Outline

• From CAPRISA with Love…
• HIV Vaccines past to present
• Broadly neutralizing antibody studies
• CAPRISA’s BnAb programme
• Future Vaccine and BnAb concepts
• Conclusions
CAPRISA’s Leadership and Facilities

Headquarters

Clinical research facilities

DDMRI  eThekwini  Vulindlela  Springfield  Umlazi

www.caprisa.org
CAPRISA’s goal & affiliations

Goal: To undertake *globally relevant & locally responsive* research that contributes to understanding HIV pathogenesis, prevention & epidemiology as well as TB-HIV treatment.

CAPRISA hosts a DSI-NRF Centre of Excellence in HIV Prevention

CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit

CAPRISA hosts a DoH-MRC Special Initiative for HIV Prevention Technology

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy
From CAPRISA with Love…
Joint projects and opportunities

• Improving HIV and STI care with point of care testing
  o Andy Gibbs and Beth Spooner
• Making an impact on TB and MDR-TB
  o Marion Loveday and Nesri Padayatchi
• ENSEMBLE COVID-19 Trial
  o 5 trial sites
• SISONKE Phase 3b JnJ vaccine implementation study
  o National and Regional leadership
Potential impact of an HIV vaccine
1.7 million people became newly infected with HIV in 2018

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

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

<table>
<thead>
<tr>
<th>Vaccine efficacy</th>
<th>HIV infections averted (2027–2070)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>8.4 million</td>
</tr>
<tr>
<td>40%</td>
<td>10.6 million</td>
</tr>
<tr>
<td>50%</td>
<td>12.6 million</td>
</tr>
<tr>
<td>60%</td>
<td>14.5 million</td>
</tr>
<tr>
<td>70%</td>
<td>16.1 million</td>
</tr>
<tr>
<td>80%</td>
<td>17.7 million</td>
</tr>
<tr>
<td>90%</td>
<td>19.0 million</td>
</tr>
</tbody>
</table>

History of HIV Vaccine Research

- 1983: HIV discovered
- 1987: First HIV vaccine clinical trial at the NIH
- 1998: VaxGen initiated Phase 3 trial of AIDSVAX (VAX004) in North America/ Netherlands with 5,400 volunteers followed by AIDSVAX (VAX003) involving 2,500 volunteers in Thailand.
- 2000: NIH forms HVTN
- 2003: The U.S. and Royal Thai governments initiate RV144, a Phase 3 ‘prime-boost’ trial (ALVAC-AIDSVAX B/E)
- 2007: Step and Phambili trials (human Ad5 vector expressing 3 HIV proteins) halted due to safety concerns and later on due to lack of efficacy.
- 2009: RV144 reveals modest preventive effect in humans.
- 2010: The Pox-Protein Public-Private Partnership (P5) formed to build on RV144.

Pox-Protein Public Private Partnership (P5) Studies

- prime-boost regimens (DNA or ALVAC prime +/- protein co-administration)
- protein doses
- adjuvants (MF59, AS01B and alum) or no adjuvant
- delivery methods (needle & syringe versus Biojector®)
HVTN 702: The Journey of Hope

**SOUTH AFRICA**

Biggest HIV vaccine trial halted after early results show it fails to protect against infection

- Started Oct 2016
- Fully enrolled: **N=5407**
- No safety concerns
- Interim analysis: No efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Primary vaccine regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M0</td>
<td>M1</td>
</tr>
<tr>
<td>1</td>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV</td>
</tr>
<tr>
<td>2</td>
<td>2700</td>
<td></td>
<td>Placebo</td>
</tr>
</tbody>
</table>
HVTN 108 Study Design

### Groups

**Priming with DNA**
- **T1**: MF59-100μg protein
- **T2**: AS01B-100μg protein
- **T3**: AS01B-20μg protein

**Co-admin with DNA**
- **T4**: MF59-100μg protein
- **T5**: AS01B-100μg protein
- **T6**: AS01B-20μg protein

**No DNA**
- **T7**: AS01B-20μg protein
- **P1**: Placebo

### Study Products

**DNA-HIV-PT123**: ZM96 env gp140, gag and nef

**Protein**: bivalent subtype C Env gp120 (20 μg or 100 μg each of TV1.C and 1086.C)

**Adjuvant**: MF59 or AS01B

### Comparisons

1. Adjuvants
   - MF59 vs AS01B

2. High vs. low dose Env gp120 protein with AS01B

3. DNA prime-protein boost vs. co-administration vs. protein only (TBD)

### Immunogenicity Analyses

- Months: 0, 1, 3, 6, 6.5, 12

- DNA + gp120/adjuvant

- DNA + Placebo

- DNA + gp120/adjuvant

- OR

- Placebo

- DNA + gp120/adjuvant

- Placebo

- DNA + gp120/adjuvant
Safety Summary

Maximum local reactogenicity events higher in AS01\textsubscript{B} than MF59 regimen

- No clinically significant differences in AEs or SAEs between groups.
- 3.6% of participants discontinued vaccinations due to reactogenicity events.
- Most severe events at US sites.
High HIV-specific IgG response rate and magnitude to clade C Env (prime sequence) across groups at 6.5M

- Higher magnitude responses in AS01\textsubscript{B} group (T2) vs. MF59 group (T1)

Statistically significant difference
CD4+ T-cell response rates and magnitude to Any Env* higher in the AS01B- than MF59-adjuvanted regimens at 6.5M & 12M

Month 6.5

Month 12

Low dose protein elicited higher magnitude responses than high dose.

*ANY ENV defined as max of 1086 gp120, TV1 gp120 and Env ZM96.
HVTN 705/HPX 2008 Mosaic Vaccine Trial
Phase 2b trial of Ad26.Mos4.HIV & alum-adjuvanted clade C gp140 to prevent HIV in African women

Protocol status
- First enrollment: Nov 2017
- Fully enrolled: N=2637
- DSMB asked to continue
- Phase 3 study (Mosaico) started among MSM and transgender in Americas

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Prime</th>
<th>M3</th>
<th>Boost</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M0</td>
<td>M3</td>
<td>M6</td>
</tr>
<tr>
<td>2</td>
<td>1300</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vectors that elicit optimal immune responses
Mosaic Inserts for global coverage (Gag-Pol-Env)
Trimeric gp140 env proteins for improved humoral immunity

HVTN 705/HPX2008 will be using Clade C gp140
**CAPRISA HIV vaccine & broadly neutralizing antibody research**

<table>
<thead>
<tr>
<th>Year</th>
<th>Efficacy Trials</th>
<th>Concepts</th>
<th>BnAb Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>HVTN 702 (Uhambo - Phase 3) ALVAC/ bivalent C-gp120/ MF59 N=354; N Naicker (PI)</td>
<td>HVTN108 (Phase 1/2a) N=16; N Garrett (Chair) DNA and gp120 with MF59 or AS01B</td>
<td>CAPRISA 012 Trials (012A, B and C) (Phase 1/2); CAP256V2LS +/- VRC07LS or PGT121 SS Abdool Karim (PI); S Mahomed (PD)</td>
</tr>
<tr>
<td>2020</td>
<td>HVTN 705 (Imbokodo - Phase 2b) Ad26/ MVA mosaic N=60; N Garrett (PI)</td>
<td>HVTN107 (Phase 1/2a) N=20; N Naicker (PI) ALVAC/ bivalent gp120 alone, with MF59 or alum</td>
<td>AMP Study (HVTN703, HPTN081) (Phase 2b) VRC01 mAb; N=207; H Dawood, N Garrett (PIs)</td>
</tr>
<tr>
<td>2021</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**More than 3000 participant visits conducted in 2020!**

In Collaboration with the HIV Vaccine Trial Network (HVTN), National Institute of Health, US, and the EDCTP
Antibody Mediated Prevention Phase 2b trials

- Enrollment and follow up complete (Total N=1,900, CAPRISA N=207)
- Primary Outcomes
  - Safety & Tolerability of VRC01 infusion
  - Efficacy to prevent HIV infection

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>HVTN 704/HPTN 085</th>
<th>HVTN 703/HPTN 081</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSM &amp; TG in the Americas</td>
<td>Women in sub-Saharan Africa</td>
<td></td>
</tr>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>633</td>
<td>1533</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>633</td>
<td>1533</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>634</td>
<td>1534</td>
</tr>
<tr>
<td>Total</td>
<td>2700</td>
<td>1900</td>
<td>4600</td>
</tr>
</tbody>
</table>

10 infusions total - given every 8 weeks
Study duration: ~22 months
In Vitro Sensitivity to VRC01 Predicts Efficacy

- Consistent evidence that VRC01 conferred prevention efficacy
  - Against viruses measured to be neutralization sensitive
  - Not against viruses measured to be neutralization resistant

- Monotone pattern with VRC01 protection wearing off with IC50, IC80, reciprocal of instantaneous inhibitory potential (IIP)
- Thus, the TZM-bl target cell assay discriminates prevention efficacy
Estimated Prevention Efficacy Over Time by IC80 Efficacy Declines with IC80 Category (Pooled Trials)

A

Pooled VRC01 vs. Control

<table>
<thead>
<tr>
<th>Weeks Since Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>-50</td>
</tr>
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</table>

B

<table>
<thead>
<tr>
<th>Pre-Specified IC80 Category</th>
<th>Treatment Arm</th>
<th>No. of HIV-1 Inf.</th>
<th>No. of Person-Years</th>
<th>Rate per 100 Person-Years</th>
<th>PE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 μg/ml</td>
<td>Control</td>
<td>19</td>
<td>2203</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>9</td>
<td>4427</td>
<td>0.20</td>
<td>75.4 (45.5, 88.9)</td>
</tr>
<tr>
<td>1-3 μg/ml</td>
<td>Control</td>
<td>10</td>
<td>2203</td>
<td>0.43</td>
<td>4.2 (−108.7, 56.0)</td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>19</td>
<td>4427</td>
<td>0.43</td>
<td>4.2 (−108.7, 56.0)</td>
</tr>
<tr>
<td>&gt;3 μg/ml</td>
<td>Control</td>
<td>35</td>
<td>2203</td>
<td>1.59</td>
<td>3.3 (−48.0, 36.8)</td>
</tr>
<tr>
<td></td>
<td>VRC01 Pooled</td>
<td>70</td>
<td>4427</td>
<td>1.58</td>
<td>3.3 (−48.0, 36.8)</td>
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</tbody>
</table>
CAP256V2LS: A long journey of discovery

Establishing cohort
- Establishing a Cohort at High Risk of HIV Infection in South Africa: Challenges and Experiences of the CAPRISA 002 Acute Infection Study

Identification of CAP256
- Evolution of an HIV glycan–dependent broadly neutralizing antibody epitope through immune escape
- Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies

Pre-clinical efficacy studies
- Broadly neutralizing antibodies targeting the HIV-1 envelope V2 apex confer protection against a Chimeric SHIV challenge

Isolation of CAP256-VRC26.25
- New Member of the V1V2-Directed CAP256-VRC26 Lineage That Shows Increased Breadth and Exceptional Potency

GMP production
- CAPRISA 012 Ph I/II SAMBA trial

2004
- PID: 256 enrolled

2006
- PID: 256 tested HIV+

2008
- PID: 256 Initiated on ART

2010
- Identification of bNAbs

2012
- Potent bNAbs isolated from CAP256
- Cloning and development of CAP256-VRC26.25LS in partnership with NIH/VRC

2014
- Cloning and development of CAP256-VRC26.25LS in partnership with NIH/VRC

2016
- CAP012 passive immunisation trial of CAP256-VRC26.25LS, VRC07 and PGT121

Clinic
- Laboratory
- Clinic
CAPRISA bnAb Programme

SAMBA: a sequence of mAb trials for HIV prevention

**CAPRISA 012A**: Phase I study to assess safety and PK of VRC07-523LS and PGT121 administered subcutaneously in HIV-negative women

**CAPRISA 012B**: Phase I study to assess safety and PK of CAP256V2LS administered subcutaneously and intravenously in HIV-negative and HIV positive women

**CAPRISA 012C**: Phase II study to assess extended safety and PK of subcutaneously-administered CAP256V2LS in combination with VRC07-523LS and/or CAP256V2LS in combination PGT121 in HIV-negative women
Assessing the safety and pharmacokinetics of the monoclonal antibodies, VRC07-523LS and PGT121 in HIV negative women in South Africa: study protocol for the CAPRISA 012A randomised controlled phase I trial


Main objectives:
- Evaluate safety of VRC07-523LS & PGT121 subcut
- Characterize PK profile of Abs
- Assess the acceptability of SC injections
- Concentration & functional activity of Abs in plasma & genital samples

Study progress:
- Study fully enrolled
- 100% Retention
- DSMB: No safety concerns
- Preliminary PK analysis completed
- Expected study end July 2020

<table>
<thead>
<tr>
<th>Group</th>
<th>Regimen</th>
<th>N</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VRC07-523LS / Placebo</td>
<td>4/1</td>
<td>5 mg/kg SC one dose</td>
</tr>
<tr>
<td>2</td>
<td>VRC07-523LS / Placebo</td>
<td>4/1</td>
<td>10 mg/kg SC one dose</td>
</tr>
<tr>
<td>3</td>
<td>VRC07-523LS / Placebo</td>
<td>4/1</td>
<td>5 mg/kg SC with one repeat dose at 12 weeks</td>
</tr>
<tr>
<td>4</td>
<td>VRC07-523LS / Placebo</td>
<td>4/1</td>
<td>10 mg/kg SC with one repeat dose at 24 weeks</td>
</tr>
<tr>
<td>5</td>
<td>PGT121 / Placebo</td>
<td>4/1</td>
<td>3mg/kg SC one dose</td>
</tr>
<tr>
<td>6</td>
<td>PGT121 / Placebo</td>
<td>4/1</td>
<td>3mg/kg SC with one repeat dose at 12 weeks</td>
</tr>
<tr>
<td>7</td>
<td>VRC07-523LS + PGT121 / Placebo</td>
<td>4/1</td>
<td>5 mg/kg SC + 3mg/kg SC one dose</td>
</tr>
</tbody>
</table>
# CAPRISA 012B trial

**First-in-human CAP256V2LS antibody trial**

## Aim:
- Determine safety, tolerability and PK of mAb CAP256V2LS given IV and SC to HIV positive & negative women in SA

## Study update:
- Groups 1a to 3b fully enrolled
- Acceptable safety profile
- **CAPRISA 012C** with CAP256V2LS and VRC07-523LS expected to start in June 2021

## Groups

### Group 1: Dose escalation of IV administration of CAP256V2LS

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Regimen</th>
<th>N=66</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>HIV negative</td>
<td>CAP256V2LS</td>
<td>4</td>
<td>5 mg/kg IV one dose</td>
</tr>
<tr>
<td>1b</td>
<td>HIV negative</td>
<td>CAP256V2LS</td>
<td>4</td>
<td>10 mg/kg IV one dose</td>
</tr>
<tr>
<td>1c</td>
<td>HIV positive</td>
<td>CAP256V2LS</td>
<td>4/2</td>
<td>20 mg/kg IV one dose</td>
</tr>
<tr>
<td>1d</td>
<td>HIV positive</td>
<td>CAP256V2LS</td>
<td>4/4</td>
<td>20 mg/kg IV one dose</td>
</tr>
</tbody>
</table>

### Group 2: Dose escalation of SC administration of CAP256V2LS

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Regimen</th>
<th>N=66</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>HIV negative</td>
<td>CAP256V2LS</td>
<td>4</td>
<td>5 mg/kg SC one dose</td>
</tr>
<tr>
<td>2b</td>
<td>HIV negative</td>
<td>CAP256V2LS*</td>
<td>4</td>
<td>5 mg/kg SC one dose</td>
</tr>
<tr>
<td>2c</td>
<td>HIV negative</td>
<td>CAP256V2LS*</td>
<td>4</td>
<td>10 mg/kg SC one dose</td>
</tr>
<tr>
<td>2d</td>
<td>HIV negative</td>
<td>CAP256V2LS*</td>
<td>4</td>
<td>10 mg/kg SC with one repeat dose at 16/24 weeks*</td>
</tr>
<tr>
<td>2e</td>
<td>HIV negative</td>
<td>CAP256V2LS*</td>
<td>4</td>
<td>20 mg/kg SC one dose</td>
</tr>
<tr>
<td>2f</td>
<td>HIV negative</td>
<td>CAP256V2LS*</td>
<td>4</td>
<td>20 mg/kg SC with one repeat dose at 16/24 weeks*</td>
</tr>
</tbody>
</table>

### Group 3: Dose escalation of the two antibody combinations

<table>
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<tr>
<th>Group</th>
<th>Participants</th>
<th>Regimen</th>
<th>N=66</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>HIV negative</td>
<td>CAP256V2LS* + VRC07-523LS*</td>
<td>4/1</td>
<td>10 mg/kg SC / 10 mg/kg SC one dose</td>
</tr>
<tr>
<td>3b</td>
<td>HIV negative</td>
<td>CAP256V2LS* + VRC07-523LS*</td>
<td>4/1</td>
<td>20 mg/kg SC / 20 mg/kg SC one dose</td>
</tr>
<tr>
<td>3c</td>
<td>HIV negative</td>
<td>CAP256V2LS* + PGT121*</td>
<td>4/1</td>
<td>20 mg/kg SC / 5 mg/kg SC one dose</td>
</tr>
</tbody>
</table>

### Group 4: Three antibody combination

<table>
<thead>
<tr>
<th>Group</th>
<th>Participants</th>
<th>Regimen</th>
<th>N=66</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>HIV negative</td>
<td>CAP256V2LS* + PGT121* + VRC07-523LS</td>
<td>4/1</td>
<td>20 mg/kg SC / 5 mg/kg SC / 20mg/kg SC one dose</td>
</tr>
</tbody>
</table>

* Higher doses will be administered with ENHANZETM dispersing agent by Halozyme
HIV–specific neutralizing antibody targets with bnAb candidates

The Journal of Infectious Diseases, Volume 223, Issue 3, 1 February 2021, Pages 370–380
Intra-host evolution of BnAbs

Sequential HIV vaccination strategies

CoVID-19 learned from HIV Science, can HIV field now learn from success of COVID-19 vaccines?

**HIV Vaccine Approaches in COVID-19 Vaccine Development**

Vaccine approaches originally developed for HIV vaccine design are at the forefront of COVID-19 vaccine development. There are over 100 vaccine candidates in development against COVID-19, many of the vaccines and approaches in human trials have roots in HIV research. Below are some of the approaches moving forward in human trials.

**Antibodies**

The AMP trials, with results due in October, are now testing infusions of an HIV-neutralizing antibody every two months as a prevention method. Antibody approaches like this, including convalescent plasma, and neutralizing antibody infusions and injections, are being developed for both prevention and treatment of COVID-19.

**Chimp adenovirus vector**

A vaccine developed at Oxford University from a virus that infects chimpanzees is being developed for therapeutic and preventive clinical trials against HIV and a number of other diseases. That chimpanzee virus platform has been adapted as a COVID-19 vaccine candidate and is now in clinical trials.

**DNA**

HIV vaccine approaches using a DNA platform are now being explored for COVID-19. Inovio has begun testing its DNA vaccine platform, originally developed for HIV vaccines, for use as a COVID-19 vaccine.

**Human adenovirus vectors**

Multiple adenovirus subtypes have been developed as HIV vaccine candidates, most notably, Janssen’s Ad26 candidate, which is now in two large HIV vaccine efficacy trials. Janssen is now adapting its Ad26 as a COVID-19 vaccine. There are also several other adenovirus-based COVID-19 vaccines in development, such as the Ad5 adenovirus being tested by a Chinese military.

**mRNA**

Messenger RNA (mRNA) vaccines, potentially more potent than DNA platforms, have been developed as HIV vaccine candidates. Now, several mRNA vaccine candidates against COVID-19 are in clinical trials sponsored by Moderna, CureVac and Pfizer/BioNTech.
Unique Challenges to HIV Vaccines

- HIV attacks CD4+ T-cells thereby weakening the conductors of the immune system in clearing the infection
- Continuously mutates and recombines resulting in an extensive diversity of viral strains
- No good model of natural clearance of infection prevents discovery of correlates of protection
- This is the era of new vaccine concepts (see example of mRNA vaccines for the prevention of COVID-19)
Conclusions

• CAPRISA likes the MRC and are looking forward to working with you over the coming years.

• HIV Vaccine research has had its ups and downs but we are eagerly awaiting the Ad26 mosaic vaccine results.

• Everyone talks about broadly neutralizing antibodies, but combinations will be required to prevent infection.

• We may require sequential vaccinations to shepherd the immune system to make them.
Acknowledgements

Investigators

• Nivashnee Naicker and Sharana Mahomed
• Salim & Quarraisha Abdool Karim and the CAPRISA study teams
• Lynn Morris, Penny Moore and the Neutralizing Antibody team (NICD)
• Carolyn Williamson, Melissa-Rose Abrahams & Viral Diversity team (UCT)
• Wendy Burgers and the Cellular Immunity teams (UCT)
• Jo-Ann Passmore and the Mucosal Immunology team (CAPRISA, UCT)
• Natasha Samsunder and the Laboratory and Support teams (CAPRISA)

Vaccine & Pathogenesis Team

Contact: nigel.garrett@caprisa.org