Where Are We Now?

An estimated 2 million people are newly infected with HIV every year.

In sub-Saharan Africa, 1 in 20 adults is living with HIV.

Women still make up almost 60% of new HIV infections in sub-Saharan Africa. In many developing countries, women still lack the power to negotiate currently available approaches to protect themselves against HIV.
Research Vision and Mission

Vision
To end the AIDS epidemic through the discovery and implementation of high-impact public health tools, technologies and interventions.

Mission
Promote research, development, evaluation and the use of high-impact public health tools, technologies, and interventions for HIV and AIDS prevention, care, and treatment.
Research Goals

Accelerate development and clinical testing of novel HIV vaccine candidates and build global capacity for vaccine research

Develop, test, and introduce microbicides for women to reduce the risk of HIV infection

Strengthen the programmatic evidence base for HIV and AIDS prevention, care, and treatment to achieve epidemic control
HIV Vaccine Research
Development of enhanced bnAbs as a prevention tool for young women and adolescent girls

Devin Sok, PhD | Director, Antibody Discovery and Development
USAID Webinar | 21 March 2018
Program goal
Develop an enhanced bnAb prevention product that has a higher likelihood for efficacy, acceptability, and affordability of use among adolescent girls and young women

INVESTIGATORS

Devin Sok, PhD
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Rajat Goyal, PhD
Director, Country of India

Anatoli Kamali, MD
Regional Director, Africa
Neutralizing antibodies bind to the HIV Env trimer to prevent HIV from infecting target cells.

Neutralizing antibody = nAb

Env trimer = (gp120 + gp41) x 3
Protocol G catalyzing the vaccine field

1. Screening for Potent Antibodies
2. Ab Isolation
3. Transformational Vaccine Concepts
4. End-to-End bnAb Discovery to Development
5. Clinical Evaluation
6. Output: Abs for Prevention
7. Translation
8. Sample Management

End-to-End bnAb Discovery to Development

Screen donors for antibodies
Serum samples were screened for neutralization activity on a representative panel of global HIV isolates at Monogram Biosciences.

> 200 broadly neutralizing antibodies were isolated using innovative techniques. Over 80 bnAbs were isolated from Protocol G. 2009 - Present
Still active in HIV vaccine research, but can antibodies be used in the meantime for HIV prevention?

- chronic infection
- therapy or prophylaxis
- vaccination
- identify broadly neutralizing antibodies
- map epitope on HIV Env
- design immunogen based on epitope
Innovation in antibody discovery has led to the discovery of increasingly potent antibodies, which has made the use of antibodies for prevention a possibility.
HIV Prevention Toolbox

A single product or approach will not stop the pandemic

We need a diversity of prevention options and programs in order to address the diverse needs of adolescent girls and young women in sub-Saharan Africa.

EXISTING PREVENTION PRODUCTS

ARV-BASED MICROBICIDES
- Tenovofir gel
- Dapivirine ring

PrEP
- Tenofovir
- Cabotegravir
- Rilpivirine

PMTCT
- Antiretrovirals

CASE FOR ADDING ENHANCED BNABS TO PREVENTION TOOLBOX

LONG-ACTING
- Reduced frequency of administration

MECHANISM OF PROTECTION
- Protection at the site of infection
- Elimination of infected cells distally from the site of infection

LOW TOXICITY
- Growing market of biologics
- Very few cases of adverse side effects, generally well-tolerated

DISCREET
- Subcutaneous delivery every 3 to 4 months
HIV bnAbs for prevention

What are the roadblocks for using broadly neutralizing antibodies for prevention?

**AFFORDABILITY**
- Lower dose required to afford protection
- Long acting to reduce frequency of administration
- Lower manufacturing costs

**OPTIMAL TARGET PRODUCT PROFILE**
- Subcutaneous delivery to ease delivery
- Safety and limited adverse side-effects
- Stability to ensure delivery to target regions and supply chain
- Efficacy to ensure broad protection against diversity of HIV

**ADOLESCENT GIRLS AND YOUNG WOMEN**
- Product development to ensure efficacy in women
- End user research to ensure acceptability by women most at risk

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MAIN RESEARCH ACTIVITIES
- IMPROVED POTENCY
- EXTENDED HALF LIFE
- BINDING AT LOW PH
- POLYREACTIVITY
- END USER RESEARCH

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**MAIN RESEARCH ACTIVITIES**

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<thead>
<tr>
<th>IMPROVED POTENCY</th>
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<td>EXTENDED HALF LIFE</td>
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The more potent the antibody, the less that will be needed to confer protection

HIGHER POTENCY = LOWER DOSE

LOWER DOSE = LOWER MANUFACTURING COST

POTENCY THROUGH DIRECTED EVOLUTION

Passive transfer shiv challenge studies

In vitro neutralization (IC80) correlates with the dose required to afford protection against the challenge virus
The more potent the antibody the less it will cost per dose

Cost comparison between ARVs and monoclonal antibodies

ARV costs ($60-122/year for first-line) are estimated based on WHO ARV regimen guidelines for adults. Calculations were done assuming an average weight of 62 kg* per individual and a manufacturing cost of $30/g** of antibody.

*London School of Hygiene & Tropical Medicine
**IAVI Report - Making it to Manufacturing

<table>
<thead>
<tr>
<th>WHO ARV regimen for adults</th>
<th>1st line ARV</th>
<th>Every Year</th>
<th>Every 4 Mo</th>
<th>Every 3 Mo</th>
<th>Every 2 Mo</th>
<th>Every 1 Mo</th>
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<td>$60-122</td>
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<tr>
<td>30 mg/kg</td>
<td>1 mAb</td>
<td>$ 55.80</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2 mAb cocktail</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3 mAb cocktail</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>1 mAb</td>
<td>$ 18.60</td>
<td>$ 55.80</td>
<td>$ 74.40</td>
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<tr>
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<td>2 mAb cocktail</td>
<td>$ 37.20</td>
<td>$ 111.60</td>
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<tr>
<td></td>
<td>3 mAb cocktail</td>
<td>$ 55.80</td>
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<tr>
<td>1 mg/kg</td>
<td>1 mAb</td>
<td>$ 1.86</td>
<td>$ 5.58</td>
<td>$ 7.44</td>
<td>$ 11.16</td>
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<td>$ 14.88</td>
<td>$ 22.32</td>
<td>$ 44.64</td>
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<tr>
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<td>3 mAb cocktail</td>
<td>$ 5.58</td>
<td>$ 16.74</td>
<td>$ 22.32</td>
<td>$ 33.48</td>
<td>$ 66.96</td>
</tr>
</tbody>
</table>
Increasing the potency of antibodies

Comparing the breadth and potency of the engineered bnAb compared to others

**ePGT121**

- **PGDM1400**
- **PGT151**
- **PGT128**
- **PGT121**
- **3BNC117**
- **PG9**
- **PGT135**
- **2G12**
- **b12**

**coverage (%)**

**potency (median IC<sub>50</sub> µg/ml)***

- **1992 - 1996 | hybridoma or phase display**
- **2009 | B cell activation and screening**
- **2010 - 2011 | Ag memory B cell sorting with RSC or gp120 baits**
- **2011 - 2012 | B cell activation and screening or memory B cell sorting with gp120 baits**
- **2014 - 2016 | B cell activation and screening or memory B cell sorting with native trimer baits**
Investments in HIV research fuels prevention research for other infectious diseases

Proof of principle for epitope-focused vaccine design

Isolation of potent neutralizing antibodies from a survivor of the 2014 Ebola virus outbreak

Rational vaccine design for RSV

Ab discovery for Ebola

Zika virus activates de novo and cross-reactive memory B cell responses in dengue-experienced donors
Thomas F. Rogers, Eileen C. Goodwin, Bryan Erney, Devin Sok, Nathan Beutler, Alexander Strubel, Rebecca Nedelloc, Khoo Le, Michael E. Brown, Dennis R. Burton, and Laura M. Walker
Program Goal
Develop enhanced broadly neutralizing antibodies (ebnAbs) for use as prophylaxis for adolescent girls and young women

End-to-End Platform
- Product development pipeline
- End-user feedback to inform development decisions
- Leverage USAID’s previous investment in discovering mAbs to produce an intervention that is accessible to high-incidence women

DISCOVERY
Leverage: Protocol G Samples
Activities:
- bnAb engineering (IAVI, TSRI, IPI, UPenn)
- Passive protection study (IAVI, TSRI, WPRC, UPenn)
- End user research (IAVI, Regional African Centers)
- Antibody evaluation (IAVI, THSTI, NCBS)

STATUS: Complete
Years: 2 / 3

ENGINEERING & OPTIMIZATION
Leverage: South-south collaboration, Indian partners for antibody evaluation, African partners for end user research, Antibody discovery and engineering experience
Activities:
- bnAb engineering (IAVI, TSRI, IPI, UPenn)
- Passive protection study (IAVI, TSRI, WPRC, UPenn)
- End user research (IAVI, Regional African Centers)
- Antibody evaluation (IAVI, THSTI, NCBS)

STATUS: Ongoing
Years: 2 / 3 / 4

PRECLINICAL EVALUATION
Leverage: US and Indian partners for preclinical evaluation
Activities:
- Passive protection study (IAVI, TSRI, WPRC, UPenn)
- pK analysis of antibodies in macaques (IAVI, TSRI, WPRC)
- Evaluation of macaque experiments (IAVI, THSTI, NCBS)

STATUS: Ongoing
Years: 4 / 5

MANUFACTURING
Leverage: Collaboration with government of India and partnerships with Indian manufacturers (e.g., Serum Institute), Expertise of IAVI’s Vaccine Development Center
Activities:
- Low cost manufacturing (IAVI, Indian partners)

STATUS: Ongoing
Years: 5+

CLINICAL TRIALS
Leverage: Clinical CRCs in Africa for evaluation of clinical trials, expertise of IAVI’s Vaccine Development Center, IAVI’s IND applications for existing bnAbs
Activities:
- Evaluation of clinical trials (IAVI, THSTI, IAVI African CRCs)

STATUS: Ongoing
Years: 5+

Institutions: International AIDS Vaccine Initiative (IAVI), The Scripps Research Institute (TSRI), Institute for Protein Innovation (IPI), Wisconsin Primate Research Center (WPRC), University of Pennsylvania (UPenn), Translational Health Science and Technology Institute (THSTI), National Center for Biological Sciences (NCBS)
IAVI gratefully acknowledges the generous support provided by the following major donors:

- USAID
- PEPFAR
- Bill & Melinda Gates Foundation
- THE WORLD BANK
- The World Bank
- The Global Fund
- The European Union
- Ministry of Foreign Affairs of the Netherlands
- Ministry of Foreign Affairs of Denmark
- Ministry of Foreign Affairs of India
- Ministry of Foreign Affairs of Norway
- Ministry of Foreign Affairs of The Netherlands
- Ministry of Science & Technology, Government of India
- National Institute of Allergy and Infectious Diseases
- Norwegian Ministry of Foreign Affairs
- Robert Wood Johnson Foundation
- The Starr Foundation
- U.K. Department for International Development
- The U.S. President's Emergency Plan for AIDS Relief through the U.S. Agency for International Development
- The World Bank
- And many other generous individuals from around the world

As of June 2017
Implementation Science Research
USAID HIV Implementation Science

Leading IS research activities

- Implementing research aligned with PEPFAR and OHA’s priority objectives of achieving epidemic control, support for OVC, sustainable financing and data quality

Promoting capacity strengthening for IS

- Creating partnerships with local researchers and institutions, and providing opportunities to further their research agendas and build long term sustainability

Catalyzing partnerships and IS data utilization

- Engaging key stakeholders before and during all IS studies and working together to interpret findings and decide upon programmatic recommendations

Disseminating IS findings

- Sharing the results of USAID funded research across multiple platforms, leveraging different approaches for different audiences, and aligning research data to epidemic control objectives
Results Highlights- IS Annual Program Statement

Partners Demonstration Project (U of Washington):
• High uptake of PrEP for serodiscordant couples
• High viral suppression for partners on ART
• 95% reduction in HIV incidence

Engage4Health (ICAP):
Interventions to improve linkage and retention

Kabeho Study (EGPAF):
Real world evaluation of PMTCT Option B+ implementation

* Graphics by Project SOAR
Objective: Develop and Evaluate Integrated Stigma Mitigation Interventions (ISMI)

- Specific Aim 1: Systematically review the literature for existing stigma metrics that have been used for MSM and FSW.
- Specific Aim 2: Use mixed methods approaches to characterize unbiased estimates of the current coverage of HIV prevention and treatment services as well as barriers and facilitators to the uptake of these services among MSM and FSW in Senegal.
- Specific Aim 3: Use a prospective cohort (followed 24 mo) of MSM and FSW in Senegal to evaluate ISMI
Anticipated Health Care Stigma Among Men Who Have Sex With Men

Felt afraid to seek health services:
- Visit 1: 10.1%
- Visit 2: 8.9%
- Visit 3: 5.7%
- Visit 4: 1.7%
- Visit 5: 1.2%
- Visit 6: 0.6%

Avoided health services:
- Visit 1: 10.1%
- Visit 2: 9.0%
- Visit 3: 4.3%
- Visit 4: 2.6%
- Visit 5: 1.2%
- Visit 6: 0.6%

P < 0.001 for both categories.
HIV outcomes among men who have sex with men

HIV status of cohort participants:
- 40.3% (73/181) living with HIV

HIV incidence over 24 months:
- 5.4/100 person-years

Self reported currently being on ART:
- 95.4% at visit 1 of cohort
- Did not significantly change over time

Viral Suppression among MSM living with HIV

- Visit 1: 35.4%
- Visit 2: 74.6%
- Visit 3: 71.2%
- Visit 4: 68.1%
- Visit 5: 64.7%
- Visit 6: 60.5%

P = 0.035
Project SOAR Overview

Project SOAR (Supporting Operational AIDS Research)

- 2014-2019
- 58 activities/studies in 23 countries
- Consortium of research partners- led by Pop Council:
  - Key partners: EGPAF, Johns Hopkins University, University of North Carolina, Avenir Health, Palladium
  - Over 30 local research partners

- http://www.projsoar.org/
Project SOAR: Strong Emphasis on Research Utilization

RESEARCH
Empirical
Objective

RU
Highlights context
Engages stakeholders
Supports use of findings
Builds ownership

PROGRAM
Practical
Urgent
Action-Oriented

POLICY
Bargaining
Lobbying
Compromising

30
How IS Contributes to Achieving 90-90-90

- Assessing new innovations
- Measuring feasibility, impact and cost
- Addressing country-level key program gaps and questions

Identify PLHIV
- Self testing
- Reaching men
- Novel size estimation for KPs
- Early infant diagnosis

Initiate ART
- Test and Start
- Enhanced linkage to care
- Differentiated service delivery

Retain & Viral Suppression
- Stigma mitigation
- Adolescent transition
- Family ART
- Community adherence groups
Updating the PLHIV Stigma Index

• Stigma Index was developed by IPPF, UNAIDS, GNP+, ICW; launched in 2008
• Questionnaire-based methodology to quantify stigma and discrimination – implemented by PLHIV among PLHIV
• Complements experiences of individuals with the collective diverse experiences of a community of PLHIV
• Provides for evidence-informed advocacy, policy reform, and service delivery
• Builds capacity of PLHIV networks
• USAID/PEPFAR supported an update in 2017, coordinated by Project SOAR, eg questions on key populations and HIV treatment
Stigma Index Pilot Results 2017: Stigma Affects HIV Care Cascade

- Hesitated to get tested due to fears
- Delayed entering care

Delayed entering care because:

- Not ready to deal with HIV infection (16–33%)
- Worried others would find out status (11–13%)
- Afraid health workers would treat me badly or disclose status without consent/had a bad experience with a health worker previously (4–11%)
Stigma Toward Key Populations Impedes Health Seeking Behavior

<table>
<thead>
<tr>
<th>Country</th>
<th>MSM</th>
<th>Sex workers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>47%</td>
<td>21%</td>
</tr>
<tr>
<td>Senegal</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>Uganda</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Cameroon</td>
<td>42%</td>
<td>22%</td>
</tr>
<tr>
<td>Senegal</td>
<td>26%</td>
<td>15%</td>
</tr>
<tr>
<td>Uganda</td>
<td>14%</td>
<td>8%</td>
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Microbicide Research
What is a Microbicide?

Biomedical products that women can use to protect themselves from HIV infection
Microbicide Development

- **T1 - Translation to Human** (Move a molecule into product)
- **T2 - Translation to Patients/Practice** (Generate the “real world” evidence)
- **T3 - Translation to Program** (Introduce in existing health systems and scale-up)

- **Minimize delays** in introducing HIV/AIDS prevention
- Better **prepare national health systems to deliver** new HIV prevention products to Women
Considerations for Microbicide Priorities

**PLANNING AND BUDGETING**
- Cost of goods

**SUPPLY CHAIN MANAGEMENT**
- Stability
- Packaging

**DELIVERY PLATFORMS**
- HCW training required
- Frequency of visits
- Prescription vs OTC
- Self administered

**UPTAKE AND ADHERENCE**
- Acceptability
- Discretion*
- Reversibility*
- Ease of use
- Access channels*
- Additional benefits
- Product Choice

**EFFECTIVE USE & MONITORING**
- Dosing frequency*
- Side effects

*Greater diversity in these attributes = greater potential health impact*
## Potential Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Target dosing</th>
<th>Active Ingredients</th>
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<tbody>
<tr>
<td>Vaginal Ring</td>
<td>1 month</td>
<td>Dapivirine</td>
</tr>
<tr>
<td>Oral Tablets</td>
<td>On-demand</td>
<td>F/TAF, TAF</td>
</tr>
<tr>
<td>Microarray Patch</td>
<td>≤ 3 months</td>
<td>TBD</td>
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<tr>
<td>Biodegradable Implant</td>
<td>1 year</td>
<td>TAF/LNG</td>
</tr>
<tr>
<td>Vaginal Inserts</td>
<td>On-Demand</td>
<td>TAF, EVG, GRFT</td>
</tr>
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Spotlight: Dapivirine Ring Timeline

- **2016**: Open-label extension study: DREAM
- **2017**: Open-label extension study: HOPE
- **2018**: African adolescents study: REACH
- **2019**: Supporting Safety and PK Studies
  - EMA Art 58
  - WHO PQ
  - FDA
  - S. Afr. MCC (SAHPRA)

African NRAs (submission & approval)
Preparing for Introduction

To accelerate introduction and access with advances in biomedical technologies and new approaches for HIV prevention.
Incorporating End-User Preferences

Research to increase product uptake and use
Thank you!

Questions?
Q&A

Please submit your questions in the chat box on the screen to the right.

Any questions not addressed during the session can be submitted to info@ghpod.com and will be answered by email.
Thank you for joining us today!

Please join us for our third seminar
Global Health Grand Challenges
Wednesday, March 28, 12-1PM
https://ghpod.adobeconnect.com/usaid_gh_rd/