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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

UNAIDS
CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

Overview of Microbicide Development

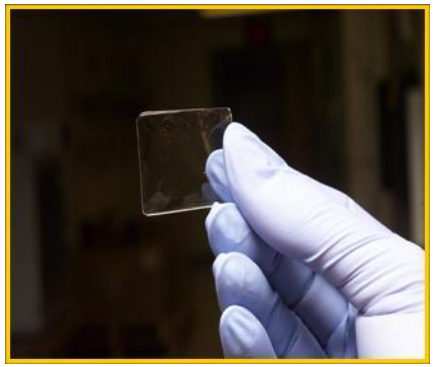
Dr Leila E Mansoor (PhD)
Senior Scientist: CAPRISA

Annual Workshop in Advanced Clinical Care (AWACC)
Durban, South Africa: 06-07 October 2016

A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections including HIV

Vaginal gel applicator

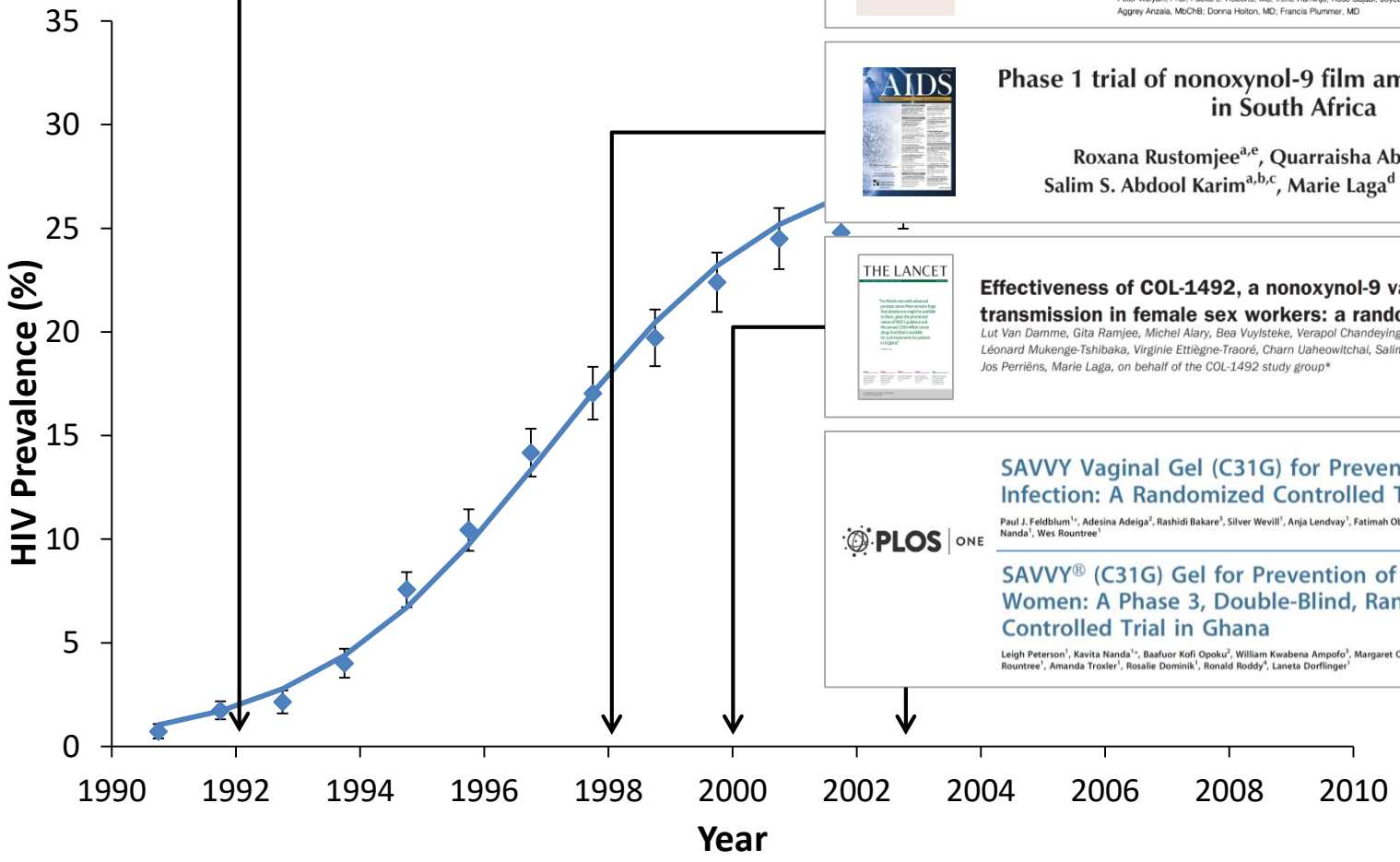
Vaginal ring



Vaginal film

Microbicides containing antiretroviral drugs = Topical PrEP (Pre-exposure prophylaxis)

History of microbicide effectiveness trials: Surfactants



JAMA

Efficacy of Nonoxynol 9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes

Joan Kreiss, MD, MSPH; Elizabeth Ngugi, PhD; King Holmes, MD, PhD; Jeckoniah Ndinya-Achola, MbChB; Peter Waiyaki, PhD; Pacita L. Roberts, MS; Irene Ruminjo; Rose Sajabi; Joyce Kimata; Thomas R. Fleming, PhD; Aggrey Anzala, MbChB; Donna Holton, MD; Francis Plummer, MD

AIDS

Phase 1 trial of nonoxynol-9 film among sex workers in South Africa

Roxana Rustomjee[a,e], Quarraisha Abdool Karim[a], Salim S. Abdool Karim[a,b,c], Marie Laga[d] and Zena Stein[c]

THE LANCET

Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial

*Lut Van Damme, Gita Ramjee, Michel Alary, Bea Vuylsteke, Verapol Chandeying, Helen Rees, Pachara Sirivongrangson, Léonard Mukenge-Tshibaka, Virginie Ettiègne-Traoré, Charn Uaheowitchai, Salim S Abdool Karim, Benoît Mâsse, Jos Perriëns, Marie Laga, on behalf of the COL-1492 study group**

PLOS ONE

SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria

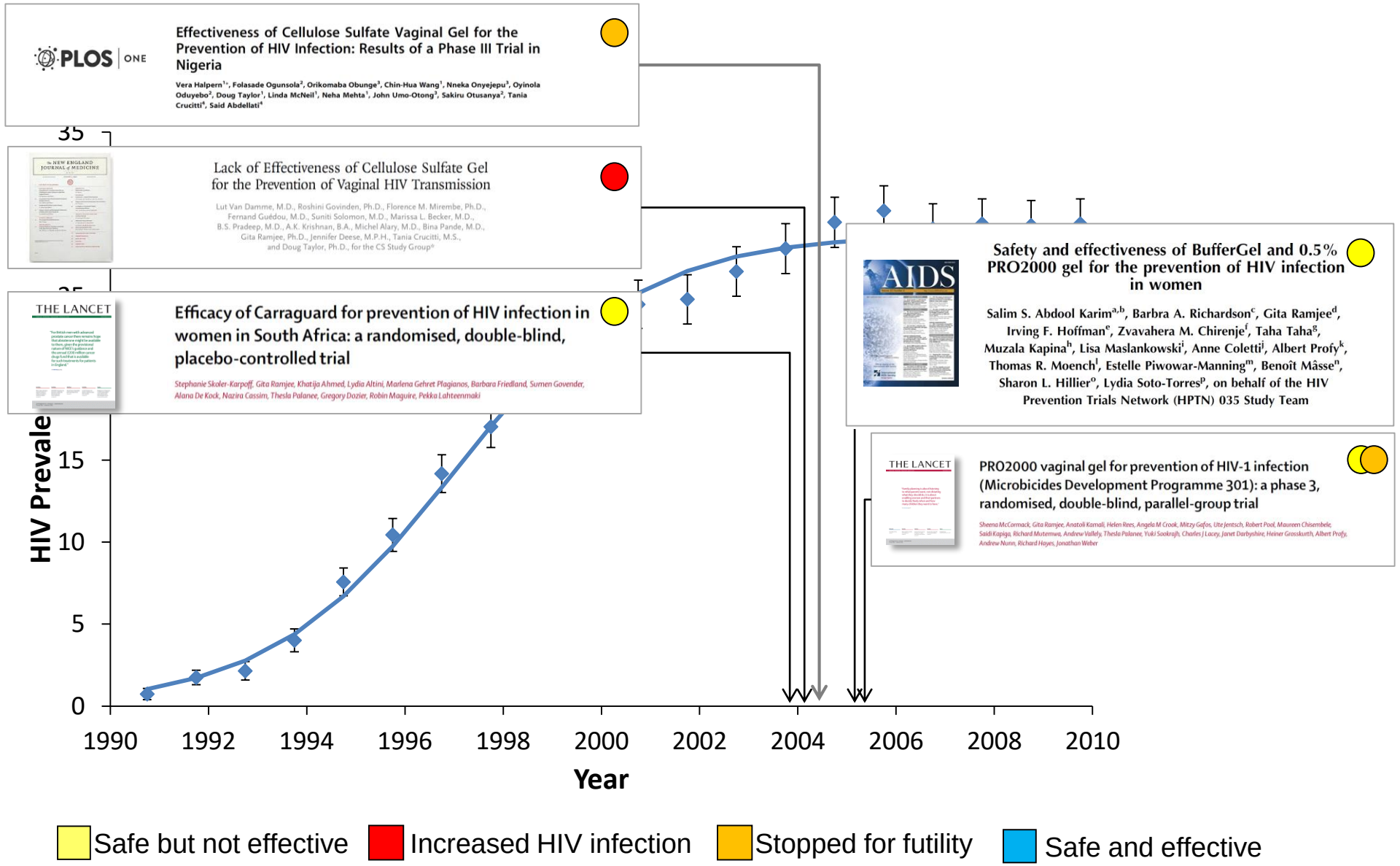
Paul J. Feldblum[1*], Adesina Adeiga[2], Rashidi Bakare[3], Silver Wevill[1], Anja Lendvay[1], Fatimah Obadaki[2], M. Onikepe Olayemi[3], Lily Wang[1], Kavita Nanda[1], Wes Rountree[1]

SAVVY® (C31G) Gel for Prevention of HIV infection in Women: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial in Ghana

Leigh Peterson[1], Kavita Nanda[1*], Baafuor Kofi Opoku[2], William Kwabena Ampofo[3], Margaret Owusu-Amoako[3], Andrew Yiadom Boakye[2], Wes Rountree[1], Amanda Troxler[1], Rosalie Dominik[1], Ronald Roddy[4], Laneta Dorflinger[1]

Safe but not effective | Increased HIV infection | Stopped for futility | Safe and effective

History of microbicide effectiveness trials: Viral entry blockers and buffers



AIDS 2010: Proof-of-concept that an antiretroviral can prevent HIV infection

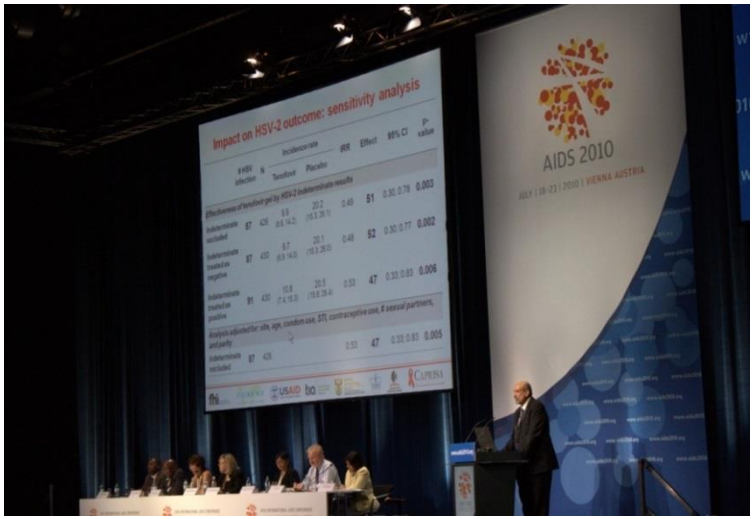
RESEARCH ARTICLES

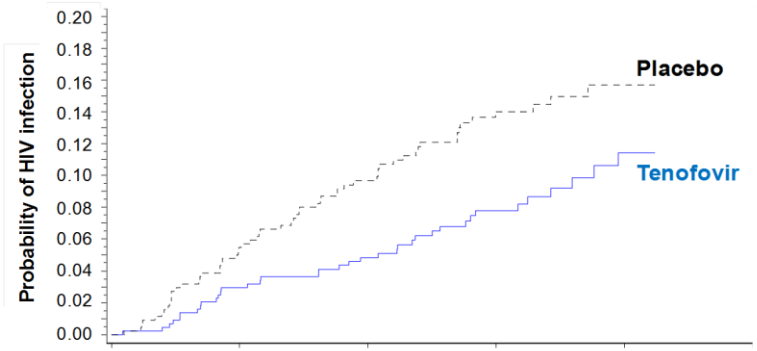
3 SEPTEMBER 2010 VOL 329 SCIENCE

Science
AAAS

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,[1,2]*† Salim S. Abdool Karim,[1,2,3]* Janet A. Frohlich,[1] Anneke C. Grobler,[1] Cheryl Baxter,[1] Leila E. Mansoor,[1] Ayesha B. M. Kharsany,[1] Sengeziwe Sibeko,[1] Koleka P. Mlisana,[1]





Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 9.4	5.6 vs 9.1
Effectiveness (p-value)	**47% (0.069)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

Antiretroviral (PrEP) effectiveness microbicide clinical trials

Phase	Trial name	Candidate(s)	Countries	Number of women	Results
Completed Trials					
IIb	CAPRISA 004 (RCT)	Tenofovir gel (coital)	South Africa	1085	AIDS 2010 39% (6; 60)
	MTN 003 VOICE Trial (RCT)	Tenofovir gel (daily) * and daily oral PrEP (tenofovir or Truvada)	South Africa, Uganda, Zimbabwe	5029	CROI 2013 15% (-21; 40)
III	FACTS 001 (RCT)	Tenofovir gel (coital)	South Africa	2059	CROI 2015 0% (-40, 30)
	MTN 020 ASPIRE Trial (RCT)	Dapivirine vaginal ring (every 4 weeks)	South Africa, Malawi, Uganda, Zimbabwe	2629	CROI 2016 31% (1; 51)
	IPM 027 Ring Study (RCT)	Dapivirine vaginal ring (every 4 weeks)	South Africa, Uganda	1959	CROI 2016 27% (1; 46)

Antiretroviral (PrEP) open label extension (OLE) microbicide trials

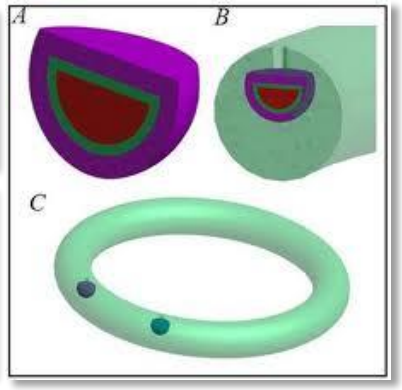
Phase	Trial name	Candidate(s)	Countries	Number of women	Comment
Completed Trials					
IIIb	CAPRISA 008 (OLE RCT)	Tenofovir gel (coital)	South Africa	382	Results presented at AIDS 2016
▪ Adherence was higher (79.9%) in the FP service compared to the trial clinic (73.9%). ▪ Most women (75.3%) expressed a preference for receiving HIV prevention from FP service clinics. ▪ Integration of PrEP into FP services is feasible, acceptable and can achieve good adherence, similar to those achieved in clinical trial settings. ▪ This clinical trial evidence may be helpful to policy makers and health care providers planning on implementing oral PrEP scale-up.					
Ongoing Trials					
IIIb	MTN 025 HOPE Trial (OLE)	Offered Dapivirine vaginal ring (every 4 weeks)	South Africa, Malawi, Uganda, Zimbabwe	± 2000	Initiated: Q3 2016
	IPM 032 DREAM Trial (OLE)	Dapivirine vaginal ring (every 4 weeks)	South Africa, Uganda	± 1400	Initiated: Q3 2016

Microbicide product pipeline

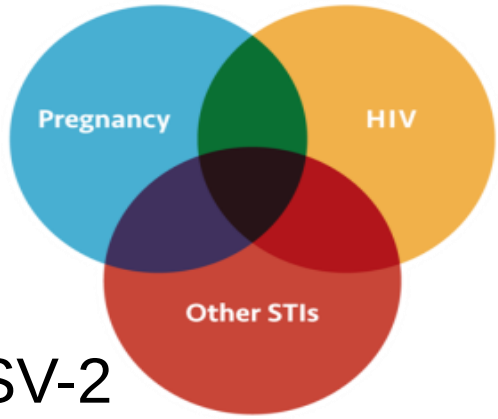
- **Microbicide film formulations:**
  - Multiple ARVs being evaluated in early stage development as vaginal films
    - Dapivirine, tenofovir, maraviroc, IQP-0528, RC-101
  - Phase 1 clinical evaluation of dapivirine film vs dapivirine gel: ongoing

- **Rectal gel formulations:**
  - Multiple ARVs being evaluated in phase I / II trials as rectal gels
    - Tenofovir, maraviroc, dapivirine, UC-781
  - Phase I expanded safety study of 1% rectal tenofovir gel showed product is safe and acceptable. Pericoital use is preferred.

- **Intravaginal ring formulations:**
  - With tenofovir and/or other antiretroviral agents
  - Maraviroc + CMPD 167 silicone matrix IVRs
  - MC1220 (NNRTI) silicone matrix IVR
  - MIV-150 (NNRTI) silicone matrix IVR
  - MIV-160 (NNRTI) EVA matrix IVR
  - Tenofovir 90 day polyurethane IVR
  - Tenofovir silicone “POD” IVR
  - Tenofovir + IQP-0528 polyurethane matrix IVR
  - Tenofovir disoproxyl fumarate polyurethane reservoir IVR



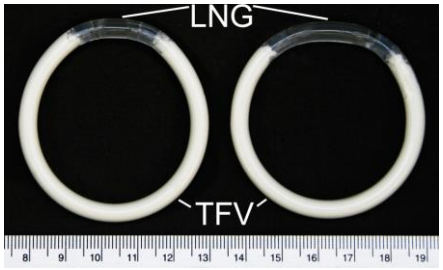
Multi-purpose prevention technologies



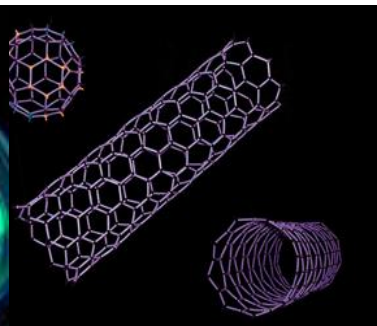
- **A single product, configured for at least two SRH prevention indications**:
  - Contraception
  - Protection against HIV
  - Protection against other STIs e.g. BV, HSV-2
  - Other health benefits
- Greater efficiency in terms of cost, access and delivery of SRH prevention products
- Capitalize on the demand in populations for one product for one indication to achieve uptake and use of a second “product” for a different indication eg. a ring to prevent pregnancy that also prevents HIV

MPT products in development

- **Vaginal Rings**
  - Tenofovir and levonorgestrel (LNG)
  - Dapivirine and levonorgestrel
- **MIV-150 products - Population Council**
  - MIV-150 (NNRTI), zinc acetate, LNG, carrageenan in IVR
    - or gel
  - Combination dependent prevention of HIV, HSV, HPV, pregnancy
- **Barrier microbicides**
  - SILCS diaphragm with microbicide gel
  - SILCS diaphragm releasing a microbicide
- **Other MPT products/technology options**
  - Rectal specific microbicides, implants, lactobacillus GMO,
    - Verselle gel delivery, broad spectrum natural products,
    - non-hormonal contraceptives and vaginal ring/film with monoclonal antibodies.



Courtesy J. Romano



HIV prevention with ARVs (since 2010)

HIV prevention (before 2010)

HIV PREVENTION

Microbicides for women

Abdool Karim Q, Science 2010

Oral pre-exposure prophylaxis

Grant R, NEJM 2010 (MSM)
Baeten J, NEJM 2012 (Couples)
Thigpen M, NEJM 2012 (Heterosexuals)

Dapivirine intravaginal ring

Baeten J, NEJM 2016

Treatment for prevention

Cohen M, NEJM 2011

Male circumcision

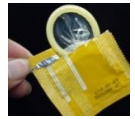
Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007

Treatment of STIs

Grosskurth H, Lancet 2000

Female Condoms

Male Condoms



HIV Counselling &Testing

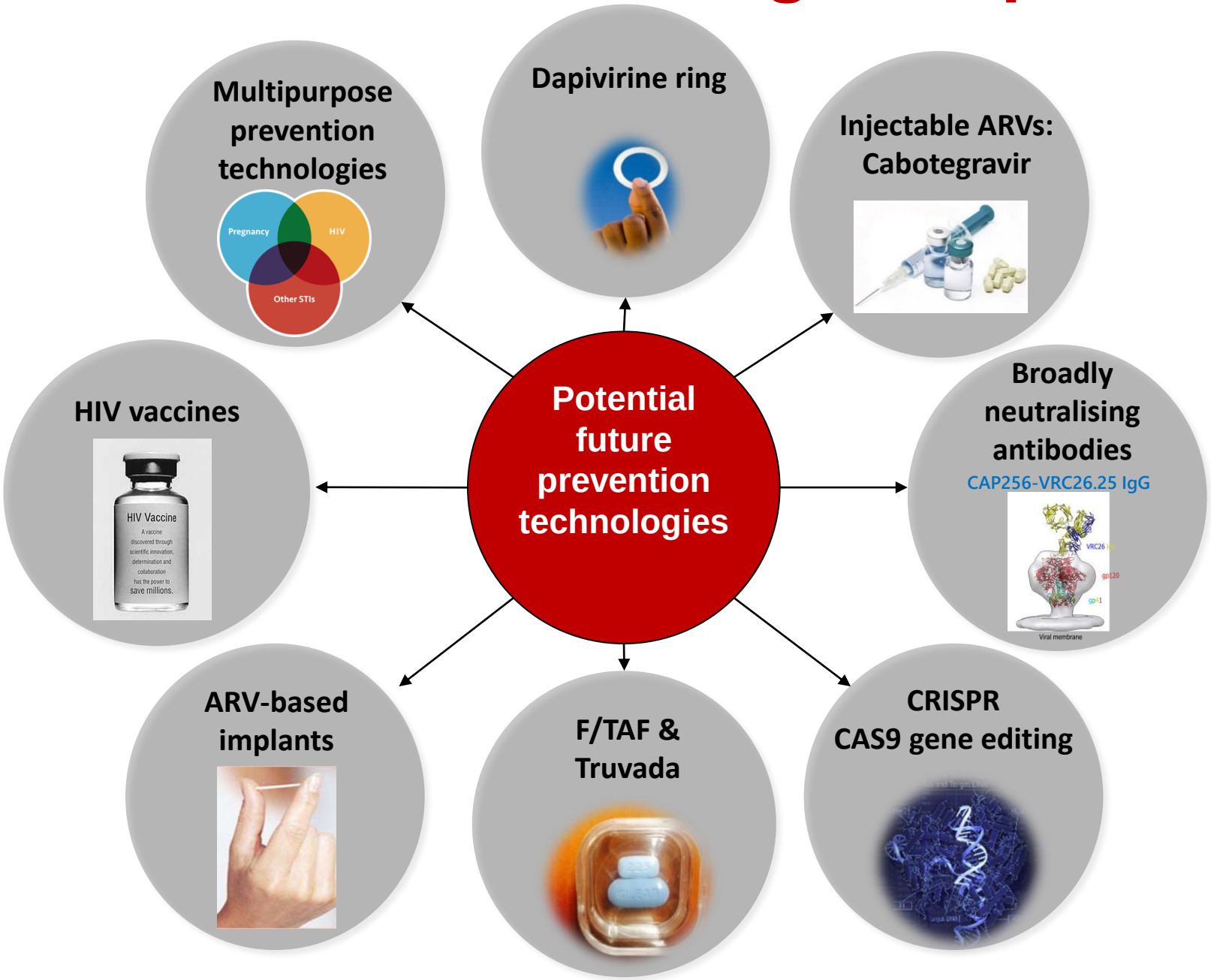
Coates T, Lancet 2000

Behavioural Intervention

- Abstinence
- Be Faithful

Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, Vaccines, etc. have not been included

The world needs a range of options…



Acknowledgements

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

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  - **South African Department of Science and Technology (DST)**
  - **Fogarty International Center, NIH**
  - **Howard Hughes Medical Institute (HHMI)**
  - **Gilead Sciences (Tenofovir API)**
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Quiz Question 1

1. **Name an antiretroviral microbicide product that has shown to prevent HIV infection?**

   A. **Dapivirine intravaginal ring**
   B. **Carraguard vaginal gel**
   C. **Tenofovir vaginal gel**
   D. **Maraviroc vaginal film**
   E. **SAVVY vaginal gel**

Quiz Question 2

2. **Should a range of HIV prevention options become available, which one method would you choose?**

   A. **Long-acting injectable – received every 2 months**
   B. **Vaginal ring – changed every 30 days**
   C. **Implant – changed every 6 months**
   D. **Vaginal gel – used coitally**
   E. **Oral tablet – taken daily**

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Overview of HIV Vaccine Development

AWACC

Dr Kathy T Mngadi

CAPRISA,
School of Laboratory Medicine UKZN

HIV VACCINE TRIALS NETWORK

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 6, 2014

Ending AIDS — Is an HIV Vaccine Necessary?

Anthony S. Fauci, M.D., and Hilary D. Marston, M.D., M.P.H.

In the past decade, according to the 2013 Global Report of the Joint United Nations Program on HIV/AIDS (UNAIDS), the numbers of AIDS-related deaths and new human immunodeficiency virus (HIV) infections have fallen by about one third from their peaks — accomplishments made possible by the accelerated implementation of effective prevention and treatment tools.

Of particular note, the scale-up of antiretroviral therapy (ART) averted 5.4 million deaths in low- and middle-income countries between 1995 and 2012. HIV prevention efforts have expanded from a narrow agenda of providing condoms and clean needles to use of a comprehensive toolkit of preventive interventions that have had a profoundly positive effect on the pandemic. For example, improved approaches to the prevention of mother-to-child transmission have averted the deaths of more than 1 million children worldwide. The rate of male acquisition of HIV can be diminished by two thirds through voluntary medical male circumcision. Postexposure prophylaxis with antiretroviral medication, when adhered to, significantly reduces the risk of HIV infection. Finally,

"Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of non-vaccine prevention methods and the development and deployment of a safe and effective HIV vaccine."

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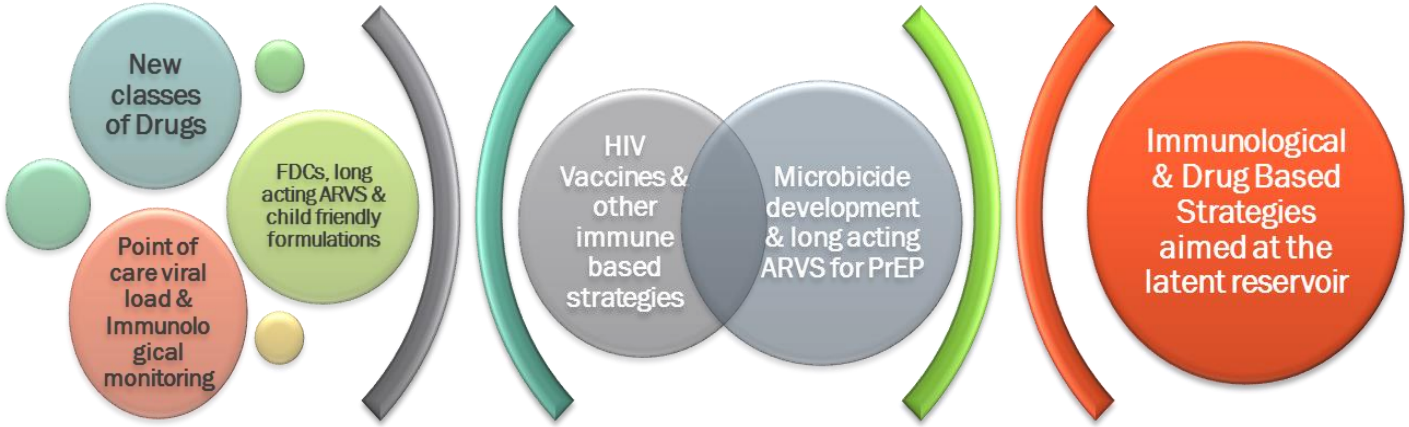
The Space for HIV Vaccines



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

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Quick Quiz

- How many HIV vaccines have been tested for efficacy in South Africa?

A. One
B. Two
C. Five
D. More than 5

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Recent History of HIV Vaccine Development

Study/ location	Vaccine/s	Risk Group/HIV incidence	Result
Vax003 Thailand	AIDSVAX B/E gp120 in alum	IDUs 3.4%	No VE
Vax004 US/Europe	AIDSVAX B/B gp120 in alum	MSM/high risk women 2.6%	No VE
HVTN 502 Americas	MRKAd5 HIV-1 gag/pol/nef	MSM/high risk women 3%	Halted for futility; early transient increased infection in vaccinees
HVTN 503	MRKAd5 HIV-1 gag/pol/nef	Heterosexual men & women 3.7%	No VE; late increased HIV infection in unblended male vaccinees
RV144 Thailand	ALVAC-HIV vCP1521, AIDSVAX B/E rgp120 in alum	Heterosexual men and women with variable risk 0.28%	31.2% VE at 42/12; 60% VE @ 12/12
HVTN 505	DNA, rAD5 (A,B,C)	Circumcised MSM Ad5 neg 1.8%	Halted at interim analysis for futility

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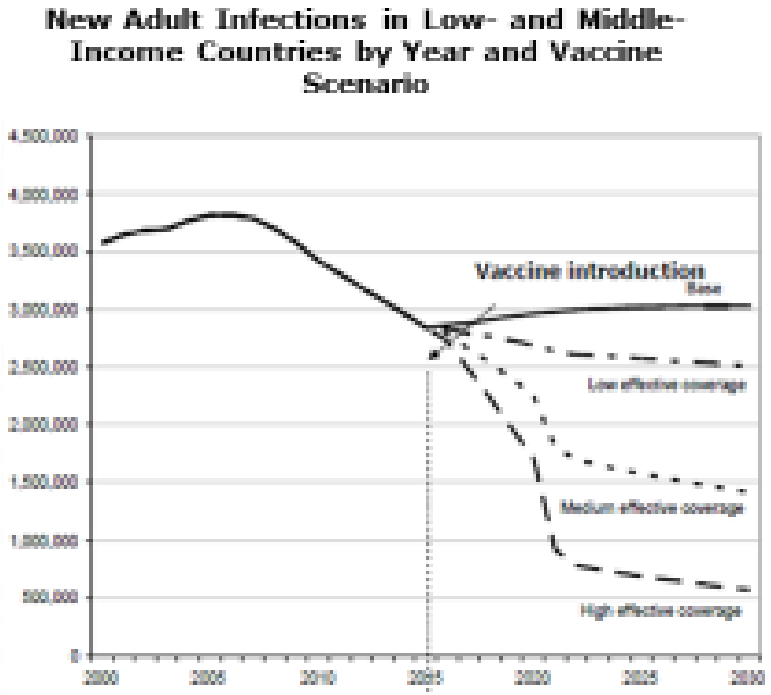
Potential Impact of a Vaccine



	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):1147-1155 (2007)

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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:

Continue to build public-private partnerships critical for success.

1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.

NOVARTIS gsk MHRP HIV VACCINE TRIALS NETWORK BILL & MELINDA GATES foundation National Institute of Allergy and Infectious Diseases SANOFI PASTEUR SAMRC SOUTH AFRICAN MEDICAL RESEARCH COUNCIL

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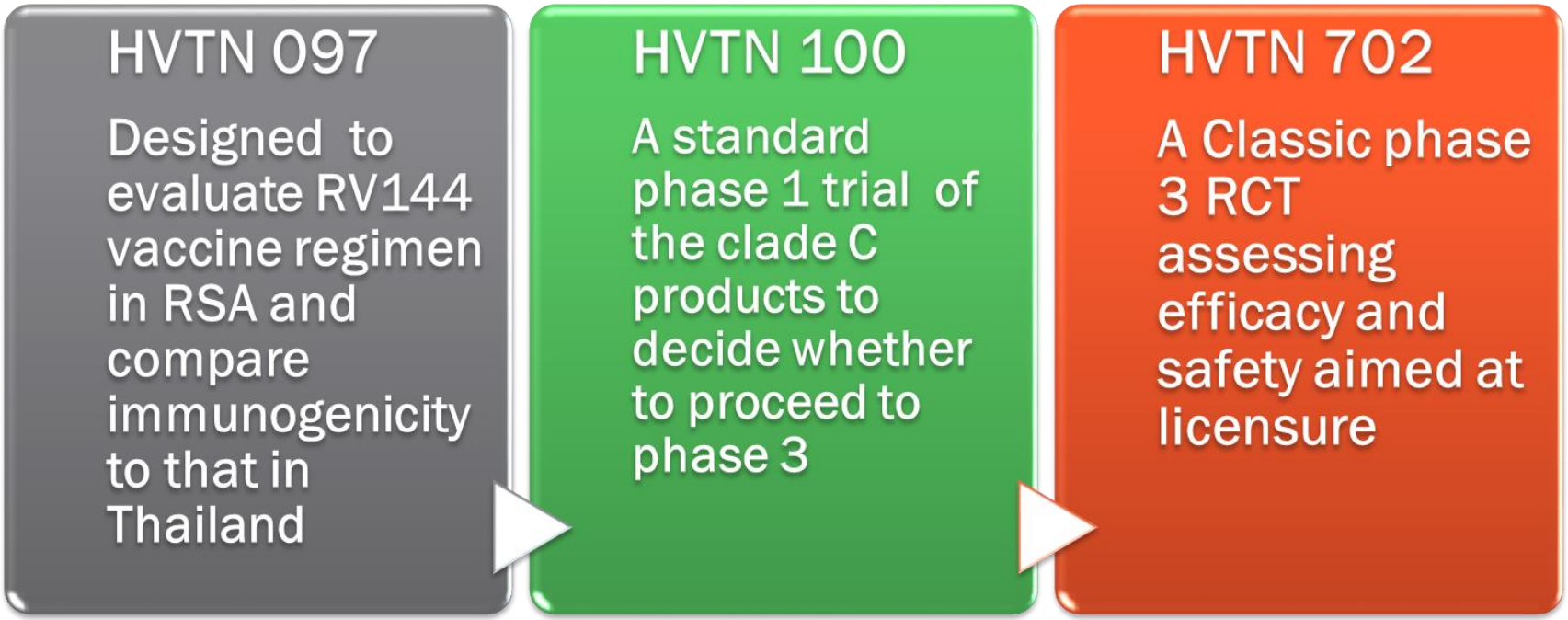
Current Vaccine Development in HVTN



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Mosaic Vaccine Development

Different HIV-1 clades dominate in different geographic regions

Adolescents (11-17 years) /Adults (18-65 years) in endemic countries and populations at risk in Western world

1

Vectors that elicit optimal immune responses

Low seroprevalent Ad26
Ad26.HIV-Gag-Pol
Ad26.HIV-Env

(MVA.HIV-Gag-Pol-Env)

2

Mosaic inserts for global coverage

3

Trimeric env protein for improved humoral immunity

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

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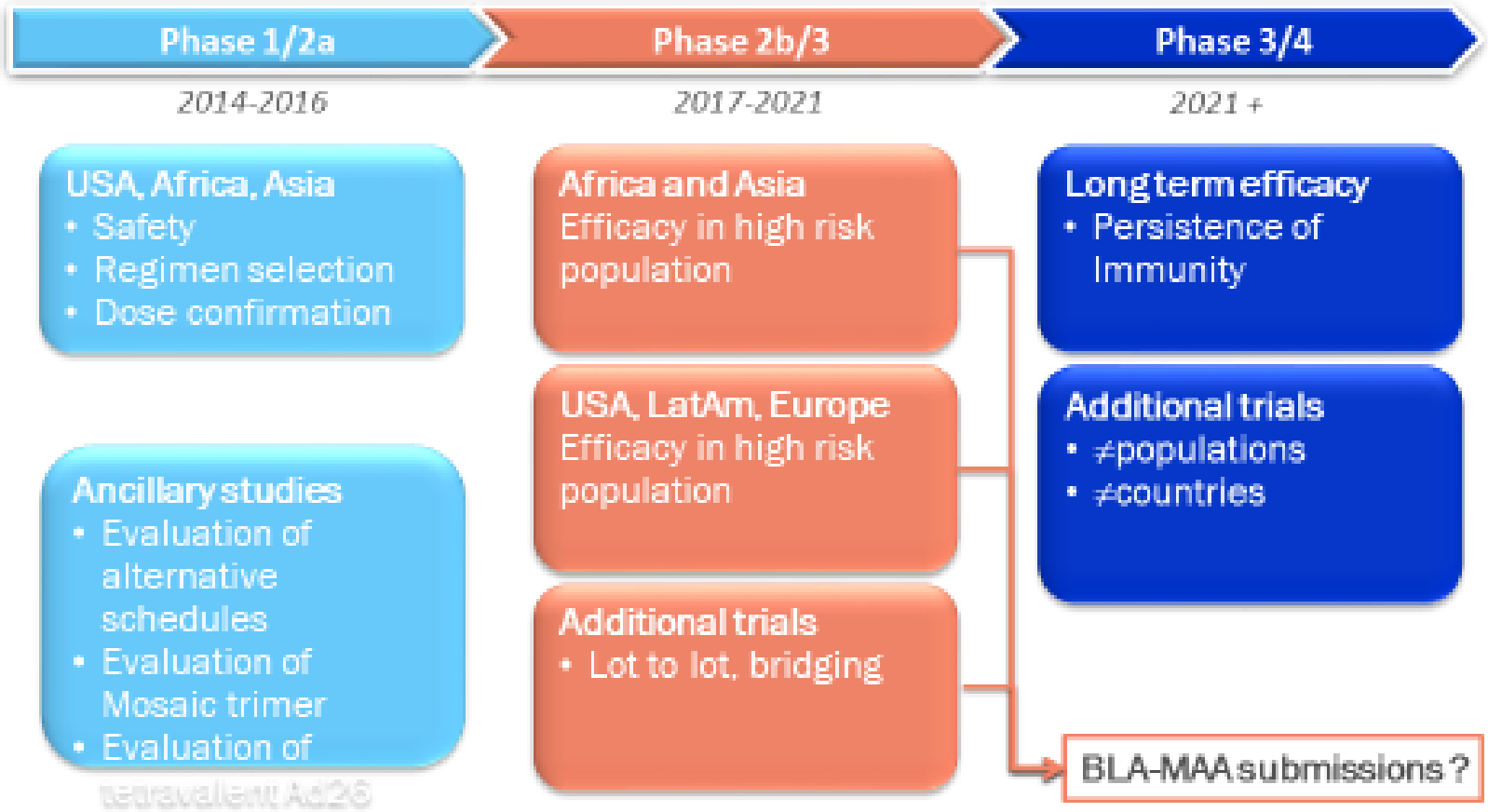
High Level Clinical Development Plan



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Janssen and Collaborators

Janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

BIDMC Harvard

MHRP

IAVI

Ragon

NIAID/HVTN

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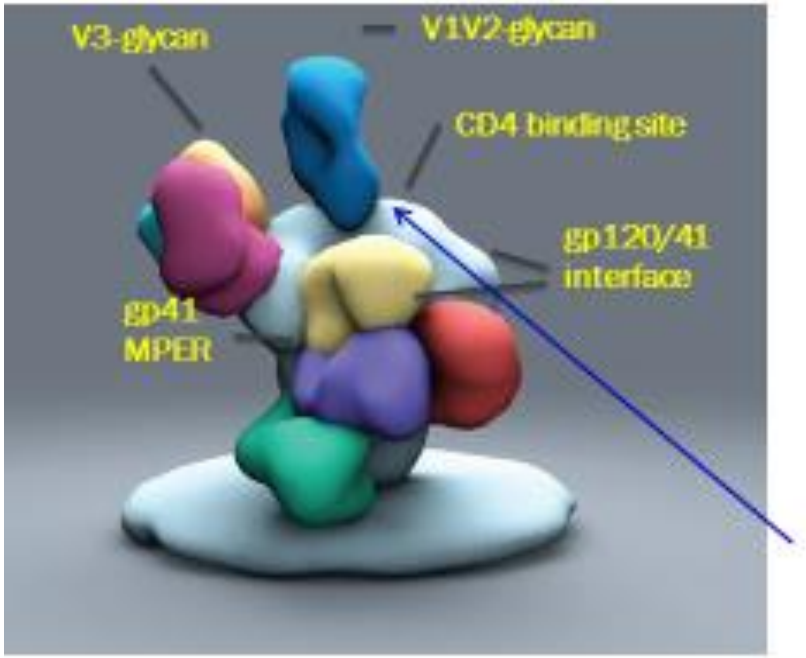
Passive Immunisation



Christina Corbaci, Andrew Ward,

Prevention

- ❑ Can mAb prevent infection in high risk adults (PrEP)
- ❑ Can mAb protect infants during childbirth and breastfeeding
- ❑ What level of antibody is needed (ug/ml) to protect
- ❑ How long will the antibody work (weeks, months?)

Possible that Single mAb could protect

Treatment

- ❑ Does mAb have virologic effect; i.e., lower viremia
- ❑ Used for treatment interruption; e.g., ART sparing
- ❑ Can mAbs impact the viral reservoir; e.g. used with latency reversing agents
- ❑ Can mAbs be used with ART as part of approach to functional cure

Likely want combinations to maximize effect and avoid escape

VRC01 and 3BNC117 in trials
CAP 256 in clinical trials in 2017/18

AMP STUDY

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Quick quiz

- How long did it take to develop a licenced Influenza vaccine?

A. 10 years
B. 20 years
C. 50 years
D. 90 years

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Vaccine Research in Perspective

VACCINE	DISCOVERY OF VIRUS	VACCINE DEVELOPED FOR HUMAN USE	YEARS TO VACCINE
H. Influenzae-B	1892	1985	93
Herpes (HSV-1)	1919	Not available	>90
Pertussis	1906	1926	20
Polio	1909	1954	47
Yellow Fever	1900	1935	35
Influenza	1933	1945	12
Measles	1911	1957	46
Hepatitis A	1973	1995	22
Hepatitis B	1967	1984	17
HPV	1974	2007	33
HIV	1983	Not available	>30

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Vaccine team at ECRS

HIV VACCINES THE WORLD'S BEST HOPE TO END AIDS

Questions??

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