Ending the HIV/AIDS Pandemic: An Achievable Goal
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National Institute of Allergy and Infectious Diseases
National Institutes of Health
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Seven Original Centers for AIDS Research (CFARs), 1988

Centers for AIDS Research (CFARs), 2015
Total NIH Funding (FY 2015): $47.7M (est.)

The DC Developmental CFAR Receives NIH Funding to Become a Full Center for AIDS Research

Current Status of the Global HIV/AIDS Pandemic
- 76 million total HIV infections
- 34 million total AIDS deaths
- 37 million people living with HIV
- 1.2 million AIDS deaths in 2014
- 2.0 million new HIV infections in 2014

The mission of the DC CFAR is to expand our multi-institutional effort to support research aimed at ending the HIV epidemic in Washington, DC and beyond in partnership with local government and community.
HIV/AIDS in the United States

- 1.2 M people living with HIV, of whom ~13% are unaware of their infection
- 658,000 people have died of AIDS
- ~50,000 new HIV infections/yr for past two decades
- MSM, African Americans bear the greatest burden of HIV
- Youths 13-24 years old account for >25% of new infections

Source: CDC

Diagnoses of HIV Infection by Transmission Category, United States and 6 Dependent Areas, 2013

<table>
<thead>
<tr>
<th>Transmission Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-to-male sexual contact</td>
<td>65%</td>
</tr>
<tr>
<td>Heterosexual contact (females)</td>
<td>8%</td>
</tr>
<tr>
<td>Heterosexual contact (males)</td>
<td>4%</td>
</tr>
<tr>
<td>Injection drug use (males)</td>
<td>17%</td>
</tr>
<tr>
<td>Male-to-male sexual contact and IDU</td>
<td>3%</td>
</tr>
<tr>
<td>Injection drug use (females)</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

(N=48,145) Source: CDC

HIV Epidemic in the District of Columbia (D.C.), 2013

16,423 persons living with HIV in D.C. as of Dec. 2013

\[
= \frac{16,423}{646,449} = 2.5\% \text{ HIV prevalence}
\]

- WHO defines 1% HIV prevalence as a generalized epidemic

Proportion of D.C. Residents Diagnosed and Living with HIV by Race/Ethnicity and Sex, 2013

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Black Males</th>
<th>Hispanic Males</th>
<th>Black Females</th>
<th>White Males</th>
<th>Hispanic Females</th>
<th>White Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Prevalence</td>
<td>2.5%</td>
<td></td>
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</tbody>
</table>

Epidemic level: 1.0%

16,423 persons living with HIV


The Science of HIV/AIDS: Much Accomplished

- Natural History
- Pathogenesis
- Etiology
- Prevention
- Virology
- Treatment
- Diagnosis
- Vaccine Development
- Epidemiology

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Rounds at NIH Clinical Center, Early 1980s – AIDS Patient

- Median survival of AIDS patients: ~6-8 months

HIV Replication Cycle

- Protein synthesis, processing, and assembly
- Reverse transcriptase inhibitors
- Nucleoside reverse transcriptase inhibitors (NRTIs)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors

HIV Replication Cycle: Targets for Antiretroviral Therapy

- Integrase Inhibitors
- Fusion Inhibitors
- Reverse Transcriptase Inhibitors

FDA-Approved Antiretroviral Drugs

- NRTIs: Zidovudine, Didanosine, Stavudine, Lamivudine, Abacavir
- NNRTIs: Nevirapine, Efavirenz, Delavirdine, Rilpivirine
- PI: Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir + Ritonavir, Atazanavir, Tipranavir
- Other: Darunavir

Applications of Antiretroviral Therapy

- Treatment

Antiretroviral Therapy Helps People with HIV Live Longer

- Diagnosed HIV+ at age 25, not taking HIV medications: ~32 years
- Diagnosed HIV+ at age 25, taking HIV medications: ~71 years
- HIV-negative: ~79 years

Number of HIV-Infected People Globally Receiving Antiretroviral Therapy (ART), 2000-3/2015

- ART averted >7.8 million deaths globally, 2000-2014

Current Status of the Global HIV/AIDS Pandemic
- 76 million total HIV infections
- 34 million total AIDS deaths
- 37 million people living with HIV
- 1.2 million AIDS deaths in 2014
  - ↓42% since the peak in 2004
- 2.0 million new HIV infections in 2014

The Science of HIV/AIDS: Much Accomplished

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- Diagnosis
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- Pathogenesis
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- Treatment
- Vaccine Development

Applications of Antiretroviral Therapy

- Treatment
- Prevention

Prevention Modalities Built upon Antiretroviral Therapy

- Prevention of Mother-to-Child Transmission
- Pre-Exposure Prophylaxis
- Post-Exposure Prophylaxis
- Treatment as Prevention
**Current Status of the Global HIV/AIDS Pandemic**
- 76 million total HIV infections
- 34 million total AIDS deaths
- 37 million people living with HIV
- 1.2 million AIDS deaths in 2014
- 2.0 million new HIV infections in 2014
  ↓ 35% since 2000

**Foundation for HIV Treatment and Prevention Efforts**

**HIV Testing**
- Test positive
- Test negative
- Care Continuum
- Prevention Continuum

**HIV Care Continuum – United States and Puerto Rico**

**Estimated Percentage of HIV Transmissions Along the HIV Care Continuum, USA**
**“90-90-90” Targets for 2020**

- 90% Diagnosed
- 90% On Treatment
- 90% Virally Suppressed

**Treating HIV-Infected Individuals: A Triad of Pivotal ART Studies**

- **SMART**
  - Episodic ART inferior to continuous ART

- **HPTN 052**
  - Early ART reduces HIV transmission to uninfected sexual partners by 96%

- **START**
  - Early ART reduces serious illness/death by 57%

**SMART Study: Benefit of Continuous Treatment**
- Individual Health Benefit

**START Study: Benefit of Early Treatment**
- Public Health Benefit

**HPTN 052: Treatment as Prevention**
- Treatment for all HIV-infected individuals

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**AIDSinfo**

**Statement by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents Regarding Results from the START and TEMPRANO Trials**

- With the availability of the START and TEMPRANO trial results, the Panel’s overall recommendation remains the same: ART is recommended for all HIV-infected patients regardless of pre-treatment CD4 count.

- However, the strength of the recommendation will be changed to AI (strong recommendation based on data from randomized controlled trials) for all patients.

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**HIV Testing**

- Test positive → Care Continuum
- Test negative → Prevention Continuum

**HIV Prevention Continuum**

- Test
  - Counseling and Risk Stratification
  - Provision of Tailored Prevention Services
  - Retention in Services
  - Adherence Support

No New HIV Infections with Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting

JE Volk, CB Hare, et al.

- 657 individuals (99% MSM) began PrEP at Kaiser Permanente San Francisco Medical Center
- No new HIV infections during more than 2.5 years of observation, despite high rates of STIs and decreases in condom use

Focusing to Achieve a World Without AIDS

AS Fauci and HD Marston

“To reach the 90-90-90 goals in the United States and globally, focus should be on the populations most vulnerable to HIV and should target interventions that are most useful and sustainable for these people.”

New HIV Diagnoses by County, United States

Source: AIDSvu, 2013

“Hot Zones” of HIV in Washington, D.C.

Newly diagnosed HIV cases by census tract and ward, 2009

Source: DC Dept of Health

HIV/AIDS Progress in Washington, D.C.

- 40% decline in new HIV diagnoses, 2009-2013
- 87% decline in HIV diagnoses attributable to IDU since scale-up of DC’s needle exchange program in 2007
- No babies born with HIV in 2013
- 4x as many HIV tests in 2014 vs. 2007
- 10x more male and female condoms distributed in 2014 vs. 2007

HIV Care Continuum in the District

- Among 3,612 newly diagnosed HIV cases, 2009-2013
  - 80% of persons linked to care within 3 months of diagnosis
  - 62% retained in care
  - 47% virally suppressed in 2014
- Among 5,622 Ryan White clients in 2014, 89% were retained in care and 64% were virally suppressed
Newly Diagnosed HIV Cases by D.C. Census Tract and Ward, 2009 and 2013

D.C. Public-Private Partnership Planning Bold 2020 Goal to End the HIV Epidemic

“...We are setting a bold goal of 90-90-90-50 by the year 2020: meaning 90 percent of DC residents with HIV will know their status, 90 percent of persons living with HIV will be in treatment, 90 percent of persons with HIV will achieve viral load suppression, and the District will see a 50 percent decrease in new HIV cases.”

-- D.C. Mayor Muriel Bowser
June 30, 2015

Remaining Challenges in HIV Discovery

- Cure
- Vaccine

Towards an HIV Cure: Addressing the HIV Reservoir

Eradicate the reservoir

Control viral rebound – Sustained virologic remission
**Strategies to Eradicate HIV in an Infected Individual**

- “Flush out” the virus by activating latently infected cells
- Immunotoxic therapy directed at reservoir
- Stem-cell transplant - CCR5 Δ32 allogeneic stem-cell transplant
- Gene therapy - Zinc-finger-nuclease modification of CCR5

**Towards an HIV Cure: Addressing the HIV Reservoir**

Eradicate the reservoir

Control viral rebound – Sustained virologic remission

**Post-Treatment Control of HIV Infection: Sustained Virologic Remission**

Early suppression of HIV viremia with cART

Discontinuation of cART

Natural HIV-specific immunity

Passive transfer of HIV-specific antibodies

Therapeutic vaccination

Sustained control of HIV viremia

**An HIV Cure**

- Simple – tertiary care not needed
- Safe – not worse than current treatment
- Scalable – relevant to millions of people

**Remaining Challenges in HIV Discovery**

- Cure
- Vaccine

**Classical Vaccinology**

The response to natural infection provides the proof of concept

**HIV Vaccinology**

No proof of concept
First Signal of Efficacy in an HIV Vaccine Clinical Trial – RV144

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand
S. Reks-Ngarm, JH Kim, NL Michael, et al. for the MOPH–TAVEG Investigators

Alternative Strategies and Parallel Tracks to HIV Vaccine Development

- RV144 approach
- Structure-based vaccine design approach—broadly neutralizing antibodies (bNAds)

Immune Correlates Analysis from RV144

- IgG antibodies against the V1V2 region of the HIV-1 envelope protein associated with reduced infection
- Non-neutralizing antibodies mediate ADCC activity
- IgA antibodies correlated with increased infection

Strategies to Amplify RV144 Response

- Strength
- Breadth
- Durability

Potential approaches:
- Multiple boosts
- Modified vectors
- Adjuvants

Alternative Strategies and Parallel Tracks to HIV Vaccine Development

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Neutralizing Antibodies in HIV-Infected Individuals

- bNAs detectable in plasma are elicited in only a minority (~20%) of infected individuals
- These bNAs only appear after ~2 years of infection with active virus replication
- Most bNAs demonstrate a high degree of somatic mutation
- Certain bNAs have other unusual traits such as autoreactivity

HIV Envelope Trimer with Selected bNAs

- VRC01, 3BCN117
- PG9
- PGT128
- 10e8
- VRC01, 3BCN117
- PG9
- PGT151, 8ANC195

HIV Envelope Trimer with Target Epitopes

- V2 apex
- High-Mannose patch
- gp120/gp41 bridge
- Membrane proximal external region (MPER)
- CD4-binding site

Fundamental Challenge in HIV Vaccinology: Convert Neutralizing Epitopes to Immunogens Inducing bNAs

- Immunogen → Induction of bNAs
- Neutralizing epitopes

Cure
Treatment
Prevention
Vaccine

World Without AIDS

Controlling and Ultimately Ending the HIV/AIDS Pandemic: a Feasible Goal

GK Folkers and AS Fauci