The Year 1981...

First Encounter: Dr. Michael Gottleib
What is AIDS?

- Acquired Immune Deficiency Syndrome
  - Acquired means you can get infected with it (not inherited)
  - Immune Deficiency means a weakness in the body’s system that fights diseases.
  - Syndrome means a group of health problems that make up a disease.

- The term AIDS refers to an advanced stage of HIV infection, when the immune system has sustained substantial damage.
- Not everyone who has HIV infection develops AIDS.

Global Statics of HIV/AIDS

- Total: 33.4 million
- Adults: 31.5 million
- Women: 15.7 million
- Children under 15 years: 2.1 million

People newly infected with HIV in 2008

- Total: 2.7 million
- Adults: 2.3 million
- Children under 15 years: 430,000

AIDS deaths in 2008

- Total: 2.0 million
- Adults: 1.7 million
- Children under 15 years: 283,000

Transmission of HIV

- The most common methods of transmission of HIV are:
  - Unprotected sex with an infected partner
  - Sharing needles with infected person

- Almost eliminated as risk factors for HIV transmission are:
  - Transmission from infected mother to fetus
  - Infection from blood products
“Patient Zero” and HIV Transmission

- Gaëtan Dugas: A Canadian who worked for Air Canada as a flight attendant
- Claimed to have had over 2,500 sexual partners across North America 1972
- Diagnosed with Kaposi’s Sarcoma in June 1980
- In 1982 the CDC linked him to 9 of the first 19 cases in Los Angeles, 22 cases in NYC and 9 more in 8 other cities – Total of 40 of the first 248 cases in the U.S.

New Model: HIV Traveled to Haiti, Then U.S.

What Type of Virus is HIV?

- Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family
- Lentiviruses are transmitted as enveloped RNA viruses
- Upon target cell entry, viral RNA is converted to dsDNA by a virally encoded reverse transcriptase present in the virus particle
Major Viral Components

Binding of HIV to CD4 T-cell

Worldwide Modes of Transmission in Adults
• Up to 90% of newly transmitted HIV uses CCR5 (M-tropic)
• R5 viruses are more often transmitted sexually
• CXCR4-tropic virus emerges in ~50-60% of infected individuals within 5 yrs
• X4-tropic (T-tropic virus) associated with pronounced depletion of CD4 T cells

Understanding HIV Tropism

- Lower CD4 counts and higher viral load is seen with dual or mixed tropic virus compared to pure R5 or X4.
- X4- virus correlates with syncytia formation
- X4 – virus associated with more rapid progression to AIDS
  - CXCR4 is expressed on nearly all CD4 T cells whereas only 15-30% express CCR5. Therefore, X4 virus has a wider range of susceptible target cells
CCR5 Delta-32 mutation & Resistance to HIV

- Approximately 1% of Europeans, and even more in northern Europe, inherit the CCR5 mutation from both parents, making them resistant to HIV infection.
- 10 to 15% of Europeans carry a mutation from 1 parent making it more difficult, but not impossible for them to become infected ("elite controllers" maintain very low viral load without ART).
- People of African, Asian and South American descent almost never carry it.

"Berlin Patient" Still HIV-free 4 Years after Bone Marrow Transplant

- Timothy Ray Brown, a 40-year-old man received 2 bone marrow transplants for acute myeloid leukemia.
- Donor had a double or homozygous CCR5-delta32 mutation.
- The patient was "conditioned" by intensive chemotherapy and radiation prior to transplantation.
- Successful reconstitution of CD4+ T cells in blood and gut without any trace of HIV.
- The last direct evidence of HIV was detectable on day 60 after transplantation.

Vaginal Acquisition of HIV infection

The process of HIV infection involves several steps, including the attachment of the virus to CD4+ T cells in the mucosal epithelium, penetration into the cells, and the subsequent release of new virus particles.
HIV Dissemination to 2º Lymphoid Tissue

Seroconversion

HIV Encephalitis and Resulting Dementia
Association between I135X and HLA-B*51 in all study cohorts

- Analyzed viral sequences and HLA alleles from >2,800 subjects, drawn from 9 distinct study cohorts spanning 5 continents.
- Initial analysis of the HLA-B*51-restricted epitope, TAFTIPS1 (reverse transcriptase residues 128-135), showed a strong correlation between the frequency of the escape mutation I135X and HLA-B*51 prevalence in the 9 study cohorts ($P = 0.0001$).
HIV Tropism and Progression to AIDS

Viral Load and CD4 Cell Count

CD4 Cell Count Predict Likelihood of developing AIDS

If your CD4 cell count is high and your viral load is low, your medicines are doing a good job controlling the virus.