Basic immunology

Congenital and acquired immundeficiencies

Groups of immundeficiencies

I. Congenital

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

II. Acquired

1) Malignant transformations (tumors, especially diseases of the hematopoetic system)
2) Systemic diseases (autoimmun e disease, sarcoidosis)
3) Infectious diseases/AIDS
4) Medication caused immunsuppression (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**
- **<u>Labordiagnostics:</u>**

  Tests for T- , B - , NK-cell and neutrophil functions, Complement-assay
- **Genetic background**

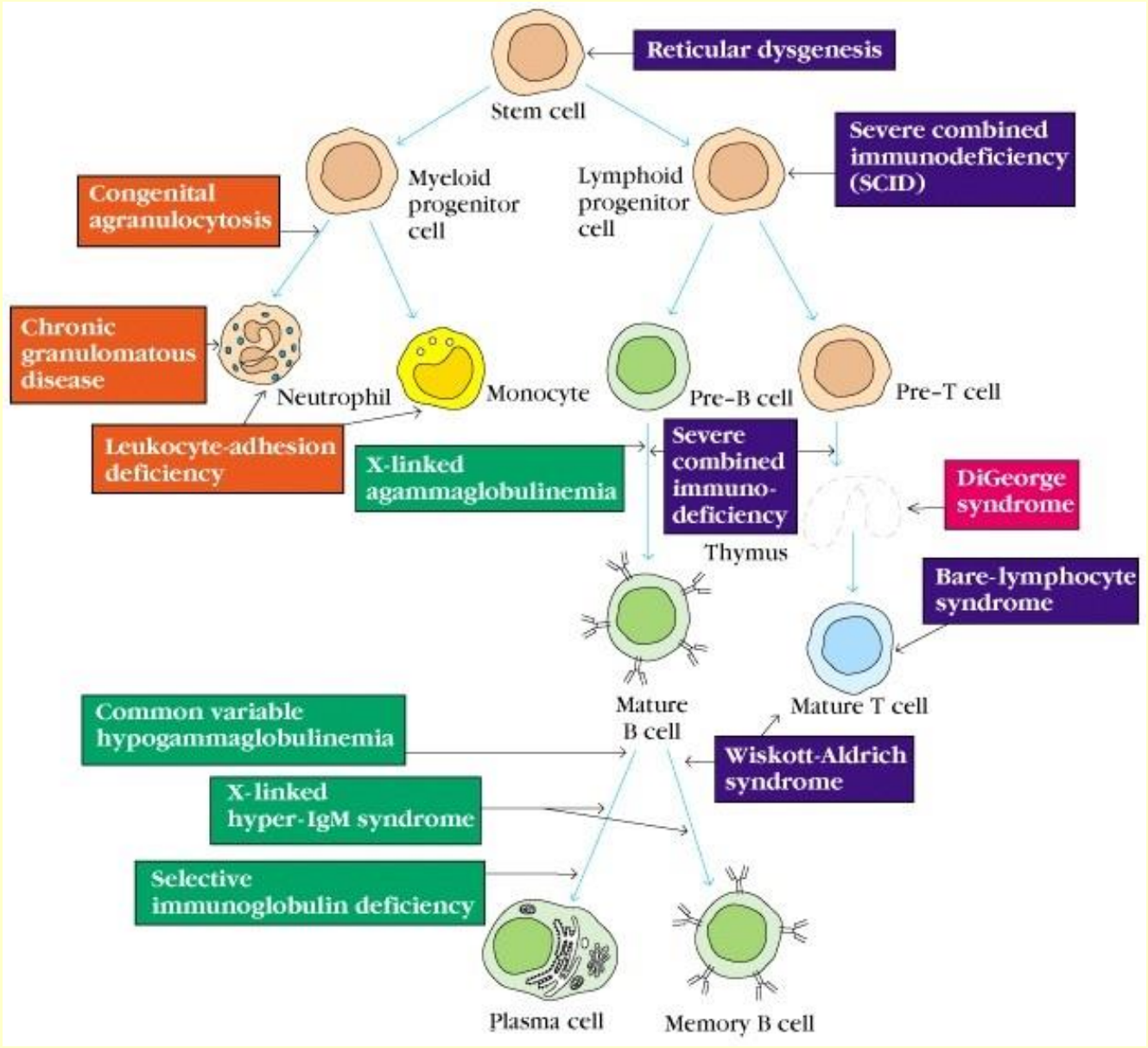
Groups of congenital immundeficiencies

Innate immune deficiencies

B – cell deficiencies

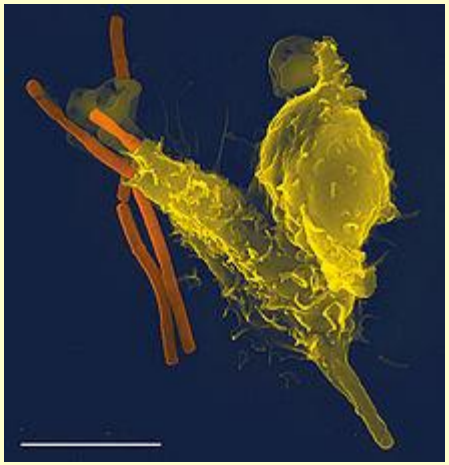
T- and B - cell deficiencies

T – cell deficiencies



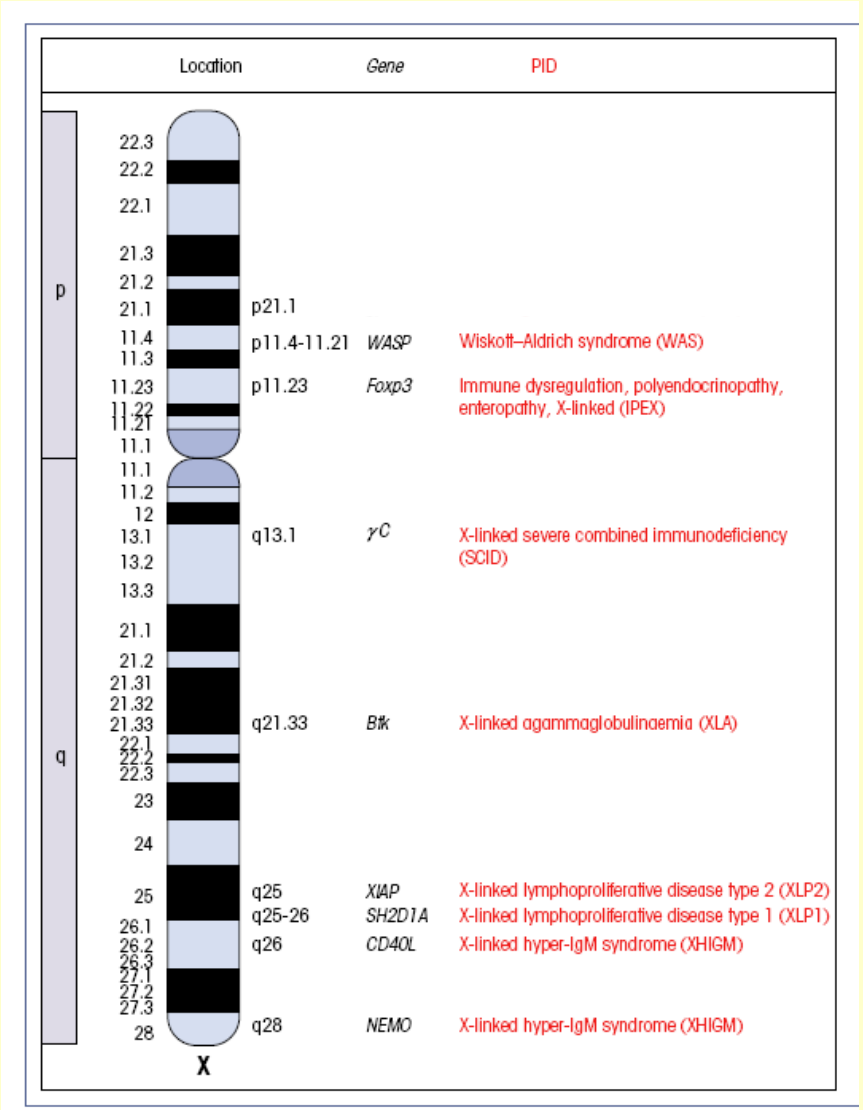
Most frequent immundeficiencies of innate immunity

- **Granulocyte/monocyte granulum- defects**
- **Intracellular killing defects**
- **Chemotaxis, adhesion defects (LAC)**
- **PAMP/TLR- defects**
- **NK-cell defects**
- **Complement-deficiencies**



Most frequent immundeficiencies of adaptive immunity

- **Usually recessive genetic diseases**
- **X –linked diseases**



Sever combined immunedeficiencies (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 – purinnucleotidephosphorilase)**
- **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

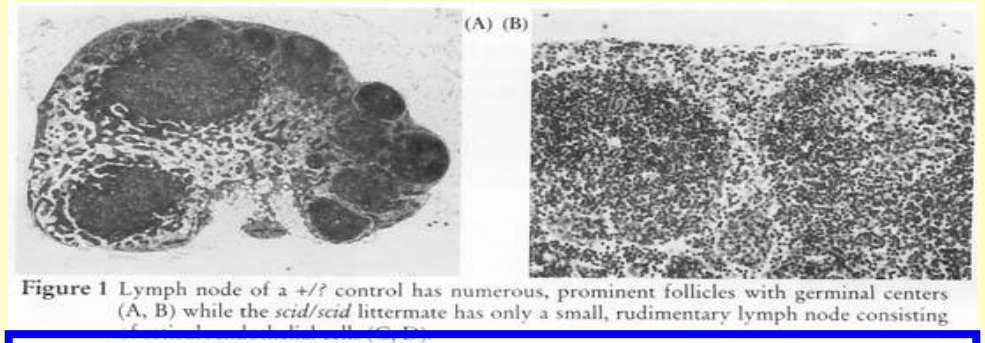
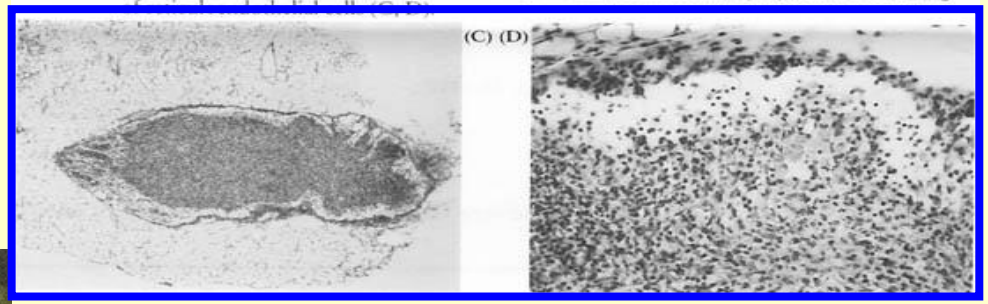
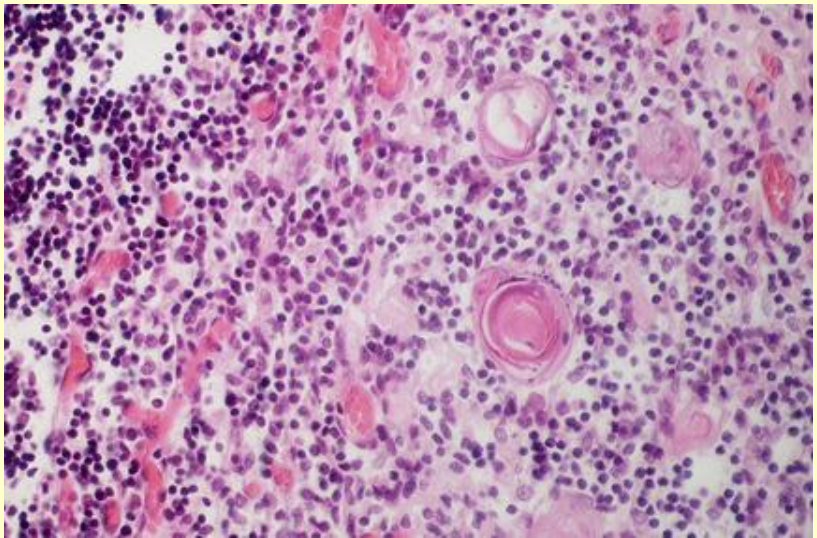


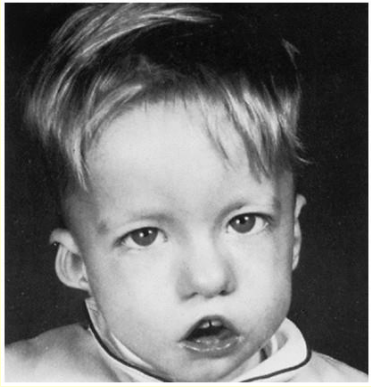
Figure 1 Lymph node of a +/? control has numerous, prominent follicles with germinal centers (A, B) while the *scid/scid* littermate has only a small, rudimentary lymph node consisting



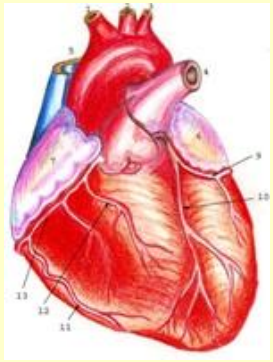
SCID

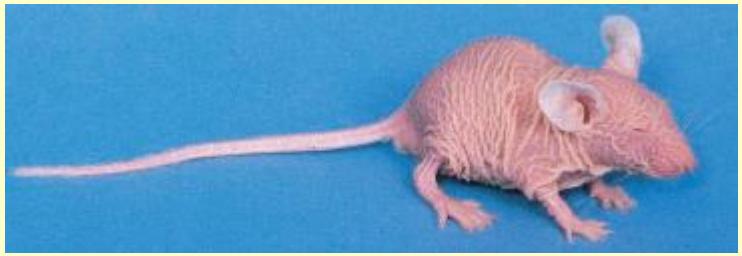


DiGeorge- syndrome



- The embryological defects of 3. and 4. pharingeal 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

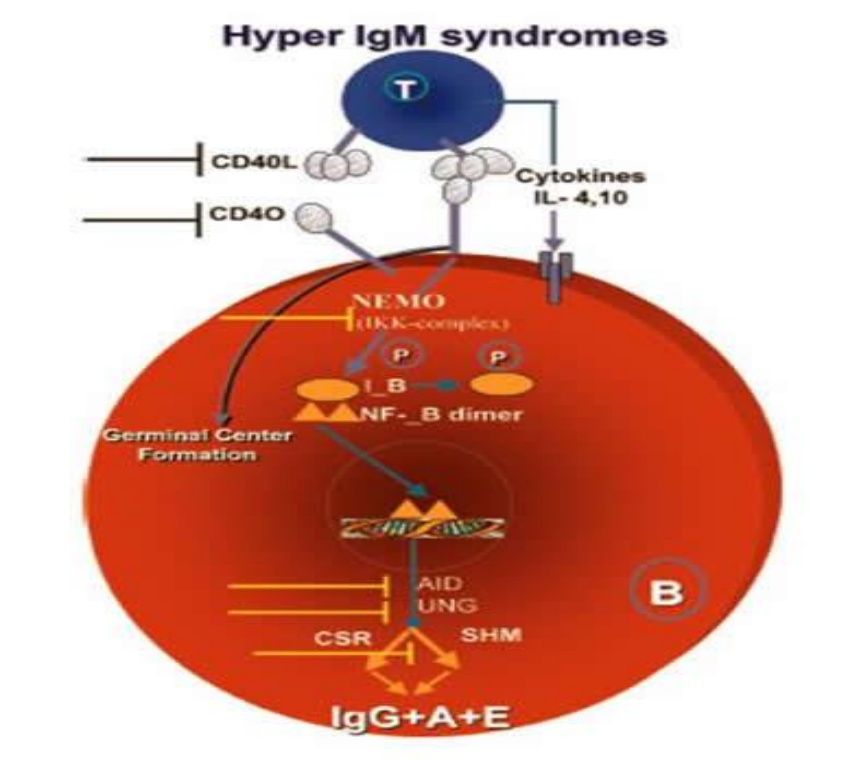
X-linked Hyper-IgM syndrome

- Defects of CD40 ligand,
- No isotype switch

X-linked Agammaglobulinaemia

- Few B cells
- Defects of Btk

(Bruton tyrosine kinase)

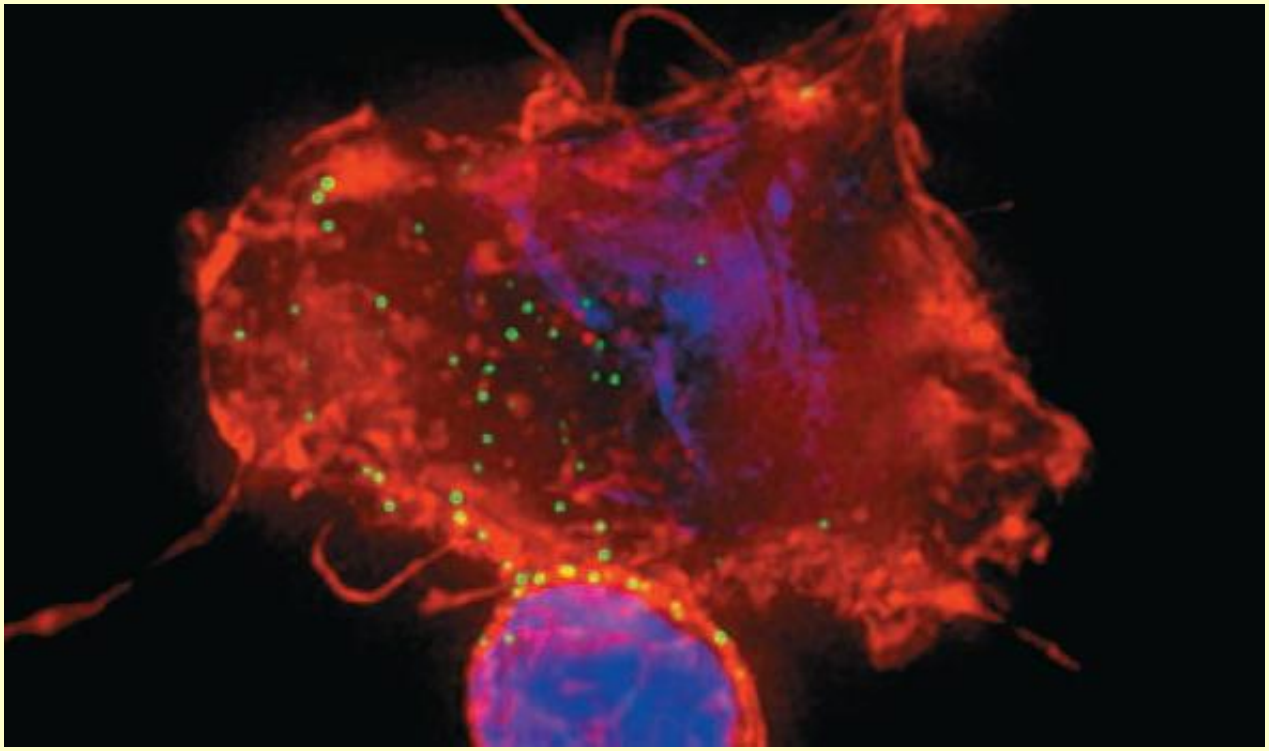


Selektive IgA deficiency

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

II. Secondary immundeficiencies

HIV-AIDS



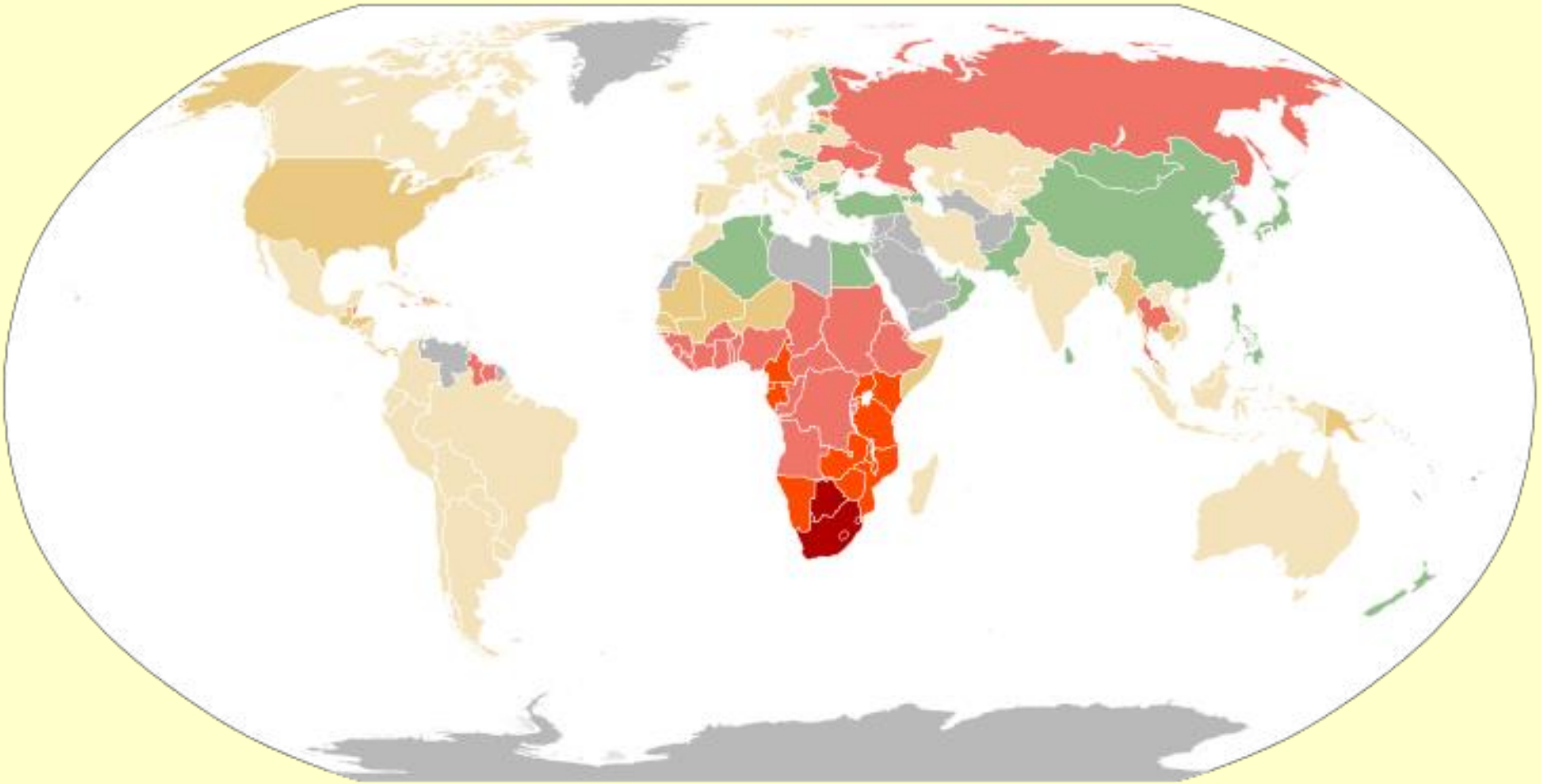
Epidemics (WHO)

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

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



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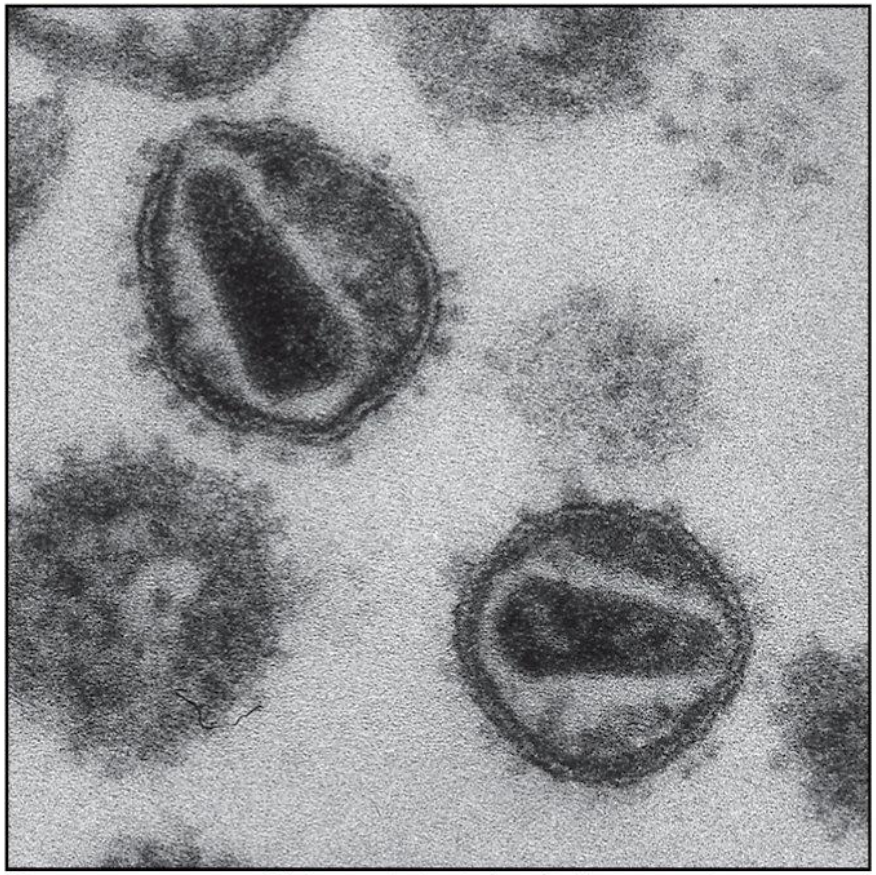
HIV

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



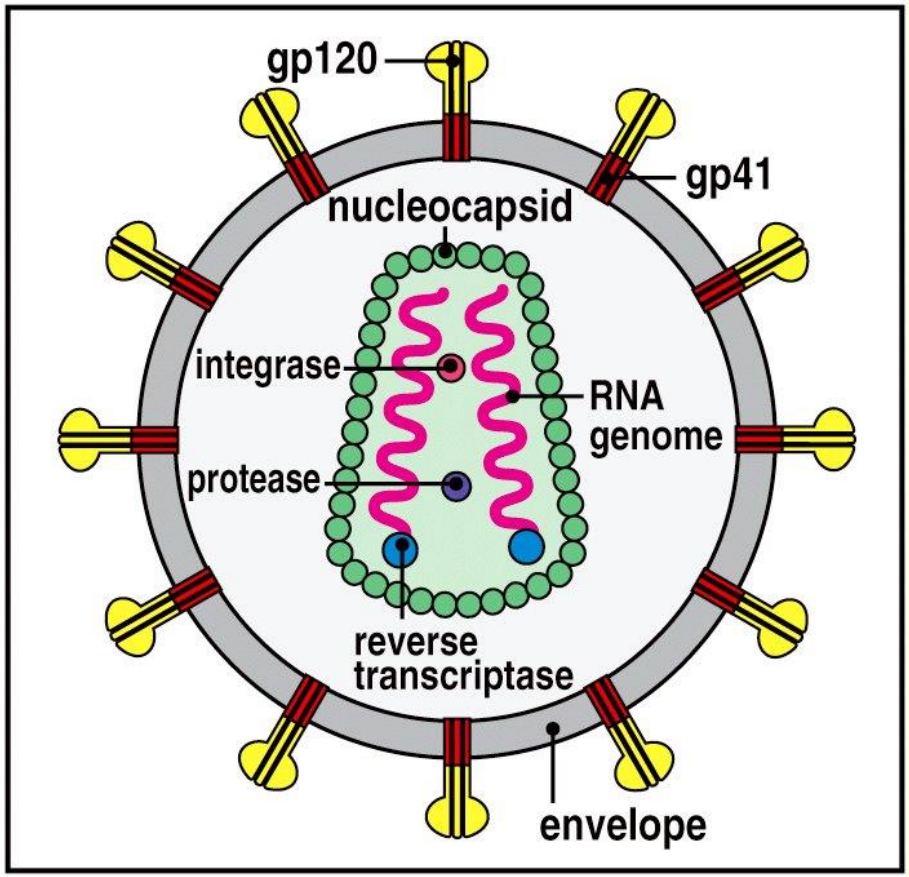
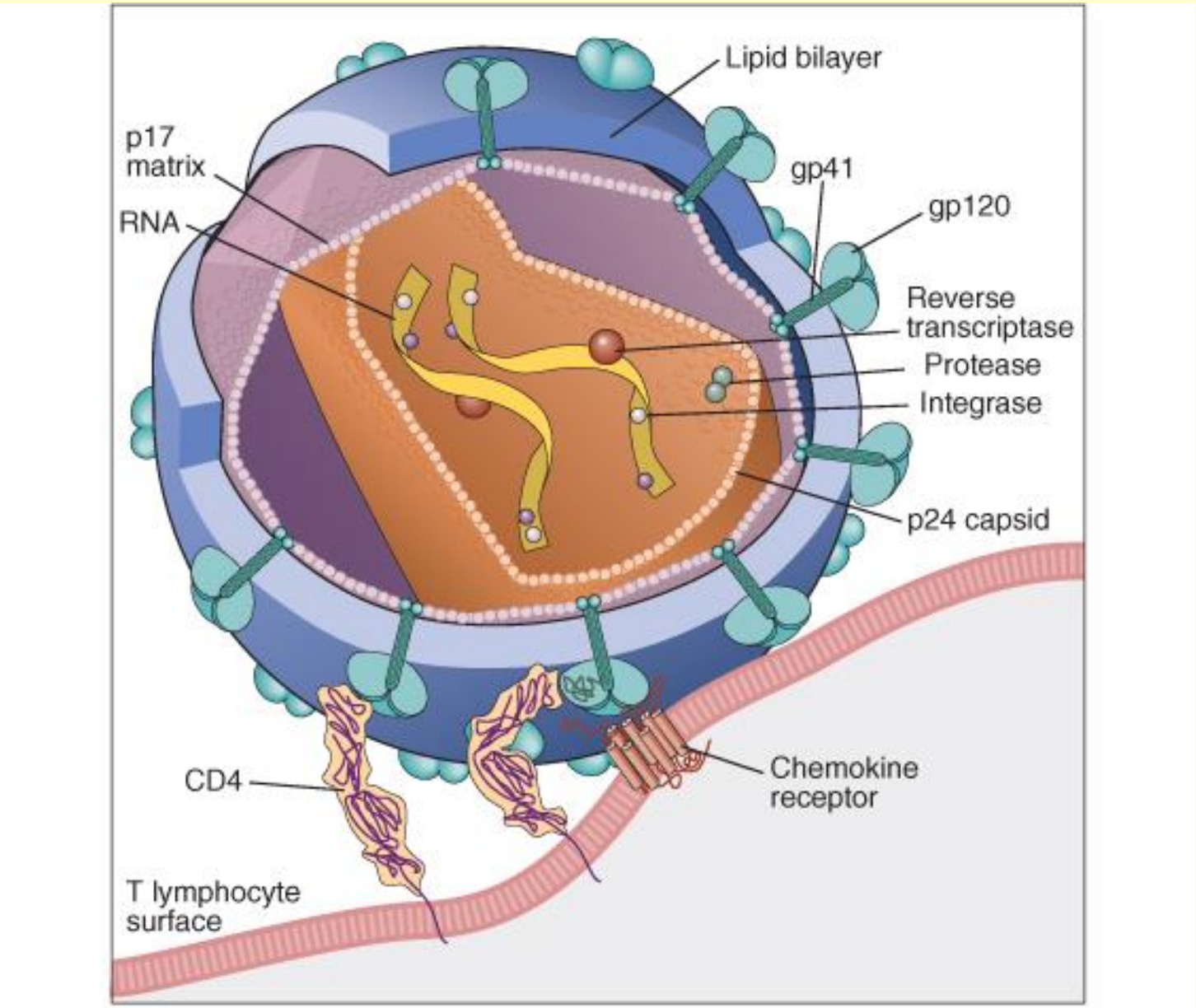


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

HIV



HIV receptors

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

The role of DC-s HIV infection

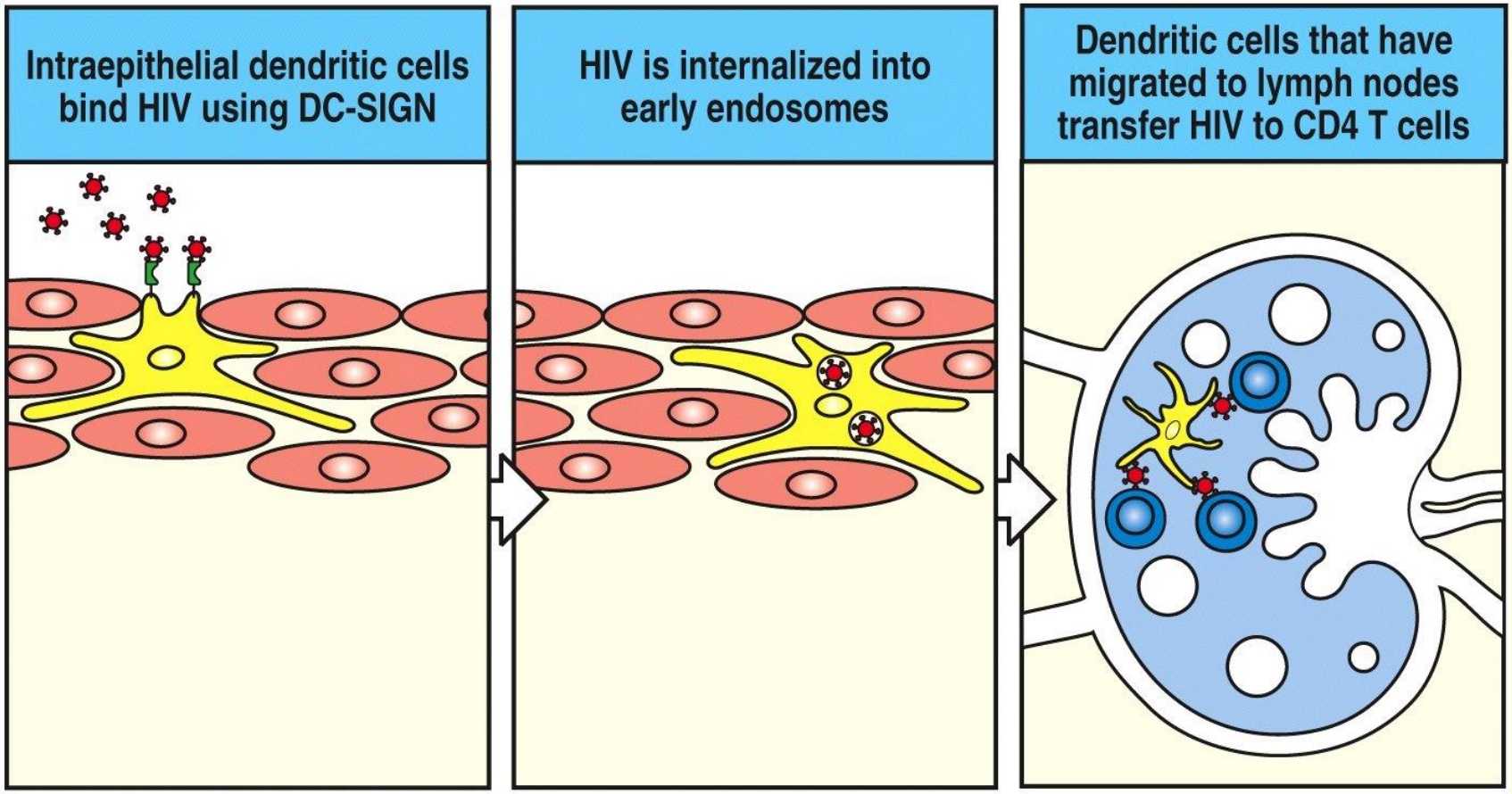
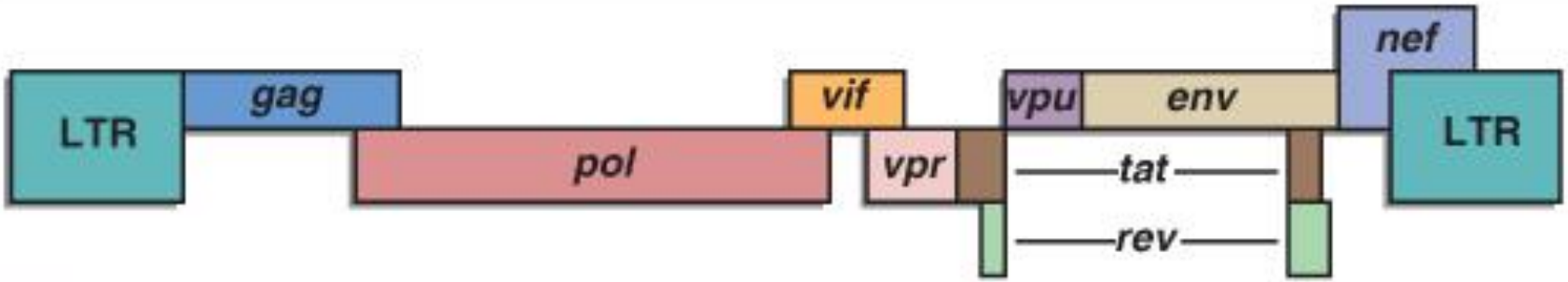


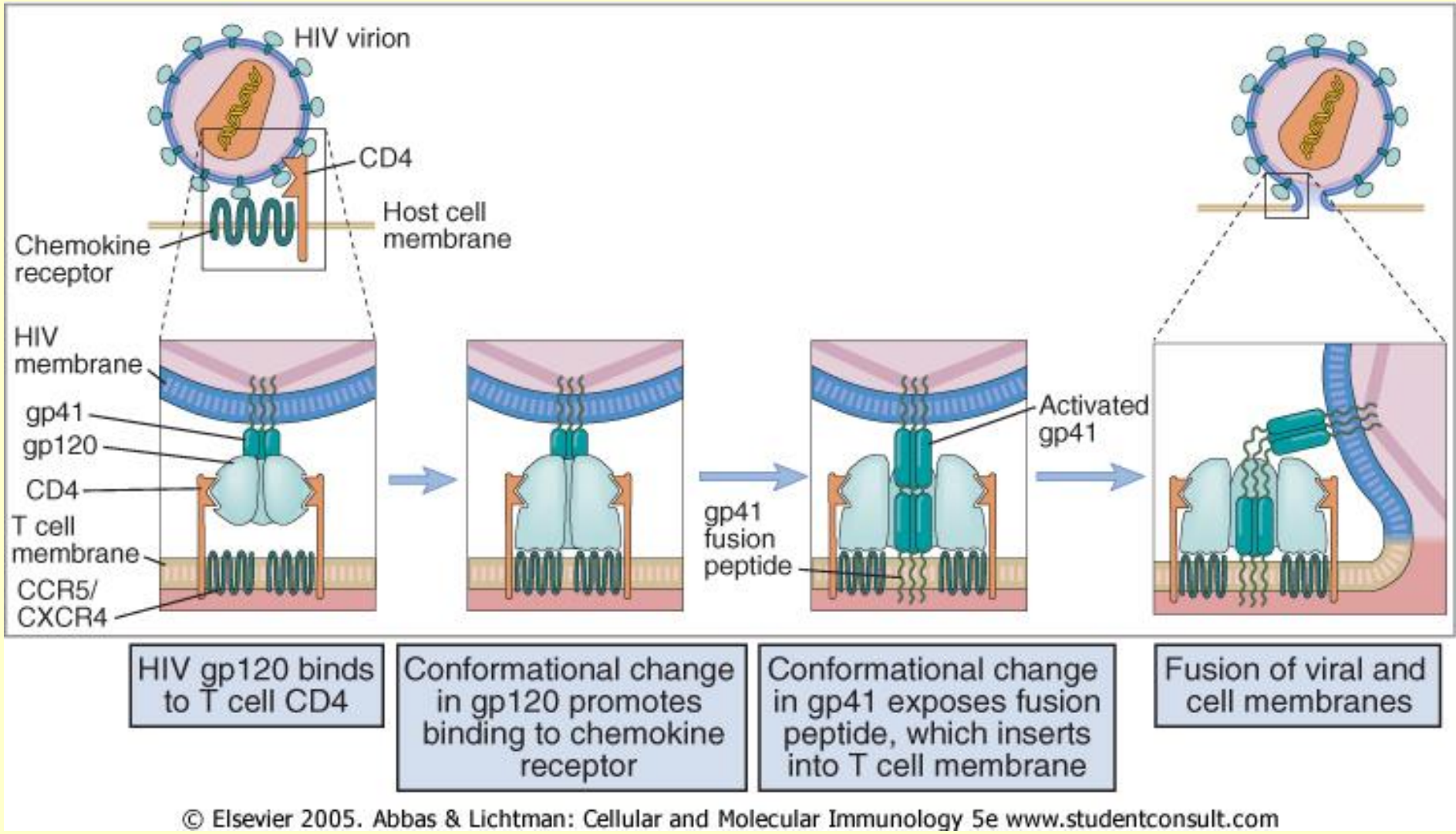
Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

Genome of HIV

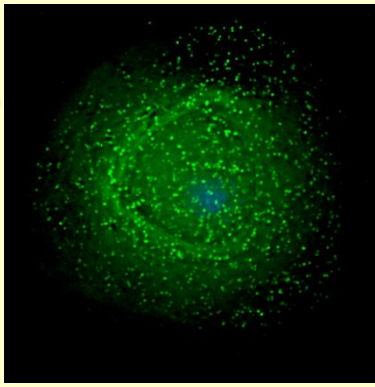


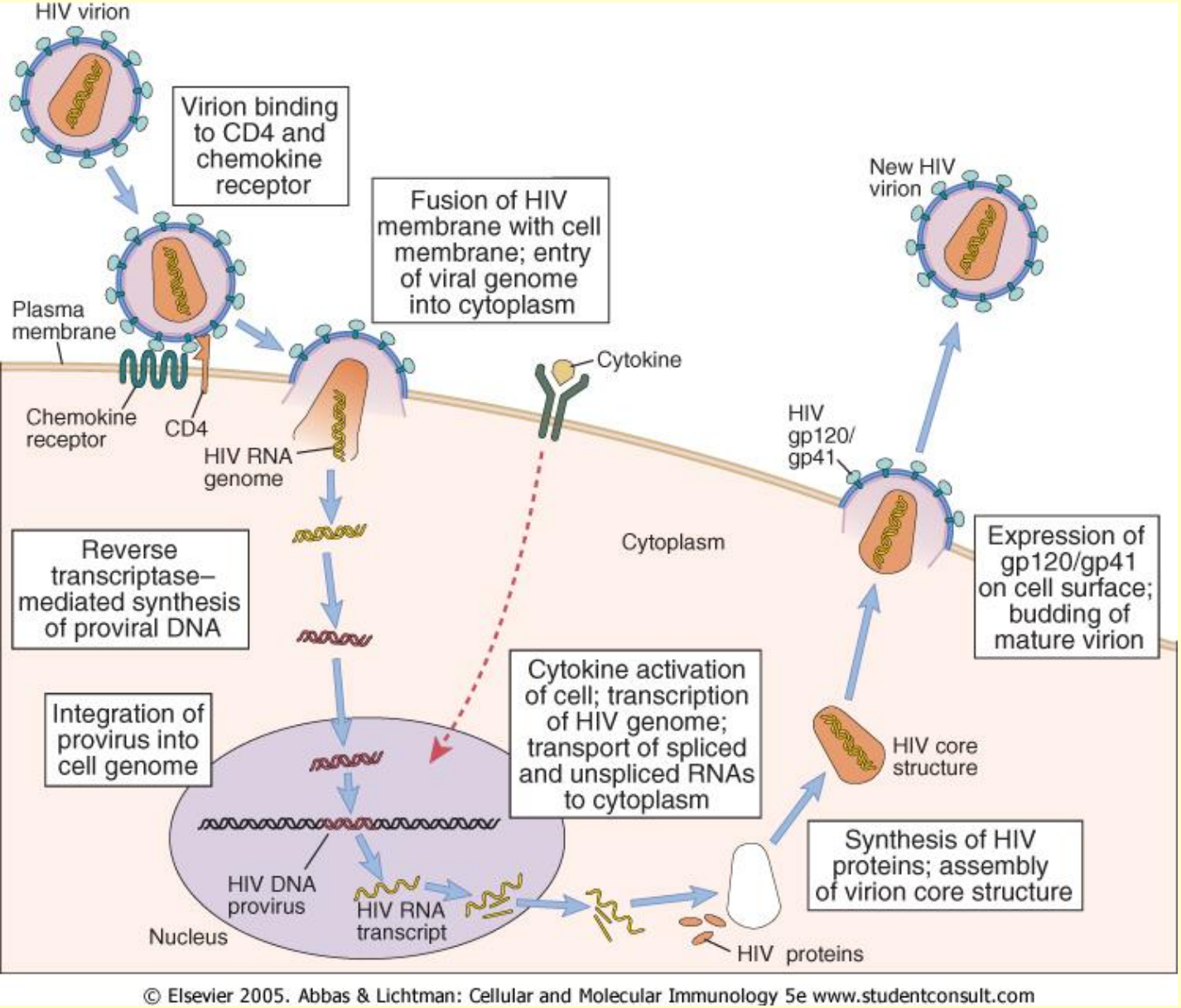
LTR	Integration of viral DNA into host cell genome; binding site for host transcription factors
gag	Nucleocapsid core and matrix proteins
pol	Reverse transcriptase, protease, integrase, and ribonuclease
env	Viral coat proteins (gp120 and gp41) mediating CD4 and chemokine receptor binding and membrane fusion
vif	Enhances infectivity of viral particles
vpr	Promotes nuclear import of viral DNA; G_2 cell cycle arrest
tat	Required for elongation of viral transcripts
rev	Promotes nuclear export of incompletely spliced or unspliced viral RNAs
vpu	Down-regulates host cell CD4 expression and enhances release of virus from cells
nef	Down-regulates host cell CD4 expression and enhances release of virus from cells; down-regulates host cell class I MHC expression

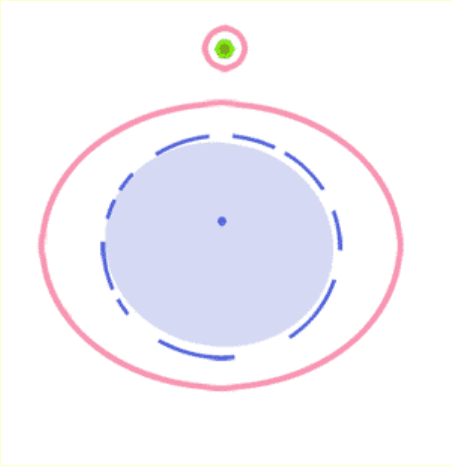
The life cycle of HIV I.

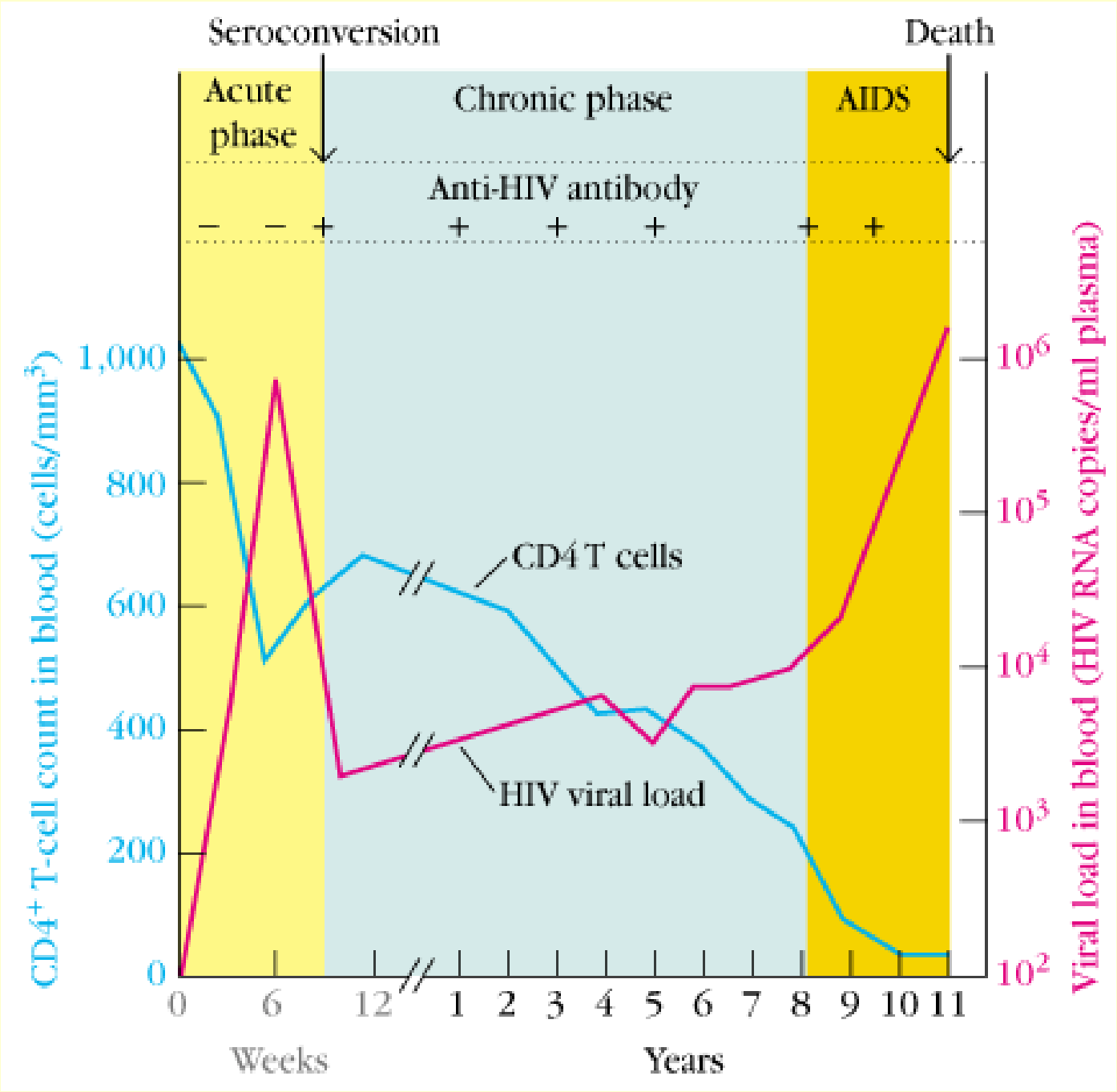


The life cycle of HIV II.

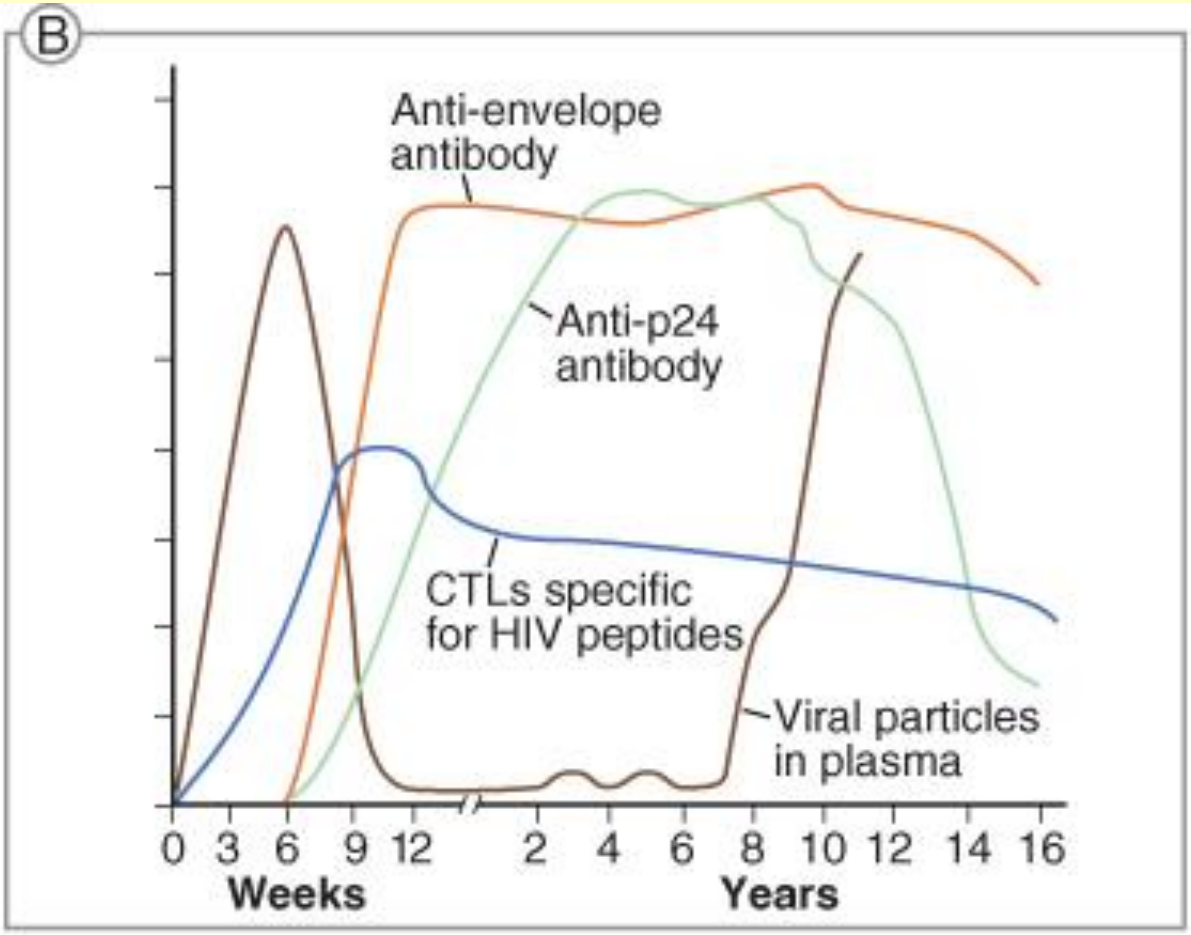







Seroconversion
Death
Acute phase
Chronic phase
AIDS
Anti-HIV antibody
– – + + + + + +
CD4 T cells
HIV viral load
CD4+ T-cell count in blood (cells/mm3)
1,000
800
600
400
200
0
Viral load in blood (HIV RNA copies/ml plasma)
10^6
10^5
10^4
10^3
10^2
0 6 12 1 2 3 4 5 6 7 8 9 10 11
Weeks
Years

Humoral amd cellular immunity against HIV



Clinical categories

CD4+ T cell numbers	A	B	C
> 500/µl	A1	B1	C1
200 - 499/µl	A2	B2	C2
< 200/µl	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

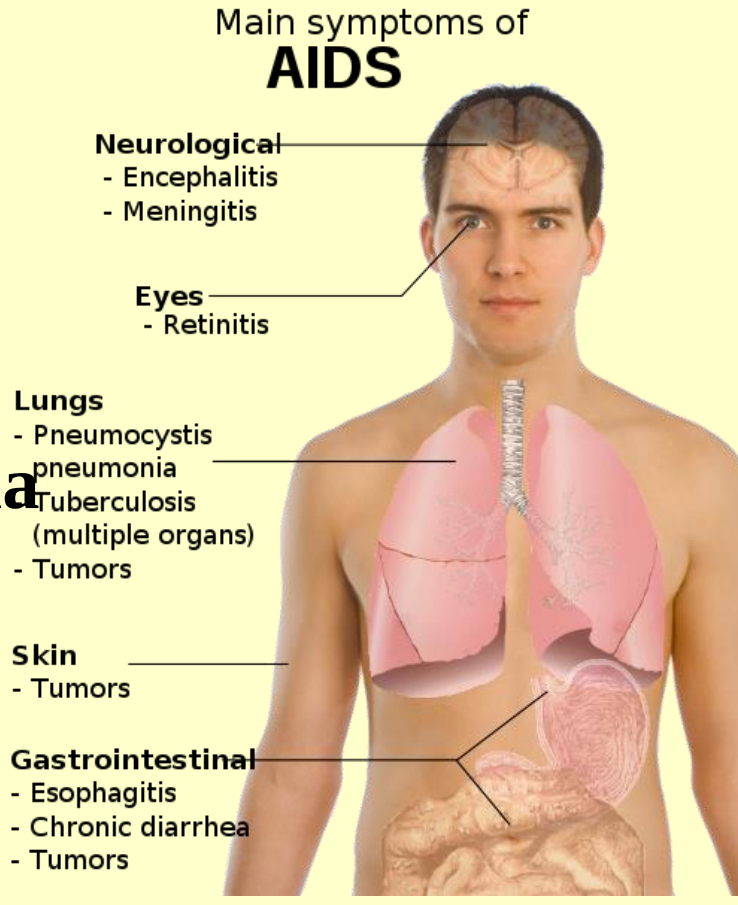
Tumors:

Kaposi-sarcoma

Non-Hodgkin-lymphoma

EBV-positive Burkitt lymphoma

Lymphoma in the CNS



Current therapeutic approaches

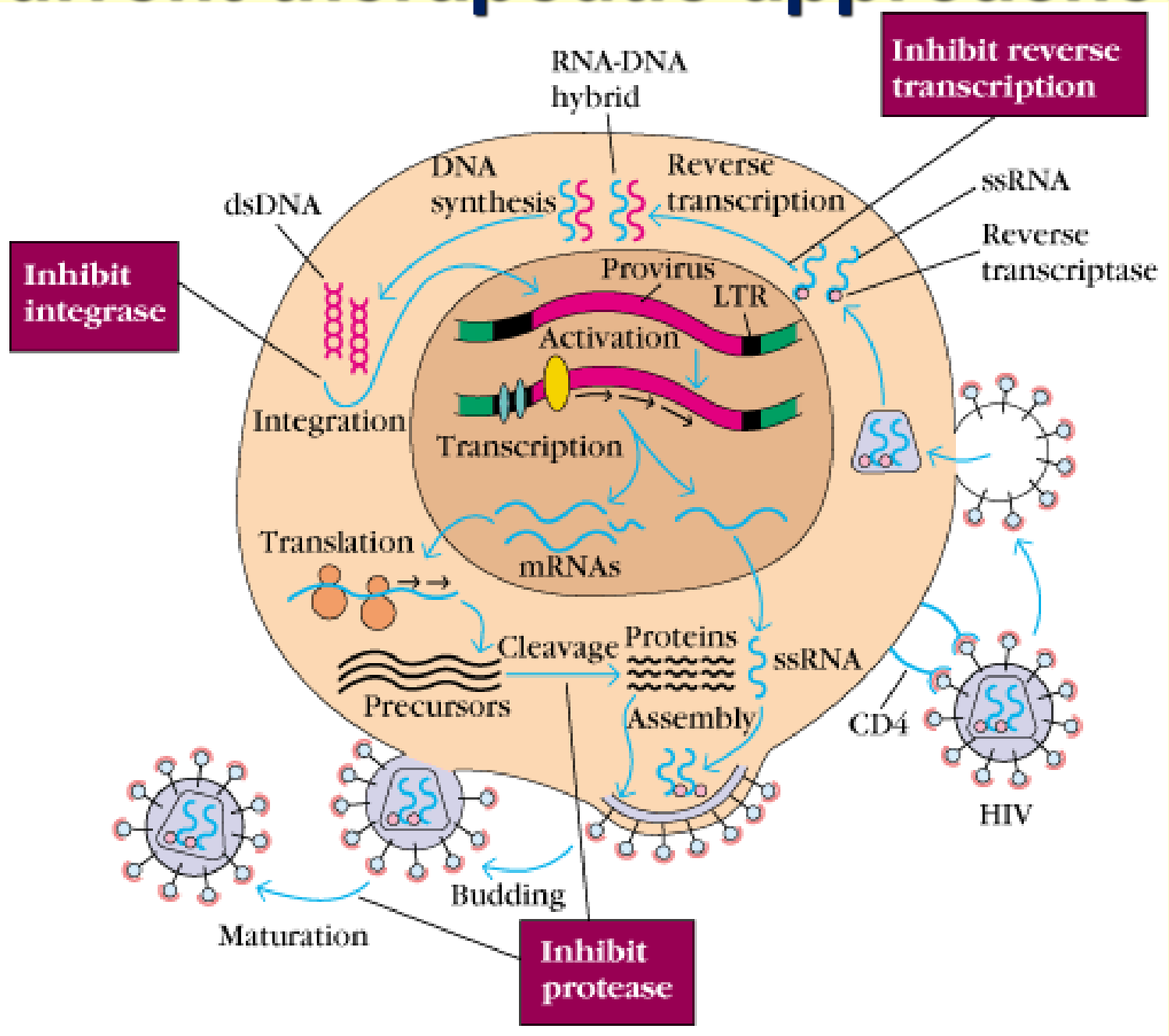
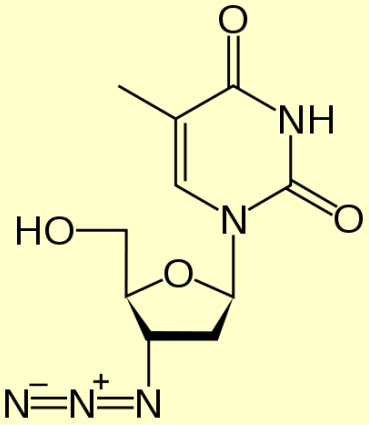


TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

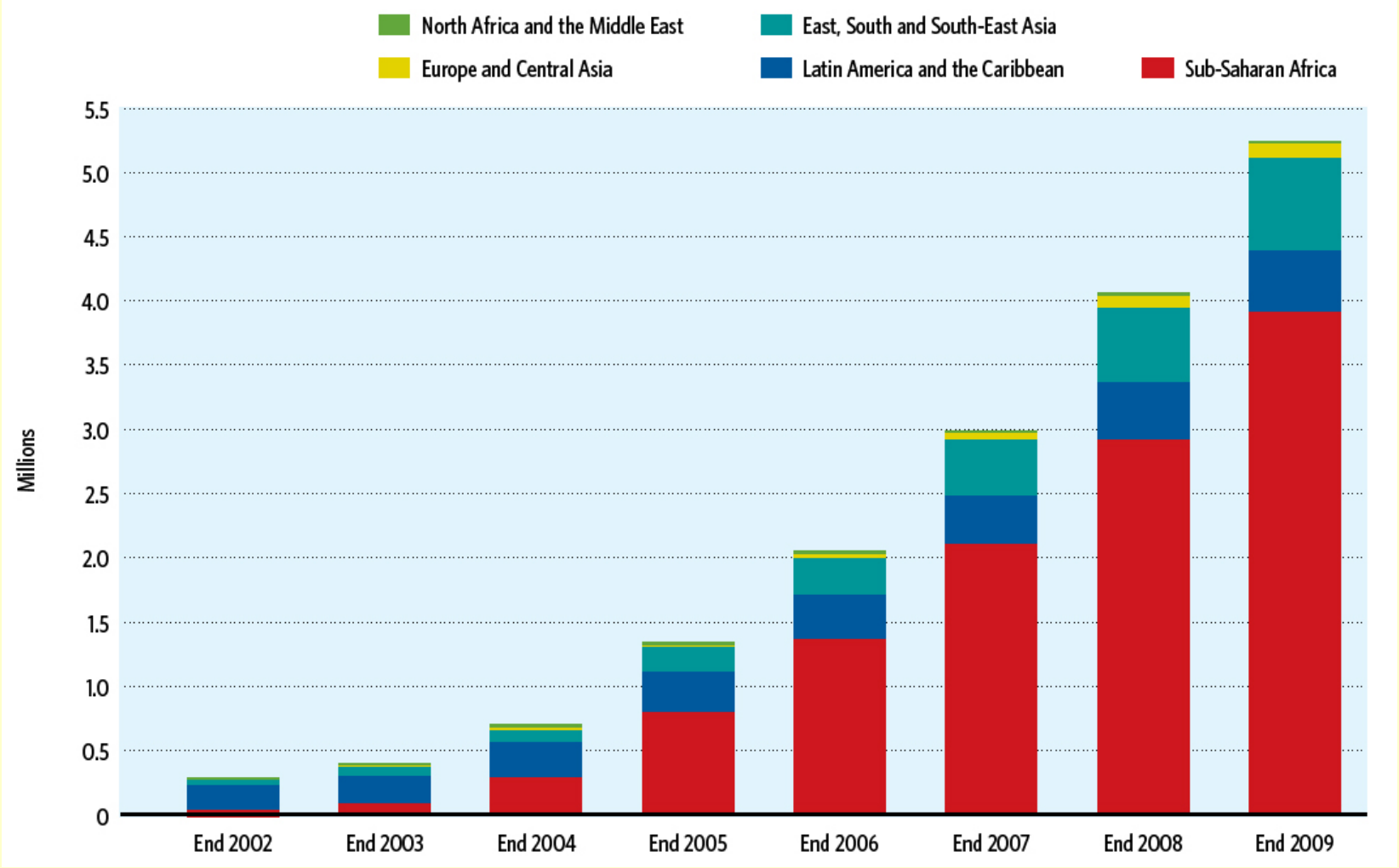
Generic name (other names)	Typical dosage	Some potential side effects
Reverse transcriptase inhibitors: Nucleoside analog		
Didanosine (Videx, ddI)	2 pills, 2 times a day on empty stomach	Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy
Lamivudine (Epivir, 3TC)	1 pill, 2 times a day	Usually 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
Reverse transcriptase inhibitors: Nonnucleoside analogues		
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
Protease inhibitors		
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.



Azithothymidin (AZT)

Antiretroviral therapy (2002-2009)



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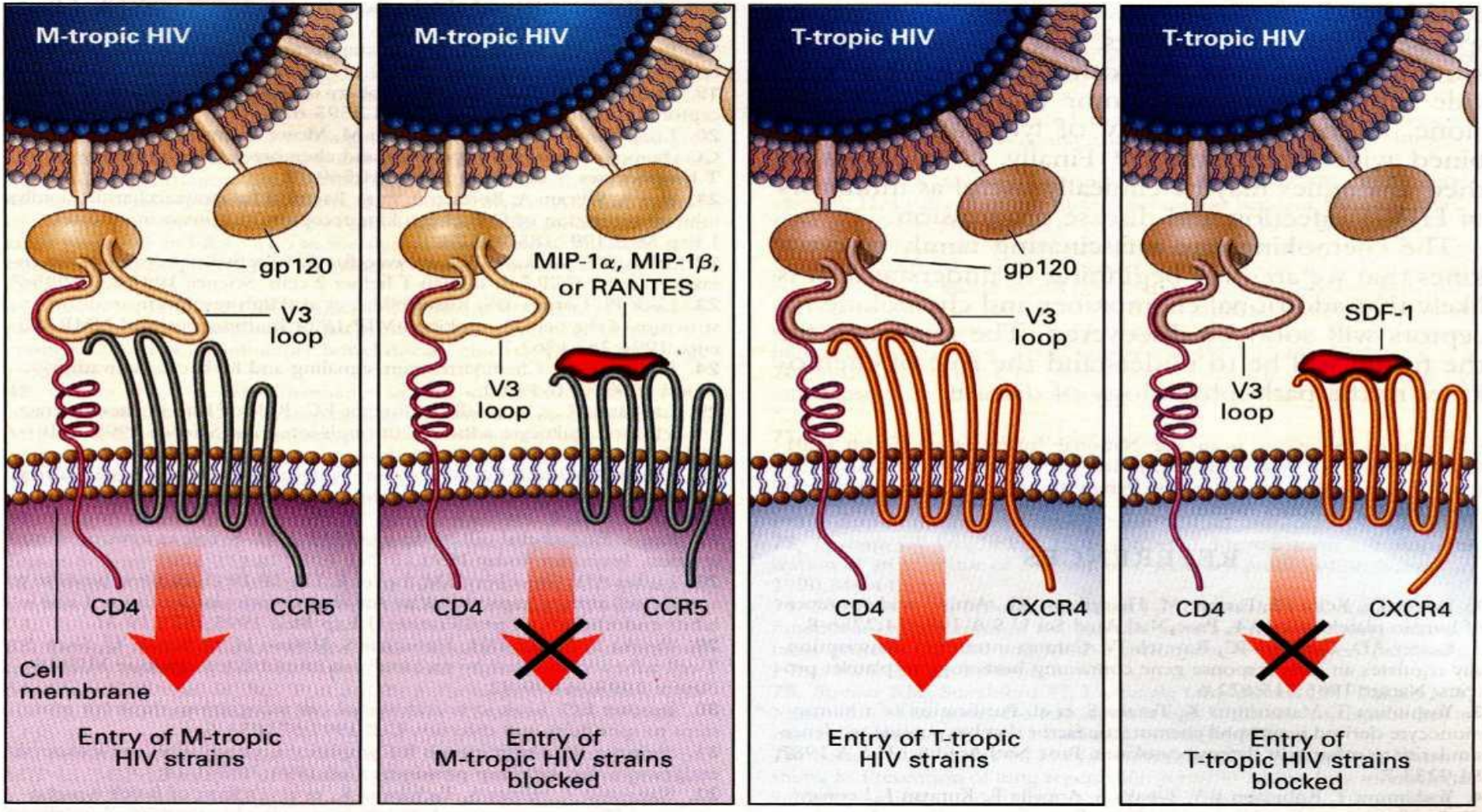
World Health Organization

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