UPDATE: HIV VACCINE TRIALS IN SOUTH AFRICA

Dr Fatima Laher, Director, Vaccines Research Centre

vaccines, rings, microbicides
**UNAIDS. Data 2018**

**DESPITE GREAT EFFORTS SO FAR, HIV IS NOT OVER**

<table>
<thead>
<tr>
<th></th>
<th>2000</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>New HIV infections</td>
<td>3.2 million</td>
<td>1.8 million</td>
</tr>
<tr>
<td>People taking HAART</td>
<td>&gt;1 million</td>
<td>21.7 million</td>
</tr>
<tr>
<td>AIDS related deaths</td>
<td>1.5 million</td>
<td>940 000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36.9 million living with HIV</td>
</tr>
</tbody>
</table>
EVEN PARTIALLY EFFICACIOUS HIV VACCINES WITH LIMITED COVERAGE COULD AVERT MILLIONS OF INFECTIONS

NEW ADULT INFECTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES BY YEAR AND VACCINE SCENARIO

Total new infections averted by an HIV vaccine between 2015-2030
30% efficacy, 20% coverage 5.5 million
50% efficacy, 30% coverage 17 million
70% efficacy, 40% coverage 28 million

EVEN PARTIALLY EFFICACIOUS HIV VACCINES WITH LIMITED COVERAGE COULD AVERT MILLIONS OF INFECTIONS

Preventative Vaccines:
- Recombinant gp120 vaccines
  - Bivalent subtype B/B
  - Bivalent subtype B/E
- Ad5 vector
  - Step
  - Phambili
- DNA+Ad5 vector vaccines
  - HVTN 505
- Pox vector+ gp120
  - Thai trial
- Pox vector + gp120 for ssA
  - Uhambo
- Ad26+gp140
  - Imbokodo
- VRC01 mAb
  - AMP

Therapeutic Vaccines:
- Tat vaccine
  - Phase 2
- mAb treatment
  - Ibalizumab

active immunisation strategies

• HETEROLOGOUS PRIME BOOST
VECTOR

- EXPRESSES PROTEINS OF SELECTED HIV GENE INSERTS

- USED AS PRIME

Image credit: slideshare

Canarypox vector
PROTEIN

- ENVELOPE PROTEIN
- GIVEN WITH ADJUVANT
- USED AS BOOST

PRIME VECTOR

ALVAC-HIV for subtypes B/E

BOOST PROTEIN + ADJUV

gp120 for subtypes B/E + alum

M0  M1  M3  M6  M12  M42
RV144: FIRST HINT OF SUCCESS – AND LESSONS

- Vaccine efficacy wanes

- **Magnitude, quality and durability** of immune responses wanes

Correlates associated with ↓HIV acquisition:
- Abs (IgG, IgG3) against envelope (vaccine-matched gp120, V1V2)
- Functionality, polyfunctionality scores of env-specific CD4+ T-cell responses

HVTN 097: IgG response to V1V2 antigens

V1V2 IgG breadth to Clades B & C lower than to Clade A/AE

Proportion of responders (%) at peak timepoint:
- 95%
- 97-99%
- 55-99%
- 66-98%

Thanks: Georgia Tomaras, HVTN Laboratory, SCHARP, HVTN 097 study team
Thailand RV144

- Vaccines can protect against HIV.
- Scientific principles of protection. Durability a challenge.
- South Africans vaccinated with Thai regimen made immune responses: waned, were not to all subtype C strains
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South Africa

Uhambo

Thailand RV144

ALVAC-HIV for subtypes B/E

M0 M1 M3 M6 M12 M42

60% efficacy 31% efficacy

gp120 for subtypes B/E + alum

ALVAC-HIV for subtypes B/C

M0 M1 M3 M6 M12 M18

gp120 for subtype C + MF59
## HVTN 100 Schema

<table>
<thead>
<tr>
<th>Grp</th>
<th>N=252</th>
<th>PART A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 0, Month 1</td>
<td>Month 3, Month 6, Month 12</td>
<td></td>
</tr>
</tbody>
</table>

### VACCINE

| 210 | ALVAC-HIV (vCP2438) + Bivalent Subtype C gp120 & MF59® |

### PLACEBO

<table>
<thead>
<tr>
<th>42</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + Placebo</td>
</tr>
</tbody>
</table>

**Healthy South African adults**

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<table>
<thead>
<tr>
<th></th>
<th>Month 6,5</th>
<th>Month 12</th>
<th>Month 12,5</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG Abs to gp120 from:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1086.C strain</td>
<td>99%</td>
<td>29084</td>
<td>100%</td>
<td>9312</td>
</tr>
<tr>
<td>TV1.C strain</td>
<td>99%</td>
<td>28113</td>
<td>89%</td>
<td>881</td>
</tr>
<tr>
<td>ZM96C strain</td>
<td>96%</td>
<td>26507</td>
<td>2%</td>
<td>948</td>
</tr>
<tr>
<td>CD4 T-cells producing IFN-G and/or IL2</td>
<td>62%</td>
<td>36%</td>
<td>70%</td>
<td>57%</td>
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Laher F et al. HVTN 100: the effects of a 12-month booster on immune responses in healthy HIV-uninfected adults vaccinated with ALVAC-HIV (vCP2438) and Bivalent Subtype C gp120/MF59® in South Africa. Late-breaker, IAS 2017.
**PRIME VECTOR**

- ALVAC-HIV for subtypes B/E
- **M0**  **M1**  **M3**  **M6**  **M12**  **M42**
  - Vaccines can protect against HIV.
  - Scientific principles of protection. Durability a challenge.
  - South Africans vaccinated with Thai regimen made immune responses: waned, were not to all subtype C strains

**BOOST PROTEIN + ADJUV**

- gp120 for subtypes B/E + alum
- gp120 for subtype C + MF59

**60% efficacy**  **31% efficacy**

**South Africa Uhambo**

- Good human safety profile
- Phase 1-2a: M12 booster prolongs immune responses to M18
- Phase 2b-3 enrolling
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<tr>
<td>M0</td>
<td>M1</td>
</tr>
<tr>
<td><strong>Ad26.Mosaic</strong></td>
<td>gp140 for subtype C + alum</td>
</tr>
<tr>
<td>M0</td>
<td>M3</td>
</tr>
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- Vaccines can protect against HIV.
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- Good human safety profile
- Phase 2b enrolling
**GLOBAL VACCINE: HIGH LEVEL DEVELOPMENT PLAN**

**Pre-clinical studies**
- At 6 weeks after exposure to SHIV, 66% of vaccinated non-human primates (Ad26 prime/Ad+gp140 boost) were HIV-uninfected vs. 0 placebo-recipients.
- Protection correlated with antibodies to HIV envelope and T-cell responses to vaccines.

**Phase 1/2a (2014-2016)**
- Multiple trials, good safety, regimen selected, dose confirmed. Humans made same type & levels of antibodies as non-human primates.
- Elicited Env-specific binding antibody responses (100%) @week 52, T-cell responses (83%) at week 50.

**Phase 2b (2017-2021)**

**Phase 3/4**

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passive immunisation strategies

• BROADLY NEUTRALISING MONOCLONAL ANTIBODIES
VRC01

- Antibody
- Broadly neutralizing: >90% HIV isolates
- Targets CD4 binding site on envelope
- Phase 2b prevention trial enrolling Africa, US, Europe
RAPID GROWTH OF bnAb FIELD

- CD4 binding site: VRC01, 3BNC117, PG04, CH103, VRC07, VRC07-523, VRC13
- gp41 MPER: 2F5, 4E10, 10e8
- gp120/41 trimer: 8ANC195, PGT151, 35022
- V1V2 Glycan: PG9&16, PGT141-145, CH01-04, CAP256-VRC26
- N332 Glycan supersite: PGT121, PGT128, 10-1074
SUMMARY

✓ Vaccines to prevent people from acquiring HIV are coming
✓ Multiple doses may be needed
✓ May be partially efficacious but would cost-effectively reduce new infections at population level
thanks to those leading the journey to an HIV vaccine

✓ CABs
✓ Protocol Teams
✓ Site staff
✓ Participants
✓ Communities
✓ SA MRC, BMGF,
  HVTN, NIH/DAIDS,
  GSK, Sanofi, Janssen