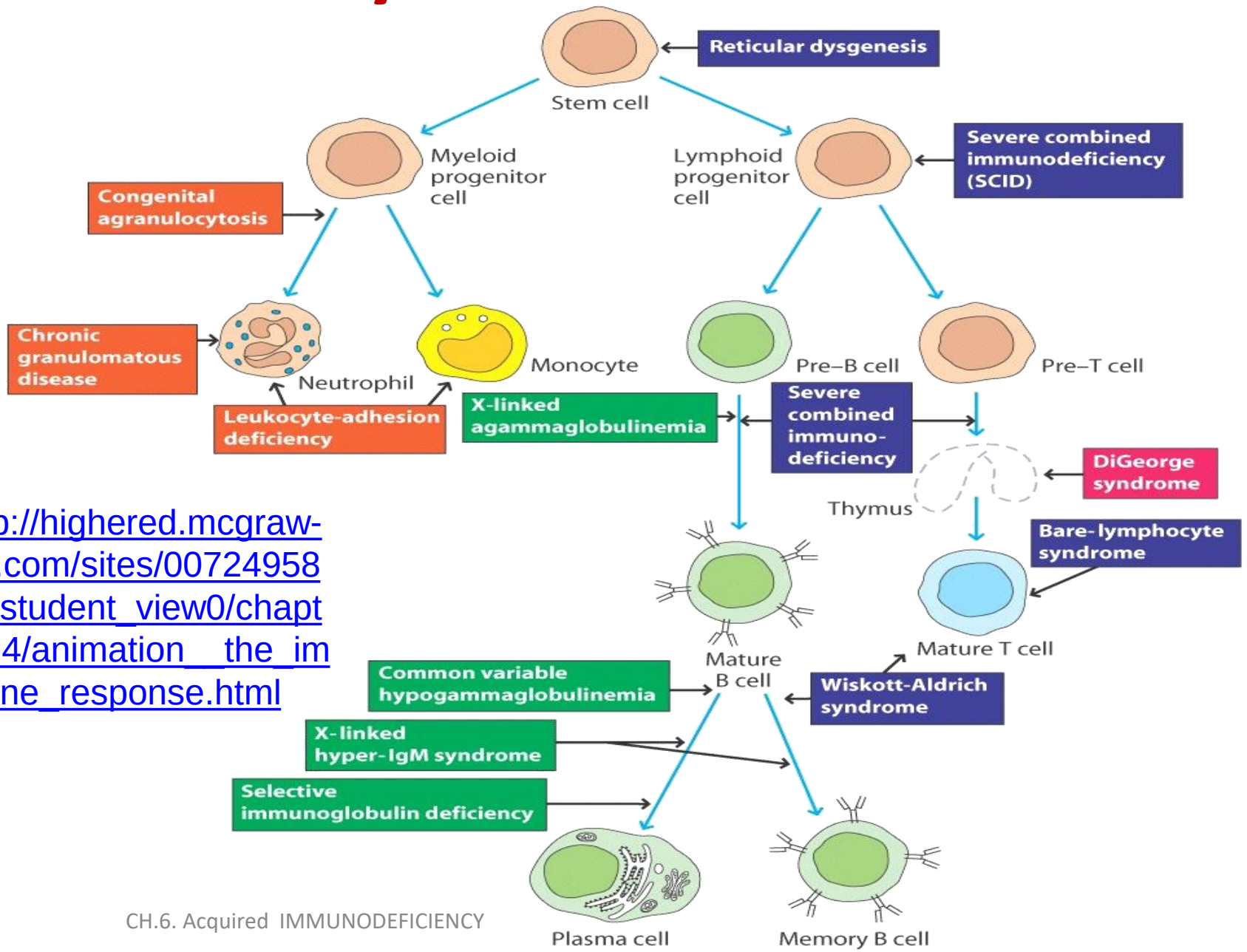
Primary Immunodeficiencies



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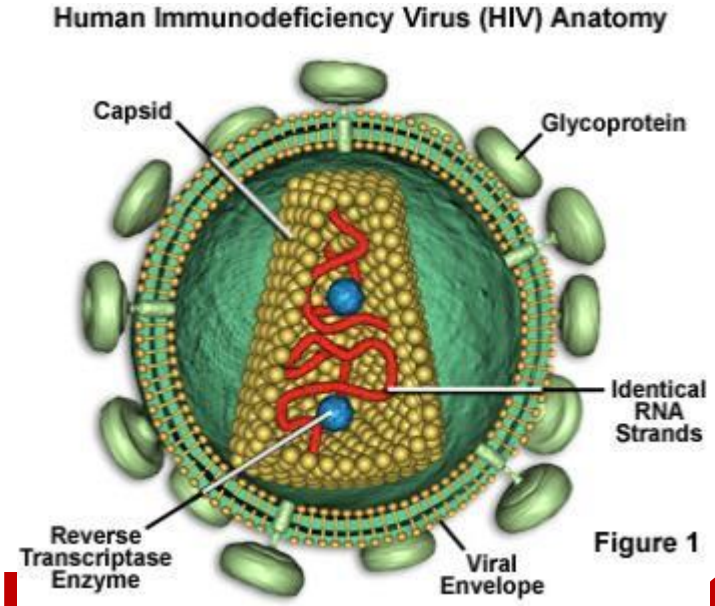


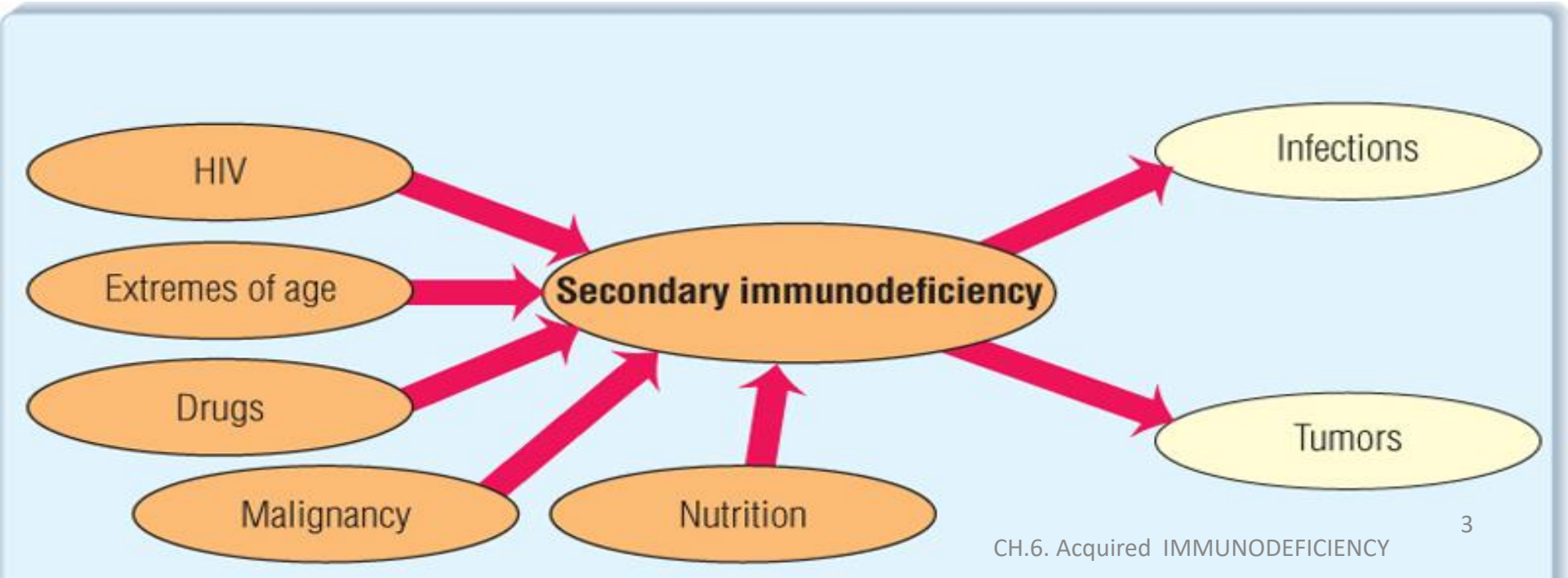
Figure 1

SECONDARY OR ACQUIRED IMMUNODEFICIENCY

A loss of previously functional immunity due to infection, toxicity, radiation, splenectomy, aging, malnutrition, etc.

Secondary Immunodeficiency

- Drug related
- Irradiation
- Disease related
  - Cancer
  - AIDS
    - HIV
    - T helper cell as target



Causes of Acquired Immunodeficiency

- **Cancer (immunoproliferative diseases)**

① Hodgkin's disease

② Multiple myeloma

③ CLL

- **Cytotoxic drugs or radiation**
  - ① X-rays
  - ② Cytotoxic drugs
- **Depression of the immune system by**
  - ① Malnutrition
  - ② Stress/emotions
  - ③Aging (thymic atrophy)
  - ④Infection
- **Splenectomy**
- **Immunosuppressive therapy**
  - ① Corticosteroids

- **Succeed some diseases SIDD**
- **Iatrogenic SIDD (**resulting from the physician's treatment **)**
- **Acquired immunodeficiency syndrome**

AIDS

Succeed some diseases

Infection：

➢**virus infection** decrease function of cellular immunity,

➢decreased function of the T cells

Malignant tumors：

➢**decreased function** of **cellular immunity**

➢decreased function of **the T cells**

➢ notablely decreased **function of the T and B cells**

Loss of proteins：

❖**Excessive consume** or **insufficient synthesis** ：

❑decreased level of **Ig，**

❑decreased function of **humoral immunity**

❖**Severe malnutrition：**

❑decreased function **of the T cells**

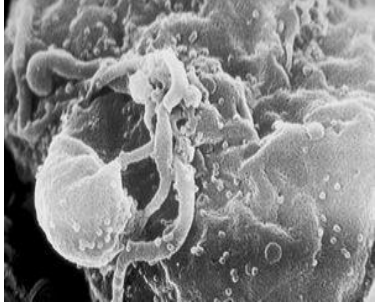
Iatrogenic Secondary Immunodeficiency Diseases.

1) Using immunosuppressive drugs、some antibiotics，

Anti-neoplastic for a long time

2) Damage by irradiation

AIDS (Acquired immune deficiency syndrome)

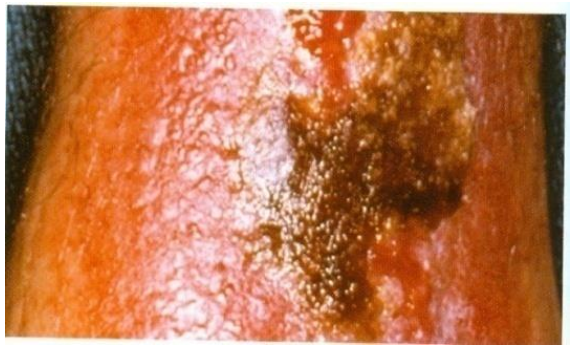


- **Acquired immunodeficiency syndrom** (AIDS or Aids) is:
  - a collection of **symptoms and infections** resulting from the **specific damage to** the **immune system** caused by the human **immunodeficiency virus (HIV**).

- **HIV** is t**ransmitted** through:
- **direct contact** of a **mucous** membrane or the **bloodstream** with:
  - a **bodily fluid** containing **HIV,** such as :
    - blood,
    - semen,
    - vaginal fluid,
    - preseminal fluid,
    - and breast milk.
  - **Not saliva, tears or sweat**

Human Immunodeficiency Virus; HIV

- **Retrovirus (RNA virus)**
- **HIV-1 (common) and HIV-2 (Africa)**
- Patients with **low CD4^{+} T cells**

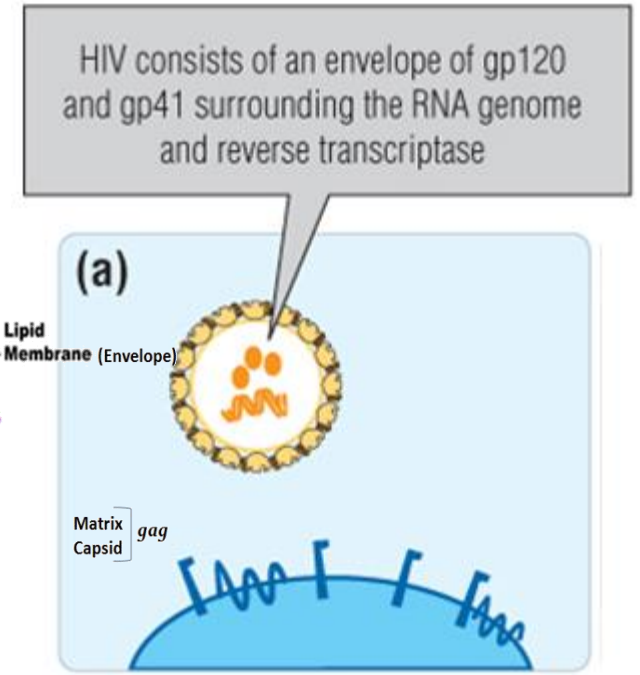


Kaposi sarcoma

- **Virus prevalent** in **homosexual, promiscuous heterosexual, I.V drug users, transfusion, infants born to infected mothers**
- **Opportunistic infections** with **Pnuemocystis carinii, Candida albicans, Mycobacterium avium**, etc.
- Patients with HIV have **high incidence of cancers** such as **Kaposi sarcoma (human herpes virus 8 (HHV8))**

HIV - virus

- SPHERICAL
  - Contains an electrodense core
  - Surrounded by lipid envelope



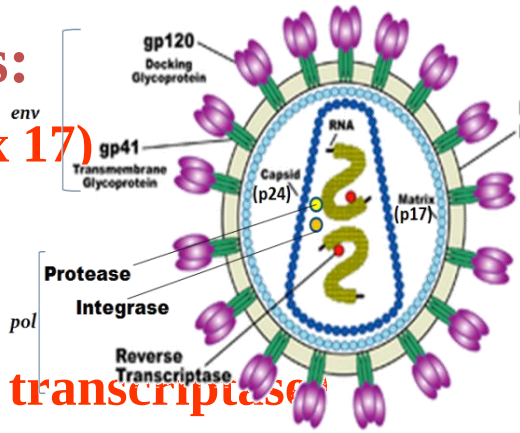
- The CORE contains:

Protein (caspid24 and matrix 17)

2 RNA

3 viral enzymes

(protease, integrase, reverse transcriptase)



Membrane: derived from the host cell membrane

Two kinds of glycoproteins: gp160 ⟹ gp120 and gp41

gp41 is a transmembrane protein,

and gp120 is an external protein, noncovalently associated with membrane.

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter24/animation__hiv_replication.html

- **HIV** is a **retrovirus** that primarily **infects vital components** of the human immune system such as
- **CD4+ T cells** (a subset of T cells),
- **macrophages**
- **dendritic cells.**

- It **directly** and **indirectly destroys CD4+ T cells**.

- When **HIV kills CD4+ T cells** so that there are:
  - **fewer than 200 CD4+ T cells per microliter (µL) of blood,**
  - **cellular immunity is lost**,
- leading to the condition known **as AIDS.**

- Pathogenesis:
- HIV→ CD4+cell→ CD4+cell lysis → **opportunistic infections and neoplasms**

Definition — The acquired immunodeficiency syndrome (AIDS) is the outcome of chronic HI infection and consequent depletion of CD4 cel defined as a **CD4 cell count <200 cells/micro presence of any AIDS-defining condition** (ta regardless of the CD4 cell count. (See 'AIDS d conditions' below.)

The term **advanced HIV** infection is often used to infection when the CD4 cell count is below 50 **cells/microL.**

AIDS-defining conditions
Bacterial infections, multiple or recurrent*
Candidiasis of bronchi, trachea, or lungs
Candidiasis of esophagus
Cervical cancer, invasive¶
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (>1 month's duration)
Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related$^{\Delta}$
Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (>1 month's duration)
Kaposi sarcoma
Lymphoma, Burkitt (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex (MAC) or *Mycobacterium kansasii*, disseminated or extrapulmonary
Mycobacterium tuberculosis of any site, pulmonary¶, disseminated, or extrapulmonary
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecii (previously known as *"Pneumocystis carinii"*) pneumonia
Pneumonia, recurrent¶
Progressive multifocal leukoencephalopathy
Salmonella septicemia, recurrent
Toxoplasmosis of brain, onset at age >1 month
Wasting syndrome attributed to HIV$^{\Delta}$

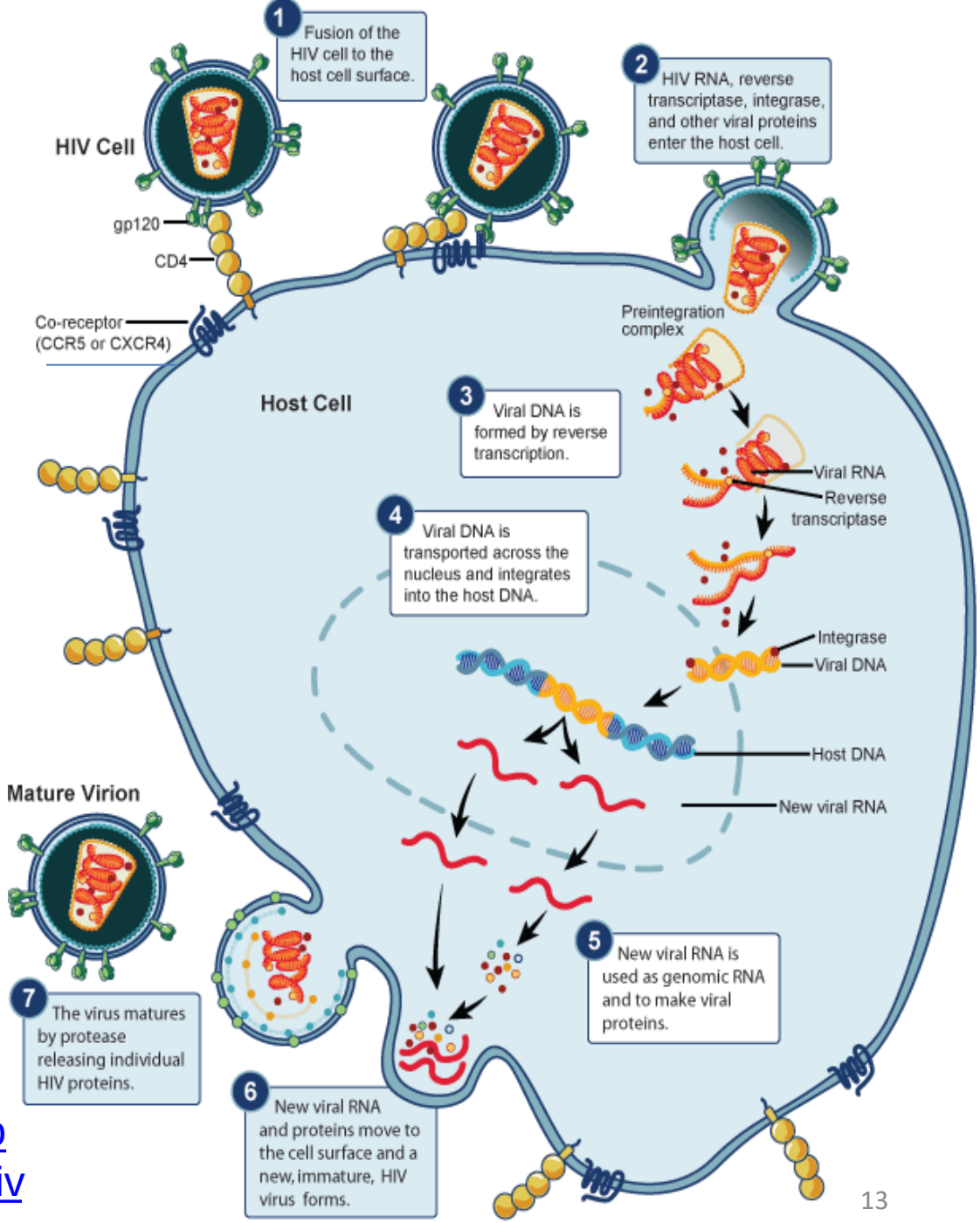
AIDS: acquired immunodeficiency syndrome; HIV: human immunodeficiency virus; MAC: mycobacterium avium complex .
* Only among children aged <6 years.
¶ Only among children aged ≥6 years, adolescents, and adults.
Δ Suggested diagnostic criteria for these illnesses, which might be particularly important for IV encephalopathy and HIV wasting syndrome are described in MMWR R

Viral Replication

- **Infects macrophages**, and **later**, **helper T cells**
- Virus **replicates and bursts out of the helper T cell**, killing it
- **Loss of helper T cells prevents B cell activation**
- Infections occur because **the immune system not functional**

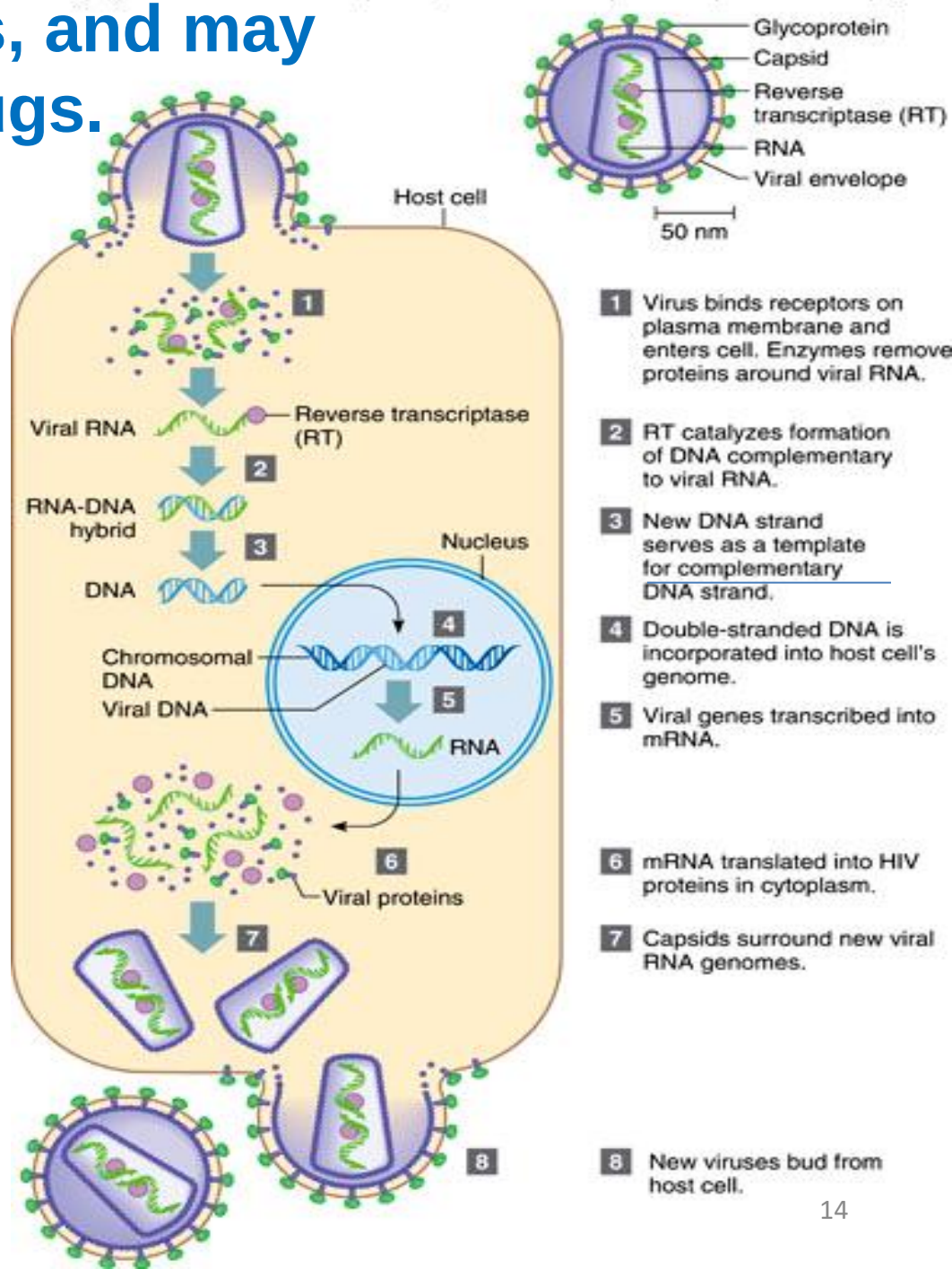
- **Replicates rapidly, mutates easily**, and **can hide**

http://www.sumanasinc.com/webcontent/animations/content/lifecyclehiv.swf



HIV continually mutates, and may become resistant to drugs.

1. ATTACHMENT
2. UNCOATING
3. DNA SYNTHESIS
4. INTEGRATION
5. TRANSCRIPTION
6. TRANSLATION
7. CLEAVAGE
8. RELEASE



ATTACHMENT

Surface of virus attaches to CD4 T cells

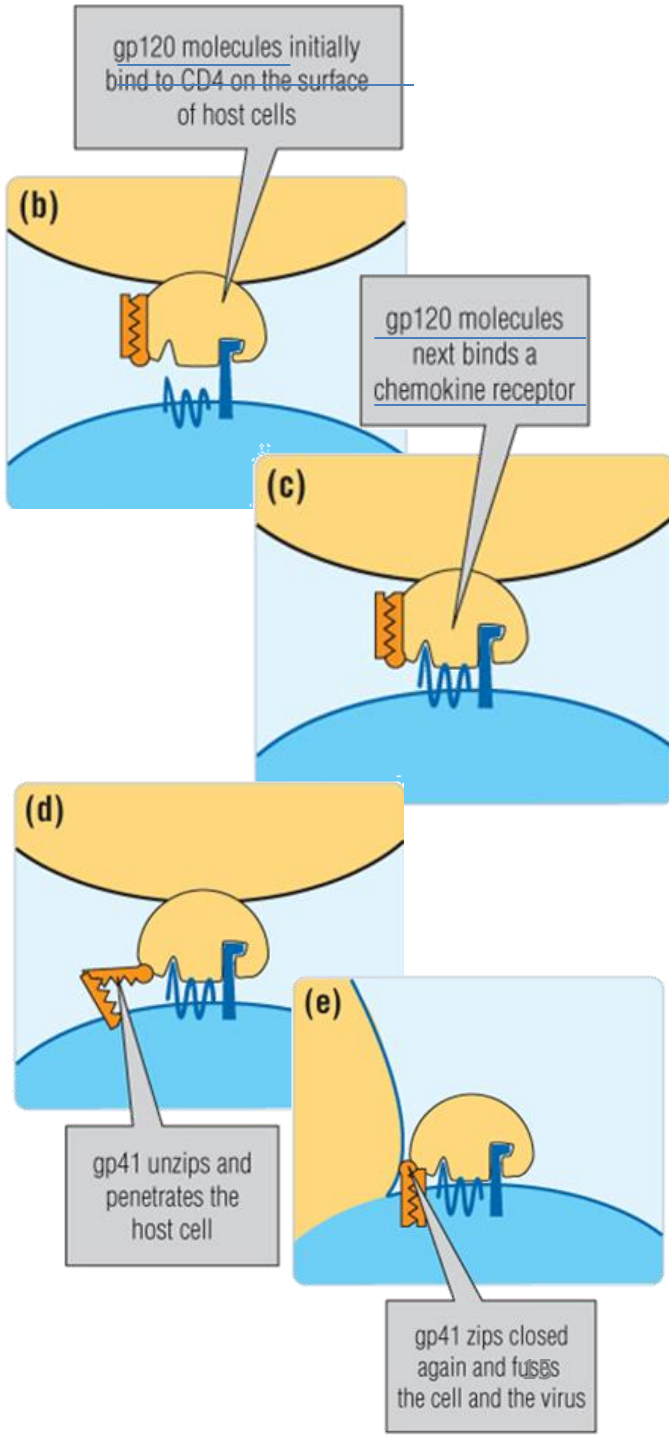
Virus GP120 & GP 41 binds to chemokines

UNCOATING

Viral envelope fuse To CD4 membrane

Contents of core enter Into CD4 cell

Single strand RNA change Into double strand DNA



DNA SYNTHESIS

Reverse transcriptase copies The viral RNA

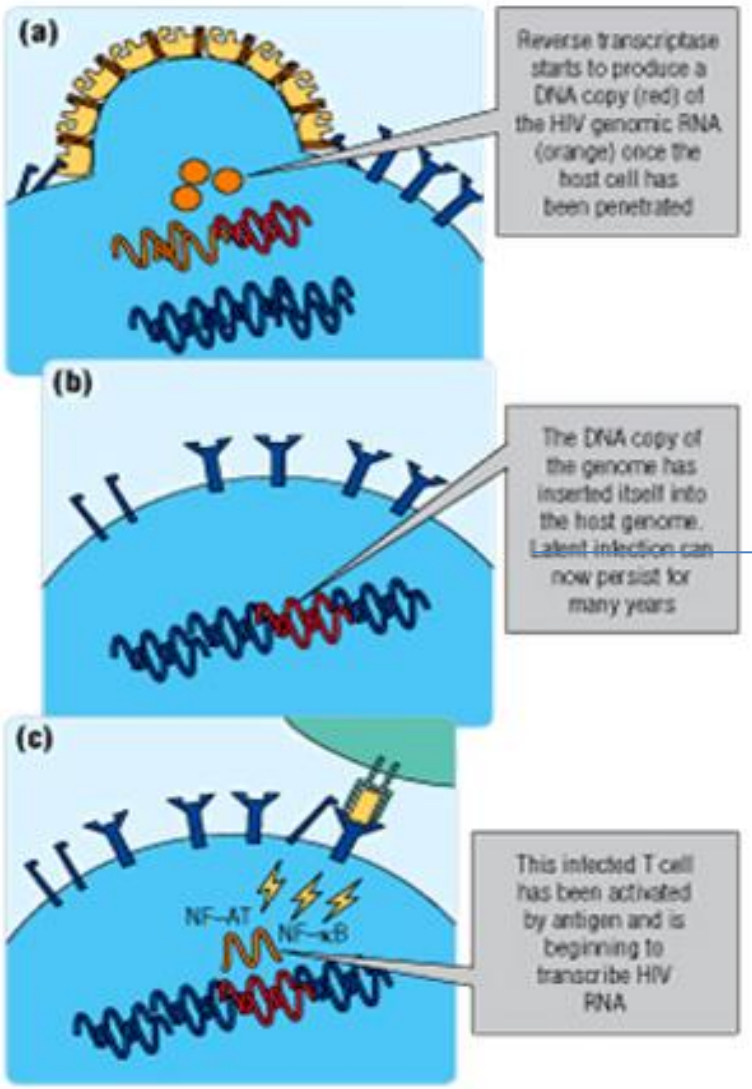
Makes a mirror image copy

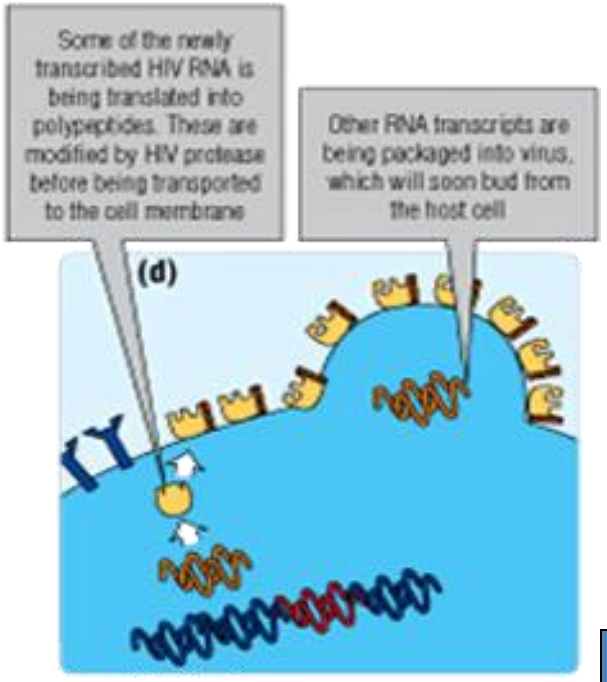
Double stranded DNA carries Instructions of viral replication

INTEGRATION

New DNA enters into nucleus Of CD4 T cell through integrase

Transcription of double Stranded viral DNA





mRNA carries instruction For building new viruses

rRNA uses instructions of mRNA

Creates polyprotein

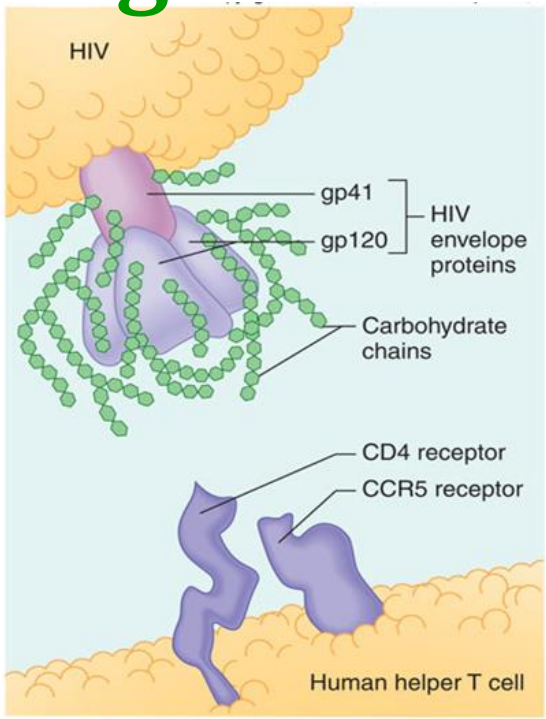
Protease cuts Polyprotein chain

Proteins and viral RNA assembled into New viruses

Kills CD4 Tcells , invades Other cells

http://www.youtube.com/watch?v=FDugpEny0Zo&feature=related

Pathogenesis and Immunological features



HIV **gp120** infect **CD4 host cells** lead to

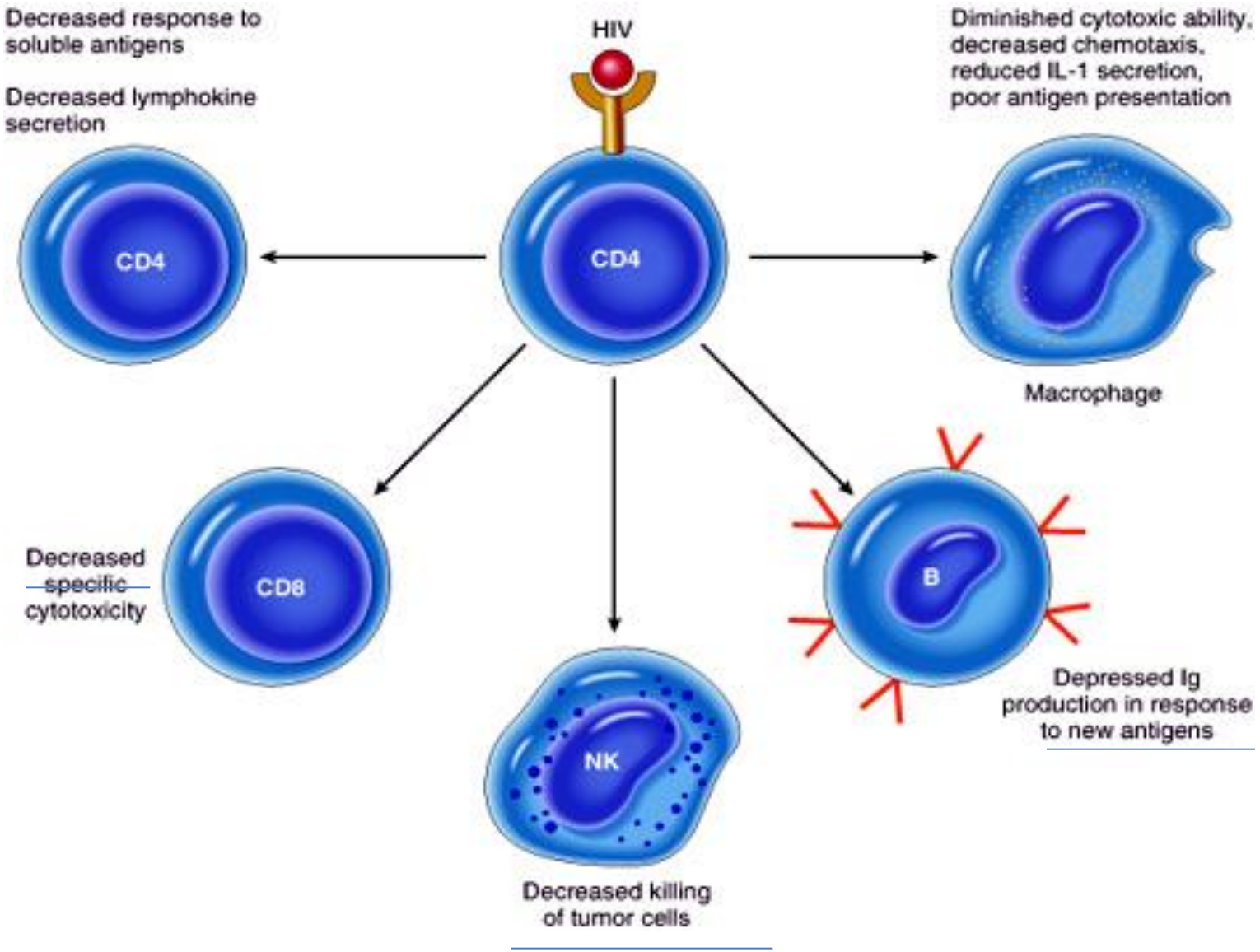
（1） **virus replication，cell death**

（2） fusion of the cells multinucleated giant cells， cell death

（3）**decrease or invert the ratio of CD4/CD8**

- The **decline of Th cells，**
- the **depletion and loss of function** of **Th cells**
- **polyclonal activation** of the **B cells**
- Mϕ increased levels of the IL-1 and TNF-a
- **Decreased number** of the **NK cells，**
- **increased incidence** of **malignant tumor、**
- **virus infection**

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter24/animation__how_the_hiv_infection_cycle_works.html



The multiple effects of loss of CD4+ T cells as a result of HIV infection

Clinical features

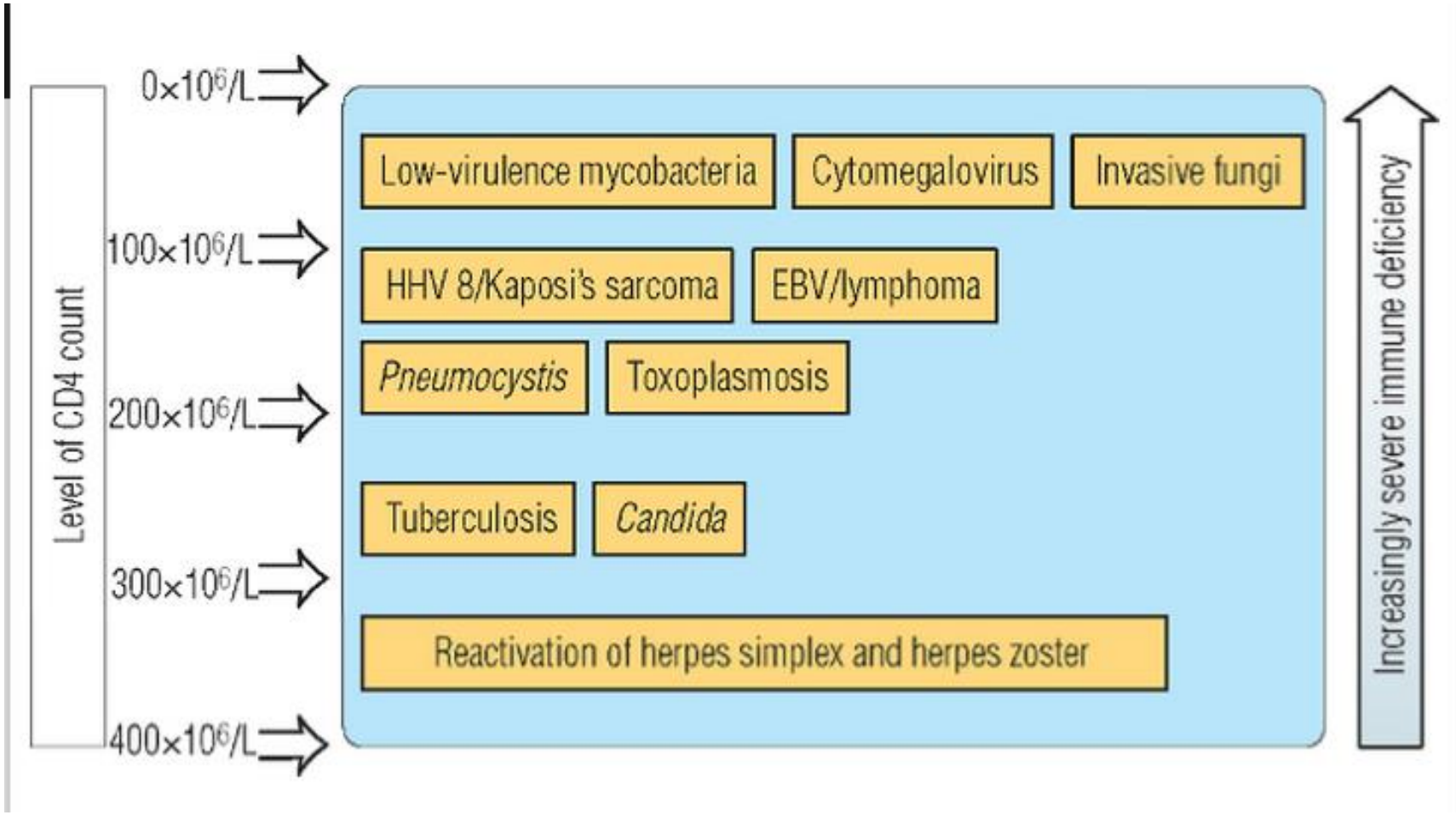
- **Infection phase：** **influenza-like symptom、infectious**
- **Abs production：** **3-20 weeks(…5 months)**
- **Latent period:** **6 month—4 year, asymptomatic**

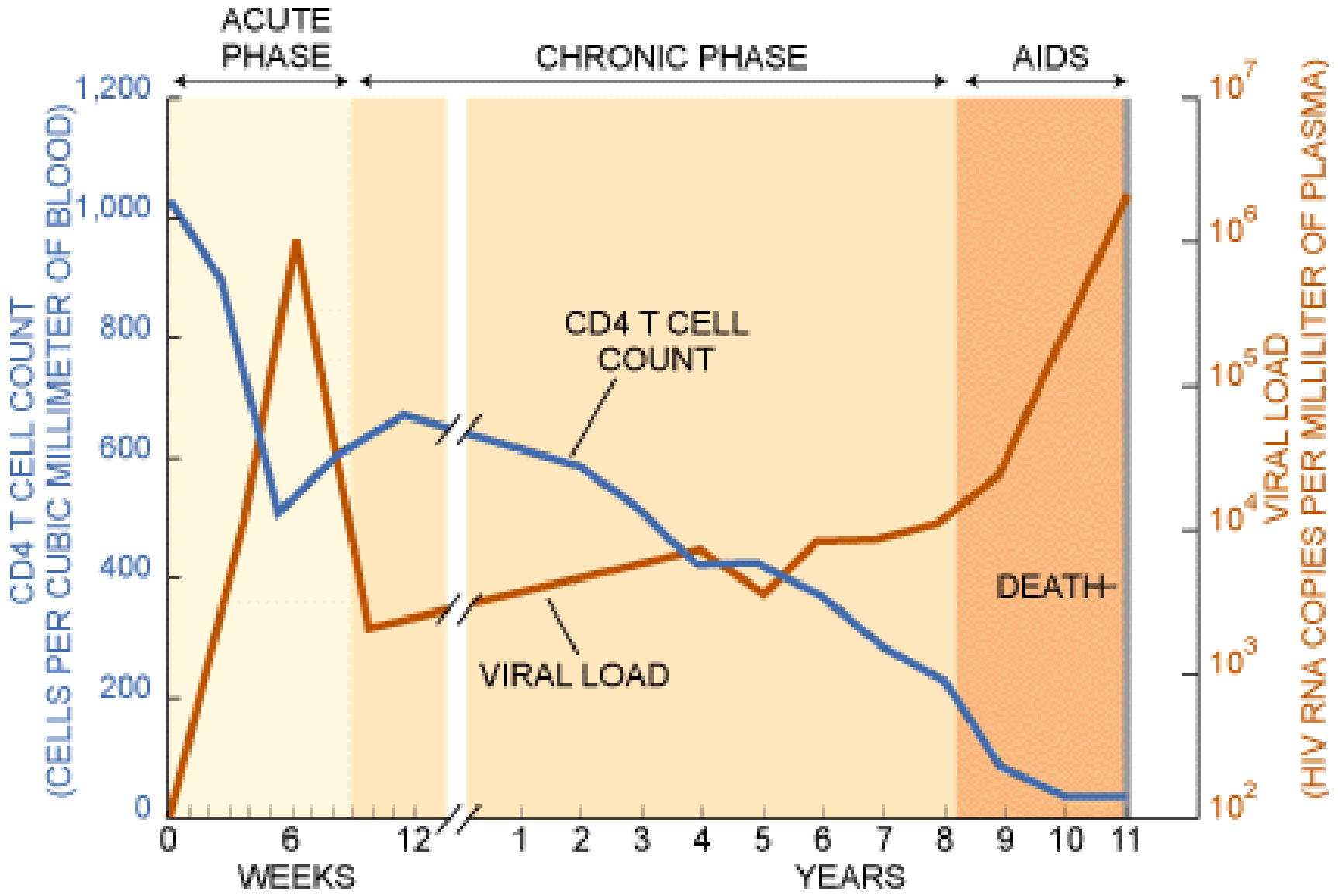
- **symptom：AIDS related complex (ARC)**

（1） opportunistic infections

（2） malignant tumors：Kaposi’s sarcoma、malignant lymphoma

（3） abnormal of the central nervous system


Level of CD4 count
0×10⁶/L
100×10⁶/L
200×10⁶/L
300×10⁶/L
400×10⁶/L
Low-virulence mycobacteria
Cytomegalovirus
Invasive fungi
HHV 8/Kaposi's sarcoma
EBV/lymphoma
Pneumocystis
Toxoplasmosis
Tuberculosis
Candida
Reactivation of herpes simplex and herpes zoster
Increasingly severe immune deficiency


ACUTE PHASE
CHRONIC PHASE
AIDS
CD4 T CELL COUNT (CELLS PER CUBIC MILLIMETER OF BLOOD)
1,200
1,000
800
600
400
200
0
CD4 T CELL COUNT
VIRAL LOAD
DEATH
VIRAL LOAD (HIV RNA COPIES PER MILLILITER OF PLASMA)
10^7
10^6
10^5
10^4
10^3
10^2
0
6
12
1
2
3
4
5
6
7
8
9
10
11
WEEKS
YEARS

Epidemiology, prevention and cure

major group at risk：

homosexual、drug abuser
infected blood or blood products

spread manner：

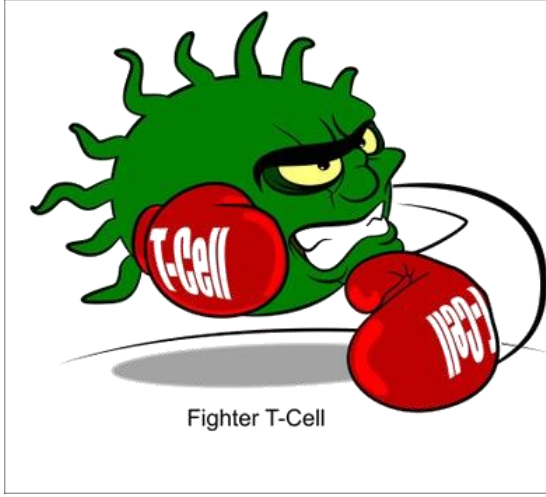
sexual contact、blood、
mother-to- child transmission

Detection

Ab detection: Abs are ineffective to control HIV

- **Virus grows intracellularly**
- Abs develop **after ~3 weeks**.
-
- Thus **cannot be used as a diagnostic test initially** (Reverse transcriptase is a sensitive test)
- **Abs are not neutralizing**

Role of T cells in development of AIDS



- **Initially Th cells control viral load**

- **Surviving Th cells** are **anergic (**T-*cell anergy* can arise when the *T-cell* does not receive appropriate co-stimulation in the presence of specific antigen recognition)

- **Destruction of infected Th cells by CTL**
  - **CTL that develop** are **ineffective** because of ➔**high viral mutations**
  - **Lack of Th affects CTL activation**
  - **Resistance to CTL by downregulation of class I MHC on target cells**

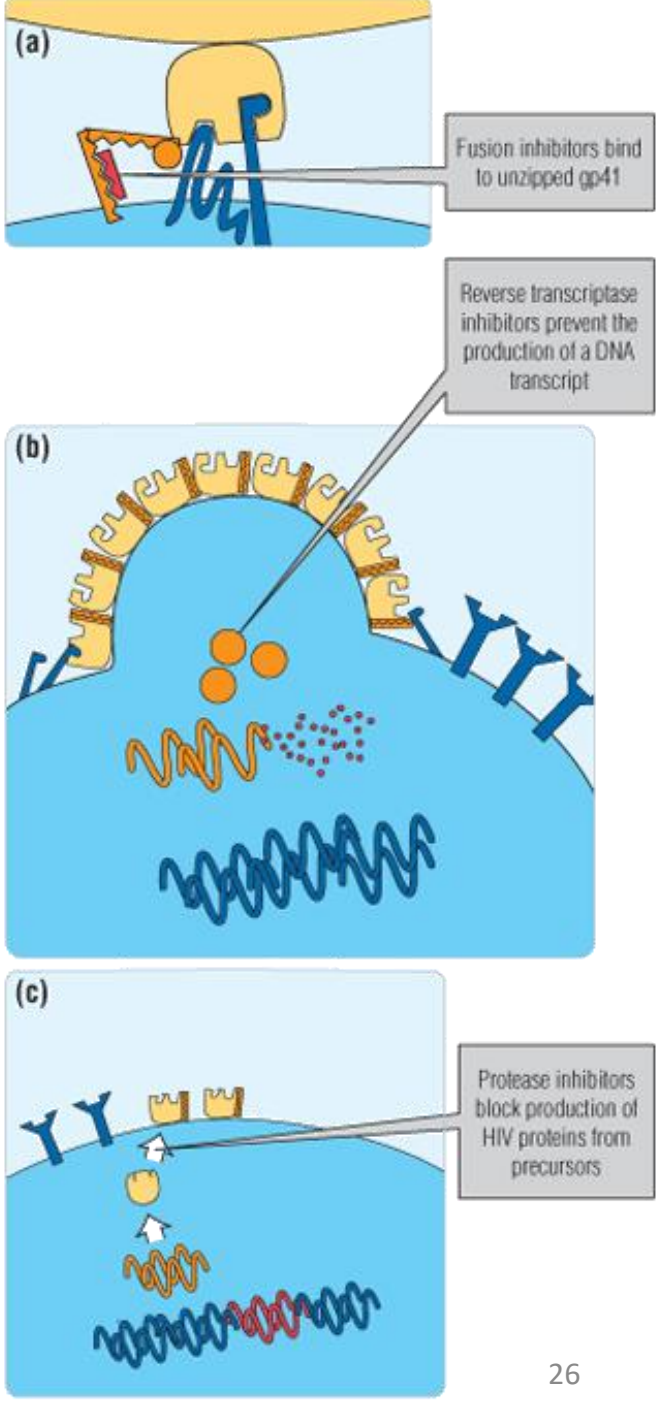
Treatment

- There is currently **no vaccine or cure** for HIV or AIDS.
- The only known methods of **prevention** are based on **avoiding exposure to the virus.**
- **Vaccines: Proteins, DNA, subunit and recombinant virus**

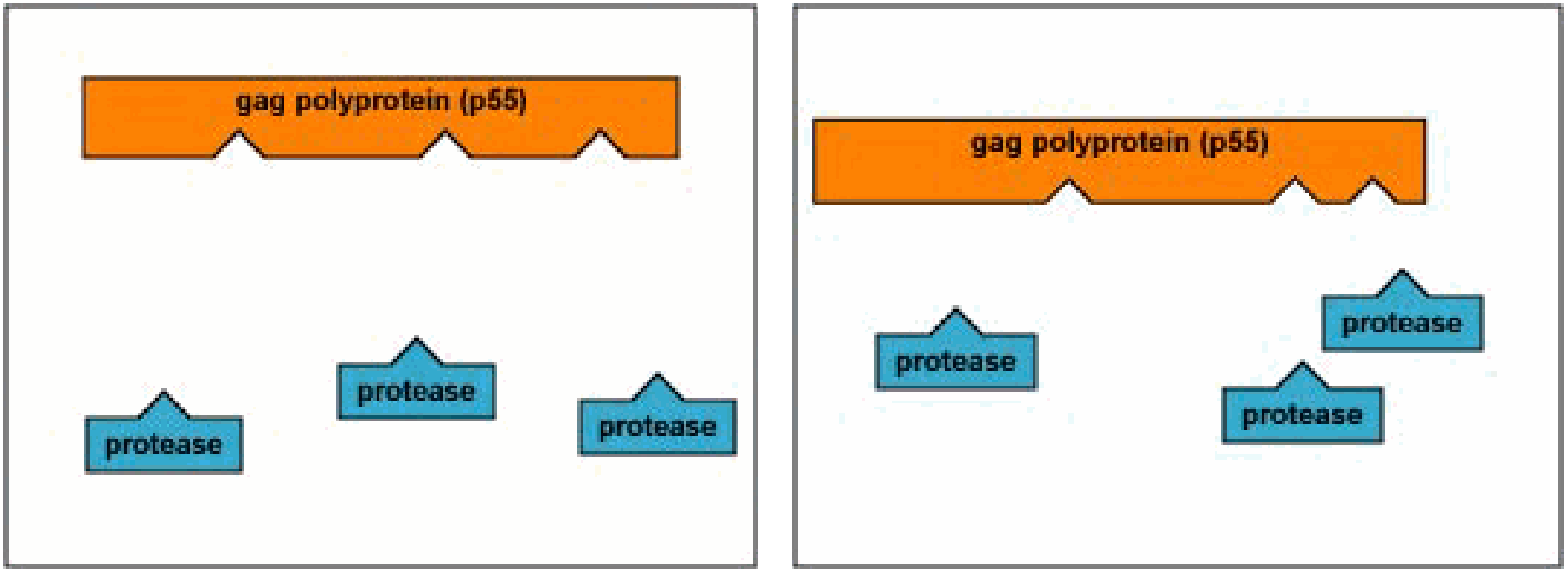
The three major classes of antiretroviral therapy are:

1. **Fusion inhibitors (one drug licensed),**
2. **Reverse transcriptase inhibitors (about 20 drugs licensed),**
3. **Protease inhibitors (eight drugs licensed).**

- *Abacavir* — a nucleoside analog reverse transcriptase inhibitors .

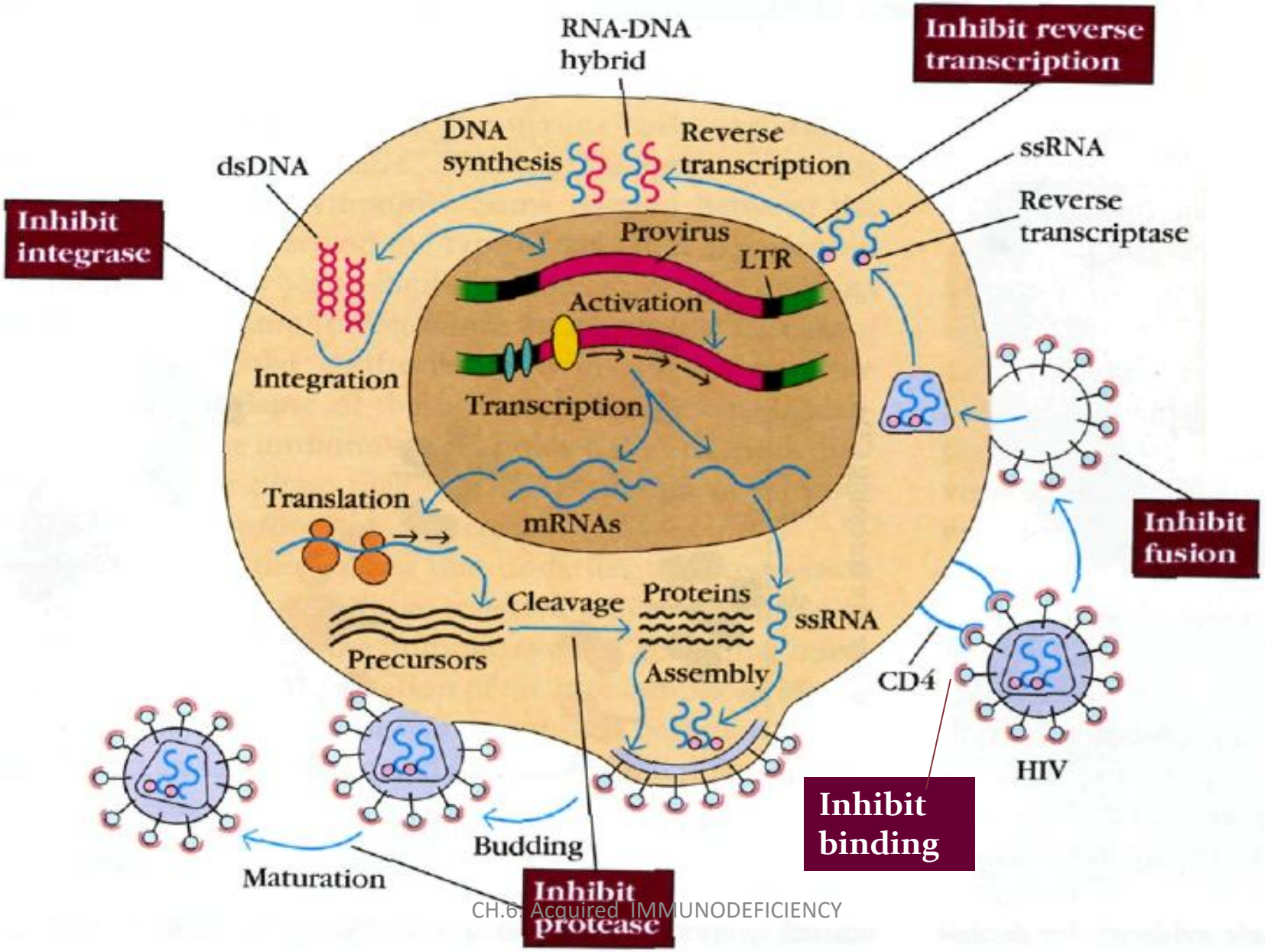


Use of Human Immunodeficiency Virus Protease Inhibitors to Inhibit Human Immunodeficiency Virus Replication



HIV genome contains three major genes, **5'gag-pol-env-3**

Therapeutic targets



Problems with therapy

1. **HIV-1 infection gives** rise to AIDS **despite the presence of Abs**
2. **Low immunogenicity of virus**
3. Vaccine alone leads to **destruction of CD4$^+$ T cells**
4. **Integration of virus in host genome**
5. **Virus undergoes mutations |(major problem)**
6. **High rate** of virus **replication** (10^9 viruses/day)
7. Live attenuated may **result in AIDS**
8. Heat killed organism is **not antigenic**
9. **Vaccine** administered through **oral or respiratory route**
   ➔ (Route of exposure to HIV is through genital tract)

10. **Lack of animal models** and in **vitro testing system**

11. **Drugs do not cross blood-brain barrier to reach virus in brain**

Summary

- **Primary immunodeficiencies** are **inherited**
- They can **affect hematopoietic stem cells, lymphoid or myeloid cells.**

- **Secondary immunodeficiencies** are due to **infections, aging, cancer or chemical exposure**
- **HIV** affects immune system by **eliminating CD4+ T cells**
- **Vaccine development has been hindered** by :
  - **lack of an experimental model,**
  - **antigenic variation**,
  - **rapid proliferation** of **the virus**

OTHER SECONDARY IMMUNODEFICIENCIES

- A **variety of other factors** can cause secondary immunodeficiency.
- These factors **often operate together.**
- This can happen very easily **during hospital admissions**, when patients are **exposed to stress, drugs**, and possibly worse than usual **nutrition**.

- **Extremes of Age**
- **Miscellaneous Factors**
  - **Drugs**
  - **B-cell Malignancy**
  - **Kidney Disease**
  - **Nutrition**
  - **Physiologic Stress**
  - **Infections**

Extremes of Age

The Immune System in the First Year of Life

➔The **specific immune** system remains **immature.**

- Although **neonates** have➔ **high numbers of T cells**, ➔these are **all naive** and so **do not respond well to antigen**

- **Fetal antibody synthesis** ➔begins at **20 weeks**, but **adult levels of IgG** are ➔not reached until about **5 years.**
- For the **first few months of life**, ➔ infants are reliant on **maternal IgG.**
- **Pregnant women** produce ➔ **increased Igs** under the effects of **estrogens.**
- **IgG** is➔ transported **across the placenta** by **specialized Fc receptors** in ➔ the **last 10 weeks of pregnancy.**
- **Breast milk** is ➔ an additional **source of protection in early life** and **protects against lung and gastrointestinal infection.**

- **Bottle-fed infants** are➔ **60 times more likely to develop pneumonia in the first 3 months of life.**

- **Premature babies** ➔ more **infection** ➔because **less time to receive maternal Ig** *during the late stages of pregnancy.*

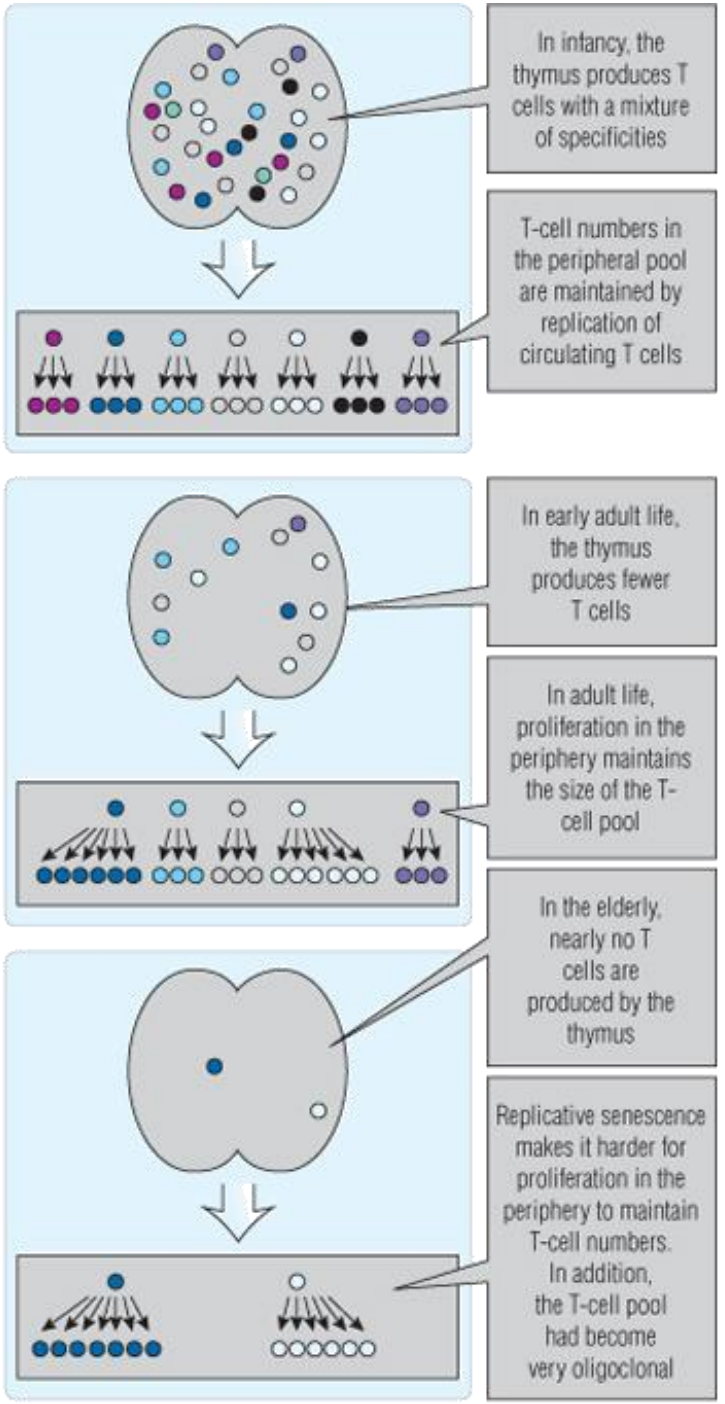
- **Immaturity of innate mechanisms** such as ➔ **lung surfactant** ➔ can increase the risk of respiratory infection.

- Many infants **develop low levels of antibody** during the **first year of life.**
  - **Transient hypogammaglobulinemia of infancy**

    ➔ caused by a **delay in maturation of Ig synthesis**, especially **IgG2**, at a time when **maternal antibody levels are falling.**

The Aging Immune System

- The **elderly** suffer **more infections** than **younger** patients.
- The mild immune deficiency that occurs with aging **mainly affects T cells.**
- **T-cell memory** is **not long-lasting**, ➔ half life of **about 50 days.**
-
- **Immune response requiring T-cell** help often ➔**require newly generated T cells.**
- **There are three reasons why the generation of new memory T cells fails in the elderly.**



- **Throughout middle age: The thymus shrinks** by about **3% a year**, and ➔ **fall in the thymic production of naive T cells**.
  - **Although Thymic output ➔ increase in response to specific circumstances** (e.g., when circulating T cells have been destroyed by drugs ➔ BUT this **cannot** be **sustained in old age.**

- **Because Fewer T cells** emerge from **the thymus** in **later life**, **➔proliferation of T cells** in the periphery is mainly responsible for **maintaining adequate T-cell numbers in adults.**
  - **However the Biological clock** is ➔ **important in limiting the number of occasions T cells can replicate.**
  - Each time a **cell divides**, ➔**shortening of telomeric DNA.** ➔ **when they are short ➔cells can no longer divide.** This ➔ ***affects T cells after about 40 divisions.***

- **In old age** ➔a herpesvirus family member called **cytomegalovirus (CMV) affects** T cells . ➔ **CMV drives increasing numbers of T cells**.
- In the elderly, the **T-cell response** becomes **very oligoclonal**, with **disproportionate numbers of T cells having CMV specificity.**
- These cells leave little room in the immune system **for other specificities.**

- Consequences of **impaired T-cell numbers and function in old age** include:
  - **poor response to vaccines,**
  - **increased infections,**
  - **possibly, increased risk for malignancy.**

B-cells:

- **Memory for preexisting antibody responses** to **effective vaccines** may ➔ **last for up to 50 or 60 years.** (e.g., responses to **smallpox vaccine** remain effective for **many decades**).

  - **Aged B cells** may show➔ signs of a **lifetime of exposure to microorganisms.**
  - **Immunoglobulin synthesis** is increased,
  - **outgrowth of B-cell clones** may ➔**lead to the presence of monoclonal immunoglobulin in the blood or B-cell malignancy .**
  - **Autoantibodies** are also more common in the elderly but are **not usually associated with disease.**

Miscellaneous Factors

Many of these factors operate together in acutely ill patients

❑ DRUGS:

- A **very common** cause of secondary immunodeficiency, ➔ **eliminating the offending drug** ➔**improve the immune response.**
- During **cytotoxic therapy for malignancy** ➔Patients develop **neutropenia**
- **Damage to T and B cells** is an expected side effect of **corticosteroids, cytotoxic drugs, and the immunosuppressive regimens** used in ➔autoimmune disease and transplant rejection prophylaxis.

- Patients should be aware ➔ **opportunistic infection.**
- **Other drugs** can cause ➔ **antibody deficiency**

❑B-cell Malignancy

- Myeloma and chronic lymphocytic leukemia
- Both may produce **large amounts of monoclonal immunoglobulin (paraprotein),** but ➔they **have low levels of antibody against pathogens**.

- Myeloma and chronic lymphocytic leukemia are **very common causes of secondary immunodeficiency** in the **elderly.**
- **Thymoma** is ➔ a **rare tumor in the** epithelial cells of the thymus **that can cause immunodeficiency.**

❑ Kidney Disease

- In **nephrotic syndrome** ➔
  - ➢ significant **renal protein loss**
  - ➢ a **reduction in blood levels of IgG and IgA with normal IgM.**

- In **severe diarrheal diseases** ➔ Igs can lost via the gut .
- **Renal failure and diabetes** ➔ cause **secondary phagocyte defects.**

❑ Nutrition

- **Deficiency of zinc and magnesium** ➔ **impairs cell-mediated immunity,** ➔ **particularly T_H1-pattern cytokine secretion.**
- ➔This can occur in **postoperative patients.**
- Although **vitamins,** especially **vitamins A and E**, are required by the immune system, their role is **less significant than mineral nutrients.**

❑ Infections

- Infections can also **cause immunodeficiency.**
- **Malaria and congenital rubella** may ➔ cause **antibody deficiency.**
- **Measles** is well known for ➔ causing **defects in cell-mediated immunity**-sometimes enough to **reactivate tuberculosis.**

❑ Physiologic Stress

- Stress has **potent affects on the adaptive immune system**.
- **Lymphocytes** have **receptors for** both:

  epinephrine (adrenaline) and corticosteroids.

➔ Secreted in response to➔ **stress**

epinephrine ➔ mediate **rapid-onset, short-term effects**
corticosteroids ➔ mediating **longer-term effects.**

- **Physiologic stress**, such as **endurance training**, can therefore ➔ **inhibit immune responses to infection.**
- **Psychological stress** can have **negative effects on the immune system in the short and long term.**
- **How important this is clinically is unclear, but physiologic stress should be considered in patients with recurrent infection.**