36 Years of HIV/AIDS: Where have we been… Where are we going?

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Circa 1900 - 1920

Chimpanzee Reservoirs of HIV-1

HIV-LB closest relatives of HIV-1 M
EK closest relatives of HIV-1 N
also sites with highest prevalence

1950 - 1980
Intestinal Cryptosporidiosis Complicated by Disseminated Cytomegalovirus Infection

LOUIS WEINSTEIN, S. MIGUEL EDELSTEIN, JAMES L. MADARA, KENNETH R. FALCHUK, BRUCE M. MCMANUS, and JERRY S. TRIER

The Division of Infectious Disease and Gastroenterology of the Department of Medicine and the Department of Pathology, Peter Bent Brigham Division of the Brigham and Women’s Hospital, and the Department of Medicine and Pathology, Harvard Medical School, Boston, Massachusetts.

Although no clear-cut evidence of immunodeficiency could be demonstrated in our patient, this could not be ruled out completely.

Received November 10, 1980. Accepted April 22, 1981.
Address for reprints: Louis Weinstein, M.D., Brigham and Women’s Hospital, 75 Francis Street, Boston, Massachusetts 02115.
© 1981 by the American Gastroenterological Association 0015-5388/81/090984-09852.50
Alternative Theories

- Drugs – e.g., Amyl Nitrites ("Poppers")
- Fungi
- Allogeneic semen as immunosuppressant
Bob Gallo, Francoise Barre-Sinoussi, and Luc Montagnier

1983-84
1985

1988 - 1996

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

The New England Journal of Medicine
VOL. 317. NO. 7, JULY 20, 1987

BW 002: 24-Week Study of AZT vs. Placebo in Patients with AIDS or ARC

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WHERE IS THE OUTRAGES
Community Activism

1988

SILENCE=DEATH

1989

“Gang of 5”

1989

1991


1992

HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy

BA Larder, G Darby, and DD Richman
5/29/2018

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Approved Antiretroviral Agents in 1996

Nucleoside RTIs
- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)

Nonnucleoside RTI
- Nevirapine (NVP)
- Delavirdine (DLV)

Protease Inhibitors
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)

NIM, 1993

T1/2 = 1.1 days

Viral Load vs. Weeks

HIV Infected Cells

Uninfected Resting CD4+ Lymphocytes

Uninfected Activated CD4+ Lymphocytes

Latently Infected CD4+ Lymphocytes

HIV infected Cells

HIV Virions

Antiretroviral Rx

1996

Perinatally Acquired AIDS Cases, 1985-2004, United States

Year of diagnosis

Note: Data have been adjusted for reporting delays and cases without risk factor information
www.cdc.gov/nchs/index.htm
1997 - 2004

**Approved Antiretroviral Agents in 2004**

**Nucleoside RTIs**
- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

**Nonnucleoside RTI**
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFZ)

**Protease Inhibitors**
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/ritonavir (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)

**Nucleotide RTI**
- Tenofovir DF (TDF)

**Fusion Inhibitor**
- Enfuvirtide (T-20)

**HIV infection results in a rapid and dramatic depletion of CCR5+ CD4+ memory T cells in gut (without evidence of increase activation/tturnover)**

**Terminal ileum, HIV uninfected**

**Terminal ileum, Week 3 HIV Infection**

Keele et al., PNAS 2008

Brenchley et al, J. Exp. Med 2004

Fiebig, AIDS 2003
Approved Antiretroviral Agents in 2011

- **Nucleoside RTIs**
  - Zidovudine (ZDV)
  - Didanosine (ddI)
  - Zalcitabine (ddC)
  - Stavudine (d4T)
  - Lamivudine (3TC)
  - Abacavir (ABC)
  - Emtricitabine (FTC)

- **Nonnucleoside RTI**
  - Nevirapine (NVP)
  - Delavirdine (DLV)
  - Efavirenz (EFZ)
  - Etravirine (ETV)
  - Rilpivirine

- **Protease Inhibitors**
  - Saquinavir (SQV)
  - Ritonavir (RTV)
  - Indinavir (IDV)
  - Nelfinavir (NFV)
  - Amprenavir (APV)
  - Lopinavir/r (LPV/r)
  - Atazanavir (ATV)
  - Fosamprenavir (Fos-APV)
  - Tipranavir (TPV)
  - Darunavir (DRV)

- **Integrase Inhibitor**
  - Raltegravir (RAL)

- **Fusion Inhibitor**
  - Enfuvirtide (T-20)

- **CCR5 Antagonist**
  - Maraviroc (MVC)

N.B.: Seven FDC are approved:
- ZDV + 3TC
- ZDV + 3TC + ABC
- ABC + 3TC
- FTC + TDF
- TDF + FTC + EFV
- LPV + TDF + FTC

When To Start Treatment? – Summary of Current Guidelines

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>symptoms of CD4 &lt;200</th>
<th>CD4 200-350</th>
<th>CD4 &gt;350</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAS-USA: JAMA 2010</td>
<td>treat</td>
<td>treat</td>
<td>Treat*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All &lt; 500 /ul No harm Rx anyone</td>
</tr>
<tr>
<td>DHHS: &lt;www.aidsinfo.nih.gov&gt;</td>
<td>treat</td>
<td>treat</td>
<td>treat*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* Split option &gt; 500</td>
</tr>
</tbody>
</table>

When to Start Therapy: Balance Has Tipped Further in Favor of Earlier Initiation

- Drug toxicity
- Preservation of treatment options
- Cost
- Harmful effects of uncontrolled viremia at all CD4 levels
- More treatment options: improved potency, tolerability, durability, simplicity
- Increased ability to suppress virus with multidrug resistance
- Diminished emergence of resistance

Randomised controlled trials of male circumcision to reduce HIV infection

- **Rakai, Uganda**
  - Gray et al. (2007) Lancet; 51% reduction in transmission

- **Kisumu, Kenya**
  - Bailey et al. (2007) Lancet; 53% reduction

- **Orange Farm, South Africa**
  - Auvert et al. (2005) PLoS Med; 60% reduction
Beyond 2011 - 2017

iPrEx: Adherence is critical to efficacy

- **Efficacy by as-treated analysis**
  (data as of Nov 21, 2010)

  - **High** (≥ 90% adherence; 49% of visits)
    - 68% efficacy
  - **Intermediate** (50-90% adherence; 33% of visits)
    - 34% efficacy
  - **Low** (< 50% adherence; 18% of visits)
    - 16% efficacy

- 9% of seroconverters had detectable drug at first HIV+ visit
- 61.5% of nonseroconverters

  Grant et al, NEJM 2010

HPTN 052

- **1763 HIV discordant couples**
  (HIV+ partner CD4 350-550)

  - **866 immediate HAART**
  - **877 delayed HAART (CD4 250)**

  All receiving HIV prevention services

  - 1 transmission
  - 3 cases of extrapulmonary TB

  - 27 transmissions
  - 17 cases of extrapulmonary TB

*96% reduction in HIV transmission to HIV-negative partner median follow-up 2 years

Prevention of Transmission

- **TEST and TREAT**
  - Testing and Linkage to Care (TLC+)

United States National AIDS Strategy...

Vaccine Strategies in Current Trials

Potential Strategies for Eradication of HIV

- Early initiation of antiretroviral therapy
- Use of virus "purging" agents
- Addition of newer classes of drugs
- Use of immune-modulating agents
- Use of HIV-specific killing agent

Ending the Epidemic with ART?

- Treatment and virologic suppression markedly reduce transmission1,2 ("Treatment as prevention")
- Modeling suggests that treating a high proportion of infected patients could end the epidemic by 20303
- UNAIDS Treatment Targets:
  - 90% diagnosed
  - 90% on treatment
  - 90% suppressed = 73% suppressed


90:90:90
Bending the Epidemic Curve

- Who’s at Risk
- Getting to 90:90:90
- Women-controlled prevention

185,000 HIV infections in U.S. in next 5 years could be prevented by expanding testing, treatment, PrEP

Four Scenarios of the Potential Impact of Expanded HIV Testing, Treatment and PrEP in the United States, 2015-2020

- Source: UNAIDS, World Health Organization, CDC, and authors' analysis

http://www.cdc.gov/std/prevention/imagenes/2016/crt_four_scenarios_graph.jpg
Beyond 2018...

What do you think?