**Discovery of HIV and Early Findings**

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**Major Epidemics of the World**

- Bubonic Plague
- Cholera
- Dengue
- Diphtheria
- Influenza
- Malaria
- Measles
- Mumps
- Schistosomiasis
- Smallpox
- Syphilis
- Tuberculosis
- Typhus
- Yellow Fever

**Factors Condusive to the Emergence of the AIDS Epidemic**

- Migration of carriers into cities - increased interpersonal contacts
- Poverty; prostitution
- International travel
- Sexual behavior
- IV drug use
- Receipt of blood and blood products

**How Does HIV Differ from Other Epidemic Pathogens?**

- Directly attacks the immune system
- Involves virus incorporation into the cellular genome
- Establishes a chronic infection before becoming pathogenic
- Involves an agent that frequently changes or modulates itself within the host.
- Can recruit other cells by direct infection or cell:cell transfer

**Seven Deadly Symptoms**

- Fever that persists for more than four or five days or comes and goes over a long period of time
- An unexplained, unexplained weight loss of 10 lbs in two months
- Persistent cough or pain in the chest
- Persistent fever or pain in the abdomen
- Abnormal bleeding or bruising
- Persistent and unexplained loss of appetite
- Persistent and severe diarrhea
- Persistent and unexplained testicular swelling

*Source: San Francisco Chronicle, August 1981*
Pneumocystis jiroveci pneumonia

HHV-8

Section of hairy leukoplakia provided by J. Greenspan, LCSO
AIDS-Associated Retrovirus (ARV)

LAV / HTLV III / ARV

ARV = HIV-1$_{SF}$

Human Immunodeficiency Virus (HIV)

Components of HIV Infection
**HIV Pathogenesis**

**Virus : Host Interactions**

**HIV: Cell Entry**

- Attachment
- Fusion
- Entry

**Coreceptor Usage by HIV-1**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Tropism</th>
<th>Coreceptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSI*</td>
<td>Macrophage</td>
<td>CCR-5, CCR-3</td>
</tr>
<tr>
<td>SI</td>
<td>T-cell line</td>
<td>CXCR-4</td>
</tr>
<tr>
<td>SI</td>
<td>Dual</td>
<td>CXCR-4, CCR-5, CCR-2b</td>
</tr>
</tbody>
</table>

* Also non-macrophage-trophic NSI Strains

**HIV Biologic Diversity**

- NSI
- X4
- R5

**Initial HIV Infection**
**Initial HIV Infection**

**HIV Replication Permits Genetic Mutations**

**Human Cells Susceptible to HIV**

**Tissues with Virus-infected Cells after Intravaginal SIV Inoculation**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Cervix</td>
<td>–</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Draining lymph node</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Distal lymph node</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Other lymph nodes</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>++</td>
</tr>
</tbody>
</table>

From Zhang, et al. Science: 286, 1353, 1999

**GI Tract**

Human cells susceptible to HIV:

- Brain: Capillary endothelial cells, Astrocytes, Microglia, Oligodendrocytes, Choroid plexus, Ganglia cells, Neuroblastoma cells, Glioma cell lines, Neurons (?), Bowel: Columnar and goblet cells, Enterochromaffin cells, Colon carcinoma cells
- Other: Myocardium, Renal tubular cells, Synovial membranes, Hepatocytes, Hepatic sinusoid endothelium, Hepatic carcinoma cells, Kupffer cells, Dental pulp fibroblasts, Pulmonary fibroblasts, Fetal adrenal cells, Retinal cells, Cervix-derived epithelial cells
- GI Tract: Cervix (epithelium ?), Prostate, Testes, Osteosarcoma cells, Rhabdomyosarcoma cells, Fetal chorionic villi, Trophoblast cells

Biologic Causes for the Spread of HIV/AIDS

Infected individuals remain healthy for many years

Virus can be transmitted by an infected cell

Virus is spread by sexual transmission

Virus mutates at a rapid rate

Virus can become resistant to immune response
**Distribution of HIV Groups**

<table>
<thead>
<tr>
<th>HIV group</th>
<th>No. of infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td></td>
</tr>
<tr>
<td>Group M</td>
<td>45,000,000 (99.6)</td>
</tr>
<tr>
<td>Group N</td>
<td>10 (0.000013)</td>
</tr>
<tr>
<td>Group O</td>
<td>10,000 (0.22)</td>
</tr>
<tr>
<td>HIV-2</td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>50,000 (0.11)</td>
</tr>
<tr>
<td>Group B</td>
<td>25,000 (0.06)</td>
</tr>
<tr>
<td>Group C</td>
<td>1 (0.000002)</td>
</tr>
<tr>
<td>Group D</td>
<td>1 (0.000002)</td>
</tr>
<tr>
<td>Group E</td>
<td>1 (0.000002)</td>
</tr>
<tr>
<td>Group F</td>
<td>1 (0.000002)</td>
</tr>
<tr>
<td>Group G</td>
<td>1 (0.000002)</td>
</tr>
<tr>
<td>Group H</td>
<td>?</td>
</tr>
</tbody>
</table>

**Multi-clade Recombinant HIV-1**

**HIV Pathogenesis**

**Virus : Host Interactions**

**Major Cells in the Immune System**

**T Lymphocyte Subsets**
Loss of CD4+ Lymphocytes in HIV Infection

1. ISOTYPE
2. CD45/CD14
3. CD3/CD4
4. CD2/CD8
5. CD3/CD16 + CD56
6. CD19

Long-term survivor
Progressor

CD4+ cell count (CD4+ cell count in ng/mL)
**HIV Isolation from Peripheral Blood of a Clinically Healthy Infected Man**

<table>
<thead>
<tr>
<th>Date</th>
<th>Virus Isolation</th>
<th>Date</th>
<th>Virus Isolation</th>
<th>Date</th>
<th>Virus Isolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/94</td>
<td>+</td>
<td>2/94</td>
<td>-</td>
<td>8/95</td>
<td>-</td>
</tr>
<tr>
<td>11/94</td>
<td>+</td>
<td>8/94</td>
<td>-</td>
<td>2/96</td>
<td>-</td>
</tr>
<tr>
<td>1/95</td>
<td>+</td>
<td>2/95</td>
<td>-</td>
<td>8/95</td>
<td>-</td>
</tr>
<tr>
<td>2/95</td>
<td>+</td>
<td>2/95</td>
<td>-</td>
<td>8/97</td>
<td>-</td>
</tr>
<tr>
<td>4/95</td>
<td>-</td>
<td>8/98</td>
<td>-</td>
<td>8/99</td>
<td>-</td>
</tr>
<tr>
<td>8/99</td>
<td>-</td>
<td>2/00</td>
<td>-</td>
<td>2/00</td>
<td>-</td>
</tr>
<tr>
<td>1/00</td>
<td>-</td>
<td>2/00</td>
<td>-</td>
<td>2/00</td>
<td>-</td>
</tr>
<tr>
<td>2/01</td>
<td>-</td>
<td>2/01</td>
<td>-</td>
<td>2/01</td>
<td>-</td>
</tr>
<tr>
<td>2/02</td>
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<td>-</td>
<td>2/02</td>
<td>-</td>
</tr>
<tr>
<td>2/03</td>
<td>-</td>
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<td>2/03</td>
<td>-</td>
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<tr>
<td>8/03</td>
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<td>2/04</td>
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<td>8/04</td>
<td>-</td>
<td>2/05</td>
<td>-</td>
<td>2/05</td>
<td>-</td>
</tr>
</tbody>
</table>

**Major Characteristics of Long-Term Survivors of HIV Infection**

- Clinically asymptomatic for ≥ 10 years; no antiviral therapy
- Normal CD4+ cell number
- Low virus load (measured by plasma viremia; infected PBMC)
- Low immune activation; normal T-reg function
- **Elite Controllers**: Undetectable plasma virus for 2-10 years

**CD8+ Cells Block HIV Replication**

**Lymphocyte Subsets**

- **CD4 Helper/inducer**
- **CD8 Suppressor/cytotoxic**

**CD8+ Cell Antiviral Activity**

**CD8+ Cell Suppression of HIV Replication in CD4+ Cells**

- **Asymptomatic**
- **AIDS**
**Resistance**

High Risk Exposed Seronegative Individuals

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**Loss over Time of CD8+ Cell Anti-HIV Response in Exposed Seronegative People**

<table>
<thead>
<tr>
<th>Virus</th>
<th>VHR</th>
<th>MR</th>
<th>LR</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1$_{SF2}$</td>
<td>13/13</td>
<td>4/10</td>
<td>0/3</td>
<td>0/10</td>
</tr>
<tr>
<td>HIV-1$_{ALA33}$</td>
<td>12/12</td>
<td>12/12</td>
<td>0/2</td>
<td>0/8</td>
</tr>
</tbody>
</table>

VHR: very high risk, multiple exposures in last 6 months
MR: moderate risk, multiple exposures within 6-12 months
LR: low risk, multiple exposures more than 1 year ago

From Stanford S. et al. PNAS 96:1030, 1999
The Ideal HIV Vaccine

- Induces:
  - Early innate response that can curtail the infection
  - Cellular and humoral immune responses against virus-infected cells as well as HIV; not autoimmune activities
  - Antibodies that neutralize HIV; not enhancing antibodies
  - Local immunity at all entry sites for HIV
- Safe with long-lasting effects

Challenges of Developing an HIV Vaccine

- HIV integrates into the cellular genome
- Infected cells transmit the infection
- Cell to cell transfer of infection takes place
- Numerous HIV variants: virus replication leads to mutations
- Virus compromises immune function

Transformation of Tomato with an HIV-2 Antigen Construct Designed for Expression in the Fruit to Produce an Edible Vaccine

Cotyledons (embryonic leaves) cut from seedlings grown under sterile conditions
Cotyledons after infection with an Agrobacterium vector containing the GGP ORF, showing signs of regeneration on a selective medium

As of December 2004, large plants expressing the GGP ORF are growing in the Weizmann Institute’s transgenic greenhouse facility.