

# **Basic immunology**

**Congenital and acquired  
immunodeficiencies**

# Groups of immunodeficiencies

## I. Congenital

- 1) Phagocyte cell deficiencies
- 2) Complement deficiencies
- 3) Severe combined immunodeficiency syndrome (SCID)
- 4) T – cell deficiencies
- 5) B - cell deficiencies

## II. Acquired

- 1) Malignant transformations (tumors, especially diseases of the hematopoietic system)
- 2) Systemic diseases (autoimmune disease, sarcoidosis)
- 3) Infectious diseases/AIDS
- 4) Medication caused immunosuppression (autoimmune diseases, transplantation)
- 5) Malnutrition
- 6) Burn

# **General clinical symptoms**

- **Recurrent infections**
- **Skin and mucosa inflammation**
- **Chronic diarrhea**
- **Tiredness**
- **Hepato-splenomegaly**
- **Autoimmunity**
- **Chronic osteomyelitis**

# **Diagnostics**

- **Anamnese, focusing on infections**
- **Familiar anamnese for inborn defects**
- **Body height, weight, development**
- **Response for vaccination**
- **Labordiagnostics:**  
**Tests for T- , B - , NK-cell and neutrophil functions,  
Complement-assay**
- **Genetic background**

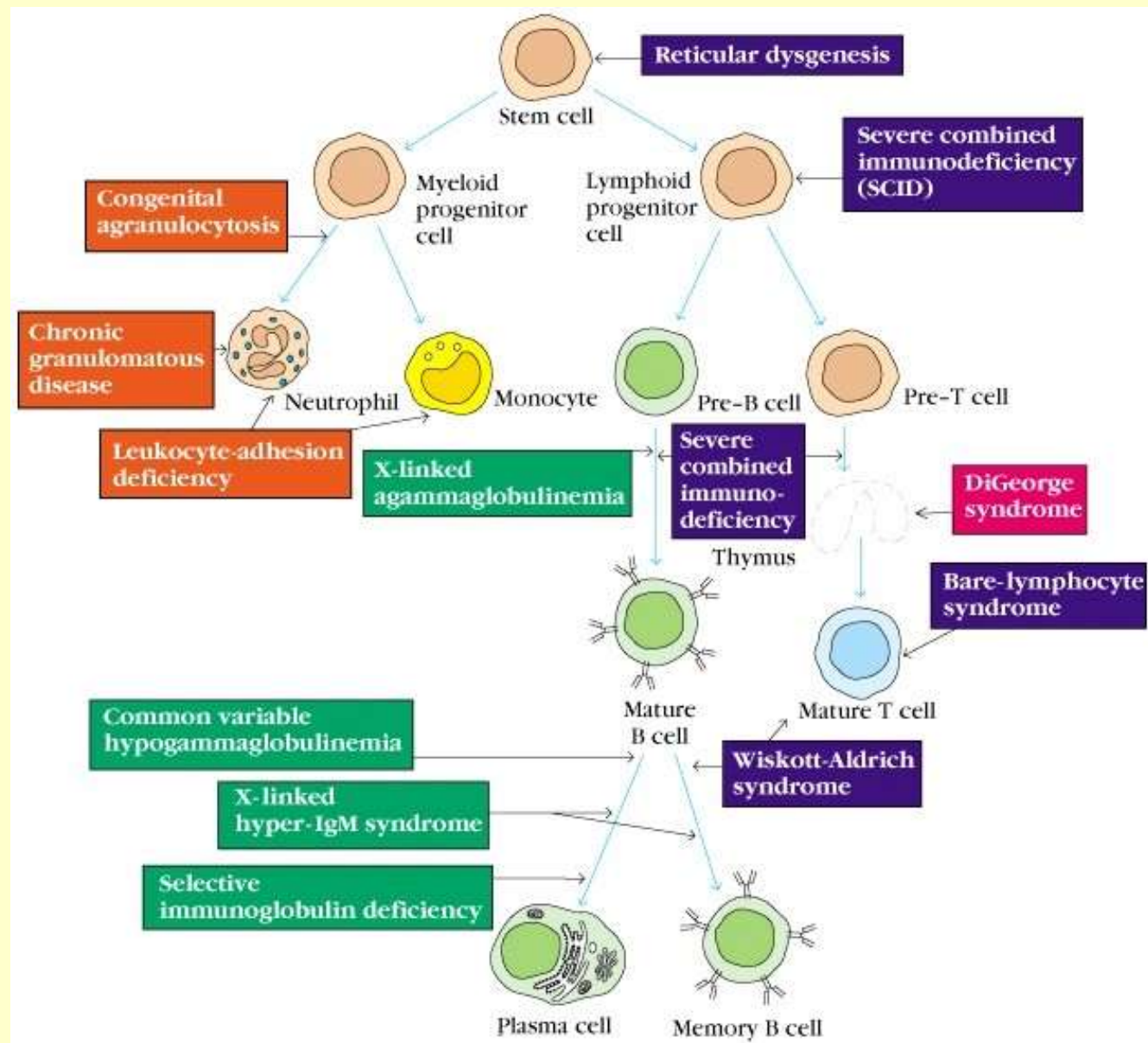
# Groups of congenital immunodeficiencies

Innate immune deficiencies

B – cell deficiencies

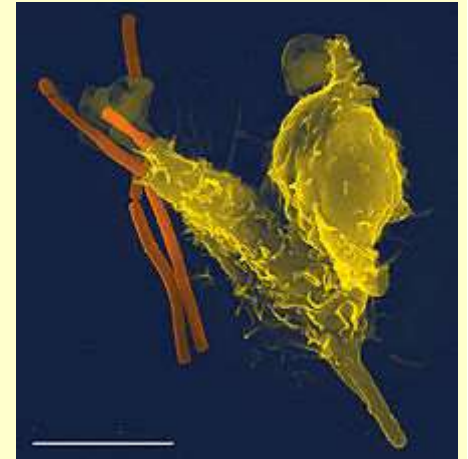
T- and B - cell deficiencies

T – cell deficiencies



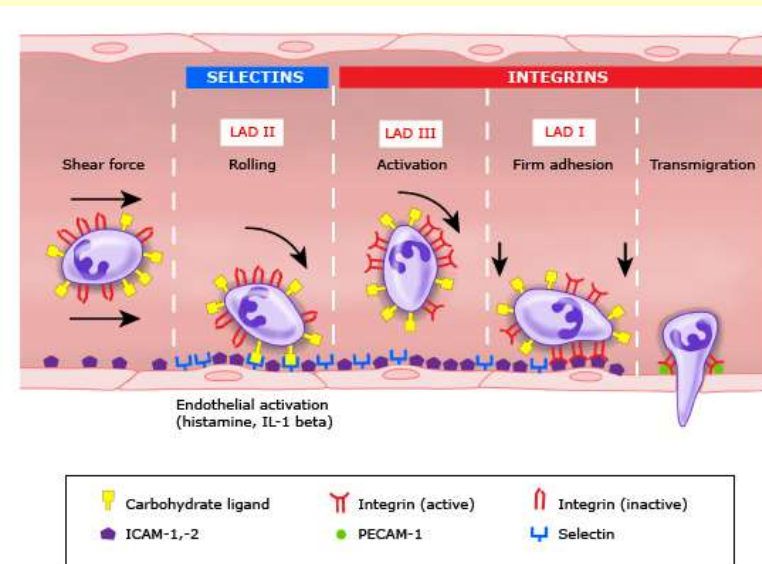
# **Most frequent immunodeficiencies of innate immunity**

- **Granulocyte/monocyte granulum- defects**
- **Intracellular killing defects**
- **Chemotaxis, adhesion defects**
- **PAMP/TLR- defects**
- **NK-cell defects**



# Defects of adhesion and chemotaxis

- LAD (Leukocyte Adhesion Deficiency) I – CD11/18 (LFA-1)
- LAD II – L-Selektin (fucosylation) – defects of ligand- Bacterial and fungi infections
- WHIM - CXCR4 /SDF-1-Receptordefects (hypogammaglobulinaemia, infections, Myelochatexis, leukopenia neutropenia)



# Chediak – Higashi syndrome

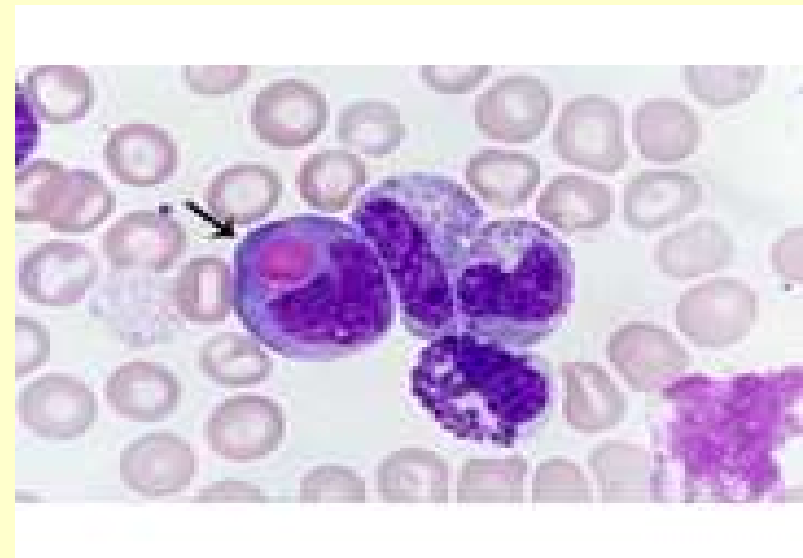
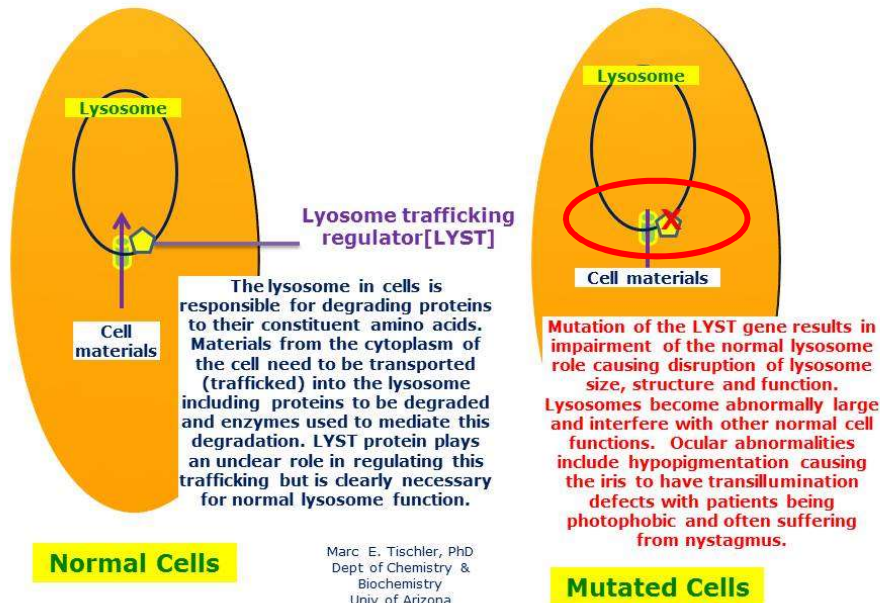
Defects of chemotaxis and intracellular bacterial killing

CHS1-Genemutation (LYST –lysosomal transport protein)

Chemotaxid defects of granulocytes and monocytes

Defects of NK-cell function

## Chédiak-Higashi Syndrome Defective gene: LYST





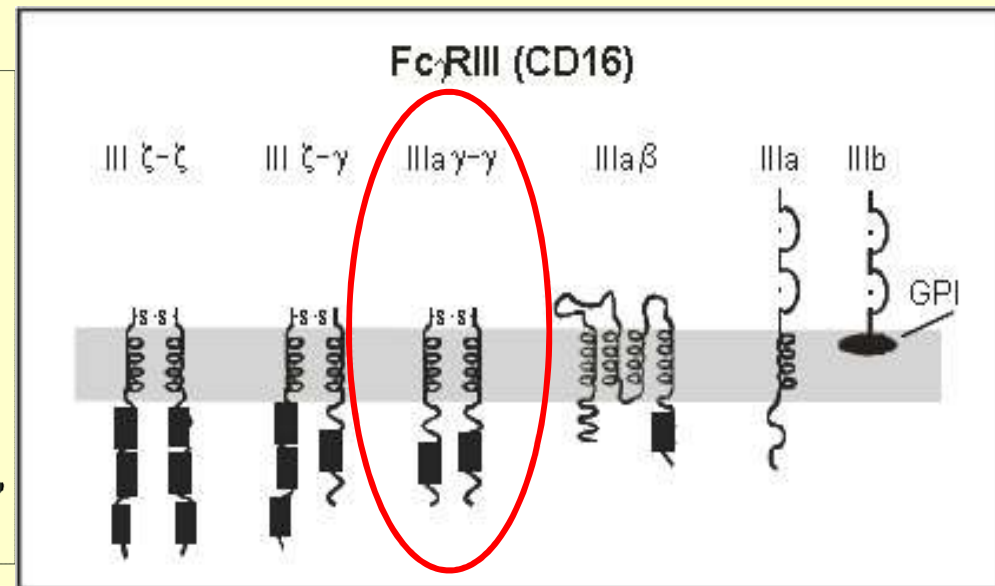
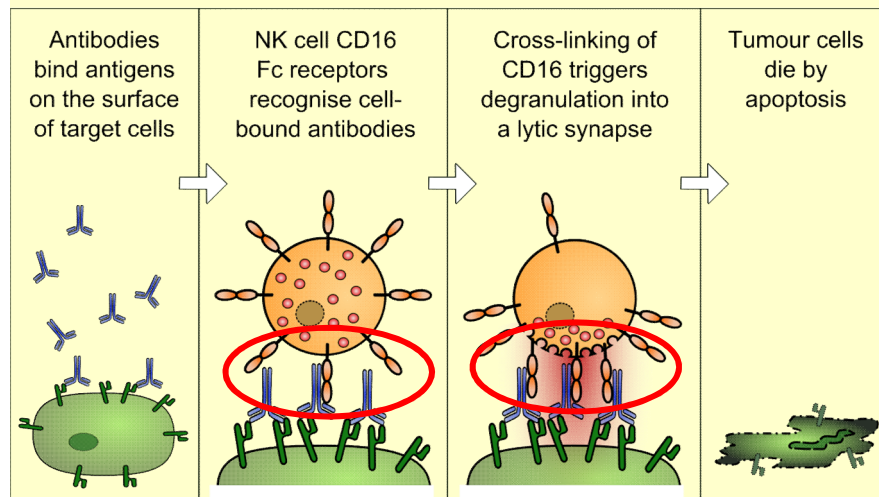
# NK-cell - deficiency

**FCGR3A-Genmutation - CD16 – FcR $\gamma$ IIIa**

**Defect affects NK-cells**

**HSV-, VZV-, EBV- Virusinfections**

**NK-cell numbers are normal**



# Complement - deficiencies

- C1-, C2-, C4-deficiencies – immunocomplex depositions
- C3-deficiency– Infection caused by encapsulated pyogenic bacteria *Pneumococcus*, *Streptococcus* or *Hemophilus*
- Terminal component (MAC) deficiencies - systemic Neisseria infections
- Lectin – pathway –deficiencies – microbial infections in the childhood (6-18 months).

Following immunosuppression, in autoimmune disease or AIDS can occurs as secunder defects in adults.

Deficiency of MBL is quite frequent, but the infection rates are not higher in the involved patients.

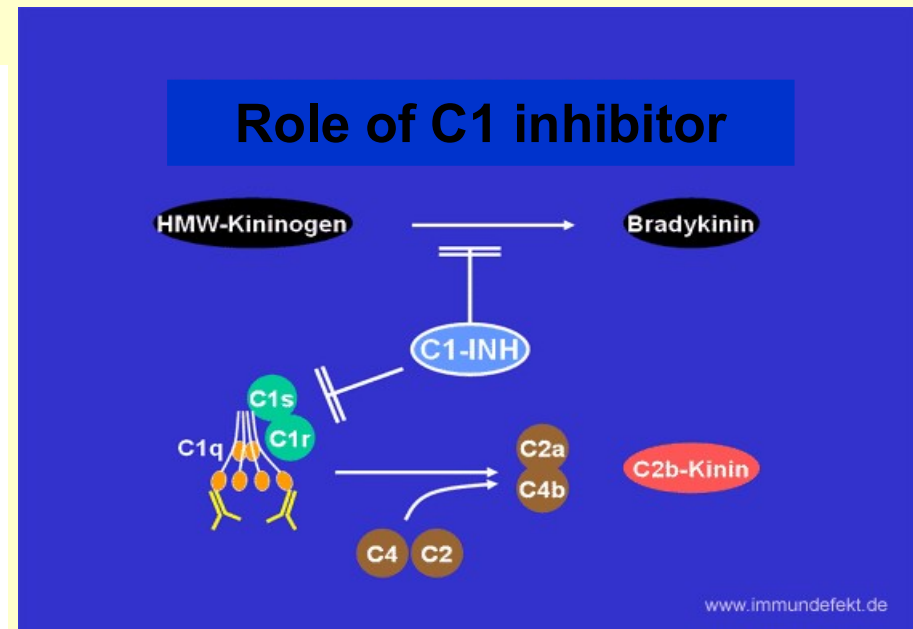
# Complement- deficiencies

## C1-inhibitor- deficiency (hereditary angioneurotic oedema)

Incidency: 2/100,000.

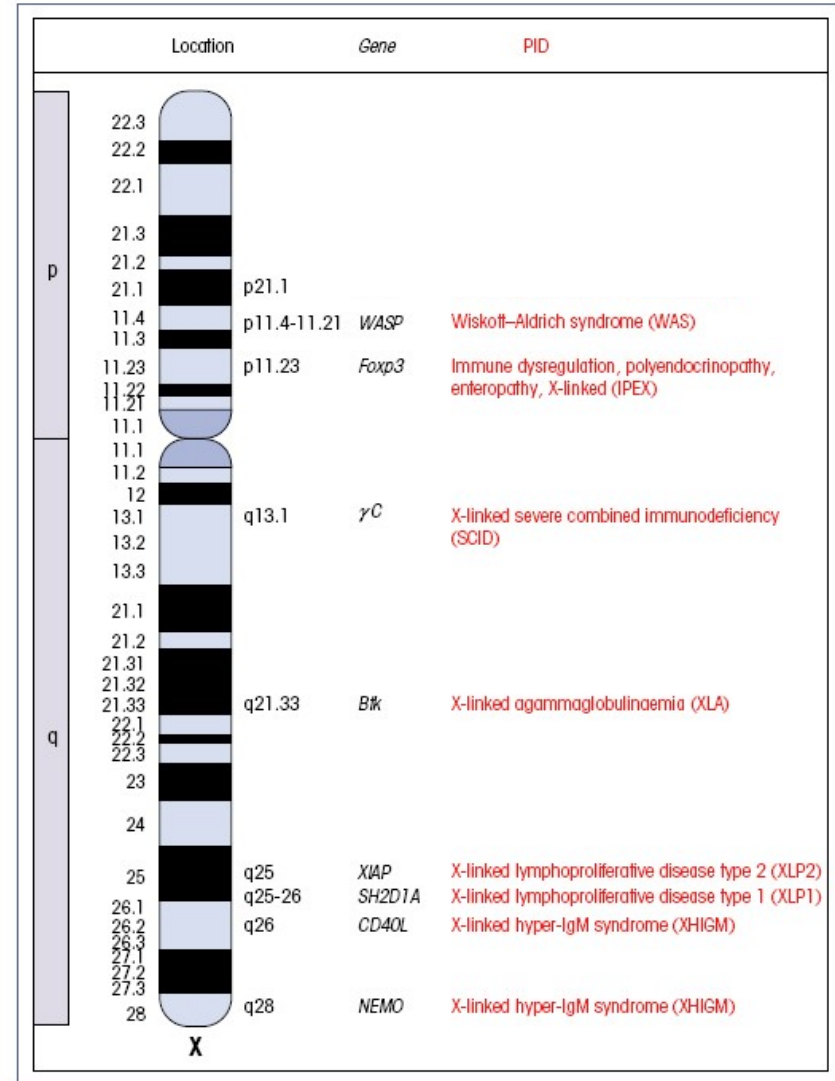
Defects of C1-esterase-inhibitor (C1-INH). Regulator protein of the classical pathway. C1-INH is not an enzyme; inhibits the initiation of several cascade system (fibrinolysis, kinin-kallikrein system, complement).

Symptoms: abdominal pain, diarrrhea, oedema-airway obstruction



# Most frequent immunodeficiencies of adaptive immunity

- Usually recessive genetic diseases
- X –linked diseases



# **Sever combined immunodeficiencies (SCID)**

- **T- and B-cell defects**
- **Higher risks for infection in 3-6 months old**
- **In SCID the skin, airways and gastrointestinal tracts are affected**
- **The thymus, lymph nodes, tonsilles are not detectable**

# Background of SCID

- **Defects of Enzymes involved in nucleotide synthesis (ADA – adenosindesaminase, PNP – purinnucleotidophosphorilase)**
- **X-linked defects – defects of common cytokine receptor gamma chain (IL-2, IL-4, IL-7, IL-9, IL-15)**
- **Autosomal SCID – DNA repair defects**
- **RAG-1-, RAG-2- deficiency (Omenn's syndrome)**
- **ZAP-70- deficiency**



# SCID



Normal

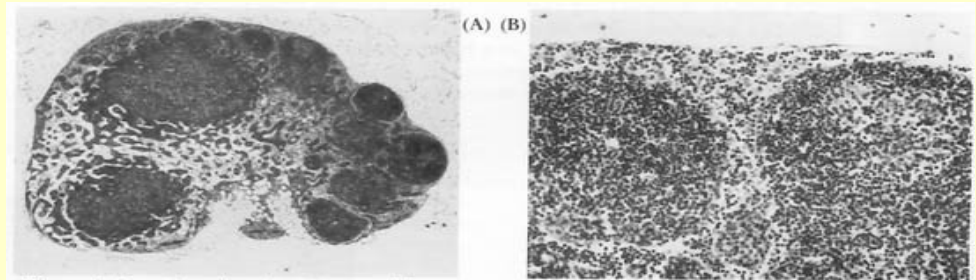
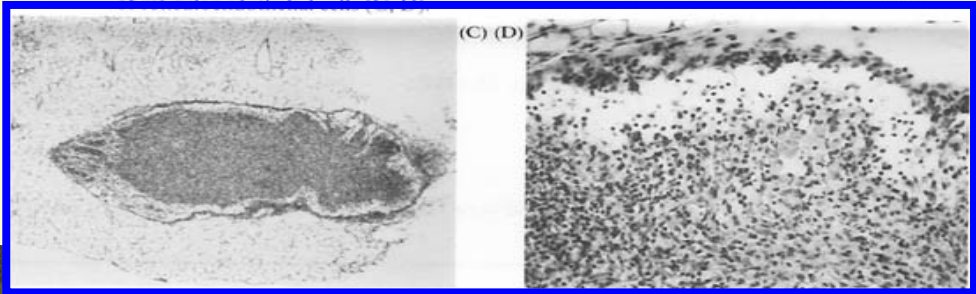
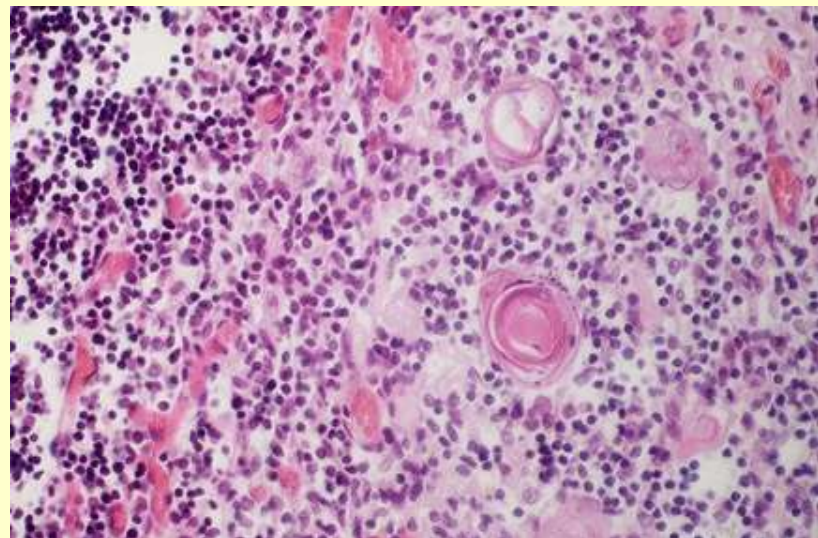


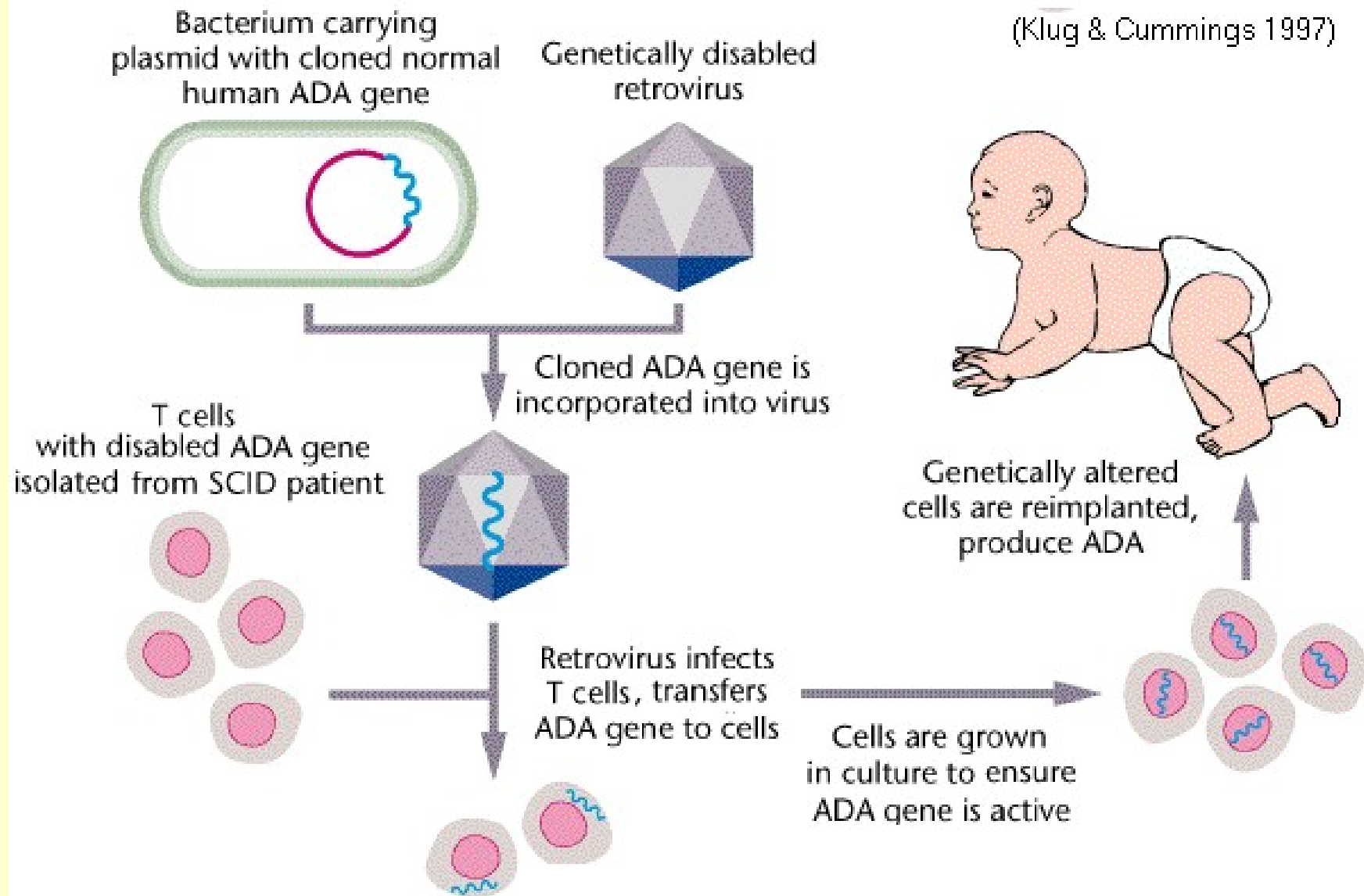
Figure 1 Lymph node of a  $+/+$  control has numerous, prominent follicles with germinal centers (A, B) while the  $scid/scid$  littermate has only a small, rudimentary lymph node consisting



SCID

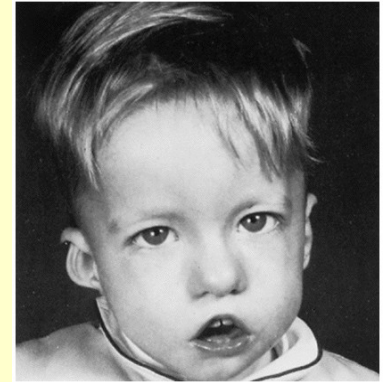


# Treatment of ADA-SCID

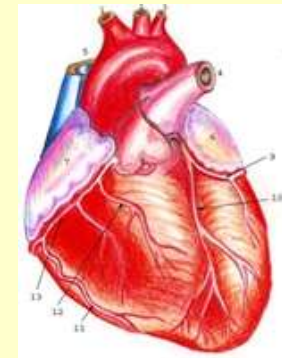




# DiGeorge- syndrome



- The embryological defects of 3. and 4. pharyngeal arches
- Embryological defects of thymus epithel
- Developmental defects of other organs (parathyroids)
- Defects in T-cell development
- Defects of T- dependent antibody production
- Defects of cellular immune response
- „Nude” micemodell



# B- cell deficiencies

## X-linked

### Hyper-IgM syndrome

- Defects of CD40 ligand,
- No isotype switch

## X-linked

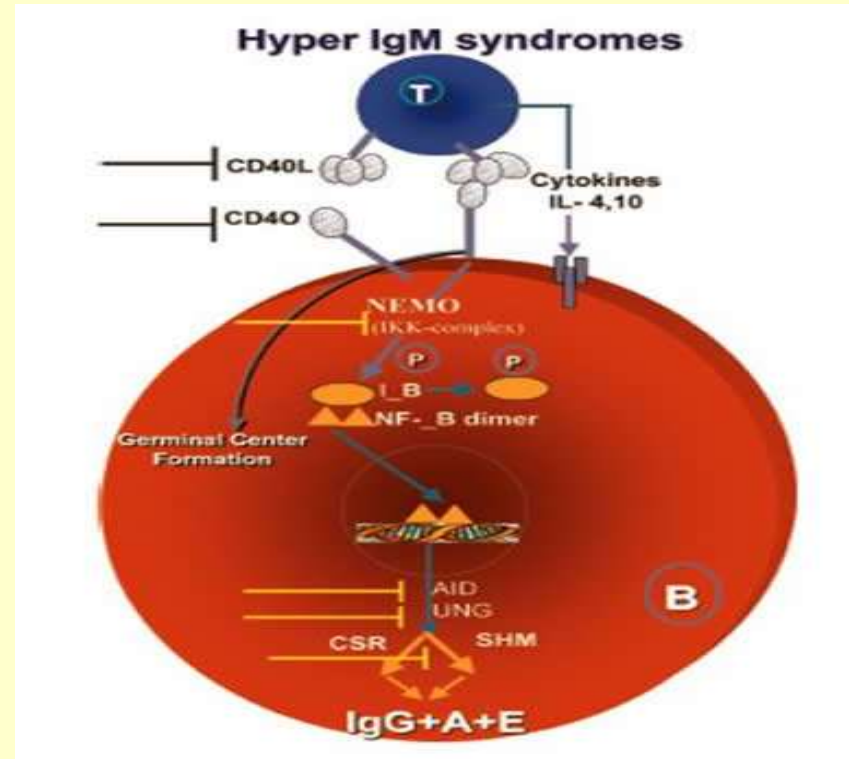
### Agammaglobulinaemia

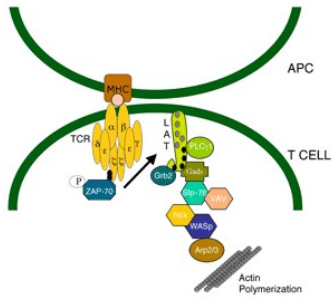
- Few B cells
- Defects of Btk

(Bruton tyrosine kinase)

### Selektive IgA deficiency

- MHC-coupled, no IgA synthesis,
- Airway infections,
- Frequency: 1/400!





# Wiskott-Aldrich syndrome

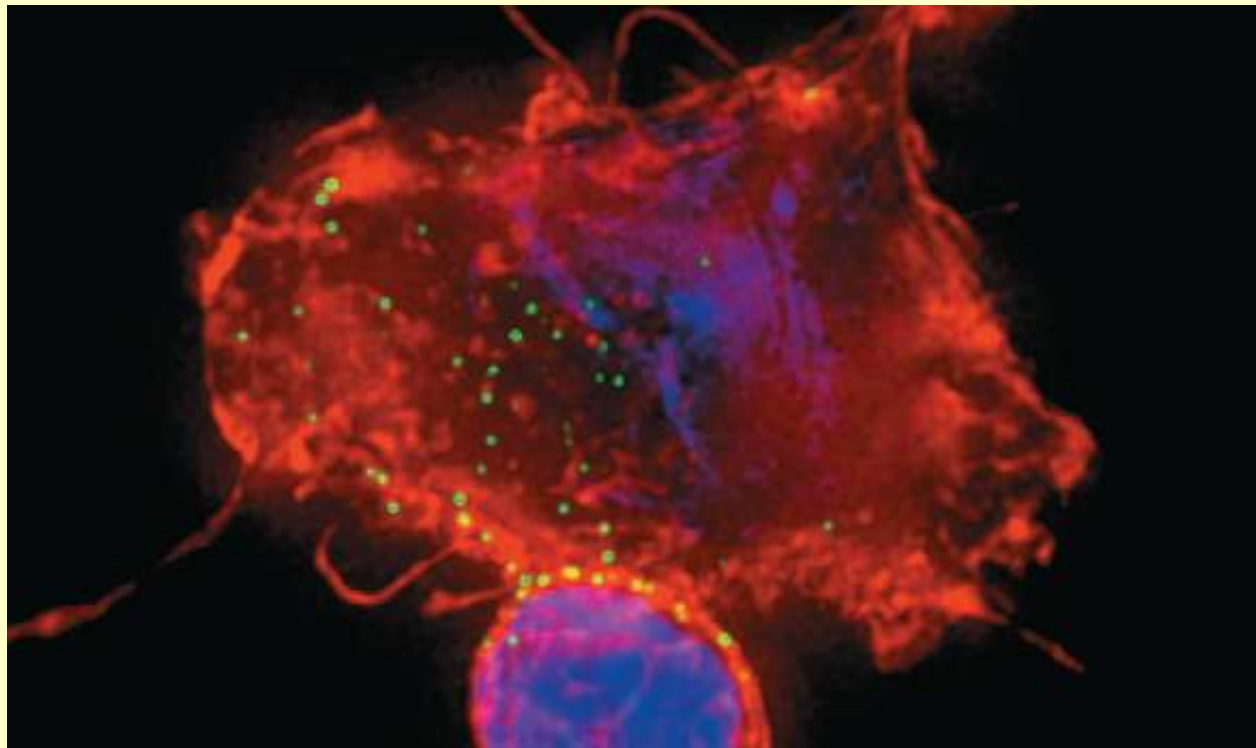


- **X-linked**
- **Low Ig production, defects in T cell activation**
- **Defects in the glycosylation of CD43**
- **Thrombocytopenic purpura**
- **Cytoskeletal defects of T-cells and platelets**



## **II. Secondary immunodeficiencies**

### **HIV-AIDS**



# Epidemics (WHO)

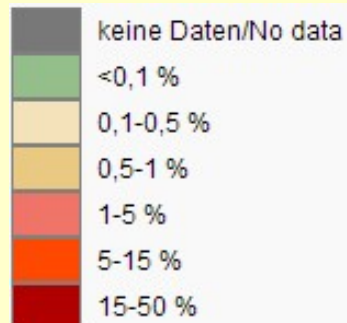
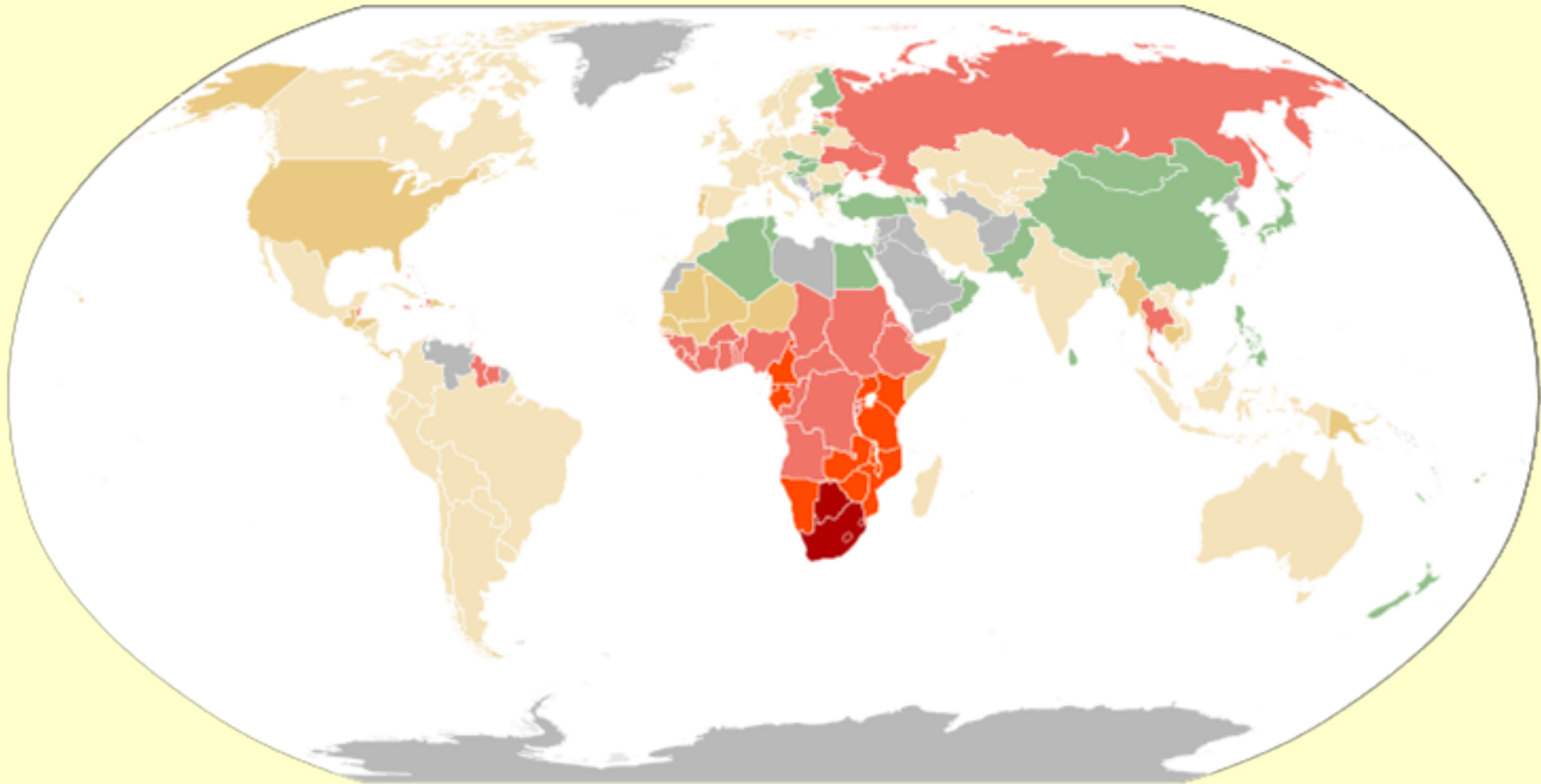
	2000	2005	2010	2011	2012	2013	2014	2015/(2016*)
<b>People living with HIV</b>	<b>28.9 million</b> [26.5 million– 31.7 million]	<b>31.8 million</b> [29.4 million– 34.5 million]	<b>33.3 million</b> [30.8 million– 36.1 million]	<b>33.9 million</b> [31.4 million– 36.7 million]	<b>34.5 million</b> [31.9 million– 37.4 million]	<b>35.2 million</b> [32.6 million– 38.1 million]	<b>35.9 million</b> [33.3 million– 38.9 million]	<b>36.7 million</b> [34.0 million– 39.8 million]
<b>New HIV Infections (total)</b>	<b>3.2 million</b> [2.9 million– 3.5 million]	<b>2.5 million</b> [2.3 million– 2.8 million]	<b>2.2 million</b> [2.0 million– 2.5 million]	<b>2.2 million</b> [1.9 million– 2.5 million]	<b>2.2 million</b> [1.9 million– 2.4 million]	<b>2.1 million</b> [1.9 million– 2.4 million]	<b>2.1 million</b> [1.9 million– 2.4 million]	<b>2.1 million</b> [1.8 million– 2.4 million]
<b>New HIV infections (aged 15+)</b>	<b>2.7 million</b> [2.5 million– 3.0 million]	<b>2.1 million</b> [1.9 million– 2.3 million]	<b>1.9 million</b> [1.7 million– 2.1 million]	<b>1.9 million</b> [1.7 million– 2.2 million]	<b>1.9 million</b> [1.7 million– 2.2 million]	<b>1.9 million</b> [1.7 million– 2.2 million]	<b>1.9 million</b> [1.7 million– 2.2 million]	<b>1.9 million</b> [1.7 million– 2.2 million]
<b>New infections (aged 0–14)</b>	<b>490 000</b> [430 000– 560 000]	<b>450 000</b> [390 000– 510 000]	<b>290 000</b> [250 000– 350 000]	<b>270 000</b> [220 000– 330 000]	<b>230 000</b> [190 000– 290 000]	<b>200 000</b> [160 000– 250 000]	<b>160 000</b> [130 000– 220 000]	<b>150 000</b> [110 000– 190 000]
<b>AIDS-related deaths</b>	<b>1.5 million</b> [1.3 million– 1.8 million]	<b>2.0 million</b> [1.7 million– 2.3 million]	<b>1.5 million</b> [1.3 million– 1.7 million]	<b>1.4 million</b> [1.2 million– 1.7 million]	<b>1.4 million</b> [1.2 million– 1.6 million]	<b>1.3 million</b> [1.1 million– 1.5 million]	<b>1.2 million</b> [990 000– 1.4 million]	<b>1.1 million</b> [940 000– 1.3 million]
<b>People accessing treatment</b>	<b>770 000</b> [680 000– 800 000]	<b>2.2 million</b> [1.9 million– 2.2 million]	<b>7.5 million</b> [6.6 million– 7.8 million]	<b>9.1 million</b> [8.0 million– 9.5 million]	<b>11 million</b> [9.6 million– 11.4 million]	<b>13 million</b> [11.4 million– 13.5 million]	<b>15 million</b> [13.2 million– 15.6 million]	<b>18.2 million</b> [16.1 million– 19.0 million] (*June 2016)  <b>17 million</b> [15.0 million– 17.7 million] (end 2015)
<b>Resources available for HIV (low- and middle-income countries)</b>	<b>4.8 billion</b>	<b>9.4 billion</b>	<b>15.9 billion</b>	<b>18.3 billion</b>	<b>19.5 billion</b>	<b>19.6 billion</b>	<b>19.2 billion</b>	<b>19 billion</b>



# Regional statistics (WHO – 2015 Dec)

Region	People living with HIV (total)	New HIV infections			AIDS-related deaths (total)	Total number accessing antiretroviral therapy
		Total	Aged 15+	Aged 0–14		
Eastern and southern Africa	19.0 million [17.7 million–20.5 million]	960 000 [830 000–1.1 million]	910 000 [790 000–1.1 million]	56 000 [40 000–76 000]	470 000 [390 000–560 000]	10 million
Latin America and the Caribbean	2.0 million [1.7 million–2.3 million]	100 000 [86 000–120 000]	100 000 [84 000–120 000]	2100 [1600–2900]	50 000 [41 000–59 000]	1.1 million
Western and central Africa	6.5 million [5.3 million–7.8 million]	410 000 [310 000–530 000]	350 000 [270 000–450 000]	66 000 [47 000–87 000]	330 000 [250 000–430 000]	1.8 million
Asia and the Pacific	5.1 million [4.4 million–5.9 million]	300 000 [240 000–380 000]	280 000 [220 000–350 000]	19 000 [16 000–21 000]	180 000 [150 000–220 000]	2.1 million
Eastern Europe and central Asia	1.5 million [1.4 million–1.7 million]	190 000 [170 000–200 000]	190 000 [170 000–200 000]	---*	47 000 [39 000–55 000]	320 000
Middle East and North Africa	230 000 [160 000–330 000]	21 000 [12 000–37 000]	19 000 [11 000–34 000]	2100 [1400–3200]	12 000 [8700–16 000]	38 000
Western and central Europe and North America	2.4 million [2.2 million–2.7 million]	91 000 [89 000–97 000]	91 000 [88 000–96 000]	---*	22 000 [20 000–24 000]	1.4 million

# Regional epidemics



**UNAIDS**  
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

UNHCR  
UNICEF  
WFP  
UNDP  
UNFPA  
UNODC  
ILO  
UNESCO  
WHO  
WORLD BANK



**World Health Organization**

# HIV

- lentivirus
- Capable of latent long-term infection
- Two subtypes : HIV-1 (common), HIV-2 (rare)

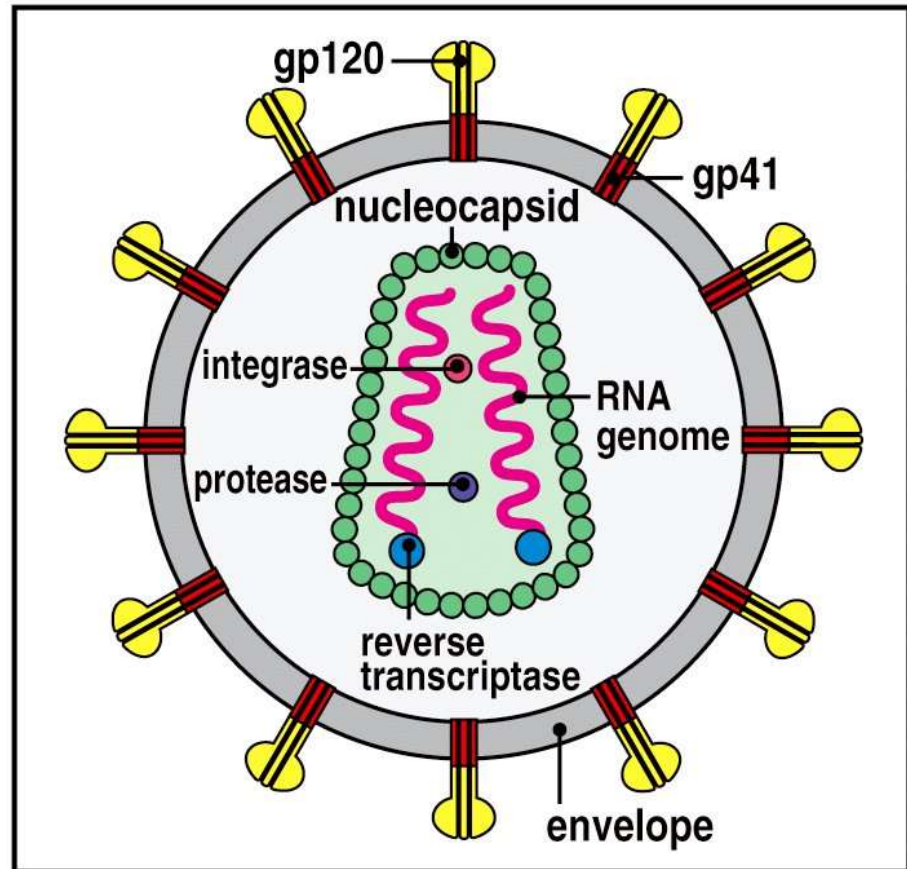
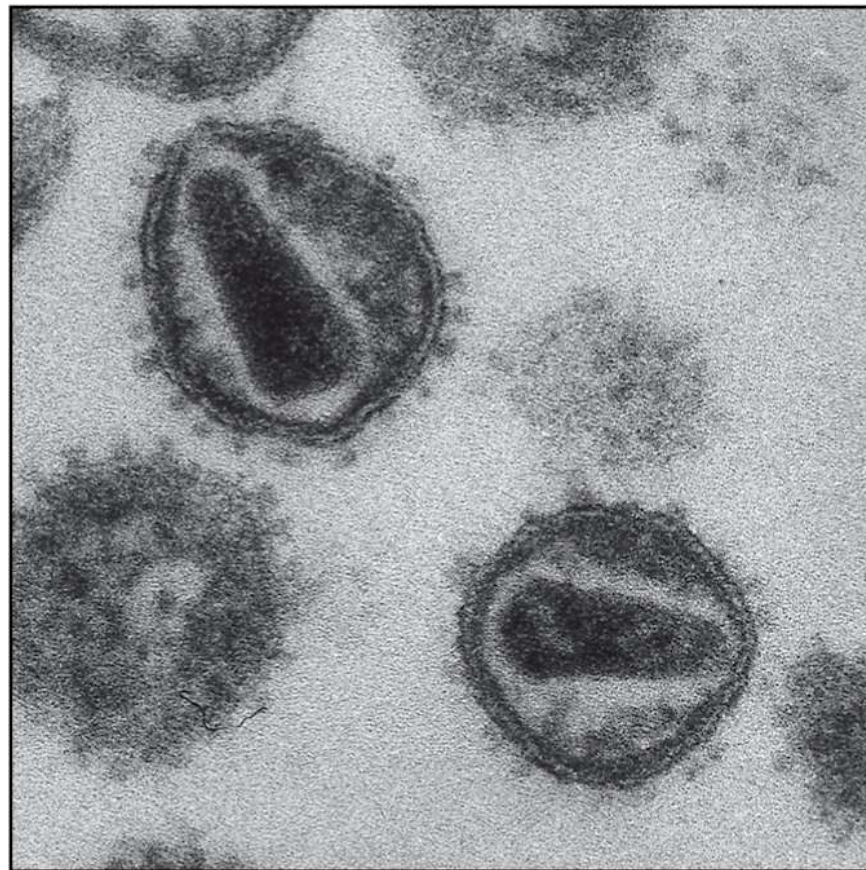
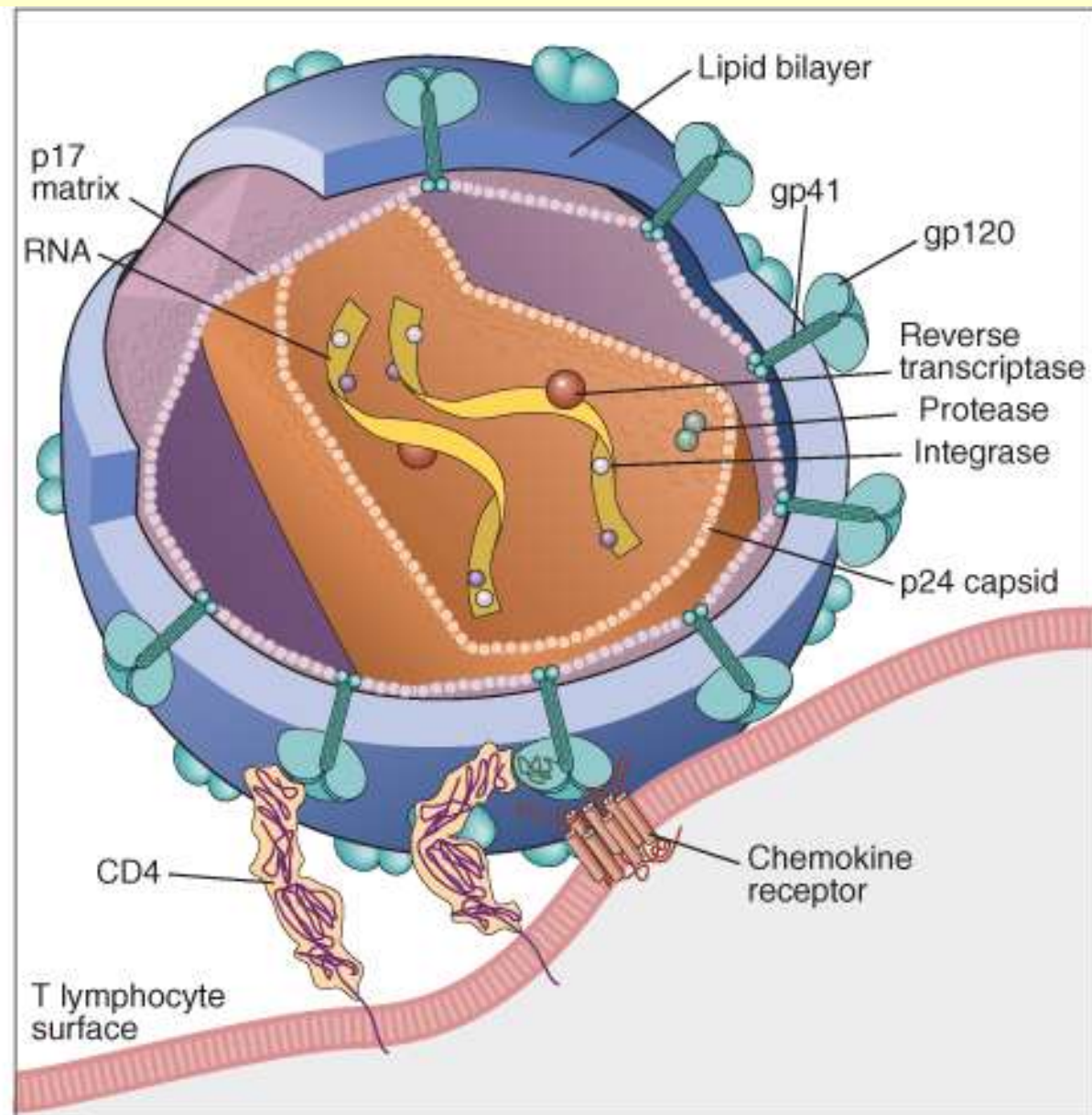


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)



# HIV



# HIV receptors

- **CD4 – gp120**
- **Chemokine receptors**
  - **CXCR4 - T cell trophic virus**
  - **CCR5 – macrophage trophikus virus**
- **DC-SIGN: dendritic cell specific intercellular adhesion molecule 3 (ICAM-3) grabbing non-integrin (Binding of HIV virus to DC-SIGN does not result direct viral entry)**

# The role of DC-s HIV infection

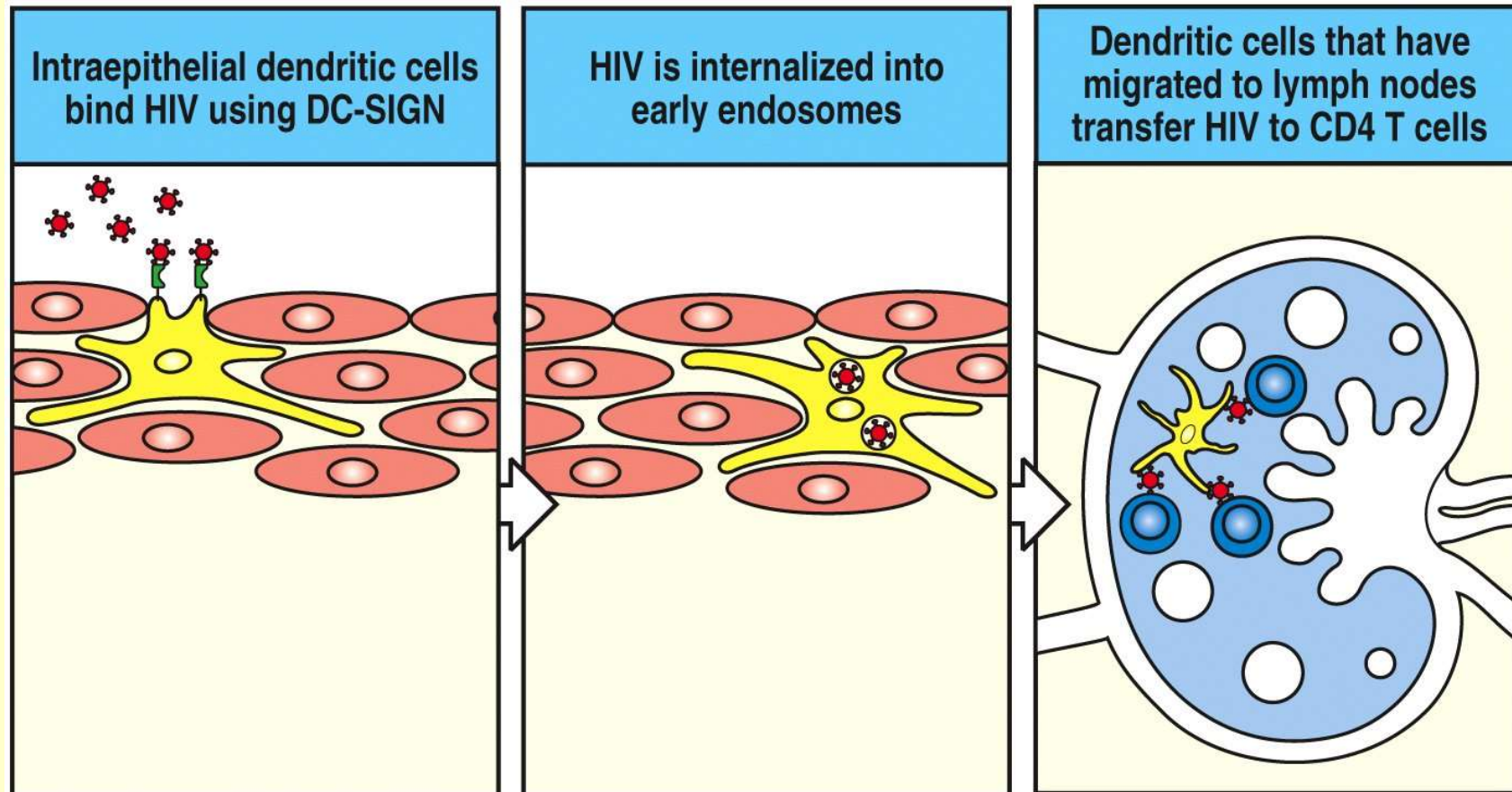
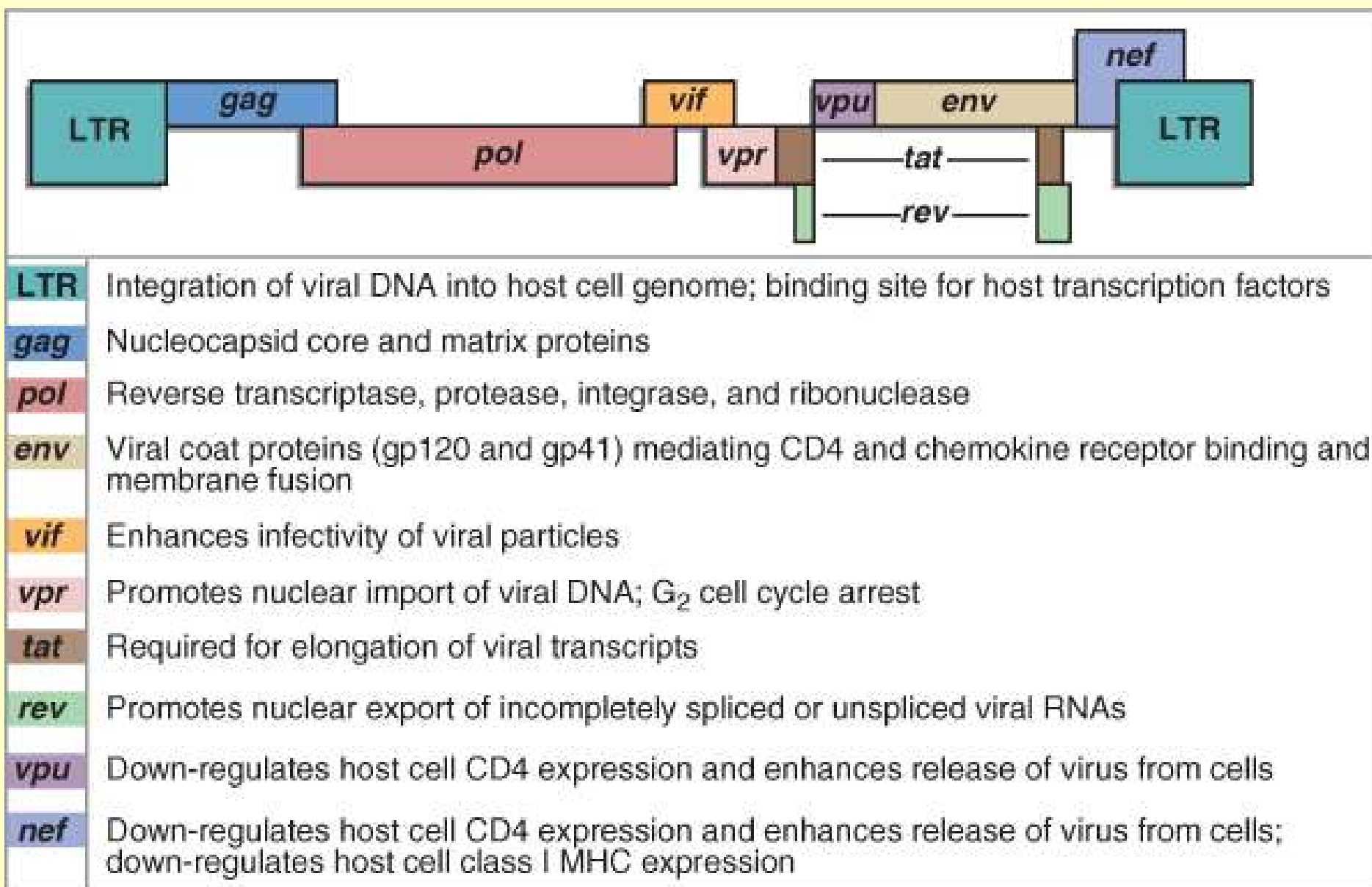
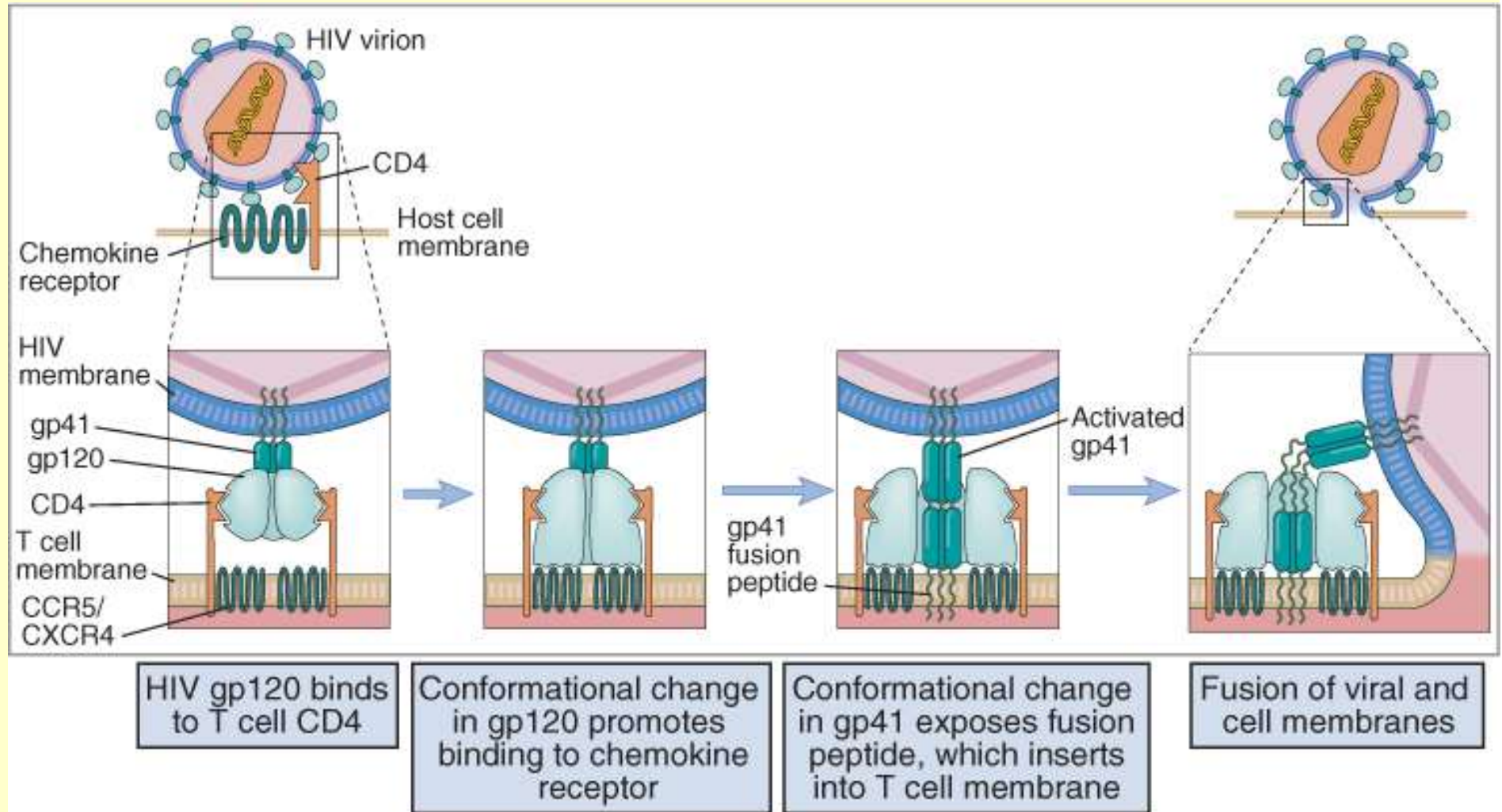


Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

# Genome of HIV

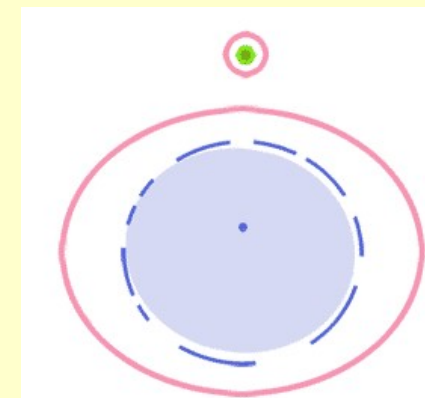
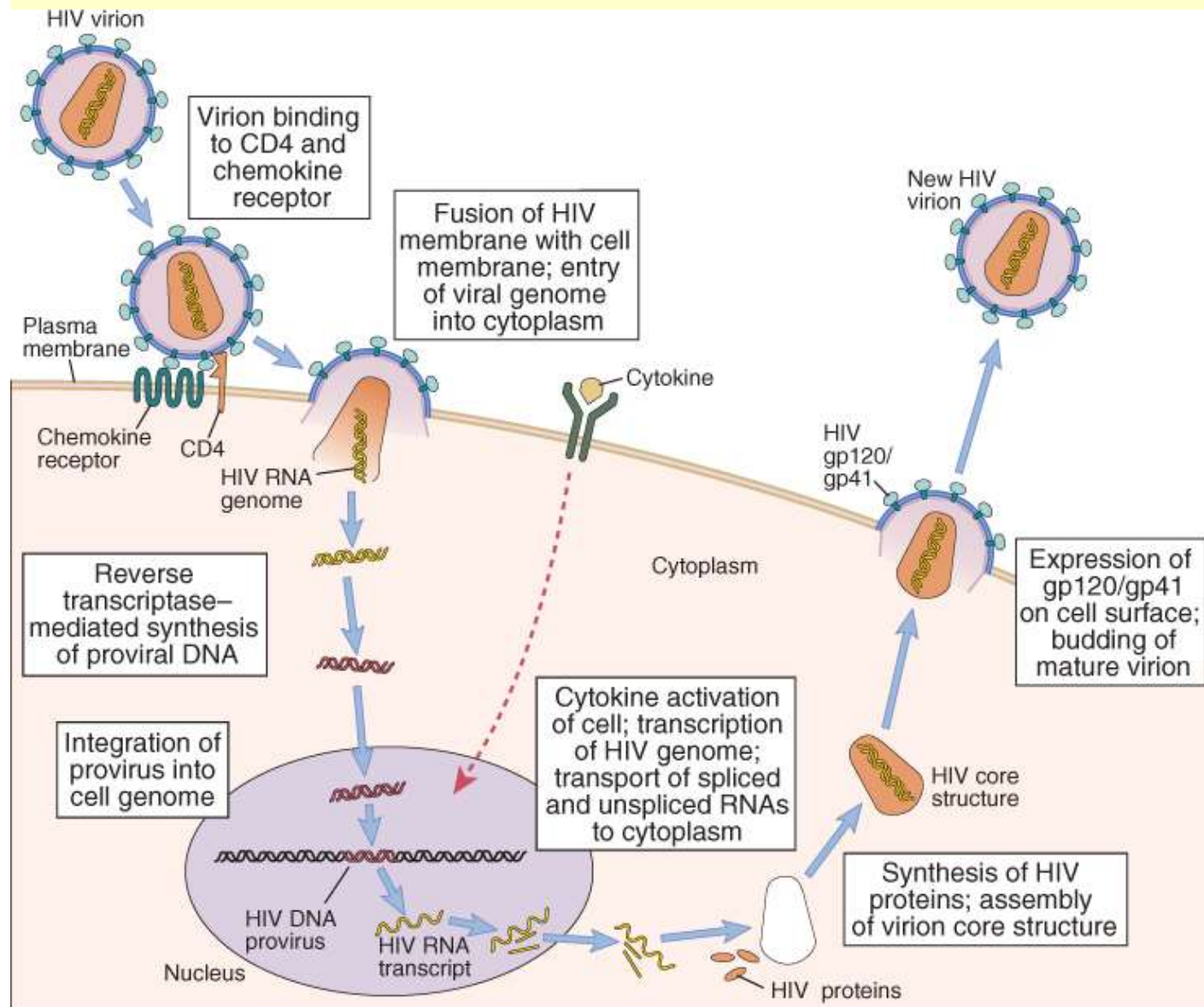
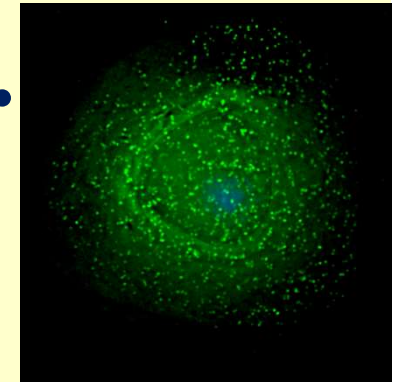


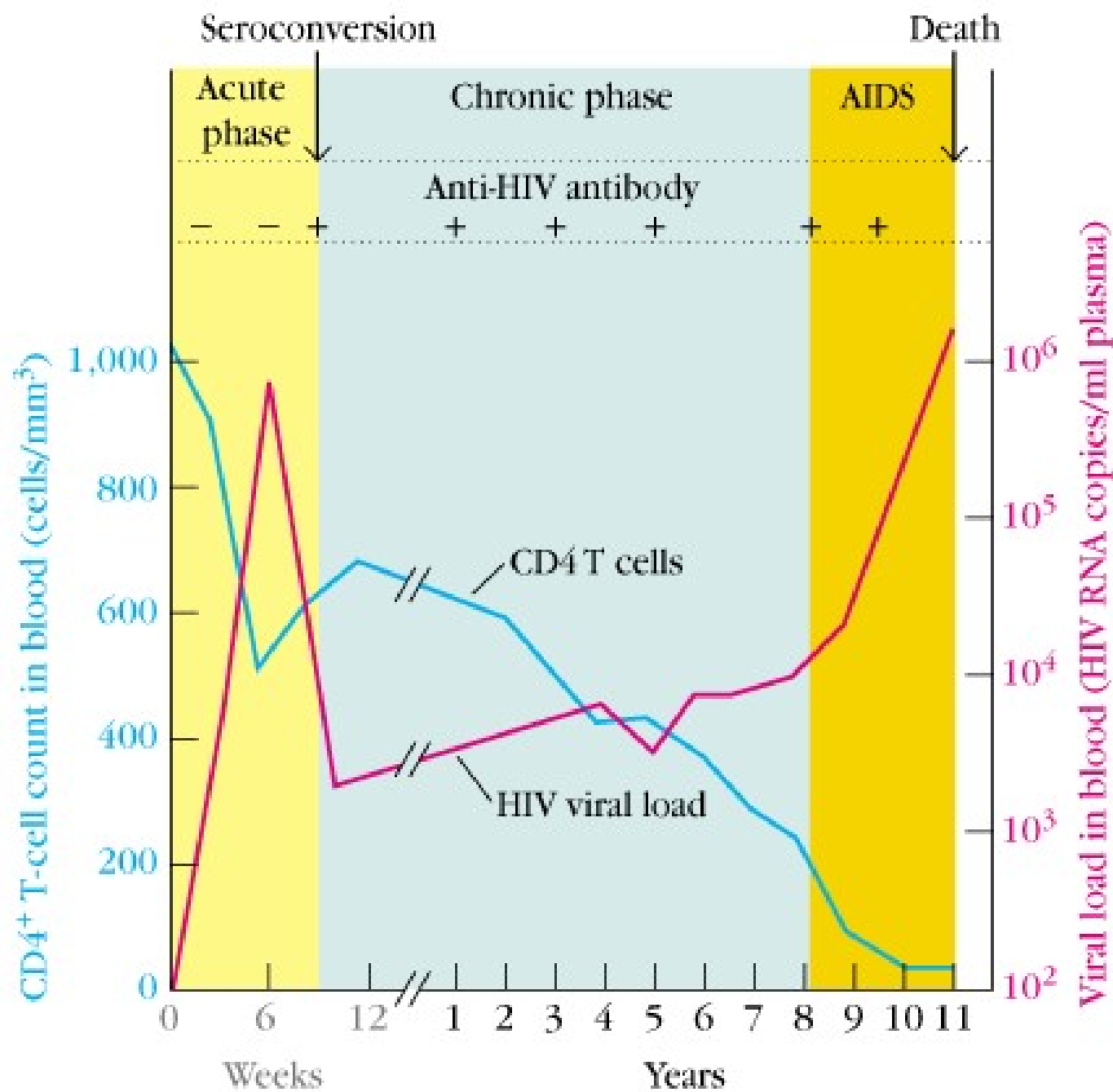
# The life cycle of HIV I.



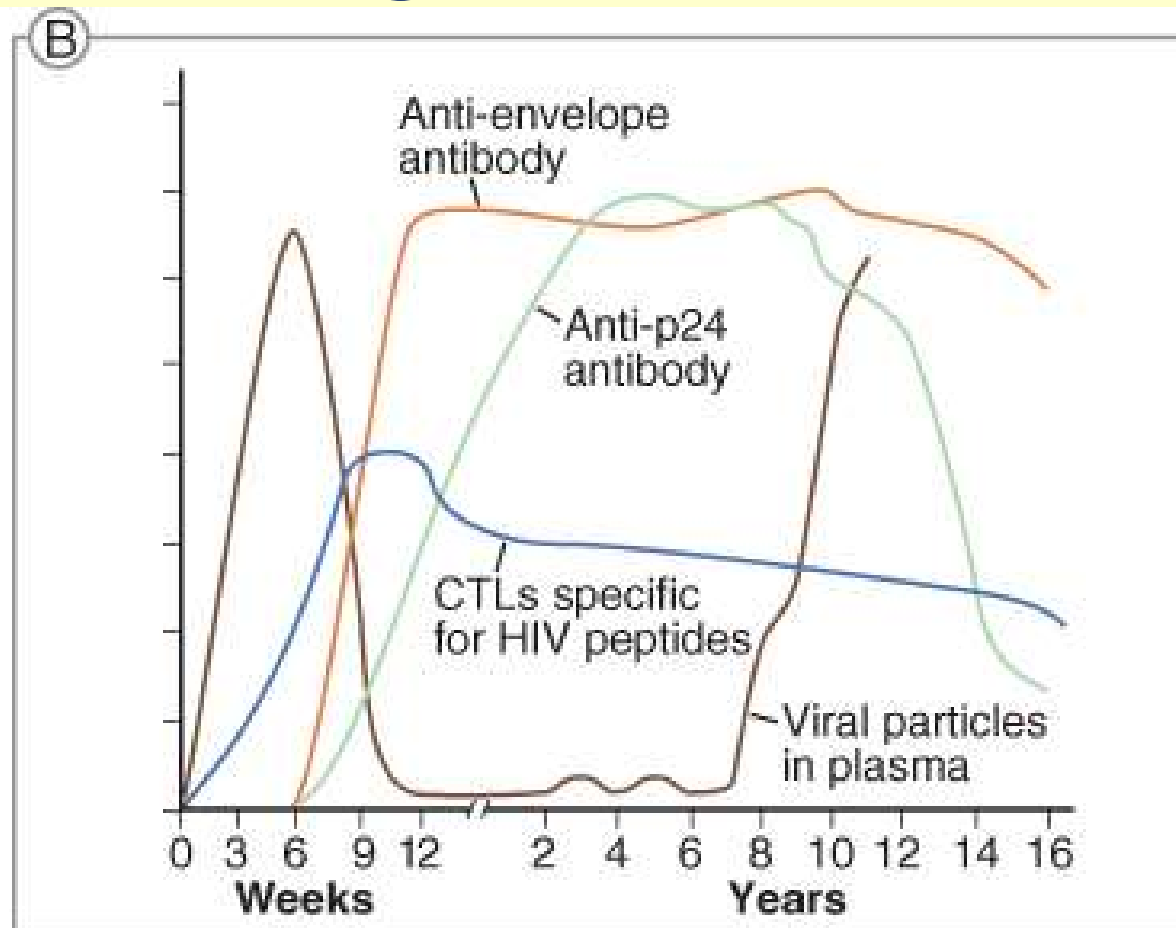


# The life cycle of HIV II.





# Humoral and cellular immunity against HIV





## Clinical categories

**CD4+ T cell numbers**

**A**

**B**

**C**

**> 500/ $\mu$ l**

**A1**

**B1**

**C1**

**200 - 499/ $\mu$ l**

**A2**

**B2**

**C2**

**< 200/ $\mu$ l**

**A3**

**B3**

**C3**

**Green categories represents AIDS syndrome**

# Complications in AIDS

## Opportunistic infections:

- **Parasites:** Toxoplasma, Cryptosporidium, Leishmania, Microsporidium
- **Bacteria:** Mycobacteria strains, Salmonella strains
- **Viruses:** HSV, CMV, VZV

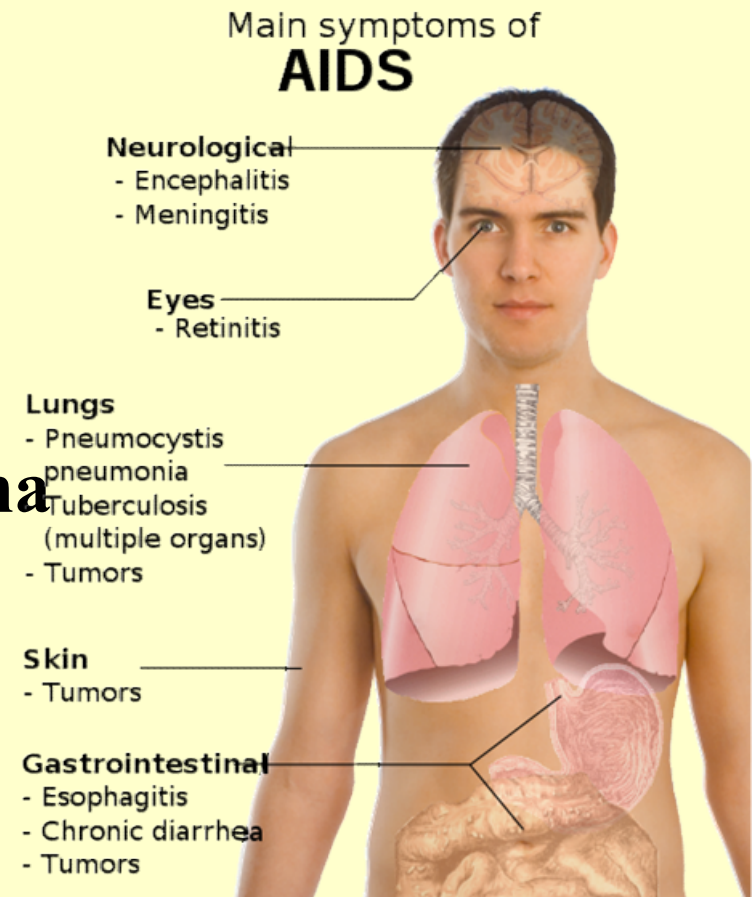
## Tumors:

**Kaposi-sarcoma**

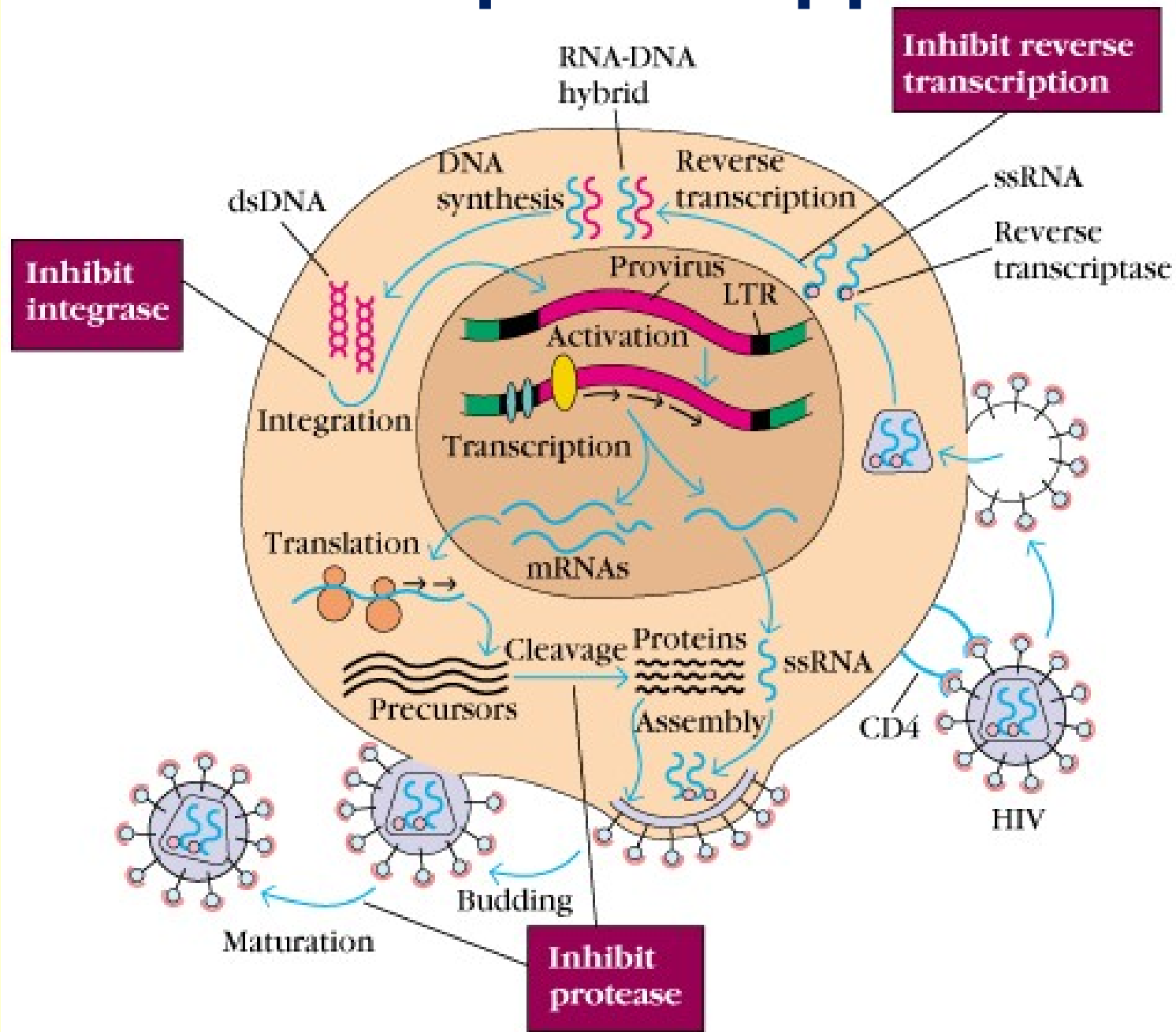
**Non-Hodgkin-lymphoma**

**EBV-positive Burkitt lymphoma**

**Lymphoma in the CNS**



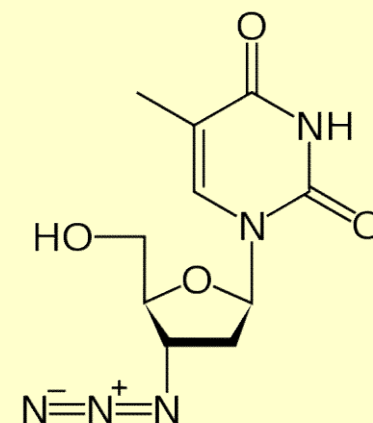
# Current therapeutic approaches



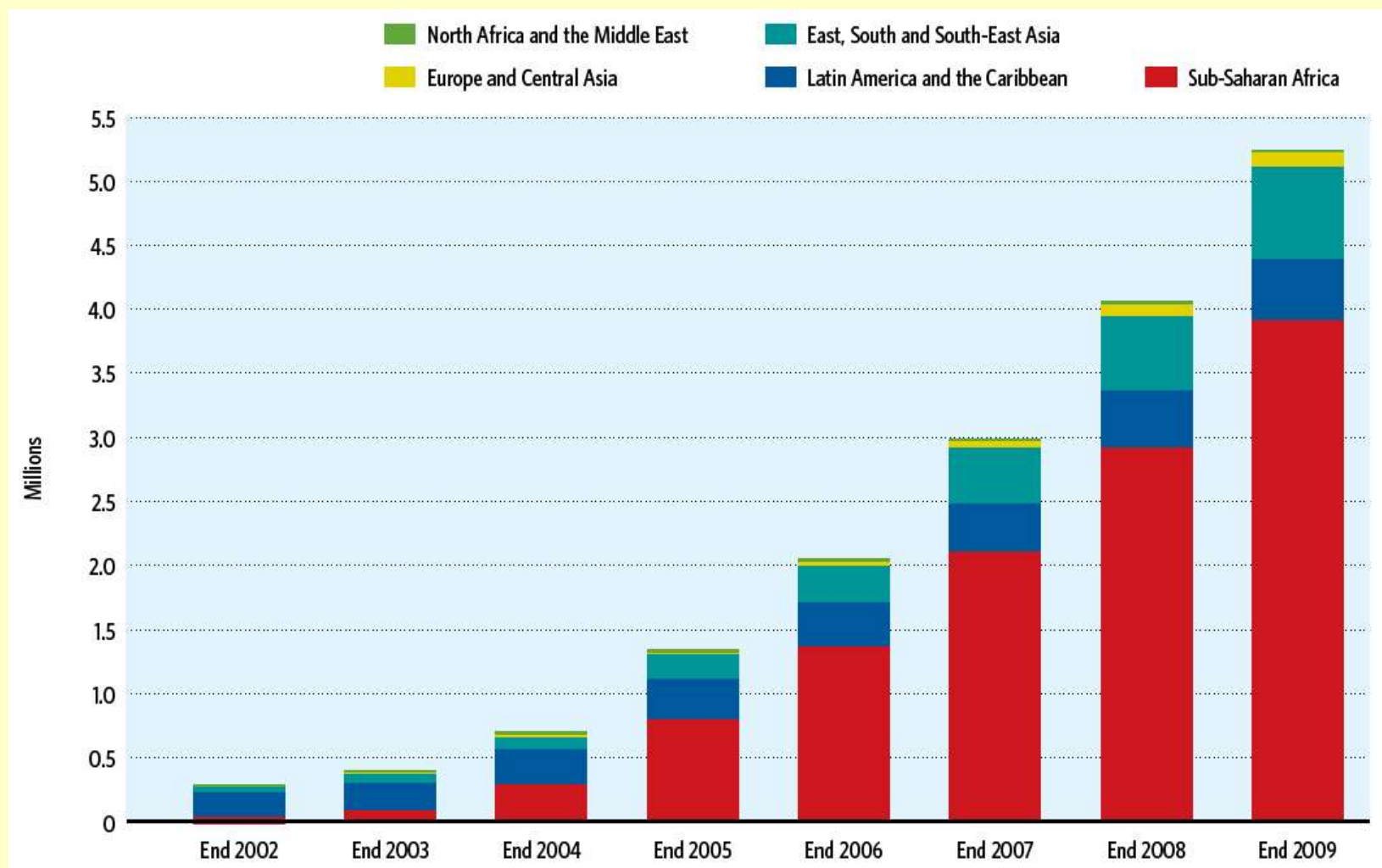
**TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE**

Generic name (other names)	Typical dosage	Some potential side effects
<b>Reverse transcriptase inhibitors: Nucleoside analog</b>		
Didanosine (Videx, ddl)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (Epivir, 3TC)	1 pill, 2 times a day	Usually none
Stavudine (Zerit, d4T)	1 pill, 2 times a day	Peripheral neuropathy
Zalcitabine (HIVID, ddC)	1 pill, 3 times a day	Peripheral neuropathy, mouth inflammation, pancreatic inflammation
Zidovudine (Retrovir, AZT)	1 pill, 2 times a day	Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia
Pill containing lamivudine and zidovudine (Combivir)	1 pill, 2 times a day	Same as for zidovudine
<b>Reverse transcriptase inhibitors: Nonnucleoside analogues</b>		
Delavirdine (Rescriptor)	4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine	Rash, headache, hepatitis
Nevirapine (Viramune)	1 pill, 2 times a day	Rash, hepatitis
<b>Protease inhibitors</b>		
Indinavir (Crixivan)	2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine	Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Nelfinavir (Viracept)	3 pills, 3 times a day with some food	Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Ritonavir (Norvir)	6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine	Nausea, vomiting, diarrhea, abdominal pain, headache, prickling sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance
Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)	6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal	Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance

SOURCE: JG Bartlett and RD Moore, 1998, Improving HIV therapy, *Sci. Am.* 279(1):87.

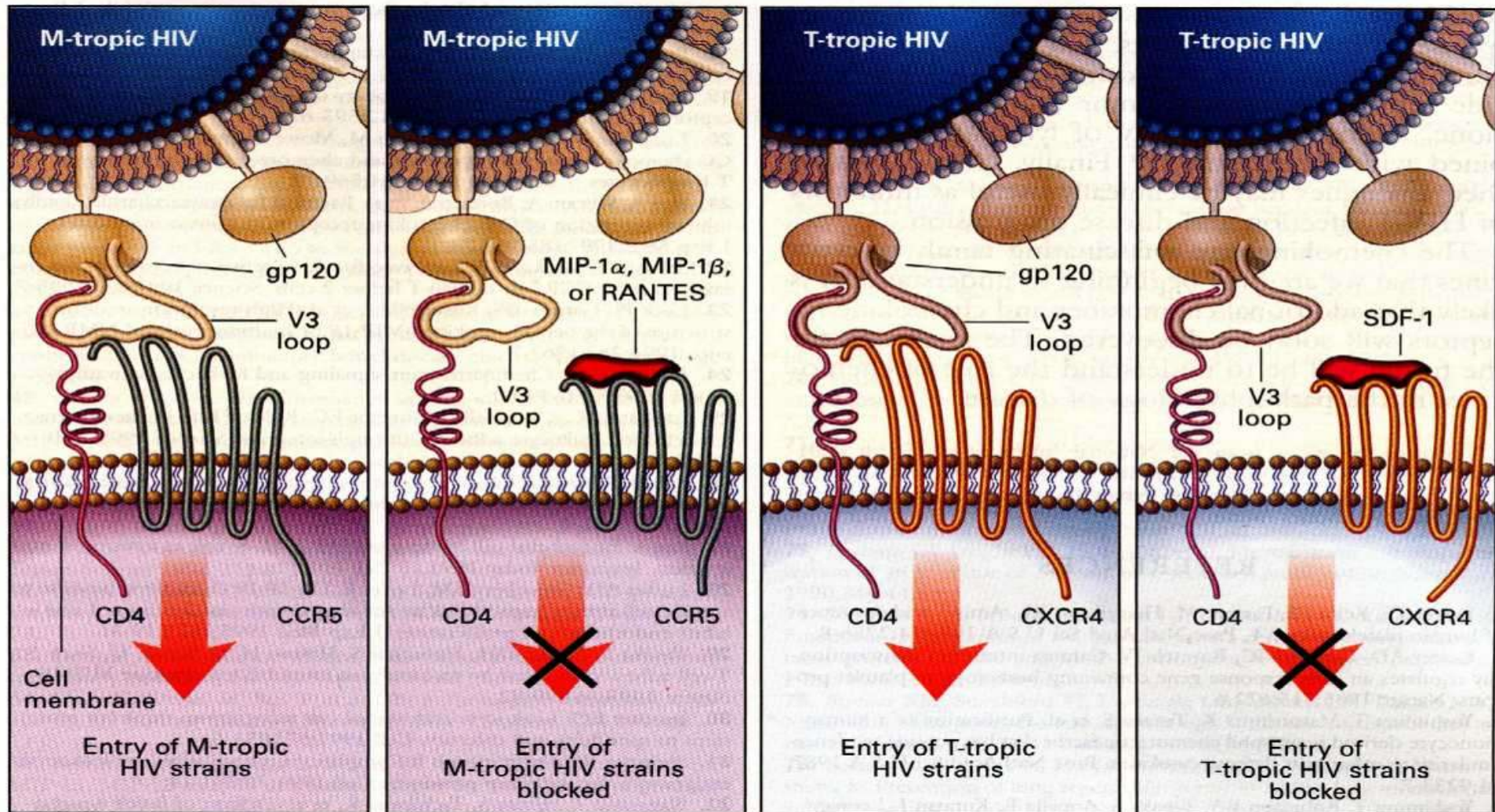
**Azidothymidin (AZT)**

# Antiretroviral therapy (2002-2009)





# Chemokine ligands can inhibit the binding of HIV to the target cells





**Dec. 1.**

## **Nobel-prize 2008**

### **HPV**



Harald zur Hausen  
*Germany*

### **HIV**



Francoise  
Barré-Sinoussi  
*France*



Luc Montaigner  
*France*