

1 Human Immunodeficiency Virus

Family: *Retroviridae*

retro = 'backwards' (RNA to DNA by reverse transcriptase)

Genus: Lentivirus

lenti = 'slow' disease progression

Single-stranded, positive-sense RNA genome

Example Species: HIV, Simian Immunodeficiency Virus

1.1 AIDS

HIV - Human Immunodeficiency Virus

AIDS - Acquired Immunodeficiency Syndrome

AIDS results from CD4+ T cell depletion causing immunosuppression and an increase in opportunistic infections

1.1.1 The Numbers

1. 86 million people have been infected with HIV
2. 40 million people have died from HIV / AIDS
3. 38 million people currently living with HIV
4. ~ 0.7% of adults aged 15-49 are living with HIV
5. 1 in 25 adults living with HIV in the 'WHO African Region'

More new HIV infections in women than in men

1.2 HIV Virion

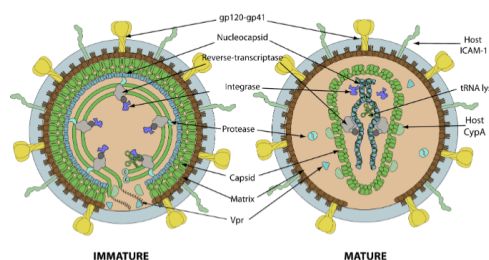


Figure 1: HIV Virion

HIV virions in their 'mature' form have a characteristic conical core structure (genome inside)

Shape of this 'core' may help in entering the nucleus through the nuclear pore

1.2.1 Mature Structure

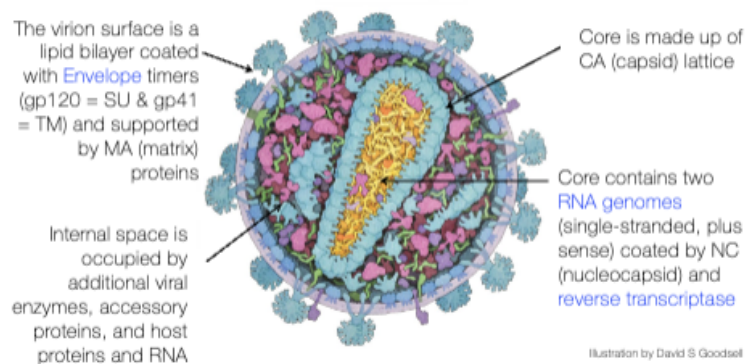


Figure 2: Mature HIV-1 virion particle

1.3 Retrovirus

Linear, single-stranded positive-sense genome of around 10kb

Host species: Humans and other primates

Transmission: Sexual contact, blood, breastfeeding

Diseases: AIDS

Retroviruses have small RNA genomes

All retroviruses use an enzyme called Reverse Transcriptase to make a DNA copy of their RNA genome

The DNA copy of the viral genome inserts itself into the host DNA genome (integration)

1.3.1 Central Dogma

Retroviruses go against the central dogma of biology (DNA → RNA → Protein)

1.4 HIV-1 Viral Genome

2 copies carried in the viral particle, each with a single strand of RNA and a few core genes + accessory genes

GAG, POL, and ENV are key genes found in all retroviruses

LTR (long Terminal Repeat) does not code for a protein, instead encoding instructions for the expression (reverse transcribing and packaging of genome)

→ Appear at ends of genome

ACC are additional ‘accessory’ genes

1.4.1 GAG, POL, and ENV [1]

Gag: Processed to form matrix protein, capsid protein, others

Pol: Processed to form reverse transcriptase, protease, integrase

Env: Processed to form gp120 (surface subunit) and gp41 (transmembrane subunit)

All retroviruses have Gag, Pol, and Env, while Lentiviruses have additional ‘accessory genes’

These proteins have specialized roles in the viral life cycle (e.g. immune evasion) and are a part of what distinguishes HIV from other retroviruses

1.5 HIV Viral Life Cycle Pt. 1

Entry: HIV infects CD4+ T cells, Macrophages, and Dendritic cells

1. gp120 (surface glycoprotein) on the virus attaches to the CD4 receptor on T cells
2. gp41 mediates membrane fusion: viral capsid and RNA genome are delivered into the cell

1.5.1 Co-Receptor

CCR5 and CXCR4 are called chemokine receptors

Trans-membrane proteins on the surface of T cells needed for the virus to fuse with cells

→ CD4 on a host cell is necessary but not sufficient to mediate viral entry

HIV envelope undergoes complicated changes in shape to mediate fusion of viral and cell membranes

CD4 is on immune cells, CCR5 is on T cells and macrophages

CXCR4 is more widely expressed

2 Origin of HIV

HIV-1 Clade M is a pandemic zoonosis

Humans have two distinct lentiviruses (HIV-1 & HIV-2)

Known from historical records, viral sequences, as well as monkey poop

HIV-1:

Group M (Major) has 12 subtypes and over 50 million cases

Groups N (non O/P), O (outlier), P (pending) have few cases

HIV-2:

2 million cases total

Groups A and B with 7 additional identified groups (1 known individual)

Less pathogenic than HIV-1 because of different origin

2.1 How Did SIV Jump to Humans?

HIV causing the global pandemic is not repeatedly spread for an animal reservoir

Likely began through chimp → human blood-blood transfer during the butchering of bushmeat

3 Timeline of HIV in the US

1. **June 1981:** MMWR report

2. **September 1982:** AIDS defined

“a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease”

3. **December 1982:** Case of AIDS after blood transfusion reported

1985: FDA instituted lifetime ban on blood donation for MSM

4. **March 1983:** CDC addresses transmission risks

‘AIDS may be caused by an infectious agent that is transmitted sexually or through exposure to blood products’

5. **January 1983:** ‘Ward86’ opens at UCSF as the first outpatient AIDS clinic

6. **June 1983:** AIDS activism begins

7. **May 1983:** HIV is discovered as the virus which causes AIDS (Nobel Prize)

January 1985: Conclusively determined that AIDS caused by HIV

1985 First public mention of AIDS by Reagan

8. **March 1987:** ACT UP (AIDS Coalition to Unleash Power) forms grassroots political group to end AIDS pandemic

9. **March 1987:** FDA approves first antiretroviral drug (Zidovudine = ‘AZT’)

10. **1992:** AIDS becomes #1 cause of death for US men aged 25-44

4 HIV Viral Lifecycle Pt. 2

4.1 Reverse Transcription and Integration

1. gp120 on the virus attaches to CD4 receptor on T cells

2. gp41 mediates membrane fusion: viral capsid and RNA genome are delivered

3. RNA genome is **reverse transcribed** into DNA and the DNA is then **integrated** into the T cell genome by integrase
4. The 'Provirus' is the integrated DNA copy of the RNA genome

Integrated virus can remain silent for a long time (**latent**)

Retroviruses stably integrate DNA into host cell chromosomes

1. Persistence: Infection is not easily cleared
2. Latency: Integrated, but silent proviruses are not seen by the immune system
3. Normal cell division increases number of infected cells (clonal expansion)

→ Reason why HIV is chronic and has no cure

4.2 Mutation Rate

Our DNA polymerases that replicate our DNA: 1 in 1 billion base pairs mutate per cell division (3 mutations per cell division)

HIV reverse transcriptase: 1 in 10,000 base pairs mutate per replication (HIV RNA genome is around 10,000 base pairs)

Approximately one mutation every time HIV replicates

Low estimate of release into blood of virions is 10 billion per day

On average every possible mutation and every possible position in the HIV genome is predicted to occur each day

Since the start of the HIV-1 group M pandemic (early 1900s), HIV sequences have massively diverged

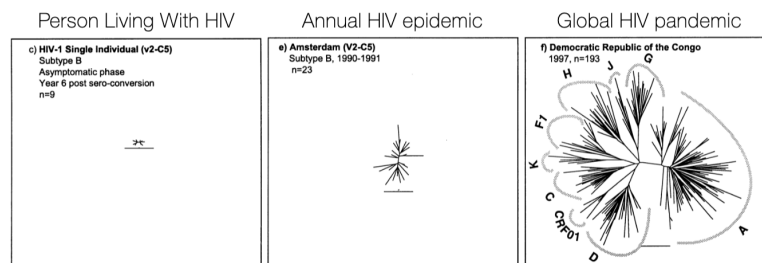


Figure 3: HIV mutation in a single individual is equivalent to that of an entire flu season

4.3 Assembly and Release

1. The integrated provirus directs the creation of new RNA viral genomes (by transcription) and new viral proteins (by translation)

2. HIV Protease cuts up a precursor protein (e.g. Pol) into smaller functional proteins (reverse transcriptase, protease, integrase)
3. New viral particles are then assembled and released from the cell to infect new cells ('budding')

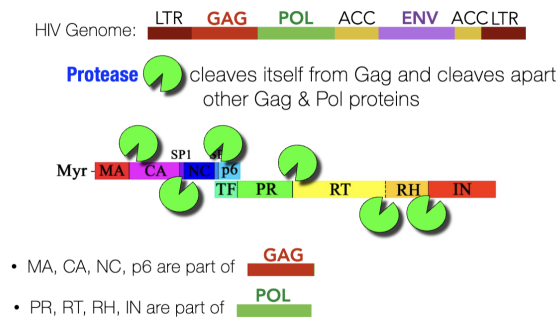


Figure 4: Protease in the HIV life Cycle (Maturation)

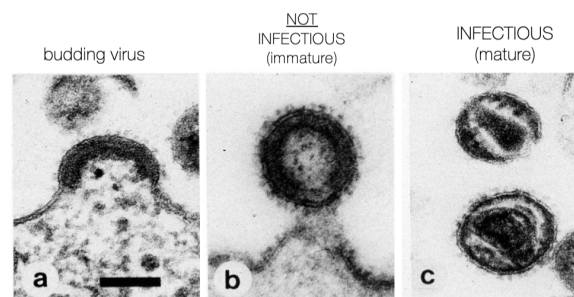


Figure 5: Mature and infectious virions

5 HIV Pathogenesis

HIV infection has 2 stages: Acute and Chronic

Acute infection:

1. flu-like symptoms (50-90% of people)
2. 2-4 weeks after infection, lasting a few days or weeks

Chronic infection:

1. Severe immunodeficiency → AIDS [item CD4 T cells are lost by direct killing by virus and immune mechanisms]

AIDS is a disease of helper CD4 T cells

Allows recruitment and activation of immune cells, helps CD8 T cells, and helps B cells make antibodies

The immune system is damaged during all infections, but in untreated people, the virus is chronic and the disease is progressive

Destruction of the immune system leads to opportunistic infections

5.1 Acute Phase

Initial peak of viremia (virus in plasma) with flu-like symptoms

5.2 Chronic Phase

Viremia is controlled and reaches a low level

Number of CD4+ T cells slowly declines as virus / immune responses kill them

CD4+ T cells reach low enough level that the immune system begins to fail

Virus replicates out of control → Further loss of immune function → opportunistic infection

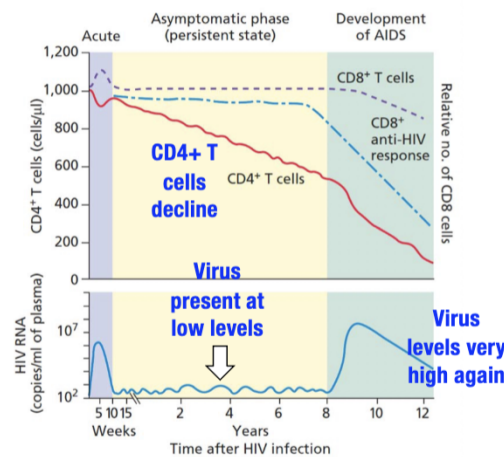


Figure 6: HIV Pathogenesis

AIDS is the result of depleted CD4+ T cells and a severely compromised adaptive immune system

→ Severe form of immunosuppression

→ TB is the leading cause of death globally among people living with HIV (opportunistic infection in PWH [People with HIV])

6 HIV Treatments

6.1 Antiretroviral Therapy (ART)

1987 AZT is the first drug to treat HIV infection (RT inhibitor)

Side effects and resistance development were major issues

Antiretroviral therapy targets multiple steps of the HIV lifecycle

1. Binding and fusion
2. Uncoating (New drug)
3. Reverse Transcriptase (AZT)
4. Integrase
5. Protease (No Maturation)

When used in combination, virus cannot as easily evolve to escape (but cannot fully cure HIV)

Known as Highly-Active Antiretroviral Therapy (HAART)

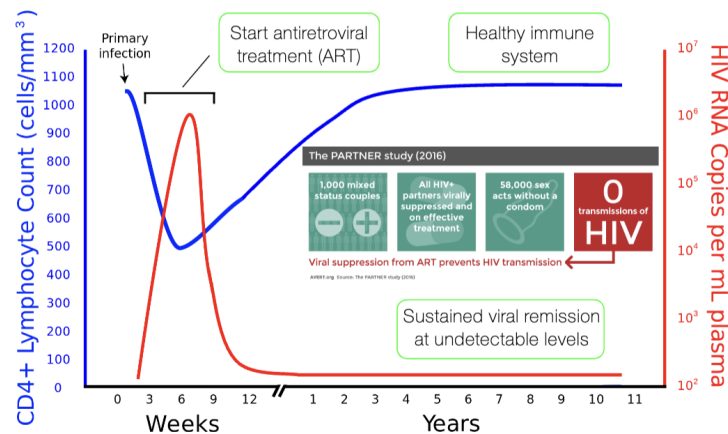


Figure 7: Treatment as prevention is more than 96% effective

Although the virus can still take over if therapies are stopped, suppressed virus cannot transmit

ART blocks viral replication, but is not a cure (can't remove integrated provirus)

Can prolong the life expectancy of PWH to near normal and can prevent transmission

→ Still have a higher risk for certain cancers / neurocognitive disorders

6.2 Current Status

Important that people know their HIV-positive **status**, are receiving **treatment**, and are virally **suppressed**

6.3 Pre-Exposure Prophylaxis (PrEP)

Can reduce chance of getting HIV from sex (99%) or injection drug use (>74%)

Requires high levels of adherence and doesn't protect against other STDs

Can be (daily) pills or shots (every 2 months)

1. Descovy or Truvada: Inhibits reverse transcriptase
2. Apretude: Integrase inhibitor
3. Lenacapivir (new): targets HIV capsid

Global access to most effective PrEP (Lenacapavir) is a major challenge

6.4 Treatment as Prevention

U = U (Undetectable = Untransmissible)

More widespread use of PrEP

UNAIDS Goals: 90:90:90 by 2025 and 95:95:95 by 2030

Better antiretroviral therapies:

1. Longer acting drugs
2. Lower toxicity
3. Better resistant profiles
4. More convenient combinations
5. Broadly neutralizing antibodies under development

6.5 HIV Cure?

Several people have been 'cured' of HIV

Why a vaccine?

1. Long-lasting protection
2. Cost-effective
3. Community immunity
4. Adherence / stigma not an issue

Why is there no HIV vaccine?

1. HIV may be hard to generate immunity to (few envelope proteins)
2. Don't know what kind of immunity should be elicited
3. HIV mutability and variability

(Very) few cases of sustained remission off ART suggest that a cure may be possible

Due to stem cell transplant (replaces immune system with that of donor)

Some people have a mutation in CCR5 gene (surface receptor) meaning HIV cannot enter cells

Hope for CRISPR gene editing?