HIV: A 60 Year Retrospective

**Important Dates in the First Decade of the AIDS Epidemic.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Reported Event</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 5, 1981</td>
<td>5 Cases of Paramyxovirus carcinoma in homosexual men</td>
<td>Initial report</td>
</tr>
<tr>
<td>July 3, 1981</td>
<td>26 Additional cases of new immunodeficiency syndrome</td>
<td>Cases in New York and California</td>
</tr>
<tr>
<td>June 18, 1982</td>
<td>Cluster in southern California</td>
<td>First report that “infectious agents [may be] sexually transmitted”</td>
</tr>
<tr>
<td>July 9, 1982</td>
<td>Initial cases in 34 Haitians</td>
<td>Mode of transmission unclear</td>
</tr>
<tr>
<td>July 16, 1982</td>
<td>Initial cases in 3 persons with hemophilia</td>
<td>Possibility of tainted blood supply</td>
</tr>
<tr>
<td>September 24, 1982</td>
<td>Term “acquired immune deficiency syndrome” (AIDS) used for first time</td>
<td>Term coined at July 1982 meeting, replacing “gay related immune deficiency” (GRID)</td>
</tr>
<tr>
<td>October 1982</td>
<td>5 Cases in women reported, including 1 with only heterosexual exposure</td>
<td>First possible heterosexual transmitted case</td>
</tr>
<tr>
<td>November 5, 1982</td>
<td>Precautions published for clinical and laboratory staff</td>
<td>“Patients resemble the distribution and modes of spread of hepatitis B”</td>
</tr>
<tr>
<td>December 10, 1982</td>
<td>Initial transfusion related case, in an infant</td>
<td>Further evidence of tainted blood supply</td>
</tr>
<tr>
<td>December 17, 1982</td>
<td>Initial vertically transmitted cases reported in 4 infants</td>
<td>Reported as “Possible that these infants had AIDS”</td>
</tr>
<tr>
<td>January 7, 1983</td>
<td>Report of heterosexual transmission to 2 female partners of injection drug user</td>
<td>Given known risk groups, occurrence in prisoners “might have been anticipated”</td>
</tr>
<tr>
<td>January 7, 1983</td>
<td>Initial cases in 18 prisoners</td>
<td>Groups at risk advised not to donate blood</td>
</tr>
<tr>
<td>March 4, 1983</td>
<td>CDC releases prevention recommendations</td>
<td>“Black Africans may be another group predisposed to AIDS”</td>
</tr>
<tr>
<td>March 39, 1983</td>
<td>CDC Council unusual cases reported in 5 persons from central Africa</td>
<td>“Very rare”</td>
</tr>
<tr>
<td>May 20, 1983</td>
<td>Isolation of a virus from a patient with AIDS</td>
<td>Occupational transmission suspected but not proven</td>
</tr>
<tr>
<td>July 15, 1983</td>
<td>Report of 4 possibly occupational cases among health care workers</td>
<td>Measures consistent with those suggested for prevention of hepatitis B should be followed</td>
</tr>
<tr>
<td>September 22, 1983</td>
<td>Infection-control guidelines published for care</td>
<td>25 Cases reported in first week</td>
</tr>
<tr>
<td>January 13, 1984</td>
<td>AIDS tabulated as “exhibit disease” for first time</td>
<td>“HTLV-III may be the primary cause of AIDS”</td>
</tr>
<tr>
<td>January 4, 1984</td>
<td>Frequent detection of HTLV-III in patients at risk</td>
<td>“HTLV-III may be the primary cause of AIDS”</td>
</tr>
<tr>
<td>March 1985</td>
<td>FDA approves commercial test to detect HIV</td>
<td>Tremendous impact on patients at risk and blood supply</td>
</tr>
<tr>
<td>1986</td>
<td>CDC provides working definition of AIDS</td>
<td>Updated in 1983</td>
</tr>
<tr>
<td>1986</td>
<td>AIDS Clinical Trials Group established by NIH</td>
<td>Now largest clinical trials group in the United States</td>
</tr>
<tr>
<td>March 1987</td>
<td>FDA approves AZT (sidozaside)</td>
<td>First drug active against HIV</td>
</tr>
</tbody>
</table>

*UN denotes United Nations, and WHO World Health Organization.

**Important Dates in the Second Decade of the AIDS Epidemic.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Reported Event</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Approval of didanosine and zidovudine</td>
<td>Second and third approved drugs; combination therapy used increasingly</td>
</tr>
<tr>
<td>1993</td>
<td>AIDS becomes leading cause of death of Americans 25–44 years old</td>
<td>AIDS supersedes unintentional injuries as cause of death in this group</td>
</tr>
<tr>
<td>January 12, 1995</td>
<td>Dynamics of HIV replication redefined</td>
<td>“Primary (therapeutic) strategy ought to be to target virally mediated destruction”</td>
</tr>
<tr>
<td>May 4, 1995</td>
<td>Identification of viral cause of Kaposi’s sarcoma</td>
<td>Human herpesvirus 8 isolated</td>
</tr>
<tr>
<td>July 15, 1995</td>
<td>First Public Health Service guidelines to prevent opportunistic infections</td>
<td>Two subsequent revisions</td>
</tr>
<tr>
<td>August 1995</td>
<td>First protease inhibitor, saquinavir, approved</td>
<td>Within 18 months, 3 additional protease inhibitors approved</td>
</tr>
<tr>
<td>1996</td>
<td>U.S. AIDS death rate decreased</td>
<td>“For the first time, deaths among persons with AIDS have decreased substantially”</td>
</tr>
<tr>
<td>May 24, 1996</td>
<td>Prognostic power of viral load determination established</td>
<td>Important laboratory determination for patient management</td>
</tr>
<tr>
<td>1997</td>
<td>President Bill Clinton seeks AIDS vaccine in 10 years</td>
<td>HIV Vaccine Trials Network established</td>
</tr>
<tr>
<td>May 7, 1998</td>
<td>First public report of lipodystrophy syndrome</td>
<td>Lipodystrophy, hyperglycemia, diabetes, and other metabolic abnormalities with increased frequency in patients with AIDS</td>
</tr>
<tr>
<td>June 1998</td>
<td>Highly approved</td>
<td>“Protective-spacing” regimen introduced</td>
</tr>
<tr>
<td>January 10, 2000</td>
<td>UN Security Council discusses AIDS</td>
<td>“AIDS threat is one security”</td>
</tr>
<tr>
<td>December 2000</td>
<td>WHO estimates 26.1 million have HIV, AIDS, with an additional 21.8 million already dead</td>
<td>5.1 million new infections in 2000; 14,500 new infections per day</td>
</tr>
<tr>
<td>March 2001</td>
<td>U.S. pharmaceutical companies substantially reduce prices and may allow generic drugs for Africa</td>
<td>Cost will be 1-10% of U.S. price</td>
</tr>
</tbody>
</table>

1959 Serum from Bantu Male @ Kinchas DRC => ZR59
Suggests single trans-species jump in 1940-1950 and radiation after WWII
YBF30 is a sequence outlier isolated from a patient in Cameroon
Map of HIV Natural Reservoirs

Disease Progression

Pathological conditions associated with HIV-1 infection

Acute phase
Mononucleosis-like syndrome: fever, malaise, pharyngitis, lymphadenopathy, headache, arthralgias, diarrhea, maculopapular rash, meningoencephalitis

Asymptomatic phase
Often none, but patients may present sporadically with one or more of the following symptoms: fatigue, mild weight loss, generalized lymphadenopathy, thrush, oral hairy leukoplakia, shingles

Symptomatic phase and AIDS
200–500 CD4+ T cells per ml; generalized lymphadenopathy, oral lesions (thrush, hairy leukoplakia, aphthous ulcers), shingles, thrombocytopenia, molluscum contagiosum, basal cell carcinomas of the skin, headache, condyloma acuminata, reactivation of latent Mycobacterium tuberculosis

Less than 200 CD4+ T cells per ml
Protozoal infections: Pneumocystis carinii, Toxoplasma gondii, Isospora belli, cryptosporidia, microsporidia

Bacterial infections: Mycobacterium avium-M. intracellulare, Treponema pallidum

Fungal infections: Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum

Viral infections and malignancies: human cytomegalovirus, recurrent bouts of oral or genital HSV, lymphoma (mostly EBV, some HHV-8), Kaposi’s sarcoma (HHV-8), anogenital carcinoma (HPV)

Neurological symptoms: aseptic meningitis, myelopathies, such as vacuolar myelopathy, pure sensory ataxia, paresthesia/dysesthesia, peripheral neuropathies, such as acute demyelinating polyneuropathy, mononeuritis multiplex, and distal symmetric polyneuropathy, myopathy; AIDS dementia complex (ADC)

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1 Adapted from Table 1 of A. S. Fauci and R. C. Desosiers, p. 587–635, in J. M. Collin et al. (ed.), The Retroviruses (Cold Spring Harbor Laboratory Press, Plainview, N.Y., 1997), with permission. HSV, herpes simplex virus; EB, Epstein-Barr virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus.
Clinical Picture

Varicella zoster

*Pneumocystis carinii*

Hairy leukoplakia

Oral candida
Modes of Horizontal Transmission

Also Vertical Transmission!

(11-60% depending on severity of maternal infection and ±breastfeeding)
• 36.1 million worldwide are infected
• Another 21.8 million have died
• 13.2 million children currently are “AIDS Orphans”
• 14,000 new infections daily (5.3 million in 2000)
• 70% of cases in sub-Saharan Africa where seroprevalence can exceed 25%
• Caribbean, Southeast Asia and Eastern Europe are other trouble areas
Virus Taxonomy

HIV belongs to the lentivirus subclass of retroviruses

- 2 copies of the +RNA strand; goes through a dsDNA intermediate
- icosahedral capsid
- enveloped
- 80-130 nm virion
Anatomy of a Retrovirus

-NEF Attenuation
Proteins

MAJOR PROTEINS:
• gag - membrane association, assembly, budding
• pol - reverse transcriptase.
• int - integrase.
• env - envelope glycoprotein.

OTHER VIRALLY EXPRESSED PROTEINS:
• tat - transcription elongation factor, regulates gene expression.
• rev - nuclear export of unspliced RNA.
• nef - “negative factor”, down regulates surface CD4 and MHC I.
• vif - blocks cytidine deamination, an innate defense against retroviruses.
• vpr - arrests cell cycle in G_{2}, promotes DNA entry into nucleus.
• vpu - ER resident TM protein, facilitates virus release, traps CD4.
• $10^9$ copies/day in fulminant AIDS
• Genome is $\sim 10^4$ nucleotides
• RT error rate is $10^{-4}$ to $10^{-6}$
• Every single-base mutation of the genome occurs at least once per day per patient
molecular intervention: RT and protease …
RT Inhibitors

Nucleoside:

Zidovudine (AZT)
Didanosine (ddI)
Zalcitabine (ddC)
Stavudine (d4T)
Lamivudine (3TC)

Non-Nucleoside:

Nevirapine
Delavirdine
Loviride
Efavirenz
Protease Inhibitors

Indinavir

Nelfinavir

Ritonavir

Saquinavir

Amprenavir
Retroviral Drug Resistance in New Patients

**Temporal Changes in the Prevalence of Drug Resistance at Baseline.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SUBJECTS IDENTIFIED WITH DRUG-RESISTANT VIRUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>no./no. of samples analyzed (%)</td>
<td></td>
</tr>
<tr>
<td>High-level drug resistance (phenotype assay)**</td>
<td>9/264 (3.4)</td>
</tr>
<tr>
<td>Any antiretroviral drug</td>
<td>6/264 (2.3)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>5/264 (1.9)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>1/264 (0.4)</td>
</tr>
<tr>
<td>PIs</td>
<td>3/264 (1.1)</td>
</tr>
<tr>
<td>Multidrug resistance</td>
<td></td>
</tr>
<tr>
<td>Major drug-resistance mutations (genotype assay)</td>
<td>17/213 (8.0)</td>
</tr>
<tr>
<td>Any antiretroviral drug</td>
<td>15/176 (8.5)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>3/176 (1.7)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>2/213 (0.9)</td>
</tr>
<tr>
<td>Multidrug resistance§</td>
<td>8/213 (3.8)</td>
</tr>
</tbody>
</table>

*Both resistance assays were performed at ViroLogic. NNRTI denotes nucleoside reverse-transcriptase inhibitor, NNRTI nonnucleoside reverse-transcriptase inhibitor, and PI protease inhibitor.

†P values are two-sided and were determined by Fisher's exact test.

‡Data are numbers (and percentages) of samples containing virus with a 50 percent inhibitory concentration (IC50) that was more than 10 times that of a reference virus.

§These results did not change when T215D, T215N, T215S, T215C, and T215E mutations were excluded from the analysis (i.e., all subjects with a revertant mutation detected at position 215 had at least one additional major drug-resistance mutation).

Where Else to Attack?

- Cell attachment, fusion, and entry
  - CD4 derivatives
  - Polymers
  - Plant lectins
  - Bicyclams
  - Chemokine analogs

- Reverse transcription
  - Nucleoside analog reverse transcriptase inhibitors:
    - zidovudine, didanosine, zalcitabine, stavudine, lamivudine, acyclic nucleoside phosphonates
  - Nonnucleoside reverse transcriptase inhibitors:
    - nevirapine, delavirdine, loviride, efavirenz

- Integration
  - Integrase inhibitors

- Transcription and posttranscriptional processing
  - Tat inhibitors

- Virion packaging and budding
  - Protease inhibitors:
    - saquinavir, ritonavir, indinavir, nelfinavir
  - Nucleocapsid inhibitors
molecular intervention: fusion …
The Model for Viral Fusion

Enfuvirtide
HIV Association with Targets

- CCR5 Homozygous Mutants are HIV resistant and otherwise healthy
- RANTES (CCR5 ligand) promoter overexpression mutants are HIV resistant
- Sdf-1 (CXCR4) overexpressors are HIV resistant

• PRO542 (Progenics): gp120 tetramer to IgG Fc that blocks CD4-gp120 interaction
• BMS-806 (Bristol-Myers Squibb): small molecule that targets the CD4 binding site on gp120
• TNX-355 (Tanox): an anti-CD4 antibody
• SCH-C, SCH-D (Schering-Plough) and UK-427,857 (Pfizer:) block CCR5
• AMD3100, AMD070 (AnorMED): block CXCR4
molecular intervention: integration …
HIV Integrase Inhibitors

• Two log reductions in viral load
• Kinetics of viral decrease faster than thought possible (cellular reservoirs)

a vaccine? …
HIV Vaccine

• >50 preparations have entered clinical trials (HIV Vaccine Trials Network)
• 1997 Clinton’s HIV vaccine challenge: 10 years
• NIH currently spends >500 million/year on trying to find an HIV vaccine
• NOTHING! (punctuated equilibrium)
• Do aspects of the immune response facilitate HIV pathogenesis?

Broadly Neutralizing Antibodies

• mAB b12: convex recombining site
• 447-52D: V3 GPGGR motif and main-chain (MHC)
• mAb 2G12: domain-swap binds oligomannose
• 2F5, 4E10: TM epitopes

SIV Cell-Based Vaccines

Restriction factors …
HIV-1 infects New World monkey cells, but not Old World monkeys: Why? Put *rhesus* cDNA library into HeLa cells and infect with GFP-labeled HIV virus. Get one clone, TRIM5α. A species restriction factor that is an E3! (J. Vir. 79(14): 8870-8877 2005) Appears to cause premature uncoating of the HIV capsid (why this is a problem is unknown).

Apobec 3G

Factor contributing to variability between cell lines in HIV infection susceptibility.

Cloned in 2002.

Cytidine deaminase enzyme; related to AID enzyme of somatic hypermutation.

Part of an ancient mechanism for anti-retroviral defense.


See also:
Other Ideas

OTHER VIRALLY EXPRESSED PROTEINS:
• tat - transcription elongation factor, regulates gene expression.
• rev - nuclear export of unspliced RNA.
• nef - “negative factor”, down regulates surface CD4 and MHC I.
• vif - blocks cytidine deamination, an innate defense against retroviruses.
• vpr - arrests cell cycle in G₂, promotes DNA entry into nucleus.
• vpu - ER resident TM protein, facilitates virus release, traps CD4.

OTHER VIRAL ENZYMES:
• RNAse H!

OTHER STRATEGIES:
• Block the virally induced inflammatory response; aids infection?
• Immunomodulation => Today’s basic science paper.
PD-1 in T-cell exhaustion …
T Cell "Exhaustion" During Chronic Infection

- Occurs with viruses that exhibit persistent viremia
- Human: HIV(retro), HBV (hepadna), HCV (flavi)
- Human Counterexamples: Cytomegalovirus, EBV
- Mouse: LCMV (arena) and Friend Leukemia Virus

- Loss of Cytolytic function, IL2, proliferation
- Loss of TNF, IFN-γ
- Clonal deletion
Lymphocytic Choriomeningitis Virus (LCMV)

- Infect neonate => "carrier"; Infect adult => infection clears
- "Wild-type" Armstrong strain causes acute infection
- In 1983 Ahmed/Oldstone isolate "strain 13" that causes chronic infection
- Strain 13 differs by mutation in polymerase, mutation in coat glycoprotein
- Predominantly infects macrophages
T-Cell Anergy

- **Signal 1:** B7 → CD28
- **Signal 2:** mature antigen-presenting cell

- **T-Cell Activation:**
  - Replaced by CTLA-4!

- **Signal 1:** immature antigen-presenting cell

- **T-Cell Apoptosis or Inactivation:**
PD-1 in Strain 13 Induced Exhaustion

(a) Gated on CD8 T cells
- Acute immune
- Chronic
- DpGP276-286 tetramer
- CD44
- TNF-α
- IFN-γ

(b) PD-1 mRNA expression (fold over naive)
- Acute immune
- Chronic

(c) Gated on DpGP276 tetramer⁺ cells
- Events
- CFSE

(d) % of maximum
- LCMV⁻
- LCMV⁺
- Chronic
- PD-L1
- PD-1
PD-1 Blockade in Early Infection

**Figure a**
- Antigen-specific CD8 T cells per spleen
  - Untx anti-PD-L1
  - Untx anti-PD-L1
  - Untx anti-PD-L1
  - Untx anti-PD-L1
  - Untx anti-PD-L1
  - Untx anti-PD-L1

**Figure b**
- Untx
- anti-PD-L1

<table>
<thead>
<tr>
<th>Peptide</th>
<th>TNF-α</th>
<th>IFN-γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>No peptide</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>NP396–404</td>
<td>0.31</td>
<td>0.41</td>
</tr>
<tr>
<td>GP33–41</td>
<td>0.59</td>
<td>1.93</td>
</tr>
<tr>
<td>NP205–212</td>
<td>7.32</td>
<td>8.71</td>
</tr>
<tr>
<td>NP166–175</td>
<td>6.34</td>
<td>6.02</td>
</tr>
<tr>
<td>GP118–125</td>
<td>2.82</td>
<td>1.53</td>
</tr>
<tr>
<td>GP109–116</td>
<td>0.81</td>
<td>0.86</td>
</tr>
<tr>
<td>GP92–101</td>
<td>2.46</td>
<td>3.12</td>
</tr>
<tr>
<td>GP70–77</td>
<td>0.55</td>
<td>2.59</td>
</tr>
<tr>
<td>GP70–77</td>
<td>0.28</td>
<td>0.72</td>
</tr>
</tbody>
</table>

**Figure c**
- log_{10}(p.f.u. mL⁻¹ serum)
- log_{10}(p.f.u. g⁻¹ tissue)
- Untx anti-PD-L1
- Untx anti-PD-L1
- Untx anti-PD-L1
- Untx anti-PD-L1
- Untx anti-PD-L1

**Graphs**
- Left: Scatter plot showing CD8 T cells per spleen.
- Middle: Graph showing log_{10}(p.f.u. mL⁻¹ serum) over time.
- Right: Bar graphs showing log_{10}(p.f.u. g⁻¹ tissue) in different organs.
LCMV in PD-1 K.O.

(a) LCMV Armstrong (acute infection)

(b) LCMV clone 13 (chronic infection)
Recent Progress

- CD8 T-Cells from HIV patients overexpress PD-1
- PD-1 expression correlates + with viral load and - with CD4 count
- Drug Treatment Reduces PD-1 levels

- IL10 blockade also clears chronic LCMV infections
- IL10 K.O. have less severe immune defects; better therapeutic target?
The Future of the Arms Race?


Immune System Overview

**Inate**
- NK cells

**Adaptive**
- APC
- B cells
- T cells

**NK cells**
- Ifn-γ induced
- IL12 from activated macrophages and dendritic cells

**APC**
- Professional

**B cells**
- γδ
- CD4 helper

**T cells**
- CD8 cytotoxic
- T_H1
  - IL2
  - Ifn-γ
  - TNFα
- T_H2
  - IL4, 10
  - TGFβ
  - Ifn-β