New developments in the search for an HIV/AIDS vaccine and other prevention research

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HIV epidemic in Uganda

1. HIV prevalence between ages 15-49 has risen and now stands at 7.3% (higher in women at 8.3%) and up from 6.4% in the 2004-05 survey.

2. HIV prevalence in some high risk groups ~ 30% and incidence ~ 5/100 PYR
Summary of presentation

• Progress in HIV vaccine research
• Progress in other NPT: microbicides, PrEP
• Test and treat and other combination prevention trials
• Future trial design challenges
• Conclusion
New prevention technologies will reduce HIV incidence… but only a vaccine will end the epidemic

Source: Imperial College and BMGF, 2010. *Assumed efficacy of 60% and uptake of 50%
Globally:

36 phase I/IIa and one lib efficacy trial

- 19 of these USA
- Most prime-boost - DNA + Viral vector (Pox and Adeno)
  - Pox mostly MVA; various adeno, 5,26, 35 etc
- Improved DNA delivery e.g electroporation
On-going trials in Africa IAVI report by October 2012

<table>
<thead>
<tr>
<th>Title</th>
<th>Phase</th>
<th>Strategy</th>
<th>Product</th>
<th>Organizer/Developer</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>073E/SAAVI 102</td>
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<td>Protein</td>
<td>Sub C gp140</td>
<td>SAAVI, HVTN</td>
<td>South Africa</td>
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<td>I</td>
<td>DNA/Viral Vector-Pox</td>
<td>SAAVI DNA-C2/SAAVI MVA-C</td>
<td>HVTN</td>
<td>South Africa, USA</td>
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<td>HVTN 086, SAAVI 103</td>
<td>I</td>
<td>Viral Vector</td>
<td>SAAVI MVA-C2/SAAVI DNA-C2/Oligomeric gp140/MF59</td>
<td>SAAVI, HVTN</td>
<td>South Africa</td>
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<td>IAVI B002</td>
<td>I</td>
<td>Protein/Protein/Viral Vector-Adeno</td>
<td>Adjuvanted GSK products and Ad35-GRIN</td>
<td>IAVI</td>
<td>Kenya, Uganda, Zambia</td>
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<td>I</td>
<td>Viral Vector-Adeno/Viral-Adeno</td>
<td>Ad26, EnvA01-Ad35-ENV</td>
<td>IAVI</td>
<td>Kenya, Rwanda, South Africa, USA</td>
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<td>I</td>
<td>DNA/Viral Vector-Adeno</td>
<td>HIV-MAG/Ad35-GRIN/ENV</td>
<td>IAVI</td>
<td>Kenya, Rwanda, Uganda</td>
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<td>PedVacc001 and PedVacc002</td>
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<td>Viral Vector</td>
<td>Pox MVA.HIVA</td>
<td>Oxford University</td>
<td>Gambia, Kenya</td>
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<td>RV262</td>
<td>I</td>
<td>DNA/Viral Vector-Pox</td>
<td>Pennvax-G/MVA-CMDR</td>
<td>USA DoD</td>
<td>Kenya, Tanzania, Uganda, USA</td>
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<tr>
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<td>Mozambique</td>
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<td>I/II</td>
<td>DNA/Viral Vector-Pox</td>
<td>HIVIS-DNA/MVA-CMDR</td>
<td>Karolinska, USA DoD</td>
<td>Tanzania</td>
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RV144 Trial- Renewed hope
Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial

Barton F. Haynes, M.D., Peter B. Gilbert, Ph.D., M. Juliana McElrath, M.D., Ph.D., Susan Zolla-Pazner, Ph.D., Georgia D. Tomaras, Ph.D., S. Munir Alam, Ph.D., David T. Evans, Ph.D., David C. Montefiori, Ph.D., Chitraporn Karnasuta, Ph.D., Ruengpueng Sutthent, M.D., Ph.D., Hua-Xin Liao, M.D., Ph.D., Anthony L. DeVico, Ph.D., George K. Lewis, Ph.D., Constance Williams, B.S., Abraham Pinter, Ph.D., Youyi Fong, Ph.D., Holly Janes, Ph.D., Allan DeCamp, M.S., Yunda Huang, Ph.D., Mangala Rao, Ph.D., Erik Billings, Ph.D., Nicos Karasavvas, Ph.D., Merlin L. Robb, M.D., Viseth Ngauy, M.D., Mark S. de Souza, Ph.D., Robert Paris, M.D., Guido Ferrari, M.D., Robert T. Bailer, Ph.D., Kelly A. Soderberg, Ph.D., Charla Andrews, Sc.M., Phillip W. Berman, Ph.D., Nicole Frahm, Ph.D., Stephen C. De Rosa, M.D., Michael D. Alpert, Ph.D., Nicole L. Yates, Ph.D., Xiaoying Shen, Ph.D., Richard A. Koup, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Jaranit Kaewkungwal, Ph.D., Sorachai Nitayaphan, M.D., Ph.D., Supachai Rerks-Ngarm, M.D., Nelson L. Michael, M.D., Ph.D., and Jerome H. Kim, M.D.
Correlate of Risk - an immune response that predicts whether vaccinees become HIV-1 infected.

It may be causally related to protection from infection, or may be only a surrogate marker for another factor.
1. Measured immune responses from:
   • 41 Infected Vaccinees
   • 205 Uninfected Vaccinees
   • 40 Placebo Recipients

**Question:** What are the immunologic measurements in vaccinees that predict HIV-1 infection over 3 year follow-up?
   • Sample Time point: **Peak Immunogenicity**
     (2 weeks after final vaccination)
   • Cryopreserved specimens
Two Correlates of Infection Risk Found
(Haynes, NEJM 366: 1275, 2012)

1. IgG antibodies that bind to a V1V2 recombinant fusion protein correlated *inversely* with infection rate. (Higher V1V2, *lower* infection rate)

2. Env binding plasma (monomeric) IgA correlated *directly* with infection rate. (Higher IgA to Env, *higher* infection rate).
Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V2

Morgane Rolland1*, Paul T. Edlefsen2*, Brendan B. Larsen3, Sodsai Tovanabutra1, Eric Sanders-Buell1, Tomer Hertz2, Allan C. deCamp2, Chris Carrico4,5, Sergey Menis4,5, Craig A. Magaret2, Hasan Ahmed2, Michal Juraska2, Lennie Chen3, Philip Konopa3, Snehal Nariya3, Julia N. Stoddard3, Kim Wong3, Hong Zhao3, Wenjie Deng3, Brandon S. Maust3, Meera Bose1, Shana Howell1, Adam Bates1, Michelle Lazzaro1, Annemarie O'Sullivan1, Esther Lei1, Andrea Bradfield1, Grace Ibitamuno1, Vatcharain Assawadarachai6, Robert J. O'Connell1, Mark S. deSouza6, Sorachai Nitayaphan6, Supachai Rerk-Ngarm7, Merlin L. Robb1, Jason S. McLellan8, Ivelin Georgiev8, Peter D. Kwong8, Jonathan M. Carlson9, Nelson L. Michael1, William R. Schief4,5, Peter B. Gilbert2*, James I. Mullins3* & Jerome H. Kim1*
1. Isolated 4 human V2 mabs (3 vaccinees)-A244 gp120

2. Crystal structures of two CH58, CH59
Hypothesis

Antibody dependent mediated cytotoxicity

Not by neutralization
Hypothesis: Monomeric IgA Can Block IgG Binding to HIV-1 Env on Infected Cells and Prevent IgG Effector Function
How To Move From a Correlate of Risk to a Causal Correlate of Protection?

To determine if the hypotheses generated from the RV144 case control study (the correlates of risk) are causal correlates, they must be directly demonstrated in new clinical trials, or antibodies tested in NHP passive protection studies, or tested in other ways.
NHP Passive Protection Trials

- CH58, CH90, CH58+CH90
Plans to move RV144 forward

On going

*Thailand:* RV 305 trial, phase II
  - Safety and tolerability of late boost of AIDSVAX B/E alone, ALVAC alone or ALVAC/AIDSVAX B/E combination in 162 participants of RV 144

Planned

*Thailand:* RV 306 same vaccine in 460 high risk MSM
  *RV 328 additional AIDSVax*

*South Africa and Mozambique:* Using subtype C prime and boost
Antibodies
Broadly neutralizing HmAb

Fig. 1. The envelope of HIV-1 carries spikes. (a) Each spike is made of three molecules of the surface glycoprotein gp120 and three molecules of the transmembrane glycoprotein gp41. Glycoprotein gp120 contains variable V1/V2 and V3 loops, as well as the binding site for CD4. (b) The binding sites of broadly acting and potent HIV-1-specific neutralizing antibodies are shown as colored circles.
**Retrovaccinology: From antibody to antigen**

Infected individual

Broadly neutralizing (protective) antibodies

Molecular characterization of interaction of antibody with pathogen antigen

Immunogen design and testing

Modified antigen

Combination of several immunogens = vaccine

Source: Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002
An innovative approach: Passive Immunity

THE FIND
Multiple broadly neutralizing antibodies against HIV

THE GOAL
Elicit those antibodies through vaccination

INTERIM STEPS
Prove concept through …

Passive immunization by injecting antibodies

Gene transfer through a vector that produces the antibodies
Progress

1. AAV 1 vector expressing gene for PG9 antibody has been developed (IAVI and NIAID) will be tested in phase 1 soon

2. Passive immunotherapy infants - GHVI consultative workshop using VRC01
   - Entebbe meeting
Other vaccines providing high levels of protection

1. Adeno/pox and Adeno/adeno vector
2. DNA + Ad5
3. Electroporated DNA + IL2 + Ad5
4. CMV-based vaccines
LETTER

Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys

Dan H. Barouch¹,², Jinyan Liu¹, Hualin Li¹, Lori F. Maxfield¹, Peter Abbink¹, Diana M. Lynch¹, M. Justin Iampietro¹, Adam SanMiguel¹, Michael S. Seaman¹, Guido Ferrari³, Donald N. Forthal⁴, Ilnour Ourmanov⁵, Vanessa M. Hirsch⁵, Angela Carville⁶, Keith G. Mansfield⁶, Donald Stablein⁷, Maria G. Pau⁸, Hanneke Schuitemaker⁸, Jerald C. Sadoff⁸, Erik A. Billings⁹, Mangala Rao⁹, Merlin L. Robb⁹, Jerome H. Kim⁹, Mary A. Marovich⁹, Jaap Goudsmit⁸* & Nelson L. Michael⁹*
Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys

Dan H Barouch¹,², Kara L O’Brien¹, Nathaniel L Simmons¹, Sharon L King¹, Peter Abbink¹, Lori F Maxfield¹, Ying-Hua Sun¹, Annalena La Porte¹, Ambryice M Riggs¹, Diana M Lynch¹, Sarah L Clark¹, Katherine Backus¹, James R Perry¹, Michael S Seaman¹, Angela Carville³, Keith G Mansfield³, James J Szinger⁴, Will Fischer⁴, Mark Muldoon⁵,⁶ & Bette Korber⁴,⁶

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Conclusion

1. There is some progress in understanding correlates of risk and mechanisms in RV144 relevant for vaccine design
2. There is progress in moving bNab to vaccine design
3. Optimised HIV vaccines can block acquisition in heterologous neutralization resistant SHIV in NHP
CAPRISA 004 effectiveness by adherence

- 1% tenofovir gel – coitally dependent regimen (BAT24)
- HIV: overall 39% reduction (6-61%, p=0.017)
- High adherers (>80% gel use): 54% lower, p=0.025
- Intermediate (50-80% gel use): 38% lower, p=0.34
- Tenofovir vaginal concentrations:
  - Need to achieve high levels >1000 ng/ml
Post CAPRISA 004

- WHO/UNAIDS meeting – priority next steps
  - Additional safety studies e.g. among young women
  - FACTS trial to confirm findings (same regimen)
  - Simplified dosing and less frequent HIV testing (MDP 302)
1. Phase III testing 1% tenofovir gel, same regimen as CAPRISA 004
2. 2900 heterosexual women
3. Launched October 2011 and results expected 2014
Next generation microbicides

Formulations:
- Gel formulations been mainly evaluated as “coitally-dependent”
- Coitally –dissociated” formulations – offer sustained delivery (IVR, injectable, implants)
  - IVR most advanced of all
Why a ring?

• Long-acting: monthly or longer
  – Could potentially improve adherence
  – Better adherence → better effectiveness

• Easy to use, comfortable
  – Flexible ring, can be self-inserted
  – Rarely felt by women or their male partners
  – Little or no impact on sexual activity

• Suitable for developing world
  – Relatively low manufacturing cost
  – Good safety and acceptability data
IPM 027- Dapivirine ring

- Phase III safety and efficacy in 1650 women; results expected early 2015
  - Uganda (MRC to join)
ASPIRE (MTN 020)

• Phase III safety and efficacy study in 3,476 women, results expected early 2015
  – Uganda (MUJHU)
Prevention of HIV-1 Infection with Early Antiretroviral Therapy

Test and treat

- Garnett et al Lancet 2009-mathematical modelling UTT may substantially reduce, even eliminate sexual transmission at population level
The PopART

- A 3-arm trial in Zambia and South Africa with 8 clusters in each arm and includes house-to-house universal voluntary HIV testing and immediate ART to all who test HIV-positive, VMMC for HIV negative men, counselling and condom promotion, strengthening PMTCT services and syndromic STI treatment.
PopART

- Arm A clusters receive the full intervention package,
- Arm B receive the full intervention but ART is only initiated to those with CD4<350 cells/μl or WHO stage 3/4, and arm
- C receives national standard of care
The Treatment as Prevention (TASP) trial in Kwazulu Natal

• A 2-arm trial with 16 clusters per arm.

  Arm A clusters receive expanded testing, VMMC, immediate ART to all HIV positive, IEC and STI treatment are implemented.

  Arm B receives same intervention package except that ART is provided at CD4 <350 cells/µl.
Other combination prevention studies
The Iringa Combination trial in Tanzania

- Is a 2-arm trial with 24 clusters per arm. Interventions include expanded testing and linkage to care, ART at CD4 <350 cells/μl, information education and communication (IEC), VMMC, conditional cash transfers and targeted outreach versus the national standard of care.
The Harvard School of Public Health-Botswana trial

- A 2-arm study with 10 clusters per arm, enrolling 18-49 year olds in rural communities.
- Arm A receives expanded testing and linkage to care, ART at CD4<350 cells/µl or viral load >10,000 copies/µl, and VMMC for HIV-uninfected adults.
- Arm B receives standard of care according to national guidelines. A key feature of this trial is that it focuses on individuals with high viral load who are most likely to be the main transmitters.
Preexposure Prophylaxis

- TDF2 and Partners PrEP efficacy 62-75%
- FEM-PrEP – discontinued due to lack of efficacy
- VOICE TDF alone stopped

- FDA approved TDF/FTC or Truvada for use as preexposure prophylaxis among sexually active adult men and women
Trial design challenges

• Future efficacy trials- large and expensive
  – Kublin J. et al It will require 5100 volunteers in S. Africa at 20 sites to observe a 50% efficacy with 4% incidence in a setting of male circumcision, increased ART uptake, possible PreP
  – Most cohorts have much lower incidence
Short-Course Antiretroviral Therapy in Primary HIV Infection

The SPARTAC Trial Investigators*
Conclusion

• In the coming years we will have a number of additional prevention approaches

• This is causing excitement even talking about an end to the epidemic !!!

• But we think for longer term control of HIV we need a vaccine