Advanced Clinical Development of HIV Vaccines

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CAPRISA ECRS

Plenary Session: Progress Towards Commonalities in Vaccine Development Against HIV, TB and Malaria

Global Vaccines and Immunization Research Forum (GVIRF)

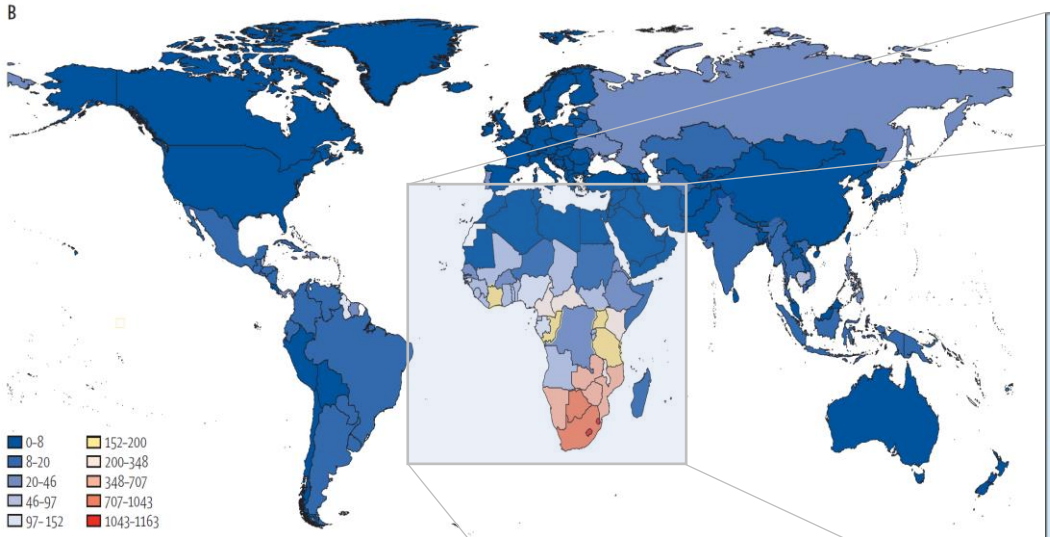
March 20-22, 2018 in Bangkok, Thailand

HIV VACCINE TRIALS NETWORK

CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

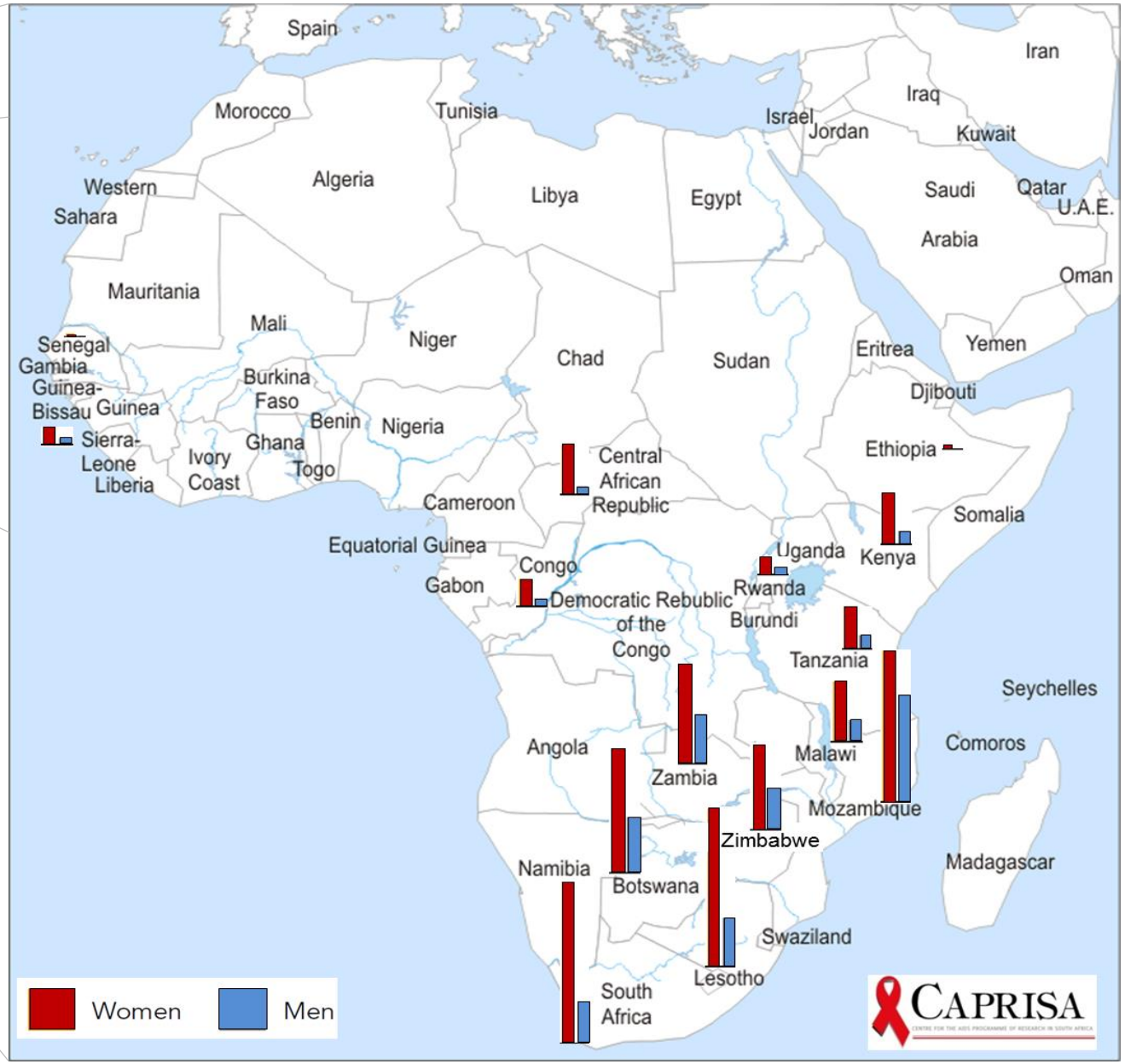
HIV Prevalence in 15-24 year old Men and Women



Global Burden of Disease, Lancet HIV 2016

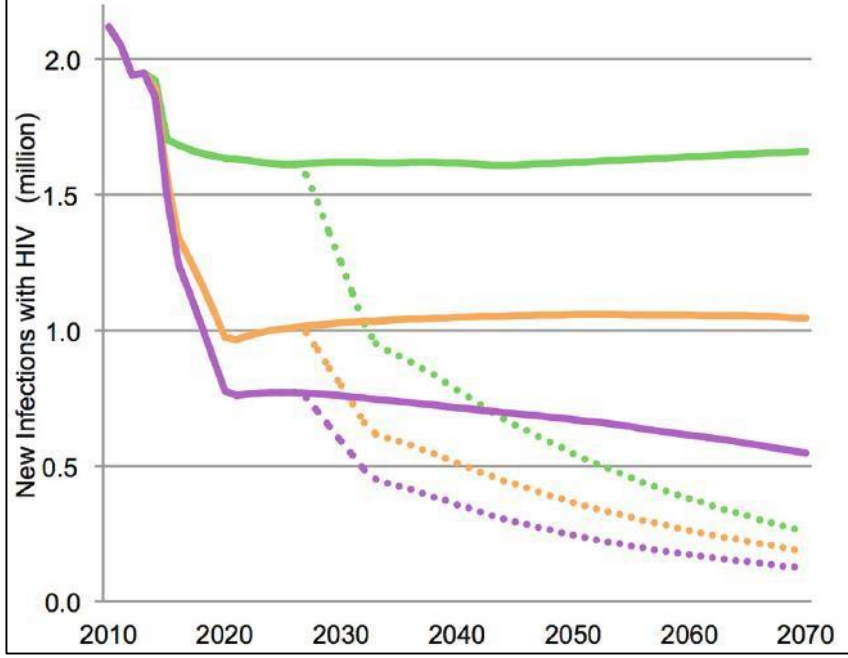
HIV Prevalence in 15 – 24 year men and women (2008–2011)

Young women have up to 8 times more HIV than men



Potential impact of an HIV vaccine

Reduction of new annual HIV infections with & without a vaccine under different prevention scale-up scenarios

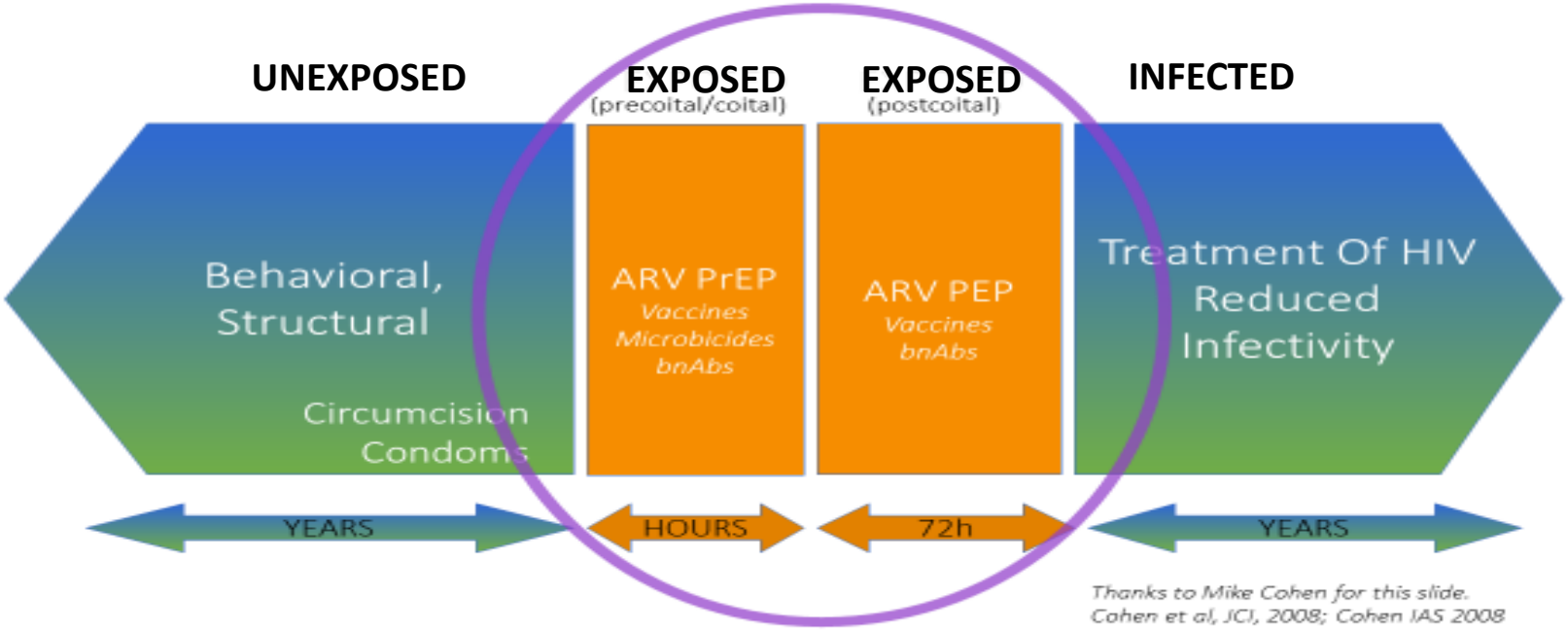


	In thousand	Annual new HIV Infections, 2070	Cumulative HIV infections, 2013-2070
Current Trends	No vaccine	1,659	95,119
	With Vaccine	257	52,331
	Reduction	*-1,402*	*-42,788*
		-84.5%	***-45.0%***
50% Scale-Up IFE	No vaccine	1,044	63,242
	With Vaccine	184	36,153
	Reduction	*-860*	*-27,088*
		-82.3%	***-42.8%***
Full Scale-Up IFE	No vaccine	547	44,442
	With Vaccine	122	28,284
	Reduction	*-424*	*-16,158*
		-77.7%	***-36.4%***

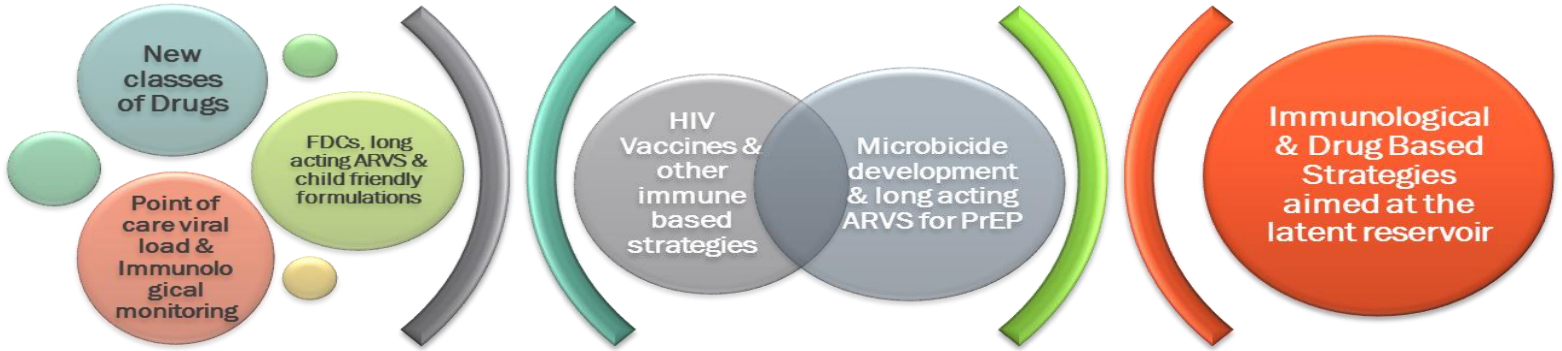
- **Assumptions**: Vaccine introduction in 2027, 50% coverage, 70% efficacy
- IFE = UNAIDS' Investment Framework Enhanced includes scale-up of PrEP, TasP, and other prevention methods

Harmon, et al. PLOS One. 2016

The Gap to fill: The Space for HIV Vaccines



Thanks to Mike Cohen for this slide.
Cohen et al, JCI, 2008; Cohen IAS 2008



Innovations in the management of HIV that will impact on community viral load and infectiousness: prevention of secondary transmission

Innovations in the Prevention of Sexual Acquisition that will be required when secondary transmission is not averted

HIV Cure: the ultimate control of the HIV epidemic will be in the elimination of viremia in those infected

Gray, G et al Plos Biol, 2016

The New England Journal of Medicine
Published at www.nejm.org -- October 20, 2009

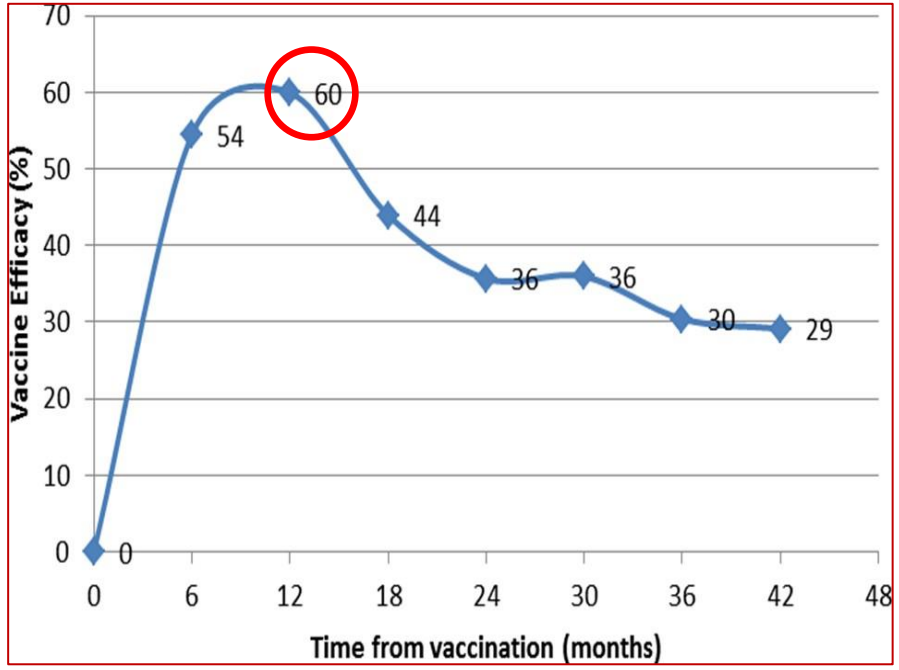
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim et al. for the MOPH–TAVEG Investigators

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

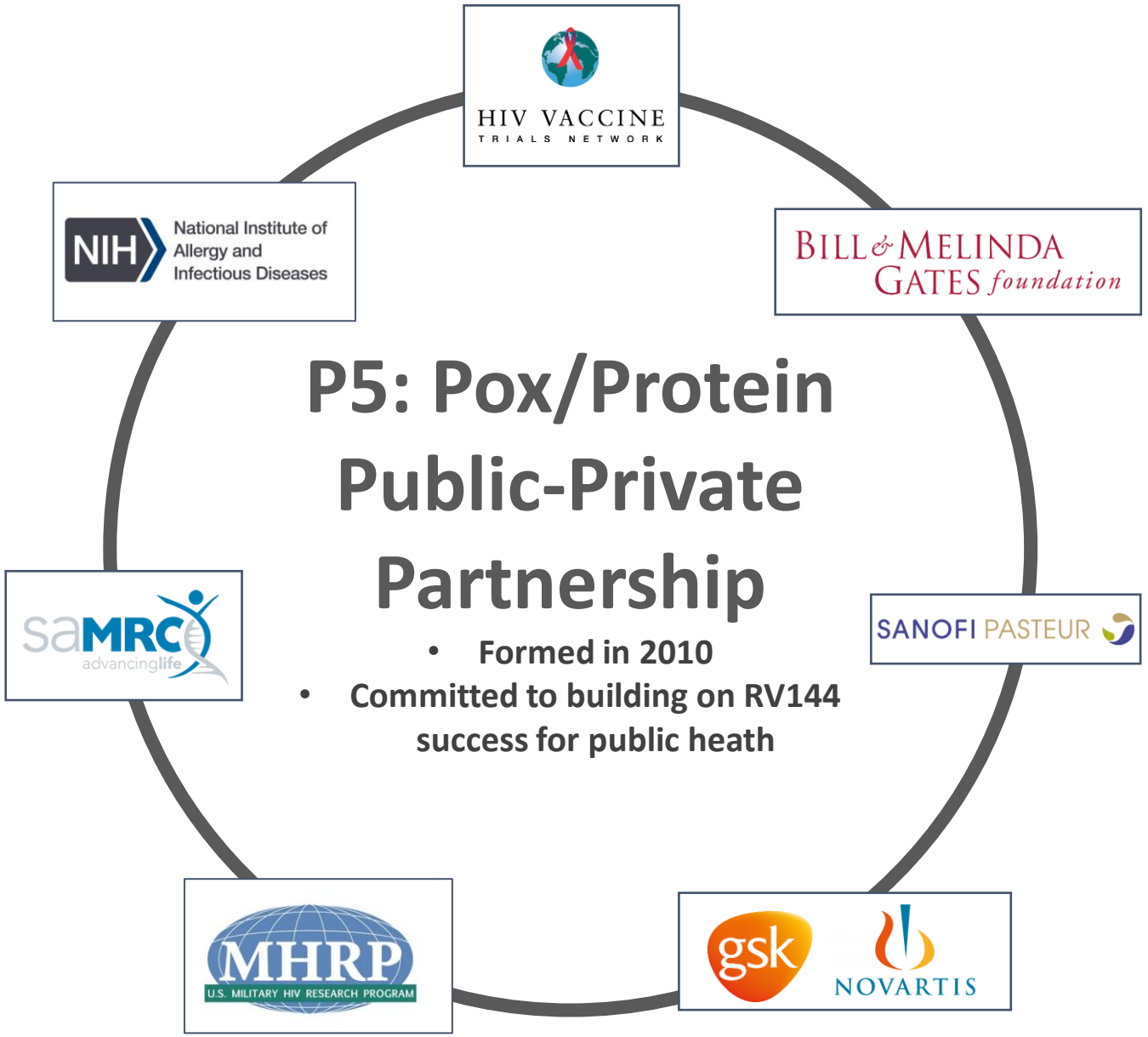


Vaccine efficacy decreases over time

	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

Data from Robb et al, Lancet Infectious Diseases, 2012.

P5 Partnership(2010)



Overarching Goals:

1. Improve vaccine efficacy and durability

- Alternative adjuvant offers the potential to impact magnitude, quality & durability of response → **MF59**
- Additional boosting may increase the level and durability of protection → **additional (12- and 18-mo) boosts**
- Alternative prime (e.g. DNA) and/or boost proteins/adjuvant may improve immunogenicity → **being evaluated in separate (parallel) Phase 1 studies**

2. Verify correlates of vaccine protection

- Immune correlates analysis based on COR in RV144

Phase 1 trials underway

HVTN 107: compare MF59® vs. alum **adjuvants.**

HVTN 120: compare MF59® vs. AS01B **adjuvants.**

HVTN 111: clade C **DNA** prime + subtype C gp120/MF59® boost.

HVTN 108: **DNA-**prime and DNA&protein boost, DNA&protein coadministration, protein prime & boost.

will changing adjuvants change immune response?

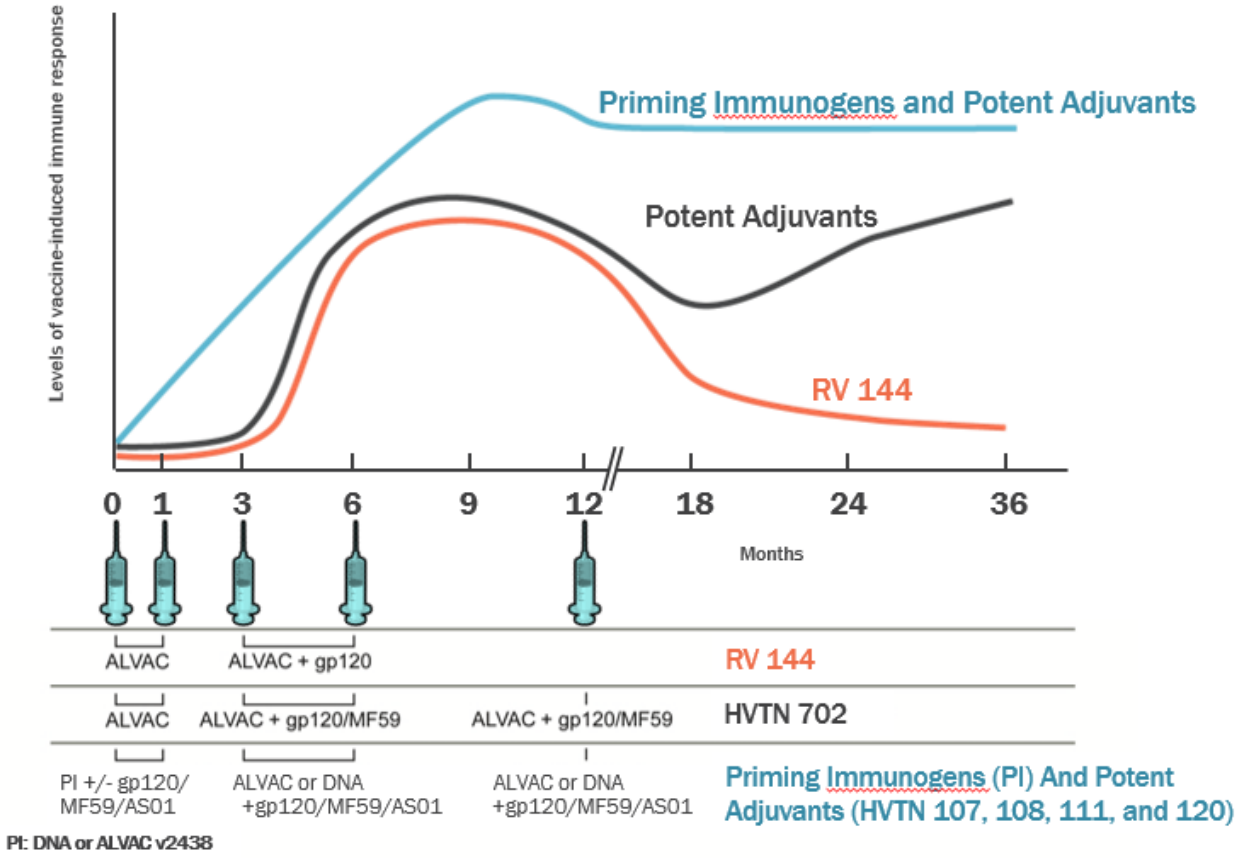
Using DNA instead of a vector?

P5 LEAD Vaccine Products

VACCINE	PRODUCT DESCRIPTION
ALVAC-HIV (vCP2438) Sanofi Pasteur	Canarypox viral vector prime expressing ZM96 gp120 (clade C strain) linked to gp41, and gag and pro (clade B LAI strain)
gp120 proteins + MF59* GSK (previously Novartis)	Bivalent clade C TV1 gp120 Env and clade C 1086 gp120 Env proteins with MF59 adjuvant

*The regulatory file for MF59 is now managed by Seqirus, a CSL company

Improvements in future vaccine efficacy trials



Strategy for the Phase 2b/3 Program

uhambo
A JOURNEY OF HOPE TO PREVENT HIV

HVTN 097

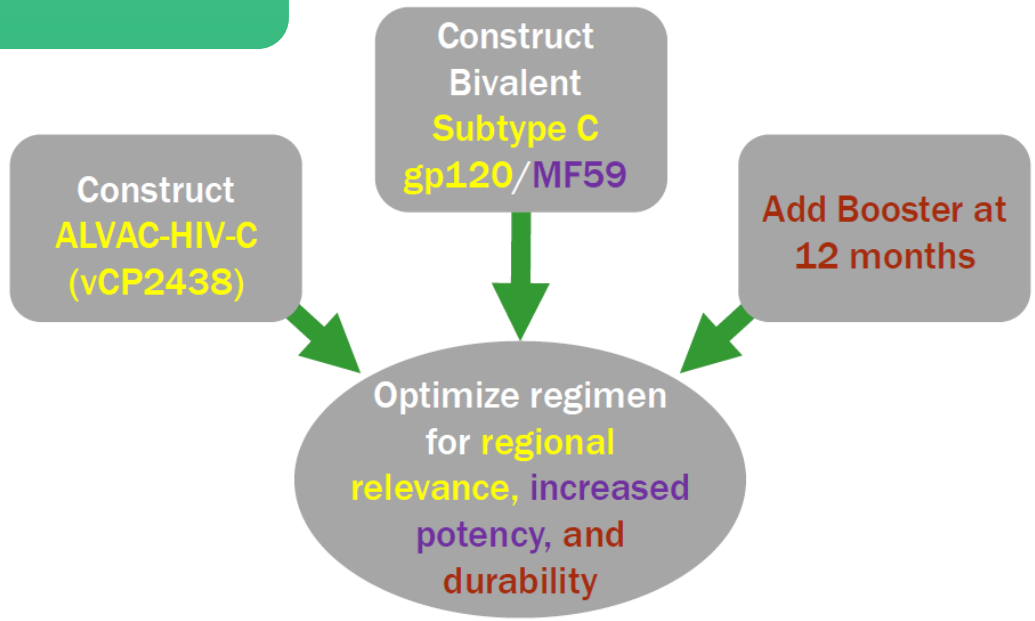
Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand

HVTN 100

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

HVTN 702

A Pivotal Efficacy study assessing efficacy and safety aimed at supporting licensure and discovery of correlates



PRE-SPECIFIED GO/NO-GO CRITERIA FOR HVTN 702:
HVTN 100 must meet all these conditions

Variable Measured at Mo 6.5	Rationale	Go Criteria Threshold (LL of 95% CI)
Env Ab Response Rate (≥2 of 3)	Adequate Ab take to vaccine Env	≥ 75%
Env Ab Magnitude (≥2 of 3)	Non-inferior Ab magnitude vs. RV144	GM ratio (new/RV144) ≥50%*
Env CD4 Response Rate (1 of 1)	Non-inferior CD4 T cell take vs. RV144	Difference within 30%*
Env V1V2 Response Rate (≥1 of 3)	Adequate to predict achieving Est. VE=50% for 2 years if V1V2 Ab is a predictive immune correlate	≥ 56%

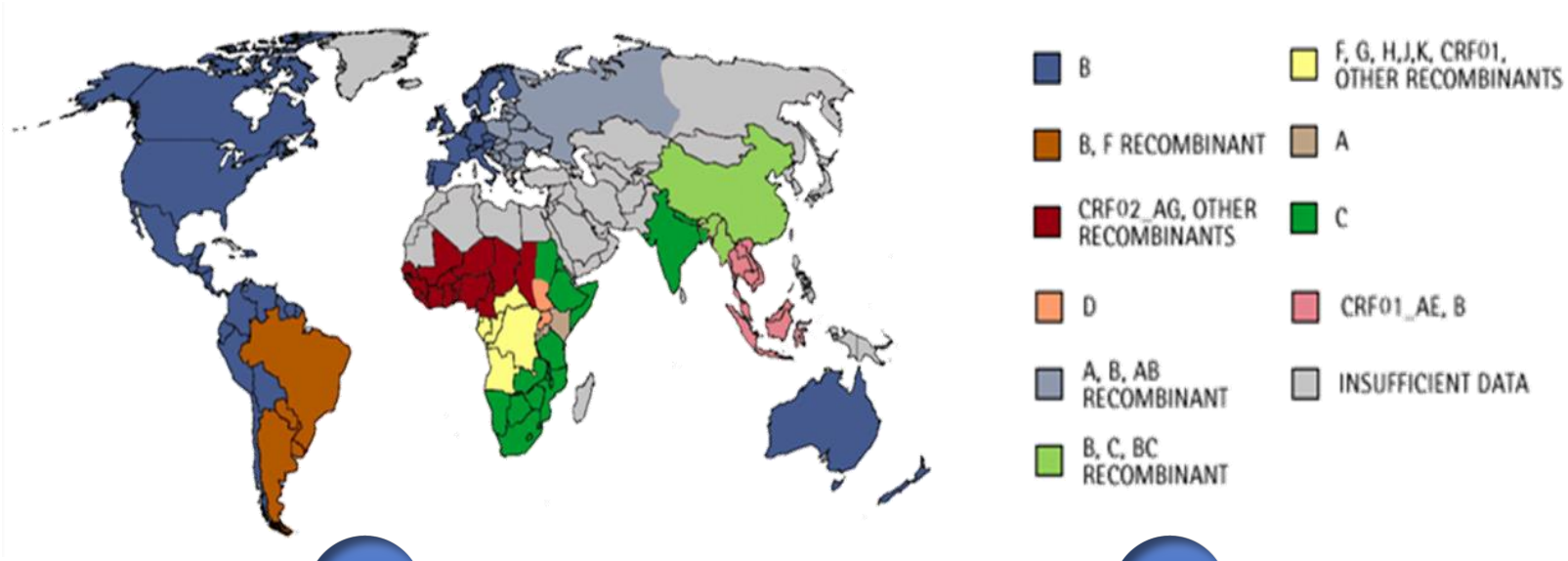
*Non-inferior to RV144 responses based on contemporaneous assessment of clade C vaccinee samples vs. RV144 vaccinee samples by the same lab

Phase 2b/3 study SCHEMA: HVTN 702

Group	N	Primary vaccine regimen				Booster	Booster
		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**						

- 18 month boost predicted to generate a higher average immune response and 14 – 18% higher predicted VE (based on V1V2 response)

Vaccine Aiming at Protection Against all Clades of HIV-1



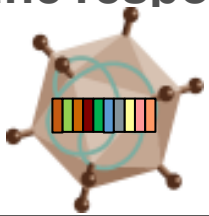
IMBOKODO

HVTN705/HPX2008

Different HIV-1 clades dominate in different geographic regions

1

Vectors that elicit optimal immune responses

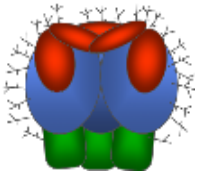


2

Mosaic inserts for global coverage (*gag-pol-env*)

3

Trimeric Env protein(s) for improved immune responses



Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys — Cell

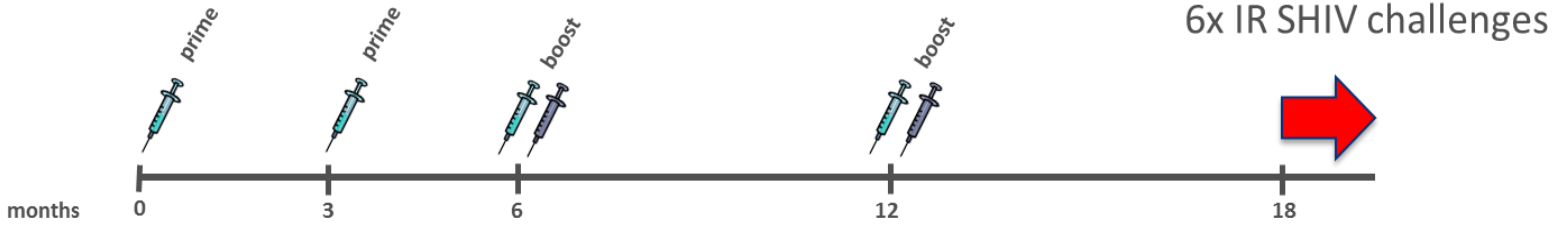
nature medicine

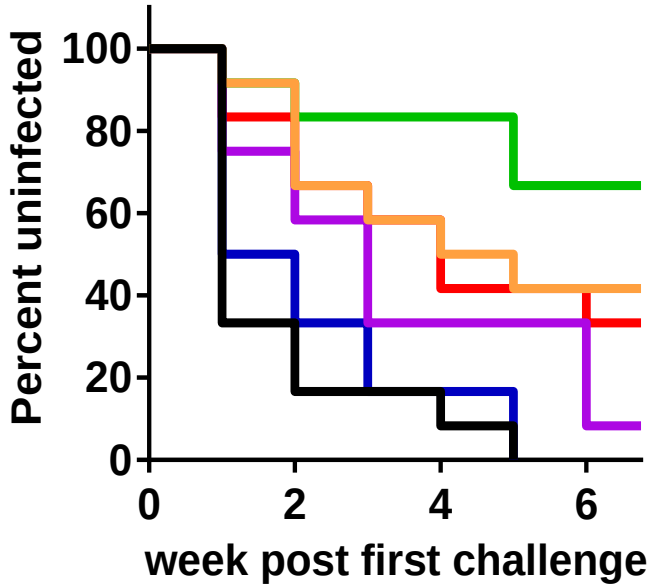
Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H Barouch et al., 2010

The Ad26/Ad26+gp140 HIV Vaccine Regimen Provides Substantial Protection in Non-Human Primates

- The vaccine candidates are very effective in preventing HIV infection in NHP models
  - Protection was confirmed in several studies





Regimen	Per-exposure risk reduction versus sham	Full protection after 6 challenges	N	
Ad prime / Ad boost	35%	0%	12	
Ad prime / gp140 boost	84%*	33%	12	
Ad prime / Ad+gp140 boost	94%*	66%†	12	Lead regimen
Ad prime / MVA boost	71%	8%	12	
Ad prime / MVA+gp140 boost	87%*	42%	12	
Sham	N/A	0%	12	

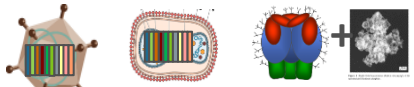
*Statistically significant vs Sham in a Cox proportional hazard model and Log-rank test; †Statistically significant vs Sham in a 2-sided Fisher's exact test

Summary of the studies informing decision to proceed with Imbokodo

NHP → APPROACH wk28 → APPROACH wk52 → TRAVERSE → Start Imbokodo Q4 2017

Ad prime/Ad+gp140 boost showed highest level of protection in NHP

HIV-V-A004/APPROACH



FIH safety of trivalent Ad26.Mos.HIV and Regimen down-selection

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)

Study 13-19	APPROACH	APPROACH	TRAVERSE
	Post 3rd vacc	Post 4th vacc	Post 2nd and 3rd vacc (subset)

Go/No Go criteria towards PoC based on Ad26 prime / Ad26+HD gp140 boost

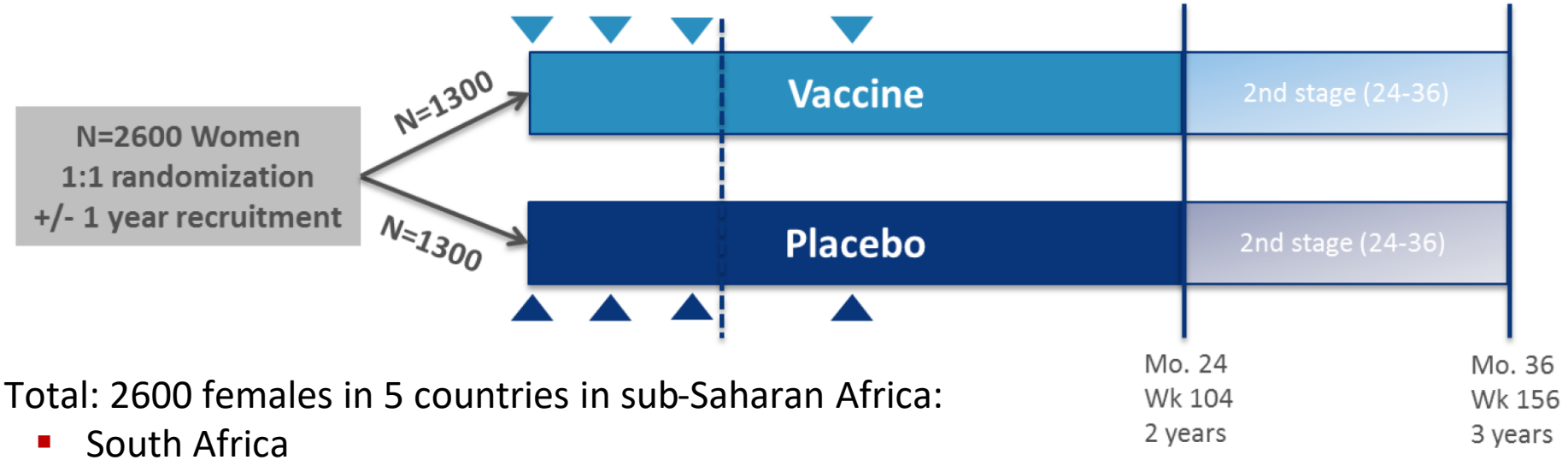
APPROACH Post 3rd

TRAVERSE

- In order to move to a PoC efficacy study, the **ELISA** and **ELISPOT** criteria have to be met
- The **ADCP** criteria, **Magnitudes** and **Env boost** would be considered **supportive**

Criteria	Endpoint	Target (LL of 95% CI)	APPROACH Results		TRAVERSE Results post 3rd	
			Post 3rd	Post 4th		
Humoral	IgG binding responses on clade C Env	≥90% (≥77%)	100% (93%)	100% (92%)	100% (90%)	✓
	ADCP responses to Clade C Env	≥56% (≥40%)	72% (57%)	80% (65%)	97% (85%)	✓
Cellular	Elispot responses to at least one ENV peptide pool	≥50% (≥35%)	77% (62%)	83% (68%)	97% (85%)	✓
Env boost	IgG to clade C Env of Ad/Ad+Env over Ad/Ad	≥1.5 fold	5.5 fold (3.5)	6.9 fold (4.5)	NA	✓
Magnitude	>2.15 log10 cPTE Env ELISPOT OR >3.8 log10 Clade C gp140 ELISA	post 3rd : ≥60% post 4th ≥75%	94%	93%	100%	✓
	Subjects should be above BOTH response thresholds	post 3rd : ≥40% post 4th ≥60%	64%	80%	94%	✓

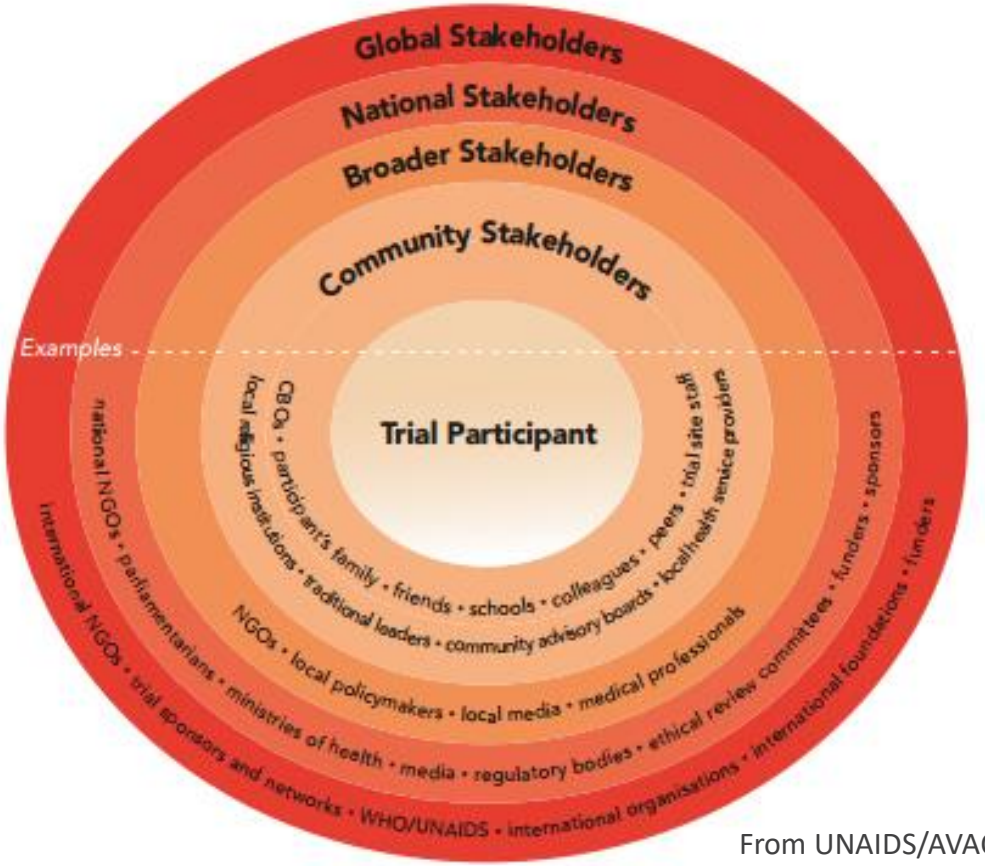
HVTN705/HPX2008
Study Design and Stages



- Total: 2600 females in 5 countries in sub-Saharan Africa:
  - South Africa
  - Mozambique
  - Malawi
  - Zimbabwe
  - Zambia
- Anticipated enrollment: approximately 17 months, 24-36 months of follow-up

- Primary Objective
- To evaluate vaccine efficacy (Months 7-24)
- To evaluate the safety and tolerability of this vaccine regimen

Science and the Community



From UNAIDS/AVAC Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials

Key Recommendations: WHO Consultation Feb 2018

- Regimens are complex and difficult to scale up, but never pre-judge community responses to new interventions – sustain community support
- Consider new models for HIV vaccine protocol design if a partially effective vaccine is licensed
- Decreased funding for prevention research conflicts with regulatory requests for cluster randomised implementation trials prior to licensure – sustainable funding models and harmonisation of regulatory approaches are ideal

Thanks to Helen Rees

While we are making encouraging progress in preventing new HIV infections, the development of a safe and effective HIV vaccine would be the ultimate game-changer.

— NIAID Director Anthony S. Fauci, M.D.

National Institute of Allergy and Infectious Diseases

#HIVVaccineAwarenessDay

Acknowledgements

Thank you to all the protocol team members site investigators, clinic coordinators, Community Engagement and Recruitment teams, pharmacists, lab support staff and PARTICIPANTS

HVTN 705/HPX2008	
Gray, Glenda	Chair
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Buchbinder, Susan	Co-chair
Tomaka, Frank	Co-chair
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Mann, Philipp	Protocol Team Leader and Core Medical Monitor
Swann, Edith	DAIDS Medical Officer
Hutter, Julia	DAIDS Medical Officer
Frahm, Nicole	Laboratory Lead
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HVTN 702	
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Mookho Malahleha	Co-chair
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John Hural	Laboratory Lead
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