The bumpy road of HIV vaccine development

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Disclosure

I have the following conflicts of interest to declare:

• I am an employee of Janssen Vaccines & Prevention B.V., a pharmaceutical company of Johnson & Johnson
Janssen Vaccines – Our Vision

Develop transformational vaccines that are first and/or best in class in areas of high unmet medical need

Help to halt HIV epidemic by preventive vaccination & contribute to a functional cure with a therapeutic vaccine

Respond fast and efficiently to outbreaks of pathogens of global concern such as Ebola

Prevent respiratory infections (RSV, Flu) impacting children, elderly and at risk patients

Prevent MDR bacterial infections such as ExPEC by vaccination as part of quest to address global AMR challenge
HIV: High unmet need
Burden in 2017

36.9 MILLION PEOPLE worldwide are currently living with HIV/AIDS

1.8 MILLION CHILDREN living with HIV

1 MILLION DIED from AIDS-related illnesses

21.7 MILLION of people living with HIV received antiretroviral drugs

1.8 MILLION NEW HIV Infections 5000 per day

Paradigms of HIV vaccine development

4 waves

- **Induction of Neutralizing Ab** (Hep B model)
  - Ends with failure of VaxGen GP120 protein efficacy trials

- **Induction of Cell-Mediated immunity**
  - Ends with failure of Merck Ad5-gag-pol-nef efficacy trials

- **Combination of Different Immune Responses** (functional Abs, memory T cells)

- **Induction of broadly Neutralizing Abs**

Still in discovery phase

- **RV144**: Viral Vector/gp120 protein: 30% efficacy
- **HVTN505**: DNA/Ad5: 0% efficacy

- Optimizing RV144 and other regimens to induce **functional non-neutralizing Abs**: efficacy in humans TBD
  - P5
  - Janssen
Our goal: a prophylactic HIV vaccine that protects against multiple clades of HIV-1

1. Vectors that elicit optimal immune responses
2. Mosaic inserts for global coverage (Gag-Pol-Env)
3. Trimeric env proteins for improved humoral immunity
Vaccine regimen selection studies

**Efficacy**
in non-human primates
*NHP study #13-19*

**Immunogenicity**
in humans, phase 1/2a
*APPROACH study*

**The plan:**

**Vaccination 1&2 at week 0, 12**

- **Ad26.Mos.HIV**
  - Ad26 with Mosaic gag-pol (mos1 & mos2) and mosaic env (mos1 & mos2) inserts

**Vaccination 3&4 at weeks 24, 48**

- **Ad26.Mos.HIV**
- **MVA-Mosaic**
  - MVA with Mosaic 1&2 gag-pol-env inserts

OR

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

OR

- **gp140 Clade C**
  - Soluble gp140 env protein with Alum
Three Parallel First-In-Human Studies

| Phase 1 HIV-V-A002/IPCAVD006/ MENSCH N=25 | Safety data MENSCH |
| Phase 1 HIV-V-A003/IPCAVD008  N=50 | Safety data HIV-V-A003 |
| Phase 1/2a HIV-V-A004/ APPROACH  N=400 | Go/no-Go heterologous boost in APPROACH |

Pre-clinical Efficacy study

- First in Human MVA.Mos
- First in Human Clade C gp140
- First in Human Ad26.Mos.HIV and heterologous regimens

NHP study 13-19

Availability of NHP challenge data

Regimen Selection
Manufacturing challenge

**Ad26.Mos.HIV**
Ad26 vectors with Mosaic 
* gag-pol or env * inserts

- Ad26.Mos2.Gag-Pol ✔
- Ad26.Mos1.Env ✔
- Ad26.Mos2.Env ✗

- 1 log lower yield compared to other Ad26 vectors at 10L scale
- Transgene instability in certain batches
- No scalable process for Ad26.Mos2.Env vector despite development efforts
Problem

Ad26.Mos2.Env cannot be produced at larger scale. Vector is poorly immunogenic.
Problem

Ad26.Mos2.Env cannot be produced at larger scale. Vector is poorly immunogenic.

Interim solution

Double dose of Ad26.Mos1.Env for NHP and APPROACH studies.

Durable Solution

Develop an alternative mos2.Env that is compatible with delivery.

-- Property of Janssen – Do not distribute --
AdVac® Vaccine components for the NHP13-19 and APPROACH studies

Ad26.Mos.HIV

- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env
- Ad26.Mos2.Env

Ad26.Mos.HIV

- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env

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# NHP13-19 - study design

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vaccination 1&amp;2 wk 0, wk 12</th>
<th>Vaccination 3&amp;4 wk 24, wk 48</th>
<th>IR SHIV challenge 6 months after 4th dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV + High Dose Clade C gp140</td>
<td>Blue arrow</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>Blue arrow</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>MVA- Mosaic + High Dose Clade C gp140</td>
<td>Yellow arrow</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>MVA- Mosaic</td>
<td>Yellow arrow</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td></td>
<td>Gray arrow</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo + High Dose Clade C gp140</td>
<td>Gray arrow</td>
</tr>
</tbody>
</table>

Barouch, Tomaka, Wegmann, et al., The Lancet, 2018

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## APPROACH - study design

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vaccination 1&amp;2 wk 0, wk 12</th>
<th>Vaccination 3&amp;4 wk 24, wk 48</th>
<th>Follow up wk 52 to 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV + High Dose Clade C gp140</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV + Low Dose Clade C gp140</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>MVA- Mosaic + High Dose Clade C gp140</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>MVA- Mosaic + Low Dose Clade C gp140</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>MVA- Mosaic</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>+ High Dose Clade C gp140</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Barouch, Tomaka, Wegmann, et al., The Lancet, 2018

-- Property of Janssen – Do not distribute --
Ad26/Ad26+gp140: A Promising HIV Prophylactic Vaccine

Immune responses associated with NHP protection compare favorably in humans

High efficacy in NHP

- **67% full protection**
- **100% infection**

Control vs. Ad26/Ad26+gp140

Number of intrarectal challenges SF162.P3 SHIV

Favorable immunogenicity in humans

Barouch, Tomaka, Wegmann, et al., The Lancet, 2018
Problem

Ad26.Mos2.Env cannot be produced at larger scale. Vector is poorly immunogenic.

Interim solution

Double dose of Ad26.Mos1.Env for NHP and APPROACH studies.

Durable Solution

Develop an alternative mos2.Env that is compatible with delivery.
Design new clade C Env antigen to replace mosaic 2 Env: Mos2s

Preclinical data: Ad26.Mos2S is highly immunogenic and increasing the breadth of humoral immunity in preclinical studies (data not shown)
Expanding breadth & magnitude of immune responses

Ad26.Mos1.Gag-Pol
Ad26.Mos2.Gag-Pol
Ad26.Mos1.Env

Ad26.Mos.HIV

Ad26.Mos2S.Env

Ad26.Mos4.HIV

-- Property of Janssen – Do not distribute --
A randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in healthy HIV uninfected adults to assess the safety/tolerability and immunogenicity of 2 different prime/boost regimens

TRAVERSE

Progress forward by moving horizontally
# TRAVERSE – study design

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Prime</th>
<th>Boost</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>55</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>+ High Dose Clade C gp 140</td>
</tr>
<tr>
<td>1B</td>
<td>11</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>22</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

**Diagram:**
- **Prime:** Weeks 0 and 12
- **Boost:** Weeks 24 and 48
- **Follow up:**
  - 140 weeks post-prime
  - 140 weeks post-boost
**Immunogenicity**

Clade C gp140 ELISA

Envelop binding antibodies

ELISA titre

Baseline Tetralvalent
Week 16

Tetralvalent
Week 28

Trivalent
Week 16

Trivalent
Week 28

Placebo
Week 16

Placebo
Week 28

Legend:
- Baseline
- Tetravalent Responder
- Trivalent Responder
- Placebo Responder
- Non-responder

D. Stieh, HIV R4P Conference, Madrid October 2018

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Immunogenicity

Significant improvement across clades & assays

Total IgG ELISA

IgG subclass Clade C ELISA

ADCP

Geometric Mean Ratio (95% CI) of 4V/3V group

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Conclusions
TRAVERSE, week 28

<table>
<thead>
<tr>
<th>SAFETY</th>
<th>HUMORAL</th>
<th>CELLULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable safety profile through 3rd vaccination</td>
<td>Tetravalent Ad26 induces more <strong>Broad and Functional</strong> HIV Env-specific humoral responses</td>
<td>Tetravalent Ad26 induces <strong>Stronger</strong> Env-specific cellular responses</td>
</tr>
</tbody>
</table>

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From Early Development to Efficacy trials

Regimen selection and “Go-No Go” criteria based on pre-clinical challenge data and immunogenicity in humans.

#makeHIVhistory

-- Property of Janssen – Do not distribute --
Establishing Magnitude Criteria for Immune Parameters that correlate with Efficacy in NHP

Principles:
- Criterion 1: ELISA log10 > 3.8
- Criterion 2: ELIspot log10 > 2.15

Regimen GO with human data from APPROACH post 3rd when:
- >60% meets Crit 1 OR Crit 2
- >40% meets Crit 1 AND Crit 2
Final Regimen selection for Ph2b based on Immunological PoC

**Ph1/2a APPROACH**

<table>
<thead>
<tr>
<th>Prime at wk 0, 12</th>
<th>Boost at wk 24, 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26.Mos.HIV 3-valent</td>
<td>Ad26.Mos.HIV 3-valent</td>
</tr>
<tr>
<td>gp140 Clade C with Alum</td>
<td>gp140 Clade C with Alum</td>
</tr>
</tbody>
</table>

ELISA vs ELISpot post 3rd Vaccination

- **ELISA Clade C**
  - Prime: 60%
  - Boost: 60%
  - Final: 40%

- **ELISpot ENV**
  - Prime: 64%
  - Boost: 70%
  - Final: 87%

---

**Final Regimen selection for Ph2b based on Immunological PoC**

- Prime at wk 0, 12
  - Ad26.Mos.HIV 3-valent
  - gp140 Clade C with Alum

- Boost at wk 24, 48
  - Ad26.Mos.HIV 3-valent
  - gp140 Clade C with Alum

- ELISA vs ELISpot post 3rd Vaccination
  - ELISA Clade C: Prime 60%, Boost 60%, Final 40%
  - ELISpot ENV: Prime 64%, Boost 70%, Final 87%
Final Regimen selection for Ph2b based on Immunological PoC

**Ph1/2a APPROACH**

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**Expanding magnitude and breadth of immune responses with 4-valent Ad26**

<table>
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<tr>
<th>Ph1/2a TRAVERSE</th>
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<tbody>
<tr>
<td>Ad26.Mos.HIV 4-valent</td>
</tr>
<tr>
<td>Ad26.Mos.HIV 4-valent</td>
</tr>
<tr>
<td>gp140 Clade C with Alum</td>
</tr>
</tbody>
</table>

ELISA vs ELISpot post 3rd Vaccination

- 94%
- 94%
- 100%
Ongoing: Imbokodo/HVTN705/HPX2008 Phase 2b Study

This vaccine is currently being evaluated for efficacy in young women in Southern Africa, with a target enrollment of 2,600.

#makeHIVhistory
Imbokodo/HVTN705/HPX2008: a phase 2b multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial

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

**Vaccine regimen:** 2x Ad26.Mos4.HIV (week 0,12), 2x Ad26.Mos4.HIV+gp140 (week 24, 48)

**Objective:** to evaluate the efficacy of the vaccine regimen in reducing the incidence of HIV infection in women

**Protective Efficacy hypothesis:** 50% (lower bound >0%) reduction in HIV-1 acquisition

Status: enrolling

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Towards the final regimen for Phase 3

From Clade C gp140 alone to Clade C + Mosaic gp140 combination

Decision to include a second protein will be based on clinical data demonstrating increased Clade B antibody responses without compromising clade C responses
**ASCENT/ HPX2003/HVTN118/IPCAVD012 study design**

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<th>N</th>
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<th>Boost</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>25</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Status: data is being analysed

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**Note:** Property of Janssen – Do not distribute.
A Few More Challenges Ahead in HIV Vaccine Development.... But Good Reasons to believe

<table>
<thead>
<tr>
<th></th>
<th>NHP Efficacy</th>
<th>Clinical efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per exposure</td>
<td>HIV-1</td>
</tr>
<tr>
<td>risk reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALVAC / gp120</td>
<td>29% <em>not significant</em>¹</td>
<td>31% RV144 trial²</td>
</tr>
<tr>
<td>DNA/Ad5</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ad26 / Ad26+gp140</td>
<td>94%³</td>
<td>Pending</td>
</tr>
</tbody>
</table>

¹ Barouch unpublished; ² Rerks-Ngarm NEJM 2009; ³ Hammer NEJM 2013; ⁴ Barouch Lancet, 2018
External Collaborators & Partners

BETH ISRAEL DEACONESS, HARVARD MEDICAL SCHOOL
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...and their teams
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All the investigators, their staffs and the volunteers for their participation in this clinical program
Diagnosed with AIDS in 1990, Martin lives in San Francisco where he continues to create new pieces.