A new disease - reports in 1981


The case histories suggested a "cellular-immune dysfunction related to a common exposure" and a "disease acquired through sexual contact."

HIV-1 and HIV-2 Origin

The human AIDS viruses HIV-1 and HIV-2 represent cross-species (zoonotic) infections from chimpanzees carrying SIVcpz\(^1\) and sooty mangabeys carrying SIVsm\(^2\), respectively.

HIV-1 and HIV-2 Origin

- Transmission across species is most likely related to the animal butchering, with animal blood contaminating wounds in humans.
- Massive migration from rural areas to urban areas, increased promiscuity and commercial sex, coupled with increased global traveling, facilitated the spreading of HIV across the world.
- HIV-1 and HIV-2 entered the human population between 1915 and 1941—most likely in the 1930s.1,2


Total: 2.8 (2.4 – 3.3) million

People estimated to be living with HIV, 2005

Total: 38.6 (33.4 – 46.0) million

Estimated deaths from AIDS, 2005

Total: 2.8 (2.4 – 3.3) million

Estimated number of people newly infected with HIV, 2005

Total: 4.1 (3.4 – 6.2) million

Source: WHO
HIV prevalence in adults in sub-Saharan Africa

HIV prevalence (%) among pregnant women attending antenatal clinics in sub-Saharan Africa, 1997/98-2004

Source: WHO

HIV Infection

Viral Infection

Mucosal surface

DC migration and maturation

Lymph Node

T-cells

Epithelial cell

Dendritic cell

Immature Dendritic Cell (iDC)
**Clinical Course of HIV Infection**

- **Acute Phase**: Immune function peaks, CD4 T Cells increase.
- **Chronic Phase**: Immune function wanes, CD4 T Cells begin to decline, T cell apoptosis increases.
- **AIDS**: T cell apoptosis becomes severe, immune function is severely compromised.
- **THERAPY**: Immune function recovers, CD4 T Cells stabilize or increase, T cell apoptosis decreases.

**Immune Escape Mechanisms**

1) Escape mutations in viral epitopes (antibody and T<sub>C</sub>)
2) Latent virus - immune system cannot detect if DNA integrated and no viral proteins made
3) Nef reduces MHC-1 levels
4) Viral Transcription Factor (Tat) modifies host cell gene expression program

**Opportunistic Infections in AIDS**

- Tuberculosis
- Kaposi's Sarcoma
- Candida esophagitis

**CXCR4 binding enables T cell infection**

**CCR5 binding enables macrophage infection**
Challenges to HIV Vaccine Development

**Prevention of infection vs clinical disease**
- Immune system cannot eliminate HIV once established
- Vaccines may prevent clinical disease, but not infection

**Viral escape**
- HIV has multiple mechanisms to escape immunity
  - variation, suppression of immune response

**Animal Models**
- Problems with best model: SIV and Macaque

Current drugs for HIV: HAART

### Retrovir (zidovudine, AZT) 1987
- Videx (didanosine, ddI) 1991
- Hivid (zalcitabine, ddC) 1991
- Zerit ( stavudine, d4T) 1994
- Epivir (lamivudine, 3TC) 1995
- Invirase (saquinavir, HGC) 1995
- Norvir (ritonavir) 1996
- Crinivir (indinavir) 1996
- Viramune (nelfinavir) 1996
- Viracept ( delavirdine) 1997
- Rescriptor ( delavirdine) 1997
- Combivir (AZT+3TC) 1997
- Fortovase (saquinavir-SGC) 1997
- Sustiva ( efavirenz) 1998
- Zagen (abacavir) 1998
- Agenerase (amprenavir) 1999
- Kaletra (Lopinavir and ritonavir) 2000
- Trizivir (AZT+3TC+abacavir) 2000
- Viread (tenofovir) 2001
- Fuzezon (enfuvirtide, T-20) 2003

HIV Vaccine Development: Advanced Trials

**Merck:** Recombinant adenovirus type 5
- Expressing Gag, Pol, Env
- Prime and boost

**NIH:** DNA / Recombinant adenovirus type 5
- Gag, Pol, Env
- Prime DNA
- Boost Recombinant adenovirus

There are now more than 30 trials ongoing in 24 countries