AOS 1: Pandemics

Global outbreaks of infectious diseases

Current major pandemics = HIV/AIDS, tuberculosis, malaria

HIV

Epidemiology

- AIDS-related deaths **decreasing** (1.7m)
    - Peaked in **early 2000s** – **before** availability of **anti-retroviral treatments** (**ART**)
      ART – not only **preventing death**, also used as a **preventative measure** to **stop transmission** (e.g. between mother → baby)
- New infections **stable (NOT decreasing)** (**37m**)
    - Peaked in **1990s** because **testing** became more available – were just discovering more people who had it (not an indication more people were getting the disease)
    - Decrease from peak globally is due to **reduction in heterosexual transmission**

Therefore to eliminate NEW HIV infections, need to do more than treat the infected.

Risk Factors

- Differs around the world
- Active homosexuals and sex workers = most at risk

Australian Statistics:

Indigenous population becoming infected **more** than non-indigenous

In both populations, **leading cause of new HIV infections = homosexual sex**

Other causes (in order, non-indigenous)

- Heterosexual sex (13%)
- Homosexual sex + injecting drug use (5%)
- Undetermined (4%)
- Injecting drug use (3%)

Increasing risk behaviour now because of **therapeutic optimism** (which is why **incidence is stable despite effective ART)**

Virology

General Information

- **Complex retrovirus** (have **primate** version too!)
    - **SIV** – closely related to HIV
      SIV SM (from Sooty Mangabey – **natural host**: infected and **healthy**) to HIV 2
      SIV CP2 (from Chimpanzee) to HIV 1O and **HIV 1M** (main one)
      *Note: the two groups are v far apart in evolutionary relationships

      We use **rhesus macaques** as models that are infected and get AIDS (infected with SIV).

Within HIV 1M, there are many different **clades** (**30%** nucleotide differences)
Significant for **vaccine generation** – different clades in different parts of the world (need to vaccinate against **dominant strain)**

- **Lentiviridae family:** Slowly cause disease
- **Small** (80-130nm)
- **Icosahedral** (capsid symmetry)
- **Envelope bound**
- **Double stranded linear + sense ssRNA (10kb)**
  Nuclear material replicated in **HOST nucleus** (after **integration**)

Although there are **2 strands** of RNA, it is STILL **SINGLE STRANDED RNA** (each strand doesn't have complementary strand – are separate)

Viroid assembled in **cytoplasm/plasma membrane**

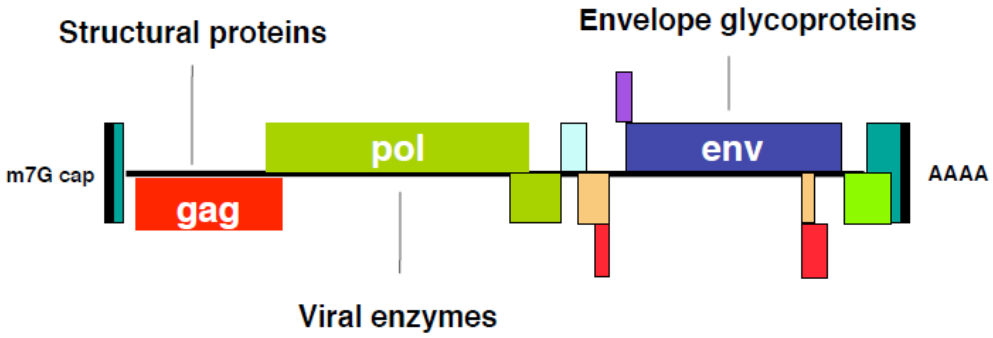
NOTE: AIDS isn't the only disease HIV causes – can also cause

- Neurologic diseases
- Arthritis
- Pneumonia

All are **slow-progression** diseases!

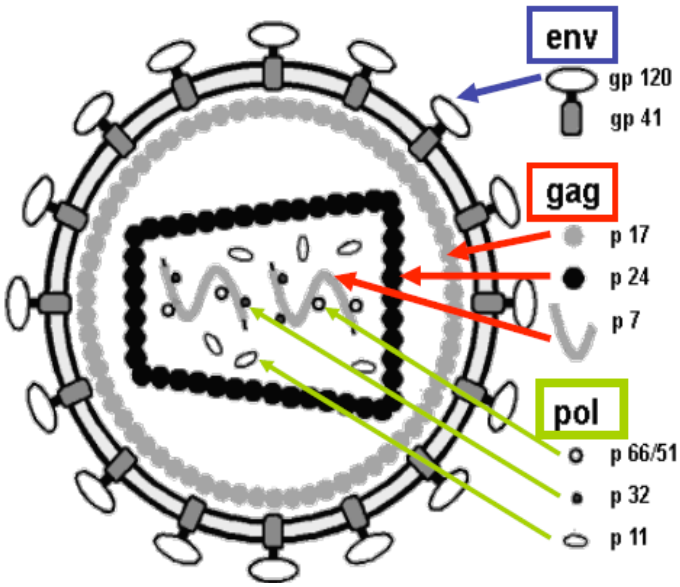
Genome Structure

All retroviruses have **common structure**



GAG: For **structural proteins** – gives **icosahedral** structure

- **P17** aka **MA**: for the **matrix**
- **P24** aka **CA:** for the **capsid**
- **P7** aka **NC:** for the **nucleocapsid**



POL: For **viral enzymes**

- **Reverse transcriptase** aka **RT** aka **p66/51**
- **Integrase** aka **IN** aka **p32**
- **Protease** aka **PR** aka **p11**

NOTE: These are **targets** for drug development!

In between POL and ENV there's a gap of **regulatory proteins** (can vary between viruses)

e.g. tat, rev, vpr, vpu, vif, nef

ENV: For **envelope glycoproteins**
– makes **gp160**, composed of 2 subunits

- **gp120** aka **SU:** Cell surface attachment – binds to **CD4 protein** on **host cell**
- **gp41** aka **TM:** Is an **anchor -** transmembrane fusion protein

Immunology

Entry to the Body

When HIV enters a person…

Hours = in **genital tract** – **first** cell it contacts = **dendritic cell**

3-4 Days = in **local lymph area** – activates **CD4+ T cells + infects them** (both activated and resting)

Get **masses** of LOCAL viral proliferation

Days-weeks = Disseminates to **lymph nodes** and lymphatic tissues

Start **detecting in blood**

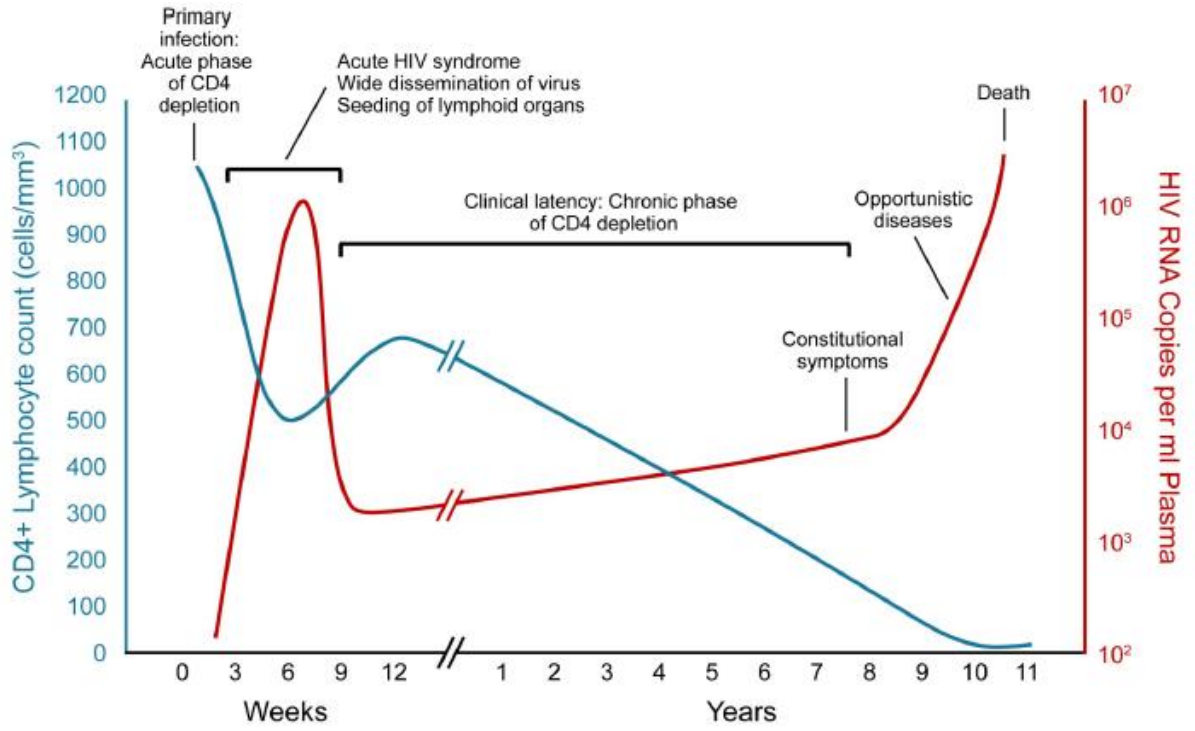
1-2 weeks = **peak plasma** virus levels + get loss of **CD4+ memory T cells**

Weeks-months-years = start **developing immune response** – get **PARTIAL** immune control
*NOTE: There is an **INITIAL ROBUST response to the virus** = partially effective immune control

Natural History/Disease Course

Red line = no. viruses in blood
Blue line = no. CD4+ T cells (count **>500 = normal)**

Note: Clinical illnesses can develop at **ANY stage of infection-**



- **<u>Primary Infection</u>** (0-10 weeks)

Initially have **acute** infection – **LOTS of CD4+ depletion** (blue line drop)

Very high **plasma viral loads** in first few months
Transmission risk increases when **viral load increases**

Peak of red = **acute** HIV syndrome – effect of the acute infection
Symptoms of **primary infection** look like **glandular fever**

Wide **dissemination** of virus, seeds lymphoid organs

*Note that viral load **drops** after this – when adaptive immune response becomes activatedch – get to stage of **clinical latency**

- **<u>Early</u>** (10 weeks-5 years), CD4+ count still **>500**

Clinical latency – viruses STILL constantly produced – just a **steady state** where virus produced = virus cleared
Because of chronic **elevated immune response** – can get **autoimmune diseases**

Initially good immune response, but **can't clear! → chronic inflammation**

- **<u>Intermediate</u>** (5-10 years), CD4+ count **between 200-500**

Towards end get **constitutional symptoms:** Fever, weight-loss diarrhoea
When CD4+ cells depleted to the point where viral load picks up again

- **<u>Advanced</u>** (>10 years), CD4+ count **<200**

When **CD4+ T cell count < 200** = **opportunistic infections/disease**

Previously, we waited until this stage to treat patient (judge by symptoms) because drugs were v toxic

Now, treat **as soon as diagnosed!**