Rev is essential for the nuclear export of intron-containing HIV RNAs (genomic RNA and mRNA)

To make all of the different proteins from a single start site the RNA transcript is differentially spliced by cellular machinery and is inefficient

Host-encoded antiviral factors block primate lentivirus replication
**Host-encoded antiviral factors block primate lentivirus replication**

Viruses encode proteins to evade or antagonize antiviral factors

**AIDS Pathogenesis: virus and host**

**SIV is not always pathogenic in its natural hosts**

Sooty Mangabey infected with SIVsm

non pathogenic

Macaque infected with SIVmac

highly pathogenic

But becomes very pathogenic in new species

What does this tell you?

**HIV Pathogenesis**

- AIDS is a disease of the helper (CD4) T cells: especially “memory” CD4 cells.
- Destruction of the immune system leads to opportunistic infections
- The immune system is fundamentally damaged during the acute infection
- HIV is a chronic infection that is not cleared
- Latency is the key reason why virus is not cleared
Memory T cells ($T_{CM}$) Have “Stem Cell” Like Qualities

<table>
<thead>
<tr>
<th>CD45RA</th>
<th>CD45RO, CCR5 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Naïve cells</strong></td>
<td></td>
</tr>
<tr>
<td>CD62L</td>
<td>CCR-7</td>
</tr>
<tr>
<td><strong>Effector cells</strong></td>
<td></td>
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<tr>
<td>Antigen</td>
<td>CD62L</td>
</tr>
<tr>
<td><strong>Memory cells</strong></td>
<td></td>
</tr>
<tr>
<td>CD28</td>
<td>T_{EM}</td>
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</tbody>
</table>

CM = central memory
EM = effector memory

Slide from Stan Riddell, FHCRC

The more complicated picture: decline of CD4+ cells in the gut is more severe than in the blood

Immune activation is a better predictor of progression than viremia

Virus in the peripheral blood peaks early after transmission and establishes a relatively stable set point

Virus peak - acute stage $\sim 10^6$
Set point $\sim 10^4$

Several weeks 4-6 months years 0.1 log10 copies/ml/year increase

Time

The amount of virus at the set point predicts disease outcome

Infection and Depletion of Gut CCR5$^+$ CD4 T Cells

- CCR5$^+$ CD4 T cells are massively depleted from gut
- The depletion is almost complete by 3rd week of infection
**HIV Disease Course**

- Total CD4 T cell counts: Bulk of CD4 T cell depletion occurs rapidly in acute infection

**HIV Pathogenesis Model**

- During acute infection, the primary target for HIV is the memory CD4 T cell compartment
- The majority of memory CD4 T cells are mucosal
- The majority of memory CD4 T cells are lost during the acute phase
- Gut CD4 T cells do not recover after the acute phase of infection
- Why is HIV disease progressive?

Loss of specialized CD4 cells in the gut affects microbial translocation across the epithelial barrier leading to immune activation.

The integrity of the gut epithelium barrier is not restored because of the decline of CD4 cells in the mucosal layer.

*Gets worse* Does not get worse, but does not return to normal
Hypothesis: The progressive nature of AIDS is due to chronic inflammation that drives
1. Increased HIV target cell proliferation
2. Gradual depletion of effector memory T cells leading to
3. Increasingly severe immune deficiency

Differences between non-pathogenic and pathogenic primate lentiviral infections:
1. Maintenance of peripheral CD4 cells despite acute loss of gut CD4 cells
2. Stabilization of gut CD4 cell numbers
3. Low levels of immune activation

The current version of this model

In nonpathogenic infections a subset of key cells are spared from viral killing

Central memory cells are critical for T cells homeostasis

CD4 cells that secrete IL-17 are critical for integrity of epithelial barrier in the gastrointestinal tract

HIV pathogenesis is due to killing of a few key cells rather than the bulk of the T cells

Reservoirs of virus in latently infected cells prevents the elimination of HIV

The latent pool is contained within memory CD4 cells

The latent pool decays very slowly (if at all)

Intensification of cART does not decrease the latent pool
(Very) few cases of transient or sustained remission off ART suggest that a cure *may* be possible.

Latency reversal in patients and other HIV Cures are still a fantasy, but

**Some (more or less) hopeful things**

- Treatment as prevention
- The PrEP trial and circumcision trials: Prevention can work
- Long acting antivirals, broadly neutralizing antibodies
- One vaccine trials that has not been a total failure...
- 90:90:90 progress

**Things you should know about this lecture**

- Restriction factors and viral proteins as determinants of HIV adaptation to humans
- The role of virus levels, CD4 cell decline and immune activation in disease progression
- Current models of pathogenesis: consequences of central memory loss and mucosal barriers
- The problem of HIV latency for cures
- Paper for next time—How does this redefine the problem of latency in curing HIV infection? Is there any “good news” here? Is this model system relevant?
  - You don’t need to look at the math. For all of the data not shown and extended data, just take their word for it.