Current Options, Future Hopes

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IAVI Clinical Laboratory Program
Biomedical HIV Prevention Forum, Abuja, Nigeria

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Outline

• Progress made to date
• Current Options
• Future Hopes
  – Microbicides
  – HIV Vaccines
  – Cure
Global HIV Epidemic - 2012

35.3 million living with HIV, 2.3 million new infections, 1.6 million deaths

Source: UNAIDS 2013
PROGRESS: New infections are falling

Increased ART coverage combined with scaled-up prevention, reduced annual HIV infections by 33% over 10 years.

Annual infections with HIV globally over time [M]
Antiretroviral Therapy coverage globally and by region

- Averted 4.2 million deaths 2002-2012
- 16 million eligible still do not have access
Investments

• **US$ 18.9 billion** was available from all sources for the AIDS response in 2012.
  – The estimated annual need by 2015 is currently between US$ 22-24 billion.

• In 2012, low- and middle-income countries increased domestic investments for HIV, accounting for 53% of all HIV related spending.

Source: UNAIDS 2013
The world has yet to reach a tipping point in the AIDS response. The number of new HIV infections in 2012 (2.3 million) substantially exceeded the increase in the number of people on HIV treatment (1.6 million). As a result, the epidemic continues to outpace the response.
THE TIPPING POINT: Global progress in reducing new HIV infections and scaling up of antiretroviral treatment

Programmatic Tipping Point
Ratio of the number of new HIV infections to the increase in new patients on treatment

Countries that have not reached the tipping point
Global and regional figures
Countries that have reached the tipping point
ARV treatment slots have exceeded the number of new infections

Nigeria
Mozambique
DR Congo
Lesotho
India
Burundi
Kenya
Global
Sub-Saharan Africa
Cameroon
Uganda
Cote d’Ivoire
Haiti
Ethiopia
Zambia
South Africa
Namibia
Malawi
Swaziland
Zimbabwe
Tanzania
Dual Pathway: to reach the tipping point

Figure 1: The dual pathway to controlling and ultimately ending the AIDS pandemic.

Fauci et al, Nature Immunology, Vol 14, Nov 13
Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission.
Selected HIV prevention technologies shown to be effective in reducing HIV transmission in randomized controlled trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>EFFECT SIZE (95% confidence interval)</th>
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<tr>
<td>Antiretroviral therapy in an HIV-positive partner HPTN 052/Africa, Asia, Americas</td>
<td>96% (73-99)</td>
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<td>Pre-exposure prophylaxis (oral emtricitabine/tenofovir; tenofovir) for heterosexual discordant couples</td>
<td>75% (55-87)</td>
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<td>Partners PrEP/Uganda, Kenya</td>
<td>67% (44-81)</td>
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<tr>
<td>Pre-exposure prophylaxis (oral emtricitabine/tenofovir; tenofovir) for heterosexual men and women TDF2/Botswana</td>
<td>63% (22-83)</td>
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<tr>
<td>Pre-exposure prophylaxis (oral emtricitabine/tenofovir; tenofovir) for men who have sex with men IPrEX/Americas, Thailand, South Africa</td>
<td>44% (15-63)</td>
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<tr>
<td>Microbicide (1% tenofovir vaginal gel) CAPRISA 004/ South Africa</td>
<td>39% (6-60)</td>
</tr>
<tr>
<td>HIV vaccine RV144/Thailand</td>
<td>31% (1-51)</td>
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Source: Adapted from Karim SS, Karim QA. Lancet, 2011.
HIV Prevention Options Timeline

**TIMELINE LEGEND**
- **Positive efficacy result**
- **Arm stopped**
- **Regulatory submission/filing**
- **Final results pending**
- **Earliest regulatory submission**
- **Possible TMC278 LA Injectable**
- **South Africa Licensure**
- **South Africa Research**
- **Thai Licensure**

* Trial end-dates are estimates; due to the nature of clinical trials the actual dates may change. For full trial details, see www.avac.org/pxrd.
** Not all trials included are effectiveness trials. Trials included on this list are mainly phase IIb, IIIb, and IV trials.
Annual number of voluntary medical male circumcisions, 2009–2012

![Graph showing the annual number of voluntary medical male circumcisions from 2009 to 2012 for various countries such as Zimbabwe, Zambia, Uganda, Tanzania, Swaziland, South Africa, and Rwanda. The graph indicates a steady increase in the number of circumcisions over the years for each country.](image)
Future Hopes

• **Deliver for today**
  - Prevent new infections with existing tools
  - Ensure access to treatment for people living with HIV
  - Mitigate societal impacts

• **Develop better tools for the future**
  - Invest in innovation for new technologies (better drugs, diagnostics, barrier methods, microbicides, vaccines)
MICROBICIDES
Current Research in Sub-Saharan Africa

- Uganda
- Rwanda
- Zambia
- Malawi
- Zimbabwe
- South Africa

Countries hosting both ring and gel trial(s)
Country hosting ring trial(s)
**AIDS vaccines are part of a sustainable, comprehensive response**

A comprehensive prevention approach - including AIDS vaccines—is critical for the affordability and sustainability of our commitments to universal access.
AIDS Vaccine Efficacy Trial- Phase IIb Pipeline: September 2012


**Candidates to Build on RV-144 Thai Trial**
- DNA + Ad5 (gag-pol, nef-Env A,B,C) : Phase IIb Efficacy (HVTN 505)

**Heterologous Prime Boost Candidates To Address HIV Variability**
- ALVAC + gp120  Licensure trial in RSA
- DNA + NYVAC + gp120 Test of Concept Trial NYVAC + gp120
- • Ad26 + MVA (mosaic antigens)
- • Chimp Ad 63 + MVA (conserved antigens)
- • epDNA + IL12+ Ad35 or chAd63

**Next Generation Candidates to Elicit bnAbs**
- • Addition of HIV trimers or Epitope based vaccines to vectors above
Follow-on Trials Based on RV144: Strategy includes development and research tracks

**RV144 FOLLOW-UP: Thailand**

*Research Studies:*
- RV144i immune correlates studies
- RV305 protein boost in volunteer-subset from RV144
- RV306 expanded immunogenicity of RV144 regimen
- RV328 AIDSvax B/E study

*Partners/Funders:* US Army, Thai government, NIH, Sanofi Pasteur, BMGF

**LICENSURE TRIAL: Thailand**

*Population:* MSM, high-risk

*Products:* ALVAC (Sanofi Pasteur) + gp120/adjuvant (such as MF59)

*Partners/Funders:* US Army, Thai government, NIH, Sanofi Pasteur, BMGF, Novartis

**LICENSURE TRIAL: South Africa**

*Population:* Heterosexual, high-risk

*Products:* ALVAC (Sanofi Pasteur) + gp120/MF59 (Novartis)

*Partners/Funders:* NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

**RESEARCH TRIAL**

*Population:* Heterosexual, high-risk

*Products:* DNA + NYVAC (Sanofi Pasteur) + protein/adjuvant (such as MF59) vs. NYVAC (Sanofi Pasteur) + protein/adjuvant

*Partners/Funders:* NIH, HVTN, Sanofi Pasteur, Novartis, BMGF

Source: This schematic comes from the Pox-Protein Public Private Partnership (P5), a collaboration spanning four continents established in 2010 to build on the results of RV144. P5 partners include the US NIAID, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, the US Military HIV Research Program, Sanofi Pasteur and Novartis Vaccines and Diagnostics.
An Effective AIDS Vaccine will likely need to stimulate broad, potent and durable **Neutralizing Antibodies** and **Cell Mediated Immunity**.
Neutralizing Antibodies: Research pathways in 2013 and beyond

HIV-infected individual

Broadly neutralizing antibodies

Reverse Engineering Vaccines

- A protein from HIV surface (envelope) interacting with an antibody.
- Molecular characterization of the interaction between HIV envelope and BNAbs
- Modified env
- Development of immunogens to mimic the portion of HIV envelope that connects with BNAbs
- Combination of several immunogens = vaccine

Passive Immunization Trials

- Development of clinical grade purified form of BNAbs
- Phase I: Safety and pharmacokinetic evaluation
- Phase II/III: Efficacy trials

Crystal Structure of a Soluble Cleaved HIV-1 Envelope Trimer

Jean-Philippe Julien,1,2,3 Albert Cupo,4 Devin Sok,2,3,5 Robyn L. Stanfield,1,2,3 Dmitry Lyumkis,1,4,6 Marc C. Deller,7 Per-Johan Klasse,4 Dennis R. Burton,2,3,5,8 Rogier W. Sanders,5,9 John P. Moore,9 Andrew B. Ward,1,2,9 Ian A. Wilson1,2,3,7,10

LETTER

doi:10.1038/nature12746

Antibody-mediated immunotherapy of macaques chronically infected with SHIV suppresses viraemia

Masashi Shingal1, Yoshikari Nishimura1, Florian Klein2, Hugo Mouquet3, Olivia K. Donau1, Ronald Plishka1, Alicia Buckler-White1, Michael Seaman1, Michael Piatak Jr2, Jeffrey D. Lifson1, Dimiter Dimitrov10, Michel C. Nussenzweig1,6,7 & Malcolm A. Martin11

ARTICLE

doi:10.1038/nature12744

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys

Dan H. Barouch1,2, James B. Whitney3, Brian Moldt4, Florian Klein2, Thiago Y. Oliveira5, Jinyan Liu1, Kathryn E. Stephenson1, Hui-Wen Chang1, Karthik Sheshur1, Sanjana Gupta6, Joseph P. Nikol1, Michael S. Seaman1, Kaitlin M. Smith1, Erica N. Borducchi1, Crystal Cabral1, Jeffrey Y. Smith1, Stephen Blackmore1, Srismoyanta Sanjutty1, James R. Perry1, Matthew Beck1, Mark G. Lewis1, William Ksiazek7, Anup K. Chakraborty1,7, Pascal Poignard1, Michel C. Nussenzweig1,6,7 & Malcolm A. Martin11

Cryo-EM Structure of a Fully Glycosylated Soluble Cleaved HIV-1 Envelope Trimer

Dmitry Lyumkis,1,2 Jean-Philippe Julien,3,4 Natalia de Val,2,3 Albert Cupo,5 Clinton S. Potter,1,2 Per-Johan Klasse,4 Dennis R. Burton,2,3,5,8 Rogier W. Sanders,5,9 John P. Moore,9 Bridget Carragher,1,2,9 Ian A. Wilson1,3,4,6,8 Andrew B. Ward1,2,9

resolution of this Env trimer in complex with bnAb PG904 against a CD4bs epitope. The structure reveals the overall organization of Env, the interaction between gp120 and gp41 subunits, and how trimer formation affects the CD4bs and its associated bnAb epitopes.

Specimen Preparation, EM Data Acquisition, and Image Processing of SOSIP Trimers

BG505 SOSIP.664 gp140 trimers were produced in HEK 293T cells and have a typical human cell glycosylation profile. The Env trimer is collagen.
Do we need a vaccine?

“The answer is absolutely yes, but the HIV prevention strategy will in fact be a unique paradigm of non-vaccine combination prevention modalities together with a safe and effective vaccine, and then and only then, will we see a durable end of HIV/AIDS.”

Anthony Fauci, Director NIAID
Implementing Combination Prevention

A range of interventions will need to be considered as part of a comprehensive prevention response:

• Behavioural interventions.
• Biomedical interventions such as circumcision, vaccines and the use of antiretroviral drugs to prevent HIV infection.
• Structural interventions which act on the factors that make people more vulnerable to HIV infection, such as poverty, gender, stigma and discrimination.
• Optimisation of surveillance, planning, delivery, monitoring and evaluation.
• Leadership, governance, advocacy and resource mobilisation.
Defining Combination Prevention: Ongoing trials in sub-Saharan Africa

- **Methods for Prevention Packages Program**
  - Home-based HIV testing and targeted referrals for VMMC, ART, STI treatment, couples counseling and oral PrEP plus topical PrEP (if effective)

- **An HIV Prevention Package for Mochudi**
  - Behavioral interventions: VCT, partner notification, concurrency reduction, VMMC, condoms and ART for those with high viral load

- **PopART/HPTN 071**
  - A strategy linking household-based HIV testing to universal community-based HIV treatment

- **Harvard School of Public Health with US CDC funding**
  - Evaluation of the impact on HIV incidence of expanding population coverage of an integrated set of HIV prevention interventions

- **Gender-Specific Combination HIV Prevention for Youth in High-Burden Settings**
  - Gender-specific HIV packages for male and female youth delivered using community-based mobile health teams

- **Acute Infection in Heterosexuals**
  - Standard vs. enhanced counseling vs. behavioral intervention plus 12-week ART to reduce viral load

- **Comprehensive HIV Prevention Package for MSM in Southern Africa**
  - Package of behavioral, biomedical and community-level interventions

- **Enhance Prevention in Couples**
  - Behavioral counseling, ART for prevention (CD4<500) plus couples counseling, VMMC

- **CHAMPS: Choices for Adolescent Methods of Prevention in South Africa**
  - Potentially PrEP, microbicides, HCT and circumcision—plus messaging and social marketing around these approaches

In addition to the trials pictured, there are also evaluations ongoing in Europe, North and South America. For a complete list, visit avac.org/pxrd.

Discovering a Cure
Remains an important aspirational goal in the HIV-research agenda

• Eradication vs functional cure
  – Early initiation of ARV – HIV infected infant

• Early treatment not always feasible – other strategies to eliminate the latently infected cells – gene therapy, stem cell transplantation, directed immunotoxic therapy
Conclusion

“Now is not the time for a ‘victory lap’ but the time for racing ahead. “

Fauci et al 2013

TOGETHER WE WILL END AIDS.
IMAGINE a World Without AIDS
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And many other generous individuals from around the world.

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