Demystifying Medicine 2019

Ending the HIV/AIDS Pandemic: Follow the Science

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The Global HIV Pandemic

- 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

HIV/AIDS in the United States

- 1.1 M people living with HIV, of whom 15% are unaware of their infection
- 703,413 people with stage 3 HIV infection (AIDS) have died
- 38,261 newly diagnosed HIV infections in 2017
- MSM, Blacks/African Americans bear the greatest burden of HIV
- Youths 13-24 years old accounted for 21% of new HIV diagnoses in 2017

Endng the HIV-AIDS Pandemic – Follow the Science

AS Fauci & HD Marston

Advances in HIV/AIDS Science 1981-2019

Treatment Prevention
Pathogenesis Diagnosis
Etiology Virology
Natural History Epidemiology

Vaccine Development

Advances in HIV/AIDS Science 1981-2019

Treatment Prevention
Pathogenesis Diagnosis
Etiology Virology
Natural History Epidemiology

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

- Median survival of AIDS patients: ~8-15 months

**HIV Replication Cycle**

**HIV Replication Cycle: Targets for Antiretroviral Therapy**

- Integrate Inhibitors
- Protease Inhibitors
- Reverse Transcriptase Inhibitors
- Fusion/Entry Inhibitors

**Evolution of Treatment Strategies for HIV Disease**

- 1987: AZT Monotherapy
- 1994: Two-Drug Therapy
- 1996: Three-Drug Therapy

**FDA-Approved Antiretroviral Drugs**

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Pharmacokinetic Enhancers</th>
<th>Multi-Class Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stavudine, Tenofovir (TDF, TAF), Abacavir, Didanosine, Zidovudine, Emtricitabine, Lamivudine</td>
<td>Atripla, Biktervy, Complera, Delvairgo, Genvyra, Jula, Odelsely, Stribild, Symfi, Symfi Lo, Symtuza, Triumeq</td>
<td></td>
</tr>
</tbody>
</table>

**Post-Attachment Inhibitor**

- Ibalizumab

**Entry Inhibitor**

- Maraviroc

**Fusion Inhibitor**

- Enfuvirtide

**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

Number of HIV-Infected People Globally Receiving Antiretroviral Therapy (ART), 2000 to 2017

>11 million deaths averted, 2000-2017

Source: UNAIDS, 2019

Advances in HIV/AIDS Science 1981-2019

Treatment
Prevention
Pathogenesis
Diagnosis
Etiology
Virology
Natural History
Epidemiology
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

The Pivotal HPTN 052 Study

Prevention of HIV-1 Infection with Early Antiretroviral Therapy
HPTN 052 Study Team

Antiretroviral Therapy for the Prevention of HIV-1 Transmission
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 350-500 compared to <250
- 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

Between the PARTNER and Opposites Attract studies, nearly 35,000 acts of condomless anal intercourse were reported in gay male couples when the HIV-positive partner had an undetectable viral load and the HIV-negative partner was not taking PrEP

Zero linked transmissions

Source: Bintson et al., Lancet HIV, July 15, 2019
PARTNER 2 Study – No HIV Transmissions When HIV+ Partner Had Undetectable Viral Load

- 783 HIV discordant 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

World Health Organization

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.

Progress in San Francisco

Abstract 93

The RAPID ART Program Initiative for HIV Diagnoses (RAPID) in San Francisco

O Bacon et al.

From 2013 to 2016:
- Median time from diagnosis to VL < 200 c/mL -- ↓ 54%, from 134 days to 61 days
- Median time from first care visit to ART -- ↓ 96%, from 27 days to 1 day

Persons Newly Diagnosed with HIV Linked to Care Within 1 Month and Achieving Viral Suppression Within 3 Months, New York City

<table>
<thead>
<tr>
<th>Year</th>
<th>Linkage to care within 1 month of HIV diagnosis</th>
<th>Viral suppression within 3 months of HIV diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td>2008</td>
<td>21%</td>
<td>56%</td>
</tr>
<tr>
<td>2009</td>
<td>41%</td>
<td>79%</td>
</tr>
<tr>
<td>2010</td>
<td>61%</td>
<td>79%</td>
</tr>
<tr>
<td>2011</td>
<td>70%</td>
<td>79%</td>
</tr>
<tr>
<td>2012</td>
<td>75%</td>
<td>79%</td>
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<tr>
<td>2013</td>
<td>78%</td>
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<tr>
<td>2015</td>
<td>79%</td>
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<tr>
<td>2016</td>
<td>79%</td>
<td>79%</td>
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HIV Pre-Exposure Prophylaxis (PrEP)

One pill per day
>95% effective in preventing HIV acquisition

Long-Acting PrEP

U.S. Preventive Services Task Force

November 20, 2018

Draft Recommendation Statement Prevention of Human Immunodeficiency Virus (HIV) Infection: Pre-Exposure Prophylaxis

Draft Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Persons at high risk of HIV acquisition</td>
<td>The U.S. PTF recommends that clinicians offer pre-exposure prophylaxis (PrEP) with effective antiretroviral therapy to persons who are at risk of HIV acquisition.</td>
</tr>
</tbody>
</table>

Grade: A
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

Long-Acting PrEP

ART-based

Broadly Neutralizing Antibodies

Broadly Neutralizing Antibodies Binding to Neutralization Epitopes on HIV Trimer


Antibody-Mediated Prevention (AMP)

VRC01 mAb Phase 2b Studies in High-Risk Men and Women

11 countries
47 sites - 4200 volunteers
100% enrolled

Enrolled MSM and TGW
Opened
April 2016
N=2700

Enrolled Women
Opened
July 2016
N=1500

The Implementation Gap in Addressing the HIV/AIDS Pandemic
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

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%

* at least 6 months of ART
** <500 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

Number of estimated HIV infections

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

Ending the HIV/AIDS Pandemic

FOCUS

Incidence “Hot Spots”

Geographic Hot Spots
Demographic Hot Spots

Demographic Hot Spots of HIV Infection: United States

Key Scientific Challenges Remaining for HIV Researchers

Key Scientific Challenges Remaining for HIV Researchers

Potential Strategies to Eradicate HIV from an HIV-Infected Individual
ART-Free Approaches Towards Durable Control of HIV Infection Requiring Intermittent or Continual Non-ART Intervention

- Therapeutic vaccination
- Passive transfer of broadly neutralizing anti-HIV monoclonal antibodies (bNAbS)

Key Scientific Challenges Remaining for HIV Researchers

- Developing strategies for achieving sustained ART-free HIV remission
- Developing a safe and effective preventive 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

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First Signal of Efficacy (31%) in an HIV Vaccine Clinical Trial – RV144

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

S. Reeks-Ngarm, JH Kim, NL Michael, et al. for the MOPH-TAVEG Investigators

Strategies to Amplify RV144 Response

- **Strength**
  - Potential approaches:
    - Multiple boosts
    - Modified vectors
    - Adjuvants
- **Breadth**
- **Durability**
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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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

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

Fundamental Challenge: Convert HIV Neutralization Epitopes to Vaccines That Induce bNAbs
How Good is Good Enough?

- 95-100%: Aspirational... and unlikely
- 31%: Not ready for prime time (RV144)
- 50-60%: Acceptable

Effectiveness

An HIV Vaccine with ~50% Efficacy Could be Highly Impactful

- With status quo of treatment and diagnosis, ~49 million new HIV cases projected between 2015 and 2035.
- The availability of an HIV vaccine could avert ~17 million of those cases.