HIV VACCINE PROGRAM
and P5 PARTNERSHIP

Considerations for a Pan-African HIV Vaccine Development Agenda
Mar. 16-17, Kigali, Rwanda

Silvija Staprans, PhD
Senior Program Officer, HIV
OUTLINE

• BMGF STRATEGY / PORTFOLIO
• EXPLORATORY MEDICINE STUDIES
• P5 PARTNERSHIP
  • Erica Andersen-Nissen’s presentation covers the HVTN trial plans
• P5 ACCESS PLANNING
Overall HIV Strategy

**Vision:** Accelerate the decline of the global burden and incidence of HIV infection by ensuring development and use of impactful prevention and treatment interventions

**Treatment**
Ensure the development and efficient use of treatment to maximize lives saved

**Prevention**
Ensure the development and efficient use of prevention interventions to maximize the reduction of new infections

**Vaccines & Immunologic Interventions**
Ensure the discovery, development and use of vaccine & immunologic interventions that are efficacious & durable in high-incidence populations

Focus of this presentation
## Vaccines & Immunologic Interventions

<table>
<thead>
<tr>
<th>Area</th>
<th>Sub-initiative</th>
<th>Focus of Investments</th>
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<tbody>
<tr>
<td><strong>Active Immunization</strong></td>
<td>Induction of broadly neutralizing antibodies to prevent infection</td>
<td><strong>Immunogens that induce bNAbs</strong> in animal models that will neutralize tier 2 strains and that can be advanced to <strong>experimental clinical studies</strong>.</td>
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<td></td>
<td>Induction of polyfunctional immune responses to prevent infection</td>
<td>P5 studies, e.g. Phase 1/2 safety and immunogenicity study; P5 correlates analysis; and <strong>other prime-boost vaccine candidates</strong>.</td>
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<td></td>
<td>Induction of immune responses to attenuate/abort infection</td>
<td><strong>CMV-based vaccines</strong>: identify correlates of protection in NHP model; phase 1 studies for prototype vector(s); identify a lead CMV-based vaccine candidate for product development.</td>
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<tr>
<td><strong>Passive Immunization</strong></td>
<td>Development of bNAbs for direct administration</td>
<td><strong>Evaluate clinical proof of mechanism for bNAbs</strong>, optimize lead candidates and enter POC studies for prevention and/or sustained viral control.</td>
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<td></td>
<td>Discovery and characterization of new bNAbs</td>
<td>Discover bNAbs targeting new epitopes or with significantly greater breadth &amp; potency; engineer Abs to improve half life and fxn; demonstrate POC in NHP models.</td>
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<td></td>
<td>Vector-based gene delivery of bNAbs</td>
<td><strong>AAV-vectored bNAb expression</strong> safety and expression.</td>
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<tr>
<td><strong>Early Discovery</strong></td>
<td>Diversify pipeline with novel innovative concepts</td>
<td>Seed pipeline with high risk/high reward concepts; advance the most promising concepts to experimental medicine trials.</td>
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<tr>
<td><strong>HIV Reservoir Biomarkers / Novel Assays</strong></td>
<td></td>
<td><strong>Identify / validate biomarker(s) of viral control</strong>.</td>
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<tr>
<td><strong>Services and Platforms</strong></td>
<td>CAVD Central Service Facilities</td>
<td>Provide high quality, standardized immune assays, statistical services, data platforms and product development support services (CMC, Reg, PM).</td>
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<tr>
<td></td>
<td>Platform Technologies</td>
<td>Evaluate and provide access to platforms to improve vaccine evaluation, effectiveness, durability or reduce costs (GH-VAP).</td>
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Can experimental medicine trials circumvent some of issues that contribute to the slow pace of vaccine development?

- Issues contributing to long development timelines include:
  - Limitation of animal models to reliably predict and mimic vaccine-induced immunity in humans
  - Poor strategies to rationally up and down select different vaccine candidates in an affordable and timely manner
  - Difficulties in defining correlates of protection
A “shift to the left” may accelerate vaccine discovery

Definition of experimental medicine studies: Small, flexible studies that can be used either to generate or test a hypothesis early in humans in order to provide critical information that contributes to accelerating discovery and/or vaccine product development
### "EXPERIMENTAL MEDICINE TRIALS" TO ACCELERATE VACCINE DISCOVERY

<table>
<thead>
<tr>
<th></th>
<th>Traditional phase I</th>
<th>Exp Med phase 0 / I</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose of the trial</strong></td>
<td>Product development</td>
<td>Scientific information; hypothesis testing</td>
</tr>
<tr>
<td><strong>Next step</strong></td>
<td>Hopefully Phase II</td>
<td>Improve Vx design / Phase I</td>
</tr>
<tr>
<td><strong>Number of Volunteers</strong></td>
<td>~20-100</td>
<td>~5-10</td>
</tr>
<tr>
<td><strong>Use of Controls/Placebo</strong></td>
<td>Yes</td>
<td>Potentially No</td>
</tr>
<tr>
<td><strong>Duration (months)</strong></td>
<td>~12-18</td>
<td>Usually &lt;12</td>
</tr>
<tr>
<td><strong>Laboratory monitoring of volunteers</strong></td>
<td>Safety/mostly regular immunogenicity</td>
<td>Safety/mostly special assays</td>
</tr>
<tr>
<td><strong>Preclinical (animal) evaluation</strong></td>
<td>Extensive (up to protection)</td>
<td>Limited (safety)</td>
</tr>
<tr>
<td><strong>Vaccine Manufacturing</strong></td>
<td>Scalable product (always?)</td>
<td>Pilot lot</td>
</tr>
<tr>
<td><strong>Product characterization</strong></td>
<td>Suitable for Ph3 trials; long term stability (always?)</td>
<td>Description of product (qualified assays): Purity, potency, stability</td>
</tr>
<tr>
<td><strong>Safety/toxicity</strong></td>
<td>Extensive</td>
<td>More limited</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>IND</td>
<td>IND (Always?)</td>
</tr>
<tr>
<td><strong>Ethics</strong></td>
<td>IRB approval; Involves large communities</td>
<td>IRB approval; Involves individuals</td>
</tr>
<tr>
<td><strong>Industrial partner</strong></td>
<td>Highly desirable</td>
<td>Desirable, but not essential</td>
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Modified from R Shattock
EXPLORATORY HUMAN STUDIES: INVERTING THE EXPERIMENTAL PARADIGM

Current paradigm

Mouse → Non-human primate → Human

New paradigm

Human → Fit-for purpose animal models → Human

HIV vaccine discovery example

Increased understanding of broadly neutralizing antibody evolution in HIV-infected humans

Evaluate candidate HIV Env immunogens for the ability to induce bNAbs in mice containing human Ab genes

Study the most promising Env immunogen(s) for the ability to induce bNAbs in small exploratory medicine study

Iterative immunogen improvement
RATIONALE FOR “HUMAN IMMUNOGENICITY TRIALS” IN HIV VACCINE DEVELOPMENT

Scientific:
- Animal models are not fully predictive of human responses
- There are germ line differences between humans and traditional animal models
- Recognized need for human immunogen discovery
- Deep sequencing and B cell cloning approaches can provide valuable information from a few subjects

Financial:
- Unsustainable to continue to put “wishful” candidates into expensive phase 3 trials
- Better allocation of resources to increase likelihood of success

Logistical:
- Increasing difficulty of conducting large scale efficacy trials

Ethical:
- Public Health need to accelerate HIV vaccine discovery and development
- Enrolling volunteers in vaccine trials with higher probability of success
- Reducing the number of volunteers exposed to unsuccessful vaccine candidates

Modified from R Shattock
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P5 PARTNERSHIP: FOUND ON THE ALVAC (CANARYPOX) PRIME – RECOMBINANT GP120 BOOST APPROACH (RV144)

Four priming injections of a recombinant canarypox vector (ALVAC-HIV vCP1521) at week 0, 4, 12, 24:
- HIV-1 Gag and Pro (subtype B LAI)
- CRF01-AE HIV-1 gp 120 (92TH023) linked to gp41-TM (LAI)

Two booster injections of a recombinant gp120 subunit vaccine (AIDSVAX B/E) at week 12, 24:
- Subtype E HIV-1 strain A244 (CM244)
- Subtype B HIV-1 strain MN
Vaccination with ALVAC and AIDSVAX
to Prevent HIV-1 Infection in Thailand

Modified Intention-to-Treat Analysis*
THAI TRIAL- CORRELATES OF RISK OF HIV INFECTION
REPORTED IN HAYNES ET AL, NEJM 2012

Follow up studies confirm and extend these observations (not shown)
P5: FORMATION OF THE PARTNERSHIP

Purpose:
To build on, substantiate & extend the RV144 results in high incidence population, and ultimately license a pox-protein based HIV vaccine with the potential for broad public health impact.

Strategy: Build public-private partnerships critical for:
1. Confirming/extending the RV144 result in high-risk, high-need populations: Development/Licensure Track
2. Incorporating knowledge from the assessment of next-generation vaccine concepts: Research/Correlates Track
P5: Potential improvements in vaccine efficacy

How will additional boosts, potent priming & adjuvants impact vaccines?

Potential Development Program Outcome

Best Case Scenario with more potent priming (research track)

Levels of vaccine-induced immune response

0 1 3 6 9 12 18 24 36

Months

ALVAC ALVAC + gp120

ALVAC ALVAC + gp120/MF59

ALVAC + gp120/MF59

RV 144 (alum)

Potent Adjuvants (MF59)

Potential Priming Immunogens (PPI)
And Potent Adjuvants (MF59, AS01B)
THE STRATEGY FOR THE ALVAC/PROTEIN PHASE 3 PROGRAM

- Optimize regimen by increasing potency & durability
- Construction of ALVAC-HIV-C (vCP2438)
- Construction of Bivalent Subtype C gp120/MF59
- Booster at 12 months

P5 designed & provided oversight for manufacture of next generation recombinant pox virus vectors & gp120 proteins
STRATEGY FOR THE PHASE 3 PROGRAM

HVTN 097: Designed to evaluate RV144 vaccine regimen in RSA and compare immunogenicity to that in Thailand.

HVTN 100: A standard phase 1 trial of clade C products to decide whether to proceed to phase 3.

HVTN 702: A classic phase 3 RCT assessing efficacy and safety aimed at licensure.

Underpinned by community, regulatory and government stakeholder engagement
P5 has worked with the HVTN in developing the clinical trials programs and planned laboratory assessments.
Projected timelines for P5 Phase 3 Program in the Republic of South Africa

HVTN 100 Ph1-2
1. ALVAC/ALVAC-gp120
2. Placebo

RSA Regulatory Review

Enrollment

Follow-up

Interim Safety Report

Phase 3 Go/No Go Decision

Final Stage 1 Efficacy Analysis

1st Efficacy/Futility Analysis
2nd Efficacy/Futility Analysis
3rd Efficacy/Futility Analysis

HVTN 702 Ph3
1. ALVAC/ALVAC-gp120
2. Placebo

RSA Regulatory Review

Enrollment

Follow-up

*Interim efficacy/futility analyses are endpoint driven—timepoints shown are approximate.
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Global Access at BMGF
A commitment to ensuring that innovations, products and information developed with BMGF funding are created and managed in alignment with the charitable purpose.

Global Access incorporates a range of business and legal issues.
• Strategic management of IP is one of many components critical to achieving Global Access.
Review ongoing efforts to develop a Global Access Plan that prepares the P5 and partners in South Africa (RSA) for the outcomes of the Phase 3 trial and helps ensure that a safe, efficacious vaccine is made available for target populations in RSA.

- Initial focus on RSA reflects the Partnership's immediate access obligations to the population in which the vaccine will be tested; however, a broader access strategy remains our ultimate objective.
- Access planning efforts in RSA will establish a precedent that will support and streamline a broader regional access strategy.
- To this end, access requirements beyond RSA will be integrated into planning efforts as the planning process advances.
1. **There is a need for timely, sustainable access to an efficacious vaccine.**
   - There should be a “plan for success” for populations most in need that is sustainable for funders, suppliers and governments.

2. **Vaccine access is a shared responsibility of P5 partners and host countries.**
   - Specific commitments and ownership are important pillars of access; a willingness to find common ground among partners is expected.

3. **There is a commitment to proactive stakeholder engagement.**
   - The access plan must recognize the needs of stakeholders; timely engagement is essential.

4. **Partners share the values of transparency and timely communication.**
   - Access discussions can be complex; it is important that issues are aired and addressed openly and respectfully.
P5 ACCESS PLANNING: P5 GAC

The P5 established the Global Access Committee (P5 GAC) and approach to guide development of a Global Access Plan that will define expectations/commitments essential to making a successful vaccine available to target populations in RSA, and ultimately, other countries in Southern Africa.

Each partner organization is represented on the P5 GAC:*

- Nina Russell (Lead; GAC Co-chair)
- Silvija Staprans (Deputy)
- Jim Tartaglia (Lead)
- Sanjay Phogat (Deputy)
- Mary Marovich (Lead; GAC Co-chair)
- Elizabeth Adams (Deputy)
- Richard Gordon (Lead)
- Michelle Mulder (Deputy)
- Susan Barnett (Lead)
- Niranjan Kanesa-Thasan (Deputy)

*GAC membership may be modified to reflect changes in the P5 partnership.
1. **Define Access Framework**, including the P5’s principles, assumptions, and guidelines for vaccine access once the Phase 3 trial in RSA concludes*.

2. **Engage Stakeholders**, including P5 partners and relevant stakeholders in RSA, to inform the development of an Access Plan.

3. **Develop an Access Plan** that addresses the regulatory, market demand, technology sharing, manufacturing and pricing requirements of a safe and efficacious vaccine.

*The GAC will focus initially on access provisions in RSA. Dialogue with a broader community of regional stakeholders will be important to ensuring that the access plan for RSA establishes a strong a relevant precedent for the region.
# P5 ACCESS PLAN: SOME KEY CONSIDERATIONS AND QUESTIONS

## Priority Populations/Targets
- At what VE level are **placebo recipients** offered vaccine and when?
- What is the **RSA’s target TPP/public health objective**? What about other high burden countries?
- Which **populations** should be vaccinated at different VE outcomes?
- What is the **forecasted demand** for each possible VE range/outcome?

## Regulatory Requirements
- What are the **regulatory requirements for licensure in RSA** and other key countries?
- What **level of efficacy** is needed to obtain regulatory approval?
- What are the implications for study design?

## Deployment Conditions
- What **other effective HIV interventions** might be or have been implemented and how will an effective HIV vaccine be integrated with them?
- **What overall deployment cost will be cost-effective** (including infrastructure, public health services, COGS)?
- In addition to engagement of country payers, might **global health buyers/payers** (e.g. Global Fund, World Bank, PEPFAR) also be engaged to support deployment?

## Manufacturing & Supply Models
- What is the **strategy for supporting rapid access to a safe and effective vaccine**?
- What are the host country’s **expectations for technology sharing**, and what capacity exists and/or can be developed?
- What are the **options for manufacturing**?
- What are the expectations for **production volumes and timing of product availability**?
- What funding sources are available to facilitate access and deployment?
The P5 GAC will initially engage key stakeholders in RSA to define local access imperatives and expectations (e.g. priority/target populations, regulatory requirements), elucidate and mitigate potential issues and share knowledge of previous access planning efforts.

In support of a robust and inclusive effort, a variety of stakeholders will be engaged, including:

- **Government** (e.g. Department of Health, Department of S&T)
- **Academic/Research Organizations** (e.g. leading universities and vaccine research units)
- **Industry** (e.g. regional vaccine manufacturers)
- **Not-for-Profit Organizations** (e.g. community-based foundations)
P5 GAC: Progress and Next Steps

**Progress:**
- Mobilized the P5 Global Access Committee
- Conducted preliminary consultations with stakeholders to gather perspectives on access imperatives and expectations.

**Next Steps:**
- Implement a robust stakeholder engagement plan to:
  1. Develop an Access Framework that defines the P5’s principles for vaccine access and provides a foundation for the Access Plan.
  2. Develop a P5 Global Access Plan that defines access considerations for potential efficacy outcomes of the Phase 3 trial.
     - The Plan will outline potential vaccine efficacy scenarios and define starting assumptions regarding timelines, principles, provisions and commitments for vaccine access within each scenario.
     - The Plan will achieve greater specificity and clarity over time, representing evolving conditions and the consensus position of P5 members.
THANK YOU!

EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE

THANK YOU!