Ending the HIV/AIDS Pandemic: Follow the Science

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**Pneumocystis Pneumonia – Los Angeles**

July 4, 1981

**Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California**
Opportunistic Infections and Kaposi’s Sarcoma among Haitians in the United States

Pneumocystis carinii Pneumonia among Persons with Hemophilia A

Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) – California

Unexplained Immunodeficiency and Opportunistic Infections in Infants – New York, New Jersey, California

Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) – New York
HIV/AIDS in the United States

- 1.1 M people living with HIV, of whom 15% are unaware of their infection
- 692,789 people with stage 3 HIV infection (AIDS) have died
- 39,782 newly diagnosed HIV infections in 2016
- MSM, Blacks/African Americans bear the greatest burden of HIV
- Youths 13-24 years old accounted for 21% of new HIV diagnoses in 2016

Source: CDC, 11/2017
In 2017:

- 36.9 million people living with HIV
- 1.8 million new HIV infections
- 940,000 deaths from AIDS-related illnesses

Since start of the pandemic:

- 77.3 million infected with HIV
- 35.4 million deaths from AIDS-related illnesses
337,342 HIV-related papers in PubMed as of October 4, 2018
Advances in HIV/AIDS Science 1981-2018

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

1. gp120 binds to CD4 and a co-receptor.
2. Fusion occurs, allowing viral entry.
3. Reverse transcriptase converts viral RNA to DNA.
4. DNA integrates into the host genome.
5. Genomic RNA is transcribed and translated.
6. mRNA is exported to the cytoplasm for protein synthesis.
7. Envelope proteins are inserted into the host membrane.

Protein Synthesis, Processing and Assembly

Mature HIV Virion
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Median survival of AIDS patients: ~8-15 months
The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex: A Double-Blind, Placebo-Controlled Trial

MA Fischl, et al.
HIV Replication Cycle: Targets for Antiretroviral Therapy

1. gp120
2. Fusion
3. Cellular DNA
4. Reverse transcriptase
5. Integrase
6. mRNA
7. Protease
8. Mature HIV virion

Fusion/Entry Inhibitors
Reverse Transcriptase Inhibitors
Integrase Inhibitors
Protease Inhibitors
FDA-Approved Antiretroviral Drugs

NRTIs
- 7 multi-drug combinations
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir (TDF, TAF)
- Zidovudine

NNRTIs
- Delavirdine
- Doravirine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

Integrate Inhibitors
- Bictegravir
- Elvitegravir
- Dolutegravir
- Raltegravir

Post-Attachment Inhibitor
- Ibalizumab

Pharmacokinetic Enhancers
- Cobicistat
- Ritonavir

PIs
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir/Ritonavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Multi-Class Combinations
- Atripla
- Biktarvy
- Complera
- Delstrigo
- Genvoya
- Juluca
- Odefsey
- Stribild
- Symfi
- Symfi Lo
- Symtuza
- Triumeq

Entry Inhibitor
- Maraviroc

Fusion Inhibitor
- Enfuvirtide

Source: AIDSinfo.nih.gov, Sept. 2018
Evolution of Treatment Strategies for HIV Disease

1987
AZT Monotherapy

1994
Two-Drug Therapy

1996
Three-Drug Therapy

RNA Change (Log10 copies/mL)

Study Week

0 8 16 24 32 40 48 56
Life Expectancy for 20-Year-Old Newly Diagnosed with HIV, 1980s and Today

1980s (no ART) 1-2 years from AIDS diagnosis

Today (on ART) ~53 years

Source: JL Marcus et al., JAIDS, 2016.
Number of HIV-Infected People Globally Receiving Antiretroviral Therapy (ART), 2000 to 2017

>11 million deaths averted, 2000-2017

Source: UNAIDS, 2018
Advances in HIV/AIDS Science 1981-2018

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- Vaccine Development
Combination HIV Prevention

- HIV Testing/Counseling
- PMTCT
- PrEP
- Blood Supply Screening
- Condoms
- Education/Behavior Modification
- Clean Syringes
- Treatment as Prevention
- Medical Male Circumcision
- STI Treatment
- Microbicides
- Treatment/Prevention of Drug/Alcohol Abuse
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Treatment as Prevention
The Pivotal HPTN 052 Study

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

HPTN 052 Study Team

- 1,763 HIV-serodiscordant 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

Antiretroviral Therapy for the Prevention of HIV-1 Transmission

HPTN 052 Study Team

- After 5+ years of follow-up, protective effect of early ART was sustained (93% lower risk)
- No linked infections when HIV was stably suppressed by ART (i.e. undetectable viral load) in HIV+ partner
PARTNER Study

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

AJ Rodger, J Lundgren et al.

- After ~58,000 condomless sex acts, no linked HIV transmissions with HIV+ partner on suppressive ART
Opposites Attract Study – No HIV Transmissions When HIV+ Partner Had Undetectable Viral Load

THE LANCET HIV
Published online July 16, 2018

Viral Suppression and HIV Transmission in Serodiscordant Male Couples: An International, Prospective, Observational, Cohort Study
BR Bavinton, AE Grulich et al. for the Opposites Attract Study Group

- 343 HIV-serodiscordant MSM couples in Australia, Thailand and Brazil
- 16,800 acts of condomless anal intercourse
- No linked HIV transmissions in 588 couple-years of followup
PARTNER 2 Study – No HIV Transmissions When HIV+ Partner Had Undetectable Viral Load

- 783 HIV-serodiscordant MSM couples in 14 European countries
- 76,991 condomless sex acts (incl. 70,743 acts of anal intercourse)
- No linked HIV transmissions with HIV+ partner on suppressive ART in 1,596 couple-years of followup
Viral Suppression for HIV Treatment Success and Prevention of Sexual Transmission of HIV

The science related to the use of ART as an additional prevention tool is clear: there is no evidence that individuals who have successfully achieved and maintained viral suppression through ART transmit the virus sexually to their HIV-negative partner(s). The preventive benefits of ART should be appropriately emphasized in HIV treatment and prevention programmes.
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Combination HIV Prevention

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Systemic PrEP
HIV Pre-Exposure Prophylaxis (PrEP)

One pill per day

>95% effective in preventing HIV acquisition
5,000 Cumulative Years of PrEP Use and No HIV Infections

- 4,991 started PrEP, 7/2012 through 2/2017 in Kaiser Permanente Northern California (KPNC) healthcare system
- No HIV infections during 5,104 person-years of PrEP use

Topical PrEP
Vaginal Ring Provides Partial Protection Against HIV in Two Large Multinational Trials

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women
JM Baeten, S Hillier et al. for the MTN-020–ASPIRE Study Team

Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women
A Nel, Z Rosenberg et al. for the Ring Study Team

- Ring reduced HIV infection risk by 27% in ASPIRE study, 31% in Ring Study
- Among subset of women older than 21 years of age, protection was higher (56% and 37%)
Long-Acting PrEP
Long-acting Antiretrovirals for Prevention

RCT of long-acting cabotegravir vs. TDF/FTC for PrEP

4500 MSM and TGW in multiple countries

RCT of long-acting cabotegravir vs. TDF/FTC for PrEP

3200 women in Sub-Saharan Africa
The Implementation Gap in Addressing the HIV/AIDS Pandemic
Disentangling overlapping memories
Larger brains are built differently than smaller brains
A neural network takes in a scene
June 15, 2018

Science

FAR FROM OVER

Three places where “ending AIDS” is a distant hope
The Global HIV Treatment Gap

36.9 million HIV-infected people (end-2017)

Treatment Gap: 15.2 million

21.7 million people on antiretroviral therapy (ART), end-2017

Source: UNAIDS, July 2018
HIV Care Continuum, United States

1.1 million people living with HIV infection

- Diagnosed: 86%
- Receiving care: 63%
- Retained in care*: 49%
- Virally suppressed**: 51%

* ≥2 tests (CD4 or VL) ≥3 months apart
** <200 copies/mL on most recent VL test

HIV Pre-Exposure Prophylaxis (PrEP) is Underutilized

- 1.1 million individuals in United States are at substantial risk for HIV and should be offered PrEP (CDC)

- Estimated number of current U.S. PrEP users: 220,000-225,000 (AVAC PrEPWatch, 8/2018)
Global Reductions in New HIV Infections are Off Target for 2020

2.2% average annual decrease in global HIV incidence, 2010-2017

Fast-Track Target for 2020 agreed upon at UN General Assembly, 2016

Source: UNAIDS, July 2018
Key Scientific Challenges Remaining for HIV Researchers

- Developing strategies for achieving sustained ART-free HIV remission
- Developing a safe and effective preventive HIV vaccine
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Pathways to Sustained ART-Free HIV Remission

- Eradicate the replication-competent HIV reservoir – classic “cure”

- Control viral rebound without eradication of HIV in the absence of ART – “sustained virologic remission”
Key Scientific Challenges Remaining for HIV Researchers

- Developing strategies for achieving sustained ART-free HIV remission

- Developing a safe and effective preventive HIV vaccine
Simultaneous Pursuit of Two Fundamentally Different Strategies Towards Development of an HIV Vaccine
Towards an HIV Vaccine: A Dual Pathway

Empirically Test a Vaccine Candidate to Identify a Correlate of Immunity: The “Classical Approach” in Vaccinology versus

Assume a Correlate of Immunity and Design a Vaccine to Induce this Correlate
Towards an HIV Vaccine: A Dual Pathway

Empirically Test a Vaccine Candidate to Identify a Correlate of Immunity: The “Classical Approach” in Vaccinology

versus

Assume a Correlate of Immunity and Design a Vaccine to Induce this Correlate
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S Rerks-Ngarm, JH Kim, NL Michael, et al. for the MOPH–TAVEG Investigators
Strategies to Amplify RV144 Response

- **Strength**
- **Breadth**
- **Durability**

Potential approaches:
- Multiple boosts
- Modified vectors
- Adjuvants
Two NIAID-Supported HIV Vaccine Efficacy Trials Now Underway

**HVTN 702, launched Nov. 2016**

- Modified RV144 prime-boost regimen: HIV clade C gp120 with MF59 adjuvant
- N=5,400 men and women in South Africa

**HVTN 705 (Imbokodo), launched Nov. 2017**

- Quadrivalent, Ad26-vectored mosaic vaccine + HIV clade C gp140
- N=2,600 women in sub-Saharan Africa
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versus

Assume a Correlate of Immunity and Design a Vaccine to Induce this Correlate
Assumption

Broadly neutralizing antibodies induced by a vaccine will afford protection against acquisition of HIV
Broadly Neutralizing Antibodies Binding to Neutralization Epitopes on HIV Trimer

V1V2 glycan
PG9
PGDM1400
PGT145
VRC38.01
CAP256-VRC26

V3 glycan
2G12
10-1074
PGT121
PGT128
PGT135

Subunit interface
35O22
8ANC195

CD4 binding site
3BNC117
8ANC131
b12
CH103
HJ16
IOMA
VRC01
VRC07-523
VRC13.01
VRC16.01
N6

Silent face center
VRC-PG05

Fusion peptide
PGT151
VRC34

Membrane Proximal External Region
2F5
10E8
4E10
DF511
Z13e1

Major Sites of bNAb Recognition (Neutralizing Epitopes) on the HIV Envelope Trimer

V1V2 glycan

V3 glycan

CD4 binding site

Subunit interface

Silent face center

Fusion peptide

Membrane Proximal External Region

Fundamental Challenge: Convert HIV Neutralization Epitopes to Vaccines That Induce bNAbs
Ending the HIV–AIDS Pandemic — Follow the Science

AS Fauci & HD Marston