HIV and AIDS

Lecture 23
Biology 4310
Virology
Spring 2021
This tragedy was facilitated (or even caused) by human interventions: colonization, urbanization, and probably well-intentioned public health campaigns.

December: At Albert Einstein Medical College in New York, pediatric immunologist Dr. Arye Rubinstein treats five black infants who are showing signs of severe immune deficiency, including PCP. At least three are the children of women who use drugs and engage in sex work. He recognizes that the children are showing signs of the same illnesses affecting gay men, but his diagnoses are dismissed by his colleagues.

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed P. carinii pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viremia. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination revealed residual P. carinii and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed P. carinii pneumonia in April 1981 after a 3-month history of fever each day and of elevated liver-function tests, CMV viremia, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 256 in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

Editorial Note: Pneumocystis pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients. The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and Pneumocystis pneumonia in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months of the diagnosis of Pneumocystis pneumonia. CMV infection has been shown to induce transient abnormalities of in vitro cellular-immune function in otherwise healthy human hosts. Although all 5 patients tested had abnormal cellular-immune function, no definitive conclusions regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection (1) of the same group had at least 1 other major concurrent infection (1). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) had CMV viremia; rates for other tests of similar age who were reported to be exclusively homosexual were 54% for seropositivity and zero for viremia (4). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than urine, but also that seminal fluid may be an important vehicle of CMV transmission (5).
AIDS

- Clusters of PCP and Kaposi’s sarcoma observed in other urban centers
- CDC established case definition of KS or opportunistic infections
- 1982 disease was called AIDS (formerly GRID)
- Found transmitted at birth and heterosexually, blood products
HIV-1 is a lentivirus

- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris; 2008 Nobel to Montagnier & Barré-Sinoussi
- 1984 blood test developed
- Electron microscopy and sequence analysis revealed HIV-1 to be a lentivirus, known group of retroviruses
Retroviridae

- Orthoretrovirinae (subfamily)
  - Alpharetrovirus (Avian leukosis virus, Rous sarcoma virus)
  - Betaretrovirus (Mouse mammary tumor virus)
  - Deltaretrovirus (Human T cell lymphotropic virus 1, 2, 3)
  - Epsilonretrovirus (Walleye dermal sarcoma virus)
  - Gammaretrovirus (Moloney murine leukemia virus)
  - Lentivirus (Human immunodeficiency virus 1, 2)
Two evolutionarily distinct groups of human retroviruses

- The lymphotropic viruses: HTLV 1, 2, 3, 4
- The immunodeficiency viruses: HIV-1, HIV-2
  - Lentiviruses, not new or unique to humans
  - Equine infectious anemia virus, causes fatal immunodeficiency of horses, isolated early 1900s
  - Bovine, feline, caprine immunodeficiency viruses
Figure 7.3 Organization of HIV-1 (A) and HIV-2 proviral DNA (B).

Vertical positions of the colored bars denote each of the three different reading frames that encode viral proteins. The LTRs contain sequences necessary for transcriptional initiation and termination, reverse transcription, and integration.

Figure 7.4 Mechanisms of Tat and Rev function.

Some regulatory sequences in the HIV LTR are depicted in the expanded section at the top. The numbers refer to positions relative to the site of initiation of transcription. The opposing arrows in R represent a palindromic sequence that folds into a stem-loop structure (TAR) in the transcribed mRNA to which Tat binds (center). Tat recruits cellular proteins that are required for efficient elongation during HIV-1 RNA synthesis. The position of the RRE in the env transcript (with bound Rev dimers) and the cis-acting repressive sequences (instability sequences, INS) in the unspliced or singly spliced transcripts are also illustrated. Mutations in the A/H11001 U-rich INS increase the stability, nuclear export, and translation efficiency of the transcripts in the absence of Rev. Response to INS appears to be cell type-dependent, but the mechanisms by which they act, and exactly how Rev counteracts their effects, are not understood.

Rev is an RNA-binding protein that recognizes a specific sequence within a structural element in the env region of the elongated transcript, called the Rev-responsive element (RRE). Rev mediates the nuclear export of any RRE-containing RNA by a mechanism discussed more fully in Volume I, Chapter 10 (Figs. 10.14 to 10.16). As the concentration of Rev increases, unspliced or singly spliced transcripts containing the RRE are exported from the nucleus. In this way, Rev promotes synthesis of the viral structural proteins and enzymes and ensures the availability of full-length products.
HIV and AIDS: Acquired ImmunoDeficiency Syndrome

- Syndrome: the occurrence together of a characteristic group or pattern of symptoms
- HIV-1 is the etiological agent of epidemic AIDS
- AIDS denialists: the hypothesis that HIV-1 causes AIDS has been tested by inadvertent infection of people with HIV-1 contaminated blood
HIV/AIDS pandemic in the US

- In the US, HIV-1 has killed over 600,000, exceeding all US combat-related deaths in all wars fought in the 20th century
- 1,140,000 million in the US are living with HIV-1; 1 in 7 don’t know it
- 37,832 new infections in 2018; 69% MSM, 24% HS, 7% IVDU

http://www.cdc.gov/hiv/statistics/overview/atalgline.html
Global summary of the HIV-1 pandemic (2018)

37.9 million people living with HIV
[32.7 million – 44.0 million]

1.7 million people newly infected
[1.4 million – 2.3 million]

0.8 million HIV-related deaths
[0.6 million – 1.1 million]

4,600 new HIV infections a day, 190 per hour

Source: UNAIDS/WHO estimates
### Global summary of the HIV-1 pandemic (2018)

<table>
<thead>
<tr>
<th></th>
<th>People living with HIV in 2018</th>
<th>People newly infected with HIV in 2018</th>
<th>HIV-related deaths 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>37.9 million [32.7 million – 44.0 million]</td>
<td>1.7 million [1.4 million – 2.3 million]</td>
<td>770 000 [570 000 – 1.1 million]</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>36.2 million [31.3 million – 42.0 million]</td>
<td>1.6 million [1.2 million – 2.1 million]</td>
<td>670 000 [500 000 – 920 000]</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td>18.8 million [16.4 million – 21.7 million]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>17.4 million [14.8 million – 20.5 million]</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Children (&lt;15 years)</strong></td>
<td>1.7 million [1.3 million – 2.2 million]</td>
<td>160 000 [110 000 – 260 000]</td>
<td>100 000 [64 000 – 160 000]</td>
</tr>
</tbody>
</table>

Source: UNAIDS/WHO estimates
37.9 million people living with HIV globally

- Africa: 25.7 million
- America: 3.5 million
- South-East Asia: 3.8 million
- Europe: 2.5 million
- Eastern Mediterranean: 400,000
- Western Pacific: 1.9 million

Source: UNAIDS/WHO estimates
Distribution of new HIV-1 infections by key population, global (2018)

- Sex workers: 6%
- People who inject drugs: 12%
- Gay men and other men who have sex with men: 17%
- Transgender women: 1%
- Clients of sex workers and sex partners of other key populations: 18%
- Remaining population: 46%

Source: UNAIDS special analysis, 2019
Decline in HIV-1 incidence and mortality over time

Source: UNAIDS/WHO estimates
Control of AIDS

Triple-drug therapy has slowed the pandemic in countries with money
ART coverage over time

Source: UNAIDS/WHO estimates
But...

- There is as yet no cure
  - Can’t clear virus from an infected individual
- There is no vaccine
  - Can’t block primary infection
- Can’t stop taking antiviral drugs
  - Reservoirs: latently infected hematopoietic progenitor cells
- Drug resistant viruses appear
- Drugs are expensive
First studies in Africa, in Zaire and Rwanda, showed that AIDS was common in Kinshasa and Kigali, where nearly 90% of sex workers were infected.
Testing of archival samples suggested that HIV-1 was present in the 1960s and 1970s in several locations in central Africa but not in West or East Africa.

- Serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998.
- Lymph node sample from DRC adult female (1960).
Out of Africa

- DRC60 and ZR59 differed by about 12%
- No doubt that HIV-1 was present in Léopoldville (Kinshasa today) by 1959–60
What was the source of HIV-1?

- SIV first isolated from chimpanzee in 1989 (SIVcpz)
- Analysis of >7,000 chimpanzee fecal samples from 90 field sites confirmed natural SIVcpz reservoir
- Only *Pan troglodytes troglodytes* and *P. T. schweinfurthii* harbor SIVcpz
- Transmitted among chimpanzees by sexual intercourse; mother to child; possibly blood-blood during aggression
- Estimated transmission probability per coital act 0.008 - 0.0015, similar to humans (0.0011)
- SIVcpz is pathogenic in natural host, disease similar to AIDS
When did SIV infect humans?

- Four separate crossover events
- M, O: First three decades of 20th century
- N, P: more recently but not enough data
How did SIVcpz infect humans?

- The cut hunter: bushmeat hunting
- Cutaneous or mucous membrane exposure to infected chimpanzee blood, body fluids
- Calculations suggest that in 1921 number of people infected with SIVcpz was <10, but probably only one spread and multiplied
- Such cross-species infections probably have occurred many times previously
- Why did this one spread?
- Leopoldville (Kinshasa) was the most dynamic city in the region, attracted large numbers of migrants and traders

- The cut hunter might have traveled there, visited a brothel, then a STD clinic

- Then amplification by non-sterile syringes, sex (some women had 1,000 clients/yr)

- Haiti and the Belgian Congo
Why did HIV-1 spread?

- European colonization of Africa beginning end of 19th century
- Establishment of large population centers, movement of adult males for labor - large scale prostitution
- Introduction of health care - colonial medicine - injections and transmission of viruses
- Egypt at turn of 20th century - well intentioned treatment for schistosomiasis spread HCV to millions
- Large scale amplification of HIV-1
HIV-2

- First isolated Guinea-Bissau, 30-40% identity HIV-1
- Restricted primarily to populations in West Africa
- Less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother-infant spread
- Crossover from sooty mangabey
- 8 distinct lineages, each arose from separate infection
HIV-1 diversity

- Four groups based on sequence alignment
- Group M (main): 99% of all HIV-1 infections
- Group O (outlier): <1% of infections, limited to Cameroon, Gabon, neighboring countries
- Group N: Only 13 cases, Cameroon
- Group P: Only 2 cases, Cameroon
- Each from an independent transmission event of SIV to humans
HIV-1 diversity

- HIV-1 group M further divided into 9 subtypes
- High-risk individuals multiply infected, recombinants emerge (CRFs) 48 so far
- No clear cut difference between subtypes in propensity to cause AIDS, except that those infected with D die faster
- Shedding of subtype C in female genital tract is higher, perhaps higher female to male transmission, extensive spread in Africa
HIV-1 subtypes

- HIV-1 evolves in one direction to numerous subtypes and recombinants
- Therefore can reconstruct sequence of progress in region or country by examining local distribution of subtypes
- Facilitated in 1990s by new tools enabling examination of nucleotide sequences from large number of isolates
- Extreme diversity of HIV-1 in central Africa, clearly the origin as had more time to diversify
HIV-1 subtypes

- Some subtypes associated in specific locations with modes of transmission
- Founder effect: subtype will *predominate* in at-risk group
- Example: subtype B found in 96% of white homosexuals in South Africa (imported from US); subtype C accounts for 81% of infections of black heterosexuals
- Subtype C (50%), B and A (10-12%), G (6%), CRF02_AG (5%), CRF01_AE (5%), D (2.5%) of all HIV-1 infections
- Subtypes F, H, J, K limited transmission (<1%)
Transmission

- Transmitted by sex, intravenous drug use, at birth ($R_0$ 2-5)
- Not spread by respiratory, alimentary, or vector routes

Mother to child at birth, ~5%
Transmission

- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
- Sex/IVDU bypass these!
## Risk of transmission of HIV-1

<table>
<thead>
<tr>
<th>Mode</th>
<th>Infection risk per 10,000 exposures</th>
</tr>
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<tbody>
<tr>
<td><strong>Sexual transmission</strong></td>
<td></td>
</tr>
<tr>
<td>Receptive anal sex</td>
<td>138</td>
</tr>
<tr>
<td>Insertive anal sex</td>
<td>11</td>
</tr>
<tr>
<td>Receptive penile-vaginal sex</td>
<td>8</td>
</tr>
<tr>
<td>Insertive penile-vaginal sex</td>
<td>4</td>
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<tr>
<td><strong>Parenteral</strong></td>
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<tr>
<td>Transfusion of infected blood</td>
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<tr>
<td>Needle sharing</td>
<td>63</td>
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<tr>
<td>Needle stick</td>
<td>23</td>
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<tr>
<td>Needle stick /AZT PEP</td>
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<tr>
<td><strong>Mother to infant</strong></td>
<td></td>
</tr>
<tr>
<td>Without AZT</td>
<td>2260</td>
</tr>
<tr>
<td>With AZT</td>
<td>&lt;1000</td>
</tr>
</tbody>
</table>
Co-receptors

R5-tropic
- R5-tropic
- β-chemokine receptor (CCR5)
- CD4
- β-chemokine (CCL3/4/5)

X4-tropic
- X4-tropic
- α-chemokine receptor (CXCR4)
- CD4
- Sdf-1

M-tropic
- M-tropic
- Macrophage
Host genes that determine susceptibility

- Ccr5-delta32 mutation protects vs HIV-1 infection
- Present in 4-16% of European descent
- Stem cell therapy cured German and London AIDS patients
  [link](http://www.virology.ws/2019/03/13/the-london-patient/)
- Disrupting *ccr5* with Crispr/cas9
Virus-dendritic cell interaction (no activation)
- Infection typically with CCR5 binding strains
- Importance of DC-SIGN (dendritic cell-specific, Icam-3 grabbing nonintegrin)

- Delivery of virus to lymph nodes
- Active replication in lymphoid tissue
- High levels of viremia and dissemination
- Down-regulation of virus replication by immune response
- Viral set point reached after ~6 months
Progression of HIV Infection

**Acute phase**
- Symptoms: Swollen lymph nodes (Lymphadenopathy), Fever, Diarrhea
- At cellular level: CD4+ T cells decline temporarily, CD8+ T cells increase temporarily (homeostasis) & anti-HIV-1 CTLs increase temporarily
  - B cells: anti-HIV-1 antibodies appear

**Chronic phase**
- Symptoms: Usually: no symptoms
  - Sporadically: fatigue, mild weight loss, generalized lymphadenopathy, rash, shingles
- At cellular level: CD4+ T cells gradually decline
  - CD8+ T cells: levels largely unaffected and CTL responses evolve
  - B cells: co-evolution of anti-viral antibodies and viral antigens
  - Acquisition of macrophage tropism
  - Infection of central nervous system (in some patients)

**Symptomatic phase**
- Symptoms: 200-500 CD4+ T cells/ml
  - Oral/skin lesions, Genital warts
  - Development of Kaposi's sarcoma, Reactivation of latent Mycobacterium tuberculosis
  - <200 CD4+ T cells/ml
  - Opportunistic infections by protozoa/bacteria/fungi/viruses
  - Weight loss, Malignancies, Neurological symptoms
- At cellular level: CD4+ T cell depletion, loss of helper function
  - HIV-1-specific CD4+/CD8+ T cell exhaustion
  - B cells: decrease/dysregulation
  - Natural killer (NK) cells: impairment of function
Effects of HIV-1 infection on intestinal mucosa
GI associated lymphoid tissue following acute infection

Absence of lymphoid cell aggregates in terminal Ileum
The variable course of HIV-1 infection

**Typical Progressor**
- Primary HIV Infection
- Clinical Latency
- AIDS

**Rapid Progressor**
- Primary HIV Infection
- AIDS

**Nonprogressor**
- Primary HIV Infection
- Clinical Latency

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Elite HIV Controllers

- Individuals who maintain normal CD4 counts and undetectable viral loads (1-30 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy
  - Estimated at 1/300 infected persons

- 20% are associated with favorable HLA (MHC) types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag

- Not associated with attenuated viruses
HIV-1 dynamics

Productively infected CD4\(^+\) lymphocytes

Latently infected CD4\(^+\) lymphocytes

Uninfected, activated CD4\(^+\) lymphocytes

Uninfected CD4\(^+\) lymphocytes

HIV-1

1.6 days per generation

1-7%

93-99%

<1%

Long-lived cell populations and T memory cells

\(t_{1/2} \sim 1.1\) days

\(t_{1/2} \sim 14.1\) days

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Principles of Virology, ASM Press
HIV-1 latency
HIV and cancer

- HIV-1 infection leads to increased incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses (EBV, HHV8, HPV), angiogenesis
Kaposi’s sarcoma

- Described 1872 by Hungarian physician
- Pre-AIDS: mainly in older Mediterranean men
- Occurs in 20% of HIV-1 infected homosexual men, 2% of HIV-1 infected women, transfusion recipients
- Infection with human herpesvirus 8 is necessary for development of KS
Induction of cancers in HIV-1 infected patients

- HIV-1 infection
- Cytokines

- Macrophages
- CD4+ T cells
- Endothelial cells
- Epithelial cells
- B cells

- ± EBV, HHV-8
- + HHV-8
- + HPV

- Lymphoma
- Kaposi’s sarcoma
- Carcinoma

- IL-6
- TNF-α
- bFGF
- IL-6
Is an HIV-1 vaccine possible?

How does HIV-1 persist despite effective anti-viral immunity?
How does it eventually outstrip immune control?
HIV-1 superinfection occurs less frequently than initial infection
HIV-1 escape from neutralizing antibody
RV144

- Prime-boost: ALVAC-HIV (gag, pol, env in canarypox vector) and AIDSVAX B/E (recombinant gp120 protein)
- 16,000 adult volunteers in Thailand
- 6 prime, 6 boost injections
- Lowered rate of HIV-1 infection by 31.2% compared with placebo
- n=51 vs n=74

HIV-1 envelope and influenza virus HA diversity

A 1996 Influenza sequence
Hemagglutinin (H3)
n=96

B HIV-1 Single Individual
Subtype B
n=9

C Democratic Republic of the Congo
1997
n=193
Broadly neutralizing antibodies

A. Autologous virus neutralization

HIV RNA (copies/ml of plasma)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>HIV RNA</th>
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<tbody>
<tr>
<td>5</td>
<td>$10^8$</td>
</tr>
<tr>
<td>10</td>
<td>$10^6$</td>
</tr>
<tr>
<td>15</td>
<td>$10^4$</td>
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<tr>
<td>2</td>
<td>$10^2$</td>
</tr>
<tr>
<td>4</td>
<td>$10^2$</td>
</tr>
<tr>
<td>6</td>
<td>$10^2$</td>
</tr>
<tr>
<td>8</td>
<td>$10^2$</td>
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</tbody>
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Time after HIV infection

Heterologous virus neutralization responses

bnAbs

B. Increasing neutralization breadth

C. V1/V2-directed

HIV-1 Env spike ectodomain

SU 3 gp120 subunits

TM 3 gp41 subunits

Transmembrane spanning region

CD4-binding site-directed

gp120 core

MPER-directed
Confronting persistence and latency

- Eradicating all HIV-1 is challenging due to long-lived latent reservoir
- Intense drug therapy + broadly nAb failed
- Shock and kill: Induce provirus expression, treat with antiviral drugs
- Block and lock: Complete and irreversible inhibition of genome transcription
~1921: Patient zero

SIV

HIV-1

75,000,000 infections
32,000,000 deaths
Next time: Unusual infectious agents