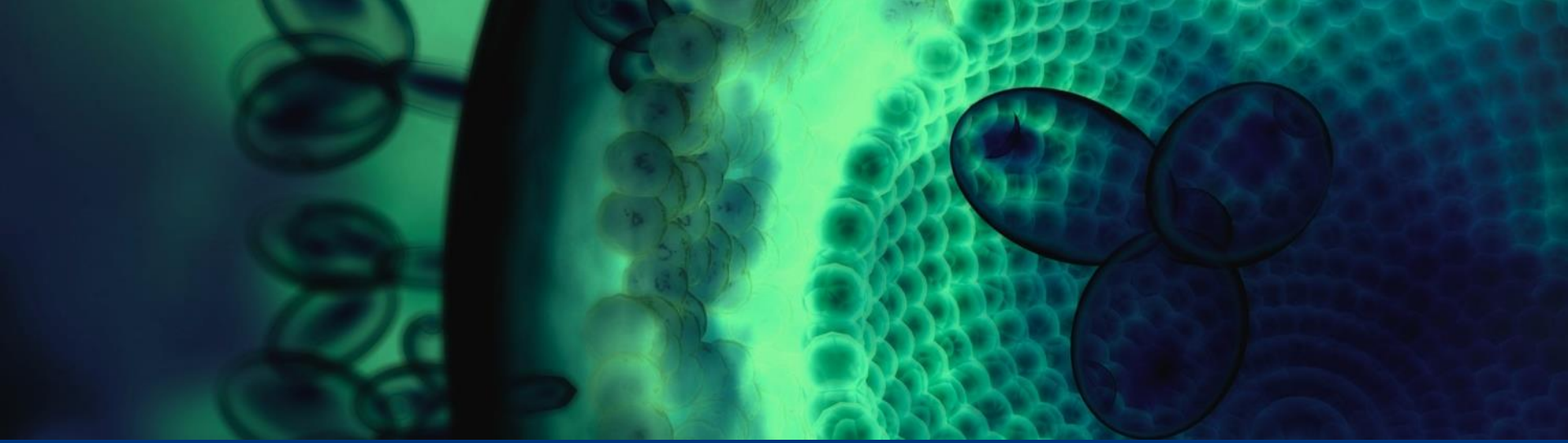


Advances in the development of a vaccine against HIV

XIV CURSO EN AVANCES EN INFECCION VIH Y HEPATITIS VIRALES

Valerie Oriol Mathieu, Global Medical Affairs Leader

Vigo, 31th January 2020

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
- I hold equity shares in Johnson & Johnson

HIV remains a high unmet need on a global scale

Global disease burden in 2018:

37.9 million people
worldwide are currently **living with HIV/AIDS**

1.8 million children
currently **living with HIV**

770,000 died
from AIDS-related illnesses

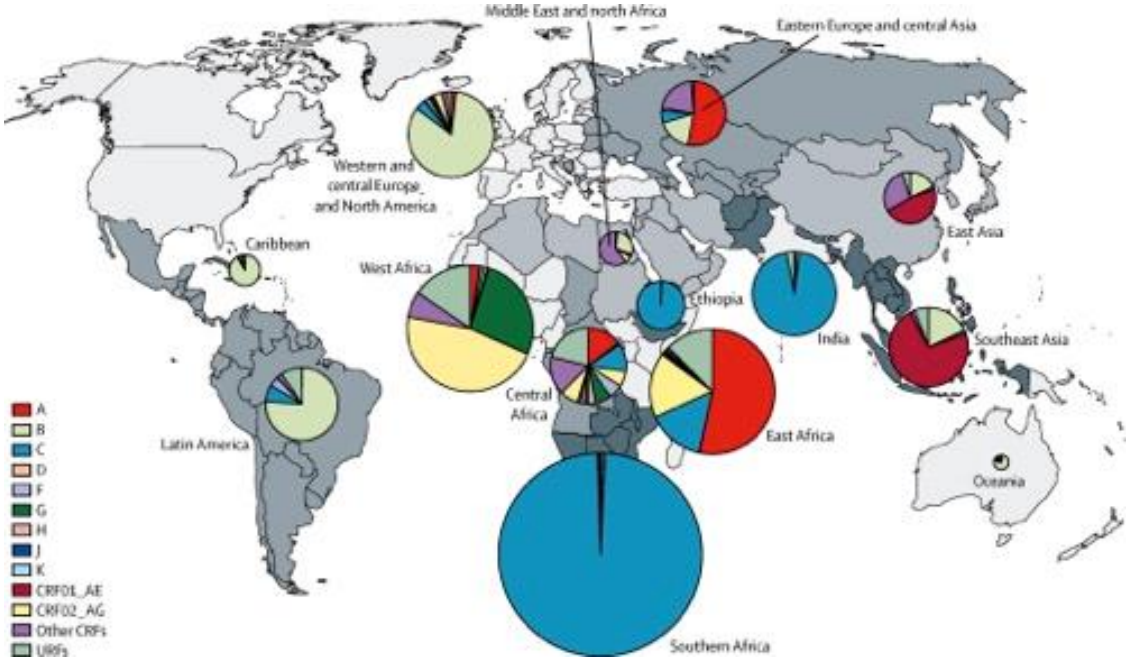
23.3 million
of people living with HIV **received antiretroviral drugs**

1.7 million new HIV infections
5000 per day

UNAIDS 2019 fact sheet: https://www.unaids.org/en/resources/fact-sheet

High diversity of HIV types, groups, subtypes (clades) and recombinants

- HIV has two major types, HIV-1 and -2
  - these are divided into groups, subtypes and recombinant forms
- Globally, >90% of HIV infections belong to HIV-1 group M viruses
  - these are classified into 9 subtypes (clades) (A-D, F-H, J, K) and >50 circulating recombinant forms (CRFs)



Hemelaar et al,Lancet Infect Dis 2019;19: 143–55

Current HIV Prevention Toolkit

Botswana, mid-nineties
https://worldlitup.com/botswana-aids/

Prevention tool (year of recommendation)

- Male and female condoms
- Behavior change including HIV testing
- Prevention of mother-to-child transmission **(PMTCT, 2000)**
- Voluntary medical male circumcision **(VMCC, 2007)**
- Post-exposure prophylaxis **(PEP)**
- Treatment as prevention **(TasP)**
- Oral pre-exposure prophylaxis **(PrEP, 2015)**

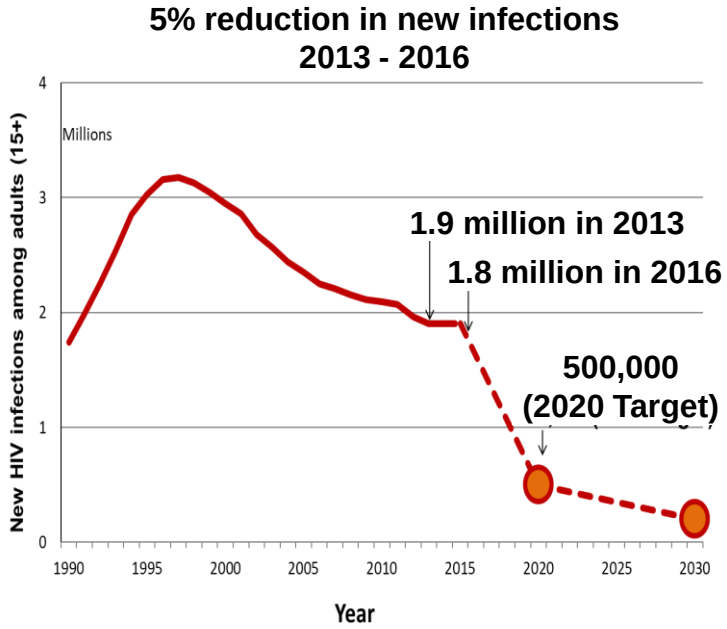


WHO Consolidated Guidelines on HIV prevention, diagnosis, treatment and care for key populations. Updated version, July 2016
Ghosn et al. HIV Lancet 2018

2020 global target in new infection reductions missed

- HIV epidemic peak is behind us, **however**:
  - Only 5% reduction in incidence between 2013 and 2016
  - High rates in adolescents and young women
  - Young people are most likely to be unaware of their infection and continue the transmission chain

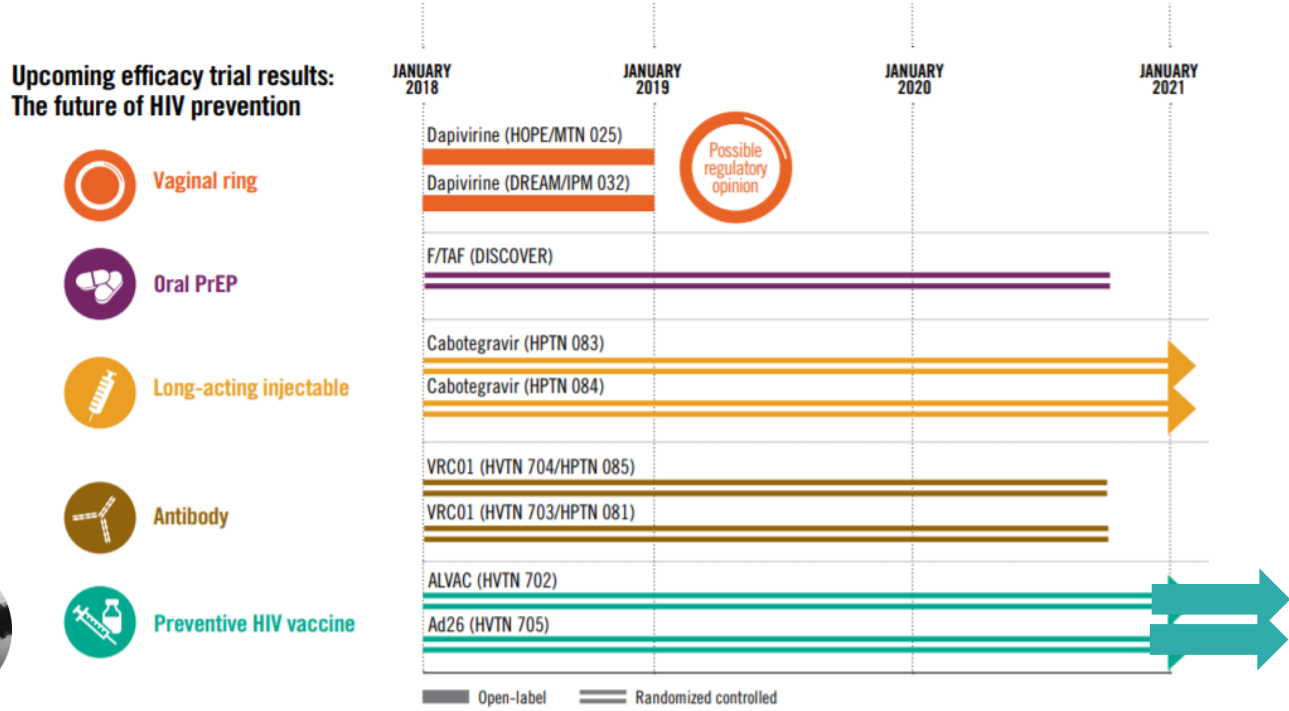
- Significant number of infections happen in regions with medium/low incidence because of large populations: **Prevention cannot focus only on high risk behavior/ populations**



1. *AVAC REPORT 2017*
2. *Adapted from: UNAIDS Data 2017 http://www.unaids.org/en/resources/documents/2017/2017_data_book*

Potential new options for HIV Prevention

- Microbicide vaginal rings (dapivirine)
- Rectal microbicides
- Injectable antiretroviral long-acting (ARV) drugs
- HIV vaccines
- Monoclonal Antibodies



1. https://www.avac.org/sites/default/files/resource-files/AVACreport2018.pdf
2. Ghosn et al. HIV Lancet 2018

Why is there no AIDS vaccine, despite 30 years of concerted worldwide research?

HIV challenges the standard vaccine approaches first and foremost because, unlike diseases such as measles and chickenpox, no one naturally recovers from infection with HIV.

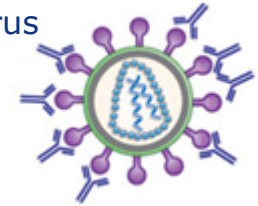
Additional complexity due to:

- Immediate and definitive HIV integration in host genome
- Lack of spontaneaous recovery from HIV infection
- Viral evasion of humoral and cellular immune responses
- Extensive HIV-1 clade and sequence diversity
- No immunogen designed/produced yet able to elicit broadly NAbs
- Immune correlates of protection unclear

The quest for immune responses:
mechanisms (or combination of mechanisms) potentially necessary to prevent HIV infection

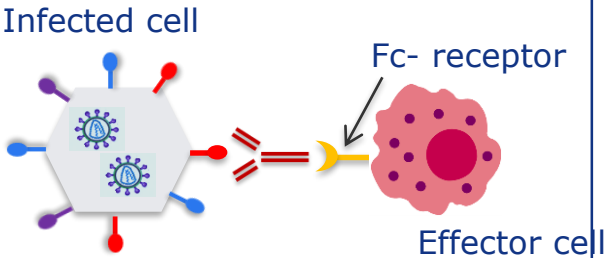
Eliciting broadly neutralizing antibodies

HIV Virus



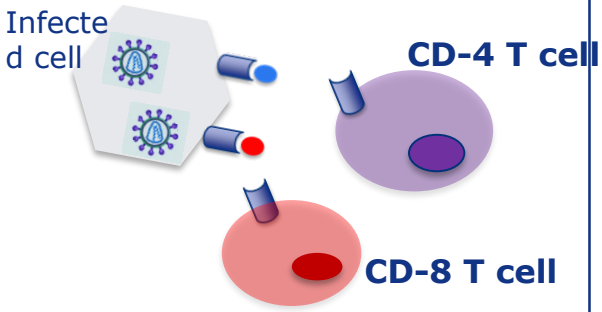
- Preventing cell infection and cell to cell viral spread
- **Broadly** neutralizing antibodies neutralize various HIV strains

Triggering other type of functional antibody responses



- Lysis or clearance of infected cells via Fc-mediated effector mechanisms

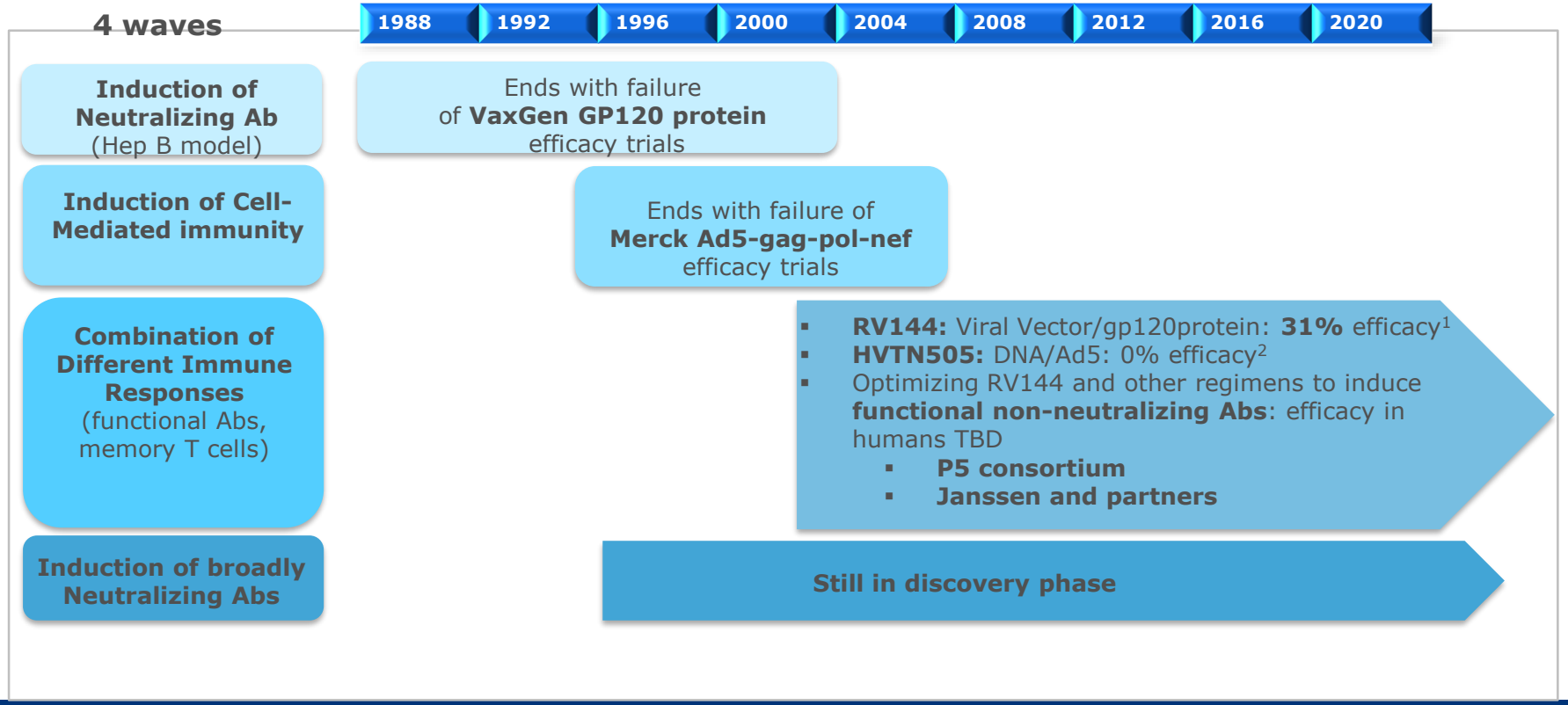
Inducing cell-mediated immunity



- Killing of infected cells by cytotoxic T cells via viral antigen presentation on MHC

Paradigms of HIV vaccine development

Evolution of HIV vaccine design to counter HIV diversity



1. Rerks-Ngarm S, et al.: Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009, 361:2209-2220.
2. Hammer SM, Sobieszczyk MK, Janes H, et al. for the HVTN 505 Study Team. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med. 2013;369(22):2083-2092
3. https://www.avac.org/infographic/hiv-vaccine-efficacy-trials-surge-activity

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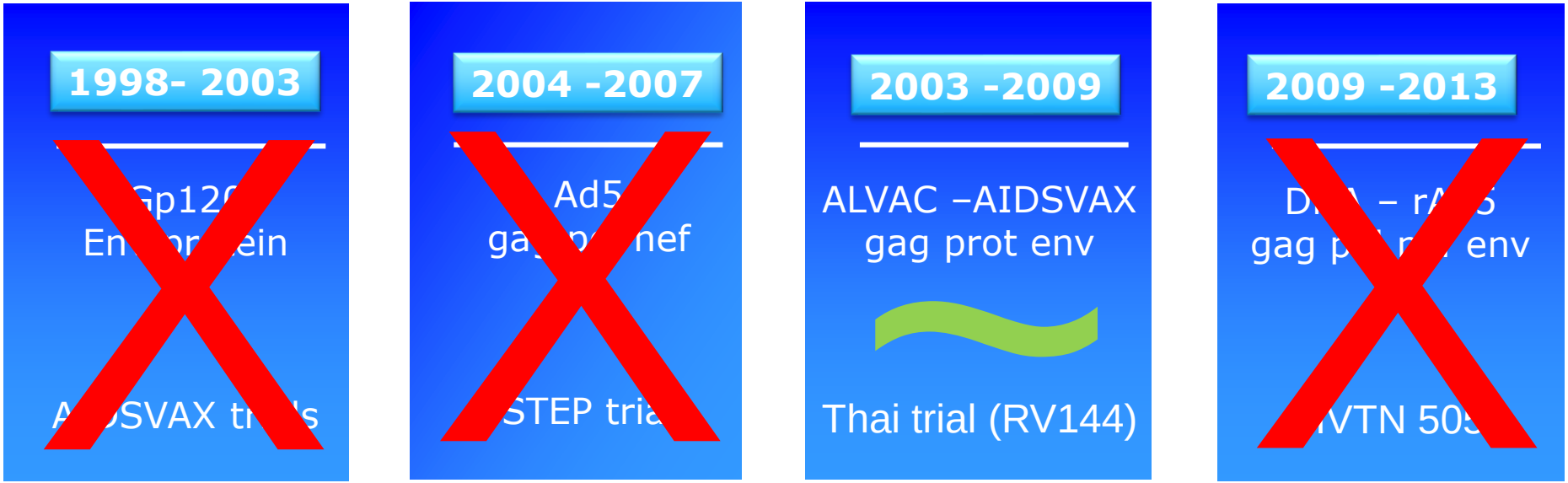
HIV vaccine efficacy studies: completed
New efforts towards HIV vaccine development are necessary



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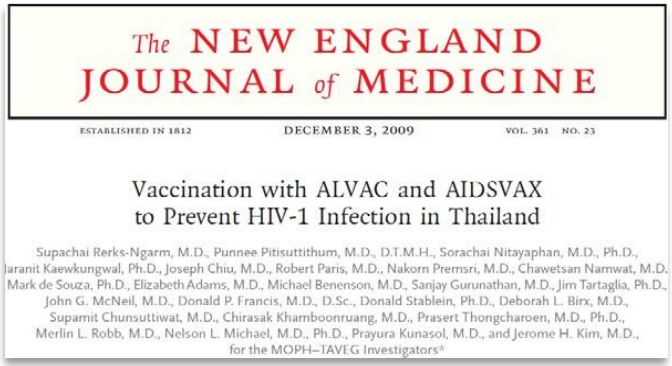
2. Hammer SM, Sobieszczyk MK, Janes H, et al. for the HVTN 505 Study Team. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med. 2013;369(22):2083-2092
3. https://www.avac.org/infographic/hiv-vaccine-efficacy-trials-surge-activity

Thai Trial (RV144)

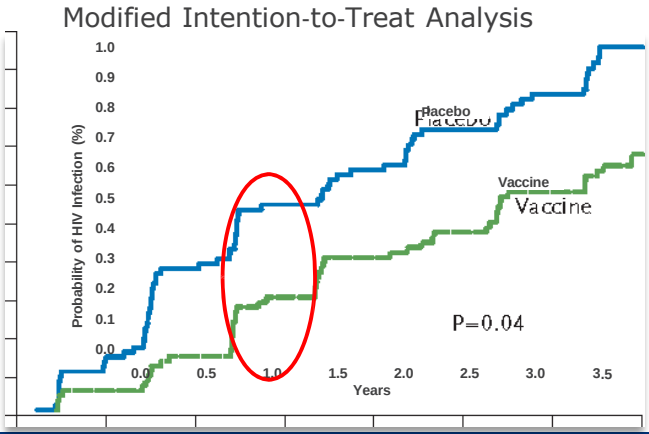


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Premsri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Birx, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH–TAVEG Investigators*



Prime: ALVAC vCP1521 (Recombinant Canarypox vector)

Boost: ALVAC vCP1521 plus VAXGEN Env protein (B/E) (Env subunit protein gp120)

Schedule: 0,1,3,6 months; 16,000+ volunteers; 1:1 vaccine: placebo; follow-up for 3 years

Efficacy against HIV infection: 31% at 42 months, 60 % at one year
Lack of durability

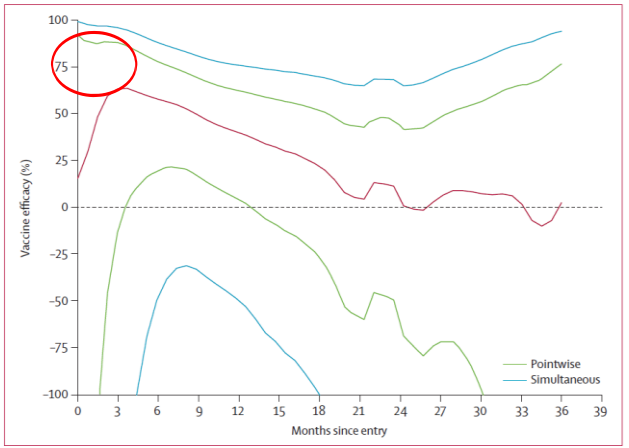


Figure 2: Vaccine efficacy point estimates over time
Vaccine efficacy rates are given over time (red line) with 95% pointwise CIs (green line) and 95% simultaneous CIs (blue line).

1. Rerks-Ngarm S, et al. New Eng J Med 2009;361;
2. Robb M, et al. Lancet Infect Dis 2012;12:531–537

HIV vaccine efficacy studies: ongoing

NIH-BMGF-HVTN Sanofi-GSK

ALVAC
gp120/MF59

gag pro env

2016 - xxxx

HVTN 702

NIH-BMGF-HVTN JANSSEN

Ad26.Mos4.HIV
gp140 Clade C/Alum

gag pol env

2017 - xxxx

HVTN 705 / HPX2008

NIH-HVTN JANSSEN

Ad26.Mos4.HIV
gp140 Clade C/Mosaic/Alum

gag pol env

2019 - xxxx

HVTN 706 / HPX3002

Our goal

A prophylactic HIV vaccine that protects against the globally relevant strains of HIV-1

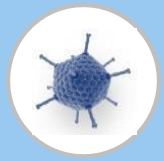
Heterologous vaccine regimen using Ad26 viral vectors expressing mosaic HIV antigens, and soluble trimeric gp140 envelope proteins

Our core technology platforms

PER.C6® cell line

- Highly permissive to human and animal viruses
- High yields (# vaccine doses) with small footprint – resulting in lower capex and lower COGs
- Formulation know-how has resulted in competitive thermostability profile
- Market authorization for PER.C6® derived product Rekovelle® (Ferring)

AdVac®



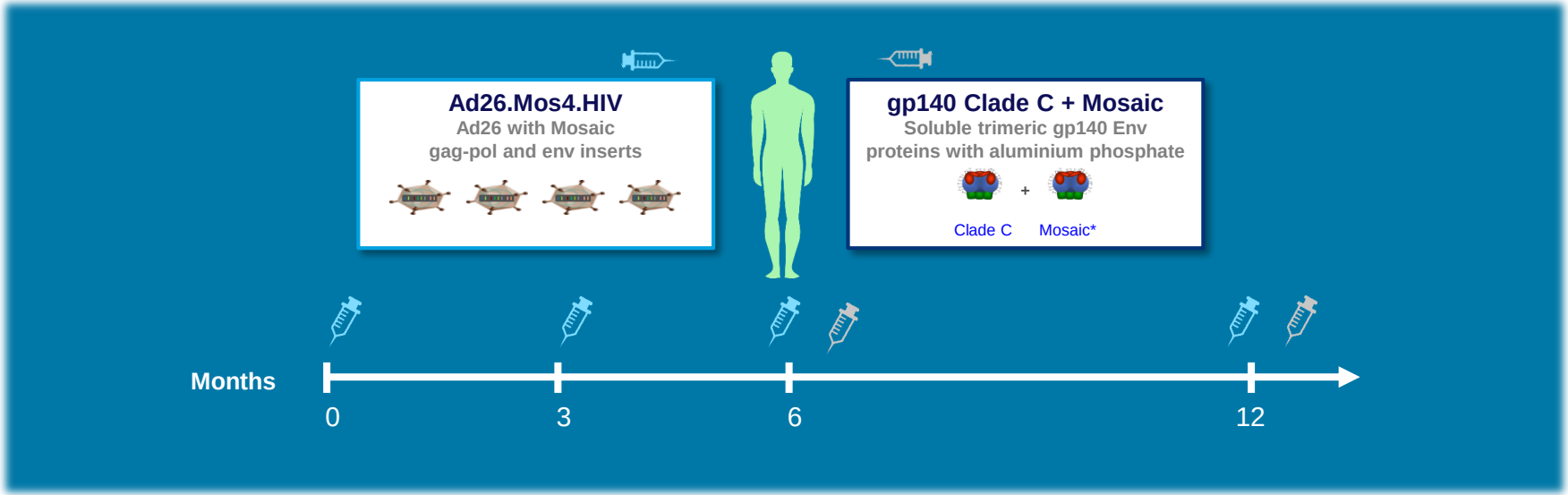
- Induction of robust, durable immune responses
  - Humoral and Cellular
- Characterization of humoral immune responses reveals unique features (ADCC, ADCP, ADCD…) in addition to neutralization
- Potential application across multiple therapeutic areas
- Safe and well-tolerated

- Platform concept; recognized by key Regulatory Authorities (FDA, MHRA):
  - Plug and Play
  - Fast from concept to FIH
  - Fast 'high output delivery' leveraging established platform process

Global HIV-1 Prophylactic Vaccine High Level TPP

- **Goal for primary efficacy**
  - High level of prevention of HIV-1 infection against the globally predominant clades
  - Immunologic responses associated with protective efficacy against multiple clades
- **Safety and tolerability**
  - Overall safe and well tolerated.
  - Mild to moderate local and/or systemic reactogenicity profile
- **Administration**
  - Intra- Muscular injection
  - Administration of 4 vaccinations over a 12 month period (Month 0 and 3 = Ad26.Mos4.HIV, Month 6 and 12 = Ad26.Mos4.HIV and Clade C + Mosaic gp140 Env), booster immunization after durability period ends
- **Storage**
  - 2-8 °C (Ad26 and protein(s)
  - Shelf life of final products: at least 24 months (2-8°C)
- **Presentation**: Separate vials for Ad26 and for protein(s) in liquid formulations
- **Indication**: Prevention of HIV-1 infection in adults (initial indication) and adolescents (later)

HIV-1 prophylactic final vaccine regimen in development



4 vaccination timepoints over a year

Adapted from Stieh D., IAS Mexico City, abst. TUAC0402LB , 2019

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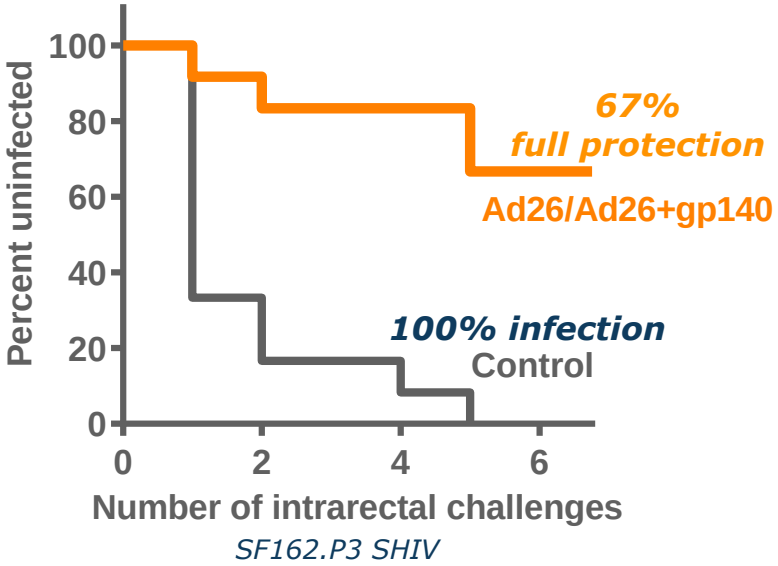
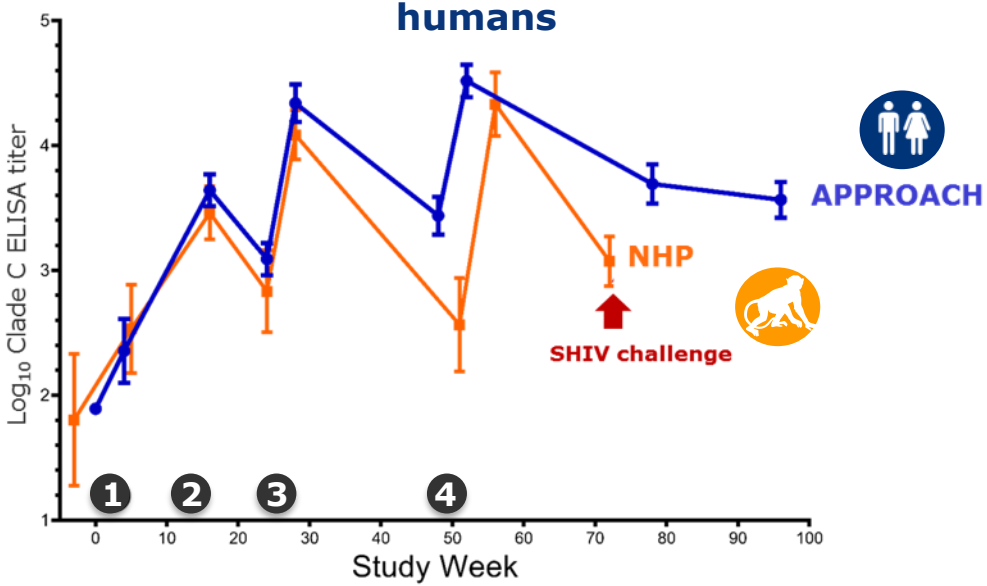
Ad26, Ad26 and gp140: A Promising HIV Prophylactic Vaccine

Immune responses associated with NHP protection compare favorably in humans

High efficacy in NHP



Favorable immunogenicity in humans



*Study # 13-19
**APPROACH: Phase 1/2a / HIV-V-A004/ IPCAVD009

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

Tomaka, 22nd International AIDS Conference, July 2018

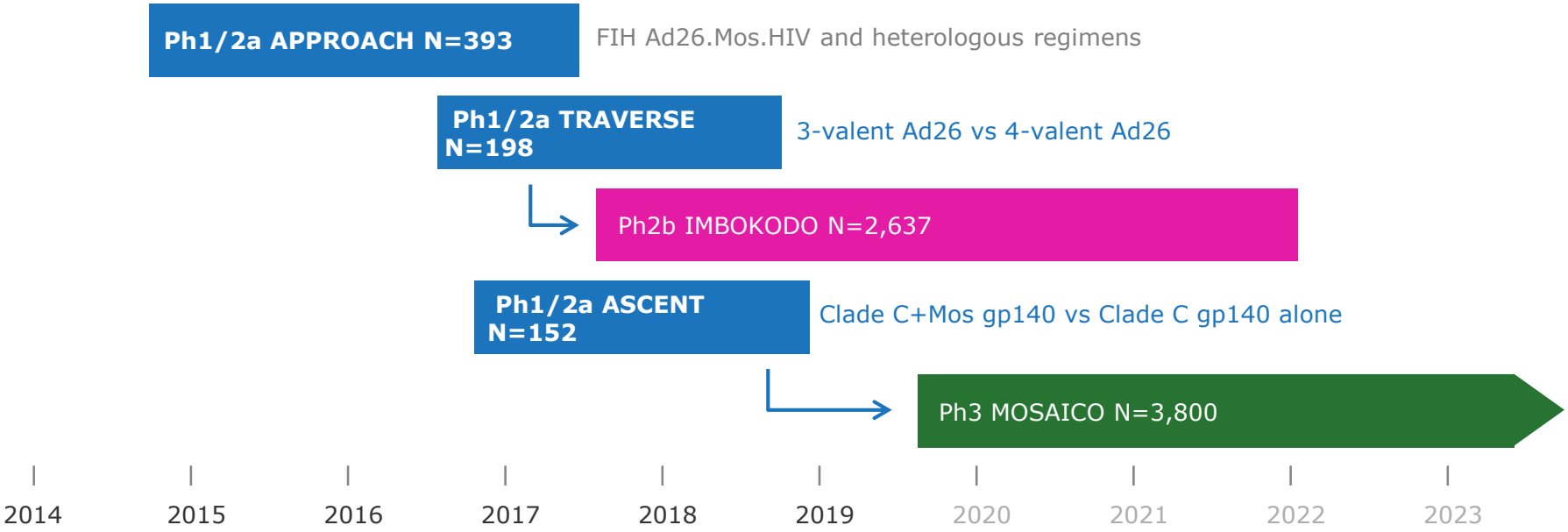
Protection in NHP elicited by Janssen's HIV Px vaccine and other candidates tested to date

	NHP Efficacy Per exposure risk reduction		Clinical Efficacy
	SIV-mac251	*SHIV-SF162P3*	*HIV-1*
ALVAC / gp120	44%[1]	29% *not significant*[2]	31% *RV144 trial*[3]
DNA / Ad5	0%[4]	-	0% *HVTN505 trial*[5]
Ad26 / gp140	90%	79%	-
Ad26 / Ad26+gp140	-	**94%[6]**	Pending

1. Franchini Nat Med 2016; 2. Barouch unpublished; 3. Rerks-Ngarm NEJM 2009 361:2209; 4. Letvin Sci Trans Med 2011 3:81; 5. Hammer NEJM 2013 22:2083; 6 . Study 10. 13-19, The Lancet, July 2018

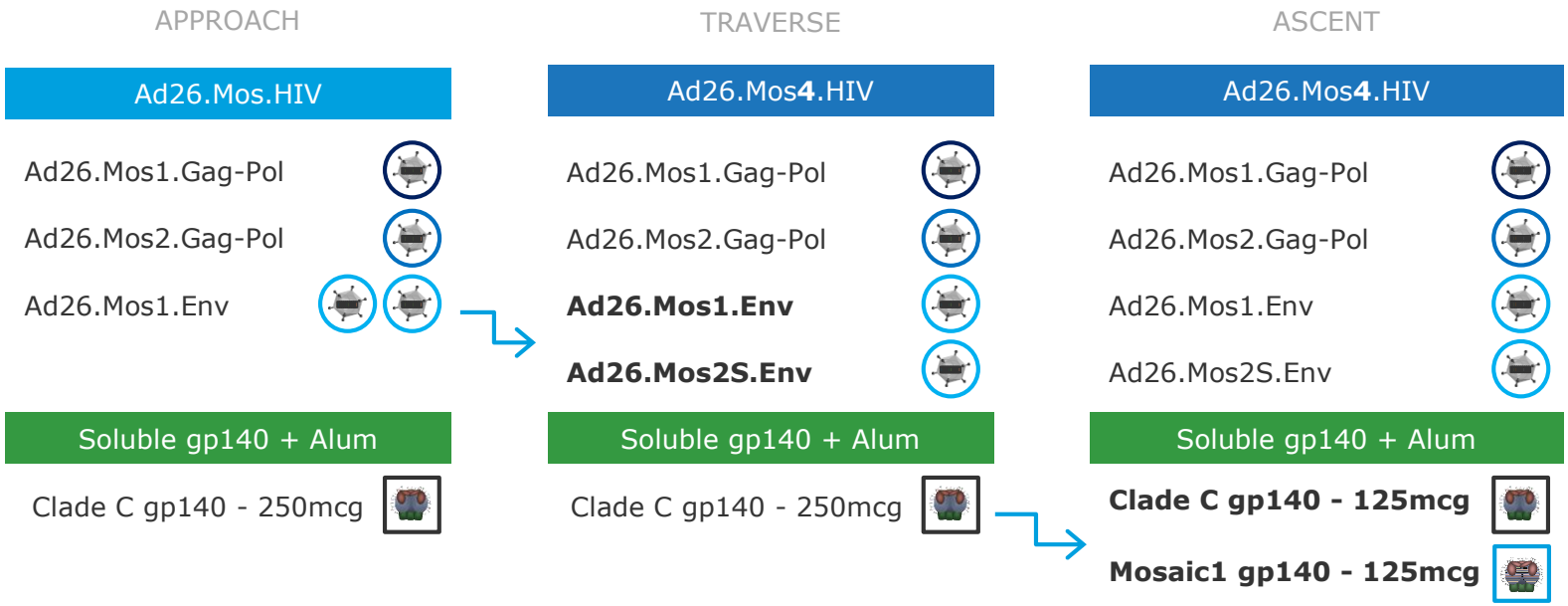
Clinical development plan

NHP #13-19
Pre-clinical study



APPROACH HIV-V-A004: NCT02315703
TRAVERSE HPX2004/HVTN117: NCT02788045
ASCENT HPX2003/HVTN118: NCT02935686
IMBOKODO HPX2008/HVTN705: NCT03060629
MOSAICO HPX3002/HVTN706: NCT03964415

Phase 1/2a clinical trials: aiming to expand the scope of global coverage



Stieh D., Mexico, IAS 2019
ASCENT HPX2003/HVTN118: NCT02935686

Safety summary from APPROACH, TRAVERSE and ASCENT

- All vaccine regimens were well tolerated
- No deaths through the end of follow-up period (LTE ongoing)
- No pausing rules met
- Rare related SAEs

- Most unsolicited events were mild and moderate

- Reactogenicity profile (Solicited Adverse Events) similar to previous experience
  - Generally, across platform, we see Solicited Adverse Events decreasing in incidence with further vaccination in the schedule
  - Injection site pain, fatigue, headache and myalgia were the most frequent reported solicited adverse events.

APPROACH HIV-V-A004: NCT02315703
Barouch DH, et al. Lancet;2018;10143:232–3;
TRAVERSE HPX2004/HVTN117: NCT02788045
Stieh D., Madrid, HIVR4P 2018
ASCENT HPX2003/HVTN118: NCT02935686
Stieh D., Mexico, IAS 2019

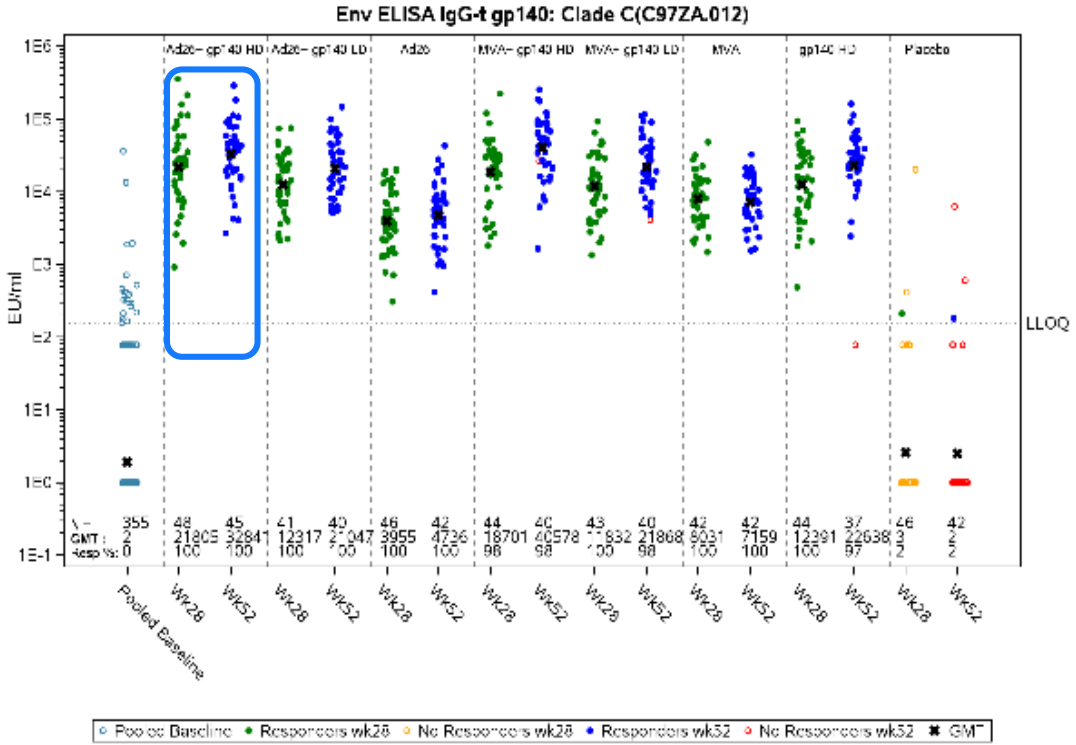
APPROACH

HIV-V-A004

Phase 1/2a Randomized, Double-Blind, Placebo-Controlled Study Evaluating Safety/Tolerability and Immunogenicity of Heterologous Vaccine Regimens using combinations of Ad26.Mos.HIV, MVA-Mosaic and gp140 Envelope Protein.

ELISA: APPROACH post 3rd & 4th vaccination

Total IgG gp140 ENV Clade C



Maintained number of responders post 4th 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

APPROACH HIV-V-A004: NCT02315703
Barouch DH et al., The Lancet, 2018;392:232–243

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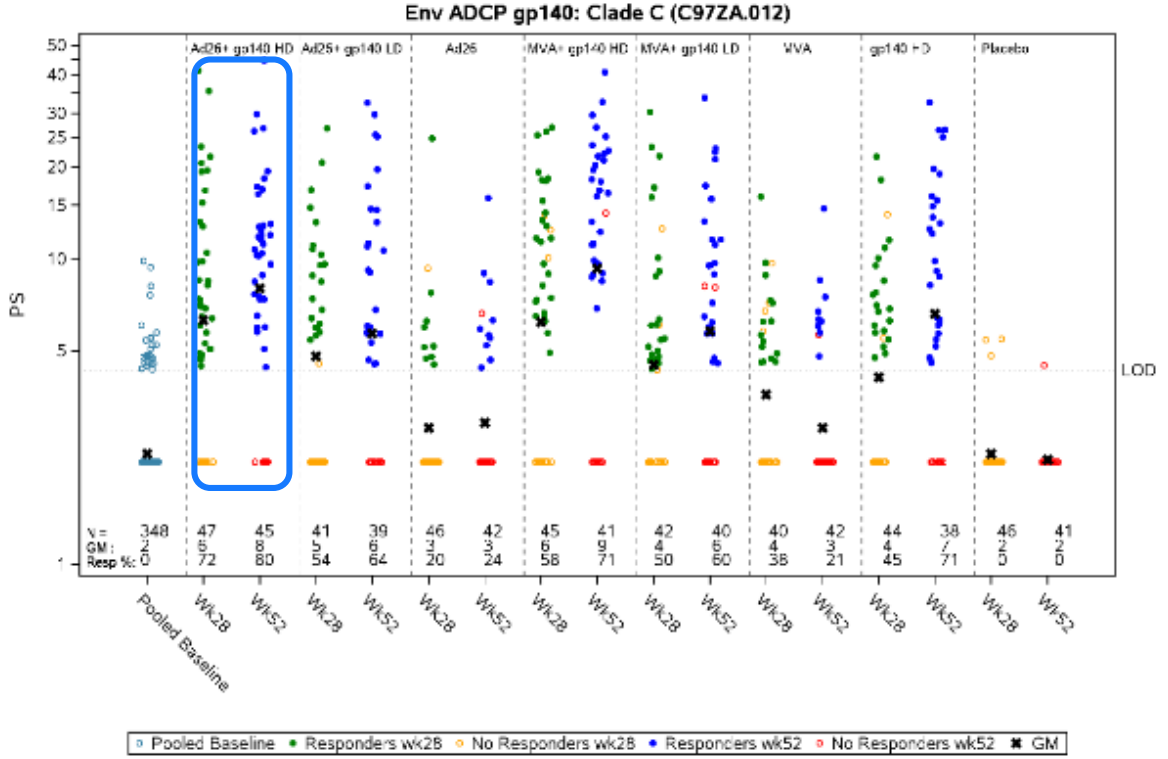
ADCP: APPROACH post 3rd & 4th vaccination

gp140 ENV Clade C



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

APPROACH HIV-V-A004: NCT02315703

Barouch DH et al., The Lancet, 2018;392:232–243

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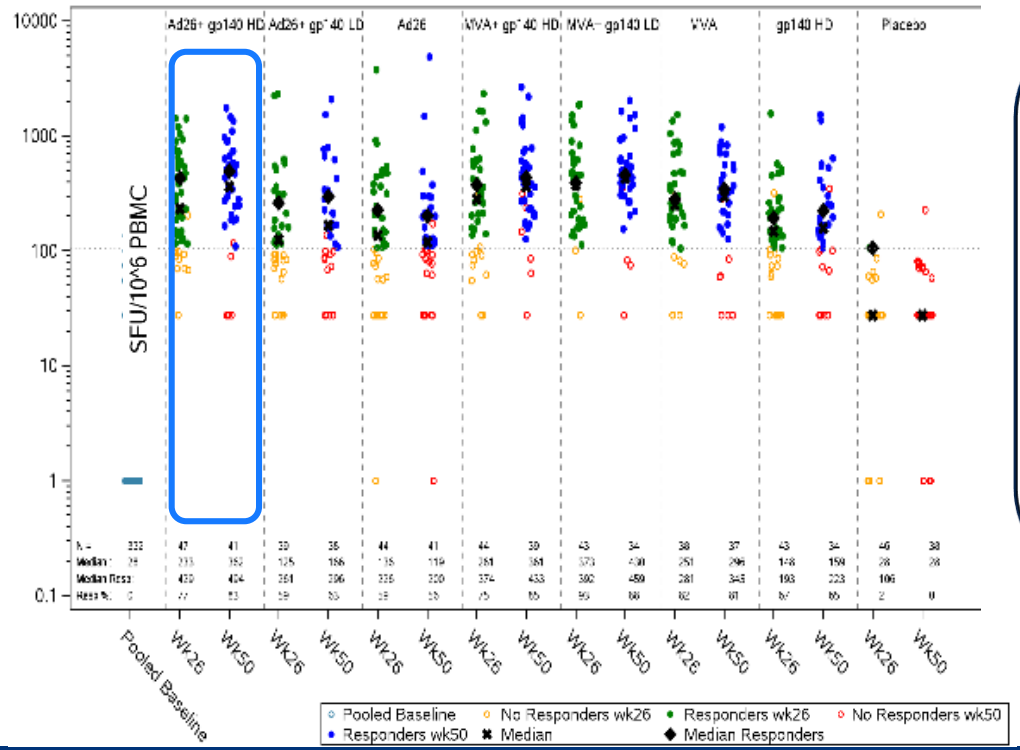
ELISPOT: APPROACH post 3rd & 4th vaccination
ENV PTE peptide pool



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 4th in ENV ELISPOT response

APPROACH HIV-V-A004: NCT02315703
Barouch DH et al., The Lancet, 2018;392:232–243

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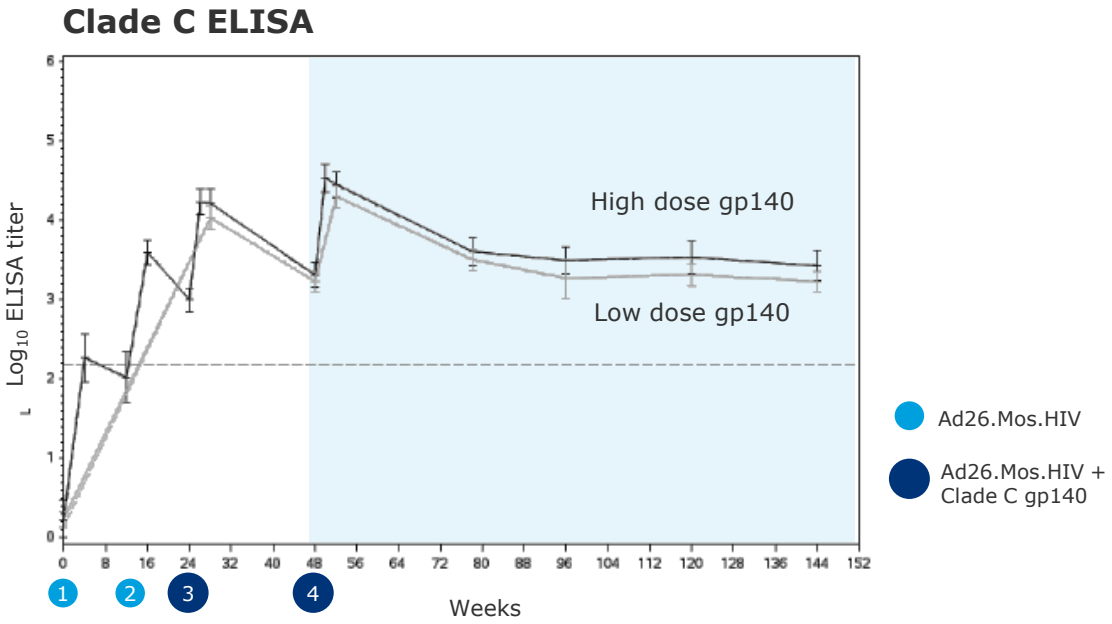
APPROACH: Durability, humoral

100% response rate is maintained for 2 years after vaccination



APPROACH HIV-V-A004: NCT02315703
Tomaka F., IAS 2019, Mexico City, Mexico

TRAVERSE

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 heterologous vaccine regimens

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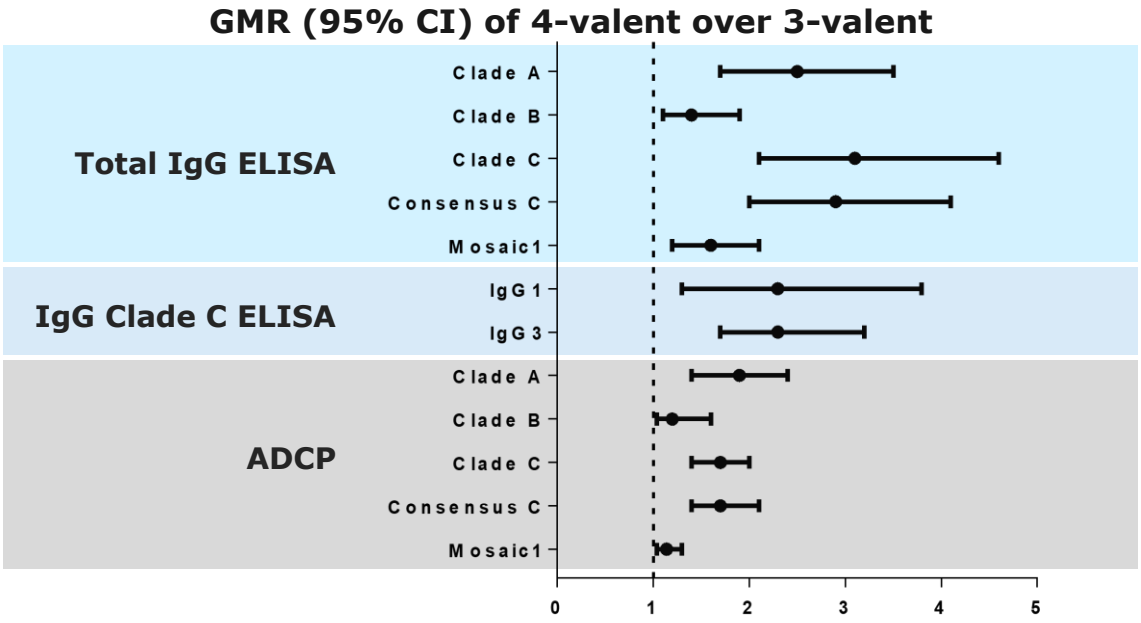
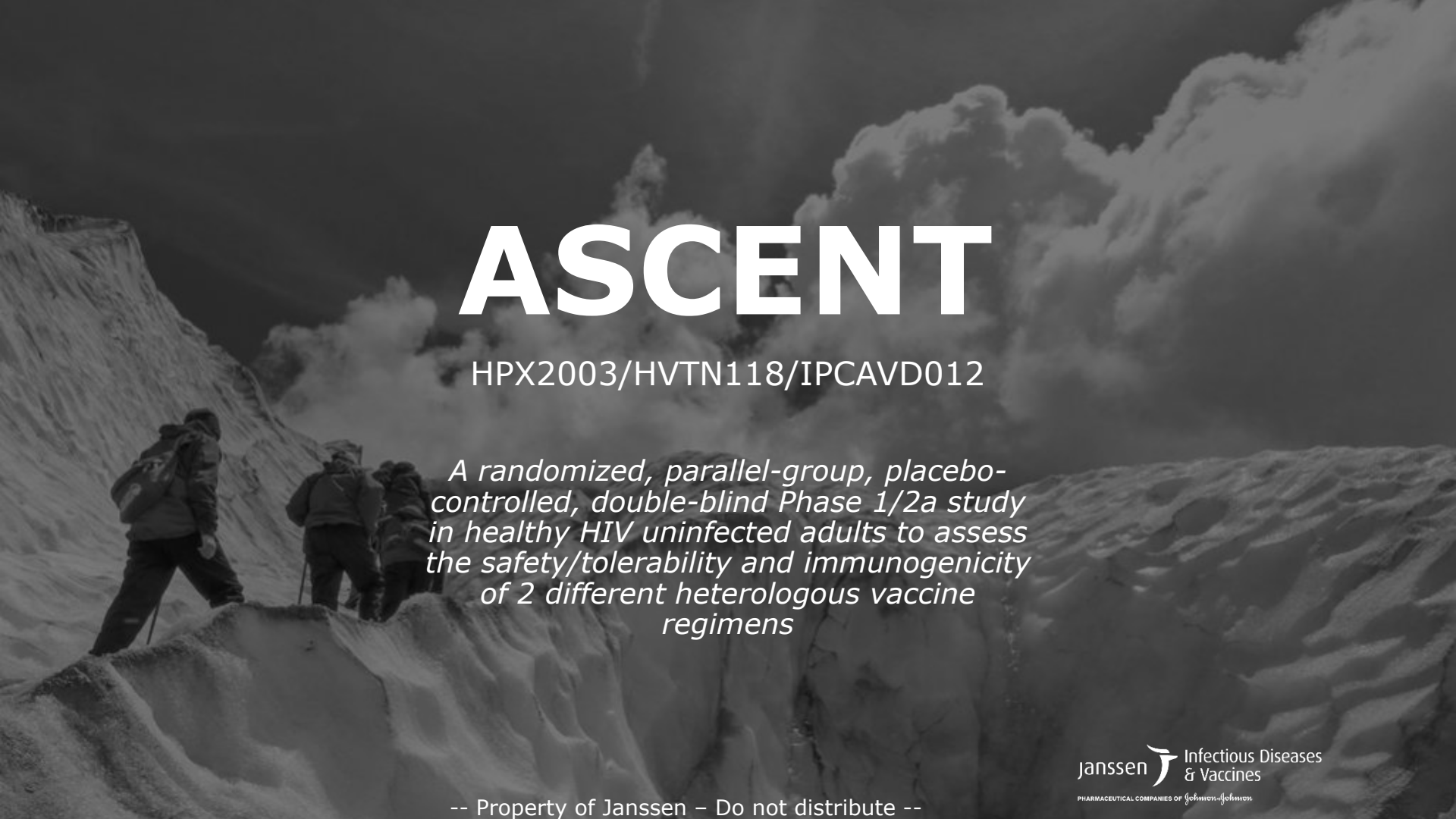
TRAVERSE Immunogenicity

Significant improvement across clades of humoral and cellular assays





ASCENT

HPX2003/HVTN118/IPCAVD012

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 heterologous vaccine regimens

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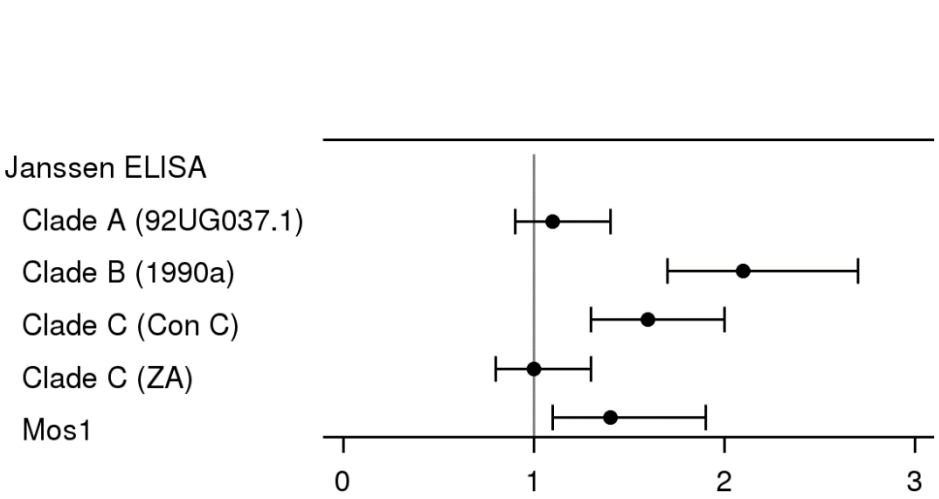
Immunogenicity

Increase in Cross Clade binding antibody responses: Pooled TRAVERSE and ASCENT analysis



	Bivalent gp140		Clade C gp140		
	N	GM	N	GM	GMR (95% CI)
Janssen ELISA					
Clade A (92UG037.1)	82	139725	110	127530	1.1 (0.9,1.4)
Clade B (1990a)	81	133424	110	62235	2.1 (1.7,2.7)
Clade C (Con C)	82	237501	110	144622	1.6 (1.3,2)
Clade C (ZA)	82	110084	110	112077	1 (0.8,1.3)
Mos1	82	137520	108	95400	1.4 (1.1,1.9)

Geometric Mean Ratio (95% CI) at Week 52 of Bivalent / Clade C gp140

IMBOKODO
Ph2b

Southern Africa

Predominantly Clade C

Heterosexual Women

Intra-vaginal transmission

MOSAICO
Ph3

Americas, Europe

Predominantly Clade B

MSM + TG

Intra-rectal transmission

Imbokodo/HPX2008/HVTN 705:

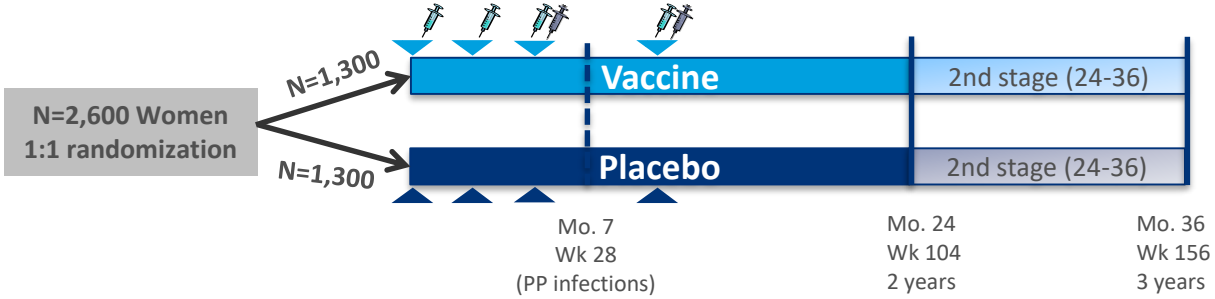
a phase 2b multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial

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+ Clade C gp140 (week 24, 48)

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

Status: fully enrolled May 2019



Mosaico/HPX3002/HVTN706:

a phase 3 multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial

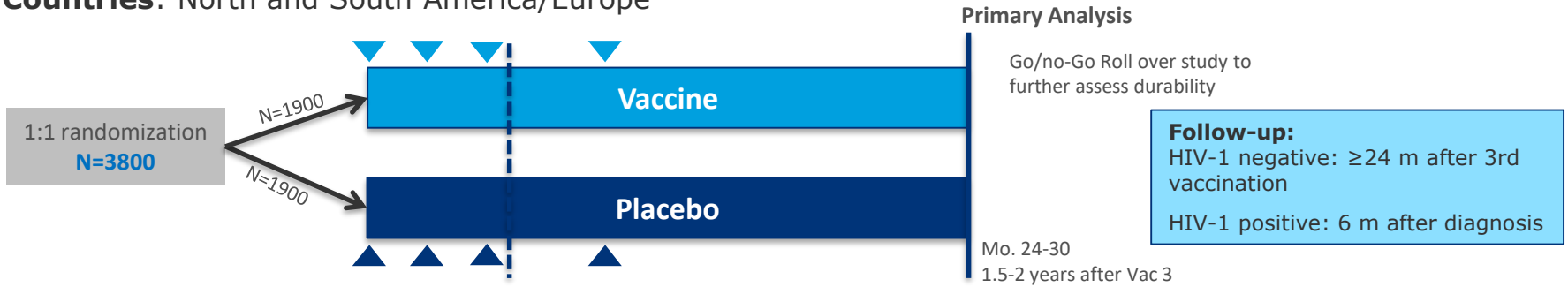
Population: Cis-gender Men and Transgender Individuals who Have Sex with Cis-gender Men and/or Transgender Individuals, age 18-60 years

Vaccine regimen: 2x Ad26.Mos4.HIV (week 0,12), 2x Ad26.Mos4.HIV and co-formulated adjuvanted clade C gp140 + Mosaic gp140 (week 24, 48)

Objective: to evaluate the efficacy of the vaccine regimen in reducing the incidence of HIV infection in HIV-1 seronegative cis-gender men and transgender individuals having sex with cis-gender men and/or transgender individuals

Status: Start Nov 2019

Countries: North and South America/Europe



Summary

- The goal is to develop a prophylactic HIV-1 vaccine that protects against the globally relevant strains of HIV-1
- The final vaccine regimen consists of 4 vaccinations:
  - 2x Ad26.Mos4.HIV (month 0, 3),
  - 2x Ad26.Mos4.HIV and co-formulated adjuvanted clade C gp140 + Mosaic gp140 (month 6, 12)
- Pre-clinical data have shown partial protection in NHP
- Available **Phase 1/2a data** show that the Janssen lead vaccine regimen is well tolerated and induces robust, broad, **functional** and **durable** humoral and cellular immune responses. Next step is to evaluate efficacy of the vaccine regimen.
- A **Phase 2b efficacy study** in 2600 women, in Southern Africa is fully enrolled and a **Phase 3 efficacy study (HPX3002/HVTN706)** in MSM and transgenders (TG), in the Americas and Europe, has recently started

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