

Future Directions in Prevention Research.

presented to
The President's Advisory Council on HIV/AIDS (PACHA).

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March 26, 2008.

[Reb ribbon with globe.]
U.S. Department of Health and Human Services.
National Institutes of Health.
National Institute of Allergy and Infectious Diseases.

Outline

- How HIV Disease is Different
- What Can Be Done to Impact the Epidemic
- Need for Prevention Research
- Developments in HIV Prevention Research
 - Prevention of Mother-To-Child Transmission (MTCT)
 - Topical Microbicides
 - Pre-exposure Prophylaxis (PrEP)
 - Circumcision
- Vaccines
- Back to Basic Research!

HIV is Different.

- The natural immune response to HIV is inadequate.
- HIV hides from the immune system.
- HIV targets and destroys the immune system.
- HIV mutates rapidly.

[gp120. gp41. Lipid Membrane. Capsid.
Reverse Transcriptase. R N A. Matrix.]

NIH Funding History, 1984-2008 (P. B.).

[Chart shows funding per fiscal year. Ranging from approximately 5 billion dollars in 1984 to 28.8 billion dollars in 2008.]

Approaches to HIV Prevention

- Education and behavior modification
- Condoms, and other barrier methods
- Treatment/prevention of drug/alcohol abuse
- Clean syringes (i.e. needle exchange programs)
- Interruption of mother-to-child transmission
- Pre-exposure prophylaxis
- Topical microbicides
- Circumcision
- Vaccination

Confronting AIDS in the twenty-first century.

Basic and clinical research.

Prevention. Treatment. Care.

San Francisco Chronicle.

Northern California's largest newspaper. May 9, 2007.

Quote by Doctor Peter Piot, UNAIDS Executive Director.

Treatment is not going to stop this epidemic. In 2005, there were six new infections for every person put into treatment. That is not sustainable. That means we are losing the battle.

HIV Prevention Research. Guiding Principles.

- Multiple strategies needed to assemble a well-rounded prevention toolkit.
- No one prevention strategy will be 100% effective, appropriate to or accepted by everyone.
- Multiple prevention strategies must be evaluated in different populations, domestically and globally, to determine the best combinations for a given population.

[Toolkit holding the words vaccine (with syringe), harm reduction, M T C T interruption, Prep, Education, microbicides, condoms, circumcision, S T I treatment, Drug/alcohol treatment, etcetera.]

Percentage of Individuals at risk with access to HIV prevention.

8 percent. Harm reduction for injection drug users.

9 percent. Condom access.

9 percent. Behavior change programs for men who have sex with men.

10 to 12 percent. Adults with access to HIV testing in Africa.

11 percent. Prevention of mother to child transmission.

Less than 20 percent. Behavior change programs for commercial sex workers.

Source: Global HIV prevention working group, 2007. WHO/UNAIDS/UNICEF, 2007

Female-controlled prevention methods are needed because social and economic disempowerment frequently prevent women from insisting on condom use.

Photo: Face AIDS. [African women taking care of a sick person.]

Mother-to-Child Transmission (MTCT) of HIV

- Mostly affects developing countries
 - Worldwide:
 - 420,000 children under 15 were infected in 2007
 - In the U.S.:
 - 142 infants were newly infected with HIV in 2006
- Routes of transmission:
 - During the mother's pregnancy
 - Childbirth
 - Breastfeeding

[Woman breastfeeding a child.]

Reuters.

February 4, 2008.

HIV Drugs Make Breast-Feeding Safer, Study Finds.

The New York Times.

February 5, 2008.

Longer Drug Regimen Found to Help Babies Avoid HIV.

"Researchers have found for the first time that the incidence of the virus among breast-fed infants can be significantly reduced by extending antiretroviral drugs for much longer periods, up to six months, according to a number of studies reported on Monday at a scientific meeting here."

Topical Microbicides.

Cream. Suppository. Gel. Film.

A substance applied vaginally or rectally that can reduce or eliminate transmission of HIV or other STD pathogens

The Need for Topical Microbicides.

- Most HIV infections are spread by unprotected sex.
- Current methods are male controlled and contraceptive.
- Women have no means to protect themselves if their partners do not use male condoms or allow female condoms to be used.
- Abstinence and being faithful are not likely to protect married women or those who are sexually abused.

Areas to Explore

- Safety (increased susceptibility?)
- Behavioral aspects (e.g. adherence, acceptability)
- Combination microbicides (similar to HAART)
- Develop long acting methods of delivery

A Role for Pre-Exposure Chemoprophylaxis of HIV Infection?

The Journal of the American Medical Association (JAMA).

Volume 296. Number 7. August 16, 2006.

Preexposure Prophylaxis for HIV: Unproven Promise and Potential Pitfalls. A.Y. Liu, R.M. Grant, and S.P. Buchbinder.

The Journal of Infectious Diseases.

Chemoprophylaxis of HIV Infection: Moving Forward with Caution.

R.M. Grant and M.A. Wainberg.

Will people at risk adhere? The importance of understanding behavior!

Timeframe for Ongoing and Planned Biomedical Prevention Trials.

HPTN 035- Phase II/IIb of vaginal PRO2000 & BufferGel (microbicide).

HPTN 052 Phase III - ART in discordant couples (ART as prevention).

MTN 003/VOICE – Phase IIb, Topical vs. oral Tenofovir or Truvada PrEP (microbicide and PrEP).

iPrEX – Phase III, Truvada among MSMs in Peru, Ecuador, South Africa, Brazil, Thailand, US (PrEP).

CDC 4370 –Phase II/III, Daily Tenofovir or placebo among IDUs in Thailand (PrEP).

CDC 4323 – Phase II Safety Study, Daily Tenofovir or placebo among MSMs in US (PrEP).

CDC 4940 – Phase III, Daily Truvada or placebo in Botswana (PrEP).

Partners Study – Phase III, Daily Tenofovir, Truvada, or placebo in discordant hetero couples (PrEP).

FEM-PrEP – Phase III, Daily Truvada or daily oral placebo in high risk women (PrEP).

Looking Ahead

- Phase II/IIb study of PRO 2000/5 (P) and BufferGel will end in summer of 2008 (HPTN 035)
- Vaginal and Oral Interventions to Control the Epidemic (VOICE) study to compare oral versus vaginal delivery of Tenofovir is currently in development (MTN-003)
- Phase III trial of Dapivirine currently in development (IPM 009)

Time.

Top 10 Medical Breakthroughs of 2007.
Number 1. Circumcision Can Prevent HIV.
[Doctors and patient in clinic.]

UNAIDS. Joint United Nations Programme on HIV/AIDS.
World Health Organization.
Paris/Geneva, 28 March 2007.

WHO and UNAIDS Announce Recommendations from Expert Consultation on Male Circumcision for HIV Prevention.

- Male circumcision should now be recognized as an additional, important intervention to reduce the risk of heterosexually acquired HIV infection in men.
- Male circumcision should be part of a comprehensive HIV prevention package.
- Adequate training, hygiene, monitoring, counseling are critical.
- Modeling studies suggest that male circumcision in sub-Saharan Africa could prevent 5 point 7 million new cases of HIV infection and three million deaths over 20 years.

JAIDS. December 15, 2007. Volume 46. Number 5.

Circumcision Status and HIV Infection Among Black and Latino Men Who Have Sex With Men in 3 United States Cities. G.A. Millet, et al.

- N equals 2,235.
- Cross-sectional data.
- No evidence that being circumcised was protective against HIV infection among black M S M or Latino M S M.

The New York Times.

February 5, 2008.

Male Circumcision No Aid to Women in Study.

Male circumcision conferred no indirect benefit to the female partners, and increased the risk if the couples resumed sex before the circumcision wound was fully healed, usually in about a month... The study did confirm that benefit of male circumcision in lowering the incidence of herpes and other genital ulcers among men.

Timeline for Efficacy Data From Current & Planned Vaccine Trials, 2007

- RV 144. Anticipated Data Availability third quarter 2009.
- HVTN 502. Anticipated Data Availability second quarter 2010.
- HVTN 503. Anticipated Data Availability second quarter 2011.
- PAVE 100. Anticipated Data Availability fourth quarter 2011.

Timeline for Efficacy Data From Current & Planned Vaccine Trials

- RV 144. Anticipated Data Availability third quarter 2009.
- HVTN 502. Stopped.
- HVTN 503. Stopped.
- PAVE 100. Under construction. Anticipated Data Availability possibly 2012.

History of HIV Vaccine Development.

Antibody Candidates.

[Arrow pointing downward.]

Cell Mediated (CD 8 + T cell) Candidates.

[Arrow pointing downward.]

Question mark.

STEP Study Results.

- Vaccine did not protect against infection.
- Vaccine did not lower the viral "setpoint."
- There were more infections in vaccinees than placebo recipients.
 - This trend was more pronounced in participants with high baseline Ad5 titers.

Next steps and future directions in HIV vaccine clinical trials.

PAVE. Evaluation of the D N A/Ad5 vaccine from the NIH.

What is PAVE?

- What is PAVE?
PAVE stands for Partnership for AIDS Vaccine Evaluation. PAVE is a voluntary consortium of United States Government (USG) agencies and key USG-funded organizations involved in the conduct of HIV vaccine clinical trials.
- What are the goals of PAVE?
PAVE's goal is to provide a forum and clearinghouse to achieve better harmony, increased efficiencies and increased cost effectiveness in the conduct of HIV/AIDS preventive HIV vaccine trials, especially phase III trials.
- Why is PAVE needed?
No one entity or institution will accomplish the goal of identifying a safe and effective HIV vaccine. Speed is critical and different expertise and sectors are required. Unnecessary duplication also needs to be avoided/eliminated. The bottom line is that there is an urgent need to increase efficiency and improve effectiveness.
- PAVE 100 is the first trial developed by this collaboration

PAVE 100 Decision-making Process

1. PAVE partners (HVTN, USMHRP, IAVI, CDC) decide their level of interest in participating in the proposed trial(s) (ongoing)
2. NIAID Director's decision on funding based on:
 - AIDS Vaccine Research Subcommittee (AVRS) technical assessments:
 - Aug 20, 2007: update on phase 2 trials
 - Dec 12, 2007: implications of STEP findings. Is further study of VRC candidate warranted? Is there equipoise in proceeding in Ad5 negative populations?
 - May 30, 2009: further assessment of new data and proposed trial(s)
 - Discussions with host country governments
 - Input from communities
 - Strategic Working Group advice on HIV/AIDS clinical trial priorities (June 2007 and May 2008)
 - Other, as needed
3. Protocol and informed consent reviews
 - NIAID Prevention Sciences Review Committee
 - U.S. FDA and host country regulatory bodies
 - Institutional review boards, ethics committees

Thank you!

Questions?

Purpose and Selected Goals of the HIV Vaccine Summit

- The summit is an important step in ongoing efforts to examine the current direction of HIV vaccine research; part of an iterative process
- NIAID is seeking input on the entire HIV research endeavor, including (but not limited to)
 - the optimal balance between vaccine discovery and development
 - NHP model development, optimization and utilization
 - Integration of clinical research with discovery
- Based upon input and feedback, NIAID will make adjustments to existing efforts to attract and support novel, high-priority science

A Comprehensive HIV Prevention "Toolbox".

[Toolkit holding the words vaccine (with syringe), harm reduction, M T C T interruption, Prep, Education, microbicides, condoms, circumcision, S T I treatment, Drug/alcohol treatment, etcetera.]