IAVI’s role and partnerships in Africa
Achievements & Way Forward

Sixth European & Developing Countries Clinical Trials Partnership Forum
*Strengthening Research Partnerships for Better Health and Sustainable Development*
9-12 October 2011, Addis Ababa, Ethiopia

Jean-Louis Excler, MD
Senior Director, Medical Affairs, International AIDS Vaccine Initiative
IAVI Partnerships “ensure” the development of a safe and effective HIV vaccine

Integrated organization that links our ...

- Industry-style labs and diverse research portfolio
- Academic, government and private-sector partnerships
- Network of clinical trial centers in Africa and India
- Advocacy and outreach from community to international level
The IAVI Model: a truly global approach - working with developing countries

• An innovative approach to research and development of health products for nations that most need them
  – Ensuring that vaccines will be available, accessible and used in countries hardest hit as quickly as possible
  – Using a “development approach”

• Create an enabling environment for research
  – Promoting national ownership and sustainable in-country commitment
  – Addressing the social and political context related to AIDS and conducting research in resource-poor settings
  – Stimulating support for and participation in clinical research

• Bring the voices of developing countries to the global call for investments in AIDS vaccine research
  ➤ Mobilizing countries as integral to the process
  ➤ Supporting strong and well-informed developing country voices
Parallel development of vaccines and testing capacity in Africa is essential for **SPEED & EFFICIENCY**
Infrastructures and Capacity Development

Site Development

- Infrastructure
- Cohort Development
- QA Programs for all lab tests
- Lab Accreditation
- Staff Development

Clinical Training

- GCP – Basic and refresher
- Advanced Courses
- Protection of Human Subjects
- Study Initiation Meetings
- Investigators Meetings

Lab training

- GCLP Courses - Basic, Advanced
- Management Training
- Training at Core Lab – Immunology
- Training at Central Safety Lab
- Audits

Documentation

- Quality Management Plans
- Standard Operating Procedures
- Study Operations Manuals
- Study Master File
- Training Files
IAVI Observational Clinical Research Studies Rationale

• Develop capacity and infrastructure to conduct HIV vaccine trials

• Trial Design: Understand the epidemiology and trial participants’ health issues

• Vaccine Design: Understand nature of newly transmitted virus and immune mechanisms of HIV control

• Engage community: civil society, medical, regulatory
1. Non-interventional Epidemiology
   a. HIV Incidence (Protocol B)
   b. Volunteer retention (B, C)
   c. Risk factor analysis (B)
   d. Clinical course of HIV infection (C)

2. Interventional Epidemiology: Phase I-III clinical trials
   (the “gold standard”)
   a. Testing vaccine products: safety, immunogenicity and ultimately efficacy

3. Assessment of Understanding
IAVI Africa HIV Research Network Experience

- CRCs in Kenya, Uganda, Rwanda, Zambia and South Africa
- More than 10 clinical trials
- First HIV vaccine trial in Kenya, Rwanda, Zambia
- 2 Phase I trials ongoing
- 2 Phase I/II iPrEP trials in Kenya and Uganda
- Prospective incidence cohorts
  - DC, MSM, FSW, MSW, STI patients, fisher folks, others*
- Early Seroconverter Cohort
- Long Term Follow-Up (LTFU) protocol
- Mucosal studies
  - Specimens: Colon and rectal biopsies, collection of mucosal secretions

*Others: clients of sex workers, multiple sex partners, youth, etc.
IAVI-sponsored Clinical Trials in Africa

Ongoing or about-to-start Phase I

• IAVI B002: Ad35-GRIN + adjuvanted protein
  – Kenya, Uganda, Zambia

• IAVI B003: Ad26-ENV + Ad35-ENV
  – USA, Kenya, Rwanda, South Africa

• IAVI B004: DNA IL-12 EP + Ad35-GRIN/ENV
  – Kenya, Uganda, Rwanda

Pending Phase I

• Ad26 + Ad35 Mosaic
Spectrum of efficacy trials and new designs

HIV infections required to evaluate efficacy

- STOC ~ 30 per protocol, ~ 40 mITT
- Ph2B TOC ~ 50 per protocol
- PAVE 100A ~ 60 weighted ITT
- RV144 ~ 129 mITT
- Vax004 ~ 200 mITT (design), ~388 mITT (actual)

Hypothesis-driven studies (e.g., reduction in viral load) and possible integration of new prevention technologies in efficacy trials (e.g., PrEP) have led to consider new efficacy trial protocol designs:

- **Phase IIB TOC** (*AIDS* 2007;21:539–46)
- **STOC** (*AIDS* 2007;21:2259–63)
- **VAXPREP** (*ARHR* 2011;27:669-80)
**HIV incidence from at-risk cohorts (April 2011)**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Enrolled</th>
<th>Year started</th>
<th>P-Y</th>
<th>HIV cases</th>
<th>Cases/100PY</th>
<th>LL</th>
<th>UL</th>
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<tbody>
<tr>
<td>Lusaka, DC</td>
<td>~1800</td>
<td>2003</td>
<td>3916</td>
<td>279</td>
<td>7.1</td>
<td>6.3</td>
<td>8.0</td>
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<tr>
<td>Kigali, DC</td>
<td>1691</td>
<td>2004</td>
<td>3379</td>
<td>99</td>
<td>2.9</td>
<td>2.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Copperbelt, DC</td>
<td>~1100</td>
<td>2004</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Entebbe, DC</td>
<td>247</td>
<td>2008</td>
<td>507</td>
<td>11</td>
<td>2.2</td>
<td>1.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Masaka, DC</td>
<td>612</td>
<td>2008</td>
<td>872</td>
<td>32</td>
<td>3.7</td>
<td>2.6</td>
<td>5.2</td>
</tr>
<tr>
<td>Kilifi, MSM</td>
<td>385</td>
<td>2008</td>
<td>575</td>
<td>41</td>
<td>7.1</td>
<td>5.3</td>
<td>9.7</td>
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<tr>
<td>Kilifi, FSW</td>
<td>116</td>
<td>2008</td>
<td>243</td>
<td>6</td>
<td>2.5</td>
<td>1.1</td>
<td>5.5</td>
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<tr>
<td>Kangemi, MSM</td>
<td>318</td>
<td>2008</td>
<td>297</td>
<td>10</td>
<td>3.4</td>
<td>1.8</td>
<td>6.3</td>
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<tr>
<td>Kangemi, other*</td>
<td>328</td>
<td>2008</td>
<td>279</td>
<td>1</td>
<td>0.4</td>
<td>0.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Rustenburg**</td>
<td>576</td>
<td>2009</td>
<td>272</td>
<td>9</td>
<td>3.3</td>
<td>1.7</td>
<td>6.4</td>
</tr>
</tbody>
</table>

DC: HIV serodiscordant couples; MSM: Men who have Sex with Men; FSW: Female Sex Workers

*Other risks (e.g. clients of sex workers, recent STD, multiple concurrent sex partners

**Mixed risk population, sexually active women, MSM, and other risks.
Hematology and Biochemistry Reference Intervals for Healthy Adults in Eastern and Southern Africa

Karita et al. PLoS ONE 2009

Hemoglobin intervals and medians by site and gender (men: blue, women: white) including U.S.-based comparison interval and cutoff for DAIDS grade one severity (vertical dashed line).

CD4 count intervals and medians by site and gender (men: blue, women: white) including U.S.-based comparison interval and cutoff for DAIDS grade one severity.
## Results from HIV prevention trials

### Study          | Length of Study | Effect size (CI) | 12 mo effect |
-----------------|-----------------|-----------------|--------------|
HIV Vaccine      | 3.5 y           | 31% (1, 51)     | 60* (22,80)  |
(Thai RV144)     |                 |                 |              |
1% TDF gel       | 2.5 y           | 39% (6, 60)     | 50 (15,72)   |
(Caprisa, Karim et al.) |          |                 |              |
TDF/FTC PrEP     | 1.2 y           | 44% (15, 63)    | 50 (28,66)   |
(iPrEx, Grant et al 2010) |      |                 |              |
Circumcision     |                 | 57% (42, 68)    |              |
(Orange Farm, Rakai, Kisumu) |         |                 |              |

*Not a part of the prespecified analysis

An HIV vaccine should be considered a component of a comprehensive approach to HIV prevention

Prof. Glenda Gray, HVTN Conference, Nov 2010

Improving Prevention of Infection

• RV144 vaccine regimen: 31% and follow-up clinical studies will be a rich source of information for vaccine design
  – Identify the nature of protective responses so we can optimize
  – Improve display of native Envelope
  – Improve immunogenicity
    • Prime boost combinations
    • Replicating vectors
    • Combine with protein based vaccine

• SHIV challenge studies may inform on the value of HIV envelopes and adjuvants

• SIV protection is possible and requires Envelope in vaccine
  SIV protection mechanisms under investigation
  – Binding antibodies
  – Antibody avidity
  – Neutralizing antibodies
  – CD4 responses
Improving Control of Viral Replication

- RV144 and Step regimens did not reduce viral load

- Vaccination can control SIV
  - Control of viral replication does not seem to require Envelope
  - Mechanisms of control are under investigation

- Improve immunogenicity
  - Replicating vectors
  - Prime boost combinations

- Dealing with diversity
  - Broadening the immune response
  - Focusing on immutable regions
IAVI’s role in the UVRI EDCTP-funded Project

• Partners: UVRI (lead partner), Liverpool School of Tropical Medicine, IAVI, WorldFish, Malawi-Liverpool-Wellcome Trust Program

• EDCTP Cash funding: € 3M (EU member state contributions came from MRC, SIDA and Irish AID)

• IAVI staff contributions: training, technical support, protocol development, project management, coordinated support from the larger IAVI network for the purposes of this project

• IAVI contribution: € 1M (in-kind)

• Project timelines: January 2008 thru Dec. 2010 (with a one-year no cost extension through Dec. 2011)
Project Objectives

- To expand and diversify high-risk cohorts by integrating new study populations from fishing communities in Uganda and Malawi.
  - Expected outcomes: Larger and more diversified cohorts for future HIV prevention research and clinical trials

- To build on capacity and infrastructure in Uganda and Malawi for the conduct of phase II/III vaccine trials and ensure transfer of technology to measure immune responses and characterize viruses.
  - Expected outcomes: increased clinical, laboratory and research capacity for the conduct of trials in Africa

- To develop Africa-based capacity for GCP/GCLP training and for technical training.
  - Expected outcomes: Regional capacity for clinical and laboratory teams to provide training and mentoring in conducting HIV prevention research and clinical trials according to ICH/GCP and GCLP in preparation for eventual accreditation
Some statistics

• More than 1,500,000 men, women and children living in fishing communities on the shores and islands of Lake Victoria in Uganda

• 70% of the population is less than 30 years old, half of the population is less than 20 years old

• Less than 25% of the people in fishing communities have access to government health services, reproductive health services, clean water and electricity

• Fishing sector comprises 8% of Uganda’s GDP,
Findings of the ‘fisherfolk study’

• HIV prevalence across 5 research sites: 27-33%
• 1000 volunteers enrolled:
  – 49% were women
  – 33% of enrolled women had transactional sex
  – Retention rate at 18 months was 77% overall
  – Of those who did not complete follow-up, 40% were women
• HIV incidence rate of 4.9 PYAR
• HIV infection rates mainly explained by high-risk behaviour
• There is an urgent need to target HIV prevention and research efforts to this vulnerable and neglected group.
HIV/AIDS in Malawi
- People living with HIV: nearly 1 million
- National HIV prevalence: 11-17%
- Subtype C
- HIV prevalence at urban areas: 25%
- AIDS accounts for 90% of hospital admissions at QEH
- Commercial sex workers, truck drivers and fishermen
- Females account for 60% of HIV infections
- 91,000 children living with HIV and over 0.5 million orphaned
- MSM epidemiology estimated at 20% but uncertain as homosexuality is a serious criminal offence punishable by imprisonment

Source: www.avert.com/aids-malawi.htm

IAVI-Malawi Collaboration
- Technology transfer between IAVI Human Immunology Laboratory, London
- T-cell responses to HIV and other gut pathogens
- ICS on sigmoid biopsies from HIV-infected subjects

Total population: 13 million
Conclusion

- Recent results of prevention trials have raised hope and generated a new impetus
- Partnerships with communities, scientists from different groups and donors are and will remain key to success
- R&D pipeline is promising
- R&D efforts must be sustained and intensified to benefit communities, in particular to vulnerable communities (e.g., fisher folks) who should receive special and sustained attention
- IAVI will continue to assist partners to diversify funding stream
- Political and donor renewed and long term commitments are vital to achieve success in the development of HIV vaccines
Acknowledgements

All study participants and the 210,000+ individuals who have received VCT through IAVI-supported activities

Principal Investigators and Clinical Staff

- Pontiano Kalibu
- Etienne Karita
- Susan Allen
- Omu Anzala
- Linda-Gail Bekker
- Evelyn Chomba
- Juliet Mpendo
- Gavin Churchyard
- Anatoli Kamali
- Noah Kiwanuka
- Shabir Lakhi
- Mary Latka
- Norbert Peshu
- Eduard Sanders
- Eric Hunter

IAVI
- Patricia Fast
- Leslie Nielsen
- Jan de Bont
- Wayne Koff
- Pauli Amornkul
- Matthew Price
- IAVI colleagues in Africa

IAVI Human Immunology Laboratory
- Imperial College, London
- Josephine Cox
- Peter Hayes
- Tony Tarragona
- Gwynn Stevens
- Jill Gilmour
Acknowledgements to our donors

IAVI gratefully acknowledges the generous support provided by the following major donors


And many other generous individuals from around the world

As of March 2011