Bioinformatics

Case Study
SIX
Human Immunodeficiency Virus

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Biology/CS/SE 123A
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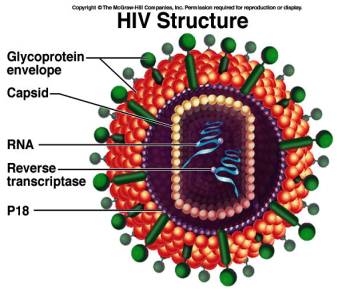
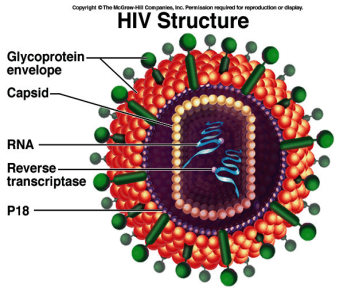
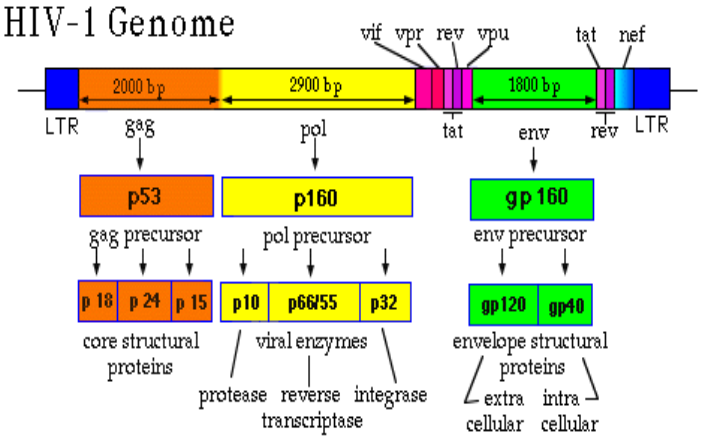
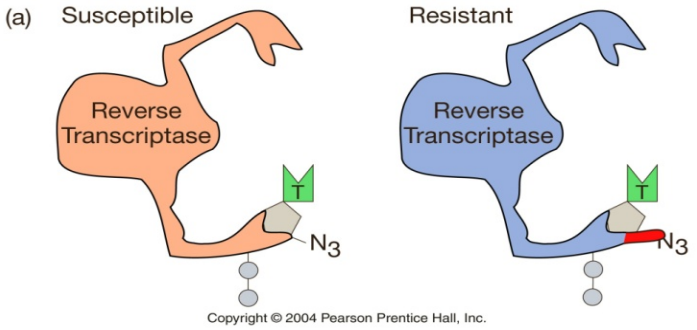




Retroviruses: HIV





- Intracellular Parasites
- gag, pol, & env genes
- HIV-1
- Immune System
- Macrophage
- T-Cells
- AIDS

What is a Virus?

Viruses: Small living particles that can infect cells and change how the cells function. Infection with a virus can cause a person to develop symptoms.

The disease and symptoms that are caused depend on the type of virus and the type of cells that are infected.

Some Terminology (I)

- **Pathogen:** patho: disease, gen: producer

  A disease producer.

  The term pathogen is commonly used to refer to infectious organisms including: bacteria, fungi, and viruses, such as HIV.
- **Virulence:** the ability of an infectious agent to produce disease. Many viruses are virulent sometimes and asymptomatic at other times.

Some Terminology (II)

Immunodeficiency: The result when the immune system fails to protect the host from disease-causing agents or from malignant cells.

Acquired immunodeficiency: is the loss of immune function and results from exposure to various agents. It is acquired because the genetic or developmental deficiency in the immune system was not present at birth.

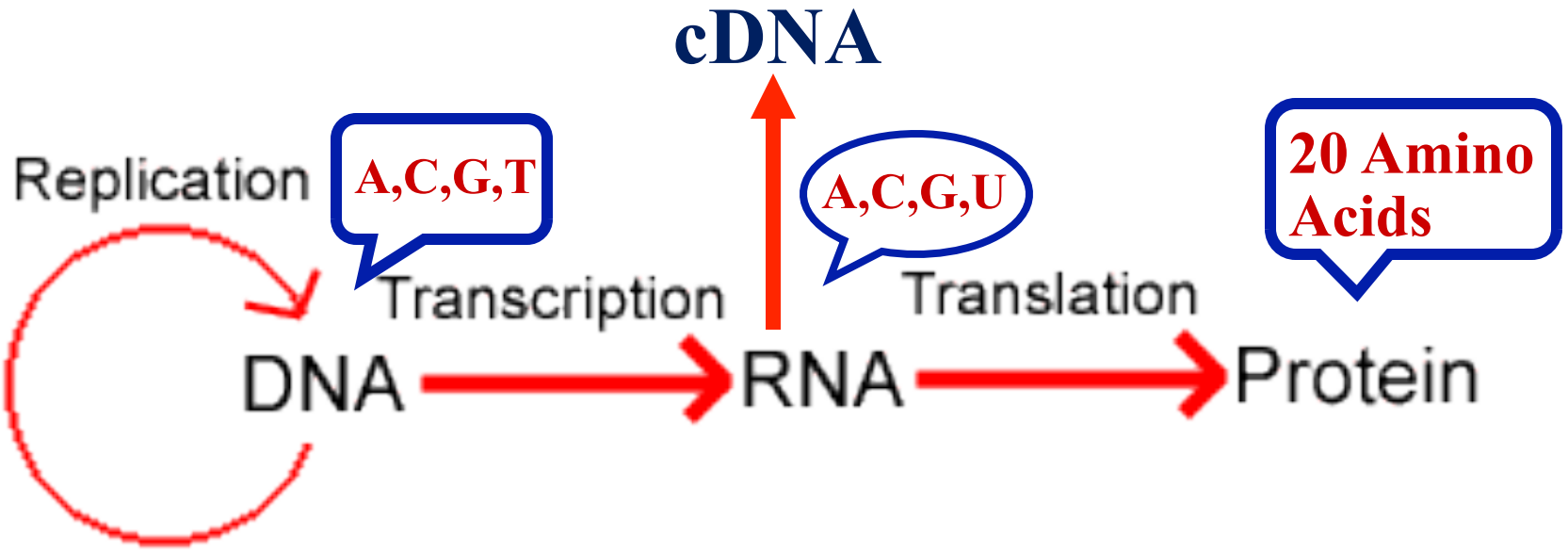
HIV Case Study

- Why have promising AIDS treatments, like drug azidothymidine (AZT) proven ineffective in the long run?
- Why does HIV kill people?
- Why are some people resistant to becoming infected or to progressing to disease once they are infected?
- Where did HIV come from?

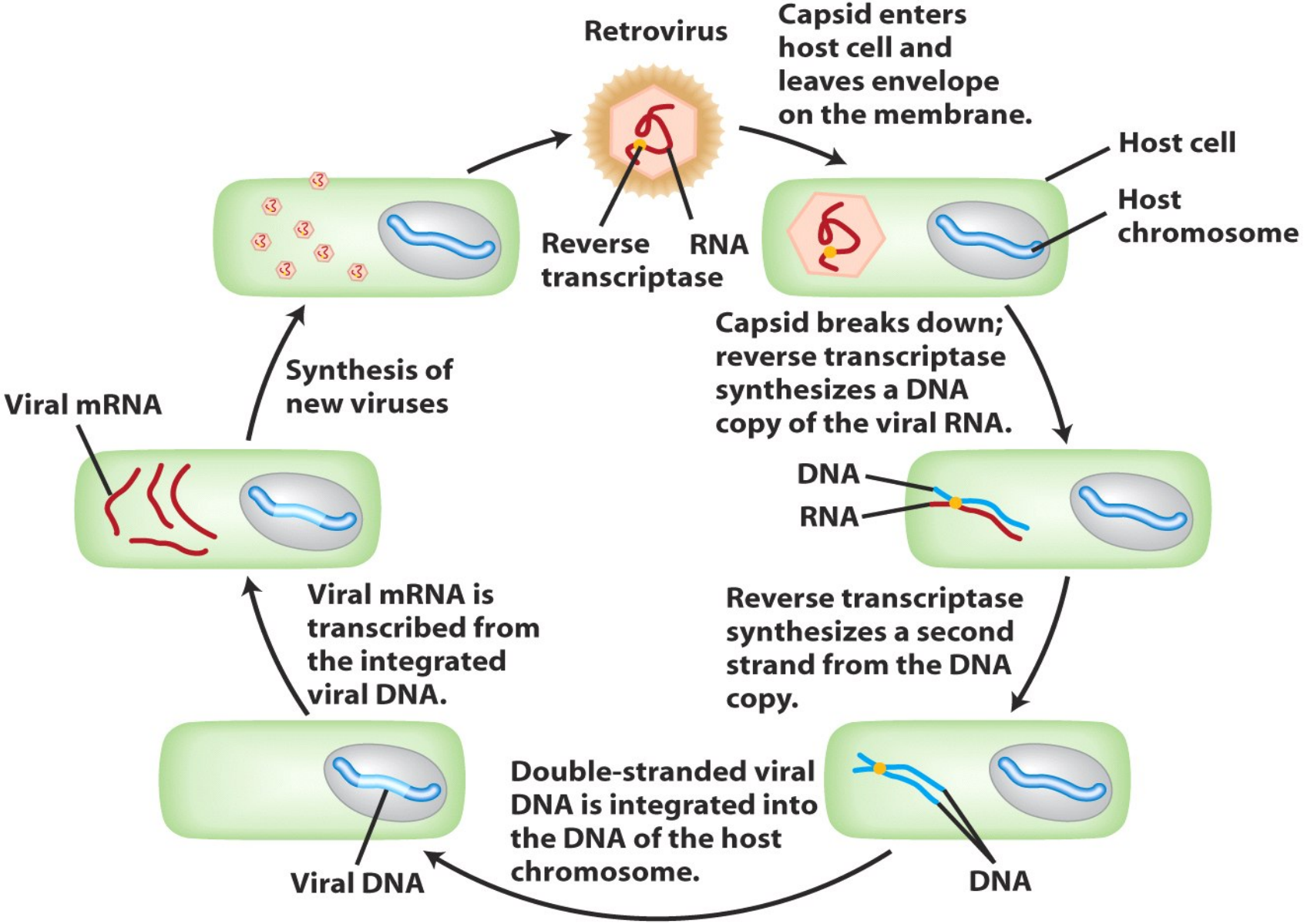
Retrovirus

- A **retrovirus** is a single-stranded RNA virus that employs a double-stranded DNA (dsDNA) intermediate for replication.
- The RNA is copied into DNA by the enzyme **reverse transcriptase.**
- The dsDNA is integrated into the host chromosomes, from which it is transcribed to produce the viral genome and proteins that form new viral particles.

Complimentary DNA



Adenine	(A)	Adenine	(A)	{A-Y}-{BJOUX}
Guanine	(G)	Guanine	(G)	
Cytosine	(C)	Cytosine	(C)	
Thymine	(T)	Uracil	(U)	


Retrovirus
Capsid enters host cell and leaves envelope on the membrane.
Host cell
Host chromosome
Reverse transcriptase
RNA
Capsid breaks down; reverse transcriptase synthesizes a DNA copy of the viral RNA.
DNA
RNA
Reverse transcriptase synthesizes a second strand from the DNA copy.
DNA
Double-stranded viral DNA is integrated into the DNA of the host chromosome.
Viral DNA
Viral mRNA is transcribed from the integrated viral DNA.
Viral mRNA
Synthesis of new viruses

HIV

- The human immunodeficiency virus (**HIV**) is the virus that causes acquired immune deficiency syndrome (**AIDS**).
- **HIV** moves from person to person when a bodily fluid containing the virus, usually blood or semen, carries the virus from an infected person directly onto a mucous membrane (membrane lining all body passages that communicate with the air) or into the bloodstream of an uninfected person.

What is HIV?

- Like all viruses, **HIV** is an intracellular parasite.
- It is incapable of an independent life and is highly specific in the cell types it afflicts.
- **HIV** parasitizes components of the human immune system: **macrophages** and **T cells**.
- **HIV** uses the enzymatic machinery and energy found in these cells to make copies of itself, killing the host cells in the process.

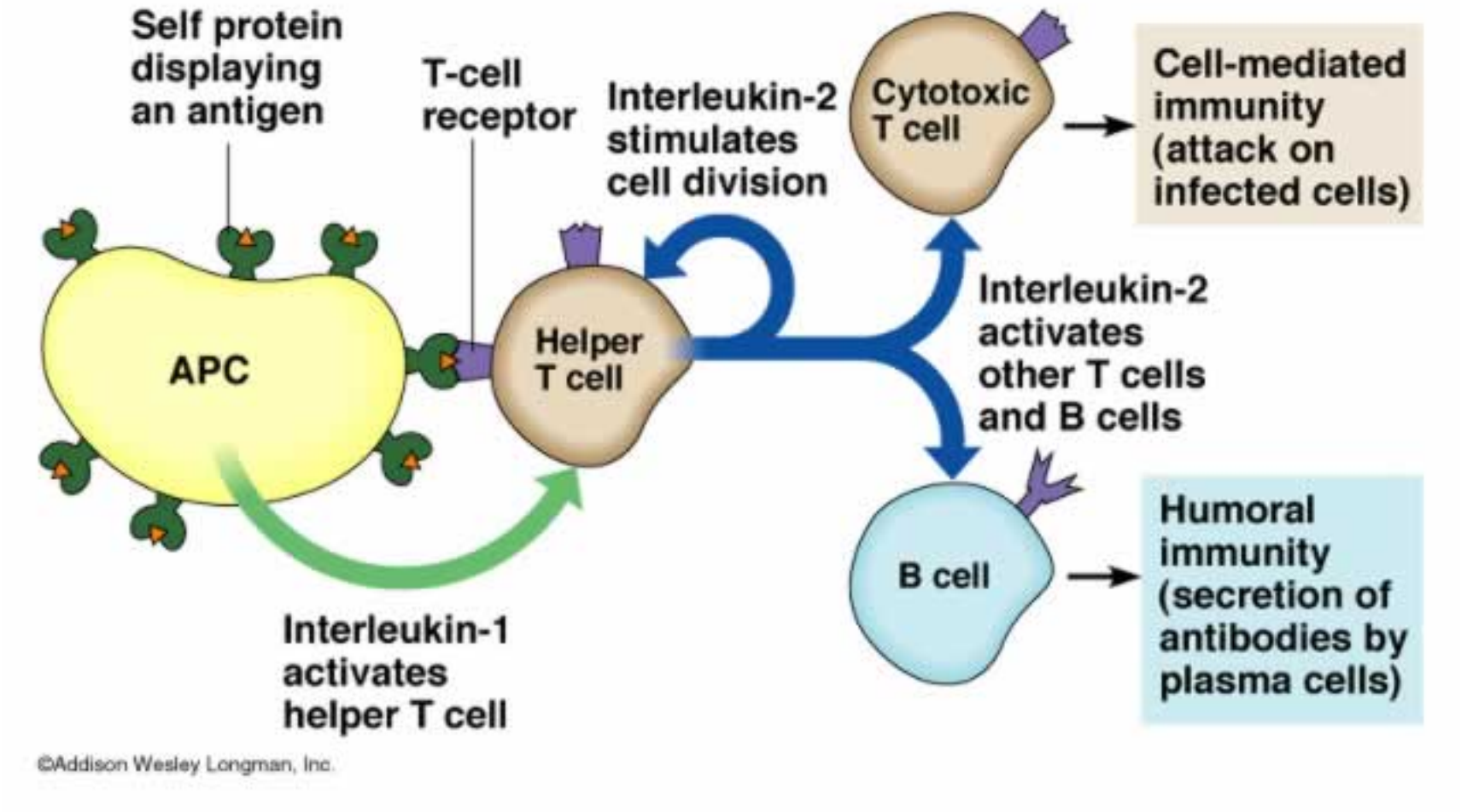
http://www.niaid.nih.gov/factsheets/howhiv.htm

HIV Transmission

- The **HIV virus** can be transmitted during heterosexual sex, homosexual sex, oral sex, needle sharing, transfusion with contaminated blood products, childbirth, and breastfeeding.
- The **HIV virus** has spread via different routes in different regions since first recognized by medical professionals in 1981.

Macrophages and T Cells

- **Macrophage** - a large immune system cell that devours invading pathogens and other intruders. Stimulates other immune system cells by presenting them with small pieces of the invaders.
- **CD4+ T cells** - white blood cells that orchestrate the immune response, signaling other cells in the immune system to perform their special functions. Also known as **T helper cells**, these cells are killed or disabled during HIV infection.


Self protein displaying an antigen
T-cell receptor
Interleukin-2 stimulates cell division
Cytotoxic T cell
Cell-mediated immunity (attack on infected cells)
APC
Helper T cell
Interleukin-2 activates other T cells and B cells
B cell
Humoral immunity (secretion of antibodies by plasma cells)
Interleukin-1 activates helper T cell
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HIV is a Lentivirus

- HIV is a retrovirus that belongs to the class of **lentiviruses:**
  - **Lentiviruses** are slow viruses. The course of infection with these viruses is characterized by a long interval between initial infection and the onset of serious symptoms.
- Other **lentiviruses** infect nonhuman species.
  - Example
    - Feline immunodeficiency virus (**FIV**) infects cats
    - Simian immunodeficiency virus (**SIV**) infects monkeys and other nonhuman primates.

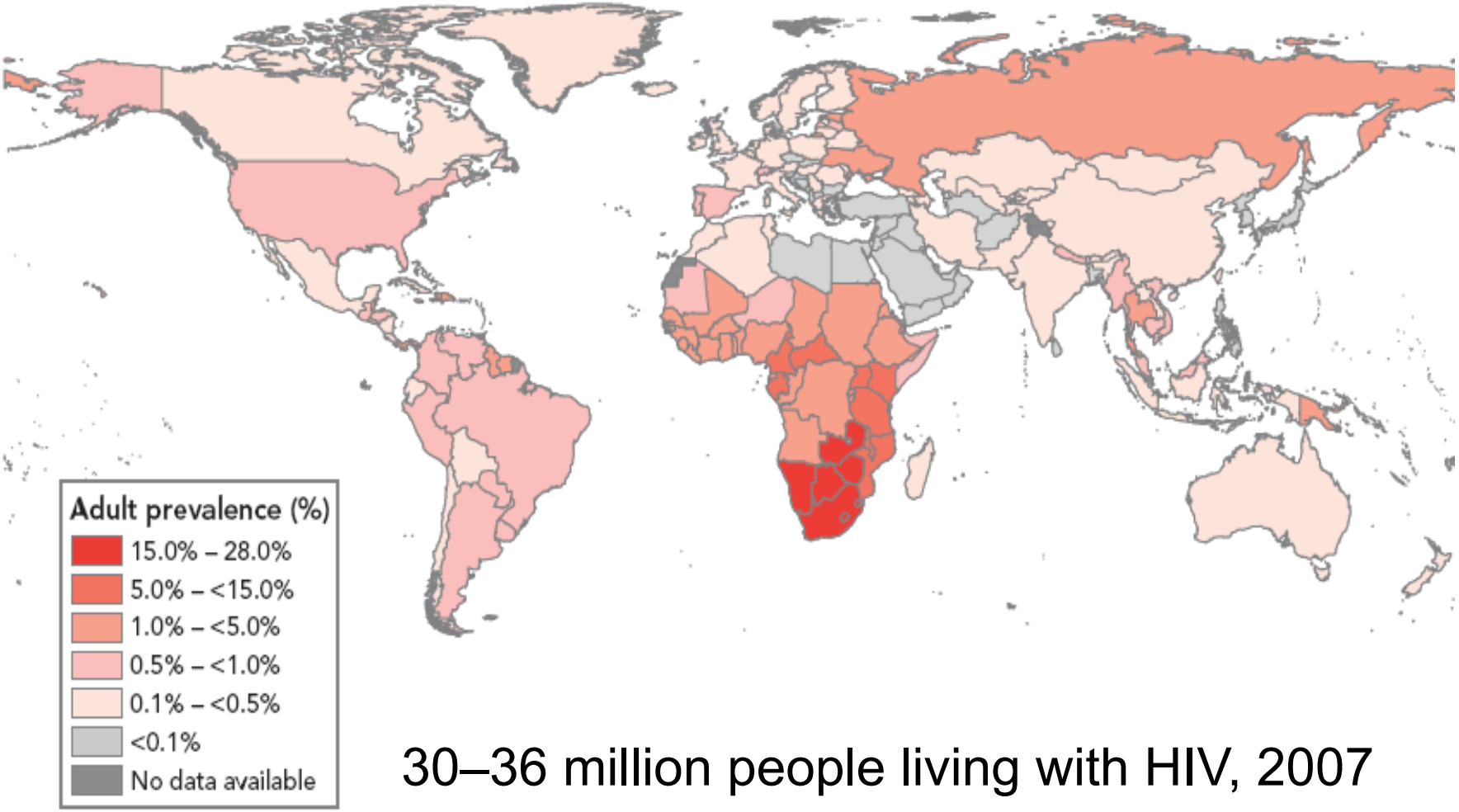
FIV and SIV

- Like **HIV** in humans, these animal viruses primarily infect immune system cells, often causing immunodeficiency and AIDS-like symptoms. These viruses and their hosts have provided researchers with useful, albeit imperfect, models of the HIV disease process in people.
- Humans inherited **HIV** from chimpanzees and mangabeys and since then, HIV has diversified and continues to do so.

How Does HIV Cause AIDS?

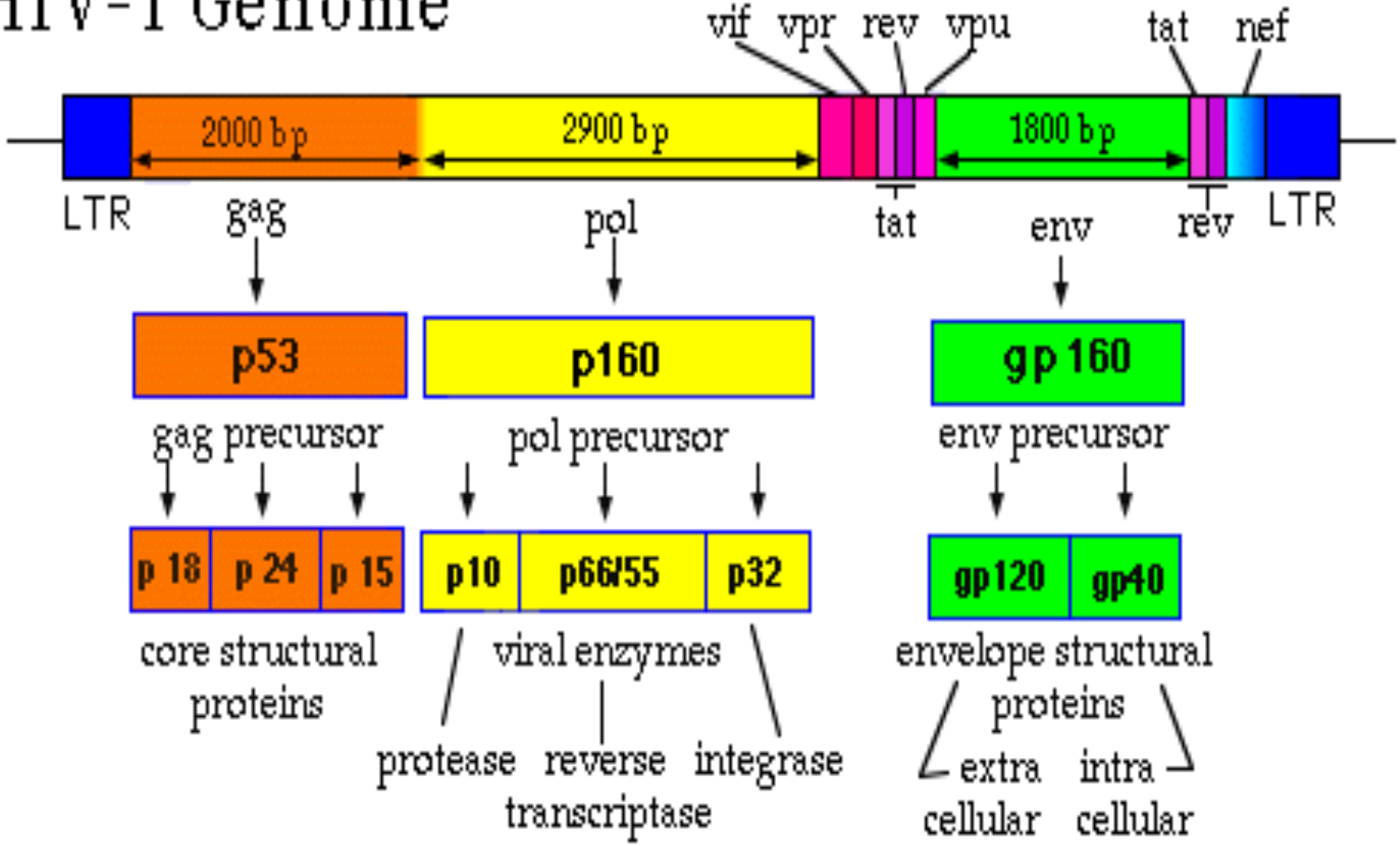
- The human body responds to HIV infection by destroying virions floating in the bloodstream and by killing its own infected cells before new virions are assembled and released.
- Ultimately, the supply of CD4 helper T cells depletes and the immune system collapses.

Geographic Distribution of HIV



30–36 million people living with HIV, 2007

HIV-1 Genome


vif
vpr
rev
vpu
tat
nef
2000 bp
2900 bp
1800 bp
LTR
gag
pol
tat
env
rev
LTR
p53
p160
gp 160
gag precursor
pol precursor
env precursor
p 18
p 24
p 15
p10
p66/55
p32
gp120
gp40
core structural proteins
viral enzymes
envelope structural proteins
protease
reverse transcriptase
integrase
extra cellular
intra cellular

Gag Pol and Env

Retroviruses encode at least three proteins that take in viral replication: the products of the **gag**, **pol**, and **env** genes.

- **gag** encodes for the core proteins, structural virion components. It plays a role in the maturation of the RNA genome.
- **pol** encodes the reverse transcriptase, the integrase, and the protease.
- **env** encodes the structural protein that surrounds the virus. This protein is necessary for the virus to leave the cell to infect other cells.

Medical Lessons from Phylogeny

- Chimpanzees are model organisms:
  - Important questions yet to be answered include:
    - How common is SIV_{cpz} in the wild?
    - How is it transmitted?
    - Why does SIV_{cpz} not make chimps ill?
- The tree is a clue as to why it has been so hard to develop an effective vaccine:
  - Many subgroups of HIV-1 exist.
  - Within a single subtype and in a single infected person, the virus also changes constantly, so a vaccine will need to protect against multiple subtypes.
  - Transmissions from chimps to humans happened repeatedly in the past and will likely continue in the future.