Retroviruses
Retroviridae

- The Retroviridae are a family of enveloped (+) sense ssRNA viruses that have been intensely studied because of their association with cancers, leukemias and the AIDS syndrome.

- The first association of viruses with cancer was in early 1900’s with the discovery by Ellerman and Bang that leukemia could be transmitted from one chicken to another by injecting leukemia cell extracts.

- In 1911 Peyton Rous showed that a bacterial free filtrate from solid tumors of chickens could cause an identical cancer in chickens inoculated with the filtrate.

- The virus causing the leukemia was subsequently shown to be avian leukosis virus and the virus causing tumors was designated Rous sarcoma virus.
### Retrovirus Classification

**Family: Retroviridae**

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Retrovirus Virions
Thin Section EM of Some Retroviruses

Type A (donut)
- MMTV

Type B (eccentric)
- ALV, RSV

Type C (central)

Type D (bar)

Lentivirus (cone)
- HIV
Retrovirus structure

- Retrovirus virions are 80-120 nm in diameter, have spherical morphology, a phospholipid envelope with knobs.
- Contain around 2000 molecules of nucleocapsid (NC) protein that bind to the two copies of (+) strand RNA genome.
- Retroviral ribonucleoproteins are encased within a protein shell built from the capsid protein to form an internal core, which can have different shapes and has a conical shape in HIV.
HIV genome organization

• Single stranded (+) sense RNA genome of about 10 kb
• 5` cap, 3` poly(A) tail
• Stop codon between gag and pol, suppressed by readthrough or frameshifting
• Looks like mRNA, but does not serve as mRNA immediately after infection
• Has a direct repeat (R) and unique (U) regions at both ends
• All retroviruses encode Gag, Pol and Env
• Lentiviral genomes encode a number of additional auxiliary proteins, Tat, Rev, Nef, Vif, Vpr and Vpu
HIV integration:
HIV / AIDS

14 000 new infections daily

Every 5 seconds...

... One person is infected

Every 15 seconds...

... One person dies
Early History of AIDS

- **June 1981** - First report of pneumocystis carinii pneumonia (PCP) in 5 young gay men in LA over Oct-80 - May-81
- **July 1981** - First reports of improbable kaposi sarcoma (KS) in 26 young gay men in NY and California
- **May 1982** - Persistent generalized lymphadenopathy noted in gay men
- **June 1982** - Non-Hodgkins Lymphoma in gay men
- **September 1982** - CDC defines ‘Acquired Immune Deficiency Syndrome’ (AIDS)
- **December 1982** - first known case of AIDS through blood transfusion first mother-to-child transmission cases reported
- **1983** – isolation of HIV by Luc Montagnier at the Pasteur Institute, official name was given in 1986

1985 – first AIDS cases diagnosed in Serbia
**Discovery of HIV**

- *Patient with swollen lymph nodes*
- *Virus detected*
- *T cells from lymph nodes were cultured*
- *Virus replication*
- *Infected cells fuse and many die*
- *Viral protein reacted with antibodies from infected patients*

**Discovery of HIV in patients**

Virus production detected in T cells by reverse transcriptase activity.

![Graph showing enzyme activity over days](image)

Barré-Sinoussi i sar. Science, 1984
HIV viral particle
HIV genome
HIV-1 cellular tropism defined by receptor usage

- **R5**
- **R5X4**
- **X4**

- Dendritic, Langerhans
- Macrophage
- Activated/effector memory
- Naive
- Astrocyte

- CD4+ T

Receptors:
- **CD4**
- CCR5
- CXCR4

‘macrophage-tropic’
‘T cell tropic’
HIV-1 diversity during disease progression

- Early HIV-1 infection is characterized by a near homogenous viral population.
  - Heterogeneous population is transmitted but there is a genetic bottleneck due to the limited number of target cells that restrict the replication of most viral types.
  - Little infectious virus is normally transmitted such that descendents of a single viral population establish infection.

- The extensive heterogeneity seen in HIV-1 during disease progression is due to:
  - Rapid viral turn over ($10^{10}$ viral particles/day)
  - High rate of incorrect nucleotide substitution during reverse transcription
  - High rate of recombination among the different HIV-1 strains

This ability to generate genetic diversity allows the virus to escape host immune responses and also to develop resistance to ARVs.
HIV-1 diversity

- M (main)
  - A1, A2, B, C, D, F1, F2, G, H, J i K
- O (outlier)
- N (new, non-M non O)
- P (pending)

- 49 circulating recombinant forms (CRFs)

- Unique recombinant forms (URFs)
HIV Genetic Diversity in Env: % difference in env gene sequence

Types 1 and 2

Groups: ~50%
M, N, O and P

Clades: 15-35%
A, B, C, D, E, F, G, H, J, K

Individual strains: 5-10%

Quasispecies
HIV in Europe
http://hiv-web.lanl.gov
Where did HIV come from?

It has been shown that HIV came from a similar virus found in chimpanzees, called Simian Immunodeficiency Virus (SIV) \(^{1,2}\).

- The 'Hunter' Theory\(^3\)
- The Oral Polio Vaccine (OPV) theory\(^{4,5}\)

What Caused the Rapid Spread of HIV?

There are a number of factors that may have contributed to the sudden spread of HIV.

**International and National Travel**
- USA. Travel by young men of the late 70s and early 80s.
- Africa. Spread along truck routes and between towns and cities within the continent.

**The Blood Industry**
- Blood transfusions became a routine part of medical practice.
  - In some countries, donors were paid to give blood, a policy that often attracted those most desperate for cash; among them intravenous drug users.
  - In the late 1960's haemophiliacs also began to benefit from the blood clotting properties of Factor VIII.

**Drug Use**
- The 1970s saw an increase in the availability of heroin following the Vietnam War and other conflicts in the Middle East, which helped stimulate a growth in intravenous drug use.
- Increased availability of drugs and the development of disposable plastic syringes lead to the establishment of 'shooting galleries'.
Pathogenesis of AIDS

Direct infection of CD4 T cells, macrophages and dendritic cells

Cytopathic to infected cells

Hyperactivation of immune response: T cells and B cells

Activation induced cell death of uninfected T cells

Preferential infection and loss of HIV specific T cells

Viral persistence despite immune response: escape

Breakdown of all T cell immune responses
Pathogenesis of AIDS
Dynamics of HIV and CD4+ T ly

HIV

- PRODUCTION: $10^{10}$ virions a day
- RESERVOIR: $3 \times 10^{10}$ virions
- $\frac{1}{2}$ life: 2 hours

CD4+ T ly

- PRODUCTION: $2 \times 10^9$ cells a day
- RESERVOIR: $4 \times 10^{10}$ CD4+ cells
- 1/2 life: productive infection - 2 days
- 1/2 life: latently infected - 150 days

DESTRUCTION

- HIV: $10^{10}$ virions a day
- CD4+ T ly: $2 \times 10^9$ cells a day
HIV Reservoirs

- These are sites where the virus can reside, with little effect of anti-HIV drugs.

- The long lifespan of some reservoir cells, such as the decades-long life of memory T cells, allows them to carry HIV for many years, providing a source for new rounds of HIV infection even in the presence of effective anti-HIV therapy.

- Establishing a cure for HIV infection will thus require a strategy that eliminates HIV from these reservoirs.
HIV cellular reservoirs

The major reservoirs of HIV-infected cells include activated and resting T cells and macrophages.

- Cell-free virus has a plasma 1/2 life of about 6 hours.
- Dendritic cell-endocytosed virus has a 1/2 life of about 6-12 hours.
- Productively infected T cells have a 1/2 life of about 1 day.
- Infected macrophages have a 1/2 life of ~ 2 weeks.
- Latently-infected (integrated) central memory T cells have a 1/2 life of months/years.
Pathogenesis of HIV infection and AIDS
HIV Transmission

1. Sexual Transmission - unprotected intercourse
   - heterosexual
   - Men who have sex with men

2. Mother to Child Transmission (MTCT)
   - In utero.
   - During delivery - with or without anti-HIV therapy.
   - Post-partum - breast feeding.

3. Contaminated Blood Products
   - Intravenous drug use (IVDU).
   - Infected blood products – blood transfusion, coagulation factors.
   - Accidental Exposure - needle stick injury.
Stages of HIV infection

• 3 phases: acute, latent (asymptomatic) and symptomatic/advanced HIV disease (AIDS)

Stage I: Acute phase

- Infected via transfer of bodily fluids from HIV-infected to uninfected person
- Rapid viral replication after infection
  - Increase in HIV viral load
  - Decrease in CD4+ T-cell counts in the bloodstream
  - ~28 days post infection:
    - CD8+ CTL response reduces viral load to a lower level
- Leads to latent phase

1 – 12 weeks
Stage II: Latent (asymptomatic) phase

- Normally can last 2 – 10 years
- Due to immune system response:
  - Slight recovery of CD4+ T-cell counts
  - Occurrence of HIV-specific antibodies
  - Help maintain HIV viral load at a lower plateau
- Patient is asymptomatic but infectious
- CD4+ cells are gradually destroyed by HIV in lymphatic organs, especially in the gut
- Progressive loss of CD4+ T-cells lead to AIDS
Stage III: AIDS

- CD4+ T-cells drop to <200 cells/mm³ in the blood, leads to the onset of AIDS
- AIDS is characterized by:
  - APC dysregulation
  - Decrease in HIV-specific CD8+ CTL
  - Decrease in HIV-specific Abs
  - Sharp increase in HIV viral load
  - Susceptibility to a variety of fatal opportunistic infections

1 – 2 years
Stage III: AIDS cont’d

Some examples of fatal opportunistic pathogens:

a) Bacteria: *Mycobacterium tuberculosis*
   • Causes tuberculosis

b) Fungi: *Pneumocystis jirovecii*
   • Causes pneumonia

c) Virus: Epstein-Barr Virus (EBV)
   • Causes B-cell lymphomas

d) Virus: Human Herpesvirus-8 (HHV-8)
   • Causes Kaposi’s sarcoma
HIV transmission risk (per episode!)

- transfusion: 95%
- vertical: 15 - 30%
- needle, IV: 0.6 - 3.0%
- Homosexual contact: 0.03% - 3.0%
- Heterosexual contact: 0.03% - 0.8%
- Needle, professional: 0.3 - 0.4%
Human T cell Leukemia Virus type I (HTLV-I)

- Associated with 2 fatal human diseases
  - Adult T cell leukemia (ATL)
    - clonal malignancy of infected mature CD4+ T cells
  - Tropical spastic paraparesis/HTLV-1 associated myelopathy
    - neurodegenerative disease
HTLV I & II
Human T cell Leukemia Virus type I (HTLV-I)

- Endemic in parts of Japan, South America, Africa, and the Caribbean
  - With an estimated 10-20 million people infected worldwide

- Asymptomatic in majority of individuals with approximately 2-5% of HTLV-I carriers developing disease 20-40yrs post infection.
  - The long clinical latency and low percentage of individuals who develop leukemia suggest that T-cell transformation occurs after a series of cellular alterations and mutations.

- Infects primarily CD4+ T cells.
HTLV 1 Transmission

• Extended close contact (cell-associated virus)

• Sexual (60% male to female \textit{versus} 1% female to male transmission)

• Blood products (screening of blood supply since 1988)

• Mother to child (breast feeding: 20% children with seropositive mothers acquire virus)