Seeking an End to HIV/AIDS: From Basic Research to Public Health Implementation

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National Institutes of Health
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Seven Centers for AIDS Research (CFARs) Established, 1988

HHS NEWS
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOR IMMEDIATE RELEASE
October 13, 1988

Robert E. Windom, M.D., assistant secretary for health, has announced that 7 Centers for AIDS Research (CFARs) are being established by universities receiving new 5-year grants from the National Institute of Allergy and Infectious Diseases (NIAID). The CFARs will promote the development of new scientific knowledge about AIDS, with the ultimate goal of improving the diagnosis, treatment and prevention of AIDS. The total costs for the first year are $6.7 million.

Seven Original CFAR Directors

- Stephen Byrn
- Murray Gardner
- King Holmes
- Eric Hunter
- Thomas Mergan
- Arye Rubinstein
- Paul Volberding

Purdue
UC, Davis
U of Washington
UAB
Stanford
Albert Einstein
UCSF

Can You Name These Guys?

U.S. CFAR and D-CFAR Sites in 2012

The World Before HIV/AIDS

Total NIH Funding (FY 2012): $37.8M (est.)
HIV Replication Cycle: Targets for Antiretroviral Therapy

Integrase Inhibitors
Protease Inhibitors
Reverse Transcriptase Inhibitors
Fusion/Entry Inhibitors

Ending the HIV/AIDS Pandemic

Interventions: Treatment and Prevention
Implementation of Interventions
Basic and Clinical Research
The End of AIDS

Attending to an AIDS Patient at the NIH Clinical Center, Early 1980s

Median survival of AIDS patients: ~6-8 months

Examples of Early Experimental Approaches to AIDS Therapy

- Suramin
- AL 721
- HPA-23
- Ribavirin
- Isoprinosine
- Thymosin
- Alpha-interferon
- Interferon-gamma
- Interleukin-2
- Thymic implantation
- Lymphocyte transfer
- Bone-marrow transplantation
- DNCB

Survival Patterns of the First 500 Patients with AIDS in San Francisco

- Estimated overall median survival time was 11 months
Antimonialotungstate (HPA-23) Treatment of Three Patients with AIDS and One With Prodrome

Rock Hudson 1925-1985

Developing AZT and Other First-Generation Nucleoside Reverse Transcriptase Inhibitors

Drs. Robert Yarchoan, Hiroaki Mitsuya, and Samuel Broder

The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex: A Double-Blind, Placebo-Controlled Trial

MA Flachl, et al.

The New England Journal of Medicine

U.S. APPROVES DRUG TO PROLONG LIVES OF AIDS PATIENTS

The first drug proved to prolong the lives of AIDS patients was given federal approval today. The drug is azidothymidine, or AZT, an antiviral drug made by the Burroughs Wellcome Company under the brand name Retrovir.

Martin Delaney, 1945-2009

The New York Times

AIDS Researcher Seeks Wide Access to Drugs in Tests

By Gene Colab

In a major shift long sought by those involved in the fight against AIDS, the chief of Federal AIDS research has called for a new system that would allow patients far greater access to experimental drugs.

Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, said such a system would provide promising drugs to some people with AIDS at the same time as the drugs are undergoing rigorous clinical trials. "I call this a parallel-track approach to clinical trials," Dr. Fauci said in a telephone interview.
HPTN 065: "TLC-Plus" - Feasibility of an Enhanced Test, Link-to-Care, Plus Treat Approach for HIV Prevention in the United States

- Testing
- Linkage to care
- Viral suppression
- Prevention for positives
- Patient and provider survey

3-year study; interventions initiated October 2010

Excellent Retention and Outcomes in Rural Rwanda

- 2-year retention rate was 92%
- 98% of patients tested at 2 years had viral load <500/mL

ML Rich et al.

Interventions: Prevention

Combination HIV Prevention

- Treatment as prevention
- PrEP
- PMTCT
- STI treatment
- Male circumcision
- Microbicides
- Testing/counseling
- Education
- Drug/alcohol treatment
- Condoms
- Harm reduction
- Blood screening

Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type 1 with Zidovudine Treatment

EM Conner et al. - ACTG 076
Estimated Number of HIV-Infected Infants, USA, 1990-2010

Pediatric HIV Diagnoses, 1980-2012, San Francisco

Progress and Challenges in Prevention of MTCT in Developing Countries

- ~600,000 pediatric HIV infections averted by ARV prophylaxis, 1995-2011
- Still, 330,000 new pediatric infections in 2011

Source: UNAIDS, 7/2012

Combination HIV Prevention

Adult Male Circumcision Significantly Reduces Men's Risk of Acquiring HIV

Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial
RC Bailey et al.

Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial
B Auvert et al.

South Africa

Adult Male Circumcision Provides Long-Lasting Protection Against HIV Infection in Rakai, Uganda

73% Effectiveness

Gray et al. AIDS 2012
Non-Vaccine Combination HIV Prevention

Biomedical Interventions

Behavior and Adherence

Combination HIV Prevention

Treatment as prevention

PMTCT

STI treatment

Male circumcision

Microbicides

Testing/counseling

Education

Drug/alcohol treatment

Condoms

Harm reduction

Blood screening

Microbicides: Mixed Results

- **CAPRISA 004** – 1% tenofovir gel before and after intercourse reduced incidence by 39%; with adherence > 80%, incidence reduced by 54%

- **VOICE** – 1% tenofovir gel daily. Study arm discontinued due to futility

- **FACTS 001** – Ongoing study in South Africa of 1% tenofovir gel before and after intercourse

Dapivirine Microbicide Rings

- Monthly use
- Two large-scale trials in 2012
  - **ASPIRE** ~3500 women in Malawi, South Africa, Uganda, Zambia, and Zimbabwe
  - **The Ring Study (IPM 027)** ~1,650 women in South Africa, Rwanda, and Malawi

Combination HIV Prevention

Treatment as prevention

PMTCT

STI treatment

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Microbicides

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Education

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Blood screening

Oral PrEP: Mixed Results

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<tr>
<th></th>
<th>Efficacy</th>
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<tr>
<td>MSM – iPrEx (Americas, Thailand, SA)</td>
<td>42%</td>
</tr>
<tr>
<td>Heterosexual discordant couples – Partners PrEP (Kenya, Uganda)</td>
<td>75%</td>
</tr>
<tr>
<td>Heterosexual men and women – TDF2 (Botswana)</td>
<td>62%</td>
</tr>
<tr>
<td>Women – FEM-PrEP (Kenya, SA, Tanzania)</td>
<td>0%</td>
</tr>
<tr>
<td>Women – VOICE (SA, Uganda, Zimbabwe)</td>
<td>0%</td>
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**Science Translational Medicine**

Predicted risk reduction

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<tr>
<th>Doses/Week</th>
<th>Reduction</th>
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<tr>
<td>2</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>96%</td>
</tr>
<tr>
<td>7</td>
<td>99%</td>
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**Emtricitabine-Tenofovir Concentrations and Pre-Exposure Prophylaxis Efficacy in Men Who Have Sex with Men**

PL. Anderson, RM. Grant et al.

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**New England Journal of Medicine**

**Prevention of HIV-1 Infection with Early Antiretroviral Therapy**

**HPTN 052 Study Team**

- 1,763 HIV-serodisordant couples in 9 countries
- 96% reduction in HIV transmission when ART started in HIV-infected partner at CD4 count of 350-550 compared to <250
- Dramatic decreases in disseminated TB in infected partners treated early

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**Interventions: Remaining Scientific Challenges**

- Vaccine
- Cure

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**Combination HIV Prevention**

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Combination HIV Prevention

- Treatment as prevention
- Vaccines
- Microbiocides
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First Signal of Efficacy in an HIV Vaccine Clinical Trial

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand
S. Rerks-Ngarm, J. H. Kim, N. L. Michael et al. for the MOPH-TAVEG Investigators

Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial
B. F. Haynes et al.

- IgG antibodies to V1/V2 region of Env may have contributed to protection against HIV-1 infection
- High levels of Env-specific IgA antibodies may have mitigated the effects of protective antibodies

Nature

Increased HIV-1 Vaccine Efficacy Against Viruses with Genetic Signatures in Env V2
M. Rolland, J. H. Kim et al.

- V1/V2-focused sieve analysis of breakthrough viruses showed selection on the part of vaccinated individuals against infection with viruses containing specific V1/V2 signature sequences
- Supports hypothesis that RV144 vaccine induced a response that selectively blocked infections with certain HIV genotypes in V1/V2 loop

Structure-Based HIV Vaccine Design: Conserved Targets Defined by Neutralizing Antibodies

- Membrane proximal region
- CD4 binding site
- Unique glycan side chain on outer domain
- V2/V3 loops quaternary epitope

Neutralizing Antibody Approach to HIV Prevention

- Structure-based Immunogen Design
- Provision of Neutralizing Antibodies
- Passive transfer of IgG
- Gene-based vectors (AAV)
Interventions: Remaining Scientific Challenges

- Vaccine
- Cure

Approaches to an HIV Cure
- Eradication → “Purge” virus
- Functional Cure
  - Enhance HIV-specific immunity
  - Modify host cells to be resistant to HIV infection

Ending the HIV/AIDS Pandemic

Implementation of HIV Interventions in Low- and Middle-Income Countries
- President’s Emergency Plan for AIDS Relief (PEPFAR)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Philanthropies and NGOs – e.g. BMGF, MSF, Clinton Foundation
- Host country programs

Impact of Scaling-Up Proven Interventions

Positive Impact of Scale-up of ARVs for PMTCT of HIV – Botswana

Number of People Receiving Antiretrovirals in Low- and Middle-Income Countries

840,000 AIDS-related deaths were averted by ART in 2011


- 38% lower risk of acquiring HIV in areas with:
  - >30% ARV coverage
  - <10% ARV coverage

Population-Level Impact of Voluntary Medical Male Circumcision (VMMC) on HIV Incidence: Rakai, Uganda

- HIV acquisition reduced by 42% in non-Muslim men following scale-up of VMMC to 35% coverage by 2011

Post-Circumcision – KwaZulu Natal, Durban, South Africa – October, 2012

Modelling the Impact of Scaling Up Selected Interventions

- ART
- Microbicide
- PMTCT
- Male circumcision
- Vaccine?

Modeling the End of the HIV/AIDS Pandemic

- Status quo

- 20??