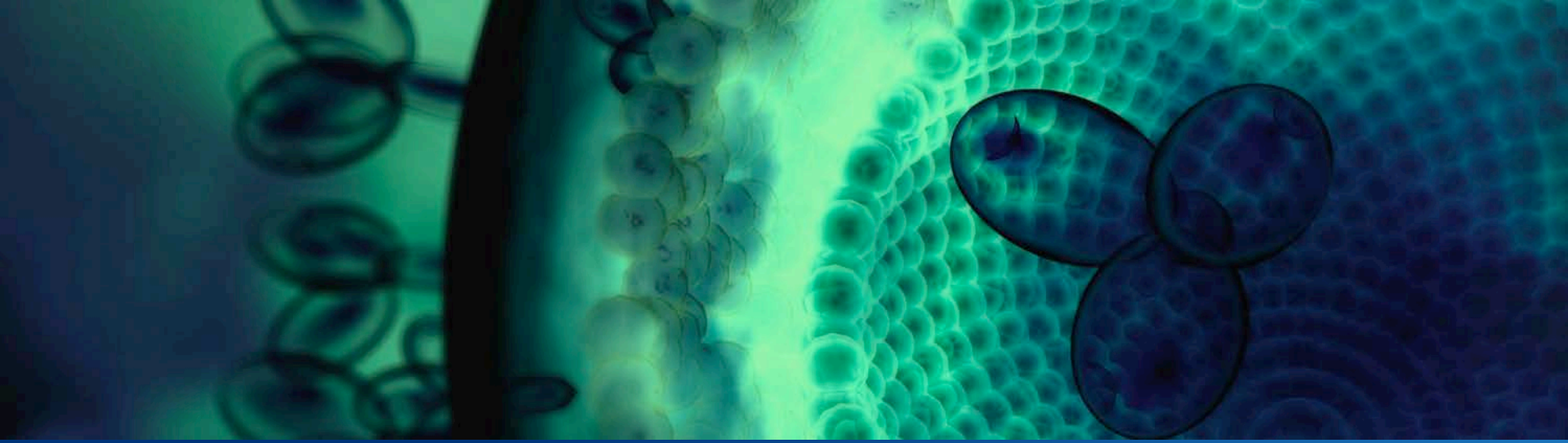


The bumpy road of HIV vaccine development

Hanneke Schuitemaker

Head Viral Vaccine Discovery and Translational Medicine

Professor in Virology, Amsterdam UMC

4th April 2019 | Janssen Vaccines and Prevention B.V.

janssen Infectious Diseases & Vaccines

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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

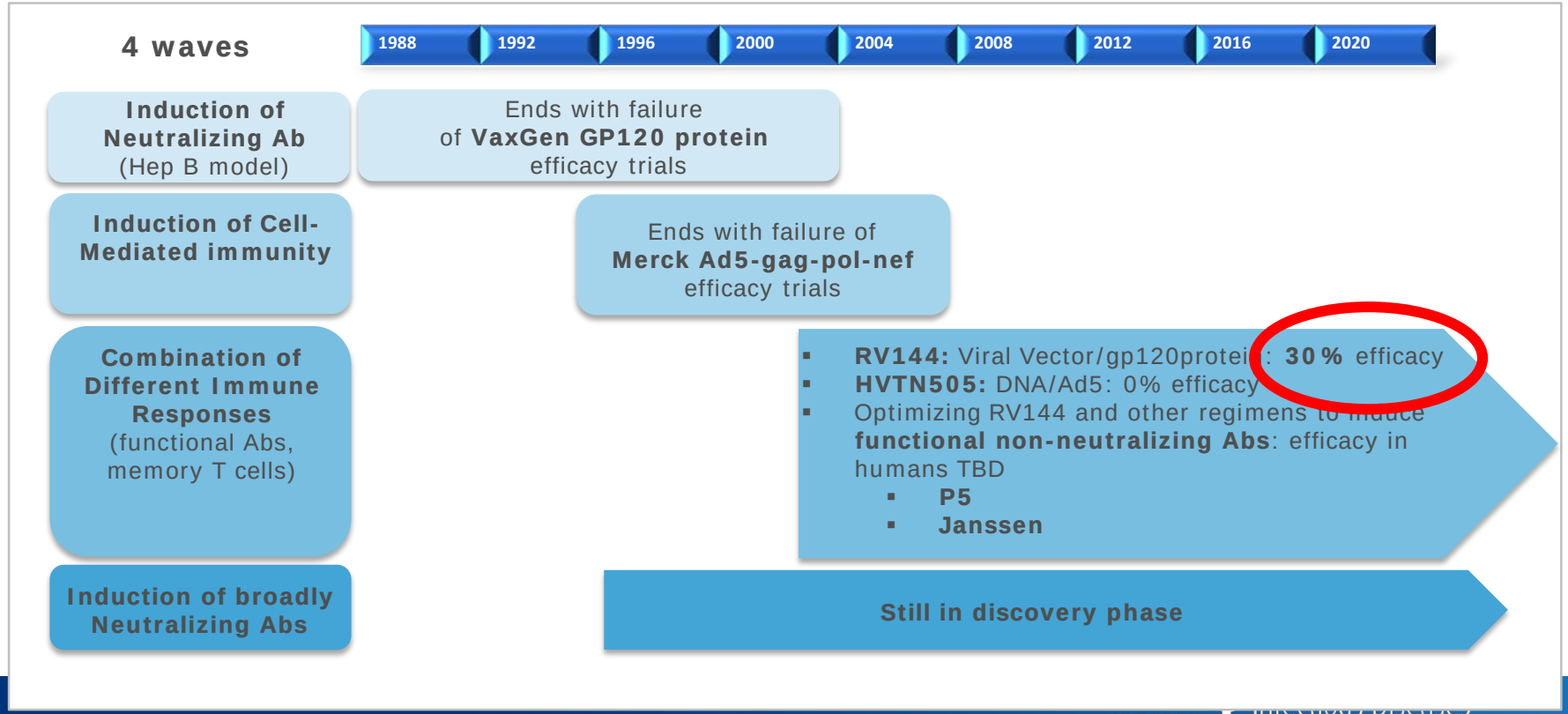
1 MILLION DIED
from AIDS-related illnesses

21.7 MILLION
of people living with HIV **received antiretroviral drugs**

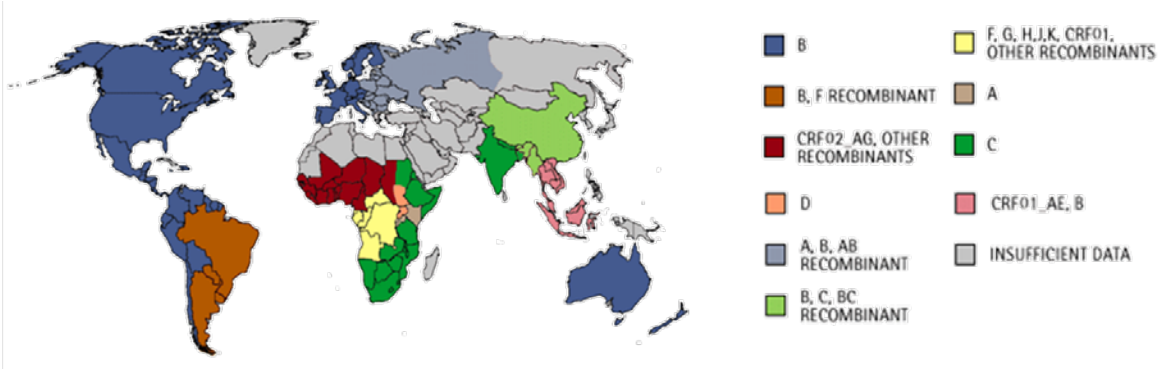
1.8 MILLION NEW HIV Infections
5000 per day

Source: http://www.unaids.org/en/resources/fact-sheet

Paradigms of HIV vaccine development

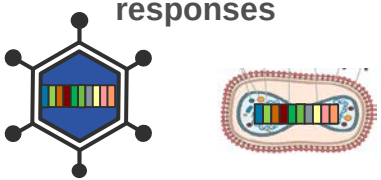


Our goal: a prophylactic HIV vaccine that protects against multiple clades of HIV-1



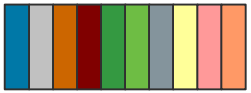
1

Vectors that elicit optimal immune responses



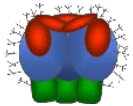
2

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

+/-/or

gp140 Clade C
Soluble gp140 env protein with Alum

OR

MVA-Mosaic
MVA with Mosaic 1&2 gag-pol-env inserts

+/-

gp140 Clade C
Soluble gp140 env protein with Alum

Three Parallel First-In-Human Studies

2014	2015				2016			
Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

Pre-clinical Efficacy study

NHP study 13-19

Availability of NHP challenge data

First in Human MVA.Mos

Phase 1 HIV-V-A002/IPCAVD006/ MENSCH N=25

Safety data MENSCH

First in Human Clade C gp140

Phase 1 HIV-V-A003/IPCAVD008 N=50

Safety data HIV-V-A003

Go/no-Go heterologous boost in APPROACH

First in Human Ad26.Mos.HIV and heterologous regimens

Phase 1/2a HIV-V-A004/ APPROACH N=400

Regimen Selection

Manufacturing challenge

Ad26.Mos.HIV

Ad26 vectors with Mosaic *gag-pol* or *env* inserts

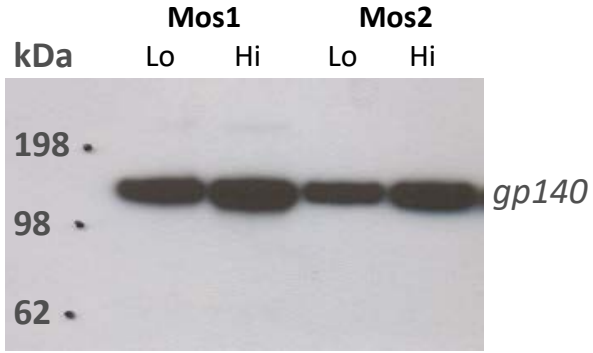
- Ad26.Mos1.Gag-Pol ✓
- Ad26.Mos2.Gag-Pol ✓
- Ad26.Mos1.Env ✓
- Ad26.Mos2.Env ✗

- 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

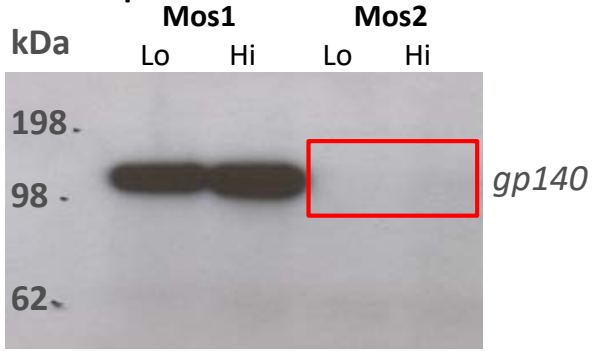
Problem

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

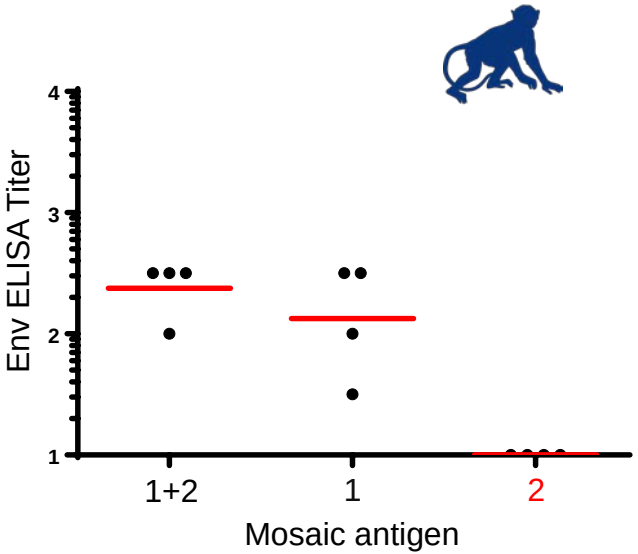
Cell lysate shows expression of Mos2 env...



... but protein is not secreted



... and is not eliciting a humoral immune reponse



Problem

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

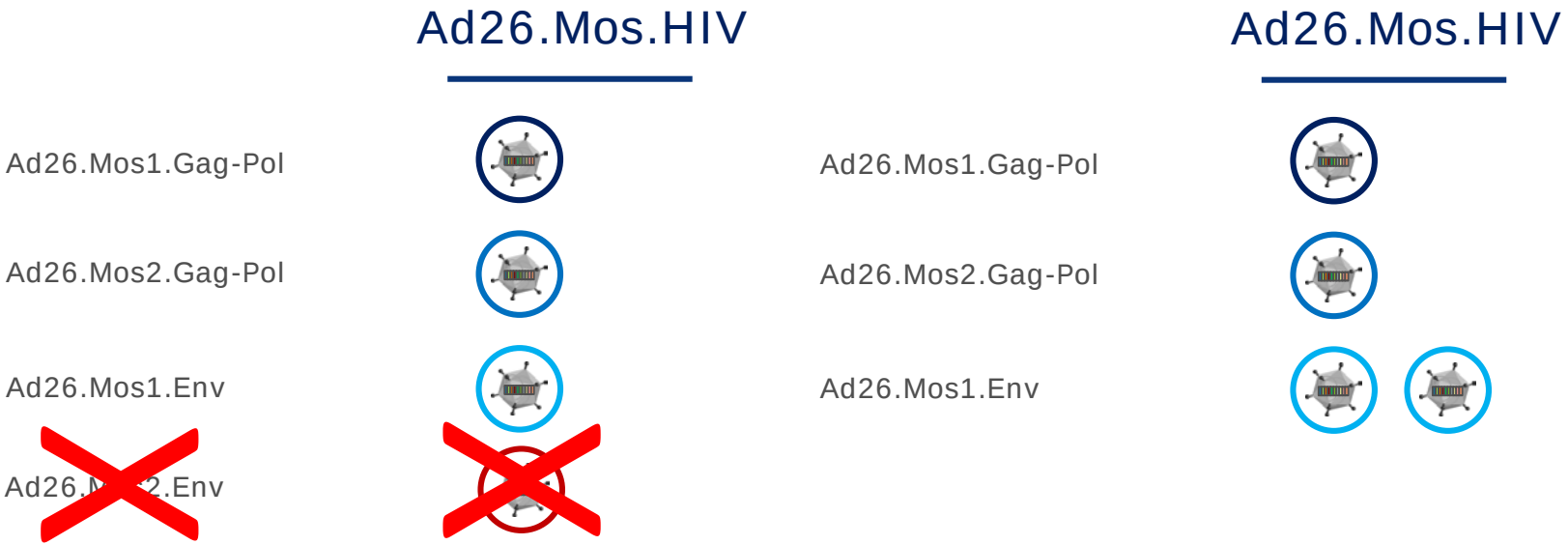
Interim solution

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

Durable Solution

Develop an alternative mos2.Env that is compatible with delivery

AdVac® Vaccine components for the NHP13-19 and APPROACH studies



NHP13-19 - study design

Group	N	Vaccination 1&2 wk 0, wk 12	Vaccination 3&4 wk 24, wk 48		IR SHIV challenge 6 months after 4th dose
1	50	Ad26.Mos.HIV	Ad26.Mos.HIV	+ High Dose Clade C gp140	
2	50	Ad26.Mos.HIV	Ad26.Mos.HIV		
3	50	Ad26.Mos.HIV	MVA- Mosaic	+ High Dose Clade C gp140	
4	50	Ad26.Mos.HIV	MVA- Mosaic		
5	50	Ad26.Mos.HIV		+ High Dose Clade C gp140	
6	50	Placebo	Placebo		

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

APPROACH - study design

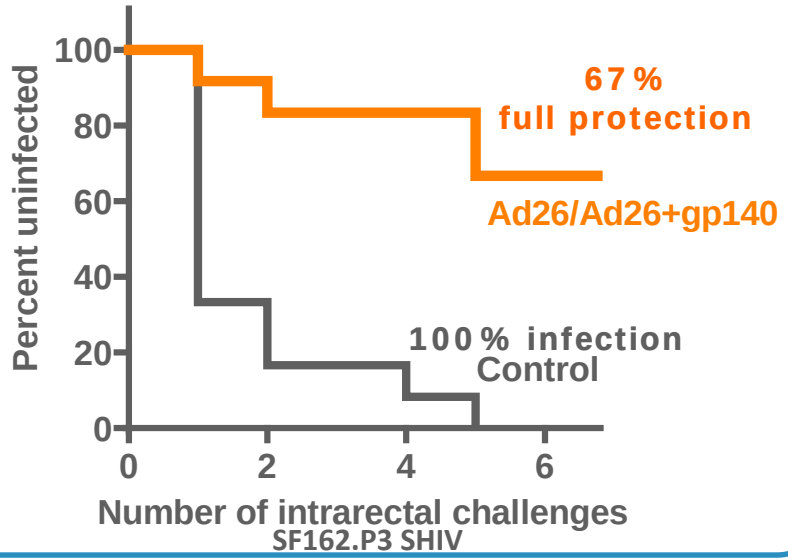
Group	N	Vaccination 1&2 wk 0, wk 12	Vaccination 3&4 wk 24, wk 48		Follow up wk 52 to 96
1	50	Ad26.Mos.HIV	Ad26.Mos.HIV	+ High Dose Clade C gp140	
2	50	Ad26.Mos.HIV	Ad26.Mos.HIV	+ Low Dose Clade C gp140	
3	50	Ad26.Mos.HIV	Ad26.Mos.HIV		
4	50	Ad26.Mos.HIV	MVA- Mosaic	+ High Dose Clade C gp140	
5	50	Ad26.Mos.HIV	MVA- Mosaic	+ Low Dose Clade C gp140	
6	50	Ad26.Mos.HIV	MVA- Mosaic		
7	50	Ad26.Mos.HIV		+ High Dose Clade C gp140	
8	50	Placebo	Placebo		

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

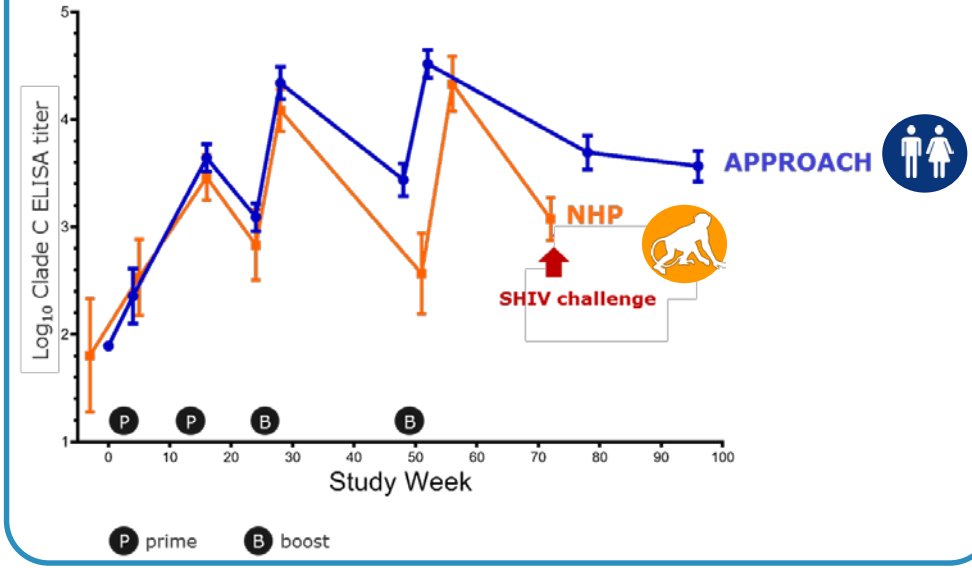
Ad26/Ad26+gp140: A Promising HIV Prophylactic Vaccine

Immune responses associated with NHP protection compare favorably in humans

High efficacy in NHP



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**

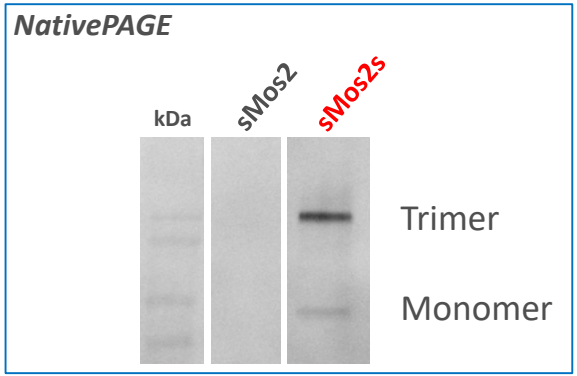
Interim solution

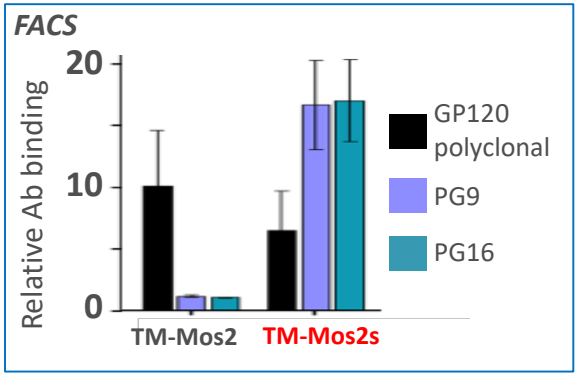
Double dose of Ad26.Mos1.Env for NHP and APPROACH studies

Durable Solution

Develop an alternative mos2.Env that is compatible with delivery

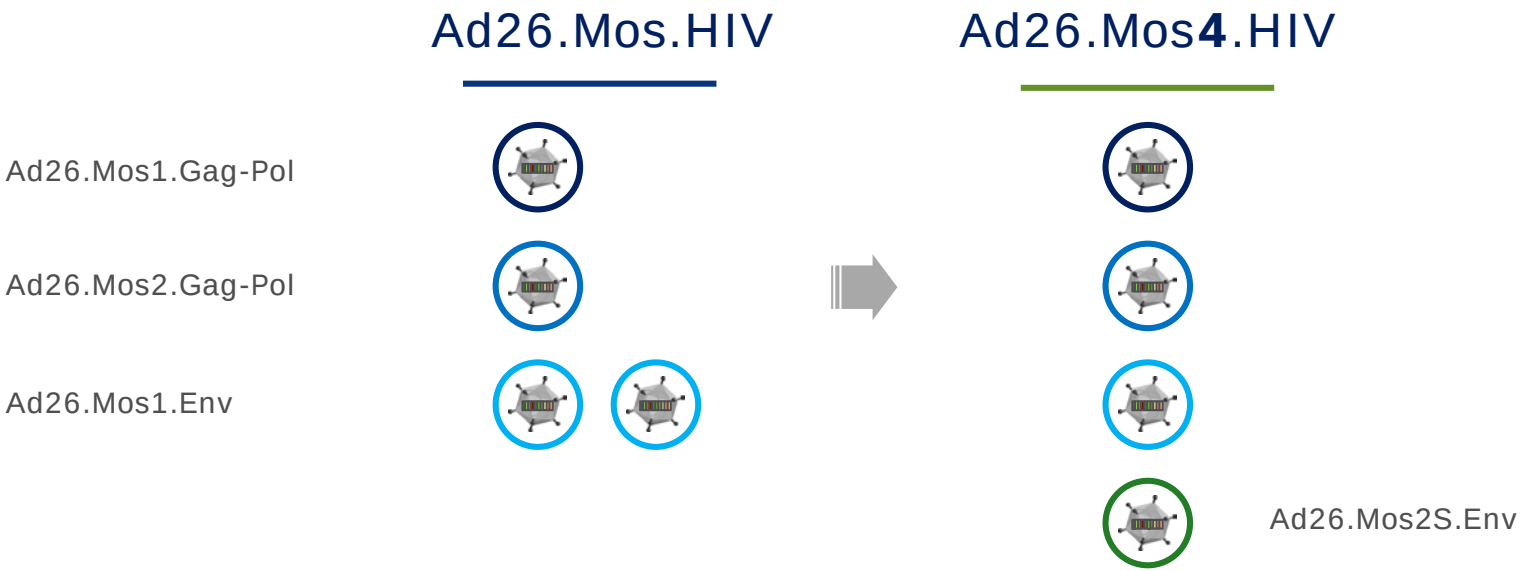
Design new clade C Env antigen to replace mosaic 2 Env: Mos2s





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



HPX2004 / HVTN117 / IPCAVD011

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

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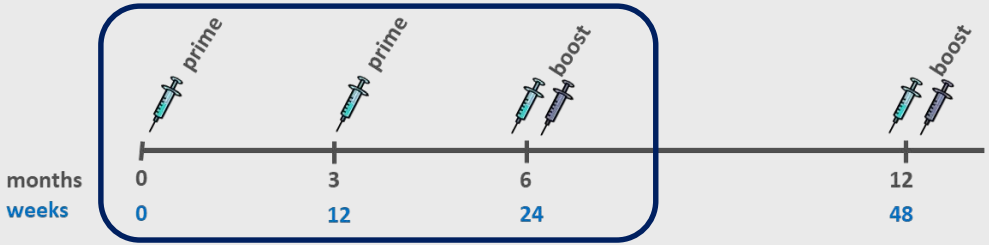
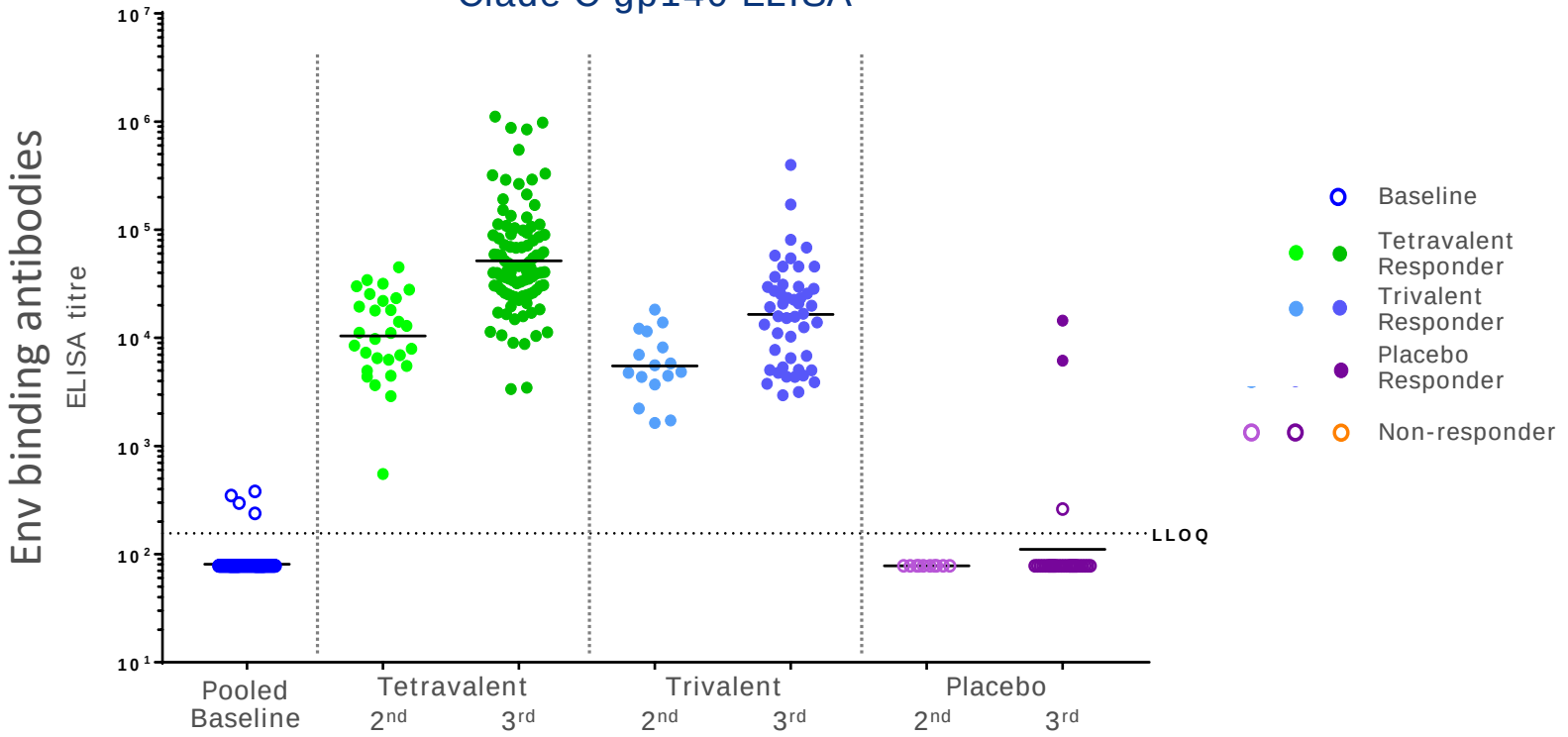
TRAVERSE – study design

Group	N	Prime wk 0, wk 12	Boost wk 24, wk 48		Follow up
1A	55	Ad26.Mos.HIV	Ad26.Mos.HIV	+ High Dose Clade C gp 140	
1B	11	Placebo	Placebo		
2A	110	Ad26.Mos4.HIV	Ad26.Mos4.HIV	+ High Dose Clade C gp 140	
2B	22	Placebo	Placebo		



Immunogenicity

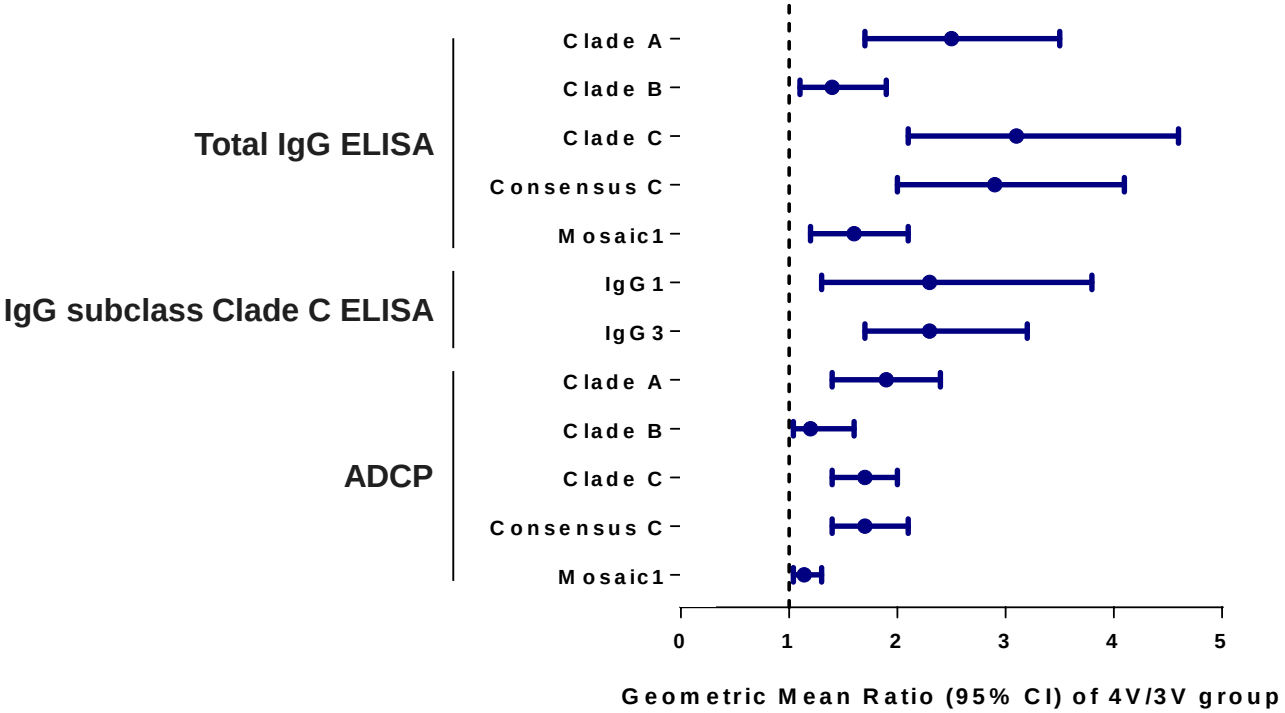
Clade C gp140 ELISA



D. Stieh, HIV R4P Conference, Madrid October 2018

Immunogenicity

Significant improvement across clades & assays



Conclusions

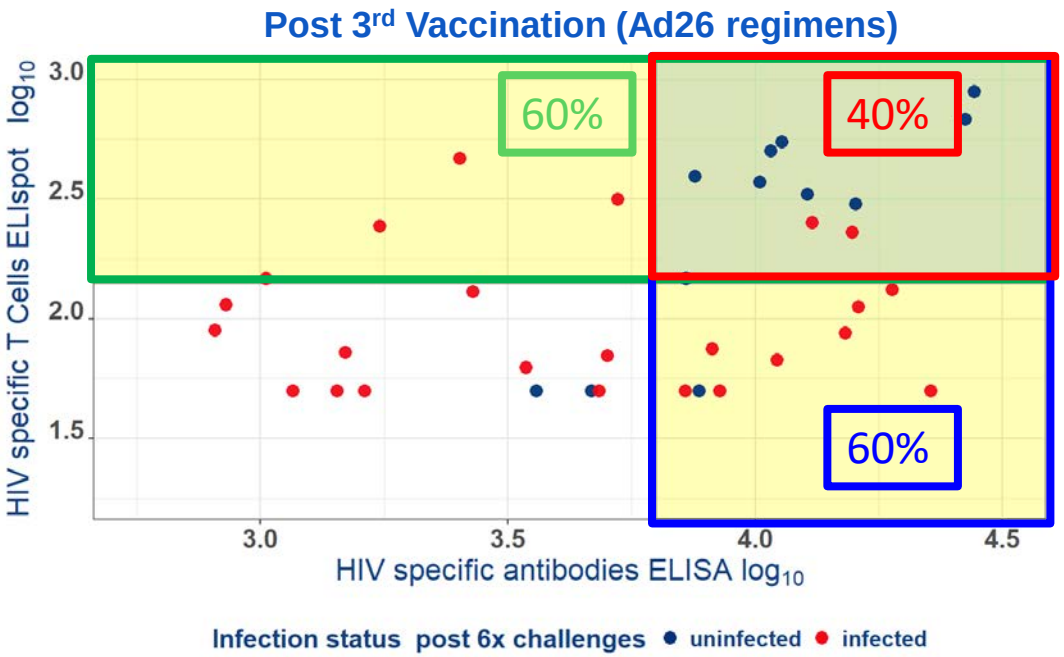
TRAVERSE, week 28

SAFETY	HUMORAL	CELLULAR
Favorable safety profile through 3rd vaccination	Tetravalent Ad26 induces more **Broad and Functional** HIV Env-specific humoral responses	Tetravalent Ad26 induces **Stronger** Env-specific cellular responses

From Early Development to Efficacy trials

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

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

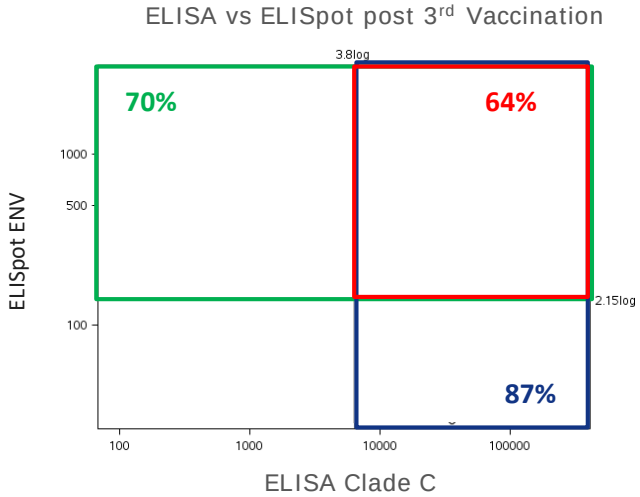
Regimen GO with human data from APPROACH post 3rd when:

>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

Prime at wk 0, 12	Boost at wk 24, 48	
Ad26.Mos.HIV 3-valent	Ad26.Mos.HIV 3-valent	gp140 Clade C with Alum



Final Regimen selection for Ph2b based on Immunological PoC

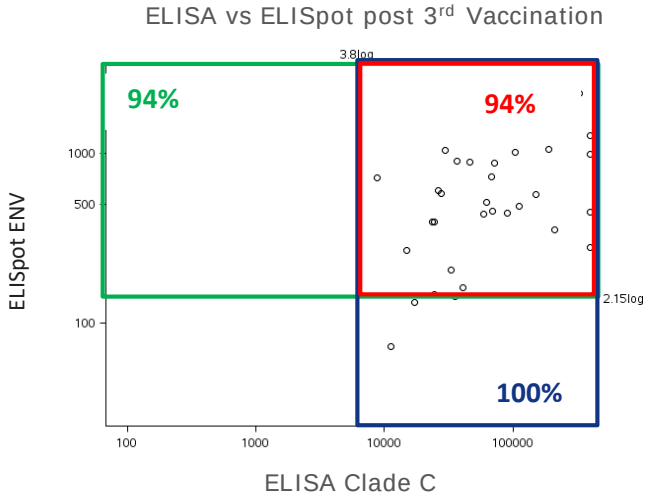
Ph1/2a APPROACH

Prime at wk 0, 12	Boost at wk 24, 48	
Ad26.Mos.HIV 3-valent	Ad26.Mos.HIV 3-valent	gp140 Clade C with Alum

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

Ph1/2a TRAVERSE

Ad26.Mos.HIV 4-valent	Ad26.Mos.HIV 4-valent	gp140 Clade C with Alum



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.

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Imbokodo / HVTN705 / HPX2008:

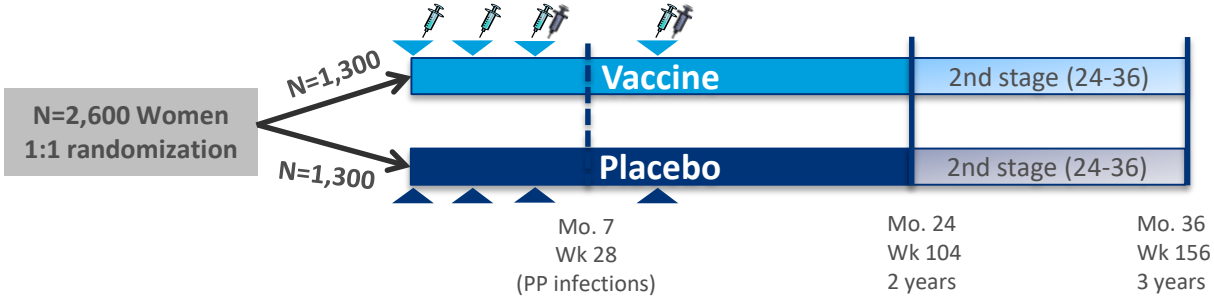
a phase 2b multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial

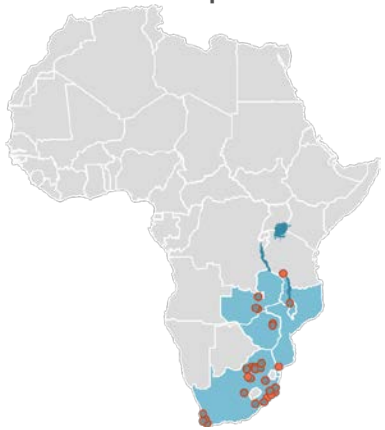
Population: Sexually active HIV-1 uninfected women (born female), age 18-35 years

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

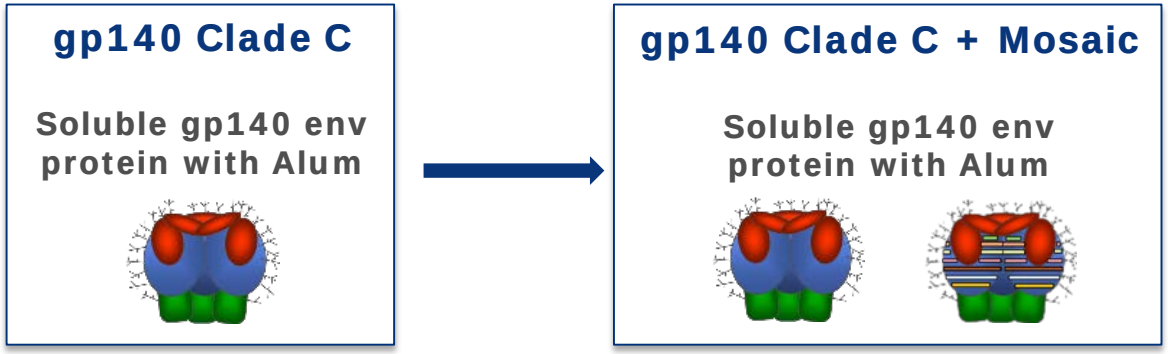




Status: enrolling

Towards the final regimen for Phase 3

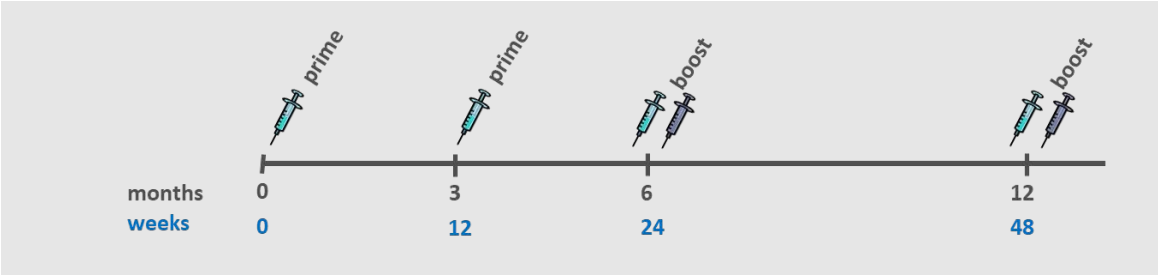
From Clade C gp140 alone to Clade C + Mosaic gp140 combination



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

Group	N	Prime wk 0, wk 12	Boost wk 24, wk 48		Follow up
1	25	Ad26.Mos4.HIV	Ad26.Mos4.HIV	+ Clade C gp 140	
2	100	Ad26.Mos4.HIV	Ad26.Mos4.HIV	+ Clade C gp 140 + Mosaic gp140	
3	25	Placebo	Placebo		



Status: data is being analysed

A Few More Challenges Ahead in HIV Vaccine Development…. But Good Reasons to believe

	NHP Efficacy Per exposure risk reduction	**Clinical efficacy** *HIV-1*
ALVAC / gp120	29% *not significant*[1]	31% *RV144 trial*[2]
DNA/Ad5	*0%*	*0%* *HVTN505 trial*[3]
Ad26 / Ad26+gp140	**94%**[4]	Pending

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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MHRP
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Bruce Walker

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Elisabeth Heger

...and their teams

#makeHIVhistory

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COMPOUND DEVELOPMENT TEAM

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John Trott
Frank Wegmann
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Danielle van Manen
Lucy Rutten

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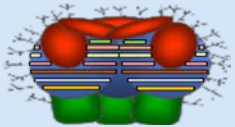
Stefan Thoelen

Johan van Hoof
Paul Stoffels



All the investigators, their staffs and the volunteers for their participation in this clinical program

Thank You

Martin Freeman, Untitled
Diagnosed with AIDS in 1990, Martin lives in
San Francisco where he continues to create new pieces.

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