

Applied immunology

**Secondary (acquired)
immunodeficiencies, HIV-AIDS**

Lecture 6

Acquired immunodeficiencies

- **Altered immune function in the course of occurred diseases (non congenital)**
- **Immunsuppression caused by a disease complication**

OR

- **Iatrogen immunosuppression caused by a complication of disease treatments**

Main causes of acquired immunodeficiencies I.

Cause	Mechanism
Human immunodeficiency virus infection	CD4+ T cell depletion
Morbilli, HTLV-1 virus	Lymphocyte infections, In the case of HTLV-1 adult T cell leukemia/lymphoma
Mycobacterium, fungi, parasites (e.g. Malaria)	Anergy towards several antigens, altered T cell function

Main causes of acquired immunodeficiencies II.

Cause	Mechanisms
Protein-calory malnutrition	Metabolic complications inhibit the normal maturation and function of lymphocytes
Bone marrow cancer, bone marrow metastasis	Normal lymphoheamatopoiesis has crowded out from the marrow
Immunosuppressants	Decreased number of lymphocytes, Inhibition of lymphocyte activation
Irradiation or chemotherapy	Decreased number of lymphoid progenitors
Splenectomy	Complication of immune response towards blood-borne pathogens

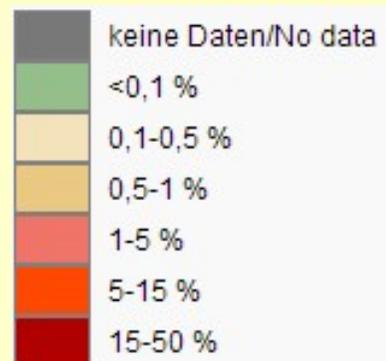
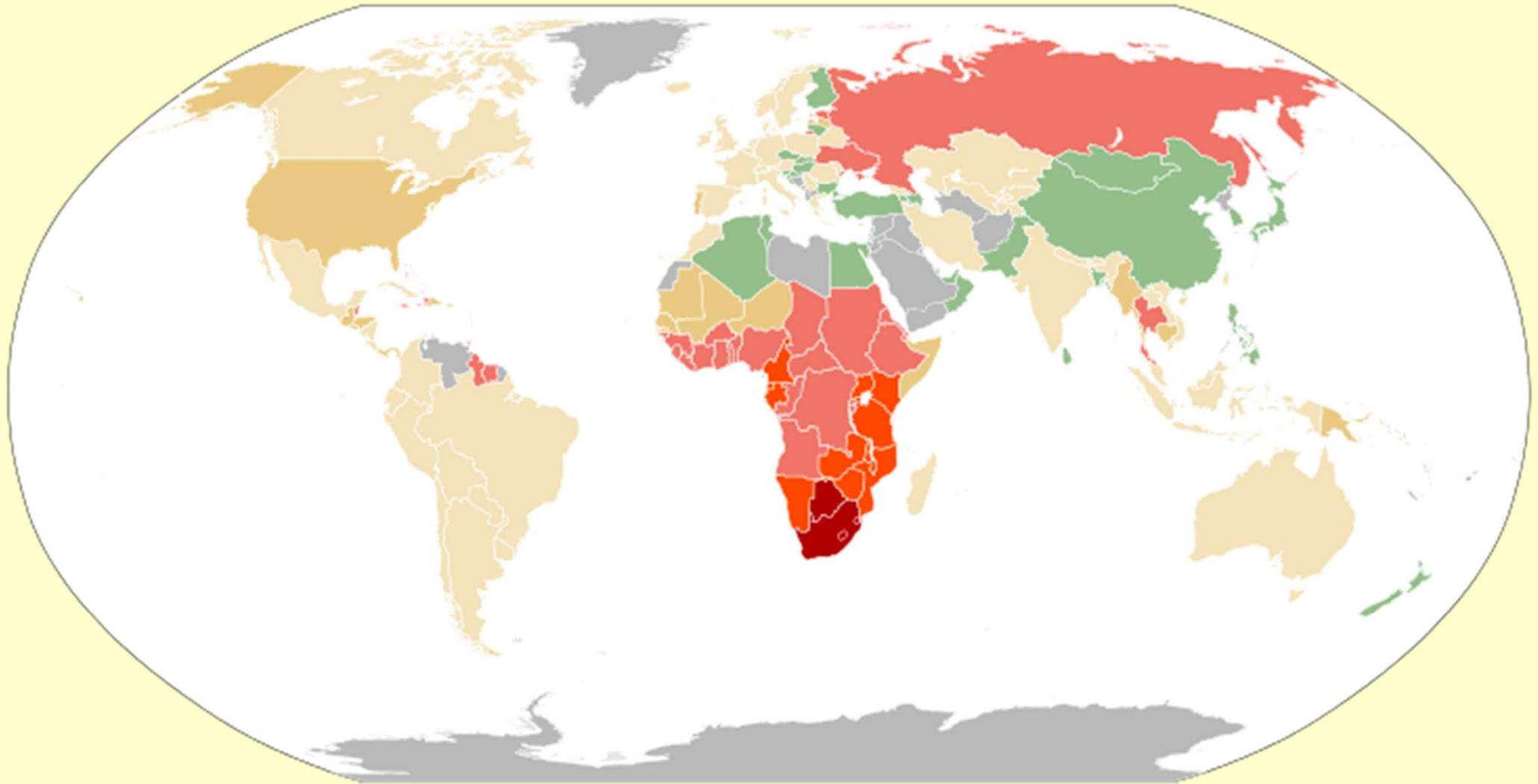
Epidemics (WHO)

	2000	2005	2010	2015	2016	2017	2018	2019	2020/ *june2021	2023
People living with HIV	25.5 million [20.5 million–30.7 million]	28.6 million [23.0 million–34.3 million]	31.1 million [25.0 million–37.3 million]	34.6 million [27.7 million–41.4 million]	35.3 million [28.3 million–42.2 million]	35.9 million [28.8 million–43.0 million]	36.6 million [29.3 million–43.8 million]	37.2 million [29.8 million–44.5 million]	37.7 million [30.2 million–45.1 million]	39 million (33.1–45.7 M)
New HIV infections (total)	2.9 million [2.0 million–3.9 million]	2.4 million [1.7million–3.4 million]	2.1 million [1.5 million–2.9 million]	1.8 million [1.3 million–2.4 million]	1.7 million [1.2 million–2.4 million]	1.7 million [1.2 million–2.3 million]	1.6 million [1.1 million–2.2 million]	1.5 million [1.1 million–2.1 million]	1.5 million [1.0 million–2.0 million]	1.3 million (1.0–1.7)
New HIV infections (aged 15+ years)	2.3 million [1.6 million–3.2 million]	2.0 million [1. 4 million–2. 7 million]	1.8 million [1.3 million–2.5 million]	1.6 million [1.1 million–2.2 million]	1.5 million [1.1 million–2.1 million]	1.5 million [1.0 million–2.1 million]	1.4 million [1.0 million–2.0 million]	1.4 million [960 000–1.9 million]	1.3 million [910 000–1.8 million]	1.2 million
New HIV infections (aged 0–14 years)	520 000 [340 000–820 000]	480 000 [310 000–750 000]	320 000 [210 000–510 000]	190 000 [130 000–300 000]	190 000 [120 000–290 000]	180 000 [120 000–280 000]	170 000 [110 000–260 000]	160 000 [100 000–250 000]	150 000 [100 000–240 000]	130 000
AIDS-related deaths	1.5 million [1.1 million–2.2 million]	1.9 million [1.3 million–2.7 million]	1.3 million [910 000–1.9 million]	900 000 [640 000–1.3 million]	850 000 [600 000–1.2 million]	800 000 [570 000–1.2 million]	750 000 [530 000–1.1 million]	720 000 [510 000–1.1 million]	680 000 [480 000–1.0 million]	630 000
People accessing antiretroviral therapy	560 000 [560 000–560 000]	2.0 million [2.0 million–2.0 million]	7.8 million [6.9 million–7.9 million]	17.1 million [14.6 million–17.3 million]	19.3 million [16.6 million–19.5 million]	21.5 million [19.6 million–21.7 million]	23.1 million [21.9 million–23.4 million]	25.5 million [24.5 million–25.7 million]	27.5 million [26.5 million–27.7 million] / *28.2 million	29.8 million
HIV resources available**	US\$ 5.1 billion	US\$ 9.3 billion	US\$ 16.6 billion	US\$ 20.3 billion	US\$ 20.7 billion	US\$ 22.3 billion	US\$ 22.0 billion	US\$ 21.6 billion	US\$ 21.5 billion	20.8 million

Regional statistics (WHO – 2022 Dec)

	People living with HIV	New HIV Infections	New HIV Infections (Adults, aged 15+)	New HIV Infections (Children, aged 0-14)	AIDS-related deaths
Global	39.0 million [33.1 million - 45.7 million]	1.3 million [1.0 million - 1.7 million]	1.2 million [900 000 - 1.6 million]	130 000 [90 000 - 210 000]	630 000 [480 000 - 880 000]
Asia and the Pacific	6.5 million [5.3 million - 7.8 million]	300 000 [220 000 - 400 000]	290 000 [210 000 - 380 000]	12 000 [8600 - 18 000]	150 000 [110 000 - 220 000]
Caribbean	330 000 [290 000 - 380 000]	16 000 [11 000 - 21 000]	14 000 [10 000 - 19 000]	1 500 [1 100 - 2 100]	5 600 [4 100 - 7 500]
Eastern and southern Africa	20.8 million [17.4 million - 24.5 million]	500 000 [370 000 - 670 000]	440 000 [330 000 - 590 000]	58 000 [38 000 - 100 000]	260 000 [200 000 - 370 000]
Eastern Europe and central Asia	2.0 million [1.8 million - 2.1 million]	160 000 [140 000 - 180 000]	160 000 [130 000 - 180 000]	... [... - ...]	48 000 [38 000 - 58 000]
Latin America	2.2 million [2.0 million - 2.5 million]	110 000 [94 000 - 130 000]	110 000 [90 000 - 130 000]	3 800 [2 900 - 4 700]	27 000 [21 000 - 35 000]
Middle East and North Africa	190 000 [160 000 - 220 000]	17 000 [13 000 - 23 000]	16 000 [12 000 - 21 000]	1 700 [1 300 - 2 100]	5 300 [4 000 - 7 100]
Western and central Africa	4.8 million [4.2 million - 5.5 million]	160 000 [110 000 - 250 000]	110 000 [66 000 - 190 000]	51 000 [34 000 - 69 000]	120 000 [96 000 - 160 000]
Western and central Europe and North America	2.3 million [1.9 million - 2.6 million]	58 000 [46 000 - 69 000]	57 000 [46 000 - 69 000]	... [... - ...]	13 000 [9 300 - 17 000]

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)**

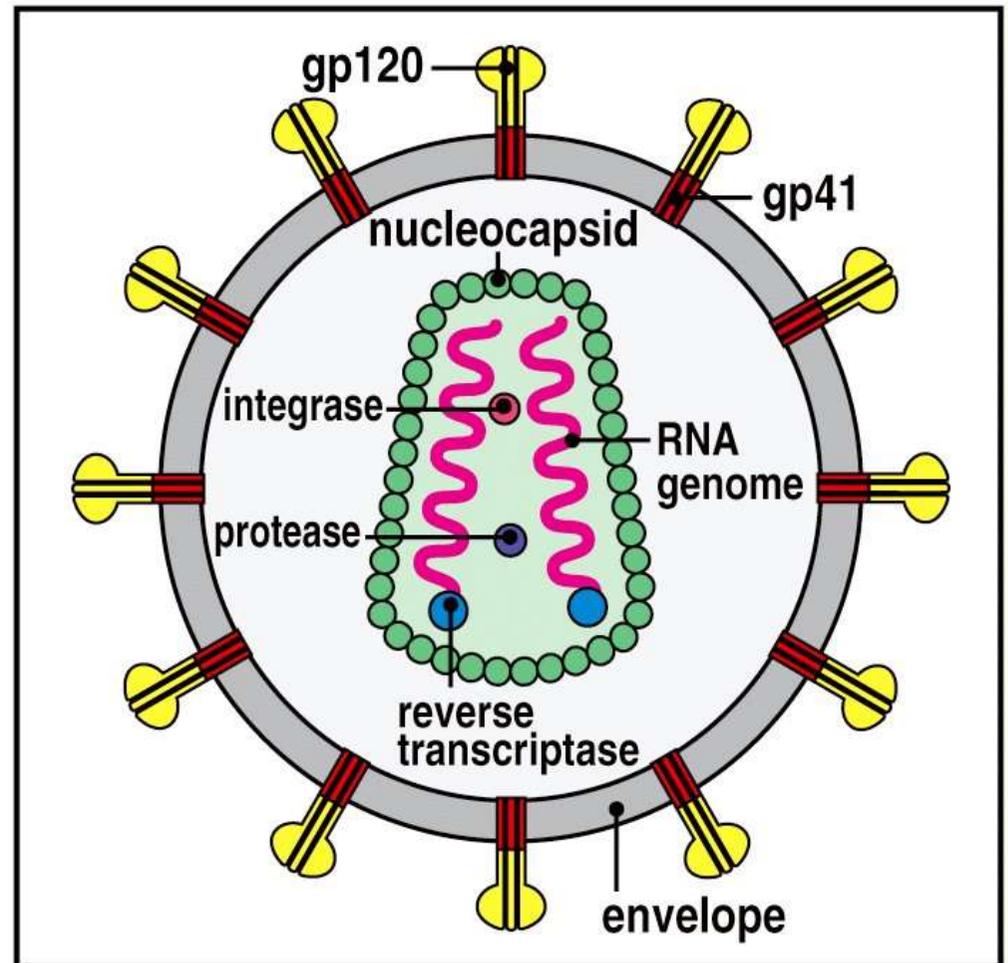
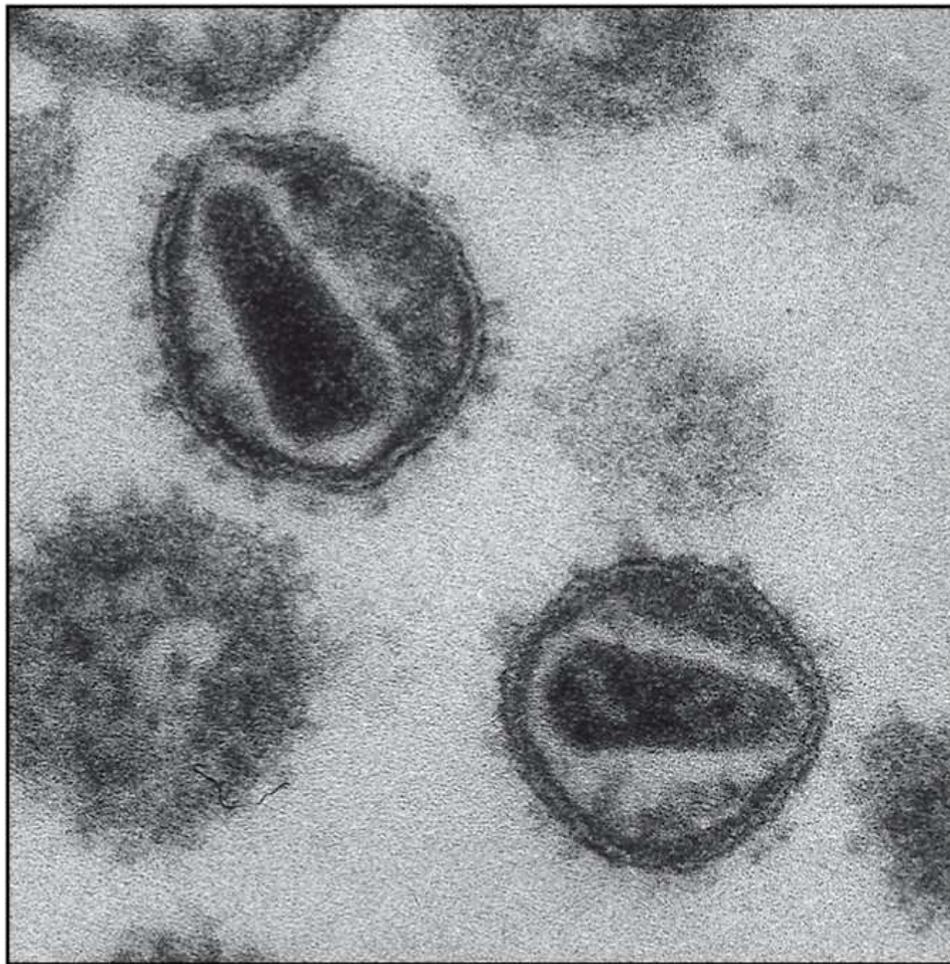
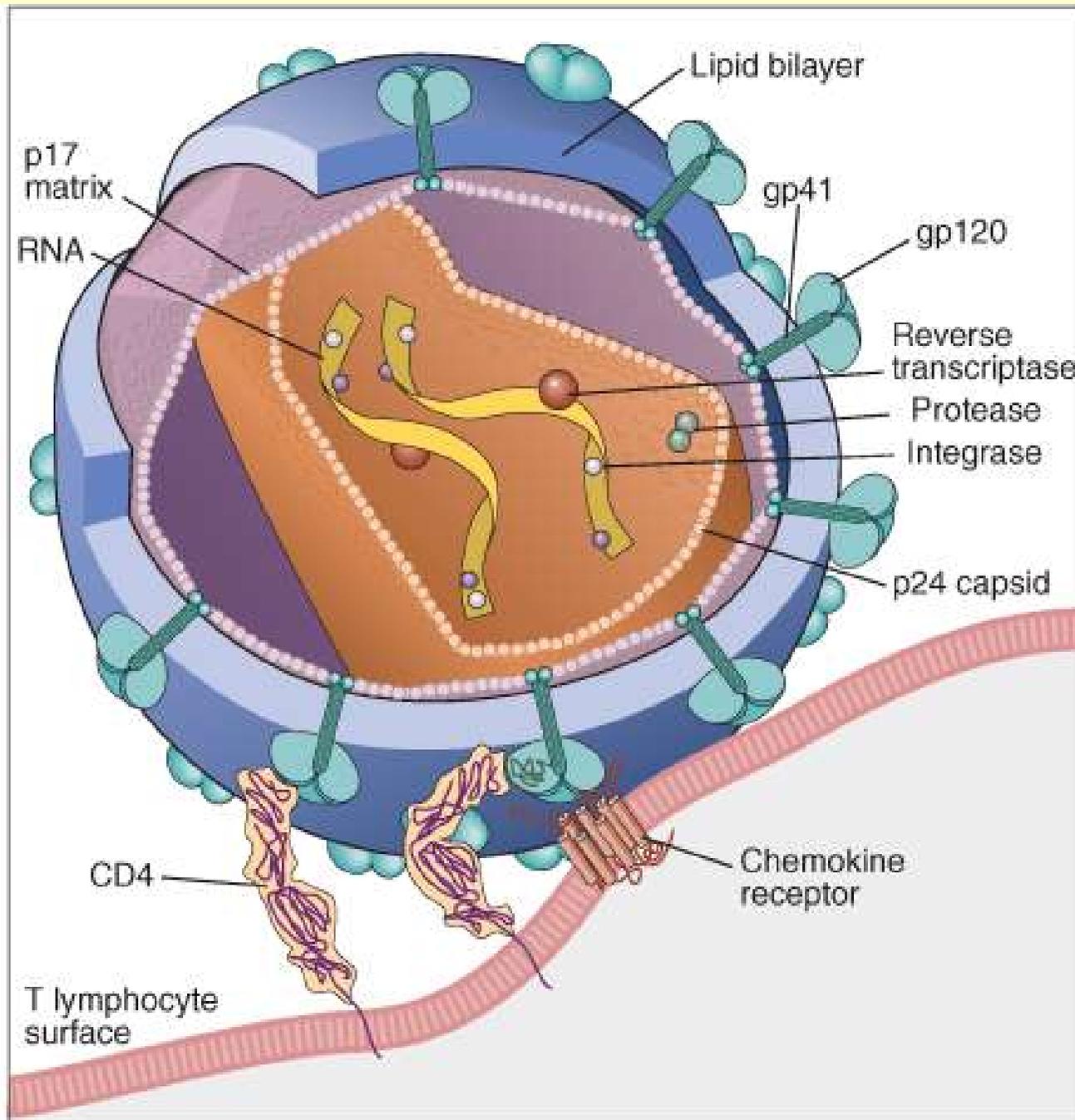


Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

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

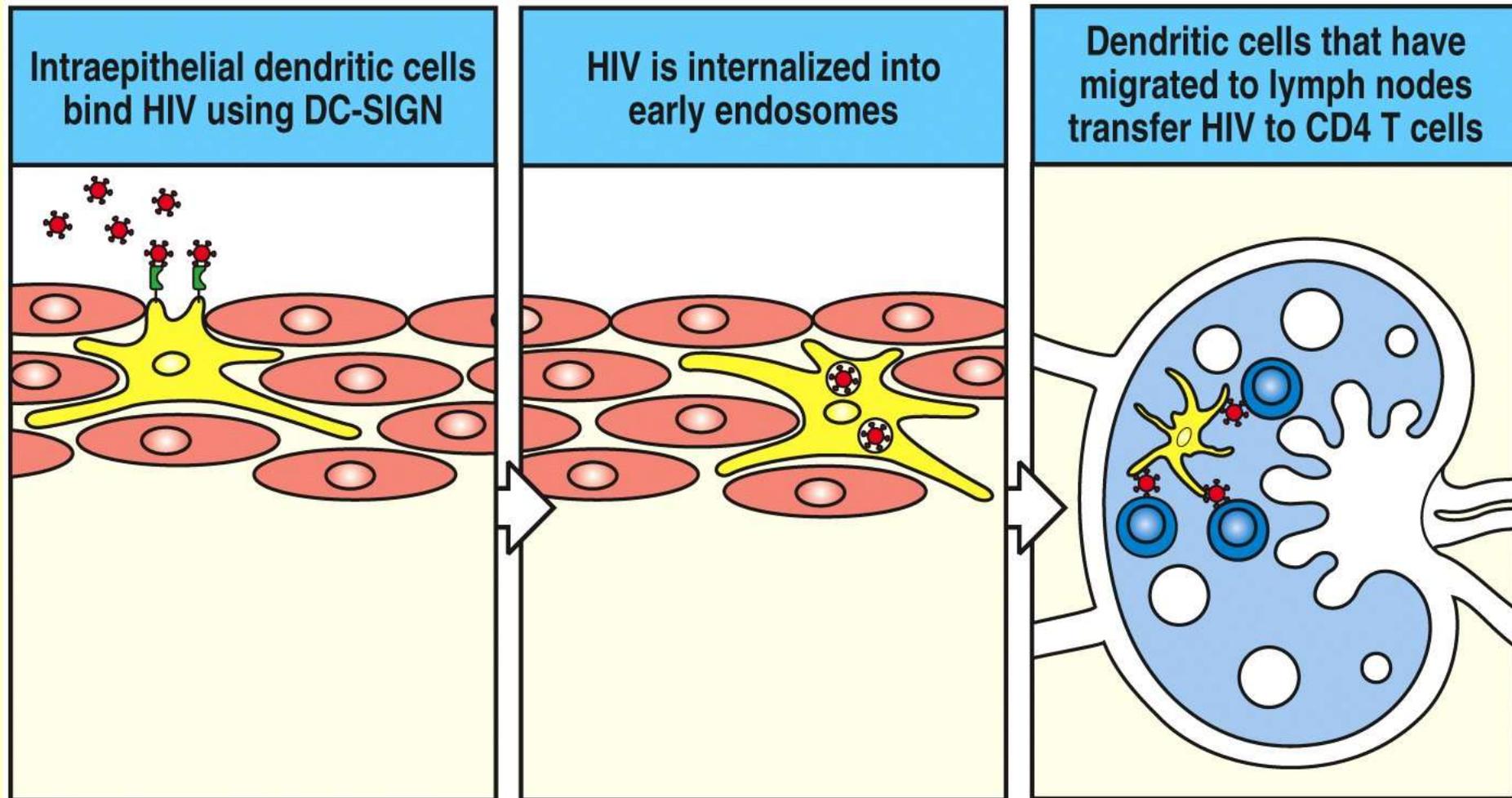
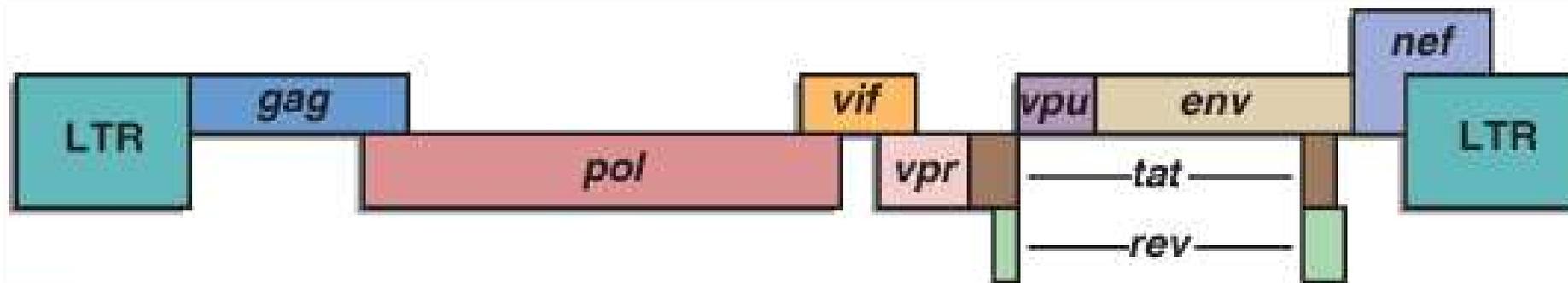


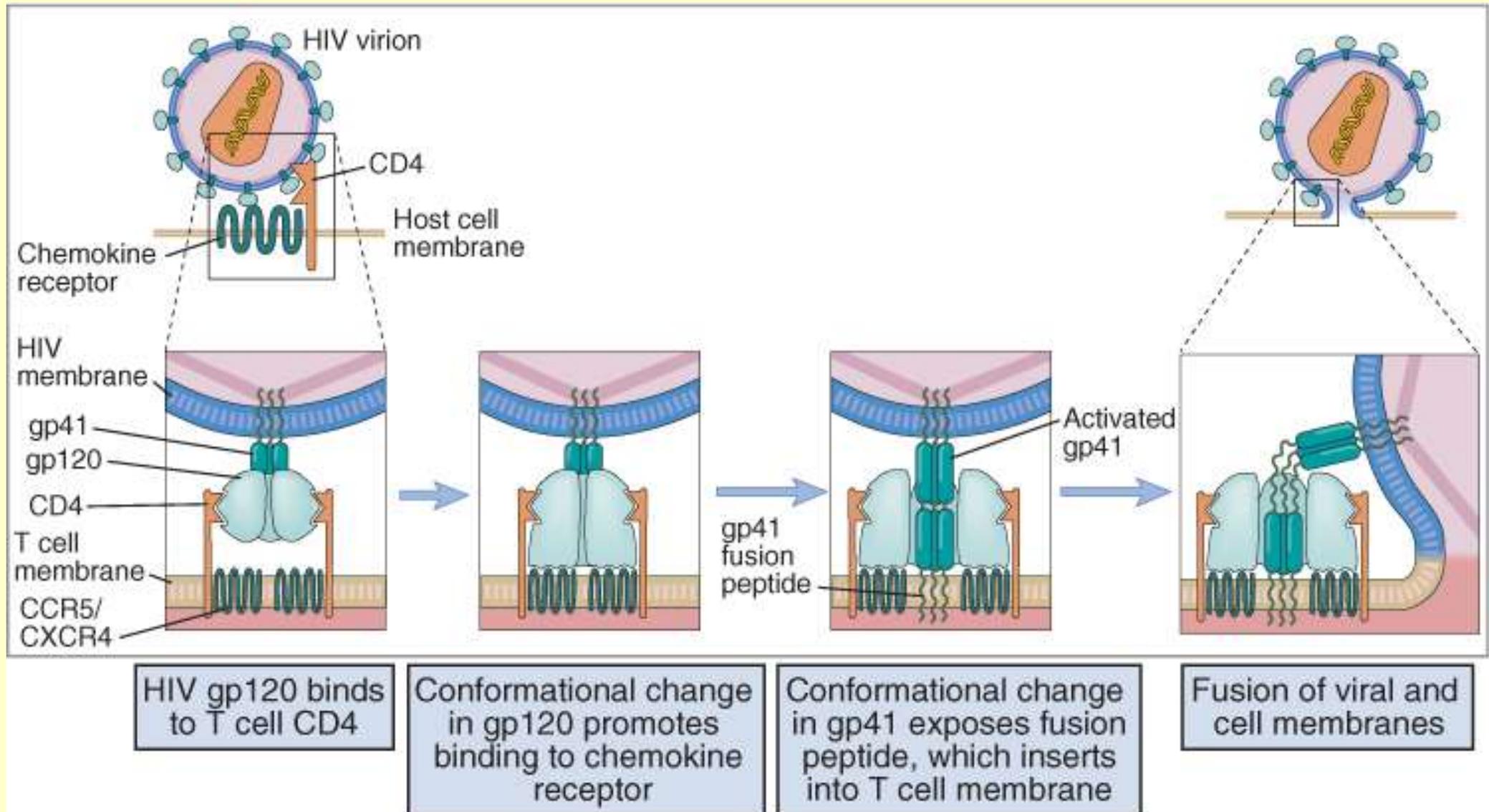
Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

Genome of HIV

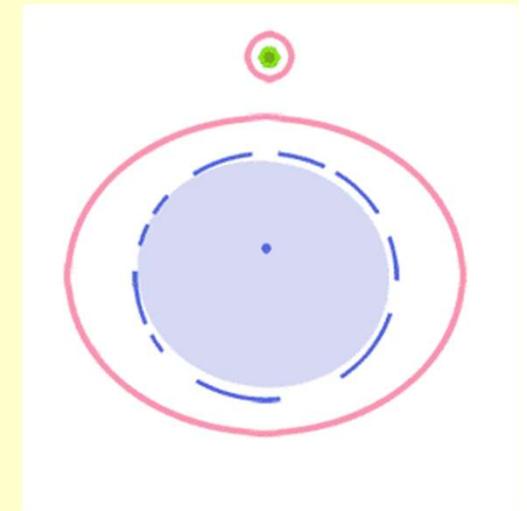
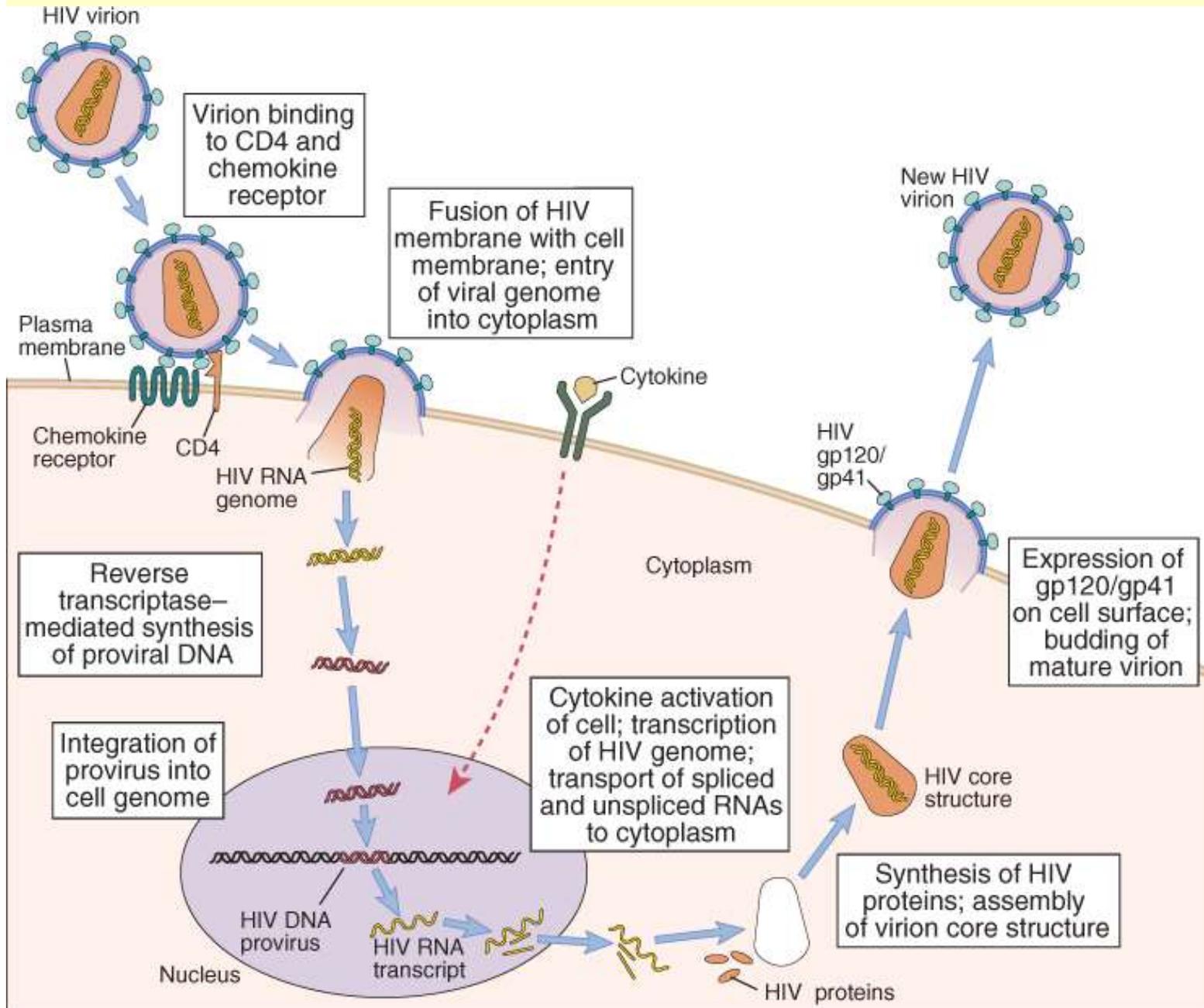
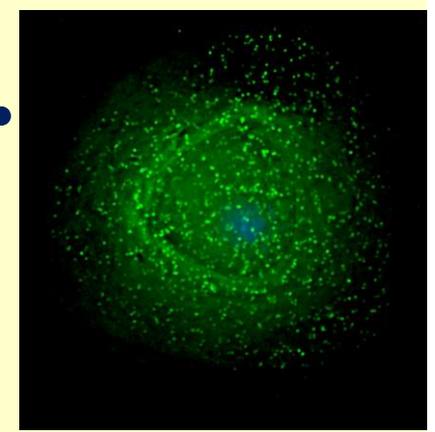


LTR	Integration of viral DNA into host cell genome; binding site for host transcription factors
gag	Nucleocapsid core and matrix proteins
pol	Reverse transcriptase, protease, integrase, and ribonuclease
env	Viral coat proteins (gp120 and gp41) mediating CD4 and chemokine receptor binding and membrane 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

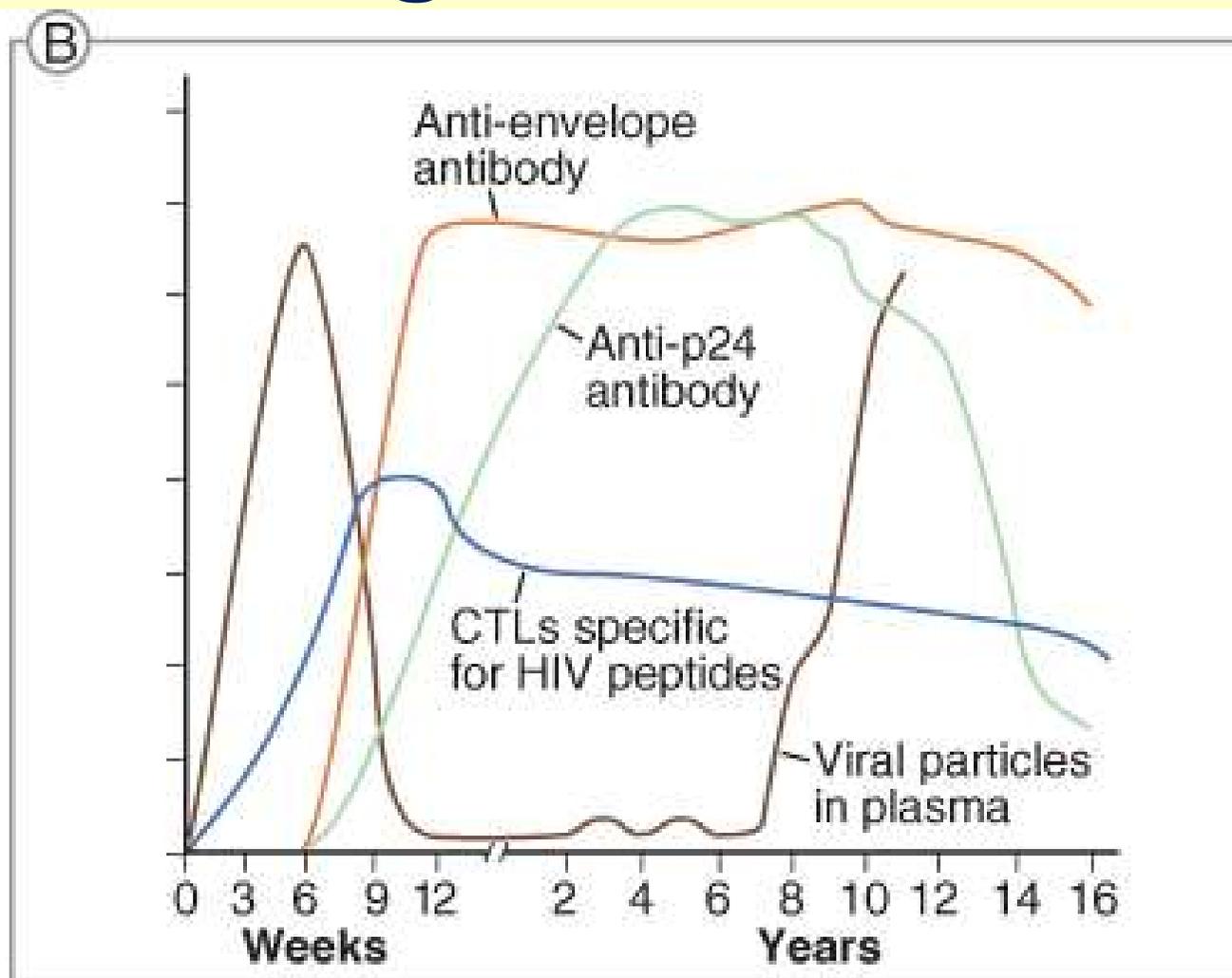
The life cycle of HIV I.



The life cycle of HIV II.



Humoral and cellular immunity against HIV



Clinical categories

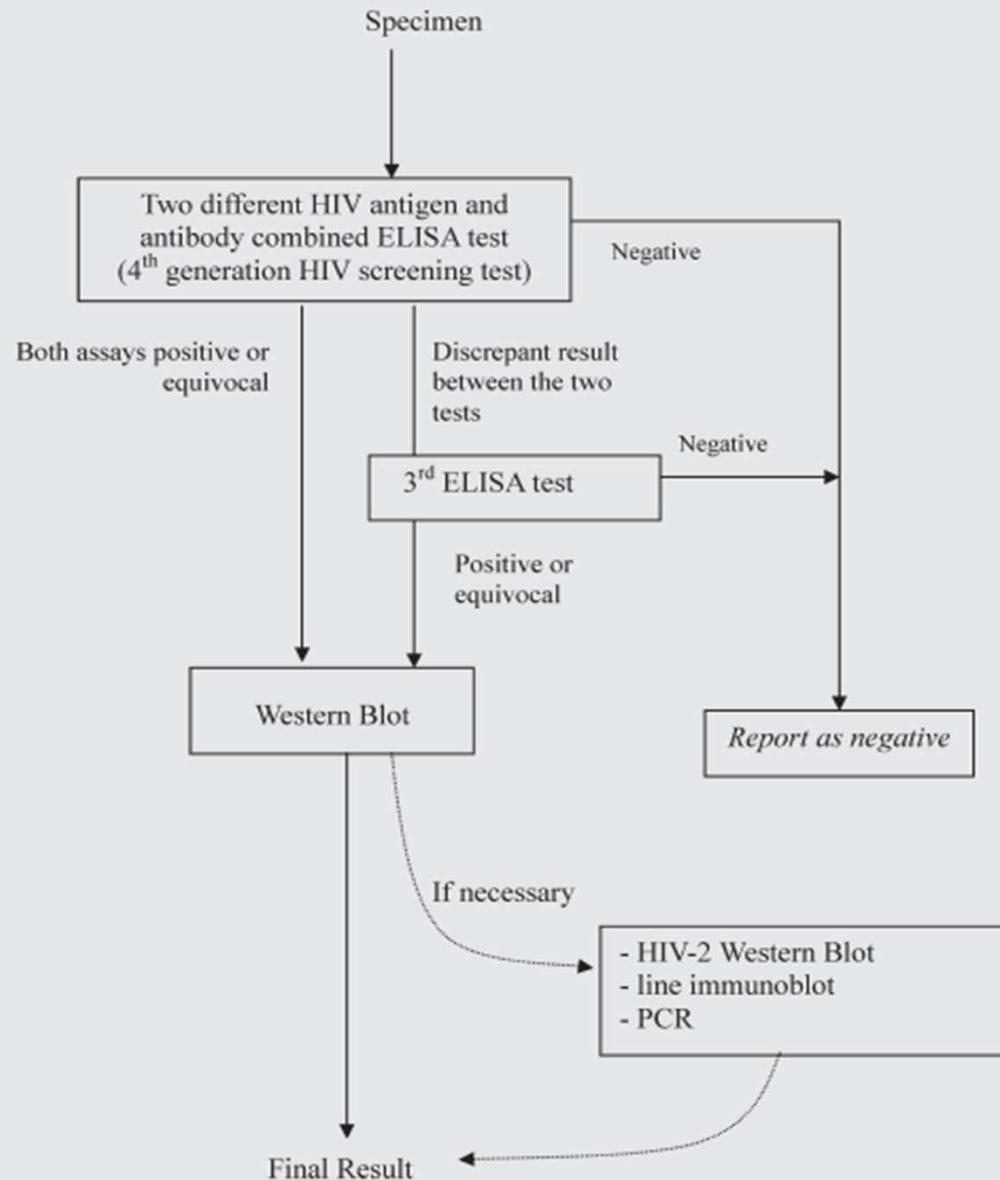
CD4+ T cell numbers

	A	B	C
> 500/μl	A1	B1	C1
200 - 499/μl	A2	B2	C2
< 200/μl	A3	B3	C3

Green categories represents AIDS syndrome

Diagnosics of HIV-infection

Algorithm 3(A) Laboratory diagnosis of HIV infection for adults
(adapted from protocol of Public Health Laboratory Centre, Centre for Health Protection, Department of Health)



Complications in AIDS

Opportunistic infections:

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

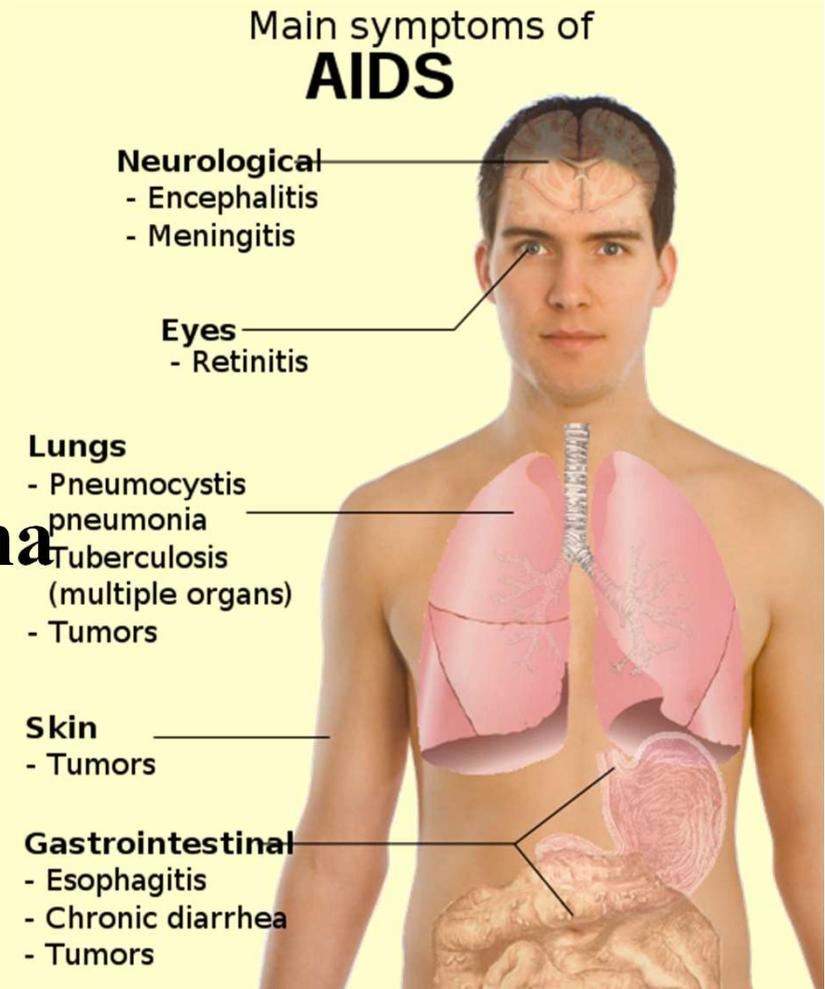
Tumors:

Kaposi-sarcoma

Non-Hodgkin-lymphoma

EBV-positive Burkitt lymphoma

Lymphoma in the CNS



Current therapeutic approaches

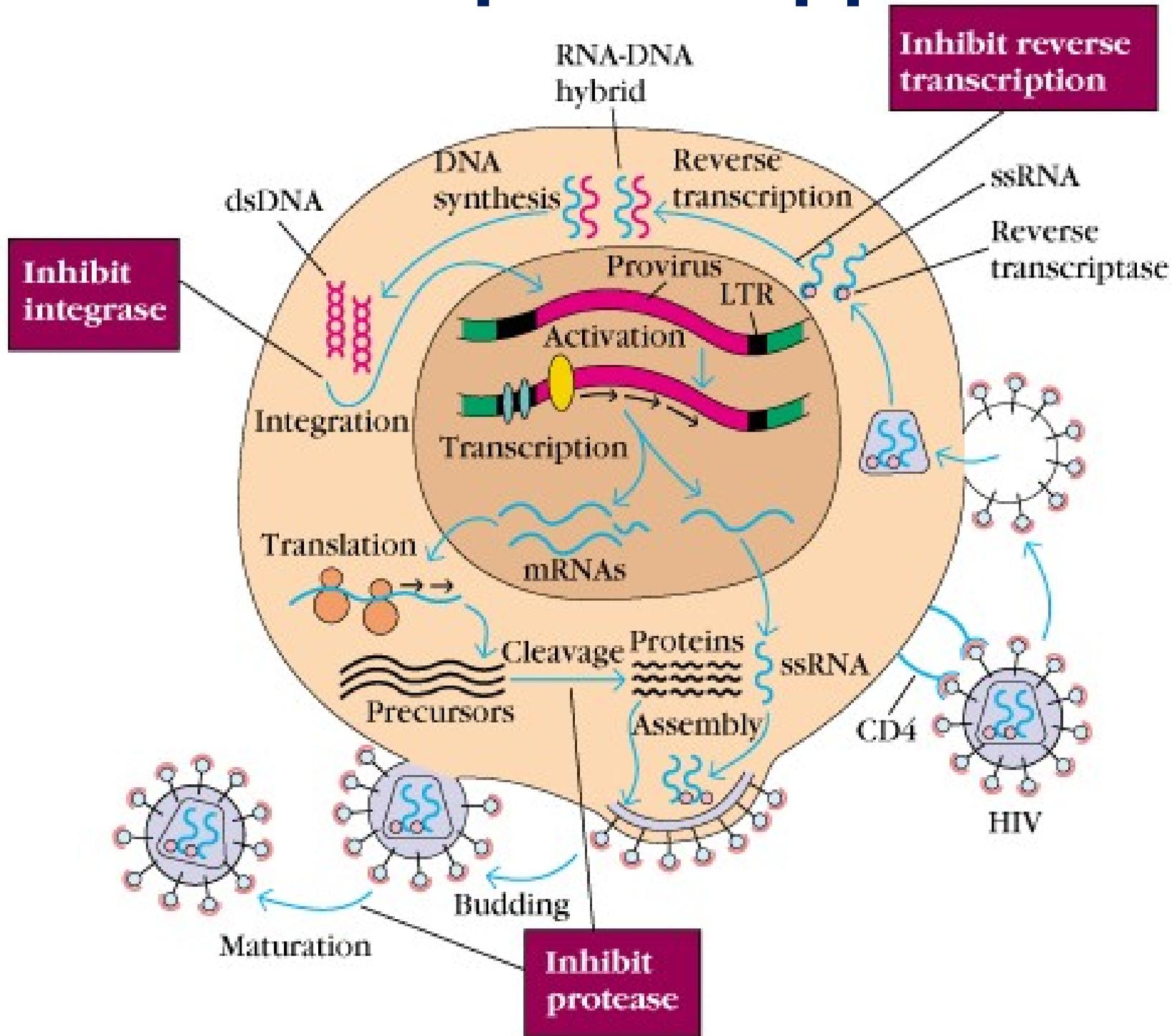
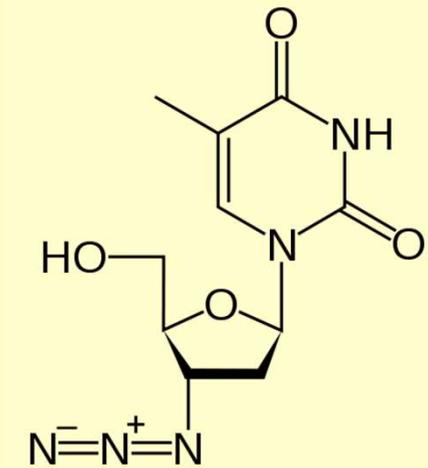
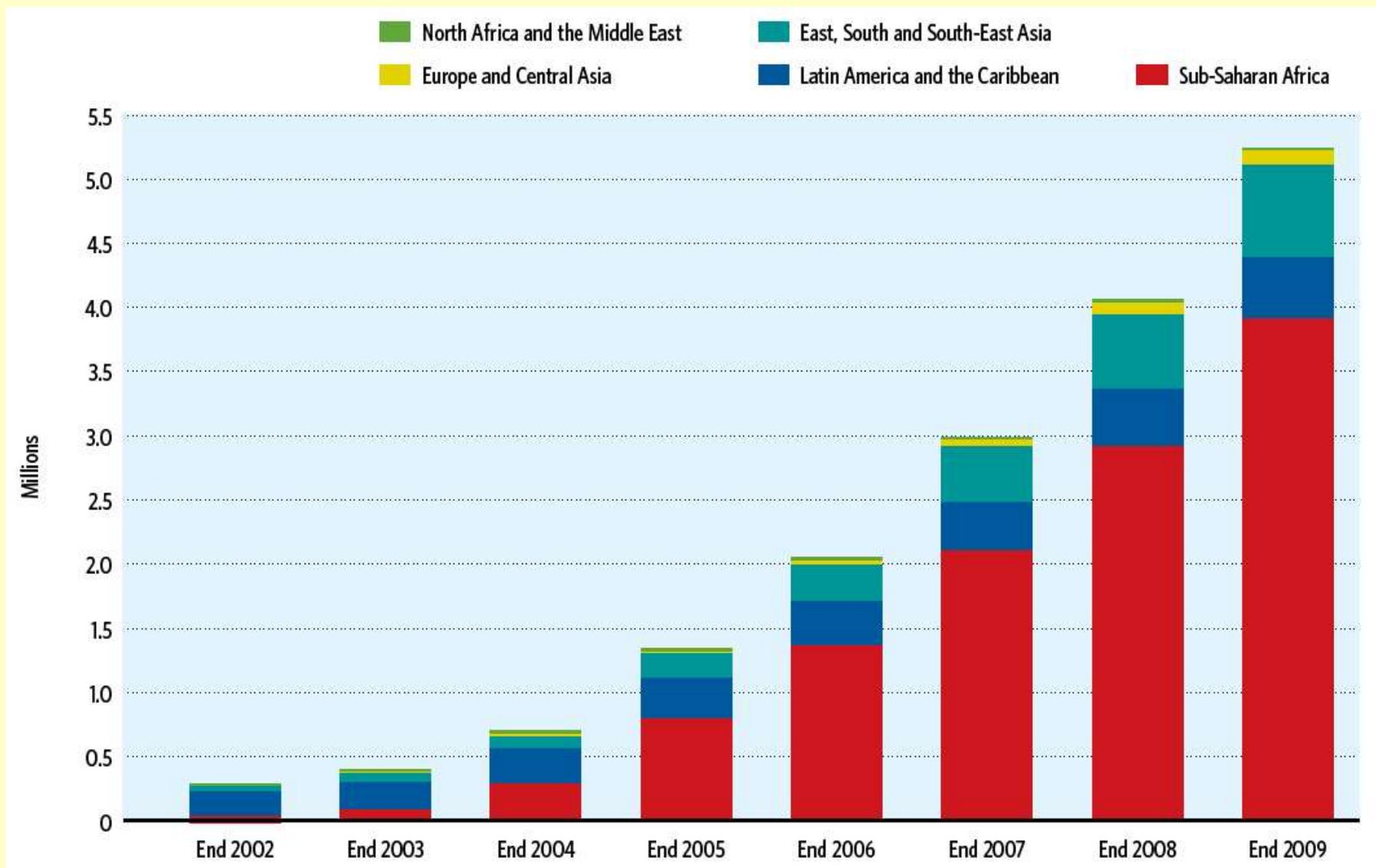


TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

Generic name (other names)	Typical dosage	Some potential side effects
Reverse transcriptase inhibitors: Nucleoside analog		
Didanosine (Videx, 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
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

**Azithothymidin (AZT)**

Antiretroviral therapy (2002-2009)



UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS

UNHCR
UNICEF
WFP
UNDP
UNFPA
UNODC
ILO
UNESCO
WHO
WORLD BANK



World Health
Organization

TABLE 19-7 VACCINE STRATEGIES UNDER STUDY

Vaccine constituents	Status	Advantages	Disadvantages
Vaccines eliciting anti-HIV antibodies			
Viral surface proteins, such as gp120	In phase I and II trials, which examine safety	Safe and simple to prepare	Vaccine-elicited antibodies have failed to recognize HIV from patients
Whole, killed HIV	Not under study in humans	Should present HIV surface proteins in a relatively natural conformation; simple to prepare	Slight risk that preparations might include some active virus; inactivated virus might shed its proteins and become ineffective
Pseudovirions (artificial viruses containing HIV surface proteins)	Close to phase I trials	Present HIV surface proteins in a relatively natural conformation	Difficult to produce and to ensure long-term stability
Vaccines eliciting cellular responses			
Live vector viruses (non-HIV viruses engineered to carry genes encoding HIV proteins)	In phase II trials	Makers can control amount and kinds of viral proteins produced	Complicated to prepare; current vaccines elicit modest immune response
Naked DNA containing one or more HIV genes	In phase I trials	Simple and inexpensive to prepare	Some worry that integration of HIV genes into human cells could harm patients
HIV peptides (protein fragments)	In phase I trials	Simple to prepare	Do not elicit strong immune response
Vaccines eliciting antibody and cellular responses			
Combinations of elements, such as pure gp120 protein plus canarypox vector	In phase II trials	Should stimulate both arms of the immune response at once	Complicated to prepare
Live, attenuated HIV	Not under study in humans; being assessed in nonhuman primates	Most closely mimics HIV; may interfere with ability of infectious HIV to replicate	Vaccine virus could potentially cause AIDS

SOURCE: D Baltimore and C Heilman, "HIV vaccines: prospects and challenges," 1998, *Sci. Am.* 279 (1):101.



Dec. 1.

Nobel-prize 2008

HPV



Harald zur Hausen
Germany

HIV



Francoise
Barré-Sinoussi
France



Luc Montaigner
France