Evaluation of lead HIV-1 vaccine regimen in APPROACH:
Phase 1/2a study testing heterologous prime boost regimens using mosaic Ad26 and MVA vectors combined with Env protein

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IAS | Paris, 24 July 2017
Disclosure

Hanneke Schuitemaker has the following conflicts of interest to declare:

- She is an employee of Janssen Vaccines and Prevention BV, a pharmaceutical company of Johnson & Johnson
- She holds equity shares in Johnson & Johnson
Goal: Global HIV-1 Prophylactic Vaccine

Key elements

1. Vectors that elicit optimal immune responses
2. Mosaic inserts for global coverage (gag-pol-env)
3. Trimeric Env proteins for improved immunity
Aim: to develop a Prophylactic vaccine offering protection against all clades of HIV-1 through an heterologous prime boost regimen

**Double Prime**

<table>
<thead>
<tr>
<th>Vaccine Configuration</th>
</tr>
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<tbody>
<tr>
<td>Ad26.Mos4.HIV</td>
</tr>
<tr>
<td>Ad26 vectors with Mosaic gag-pol or env inserts</td>
</tr>
<tr>
<td>Ad26.Mos1.Gag-Pol</td>
</tr>
<tr>
<td>Ad26.Mos2.Gag-Pol</td>
</tr>
<tr>
<td>Ad26.Mos1.Env</td>
</tr>
<tr>
<td>Ad26.Mos2S.Env</td>
</tr>
<tr>
<td>Co-formulated 1:1:1:1</td>
</tr>
</tbody>
</table>

**Double Boost**

<table>
<thead>
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<th>Vaccine Configuration</th>
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<tbody>
<tr>
<td>gp140 Clade C</td>
</tr>
<tr>
<td>Soluble trimeric gp140 Env protein with Alum</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>gp140 Clade C + Mosaic</td>
</tr>
<tr>
<td>Soluble trimeric gp140 Env proteins with Alum</td>
</tr>
<tr>
<td>Clade C + Mosaic</td>
</tr>
</tbody>
</table>

**Regimen to be selected after Phase 1/2a**

- Months: 0, 3, 6, 12
Heterologous prime-boost vaccine regimens: tested in early studies in parallel in humans (phase 1/2a study HIV-V-A004/ IPCAVD009/ APPROACH) and in NHP (study #13-19)

### Double Prime

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<td></td>
</tr>
<tr>
<td>Ad26.Mos1.Env</td>
<td></td>
</tr>
<tr>
<td>Co-formulated 1:1:2</td>
<td></td>
</tr>
</tbody>
</table>

### Double Boost

<table>
<thead>
<tr>
<th>gp140 Clade C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soluble trimeric gp140 env protein with Alum</td>
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</table>

**OR**

### Double Prime

- **Ad26.Mos.HIV**
- Ad26 vectors with Mosaic gag-pol-env inserts
- Co-formulated 1:1:2

### Double Boost

- **gp140 Clade C**
- Soluble trimeric gp140 env protein with Alum

**OR**

### Double Boost

- **MVA-Mosaic**
  - MVA vectors with Mosaic gag-pol-env inserts
  - MVA-Mosaic 1 + MVA-Mosaic 2

**Regimen to be selected after Phase 1/2a**

[Diagram showing vaccine regimens with timelines for prime and boost injections]
Studies that inform decision to proceed with a Phase 2b/Proof of Concept study

- NHP Study 13-19
  - Efficacy / correlates
- Phase 2a APPROACH
  - Safety / Immuno
  - Post 3rd vacc
- Phase 2a APPROACH
  - Safety / Immuno
  - Post 4th vacc
- Phase 2a TRAVERSE
  - Safety / Immuno
  - Post 2nd and 3rd vacc

Start PoC
The Ad26/Ad26+gp140 HIV Vaccine Regimen Provided Significant Protection Against SHIV$_{SF162P3}$ Challenges in NHP (study 13-19*)

*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

Dan Barouch, IAS HVTN Satellite, 25 July - 7am
Studies that inform decision to proceed with a Phase 2b/Proof of Concept study

- **NHP Study 13-19**
  - Efficacy / correlates
  - Post 3\(^{rd}\) vacc

- **Phase 2a APPROACH**
  - Safety / Immuno
  - Post 3\(^{rd}\) vacc

- **Phase 2a APPROACH**
  - Safety / Immuno
  - Post 4\(^{th}\) vacc

- **Phase 2a TRAVERSE**
  - Safety / Immuno
  - Post 2\(^{nd}\) and 3\(^{rd}\) vacc

Start PoC
Phase 1/2a: APPROACH

FIH of Ad26.Mos.HIV and heterologous regimens

**Countries:** USA, Rwanda, Uganda, South Africa, Thailand
**Target N:** 400
**Sponsor:** Janssen Vaccines*
**Partners:** BIDMC*, IAVI*, MHRP*, HVTN/NIAID*, Ragon*

*co-funders

**APPROACH:**
The path or route to the start of a technical climb. Although this is generally a walk or, at most, a scramble it is occasionally as challenging as the climb itself
Phase 1/2a with tetravalent Ad26 and Mosaic gp140: TRAVERSE and ASCENT

- **HPX2004/ HVTN117 / TRAVERSE**
  - **Ad26.Mos4.HIV (4-valent) vs Ad26.Mos.HIV (3-valent)**
  - **Countries:** USA, Rwanda
  - **Target N:** 198
  - **Sponsor:** Janssen Vaccines*
  - **Partners:** BIDMC*, BMGF*, HVTN/NIAID*, MHRP*, Ragon*
    *co-funders
  
  **TRAVERSE:** progress forward by moving horizontally

- **HPX2003/ HVTN 118 / ASCENT**
  - **Countries:** USA, Rwanda, Kenya
  - **Target N:** 150
  - **Sponsor:** Janssen Vaccines
  - **Partners:** BIDMC*, HVTN/NIAID*, MHRP*, Ragon*
    *co-funders
  
  **ASCENT:** a walk to the summit of a mountain
From Phase 1/2a to Proof of Concept study pre-specified Go/no-Go criteria

- Selection of criteria based on:
  - Immune correlates of protection identified in NHP studies

- Emphasis on:
  - Vaccine take as demonstrated by humoral and cellular immune responses
  - Magnitude of humoral and cellular immune responses
  - Functionality of elicited antibodies
Binding antibodies to HIV Env together with HIV Env specific T cells correlated with protection in NHP SHIV$_{\text{SF162P3}}$ challenge study.
Go/No Go criteria towards Proof of Concept based on APPROACH

- 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** are considered **supportive**

<table>
<thead>
<tr>
<th>Criteria</th>
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<th>Results post 3rd APPROACH</th>
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<tbody>
<tr>
<td>Humoral</td>
<td>IgG binding responses on Clade C Env</td>
<td>≥90% (&gt;77%)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>&gt;1.5 fold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnitude</td>
<td>&gt;2.15 log10 cPTE Env ELISPOT OR &gt;3.8 log10 Clade C gp140 ELISA</td>
<td><strong>post 3rd</strong>: &gt;60%</td>
<td><strong>post 4th</strong>: &gt;75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subjects should be above BOTH response thresholds</td>
<td><strong>post 3rd</strong>: ≥40%</td>
<td><strong>post 4th</strong>: ≥60%</td>
<td></td>
</tr>
</tbody>
</table>
**APPROACH Trial Design: a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial in healthy HIV-uninfected adults**

Primary endpoint for immunogenicity: 3rd vaccination + 4 weeks (Week 28)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Day 0 (Baseline)</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48 Booster</th>
<th>Label used in tables and figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>Ad26 + gp140 HD</td>
<td>Ad26 + gp140 HD</td>
<td>Ad26/Ad26 + gp140 HD</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>Ad26 + gp140 LD</td>
<td>Ad26 + gp140 LD</td>
<td>Ad26/Ad26 + gp140 LD</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>Ad26</td>
<td>Ad26</td>
<td>Ad26/Ad26</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>MVA + gp140 HD</td>
<td>MVA + gp140 HD</td>
<td>Ad26/MVA + gp140 HD</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>MVA + gp140 LD</td>
<td>MVA + gp140 LD</td>
<td>Ad26/MVA + gp140 LD</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>MVA</td>
<td>MVA</td>
<td>Ad26/MVA</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Ad26</td>
<td>Ad26</td>
<td>gp140 HD</td>
<td>gp140 HD</td>
<td>Ad26/gp140 HD</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo/Placebo</td>
</tr>
</tbody>
</table>

Ad26 = Ad26.Mos.HIV  
MVA = MVA-Mos  
gp140 HD = gp140 DP (250 mcg + adjuvant)  
gp140 LD = gp140 DP (50 mcg + adjuvant)

<table>
<thead>
<tr>
<th>weeks</th>
<th>prime</th>
<th>prime</th>
<th>boost</th>
<th>boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>
Safety summary

- Most solicited AEs were grade 1 and 2
  - most common were injection site pain, headache, fatigue
  - no clear differences between groups

- Most unsolicited AEs were grade 1 and 2 and were unrelated
  - no differences between groups

- Only 1 related SAE, hypersensitivity with multiple confounding factors
ELISA: APPROACH post 3rd vaccination
Total IgG gp140 ENV Clade C (C97ZA.012)

- All vaccine regimens were immunogenic: 100% responders in most groups
- Clear contribution of gp140 boost
- Clear contribution of the gp140 dose
- Detectable contribution of the vector to the gp140 boost
- Contribution of the gp140 seems more evident in the Ad26 boosted groups than in the MVA boosted groups
ELISA: APPROACH post 3rd and 4th vaccination
Total IgG gp140 ENV Clade C (C97ZA.012)

Maintained number of responders post 4\textsuperscript{th} vaccination and slight increase in ELISA titers in most groups that have gp140 in the boost

Cross-clade responses detected with very similar response patterns as observed against the vaccine component Clade C gp140
ADCP: APPROACH post 3rd and 4th vaccination
gp140 ENV Clade C (C97ZA.012)

All vaccines regimens elicited ADCP responses
Clear contribution of gp140 boost and dose
Maintained number of responders and slight increase in ADCP titers in gp140 boosted groups post 4th
ELISPOT: APPROACH post 3rd and 4th vaccination

ENV PTE peptide pool

All vaccine regimens were immunogenic: high % responders in most groups

Highest immunogenicity in Ad26+gp140HD and MVA+gp140 boosted groups

Maintained or slight increase post 4\textsuperscript{th} in ENV ELISPOT response
Go/No Go criteria towards Phase 2b/PoC based on APPROACH Lead Regimen

- 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 are considered supportive

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<td>100% (93%)</td>
<td>100% (92%)</td>
</tr>
<tr>
<td></td>
<td>ADCP responses to Clade C Env</td>
<td>≥56% (&gt;40%)</td>
<td>72% (57%)</td>
<td>80% (65%)</td>
</tr>
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<td>Cellular</td>
<td>Elispot responses to at least one ENV peptide pool*</td>
<td>≥50% (&gt;35%)</td>
<td>77% (62%)</td>
<td>83% (68%)</td>
</tr>
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<td>Env boost</td>
<td>IgG to clade C Env of Ad/Ad+Env over Ad/Ad</td>
<td>≥1.5 fold</td>
<td>5.5 fold (3.5)</td>
<td>6.9 fold (4.5)</td>
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<td>Magnitude</td>
<td>&gt;2.15 log10 cPTE Env ELISPOT OR &gt;3.8 log10 Clade C gp140 ELISA</td>
<td>post 3rd : ≥60%</td>
<td>post 4th : ≥75%</td>
<td>94%</td>
</tr>
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<td></td>
<td>Subjects should be above BOTH response thresholds</td>
<td>post 3rd : ≥40%</td>
<td>post 4th : ≥60%</td>
<td>64%</td>
</tr>
</tbody>
</table>

*PTE Env peptide pool
Studies that inform decision to proceed with a Proof of Concept study

- Study 13-19
- APPROACH
  - Post 3rd vacc
- APPROACH
  - Post 4th vacc
- TRAVERSE
  - Post 2nd and 3rd vacc
  - Q3/Q4 2017

Start PoC
Proof-of-Concept Study
HPX2008/HVTN 705

**Design:**
Multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial

**Countries:** South Africa, Zambia, Zimbabwe, Malawi, Mozambique

**Target N:** 2,600

**Population:** Sexually active HIV-1 uninfected women (born female), age 18-35 years

Susan Buchbinder, IAS HVTN Satellite, 25 July - 7am
Acknowledgements

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- Dan Barouch
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- Dale Hu
- Mary Marovich
- Michael Pensiero
- Tina Tong

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LANL
- Bette Korber

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- Nelson Michael
- Merlin Robb

Ragon Institute
- Galit Alter
- Bruce Walker

...and their teams
We thank the Principal Investigators and sites staff and all the volunteers and their families for their participation in the clinical studies.
Diagnosed with AIDS in 1990, Martin lives in San Francisco where he continues to create new pieces.