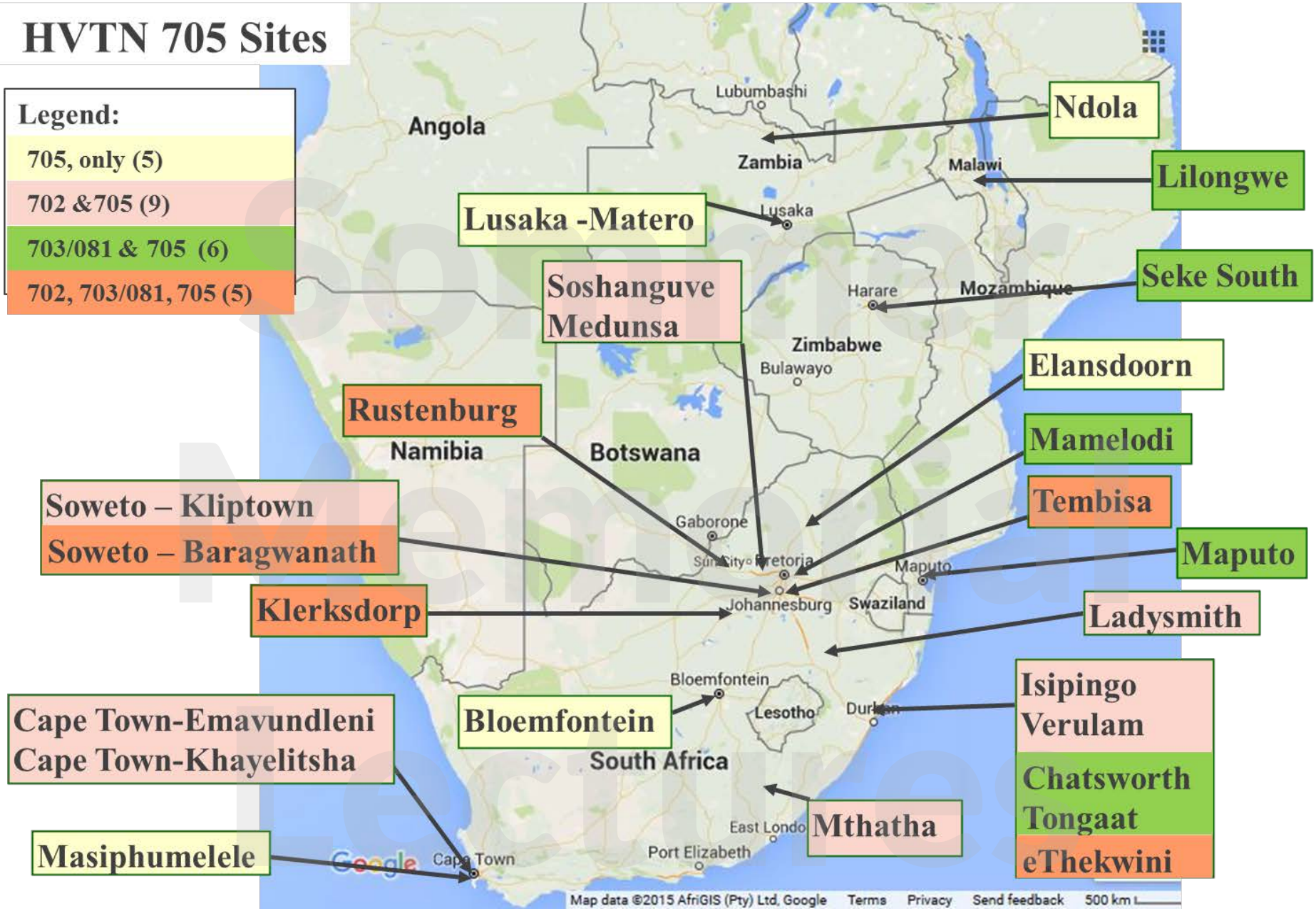
In addition, functional antibodies as assessed by **ADCP** were found to correlate with protection, as has been observed in previous studies

Note: to increase accuracy, model is based on Ad26 groups without MVA

Study Design and Stages



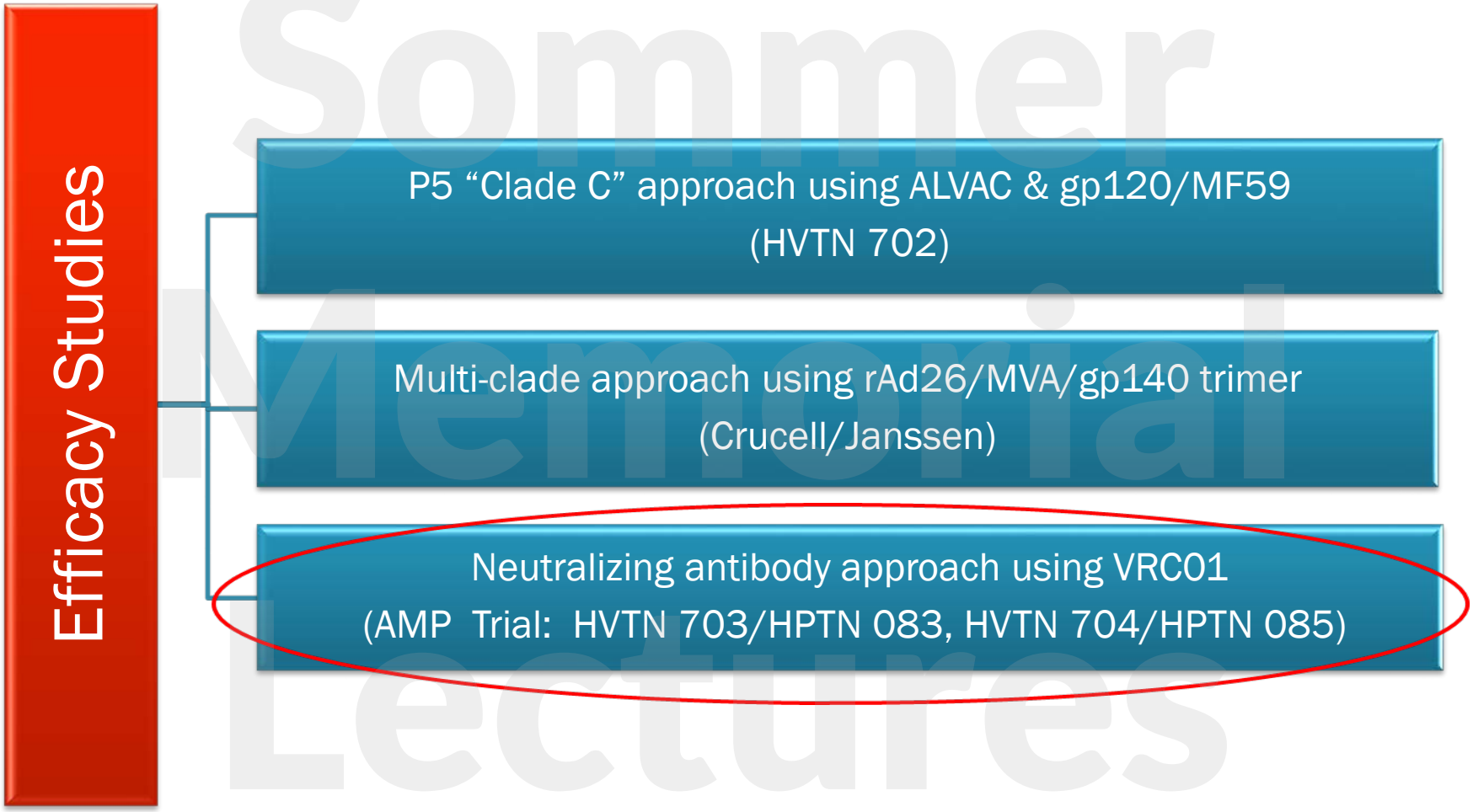
HVTN 705 Sites



Another Pause to Reflect

- 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.

Neutralizing Antibodies for HIV Prevention



Long History of Antibodies to Treat and Prevent Infectious Disease (Serum Therapy)

Behring together with his colleagues Wernicke (left) and Frosch (center) in Robert Koch's laboratory in Berlin. Photo: Courtesy of Aventis Behring WWW.nobelprize.org

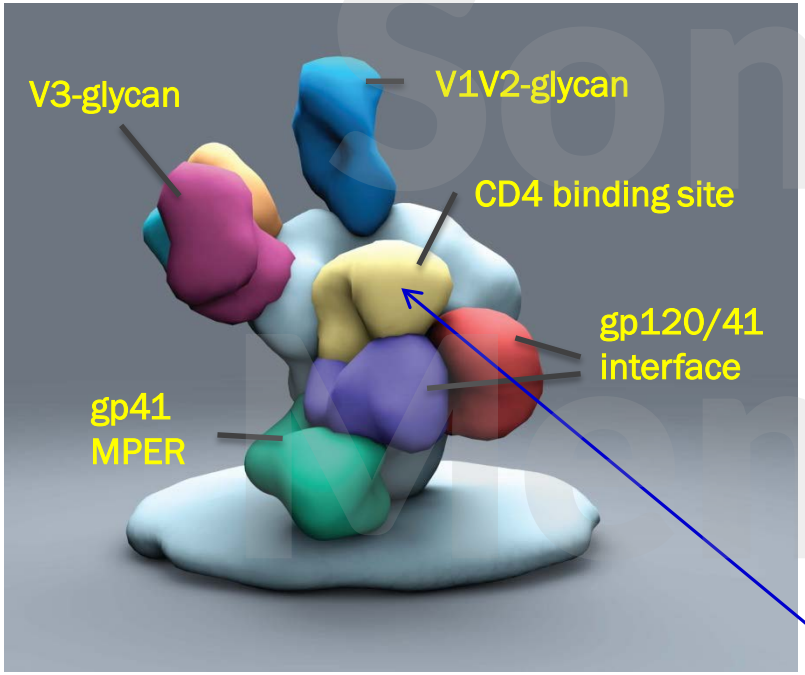
The Nobel Prize in Physiology or Medicine 1901 to Emil von Behring: "For his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths".

Pre-Antibiotic Era: Bering and Paul Ehrlich pioneered serum therapy for diseases such as diphtheria, tetanus, streptococcal infections

Nobel Prizes awarded for discoveries related to antibodies in infectious diseases:

- 1901: Serum therapy for diphtheria (Behring),
- 1908: Describing humoral immunity (Mechnikov, Ehrlich),
- 1972: Defining the chemical structure of antibodies (Edelman, Porter)
- 1984: Production of monoclonal antibodies (mAbs) (Jerne, Köhler, Milstein)
- 1987: Explaining the mechanism for antibody diversity (Tonegawa)

Neutralizing Ab to HIV-1

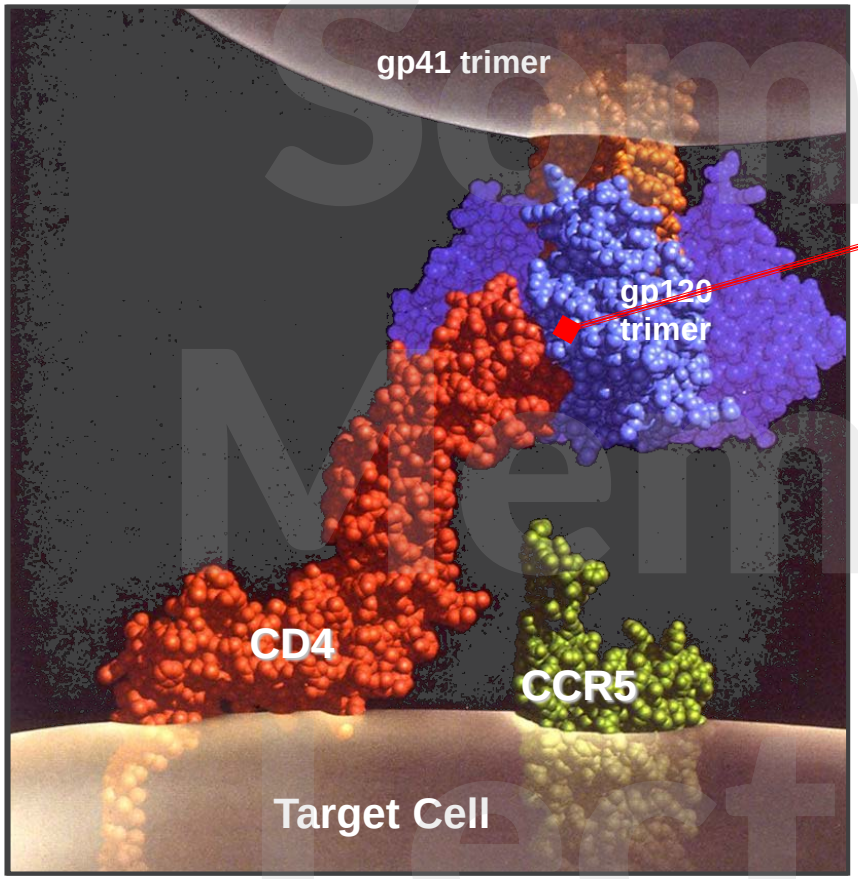


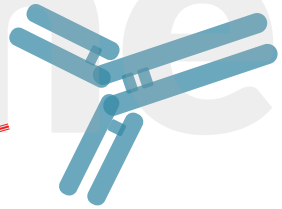
- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

antibodies that have advanced farthest in the clinic (VRC01, 3BNC117)

Christina Corbaci, Andrew Ward,

VRC01 Blocks Attachment to CD4



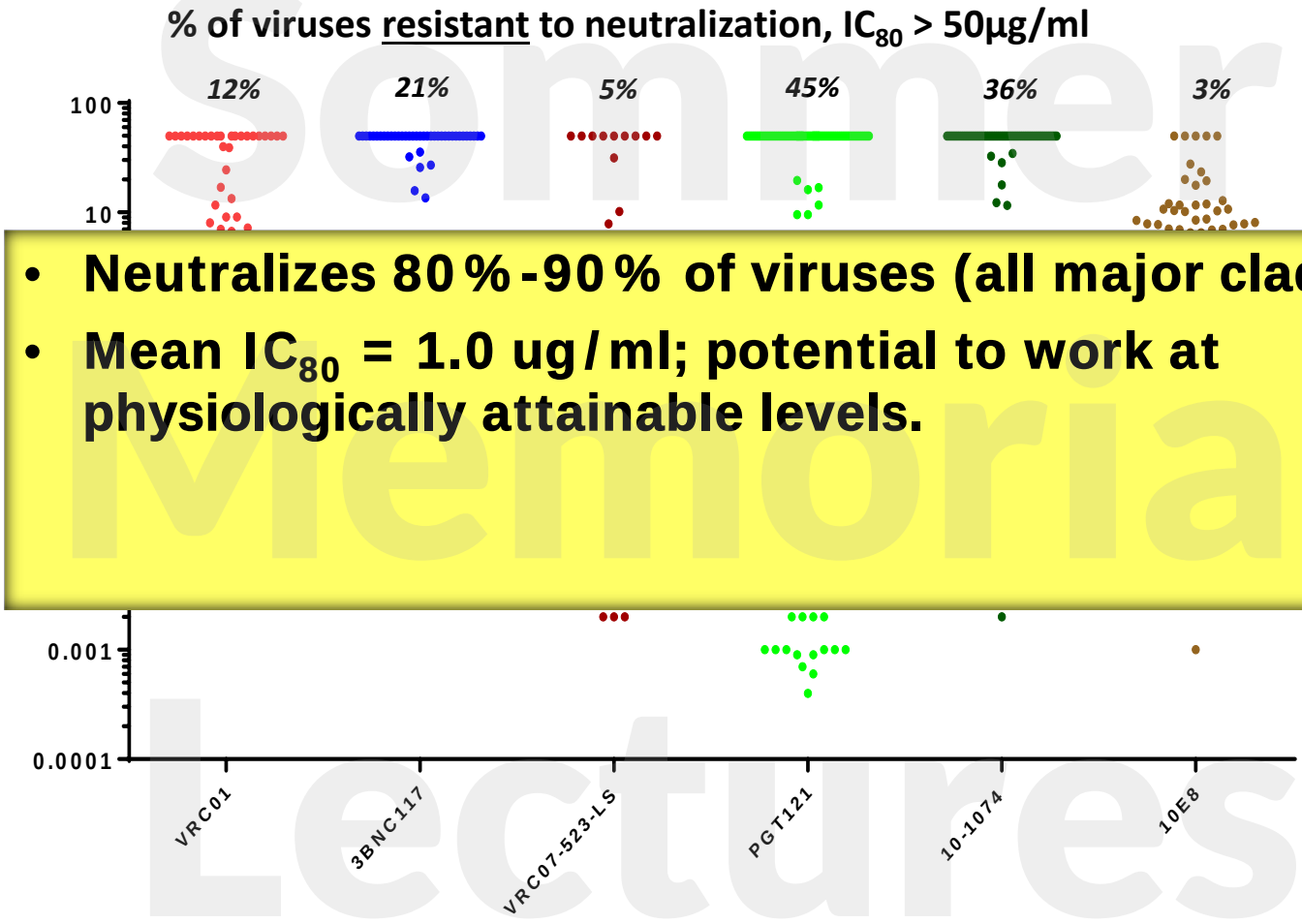


CD4 binding site on gp120 is functionally conserved: all viruses must bind CD4

VRC01 neutralizes ~ 90% of diverse viral isolates

How Potent is VRC01 *In Vitro*

Neutralization (IC_{80})



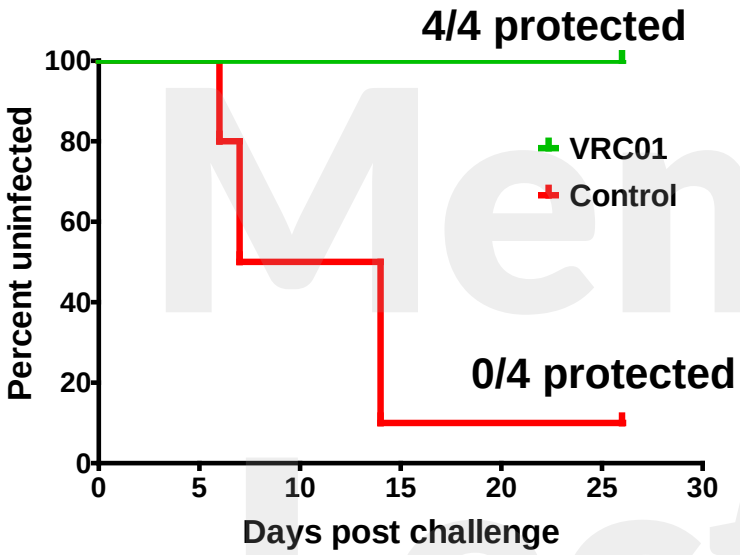
- **Neutralizes 80%-90% of viruses (all major clades)**
- **Mean IC_{80} = 1.0 ug/ml; potential to work at physiologically attainable levels.**

Panel of 170 genetically diverse Env-pseudoviruses, representing all major clades
Line shows median IC value - based on results from all viruses, including those not neutralized.

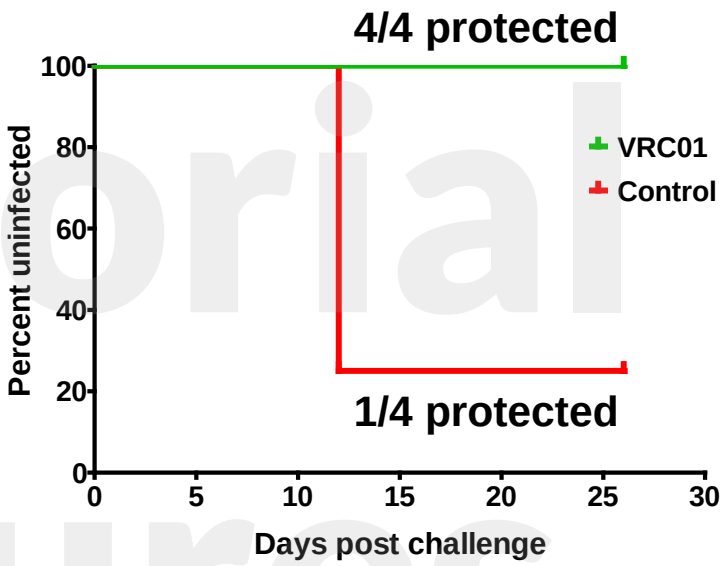
VRC01 Protects Against Mucosal SHIV-Challenge in Non-Human Primates

20 mg/kg infusion of VRC01: Challenge with SHIV SF162P3

RECTAL CHALLENGE



VAGINAL CHALLENGE



- Pegu et al. Science Transl Med (2014)
- Ko et al. Nature (2014)
- Rudicell et al. J Virol (2014)

Passive Antibody Prevention
Phase IIB Efficacy Studies

AMP = Antibody Mediated Prevention

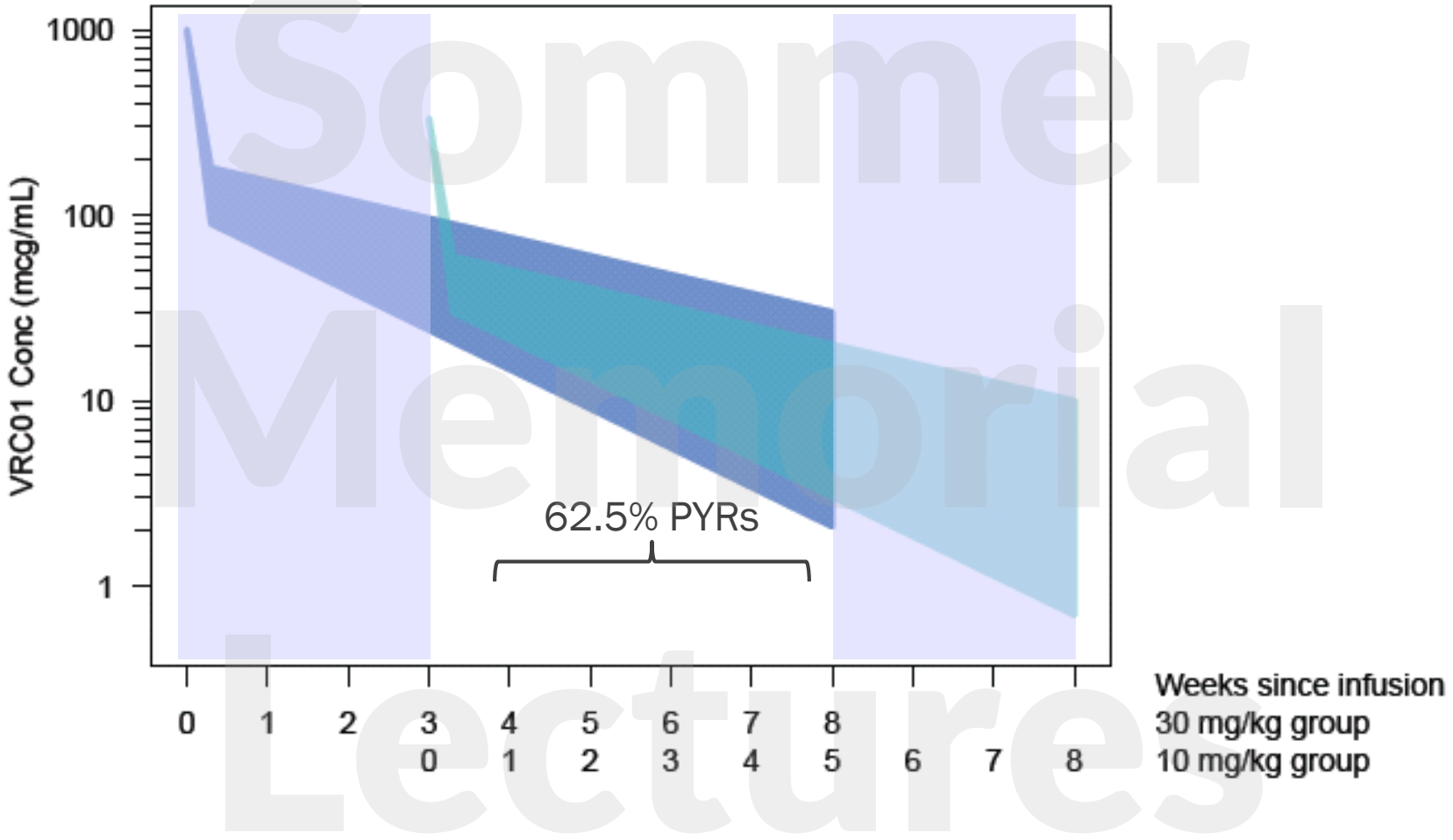
Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults: MSM in Americas & heterosexual women in sub-Saharan Africa

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

Main Hypotheses of the Trials

- **Does administration of VRC01 reduce acquisition of HIV infection in people who are at risk of acquiring HIV?**
- **If so, will the level of VRC01 required for protection vary by type of sexual exposure (men and women)?**
- **Correlates of protection:**
  - Concentration of VRC01 in serum is directly associated with the rate of protection
  - Breakthrough isolates will have greater resistance to neutralization and will exhibit molecular signatures associated with escape from neutralization

66% Overlap in Concentrations



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

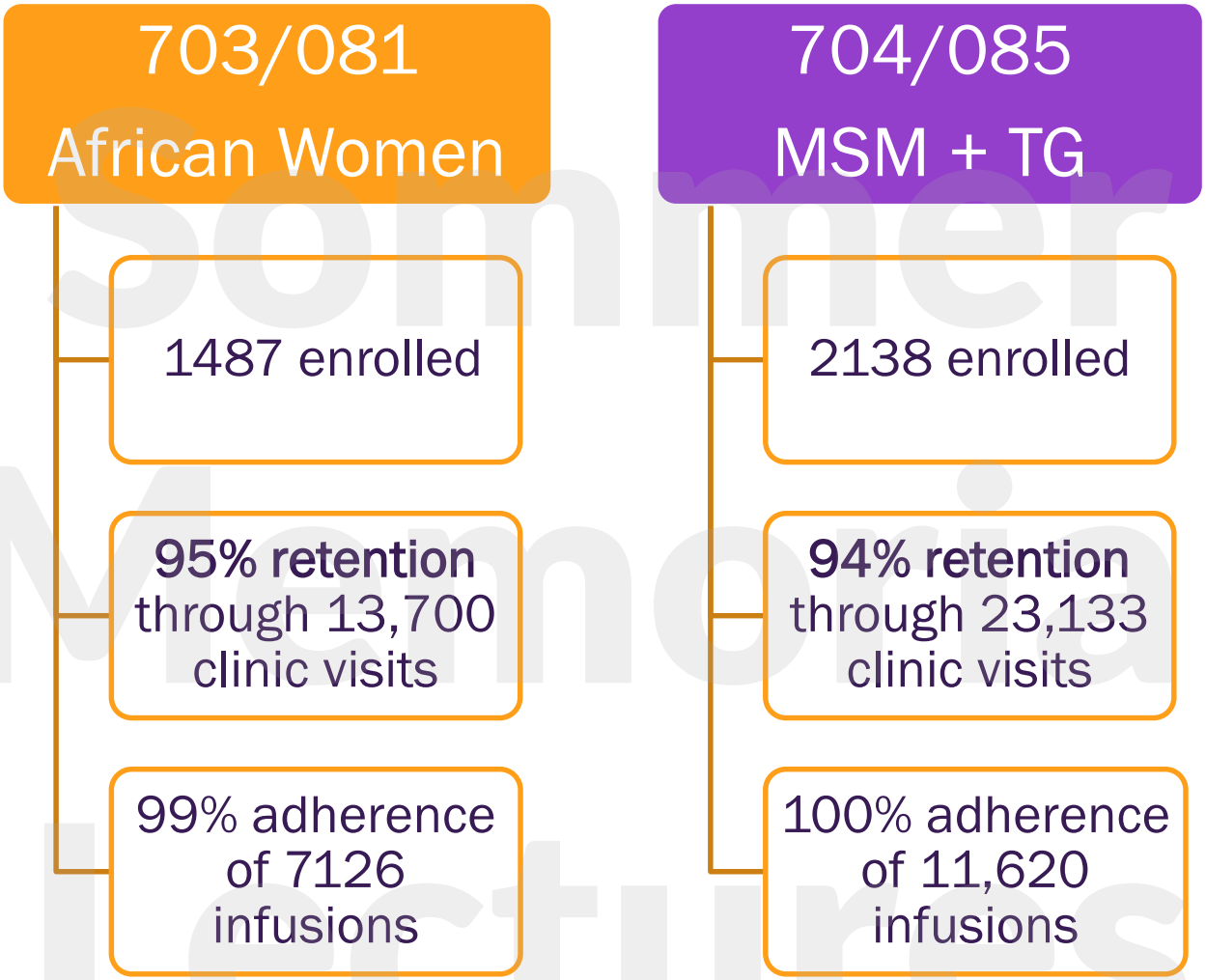
* Due to the randomization scheme, the numbers of vaccine and control recipients may differ slightly.

Study Schema for the AMP studies

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	A	A	A	A	A	A	A	A	A	A		
Group 2	30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		
Total: 2700 for the MSM + TG group; (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 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



The HIV Vaccine Field is Quietly and Efficiently Moving Along

- Three pivotal HIV vaccine related efficacy trials are either underway (AMP/702) or soon to be started (705).
- These pivotal efficacy studies will define if either or both neutralizing and/or non-neutralizing antibodies can be tweaked to provide reasonable vaccine efficacy in high risk Clade C regions of the world.
- These studies will set the stage for the entire design and development of HIV vaccines for the next decade.

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