

Virus

Class 7

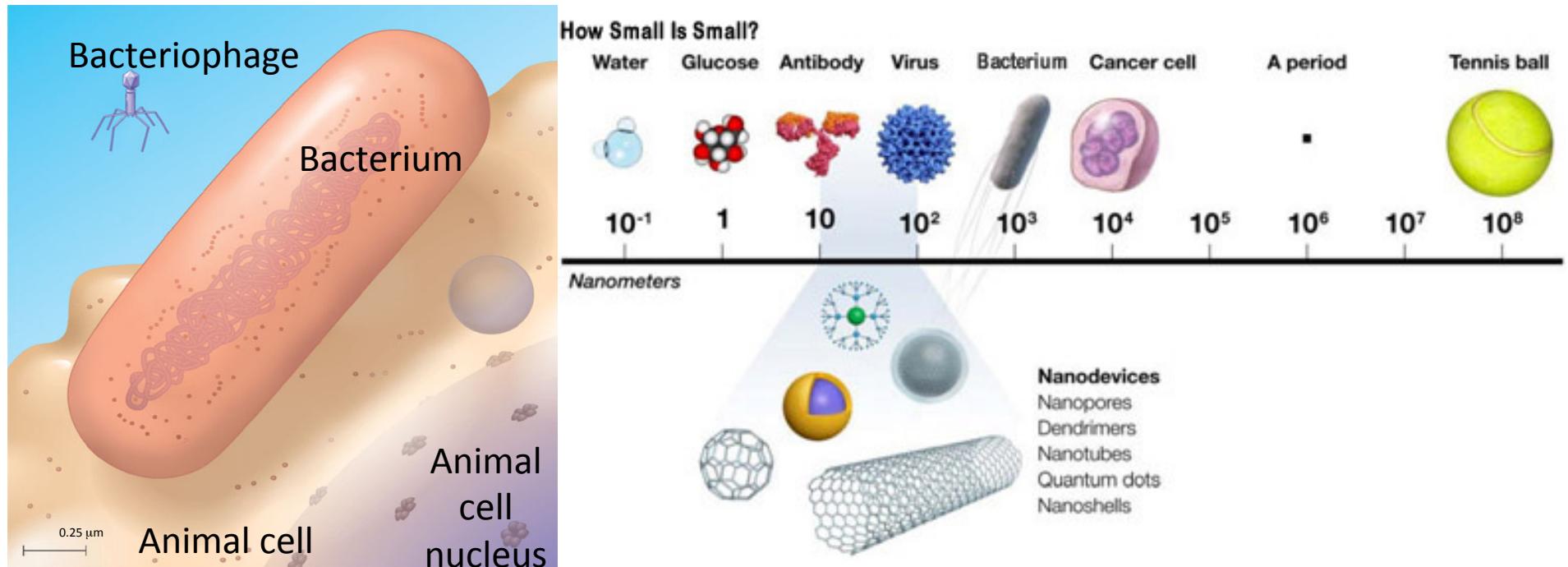
Reference: Chapters 19 (Campbell biology & slides)



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Viruses are very small

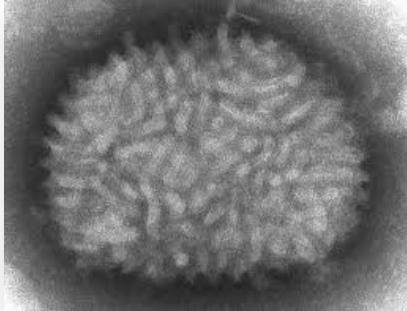
- Recall that bacteria are smaller than eukaryotes
- Viruses are smaller and simpler still



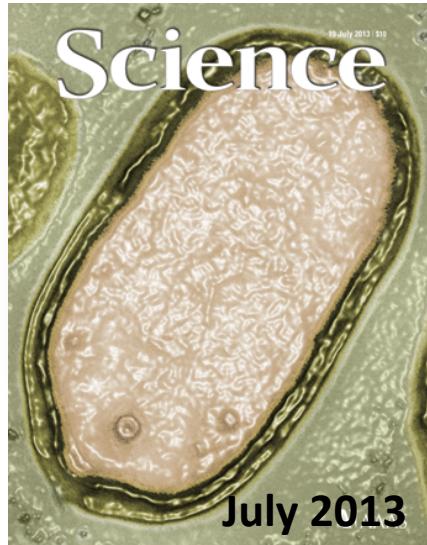
Viruses lack energy metabolism

Not all Viruses are very small!

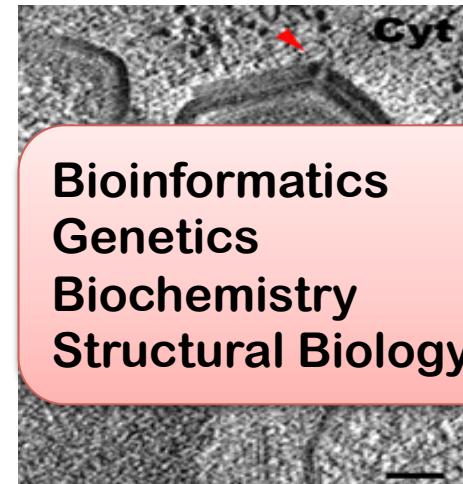
Evolution and Biology of Extremely Large DNA Viruses



Vaccinia Virus (1796)
190 kb genome



Mimivirus (2003)
1.2 Mb genome



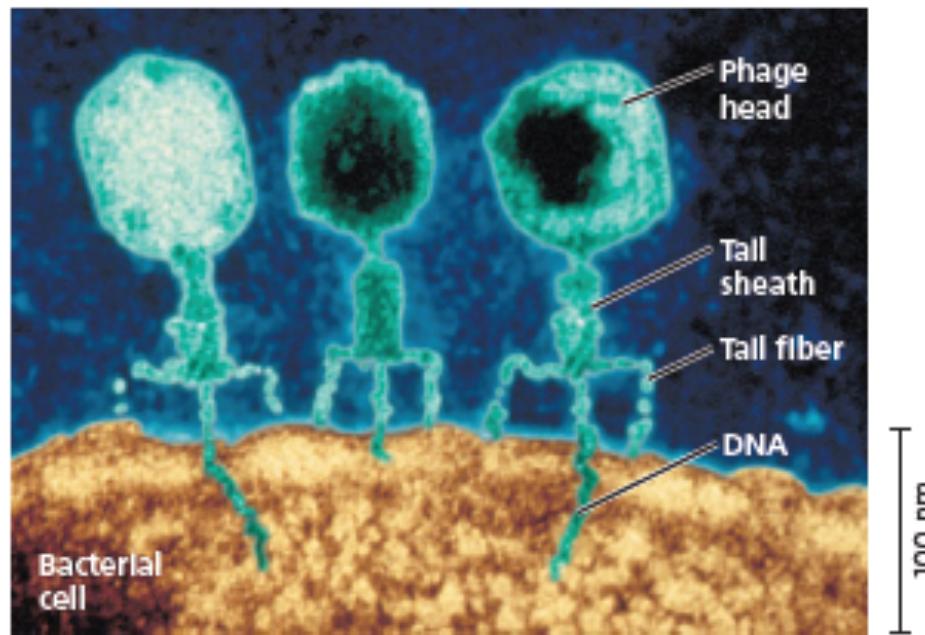
Bioinformatics
Genetics
Biochemistry
Structural Biology

Caught in the act
Mustaf et al., PLoS Pathogens
(2013), 9: e1003367

Bacteriophages

Viruses that infect bacteria are called bacteriophages

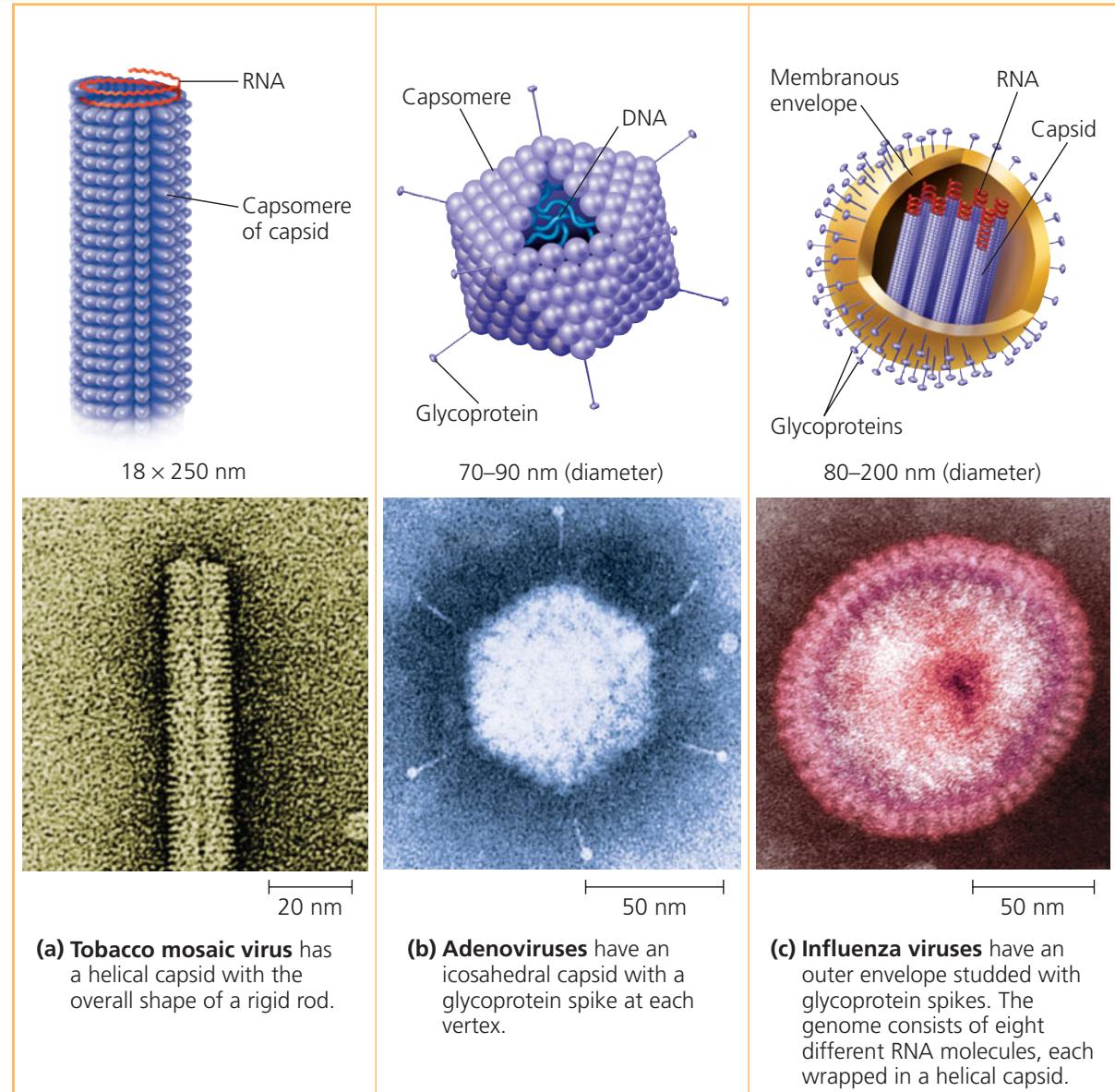
- Can infect and set in motion a genetic takeover of bacteria, such as *Escherichia coli*



Viruses infecting a bacterial cell. Phages called T2 attach to the host cell (*E.coli*) and inject their genetic material through the plasma membrane while the head and tail parts remain on the outer bacterial surface (colorized TEM).

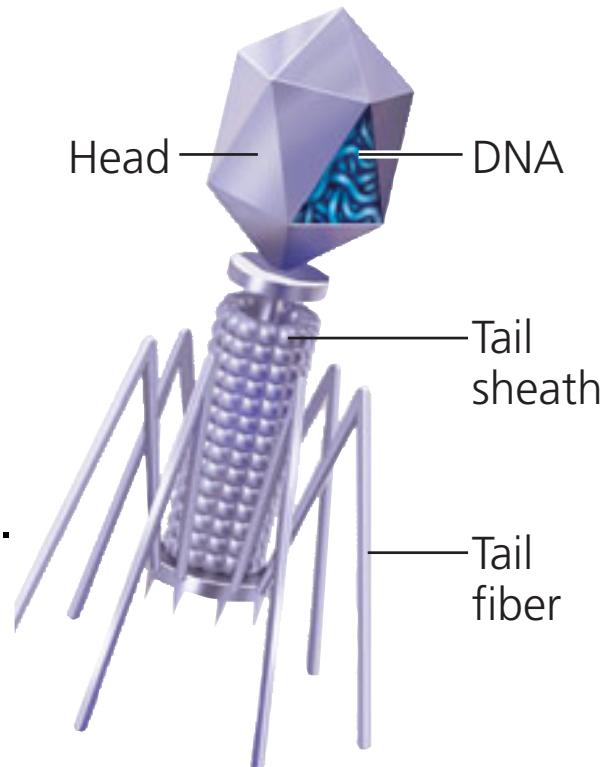
A capsid is the protein shell that encloses the viral genome can have various structures

Some viruses have envelopes
Which are membranous coverings derived from the membrane of the host cell

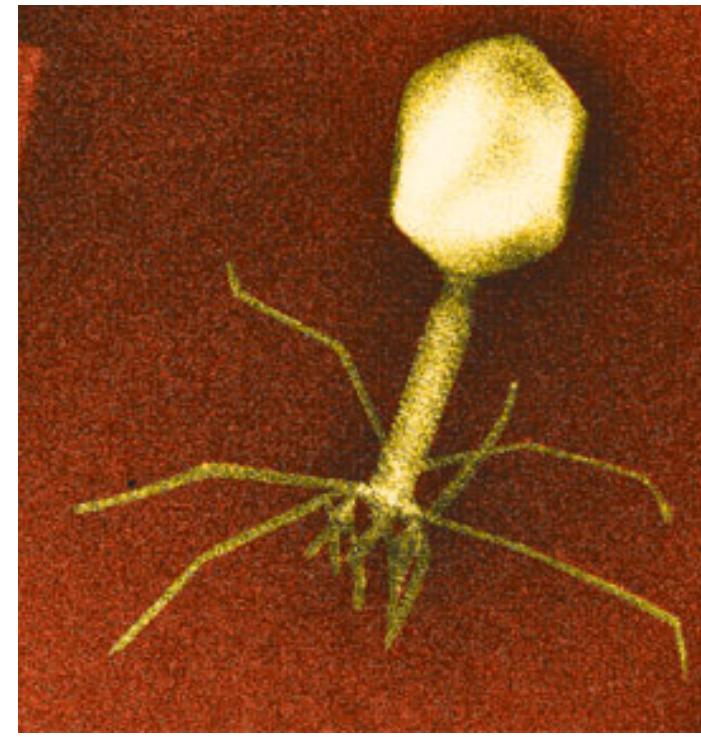


Bacteriophages have the most complex capsid structures

Bacteriophage T4.
Like other “T-even” phages, has a complex capsid consisting of an icosahedral head and a tail apparatus.



80 × 225 nm



50 nm

E. coli and its viruses (phages) are used as model systems

A micrograph of an *E. coli* cell being infected by several T4 particles

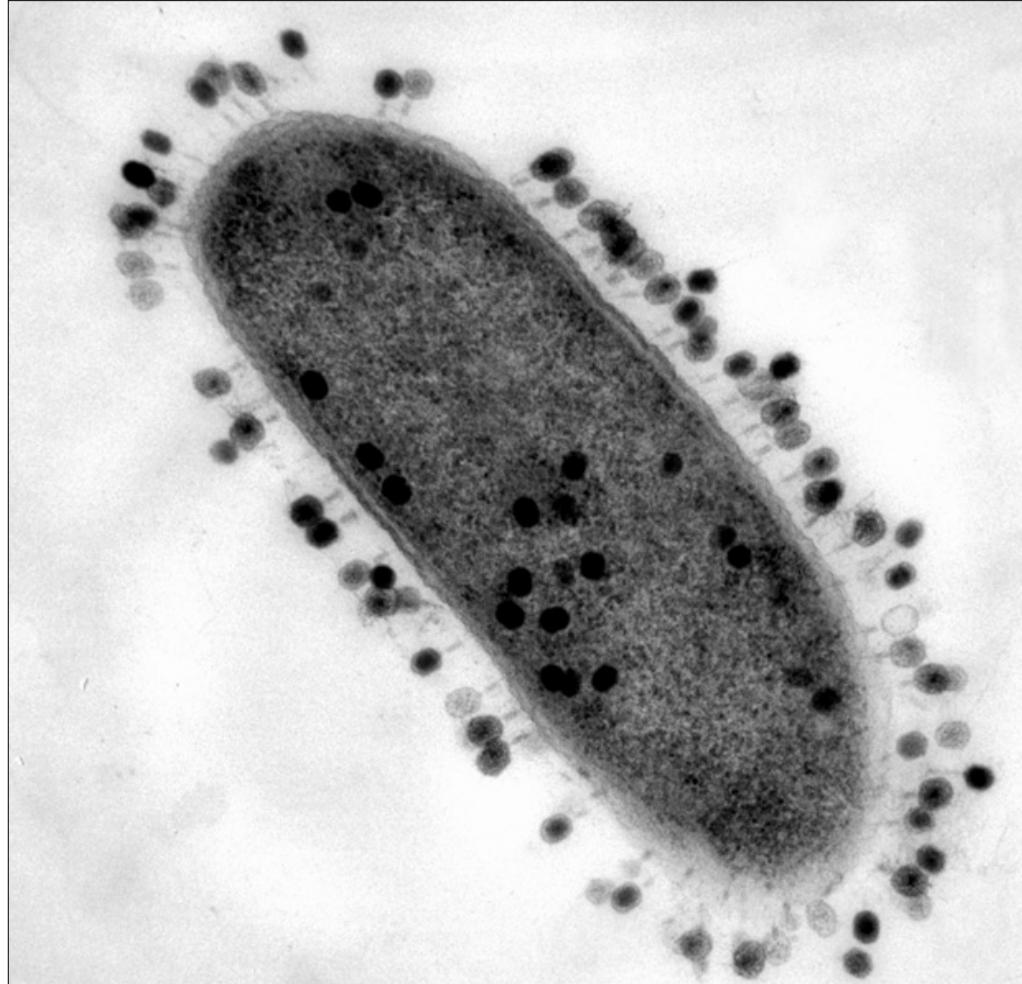
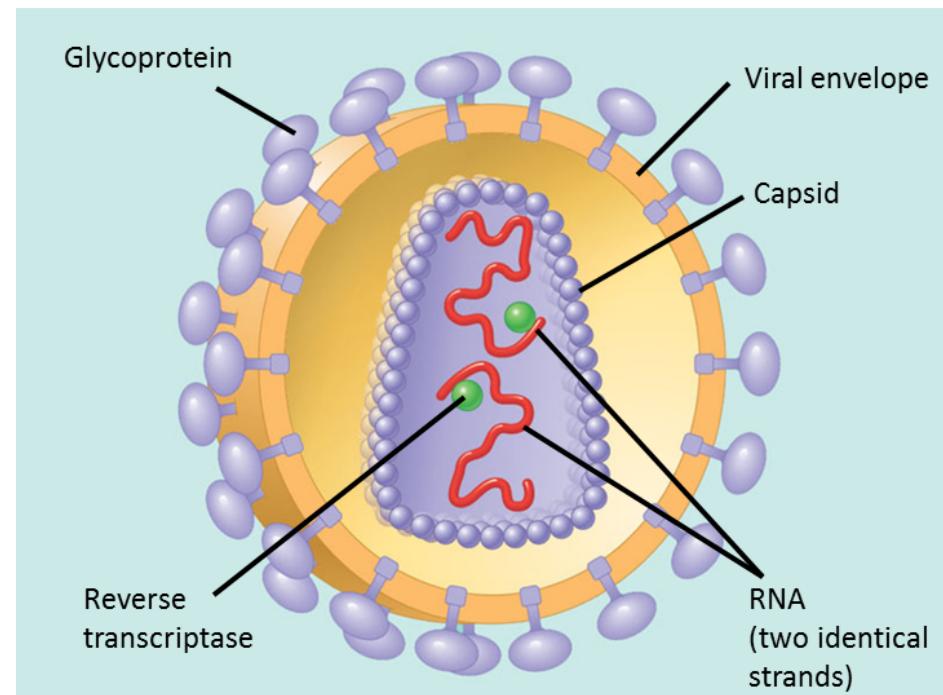


Image credit: <http://beaker.biology.washington.edu/images/research/commonsfig1.jpg>

RNA Viruses

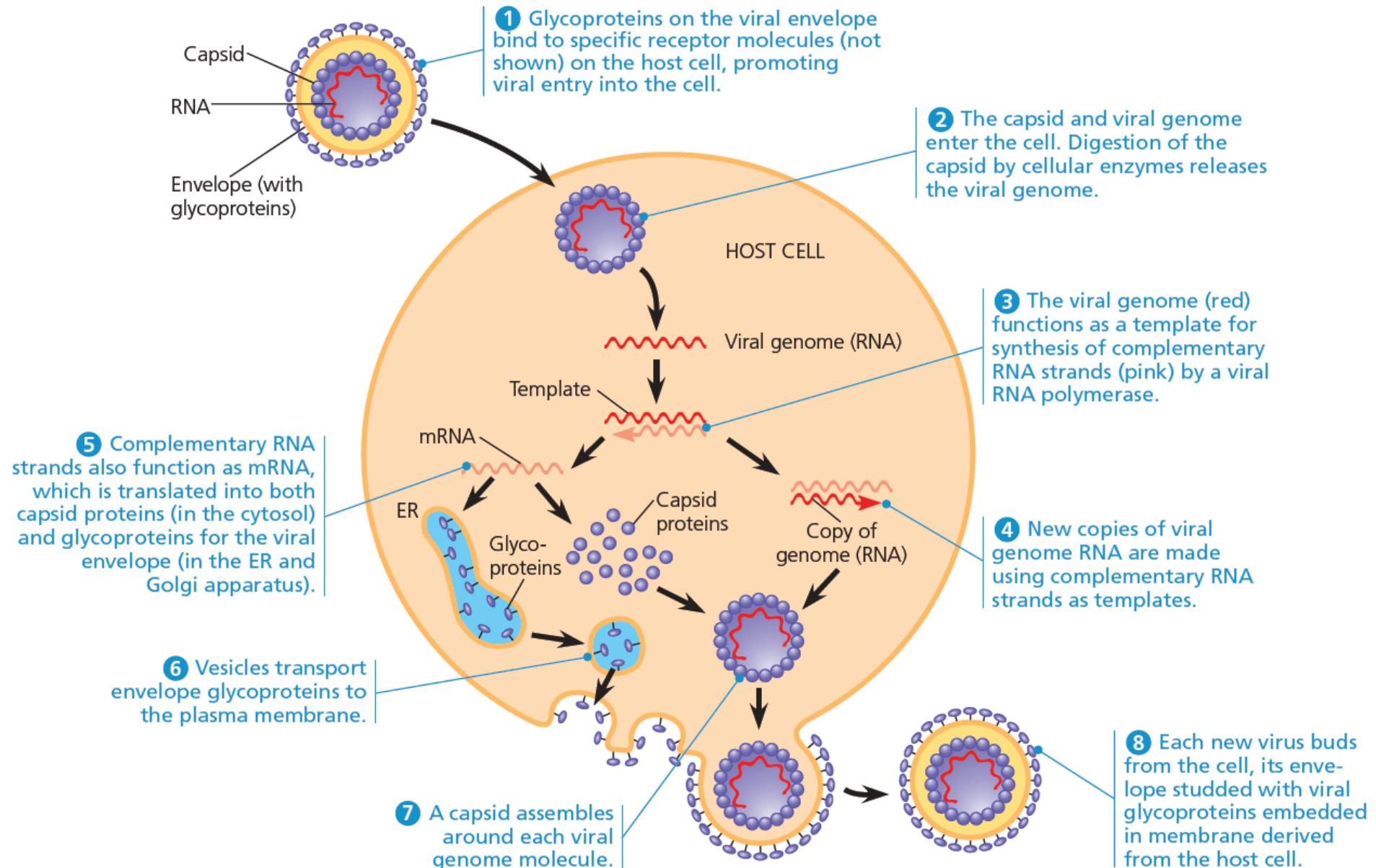
Retroviruses, such as HIV, use the enzyme called reverse transcriptase

To copy their RNA genome into DNA, which can then be integrated into the host genome as a provirus



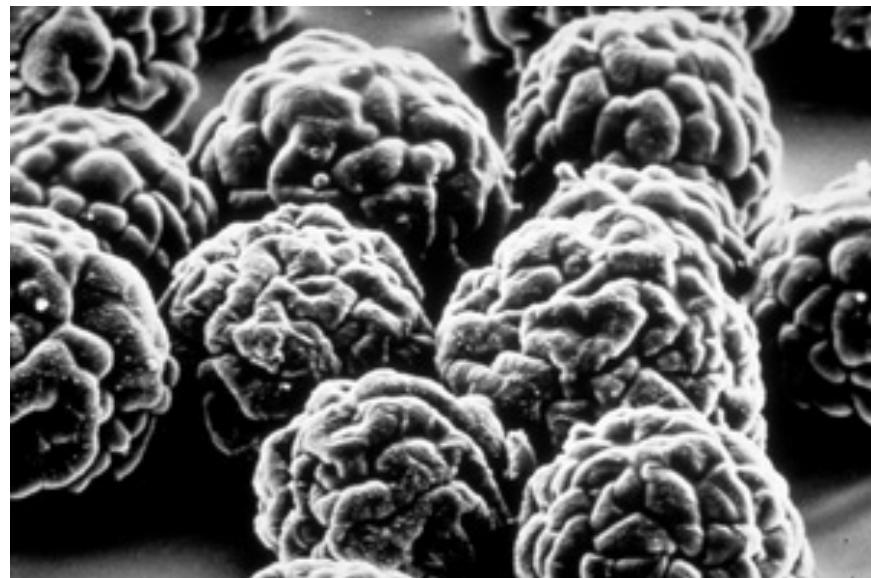
About 8 % of the human genome (240 million out of 3 billion bps) is of ancient retroviral origin (known as HERV-Human endogenous retroviruses)

The reproductive cycle of an enveloped RNA virus



Polio myelitis (infantile paralysis) is caused by poliovirus

- Poliovirus invades the nervous system, causing paralysis in one out of every 200 children
- Polio remains endemic in three countries – Afghanistan, Nigeria and Pakistan



Viral diseases in plants

More than 2,000 types of viral diseases of plants are known

Common symptoms of viral infection include

Spots on leaves and fruits, stunted growth, and damaged flowers or roots

► **Figure 19.10 Viral infection of plants.**
Infection with particular viruses causes irregular brown patches on tomatoes (left), black blotching on squash (center), and streaking in tulips due to redistribution of pigment granules (right).



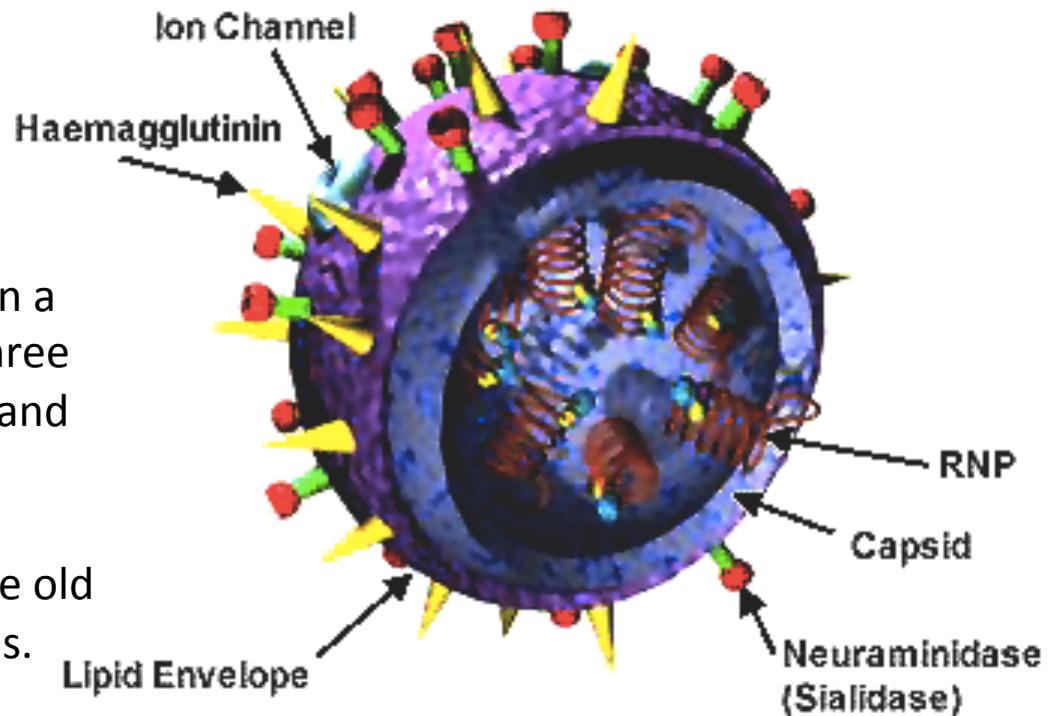
Viral diseases in Human

- Influenza virus (A, B, C): influenza
- HIV: AIDS
- Herpes simplex virus (HSV): Herpes
- Epstein bar virus: Cancer
- Respiratory syncytial virus (RSV) induced bronchiolitis
- Herpes Zoster (Varicella zoster): chicken pox
- Hepatitis B (HBV) & Hep C: Liver cirrhosis, hepatocellular carcinoma
- Several other viruses cause human diseases

Reference: info in this slide is sufficient (not available in Campbell Biology)

Influenza virus

- Influenza A, B and C
- RNA virus
- Influenza spreads around the world in a yearly outbreak, resulting in about three to five million cases of severe illness and about 2 to 5 lakhs deaths.
- Death occurs mostly in the young, the old and those with other health problems.



Source of image and text: wiki

- In the 20th century three influenza pandemics occurred: Spanish influenza in 1918, Asian influenza in 1958, and Hong Kong influenza in 1968, each resulting in more than a million deaths.
- A new type of influenza A/H1N1: pandemic in June of 2009. Larger outbreaks known as pandemics are less frequent.

Reference: info in this slide is sufficient (not available in Campbell Biology)

How influenza virus causes epidemic or pandemic?

- **Influenza:** At one time single virus type responsible for the most cases of influenza
- **Mechanism: Antigen variation**
 - **Antigenic drift:** epidemic resulting from this type is relatively mild
 - **Antigenic shift:** major changes in the viral envelop protein: Higher mortality

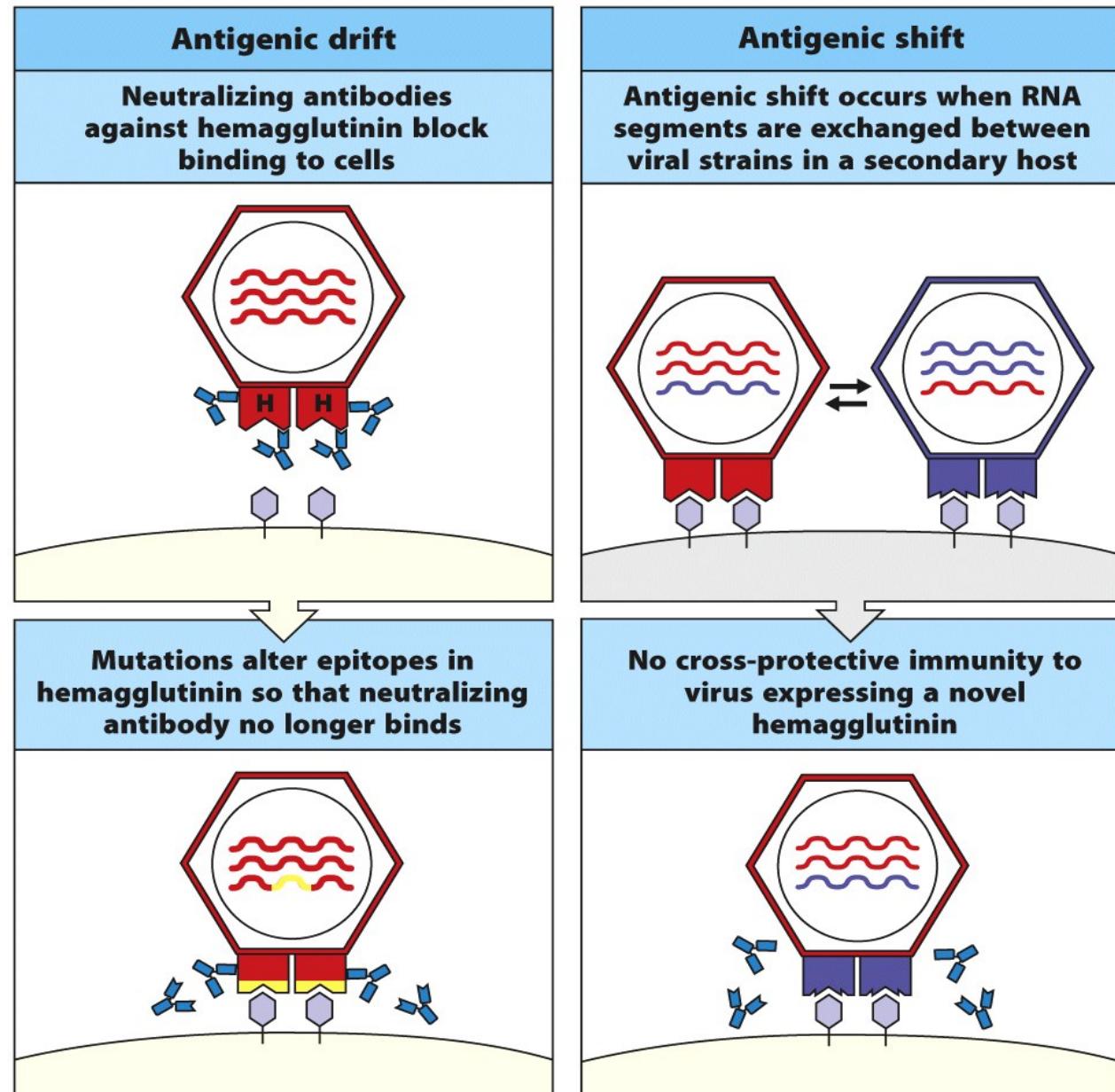
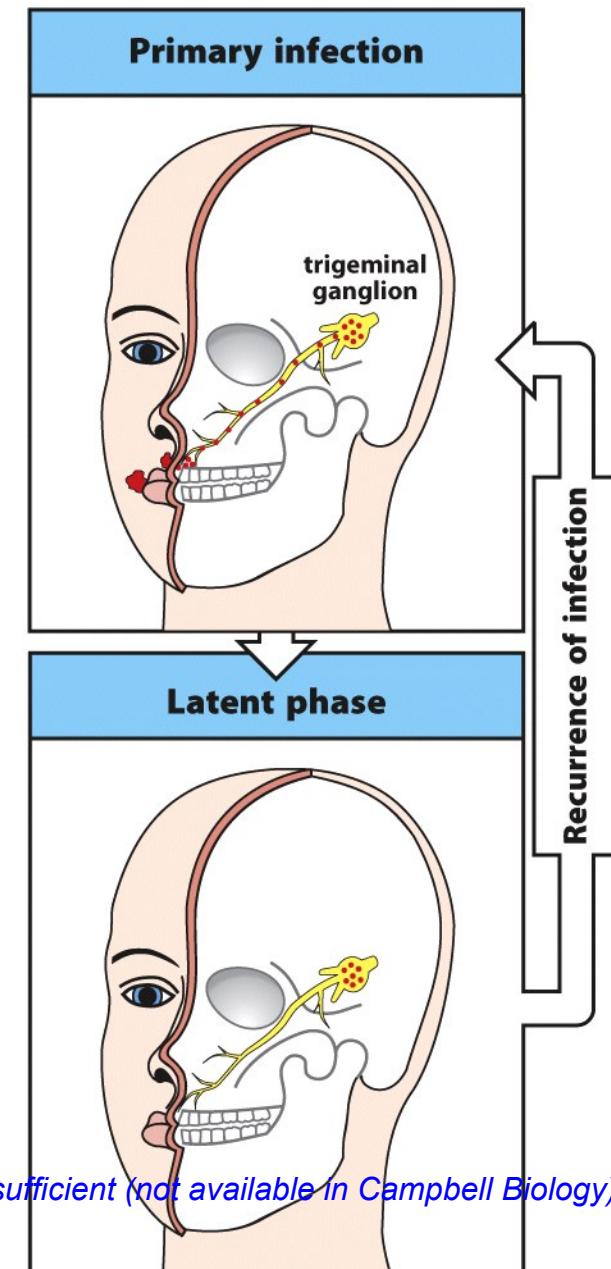


Figure 13.2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Reference: info in this slide is sufficient (not available in Campbell Biology)

How Herpes virus hides in human and cause Herpes?

- After entering to host cells, few viruses undergo **latency** (**metabolically inactive state**)
- Major class of virus: **Herpesviruses**
 - **Herpes simplex virus (HSV):**
 - cold sores,
 - infects epithelial cells and spreads to sensory neuron (latent phase) serving the infected area
 - Factors such as sunlight, infection, hormonal changes reactivate the virus, which travels down to axons of the sensory neuron and reinfects the epithelial cells
 - Cycle repeats many times
 - “Why sensory neurons for latent phase”



Reference: info in this slide is sufficient (not available in Campbell Biology)

How virus cause cancer & chicken pox?

Herpes Zoster (Varicella zoster, HZ)

- Chicken pox
- remains in latent phase in one or few dorsal root ganglion
- reactivate by stress or immuno-suppression, travels down the nerve and re-infects the skin to cause shingles (varicella rash).
- reinfection occur only once

Epstein bar virus (EBV):

- most of us infected with EBV
- Latent stage: infects memory B cells
- B cell lymphoma (cancer)

These viruses (Herpes virusis: HSV, HZ, and EBV) persist *in vivo* by ceasing to replicate until immunity wanes.

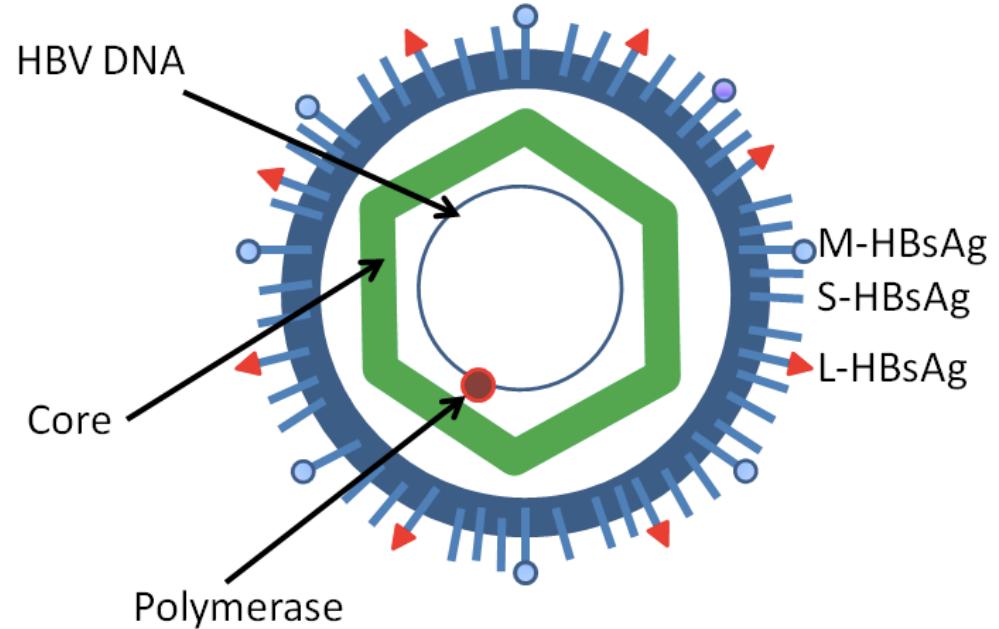
Reference: info in this slide is sufficient (not available in Campbell Biology)

How Hepatitis virus cause Liver damage?

Hepatitis B (HBV) & Hep C:

Liver cirrhosis, hepatocellular carcinoma

- Both set-up chronic infection in the liver
- Suppresses immune system by inappropriate immune cell activation (T cells)
- No proofreading activity in RNA polymerase of the virus: large antigenicity



Reference: info in this slide is sufficient (not available in Campbell Biology)

HIV: Introduction & How it infects human?

- Belongs to group of retrovirus: lentivirus
- Two copies of RNA genome
- Numerous copies of essential enzymes
- Enters cells by envelop proteins:
 - Gp120: binds to CD4 and CCR5/ CXCR4
 - Gp41: helps in fusion with PM
 - Fusion inhibitors:T20
 - How HIV escape the host immune response: “escape mutants”
 - After acute phase, HIV mutates rapidly, gives rise to many variants in a single infection
- infects immune cells (CD4 T cells, dendritic cells, and macrophages)

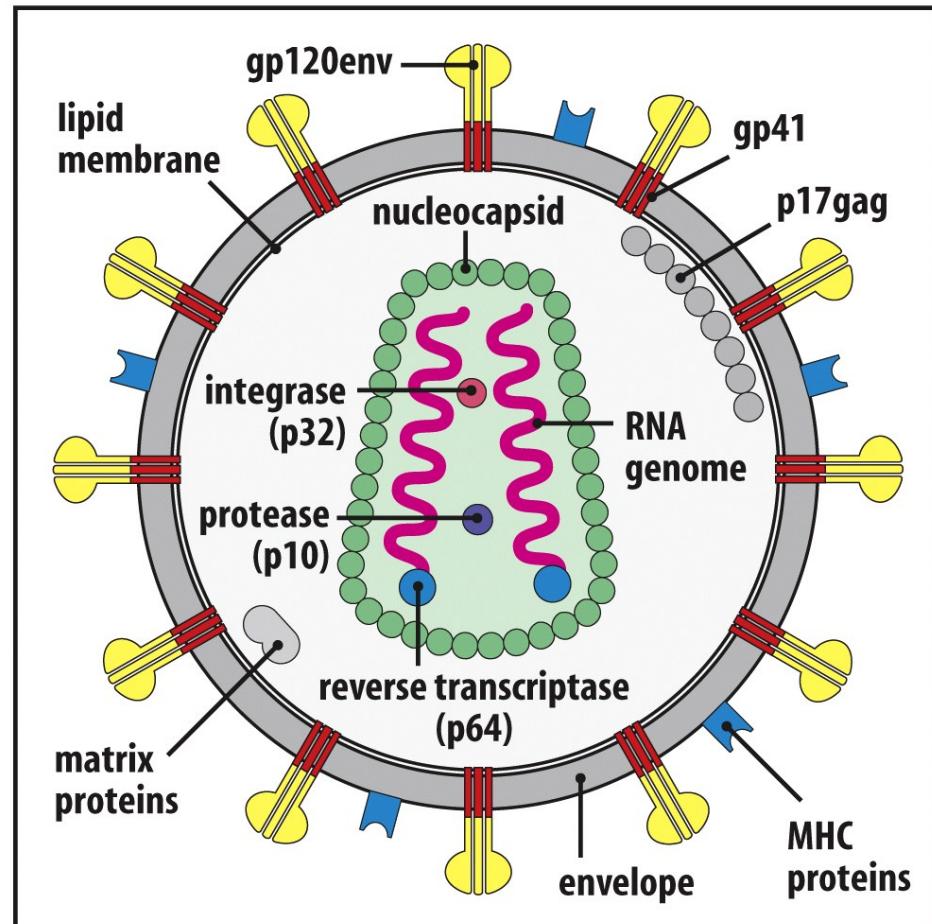
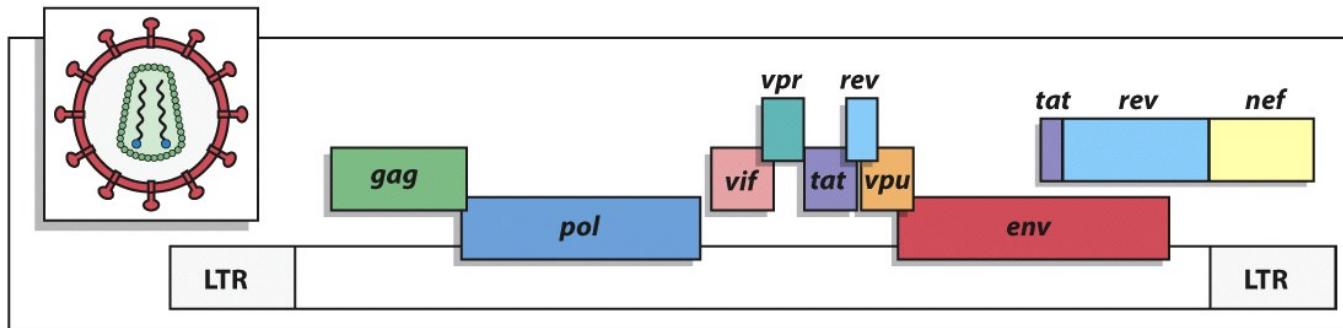


Figure 13.22 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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Genomic organization of HIV



Gene	Gene product/function	
gag	Group-specific antigen	Core proteins and matrix proteins
pol	Polymerase	Reverse transcriptase, protease, and integrase enzymes
env	Envelope	Transmembrane glycoproteins. gp120 binds CD4 and CCR5; gp41 is required for virus fusion and internalization
tat	Transactivator	Positive regulator of transcription
rev	Regulator of viral expression	Allows export of unspliced and partially spliced transcripts from nucleus
vif	Viral infectivity	Affects particle infectivity
vpr	Viral protein R	Transport of DNA to nucleus. Augments virion production. Cell-cycle arrest
vpu	Viral protein U	Promotes intracellular degradation of CD4 and enhances release of virus from cell membrane
nef	Negative-regulation factor	Augments viral replication <i>in vivo</i> and <i>in vitro</i> . Decreases CD4, MHC class I and II expression

Figure 13.26 Janeway's Immunobiology, 8ed. (© Garland Science 2012) Reference: info in this slide is sufficient (not available in Campbell Biology)

Life cycle of virus

HIV RNA is transcribed by viral reverse transcriptase into DNA that integrates into the host-cell genome.

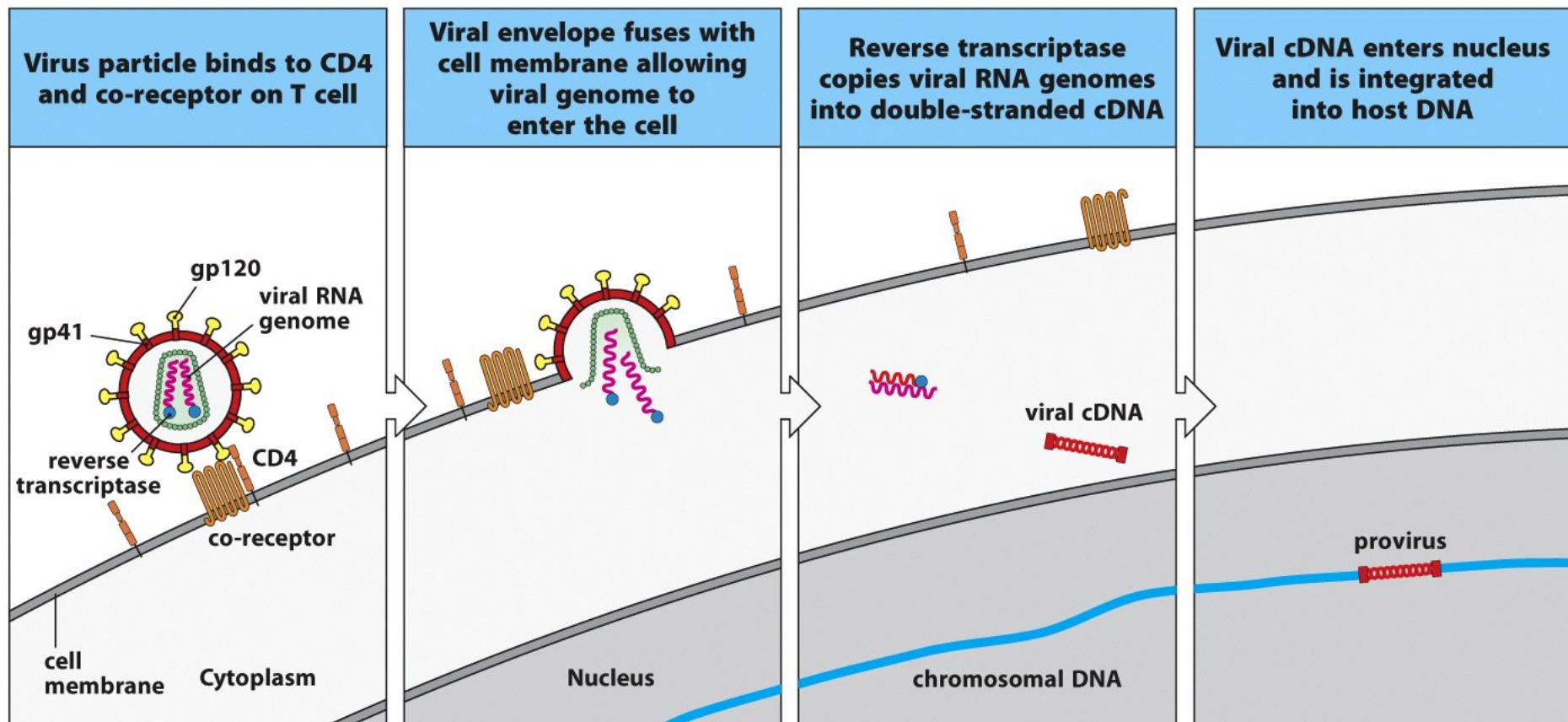


Figure 13.25 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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Life cycle of virus

HIV RNA is transcribed by viral reverse transcriptase into DNA that integrates into the host-cell genome.

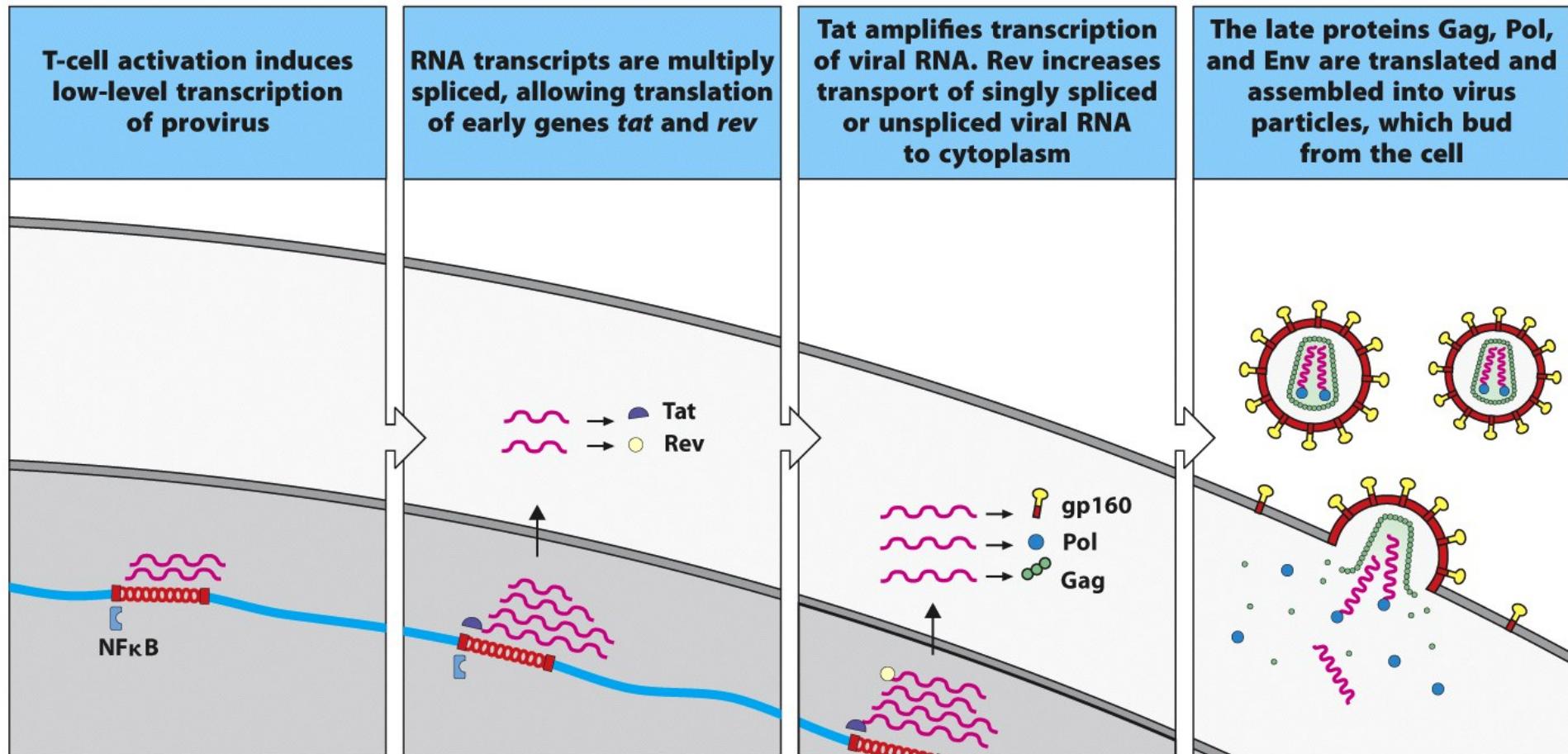


Figure 13.25 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Reference: info in this slide is sufficient (not available in Campbell Biology)

Route of HIV infection and disease progression after HIV entry

- HIV spread by transfer of body fluids (blood, mucosal fluid): pregnant mother to her baby
- HIV (retrovirus) mainly infect cells that express CD4 (receptor) along with CCR5/CXCR4 (co-receptor): “cellular tropism”
- Free virus: blood, semen ,vaginal fluid, mother’s milk
- Primary infection site?:
- Unlike other viral infection, HIV infection seems rarely to lead to an protective immune response
- Initial acute infection is somewhat controlled, but HIV continues to replicate

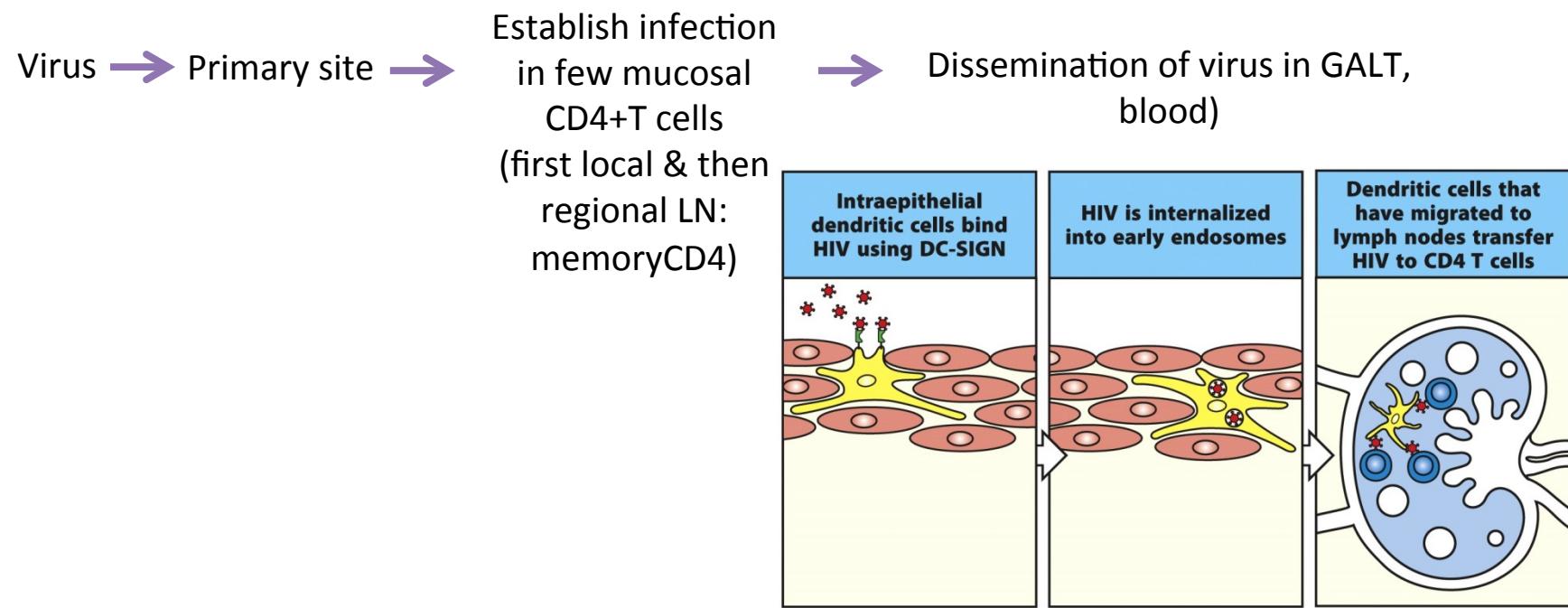


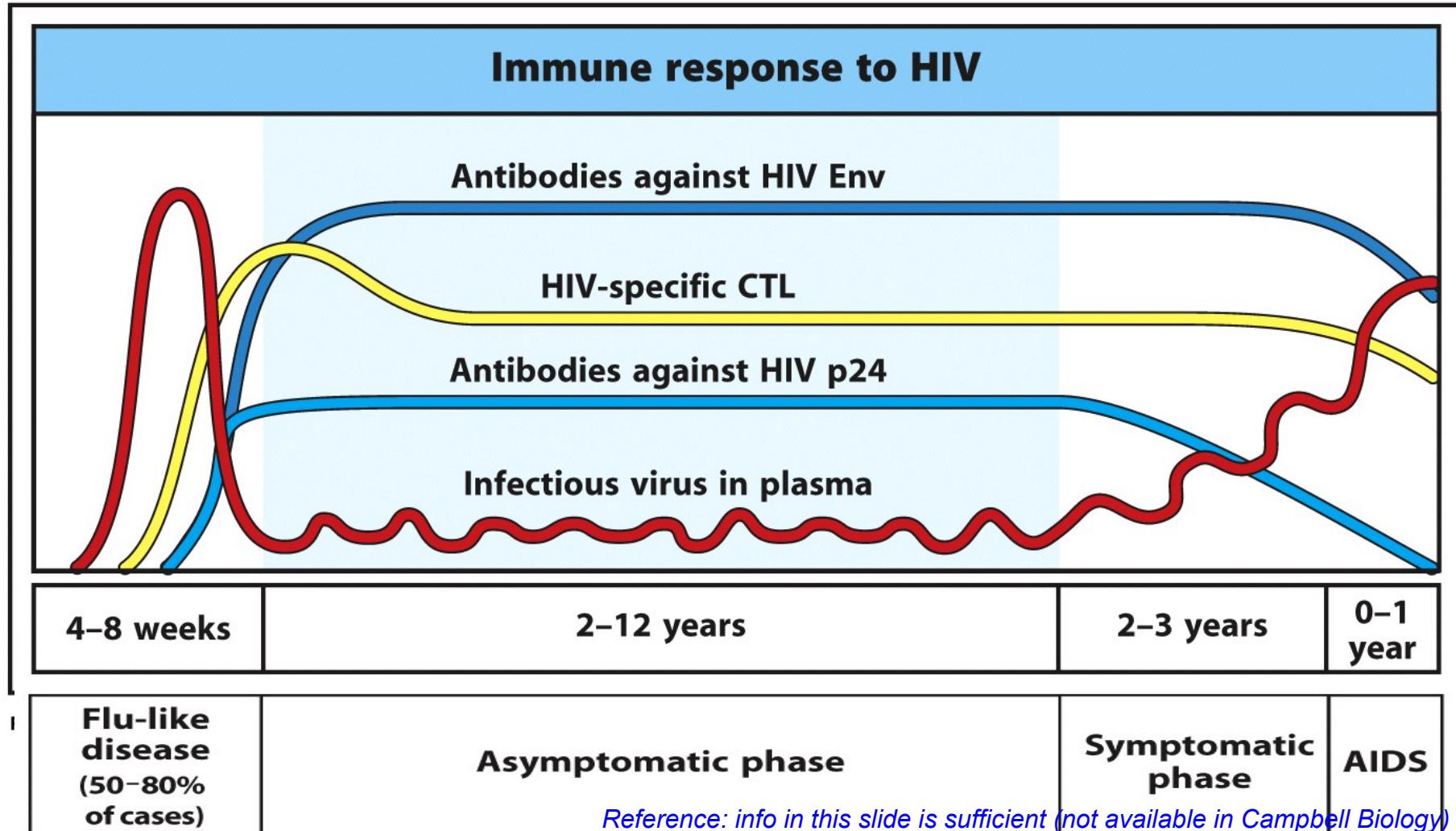
Figure 13.23 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Reference: info in this slide is sufficient (not available in Campbell Biology)

Most individuals infected with HIV progress over time to AIDS.

Course of infection

- Immune system unable to eliminate virus



How HIV causes AIDS

Mechanisms of CD4+T cell killing

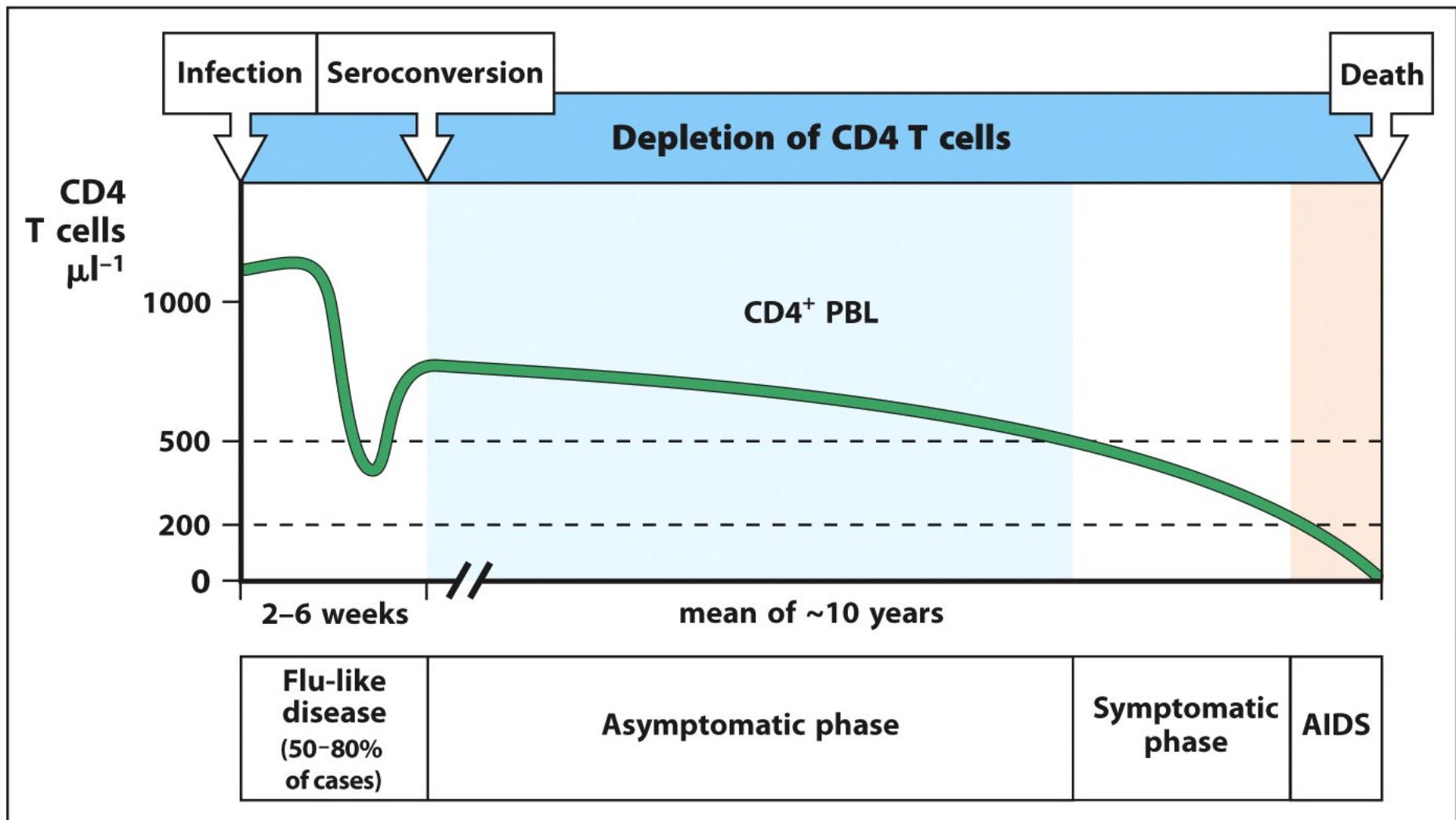


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Reference: info in this slide is sufficient (not available in Campbell Biology)

AIDS: General features & demography

- First documentation: sample of serum from Kinshasa (Republic of Congo) stored in 1959
- Official report of first case -1981, HIV discovered on 1983
- Susceptibility to infection with opportunistic pathogen
- Two types of HIV: HIV-1 (highly virulent) & HIV-2

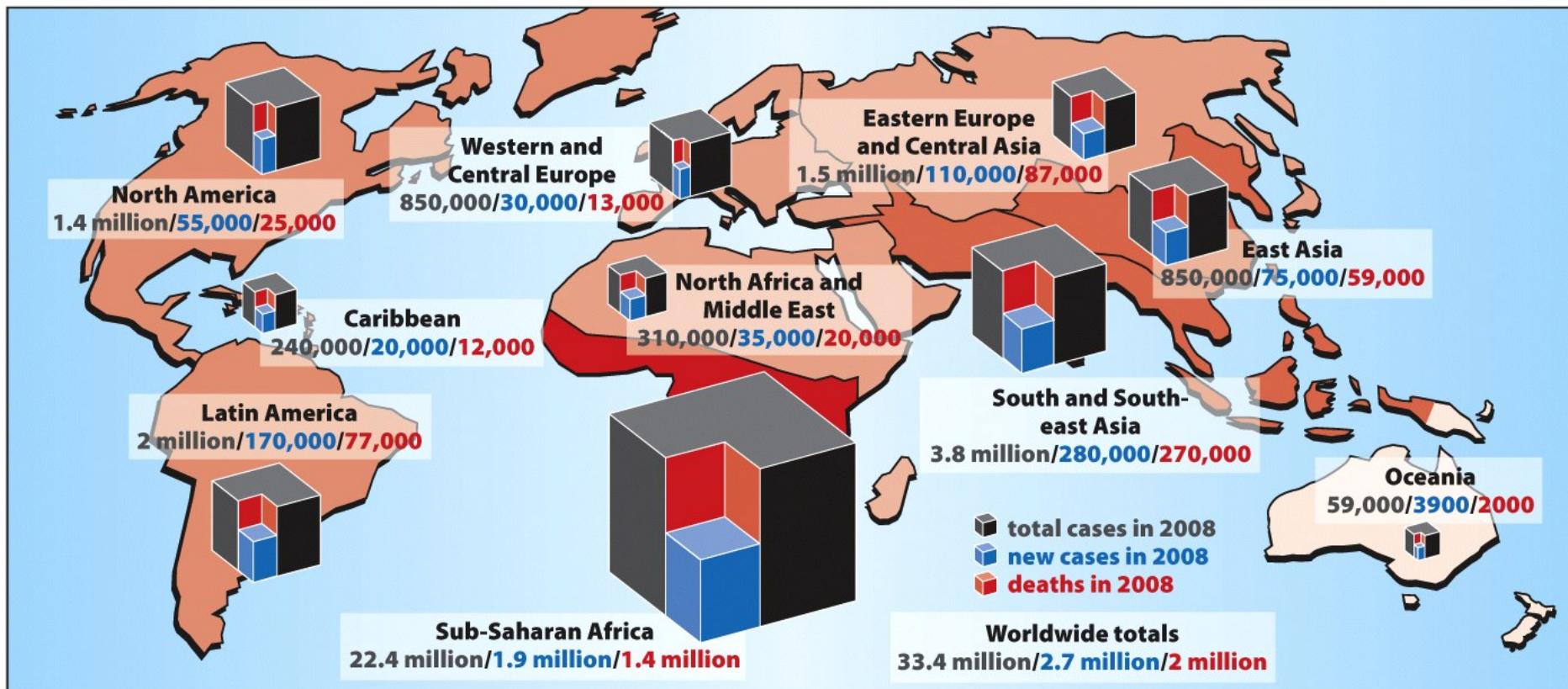


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How genetics play role in sensitivity to HIV infection?

Genetic variation in the host can alter the rate of progression of disease.

Genes that influence progression to AIDS				
Gene	Allele	Mode	Effect	Mechanism of action
HIV entry				
CCR5	Δ32	Recessive	Prevents infection	Knockout of CCR5 expression
		Dominant	Prevents lymphoma (L) Delays AIDS	Decreases available CCR5
	P1	Recessive	Accelerates AIDS (E)	Increases CCR5 expression
CCR2	I64	Dominant	Delays AIDS	Interacts with and reduces CXCR4
CCL5	In1.1c	Dominant	Accelerates AIDS	Decreases CCL5 expression
CXCL12	3'A	Recessive	Delays AIDS (L)	Impedes CCR5-CXCR4 transition (?)
CXCR6	E3K	Dominant	Accelerates <i>P. carinii</i> pneumonia (L)	Alters T-cell activations (?)
CCL2-CCL7-CCL11	H7	Dominant	Enhances infection	Stimulates immune response (?)

Figure 13.24 part 1 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Reference: info in this slide is sufficient (not available in Campbell Biology)

How genetics play role in sensitivity to HIV infection?

Genes influences progression of AIDS

Genes that influence progression to AIDS				
Gene	Allele	Mode	Effect	Mechanism of action
Cytokine anti-HIV				
<i>IL10</i>	5'A	Dominant	Limits infection Accelerates AIDS	Decreases IL-10 expression
	-179T	Dominant	Accelerates AIDS (E)	
Acquired immunity, cell mediated				
<i>HLA</i>	A, B, C	Homozygous	Accelerates AIDS	Decreases breadth of HLA class I epitope recognition
	<i>B*27</i>	Codominant	Delays AIDS	Delays HIV-1 escape
	<i>B*57</i>		Accelerates AIDS	Deflects CD8-mediated T-cell clearance of HIV-1
	<i>B*35-Px</i>			
Acquired immunity, innate				
<i>KIR3DS1</i>	3DS1	Epistatic with HLA-Bw4	Delays AIDS	Clears HIV ⁺ , HLA ⁻ cells (?)

Figure 13.24 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Reference: info in this slide is sufficient (not available in Campbell Biology)

How HIV infection cause AIDS?

The destruction of immune function increases the susceptibility to opportunistic infection and eventually to death.

Infections	
Parasites	<i>Toxoplasma</i> spp. <i>Cryptosporidium</i> spp. <i>Leishmania</i> spp. <i>Microsporidium</i> spp.
Intracellular bacteria	<i>Mycobacterium tuberculosis</i> <i>Mycobacterium avium intracellulare</i> <i>Salmonella</i> spp.
Fungi	<i>Pneumocystis jirovecii</i> <i>Cryptococcus neoformans</i> <i>Candida</i> spp. <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i>
Viruses	<i>Herpes simplex</i> <i>Cytomegalovirus</i> <i>Herpes zoster</i>
Malignancies	
<i>Kaposi's sarcoma – (HHV8)</i> <i>Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma</i> <i>Primary lymphoma of the brain</i>	

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How HIV infection (AIDS patients) are treated?

- Potential drug targets for HIV
 - Drugs that block HIV replication lead to a rapid decrease in virus titer
- Nucleoside analogs (zidovudine (AZT))
 - Target: Reverse transcriptase
 - Mechanism of action: prevents establishment of virus into new cells

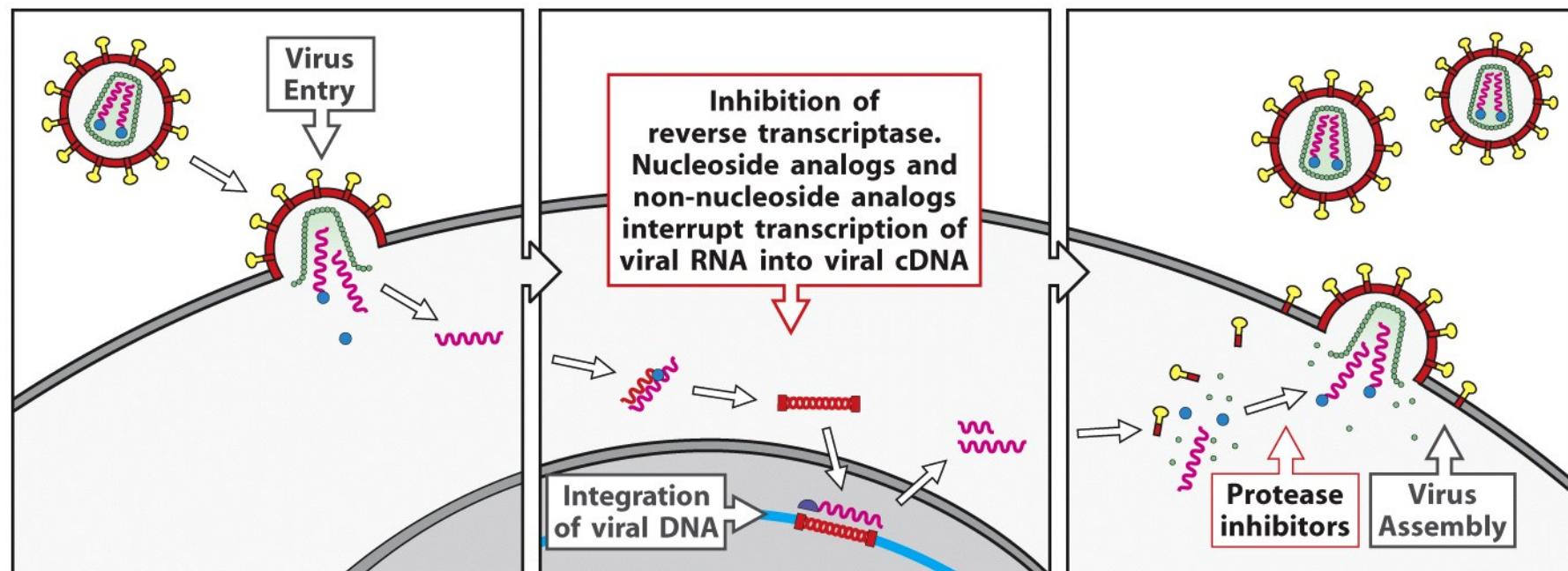
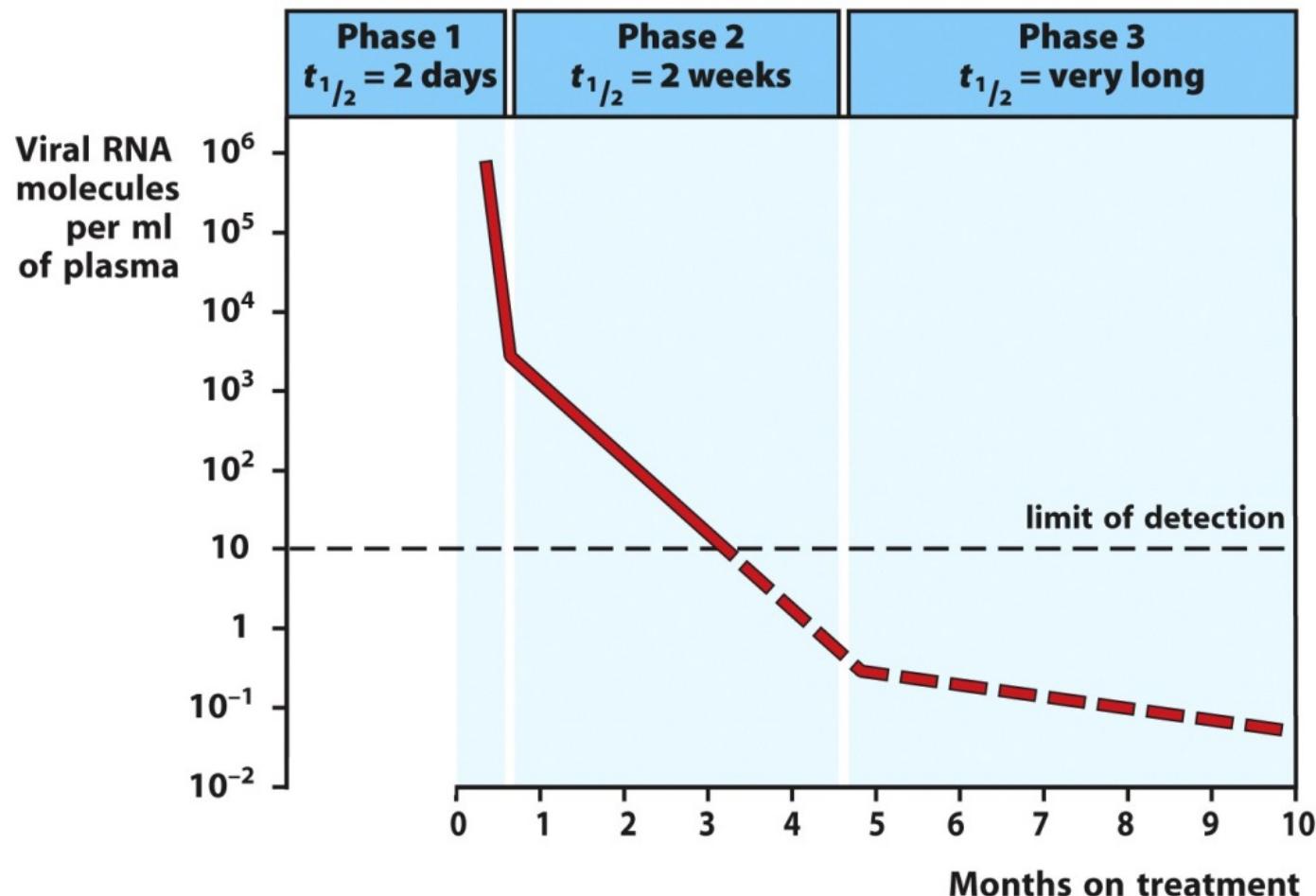


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How AIDS patients are treated?

Combination therapy (HAART therapy): cocktails of protease inhibitors & nucleoside analogs



How to control HIV infection?

Prevention and education are one way in which the spread of HIV and AIDS can be controlled.

Challenges in HIV treatment?

HIV accumulates many mutations in the course of infection, and drug treatment is soon followed by the outgrowth of drug-resistant variants.

Reference: info in this slide is sufficient (not available in Campbell Biology)

How bacteria and virus able to cause various diseases in humans?

Two possibilities:

- Either pathogen evolve ways to evade host defense mechanisms or host has a weak immune system
1. **Pathogen (bacteria and virus) mediated mechanisms that help them evading human immune system**
 - Antigen variation
 - Immunosuppression
 - Inappropriate immune activation
 - Latency
 2. **Host related immune deficiency**
 - Primary immunodeficiency
 - Acquired immunodeficiency

Reference: info in this slide is sufficient (not available in Campbell Biology)

How do we know/identify that an individual has weak immune system

- A history of repeated infections suggests a diagnosis of immunodeficiency.
- Another reasons for failure of host immune response.
- Primary immunodeficiency and secondary immunodeficiency

How primary immunodeficiency occurs in human?

Primary immunodeficiency diseases are caused by inherited gene defects

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	See text and Fig. 13.8		General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T cells	General
MHC class I deficiency	TAP mutations	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General

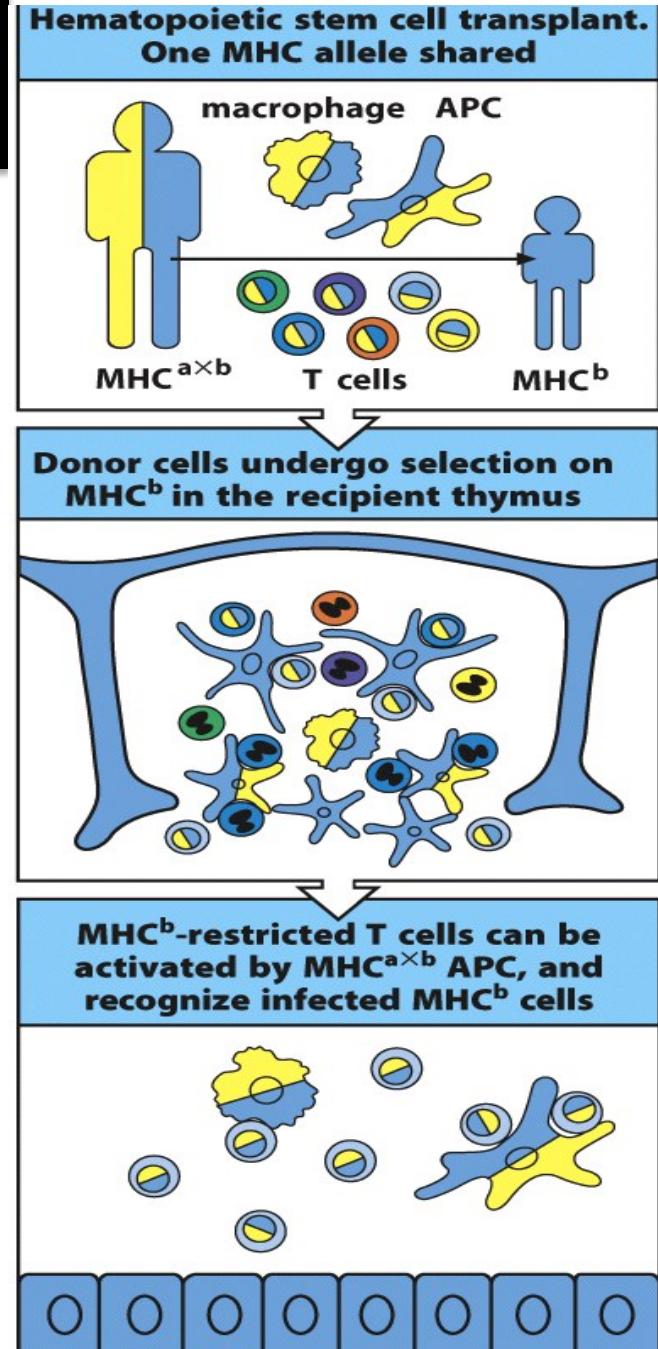
Severe combined immunodeficiency (SCID)

- Interleukin-2 receptor gamma(IL2RG) deficient (-/-) (no T cells and NK cells)
- Rag1/2-/- (no T cells and no B cells)

How to fix the primary immunodeficiency in human?

Hematopoietic stem cell transplantation or gene therapy can be useful to correct genetic defects.

- HSC derived from bone marrow/blood of a donor transferred into host
- Replacing the defective component of the patient
- **Principle of stem cell transplantation**
 - graft must share some MHC alleles with the host to restore normal immune function (MHC haplotyping is needed)
 - MHC alleles expressed by the thymic epithelium determine which T cells can be positively selected
- **Complications:** Graft versus host disease (GVHD) and Host vs graft disease (HVGD)



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Figure 13.17 Janeway's Immunobiology, 8ed. (c)

How to fix the primary immunodeficiency in human?

Somatic gene therapy

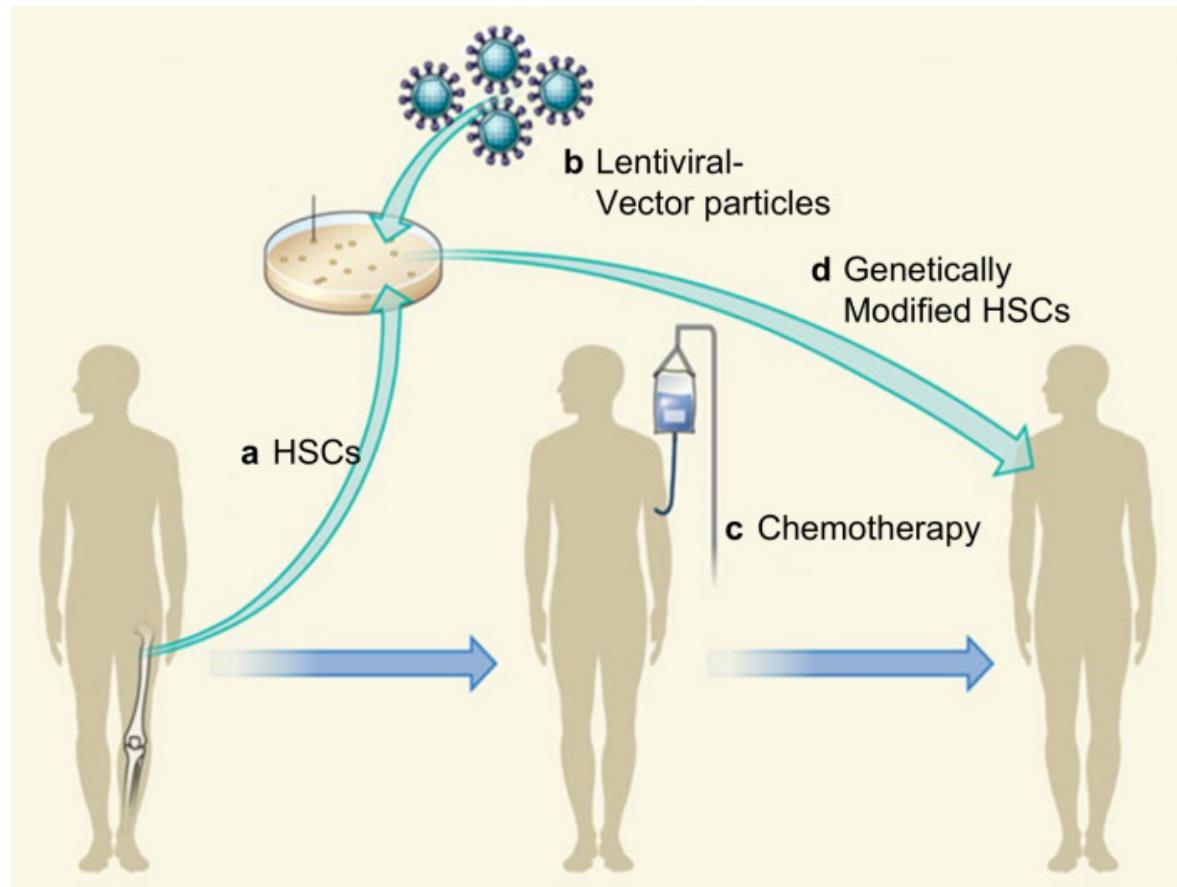
Principle:

- Correct the defective copy of gene by replacing with correct gene using retroviral vector

Severe complication:

malignancy (5/10 patient treated for X-SCID developed leukemia)

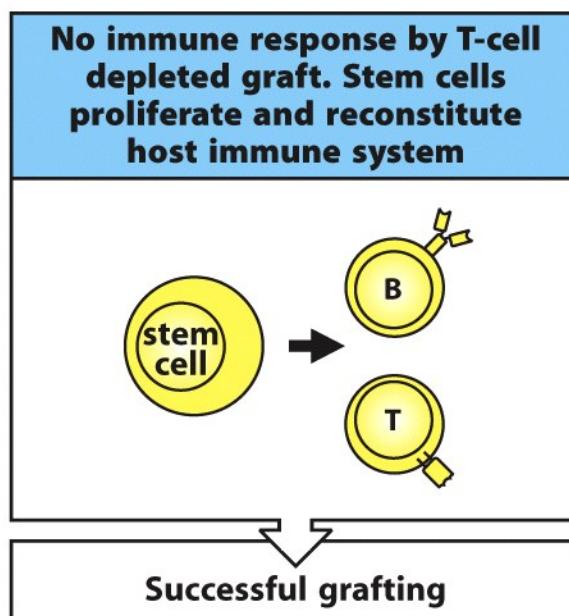
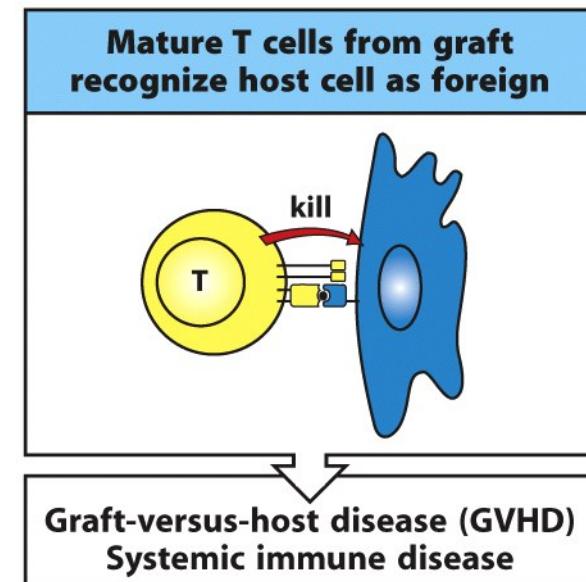
Alternate solution: induced pluripotent cells (iPS)



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Graft versus host disease (GVHD)

- Graft (donor) cells attack the host
- HSCs infusion contains T cells and other immune cells along with HSCs
- Possible solution: deplete donor T cells from the graft before infusion into a recipient



Reference: info in this slide is sufficient (not available in Campbell Biology)

Host versus graft disease (HVGD)

- HVGD: Host cells attack on graft
- When residual T cells remain in the host before transplantation
- In SCID recipient there is no problem of HVGD

Possible solution:

- Patient (recipient) conditioning by cytotoxic drugs (depletion of remaining T cells and bone-marrow cells of the recipient)

