# Basic immunology

## Secondary (acquired) immundeficiencies, HIV-AIDS

## Lecture 28

# Acquired immundeficiencies

- **Altered immune function in the course of occured diseases (non congenital)**

- **Immunsuppression caused by a disease complication**

**OR**

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

# Main causes of acquired immundeficiencies I.

| Cause | Mechanism |
| --- | --- |
| Human immundeficiency virus infection | CD4+ T cell depletion |
| Morbilli, HTLV-1 virus | Lymphocyte infections,<br>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 immundeficiencies II.

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

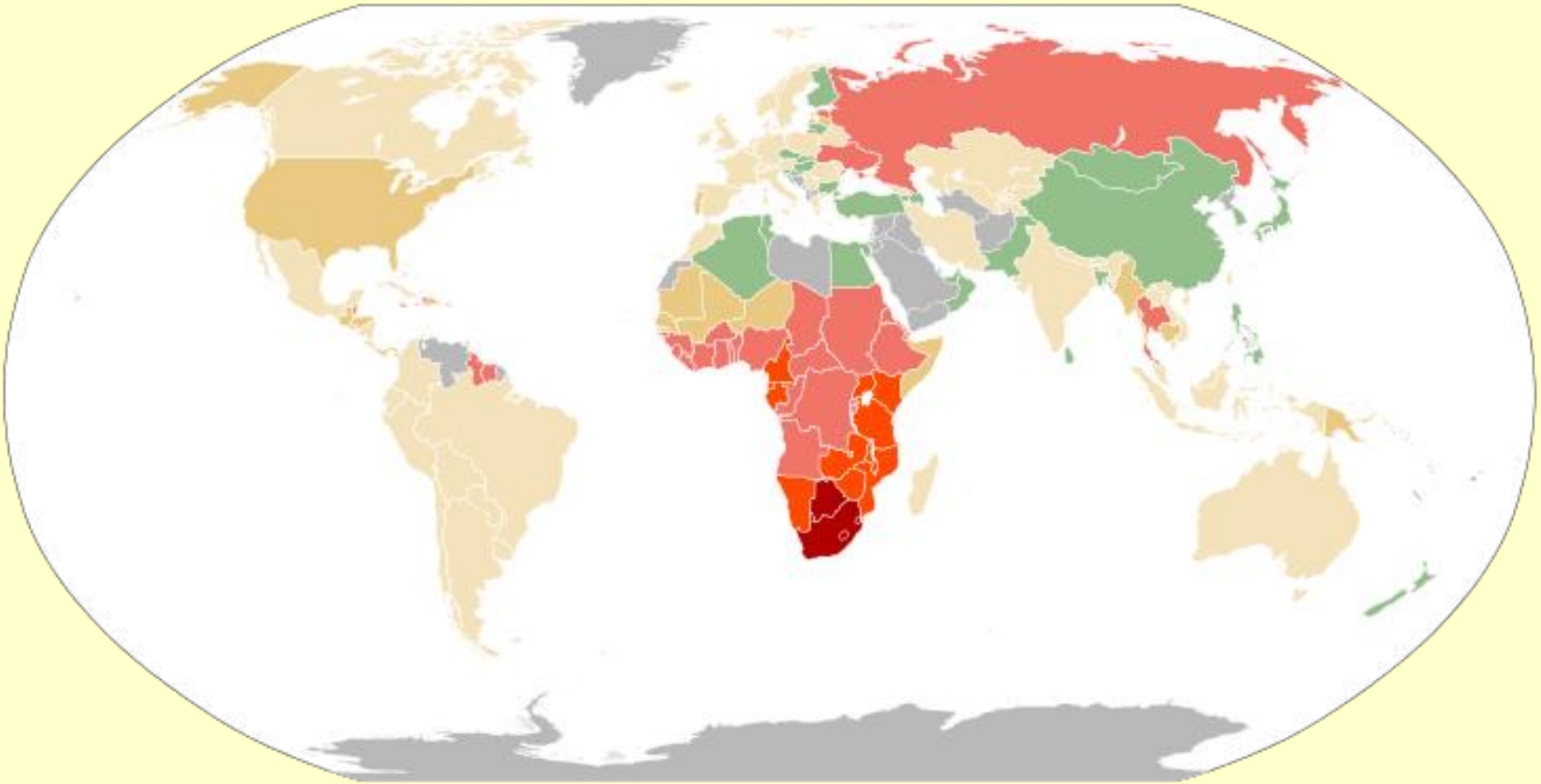
# Epidemics (WHO)

| | 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 |

# 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 [4100 - 7500] |
| 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] | 3800 [2900 - 4700] | 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] | 1700 [1300 - 2100] | 5300 [4000 - 7100] |
| 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 [9300 - 17 000] |

# Regional epidemics

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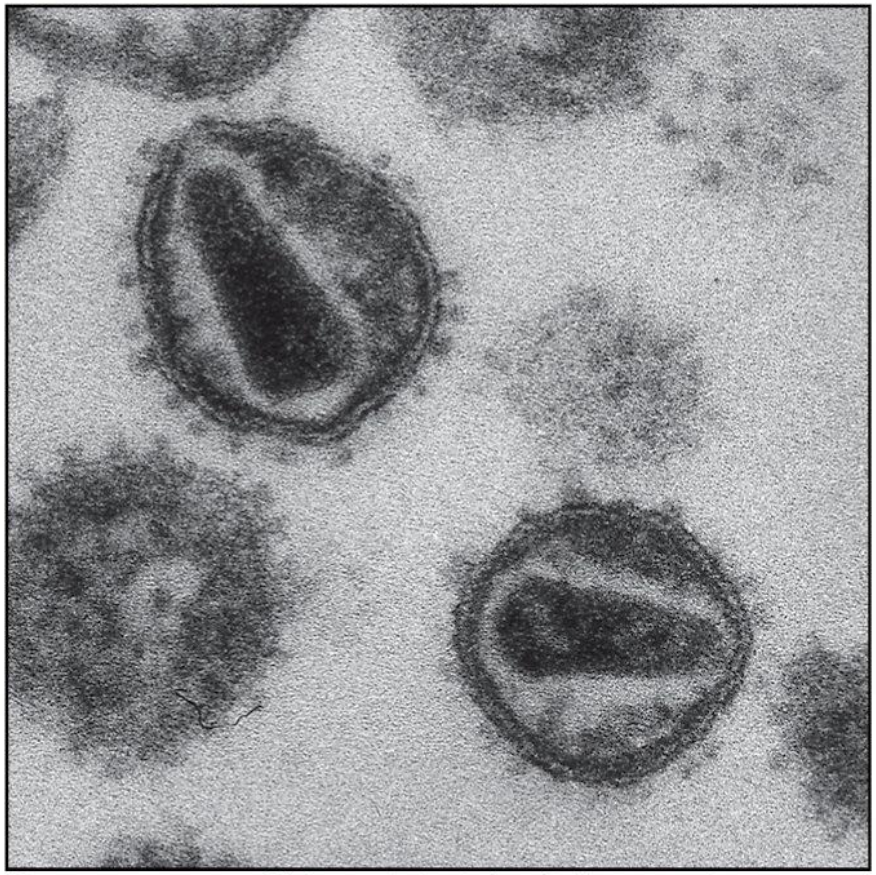
# HIV

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



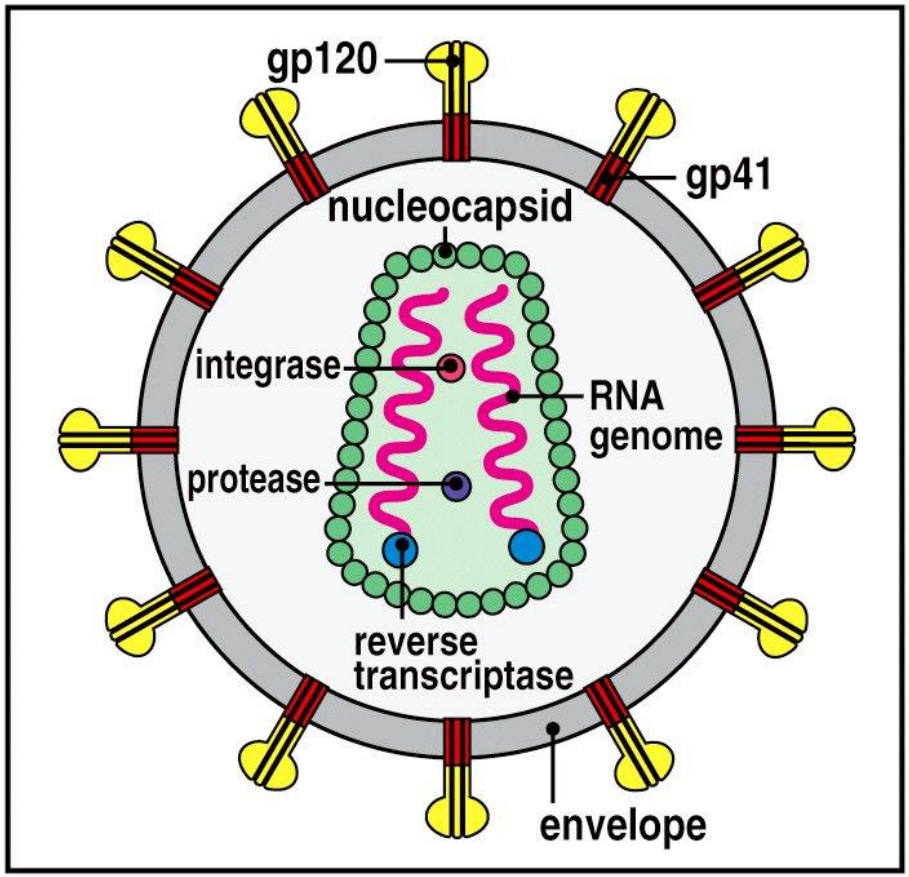
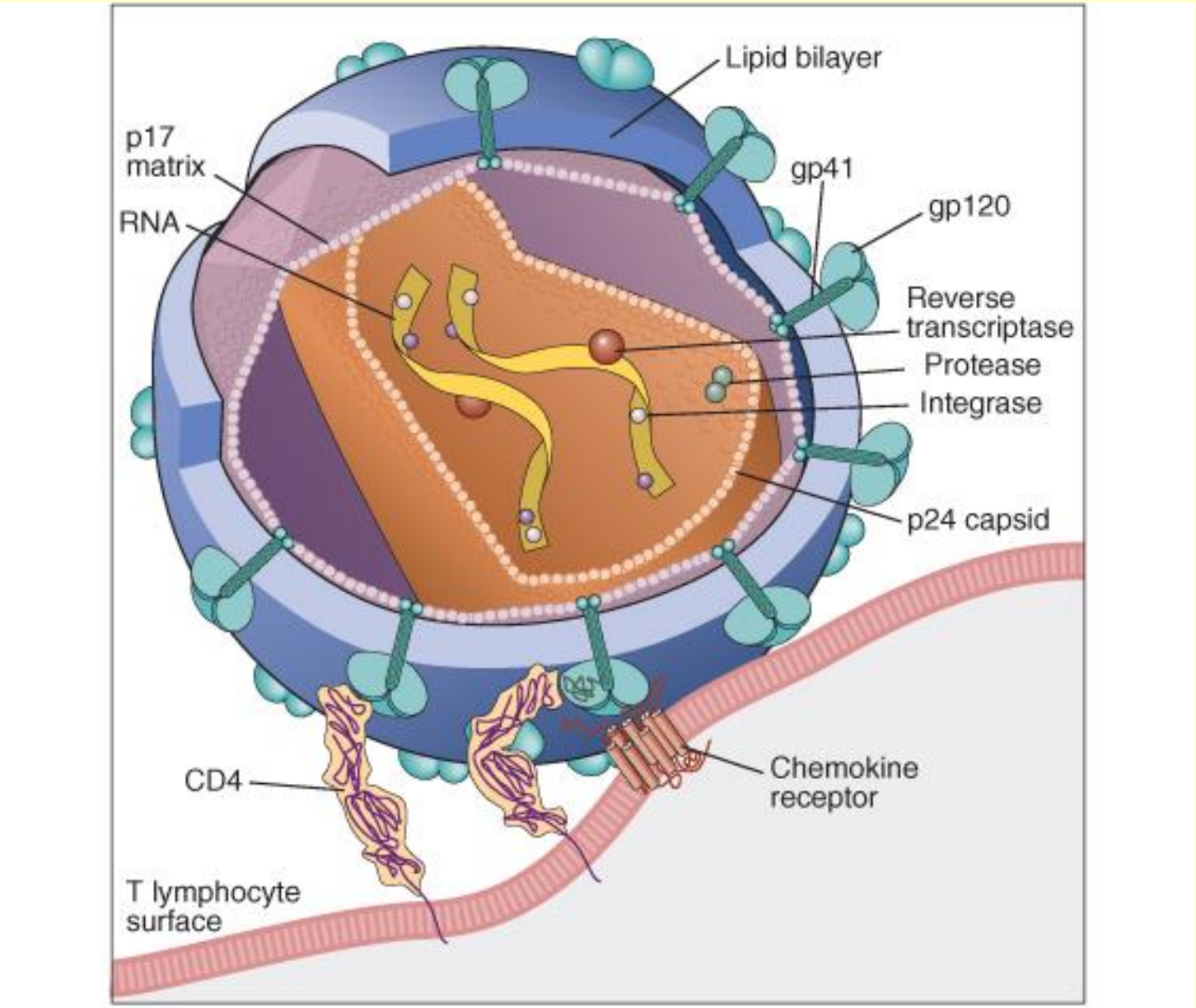



Figure 11-21 Immunobiology, 6/e. (© Garland Science 2005)

# 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

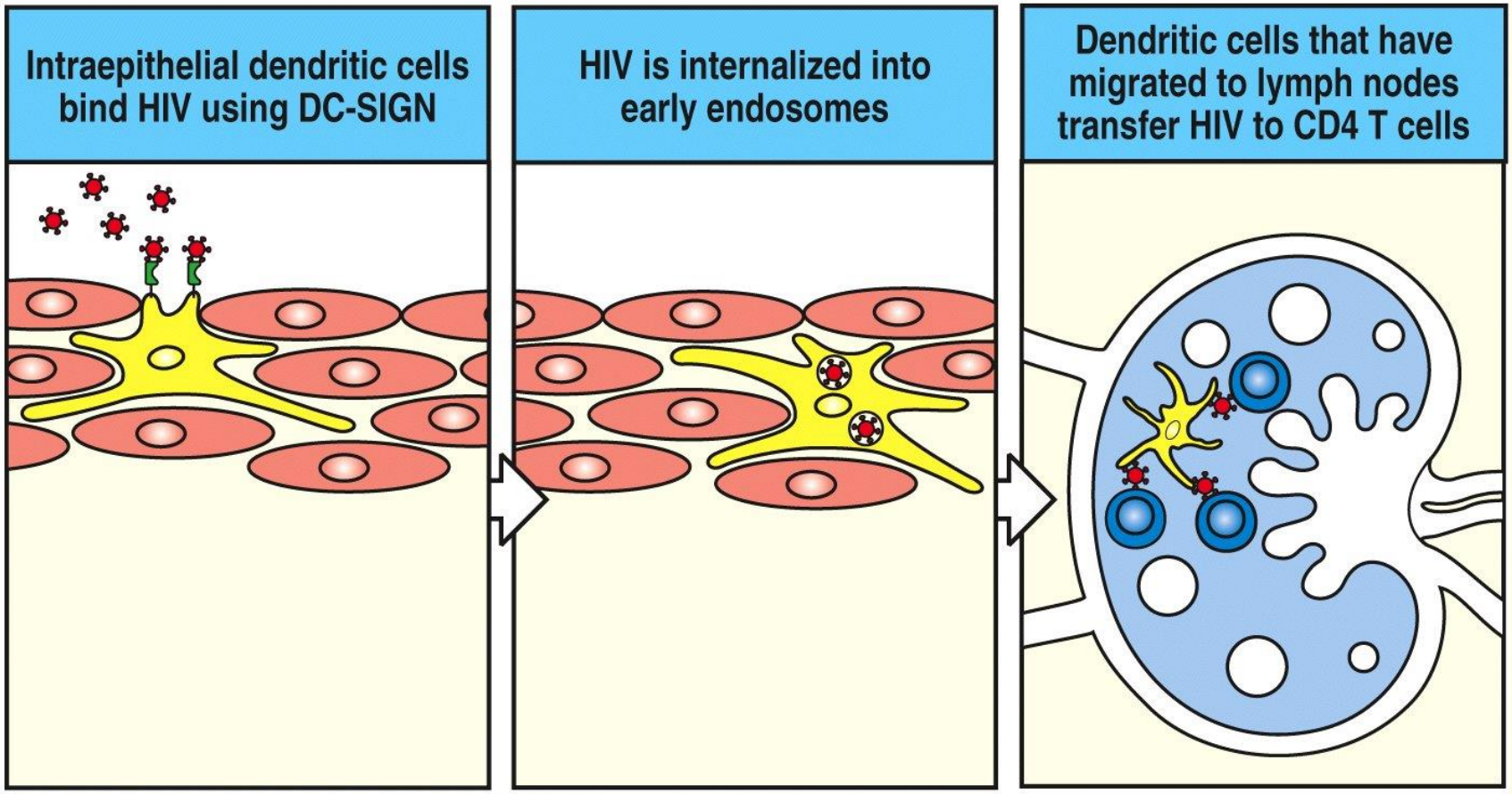
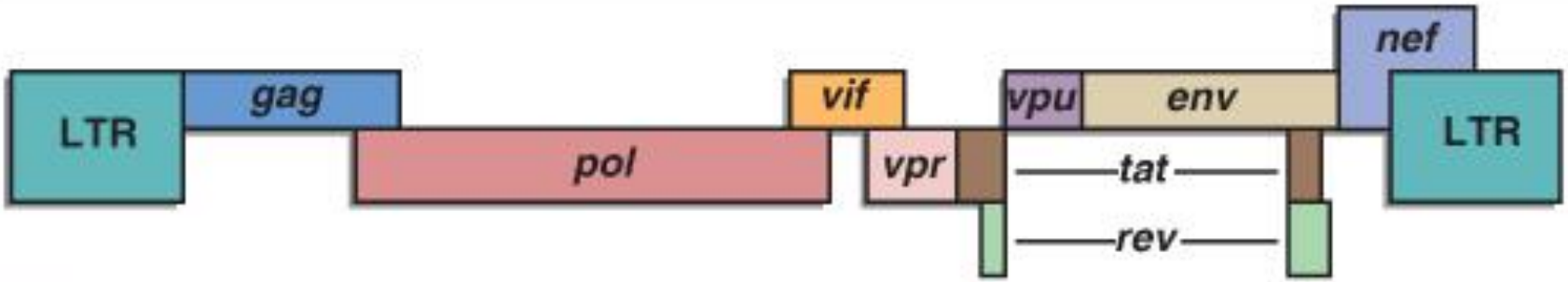


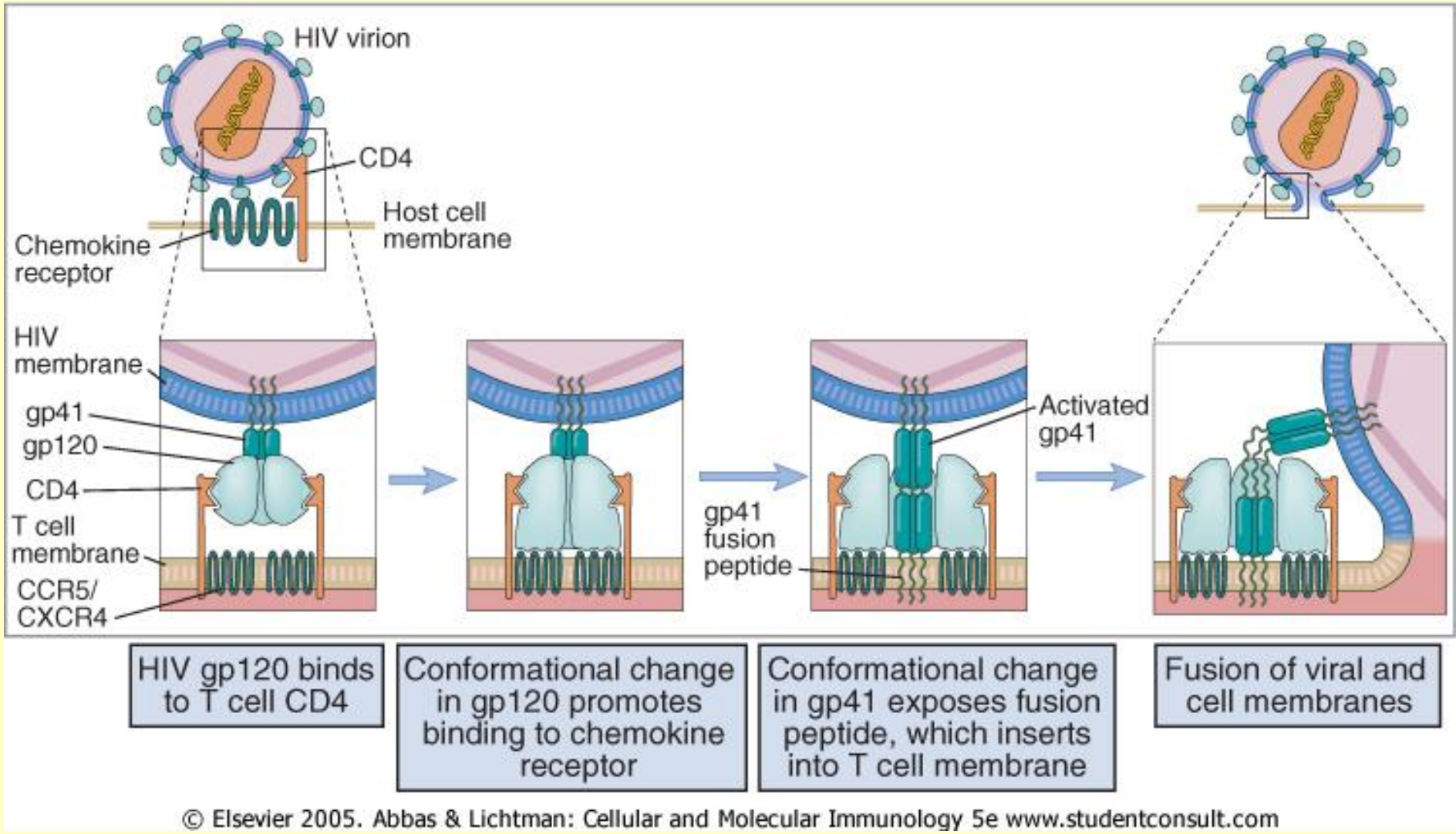

Figure 11-22 Immunobiology, 6/e. (© Garland Science 2005)

# Genome of HIV

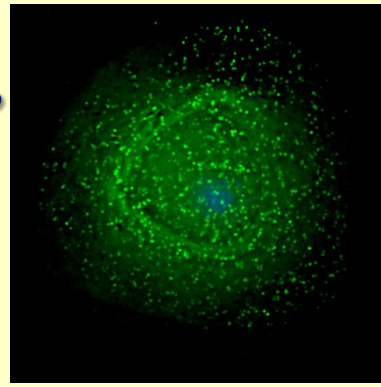


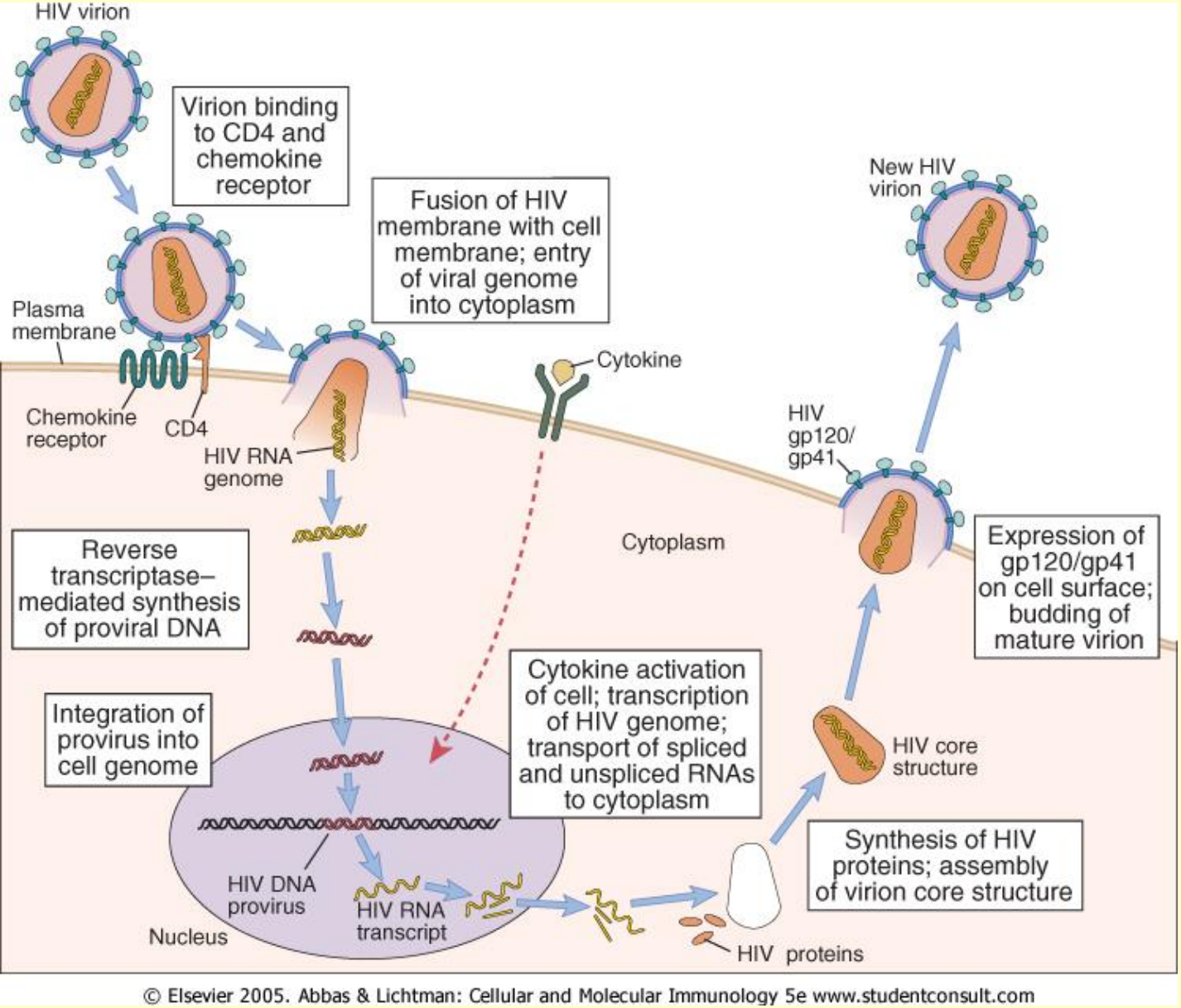

| | |
|---|---|
| LTR | Integration of viral DNA into host cell genome; binding site for host transcription factors |
| *gag* | Nucleocapsid core and matrix proteins |
| *pol* | Reverse transcriptase, protease, integrase, and ribonuclease |
| *env* | Viral coat proteins (gp120 and gp41) mediating CD4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

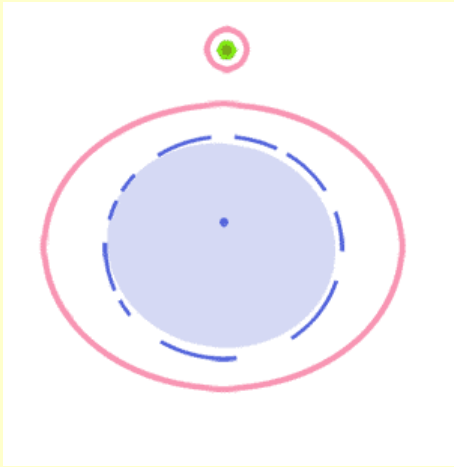
# The life cycle of HIV I.

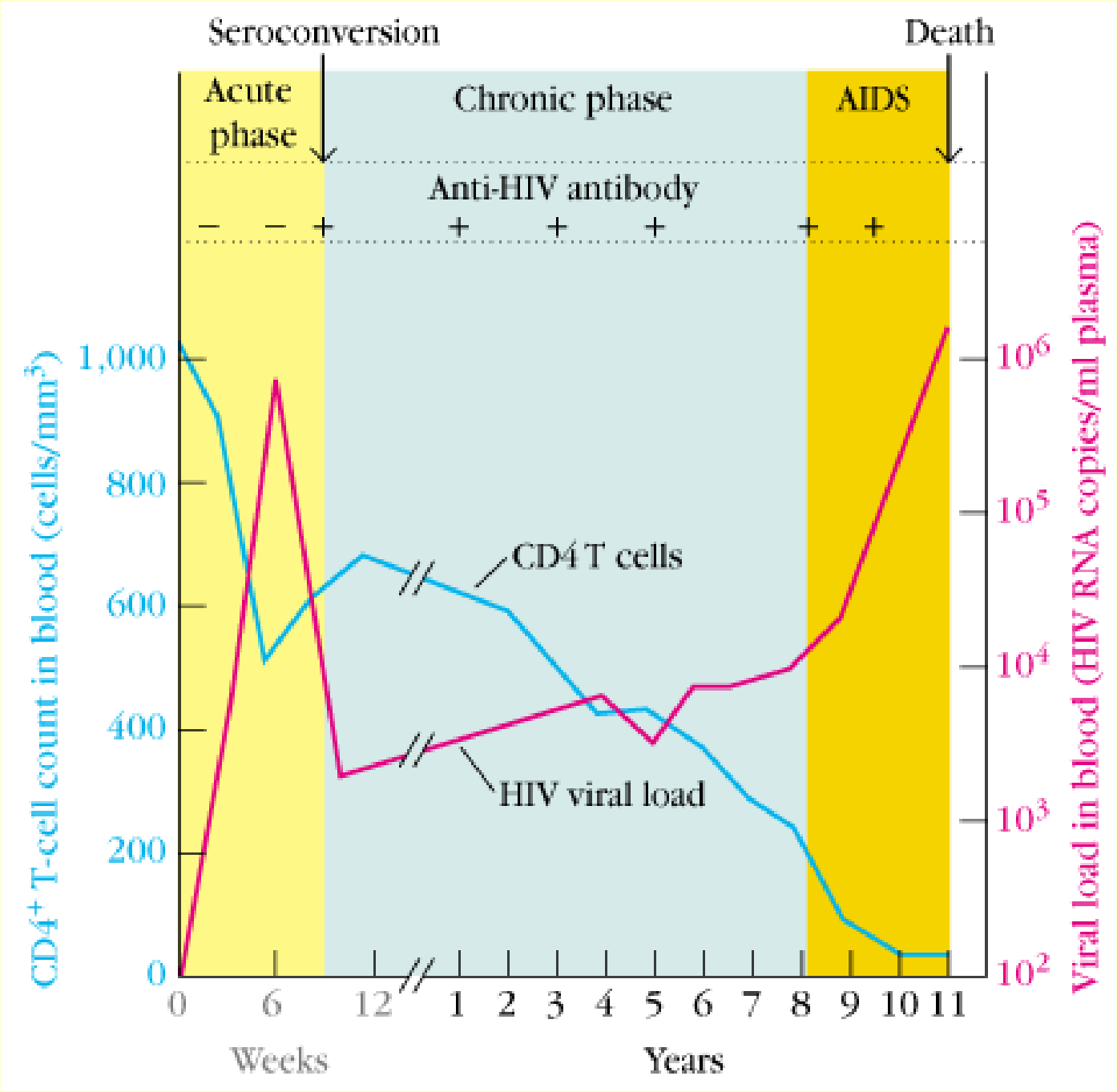


# The life cycle of HIV II.

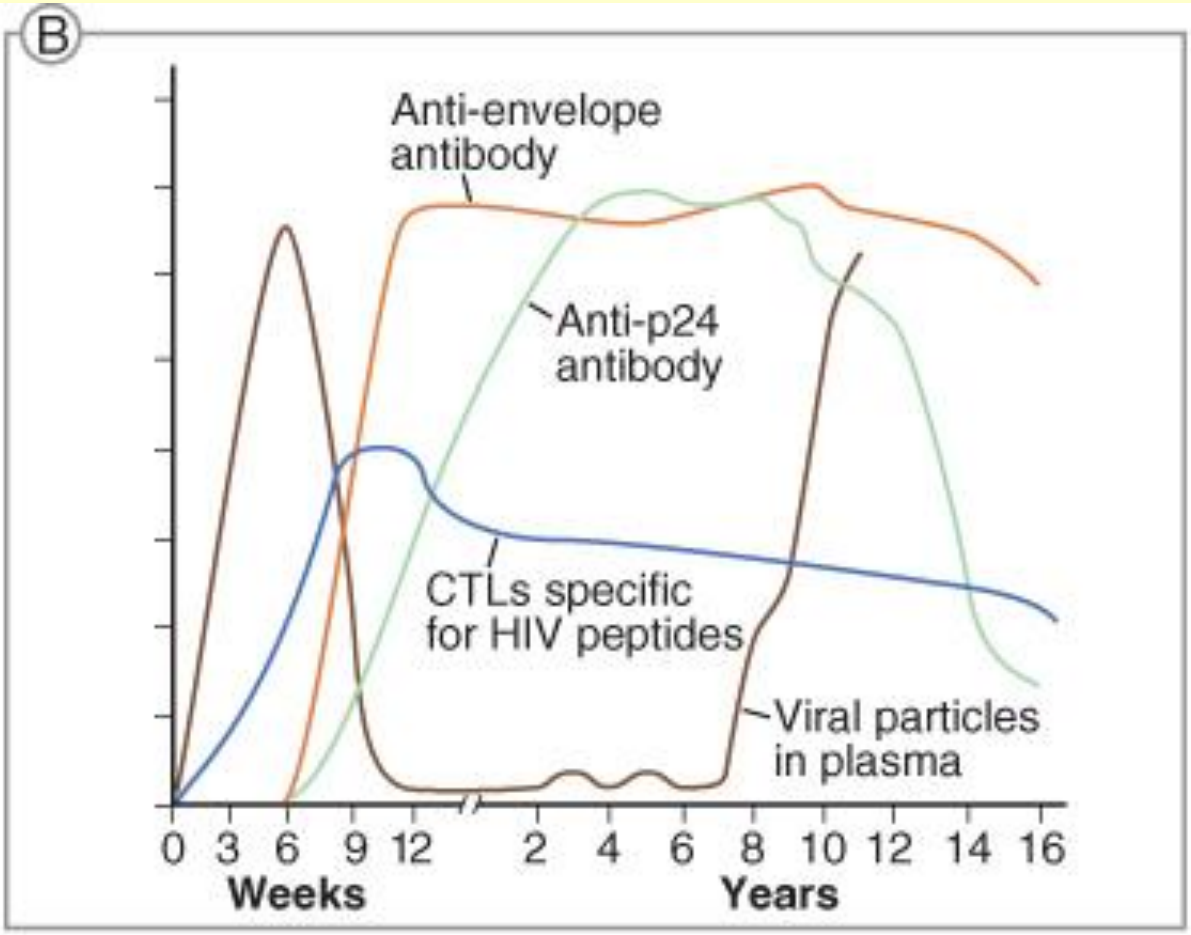





Seroconversion
Death
Acute phase
Chronic phase
AIDS
Anti-HIV antibody
– – + + + + + +
CD4 T cells
HIV viral load
CD4+ T-cell count in blood (cells/mm3)
1,000
800
600
400
200
0
Viral load in blood (HIV RNA copies/ml plasma)
10^6
10^5
10^4
10^3
10^2
0 6 12 1 2 3 4 5 6 7 8 9 10 11
Weeks
Years

# Humoral amd cellular immunity against HIV

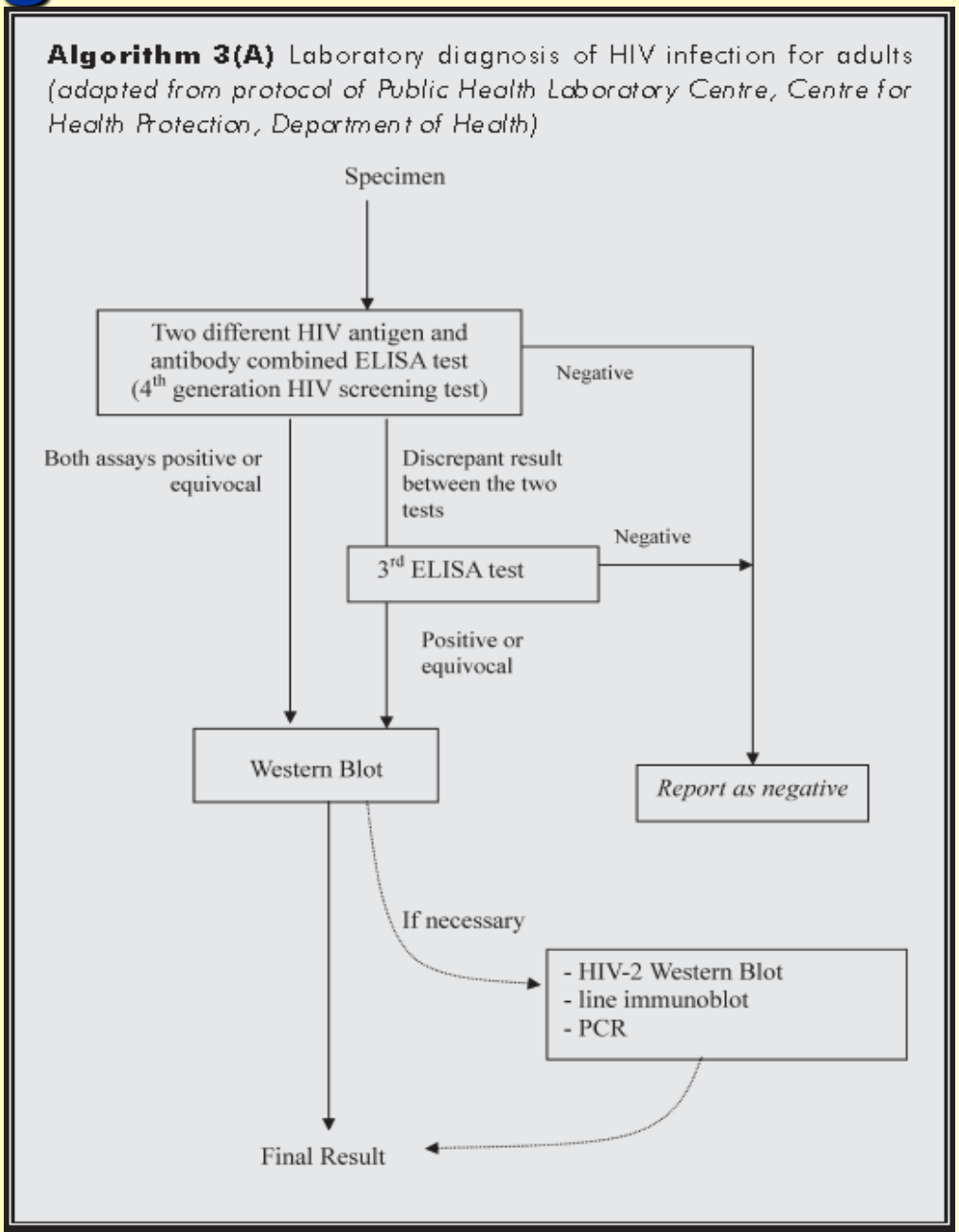


## Clinical categories

| 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

# Diagnostics of HIV-infection



# Complications in AIDS

## Opportunistic infections:

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

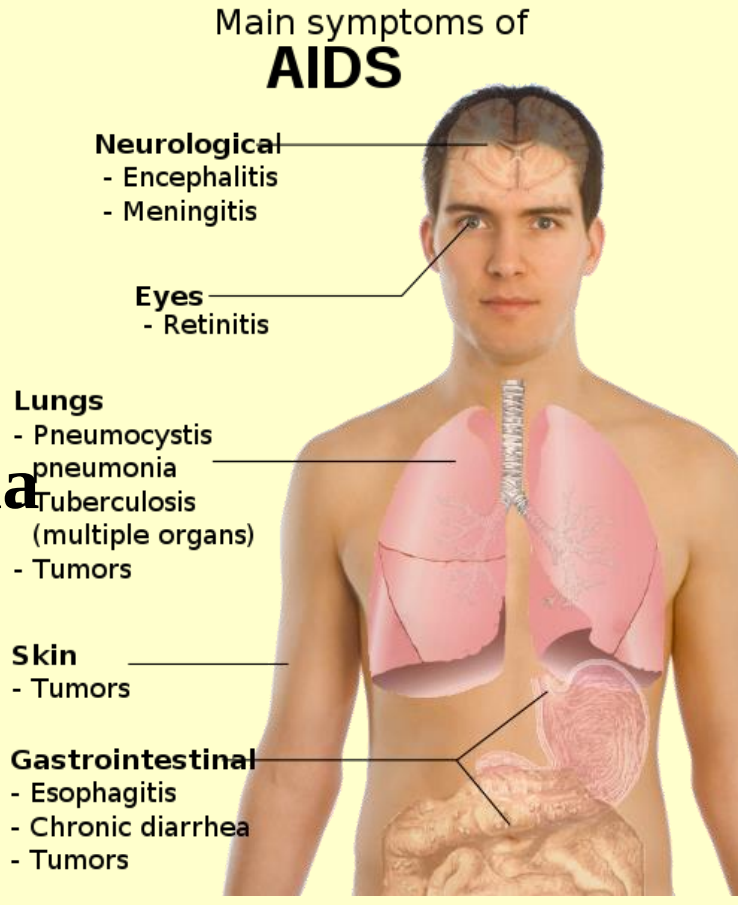
## Tumors:

Kaposi-sarcoma

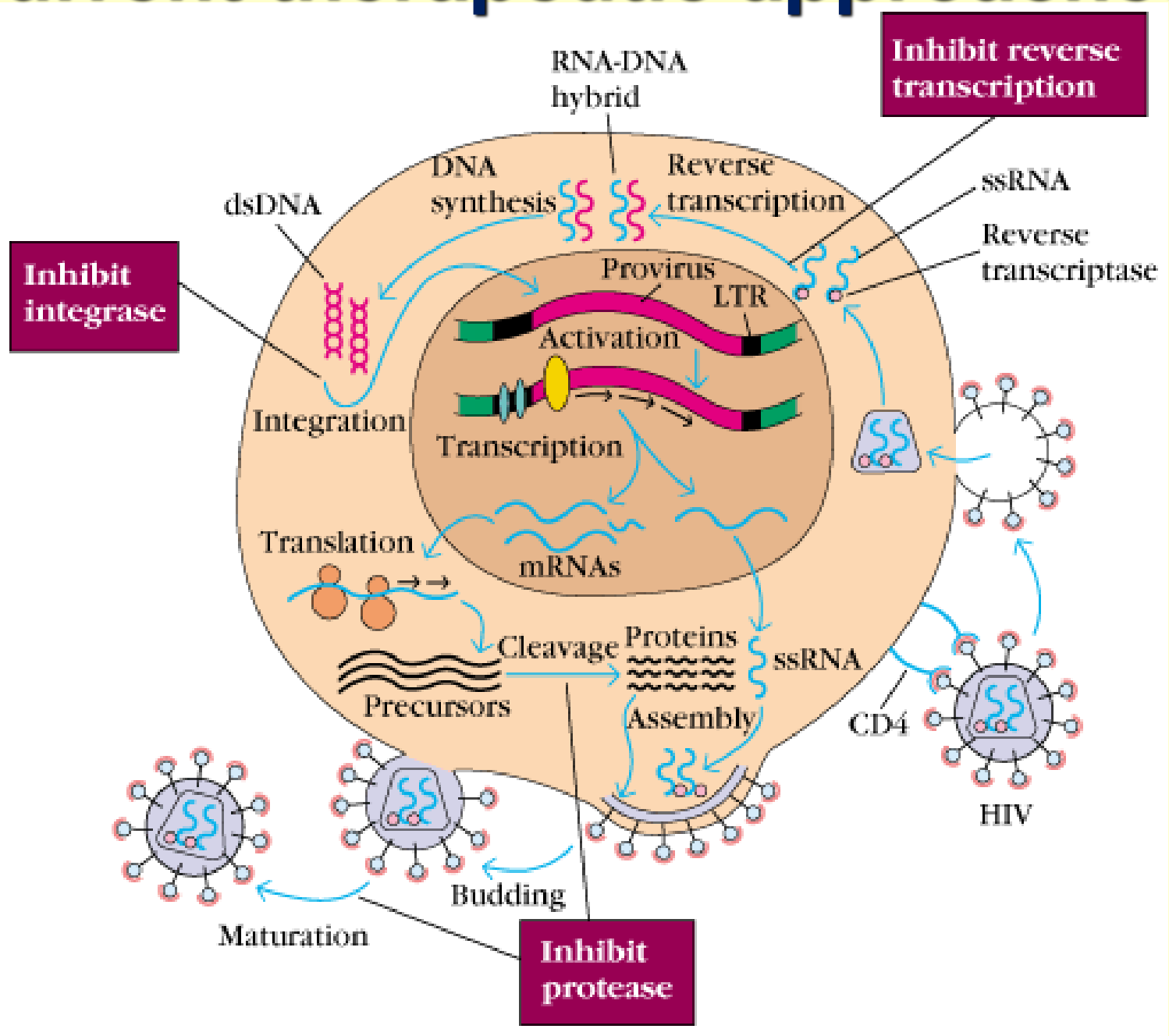
Non-Hodgkin-lymphoma

EBV-positive Burkitt lymphoma

Lymphoma in the CNS



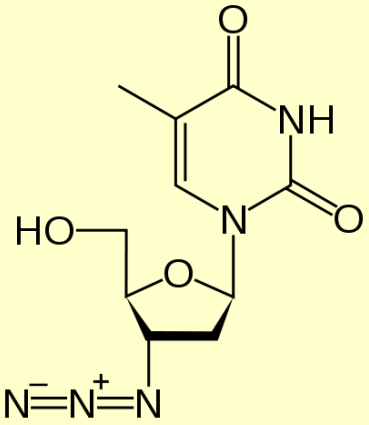
# Current therapeutic approaches



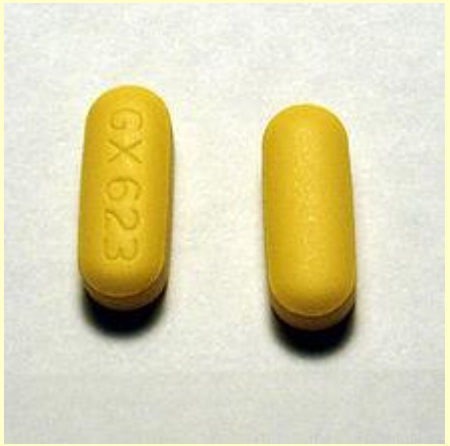
## TABLE 19-5 SOME ANTI-HIV DRUGS IN CLINICAL USE

| 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 |

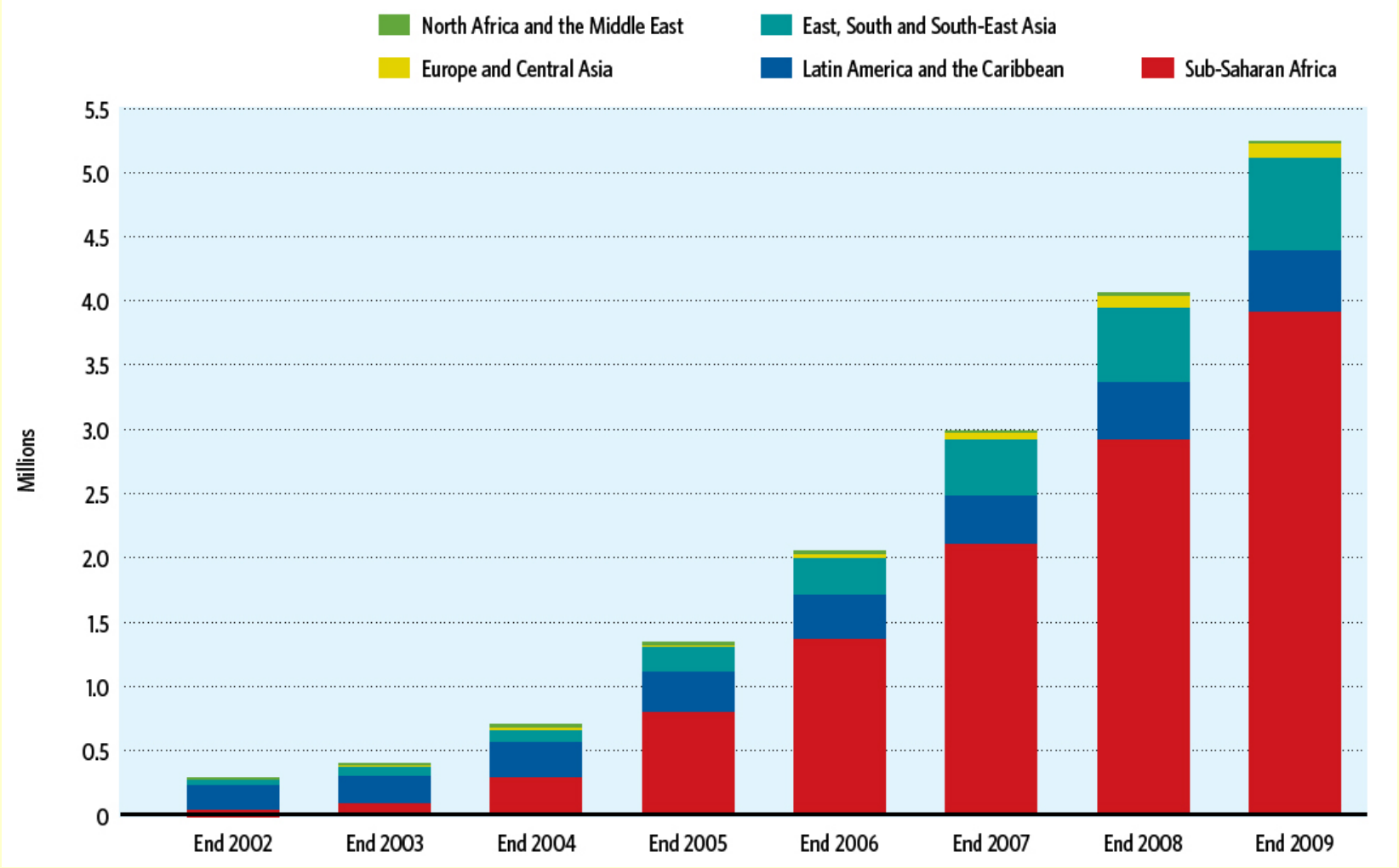
*SOURCE*: JG Bartlett and RD Moore, 1998, Improving HIV therapy, *Sci. Am.* **279**(1):87.




**Azithothymidin (AZT)**



# Antiretroviral therapy (2002-2009)

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## 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*