# 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 <em>Pneumocystis carinii</em> pneumonia in homosexual men¹</td>
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</tr>
<tr>
<td>July 3, 1981</td>
<td>26 Additional cases of new immunodeficiency syndrome²</td>
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<tr>
<td>June 18, 1982</td>
<td>Cluster in southern California³</td>
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<tr>
<td>July 9, 1982</td>
<td>Initial cases in 34 Haitians⁴</td>
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<tr>
<td>July 16, 1982</td>
<td>Initial cases in 3 persons with hemophilia⁵</td>
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<tr>
<td>September 24, 1982</td>
<td>Term “acquired immune deficiency syndrome” (AIDS) used for first time⁶</td>
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<tr>
<td>October 1982</td>
<td>5 Cases in women reported, including 1 with only heterosexual exposure⁷</td>
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<tr>
<td>November 5, 1982</td>
<td>Precautions published for clinical and laboratory staff⁸</td>
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<tr>
<td>December 16, 1982</td>
<td>Initial transfusion-related case, in an infant⁹</td>
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<tr>
<td>December 17, 1982</td>
<td>Initial vertically transmitted cases reported in 4 infants¹⁰</td>
<td></td>
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<tr>
<td>January 7, 1983</td>
<td>Report of heterosexual transmission to 2 female partners of injection-drug user¹¹</td>
<td></td>
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<tr>
<td>January 7, 1983</td>
<td>Initial cases in 16 prisoners¹²</td>
<td></td>
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<tr>
<td>March 4, 1983</td>
<td>CDC releases prevention recommendations¹³</td>
<td></td>
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<tr>
<td>March 19, 1983</td>
<td>Initial cases in 5 persons from Central Africa¹⁴</td>
<td></td>
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<tr>
<td>May 20, 1983</td>
<td>Isolation of a virus from a patient with AIDS¹⁵</td>
<td></td>
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<tr>
<td>July 15, 1983</td>
<td>Report of 4 possible occupational cases among health care workers¹⁶</td>
<td></td>
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<tr>
<td>September 22, 1983</td>
<td>Infection-control guidelines published for care of patients with AIDS¹⁷</td>
<td></td>
</tr>
<tr>
<td>January 13, 1984</td>
<td>AIDS tabulated as “notifiable disease” for first time¹⁸</td>
<td>25 Cases reported in first week</td>
</tr>
<tr>
<td>May 4, 1984</td>
<td>Frequent detection of HTLV-III in patients at risk¹⁹</td>
<td></td>
</tr>
<tr>
<td>March 1985</td>
<td>FDA approves commercial test to detect HIV</td>
<td></td>
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<tr>
<td>1986</td>
<td>CDC provides working definition of AIDS¹⁰</td>
<td></td>
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<tr>
<td>1986</td>
<td>AIDS Clinical Trials Group established by NIH</td>
<td></td>
</tr>
<tr>
<td>March 1987</td>
<td>FDA approves AZT (azidothymidine)</td>
<td>First drug active against HIV</td>
</tr>
</tbody>
</table>

## 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 zalcitabine</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 old¹⁹</td>
<td>AIDS surpasses unintentional injuries as cause of death in this group</td>
</tr>
<tr>
<td>January 12, 1995</td>
<td>Dynamism of HIV replication redefined¹⁰</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 sarcoma¹¹</td>
<td>Human herpesvirus 8 isolated</td>
</tr>
<tr>
<td>July 15, 1995</td>
<td>First Public Health Service guidelines to prevent opportunistic infections¹²</td>
<td>Two subsequent revisions</td>
</tr>
<tr>
<td>August 1995</td>
<td>First protease inhibitor, saquinavir, approved¹³</td>
<td>Within 18 months, 3 additional protease inhibitors approved</td>
</tr>
<tr>
<td>1996</td>
<td>U.S. AIDS death rate decreases¹⁴</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 established¹⁵</td>
<td>Important laboratory determination for routine 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 published report of lipodystrophy syndrome¹⁶</td>
<td>Lipodystrophy, hyperlipidemia, diabetes, and other metabolic abnormalities described with increasing frequency in patients with AIDS</td>
</tr>
<tr>
<td>June 1998</td>
<td>Efavirenz approved¹⁷</td>
<td>“Increase-saving” regimen introduced</td>
</tr>
<tr>
<td>January 10, 2000</td>
<td>UN Security Council discusses AIDS¹⁷</td>
<td>“AIDS threatens our security”</td>
</tr>
<tr>
<td>December 2000</td>
<td>WHO estimates 36.1 million have HIV–AIDS, with an additional 21.8 million already dead¹⁸</td>
<td>S.1 million new infections in 2010; 14,450 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 Africa¹⁹</td>
<td>Cost will be 1–10% of U.S. price</td>
</tr>
</tbody>
</table>

*CDC denotes Centers for Disease Control, FDA Food and Drug Administration, HIV human immunodeficiency virus, HTLV human T-cell lymphotrophic virus, and NIH National Institutes of Health.

*Each quoted statement is from the reference cited under the corresponding Reported Event.

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

¹ Each quoted statement is from the reference cited under the corresponding Reported Event.
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, mononeuropathies, polyneuropathy, multisensory symmetric polyneuropathy; myopathy; AIDS dementia complex (ADC)

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Adapted from Table 1 of A. S. Fauci and R. C. Desrosiers, p. 587–635, in J. M. Coffin et al. (ed.), The Retroviruses (Cold Spring Harbor Laboratory Press, Plainview, N.Y., 1997), with permission. HSV, herpes simplex virus; EBV, 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

- Heterosexual: 80% to 85%
- Homosexual: 5% to 10%
- Intravenous drug use: 5% to 10%
- Blood transfusions: 3% to 5%
- Unknown: 0% to 17%

Also Vertical Transmission!

(11-60% depending on severity of maternal infection and ±breastfeeding)
Incidence and Prevalence

- 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
The Lentiviruses (slow viruses)

- Sooty Mangabey
- Sykes Monkey
- Chimpanzee
- African Green Monkey
- Mandrill
- visna/maedi
- caprine arthritis-encephalitis
- equine infectious anemia
- bovine
- feline
1959 Serum from Bantu Male @ Kinchasa 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
SIV appeared after versus/velleroses (0% prevalence) split from troglodytes/schweinfurthi (25-35% infected)

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 G₂, promotes DNA entry into nucleus.
• vpu - ER resident TM protein, facilitates virus release, traps CD4.
Viral Replication Cycle

- $10^9$ 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 Base Line.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects Identified with Drug-Resistant Virus</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level drug resistance (phenotype assay)¶</td>
<td>9/264 (3.4) 14/113 (12.4) 0.002</td>
<td></td>
</tr>
<tr>
<td>Any antiretroviral drug</td>
<td>6/264 (2.3) 7/113 (6.2) 0.07</td>
<td></td>
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<tr>
<td>NNRTIs</td>
<td>5/264 (1.9) 8/113 (7.1) 0.03</td>
<td></td>
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<tr>
<td>PIs</td>
<td>1/264 (0.4) 9/113 (8.0) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Multidrug resistance</td>
<td>3/264 (1.1) 7/113 (6.2) 0.01</td>
<td></td>
</tr>
<tr>
<td>Major drug-resistance mutations (genotype assay)</td>
<td>17/213 (8.0) 26/88 (22.7) &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any antiretroviral drug</td>
<td>15/176 (8.5) 13/82 (15.9) 0.09</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>3/176 (1.7) 6/82 (7.3) 0.03</td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>2/213 (0.9) 8/88 (9.1) 0.001</td>
<td></td>
</tr>
<tr>
<td>Multidrug resistance§</td>
<td>8/213 (3.8) 9/88 (10.2) 0.05</td>
<td></td>
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</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
  - Bicyclics
  - 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

Preventing HIV Entry

- 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

Maraviroc, FDA 8/2007
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?


Early 1990's: Ab's and soluble CD4 work in lab but not on primary HIV-1 isolates. Humoral vaccine programs put on hold.

1990-2007: Attempt to produce an adenovirus based T-cell vaccine.

2006: Prospective Amsterdam study shows that strong HIV-specific memory T-Cell response does not afford any protection (maybe even a liability).

2007: The STEP and Phambili trials with MRKAd5 Trivalent HIV vaccine (gag, pol, nef) are cancelled because of lack of efficacy.
The case for Cell-Based Vaccines

Broadly Neutralizing Antibodies

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


B12 (vaginal or IV) protects monkeys from infection.
Many of the broadly neutralizing antibodies recognize parts of gp120 that bind to CD4.
The Case for a Tolerizing Vaccine

INFLAMMATION CORRELATES WITH DISEASE PROGRESSION!

HIV-1 induces a systemic immune response, primarily to bacterial antigens; the level of this immune activation at the viral setpoint is the best current predictor for disease progression.

"Elite Controllers" exhibit a lower level of systemic immune activation.

SIV infects sooty mangabeys but does not cause AIDS; the system immune activation/inflammation is also not observed.

The frequency of mother-child transmission of HIV-1 is lower than might be expected; does immunosuppression during pregnancy account for this observation?

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! \( (J. \textit{Vir.} \ 79(14): \ 8870-8877 \ 2005) \)

Appears to cause premature uncoating of the HIV capsid (why this is a problem is unknown). Human TRIM5a may have evolved away from chimpanzee in order to suppress a now-extinct retrovirus, PtERV1 (resurrection experiments).

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Apobec 3G

Vif+ virus replicates in HeLa, COS, Jurkat, 293T cells but not in H9 or CEM15 cells.

Non-permissive phenotype dominant in cell fusion experiments => inhibitor.

Apobec 3G cloned as the inhibitor by a subtractive mRNA screen in 2002. Vif overcomes the restriction imposed by Apobec3G.

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

Part of an ancient mechanism for anti-retroviral defense.

There are five additional Apobec3G like genes; they exhibit some of the strongest signals for positive selection within the human genome.

This positive selection predates lentiviruses.


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
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

![Diagram showing the process of T-cell activation and anergy.]

- **Mature antigen-presenting cell**
  - Signal 1
  - B7 binds CD28
  - T cell activation

- **Immature antigen-presenting cell**
  - Signal 1
  - T cell anergy or inactivation

- CTLA-4 replaces CD28 in the binding process, affecting T-cell activation.
The Future of the Arms Race?


Immune System Overview

Inate

NK cells

Adaptive

APC

B cells

T cells

Ifn-γ induced

professional

IL12 from activated macrophages and dendritic cells

γδ helper

CD4

CD8 cytotoxic

γδ

+ T_H1

IL2

Ifn-γ

TNFα

T_H2

IL4, 10

TGFβ

Ifn-β