HIV Prophylactic Vaccine Development Program

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Senior Director, Compound Development Team Leader, Janssen

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HIV vaccine R&D programs: Current Collaborators (in alphabethical order)

- BIDMC/Harvard
- BMGF
- HVTN
- IAVI
- MHRP
- NIH-NIAID-DAIDS
- Ragon Institute
High Level Target Product Profile Goal:
Prophylactic vaccine offering protection against all clades of HIV-1 through an heterologous prime boost regimen

1. Vectors that elicit optimal immune responses
2. Mosaic inserts for global coverage (Gag-Pol-Env)
3. Trimeric env proteins for improved humoral immunity
Proof-of-concept studies in non-human primates

Heterologous **vector-based** prime-boost regimens delivering SIV or HIV-mosaic antigens afforded partial protection against **SIVmac251** and **SHIV-SF162P3** repetitive intra-rectal challenges.

### Per-Exposure Risk Reduction

<table>
<thead>
<tr>
<th></th>
<th>Ad26/MVA</th>
<th>Ad35/Ad26</th>
<th>Sham (N=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIVmac251</td>
<td>83%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>SHIV-SF162P3</td>
<td>90%</td>
<td>16%</td>
<td>100%</td>
</tr>
</tbody>
</table>

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Barouch DH, Michael NL et al, 2012

Barouch DH, Michael NL et al, 2013
Proof-of-concept studies in non-human primates

Increase of humoral immunity by **gp140 boost** affording partial protection in stringent **SIVmac251** and **SHIV-SF162P3** challenge models

Barouch DH, Schuitemaker H et al, 2015

![Graphs showing protection against SIV challenges](image)

**SIVmac251**

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26/Env</td>
<td>90%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**SHIV-SF162P3**

<table>
<thead>
<tr>
<th></th>
<th>Per-Exposure Risk Reduction</th>
<th>Full Protection after 6 challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admos/Env</td>
<td>79%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Heterologous prime-boost HIV-1 vaccine regimen aiming at global coverage: tested in parallel in humans (ph 1/2a study HIV-V-A004/IPCAVD009/APPROACH) and in NHP challenge study

<table>
<thead>
<tr>
<th>Prime</th>
<th>Boost</th>
</tr>
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<tbody>
<tr>
<td>Ad26.Mos.HIV</td>
<td>gp140 Clade C</td>
</tr>
<tr>
<td>Ad26 vectors with Mosaic gag-pol or env inserts</td>
<td>Soluble trimer gp140 env protein</td>
</tr>
<tr>
<td>Ad26.Mos1.Gag-Pol</td>
<td>and/or</td>
</tr>
<tr>
<td>Ad26.Mos2.Gag-Pol</td>
<td>OR</td>
</tr>
<tr>
<td>Ad26.Mos1.Env</td>
<td>+/−</td>
</tr>
</tbody>
</table>

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

Regimen to be selected after Phase 1/2a
The Ad26/Ad26+gp140 HIV Vaccine Regimen Provided Significant Protection Against SHIV$_{SF162P3}$ Challenges in Non-Human Primates

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Per-exposure risk reduction versus sham</th>
<th>Full protection after 6 challenges</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad prime / Ad boost</td>
<td>35%</td>
<td>0%</td>
<td>12</td>
</tr>
<tr>
<td>Ad prime / gp140 boost</td>
<td>84%*</td>
<td>33%</td>
<td>12</td>
</tr>
<tr>
<td>Ad prime / Ad+gp140 boost</td>
<td>94%*</td>
<td>66%†</td>
<td>12</td>
</tr>
<tr>
<td>Ad prime / MVA boost</td>
<td>71%</td>
<td>8%</td>
<td>12</td>
</tr>
<tr>
<td>Ad prime / MVA+gp140 boost</td>
<td>87%*</td>
<td>42%</td>
<td>12</td>
</tr>
<tr>
<td>Sham</td>
<td>N/A</td>
<td>0%</td>
<td>12</td>
</tr>
</tbody>
</table>

*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
The Ad26/Ad26+gp140 HIV Vaccine Regimen Provided Significant Protection Against SHIV\textsubscript{SF162P3} Challenges in Non-Human Primates

![Graph showing the percentage of uninfected individuals over time for different vaccine regimens.]

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<th>Per-exposure risk reduction versus sham</th>
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*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
Binding antibodies to HIV Env together with HIV Env specific T cells correlated with protection in NHP SHIV$\text{SF}_{162P3}$ challenge study

Shaded colors and diagonal lines indicate the prediction model of infection based on ELISpot and ELISA responses.

In addition, **functional antibodies** as assessed by ADCP were found to correlate with protection, as has been observed in previous studies.
Two First-in-Human trials completed

HIV-V-A002/MENSCH
FIH safety of MVA-Mosaic (also FIH of mosaic inserts)

- MVA-Mosaic vectors induce cross-clade ELISA responses

HIV-V-A003
FIH safety of Clade C protein w/ and w/o alum

- Clade C gp140 with Alum is immunogenic in humans
Phase 1/2a: HIV-V-A004/IPCAVD009/APPROACH

FIH safety of Ad26.Mos.HIV and heterologous regimens

Countries: USA, Rwanda, Uganda, South Africa, Thailand

Target N: 400

Sponsor: Janssen

Co-funders: Janssen, MHRP, IAVI, BIDMC, Ragon, HVTN/NIAID

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
### APPROACH Trial Design: a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial in healthy HIV-uninfected adults

**Primary endpoint**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 0 (baseline)</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48 Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 7</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>gp140 (250 µg/adj)</td>
<td>gp140 (250 µg/adj)</td>
</tr>
<tr>
<td>Group 8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

*Adj=AdjuPhos

**Status:** Vaccinations completed

12 month follow-up
Expanding Breadth of Immune Responses:
Tetravalent Ad26 and Mosaic gp140

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<thead>
<tr>
<th>Prime</th>
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</tr>
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<tbody>
<tr>
<td><strong>Ad26.Mos4.HIV</strong></td>
<td>gp140 Clade C</td>
</tr>
<tr>
<td>Ad26 vectors with Mosaic gag-pol or env inserts</td>
<td>+ Soluble trimeric gp140 Env protein</td>
</tr>
<tr>
<td>Ad26.Mos1.Gag-Pol</td>
<td>OR gp140 Clade C + Mosaic</td>
</tr>
<tr>
<td>Ad26.Mos2.Gag-Pol</td>
<td>+ Soluble trimeric gp140 Env proteins</td>
</tr>
<tr>
<td>Ad26.Mos1.Env</td>
<td>Clade C + Mosaic</td>
</tr>
<tr>
<td>Ad26.Mos2S.Env</td>
<td></td>
</tr>
</tbody>
</table>

Regimen to be selected after Phase 1/2a

months
0 3 6 12

prime  prime  boost  boost

Visual representation of prime and boost regimens with corresponding insertions and boost combinations.
HPX2004/HVTN117/IPCAVD011/TRAVERSE

Ad26.Mos4.HIV (4-valent) compared to Ad26.Mos.HIV (3-valent)

Countries: USA, Rwanda
Target N: 198
FSI: July, 2016
Sponsor: Janssen
Partners: HVTN/NIAID, BIDMC, MHRP, Ragon, BMGF

Status: Enrollment completed
HPX2003/HVTN118/IPCAVD012/ASCENT

Ad26.Mos4.HIV and Mosaic gp140+Clade C gp140 compared to Ad26.Mos4.HIV and Clade C gp140 alone

Countries: USA, Kenya, Rwanda
Target N: 150
FSI: Q1, 2017
Sponsor: Janssen
Partners: HVTN/NIAID, BIDMC, MHRP, Ragon

Status: First Subjects Vaccinated
Ancillary study: HPX1002/IPCAVD010
Started in April 2016

- Phase 1 to evaluate safety/tolerability and immunogenicity of **different vaccine schedules** with Ad26.Mos.HIV and Clade C gp140

- Single Site: Center for Virology and Vaccine Research, Harvard Catalyst Clinical Research Center, BIDMC
- Co-funded by Ragon Institute, BIDMC and Janssen
- Not on critical path for efficacy trials but may inform late stage development and facilitate decision-making
- **Fully enrolled; vaccinations ongoing**
From Phase 1/2a to Phase 2b and Phase 3 Efficacy trials: regimen selection

- The optimal regimen is hypothesized to elicit a
  - well balanced immune response with both humoral and cellular immunity
  - broad coverage against HIV clades A, B and C

- For the choice of final regimen, emphasis will be on
  - immunological correlates that have been identified to correlate with a reduced risk of SIV/SHIV infection in NHP
  - immunological correlates that have been identified to correlate with a reduced risk of HIV infection in RV144
From Phase 1/2a to Phase 2b and Phase 3 Efficacy trials: “go/no go”

- For the ‘Go/No Go’ decision, emphasis will be on:
  - *Vaccine take* as demonstrated by humoral and cellular immune responses
  - *Functionality* of elicited antibodies

- Decision points to move to Ph2b will be based on APPROACH post 3rd and 4th vaccination

- Additional decision point will be based on TRAVERSE interim data

Tentative Start PoC Q4 2017-Q1 2018
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
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- Merlin Robb

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...and their teams
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- Paul Stoffels

...and their teams