Family: Retrovirus  
Genus: Lentivirus

retro = “backward” — describes the flow of information from RNA back to DNA via reverse transcriptase.

lenti = “slow” — describes the slow disease progression of the founding member of the genus, Visna virus of sheep. Actually an awful description of the virology though.

Estimation 2.1 million new infections in 2015  
Estimated 1.1 million deaths in 2015

Primate lentiviruses are widespread in African species

Old World monkeys

- SIVho
- SIVagm
- SIVcol
- SIVgum
- SIVmm

Hominids

- SIVcpz
- SIVgor

Over 45 species of African monkeys have an endemic lentivirus

Two of these have transmitted to hominids

Several different HIV-1 types infect humans

- HIV-1 type M (major) is the predominant lineage world-wide. Clades A-H.
- HIV-1 type O (other) is present in central Africa.
- HIV-1 type N (new) is rare in Cameroon.
- HIV-1 type P

> 50,000,000 cases

~ 10,000 cases

~ 50 cases

Less than 10 cases

All are independent transmissions originally from chimpanzees

But only one is responsible for the pandemic
Origins of HIV-1 groups from chimpanzee transmissions

What about this tree makes that conclusion?

Genetic Organization of Retroviruses

ALV

Gag; MA (matrix), CA (capsid), NC (nucleocapsid)

HIV-1

Pol; PR (protease), RT (reverse transcriptase), IN (integrase)

Env; SU (surface), TM (transmembrane)

Structure of the Mature HIV-1 Virus Particle

The virion surface is a lipid bilayer with protruding Env spikes.

MA (matrix) associates with the membrane. CA (capsid) forms the conical shell. NC (nucleocapsid) coats the viral RNA.

The core contains two RNA genome (single-stranded, plus sense), tRNA primers, and about 50 copies of each viral enzyme (PR, RT, and IN).
HIV entry into cells

- **Receptor is CD4**
  - Expressed on helper T cells (CD4 cells) and macrophages
- **Co-receptors are required**
  - Multiple pass membrane proteins that are normal ligands for chemokines (peptide factors that induce cell migrations)
- **CCR5**
  - Expressed on T cells and (especially memory cells) and macrophages. Induced by activation
- **CXCR4**
  - Widely expressed and constitutive

**Evidence that CCR5 is the critical co-receptor:**

There is a polymorphism in the human population in CCR5 that deletes 32 bp within the coding region present at about 10% frequency in Caucasians

\[ \Delta^{32}-\text{CCR5 polymorphism} \]

- **CCR5/CCR5**
  - Ancestral genotype
  - Heterozygotes.
  - Get infected normally
  - Progress more slowly

- **CCR5/CCR5\(\Delta^{32}\)**
  - Homozygotes for \(\Delta^{32}\text{ccr5}\)
  - Highly resistant to HIV
  - No significant side effects

**Reverse transcription**

- First jump
  - Second primer is viral RNA at polypurine tract
- Second jump
  - DNA-dependent DNA synthesis
- **Followed by formation of a fusion pore between the membranes that allows entry of viral cores into cells**
• Reverse transcriptase is very error-prone.
  • Large diversity of virus pool. Every mutation occurs every day in an HIV-infected person
  • What are the consequences of this?
• Reverse transcriptase uses both packaged RNA strands to make DNA. It is a non-prosessive enzyme that jumps from one template to another at regions of short homology.
• This leads to frequent recombination (as well as deletions and insertions)
  • Rapid fitness gains in periods of intense selection
  • Why?

Integrase (IN) covalently links viral DNA to the host chromosome

Retroviruses stably integrate their DNA into the host cell chromosome

Important consequences of integration:
1. **Persistence**: infection is not easily cleared because there is a long-lived reservoir of infected cells
2. **Latency**: integrated, but silent proviruses are not seen by the immune system

This is the key thing—why infection is chronic, why a vaccine is so difficult.
Most transcription complexes initiating at the LTR fail to elongate in the absence of the viral protein Tat.

Tat activity depends on a region called TAR in the 5’ end of the viral transcript.

Tat brings Cdk9 and CycT to the promoter via TAR to enhance phosphorylation of RNA pol II which increases elongation of the cellular transcription complex.

Rev is essential for the nuclear export of intron-containing HIV RNAs (genomic RNA and mRNA).
Protease in the HIV Life Cycle (Maturation)

Gelderblom et al., in Membrane Interactions of HIV (1992)

Basic Steps of HIV Replication

1. Attachment & receptor binding
2. Membrane fusion (entry)
3. Uncoating reverse transcription
4. Nuclear import
5. Integration
6. Transcription
7. Differential splicing
8. Nuclear export
9. Translation
10. Assembly
11. Budding
12. Maturation

Fusion inhibitors
PR inhibitors
RT inhibitors
Integration inhibitors

Fusion inhibitors
1. receptor binding
2. membrane fusion & entry
3. uncoating & reverse transcription
4. nuclear uptake
5. integration
6. transcription
7. RNA maturation
8. nuclear export
9. translation
10. assembly
11. budding
12. maturation

PR inhibitors

RT inhibitors

cART

Integration inhibitors

Things you should know about HIV replication

- Genetic organization of retroviruses
- Origins of HIV
- Replication cycle of HIV
  - early steps (entry, reverse transcription, integration)
  - regulation (tat, rev)
  - Drug targets
- Discussion paper: Why did they think there was a species-specific factor that acted against HIV?
- How did they find it (read the first paragraph of the Methods)
- How did they prove they found what they were looking for?
- Definition: pseudotype is putting the envelope of one virus on the core of another virus. This allows bypassing the normal virus receptor for something that is more widely expressed

Recent: longer acting drugs, lower toxicity, better resistance profiles, more convenient combinations