HIV
HIV origins

HIV-1 and HIV-2 result from zoonoses

SIVcpz → HIV-1

SIVsm → HIV-2
HIV-1 and HIV-2 originate from West Central and West Africa

No emergence during the slave trade

Cuts from bush meat butchering

Massive population movement and expansion of Kinshasa from 100 in 1900 to ten million today
HIV-1 groups

HIV-1 forms 4 groups based on their genetic relationship. Each group is believed to be from a separate transmission from chimpanzees or gorillas

M, N, O and P

Major, New, Outlier, P
Group M has caused the global pandemic of HIV-1. Group N has relatively few cases. Group O is epidemic in parts of Africa.

Group P in two women
Major Group M

M is split into at least 9 subtypes or CLADES; A, B, C, D, F, G, H, J, K.

There are > 50 circulating recombinant forms. Clade E is a recombinant with clade A gag and clade E envelope.
HIV-1 clade distribution

Subtypes or clades are defined on sequence alone.
Fidelity: Poor fidelity of HIV reverse transcriptase (RT). RNA polymerases, including RT do not have *proof reading* functions. HIV RT has one of the poorest fidelities of any polymerase.

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Polymerase Error Rate (per nucleotide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA</td>
<td></td>
</tr>
<tr>
<td>HIV-1</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>HTLV</td>
<td>$1 \times 10^{-5}$</td>
</tr>
<tr>
<td>Influenza A</td>
<td>$6 \times 10^{-5}$</td>
</tr>
<tr>
<td>DNA</td>
<td></td>
</tr>
<tr>
<td>Bacteriophage T4</td>
<td>$2 \times 10^{-8}$</td>
</tr>
<tr>
<td>Yeast</td>
<td>$8 \times 10^{-10}$</td>
</tr>
<tr>
<td>Human</td>
<td>$1 \times 10^{-12}$</td>
</tr>
</tbody>
</table>
Quasispecies

HIV RT introduces an average of one change per cycle of reverse transcription. *In vivo*, this means that every infected person carries a swarm of closely related viruses.
The scale of HIV variation

HIV morphology
HIV morphogenesis
Human Immunodeficiency Virus Type 1 
Composition and Morphology

HIV-1 buds

Thin-section EM

Mature HIV-1
Cryo-EM + image rec.

Envelope protein
lipid membrane

genome RNA

replication enzymes

Slide courtesy of Hans-Georg Kräusslich
L domains of retroviruses

HIV Gag

Lentiviruses:
- HIV-1 (PTAP)
- EIAV (YPxL)

Other Retroviruses:
- RSV
- MLV
- MPMV (PPxY)

HIV-1 L Domain Mutant
Formation and function of multivesicular bodies

(Raiborg et al. 2003, Curr. Opin. Cell Biol.)
(E. Conibear 2002, Mol. Cell)
ESCRT complexes and virus budding

Chen and Lamb, Virology 372: 221
Model for ESCRT-III-driven HIV-1 release
Intrinsic cellular-defense against HIV-1

- Nuclear import and integration of viral RNA, Gag and Pol proteins
- Reverse transcription
- Envelope protein
- Cytidine Deaminases
- Tetherin
- Capsid Restriction Factors
- SAMHD1
- Nuclear import and integration
- Transcription Translation
Vif 'permissive' cells: produce fully infectious virions in absence of Vif
Vif 'non-permissive' cells: produce non-infectious virions in absence of Vif

Heterokaryons: produce non-infectious virions in absence of Vif

Human cells: fully permissive to HIV-1 infection if receptors expressed
Monkey cells: strong post entry block to HIV-1 infection

Heterokaryons: strong post entry block to HIV-1 infection

Monkey Cells (COS): efficient particle production even when Vpu absent
Human cells (HeLa): poor HIV-1 particle production in absence of Vpu

Heterokaryons: poor HIV-1 particle production in absence of Vpu

Heterokaryon experiments reveal dominant antiretroviral activities
Vif (Viral infectivity factor):

- Encoded by all lentiviruses (except EIAV)

- **Required** for HIV-1 replication in all *biologically relevant targets*

- Must be expressed in the cells **producing** HIV-1

- Progeny virions have **normal morphology**

- Effects become manifest in the next **target cell**

- Dispensable in some T cell lines ("**permissive cells**")

- **Non-permissive phenotype** is **dominant** in heterokaryons
\textbf{Vif} = viral infectivity factor

\textbf{Vif-negative HIV-1:}

- Primary T cells
- Defective virions: Can enter cells, but fail to establish productive infection
- Fully infectious virions

Permissive T cell line
APOBEC3G expression explains the cell line dependence of HIV replication upon Vif
Evidence that Vif targets APOBEC3G

• APOBEC3G is **expressed** in all **non-permissive** cells (e.g. CEM-SS; primary T cells)

• APOBEC3G is **absent** from **permissive cells** (e.g. CEM)

• Ectopic expression confers **non-permissive** phenotype

• APOBEC3G has **no** effect on virion morphology

• WT HIV-1 is **insensitive** to ectopically expressed APOBEC3G
APOBEC3G attacks the nascent HIV-1 provirus

- APOBEC3G belongs to a family of **nucleic acid editing enzymes** (apolipoprotein B mRNA editing enzymes)

- APOBEC3G has **cytidine deaminase** activity for **single-stranded DNA**

- APOBEC3G targets the viral **minus-strand** reverse transcription product

- dC-to-dU mutations in the minus strand ultimately lead to **dG-to-dA** mutations in the plus strand

- **Hypermutation** renders provirus defective (eg TGG becomes a stop codon)
APOBEC3G causes a $G \rightarrow A$ mutation

Deamination of Cytosine

Cytosine $\rightarrow$ Uracil

*Thymine has CH3 here

Deamination (Apobec3g)
Vif induced proteolysis of APOBEC3G

Yu, et al.
Cell-intrinsic control of HIV-1 release:

- Anti-HIV release activity is induced by interferon α

- Activity is constitutively expressed in some cells (e.g. HeLa cells)

- Activity tethers nascent virions to cell surface, leading to re-endocytosis and degradation of virions

- Mediated by a cellular surface protein

- Counteracted by HIV-1 Vpu
HIV-1 Vpu antagonizes BST-2/tetherin
Vpu prevents re-endocytosis of virions from plasma membrane
Salient features of tetherin:

• **Broadly active** against diverse enveloped viruses

• Inserted into membrane on **both ends**

• **Dimerizes** via parallel coiled-coil

• Induced by **INFα**

• Antagonized by **HIV-1 Vpu**

• Antagonized by **SIV Nefs**

• Antagonized by some **viral Envs** (e.g. of HIV-2, Ebola)
Capsid is a critical tropism determinant in primate lentiviruses
Capsid is a critical tropism determinant in primate lentiviruses

Virus dose (log TE671 i.u.)

- HIV-1
- SIV\text{MAC}
- HIV-1(SCA) [adapted]
Capsid is targeted by TRIM5α

- **Rhesus** TRIM5α potently restricts HIV-1 but not SIV
- **Human** TRIM5α restricts N-MLV but not HIV-1

- Sensitivity determined by CA

- TRIM5α targets *incoming capsids* at early postentry step

- Triggers premature capsid *disassembly*

- Functions as an *innate immune sensor* for the CA lattice (ubiquitinates TAK1 and triggers AP-1 and NFκB signaling)
Capsid-targeted restriction factors (TRIM5)

One of a family of dozens of Tripartite Motif proteins (Poorly studied, no common themes in function)

Splice variants share a common amino-terminal domain linked to various carboxy-terminal domains
HIV tropism

HIV infects CD4⁺ cells.

These include: **T-cells**

**macrophages**

**dendritic cells**

These cells express the receptor, CD4 and coreceptors CCR5 and CXCR4.
HIV Envelope and Receptors

CD4

CCR5, CXCR4
6-helix bundle
HIV tropism

All HIV-1 strains replicate in CD4⁺ T-cells

<table>
<thead>
<tr>
<th>Virus</th>
<th>Naïve T-cells</th>
<th>Memory T-cells</th>
<th>Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>R5</td>
<td>-</td>
<td>+++</td>
<td>- to +++</td>
</tr>
<tr>
<td>X4</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
The course of HIV infection

- **Acute**
- **Asymptomatic**
- **AIDS**

The diagram illustrates the progression of HIV infection, showing the stages of primary infection, clinical latency, and opportunistic infections leading to death. The types of HIV strains are indicated: R5, X4, and R5X4.
Transmission of HIV

Main routes of transmission:
- sexual contact
- intravenous drug abusers

Vertical transmission via the placenta, at birth or via breast milk
The acute phase of replication

1. Massive replication occurs in gut lymphoid tissue.
2. CD4$^+$ CCR5$^+$ memory T-cells are main targets for infection.

From Brenchley et al. JEM 200, 749-759
Asymptomatic phase

1. Virus replication is continuous.
2. CD4 cell depletion in gut is maintained.
3. All lymphoid tissue is affected.
4. Slow decline of residual CD4$^+$ T-cells detected in blood.
5. Chronic activation of T-cells: cell death.
AIDS

---X4 variants emerge in some patients.
---R5 viruses may become more aggressive.
---CD4 T-cells decline rapidly.
---Neurological complications—severe dementias in 30% of AIDS cases
HIV immune evasion

HIV induces a strong immune response. Yet the host fails to control viral replication, which continues constantly.

HIV infects CD4+ T-cells, which orchestrate the rest of the immune system.
escape mutants
-CTLs
-neutralizing antibodies

CD4 and coreceptor binding sites on gp120 are occluded from neutralizing antibodies

vif and vpu counteract host innate inhibitory factors APOBEC3G and tetherin

Nef down-regulates MHC class I HLA-A and HLA-B (CTL targets).

HIV immune evasion

HIV can establish long-lived reservoirs
HIV pathogenesis

HIV drives a sequence of immune activation, CD4 T-cell infection and death, and more virus.

Gut leakage
Microbial translocation

immune activation

AICD
Cytopathicity

Susceptible target cells
Vaccines

The variation of HIV means that the development of a vaccine is a major challenge.

The host mounts a vigorous immune response, yet fails to ultimately contain the virus.

BUT if immunity is present at the time of transmission it could be protective or lead to control of virus replication.
The RV144 vaccine trial in Thailand

Recombinant canarypox
---engineered to express HIV-1 Gag and PR (clade B strain) and clade E envelope
---3 doses

A clade E and clade B gp120
---2 doses

16,402 low risk individuals
56 infections in the vaccine group and 76 in the placebo group

The vaccine efficacy was 31.2% (p=0.04).
Renewed hope for vaccines but immune correlates of protection are unclear

A long way to go