HIV and AIDS

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Acquired Immunodeficiency Syndrome (AIDS)

- 1981: In United States, cluster of *Pneumocystis* and Kaposi's sarcoma in young homosexual men discovered. The men showed loss of immune function.
- 1983: Discovery of virus causing loss of immune function.

The Origin of AIDS

- Crossed the species barrier into humans in Africa in the 1930s.
- Patient who died in 1959 in Congo is the oldest known case.
- Spread in Africa as a result of urbanization.
- Spread world-wide through modern transportation and unsafe sexual practices.
- Norwegian sailor who died in 1976 is the first known case in Western world.

HIV Infection

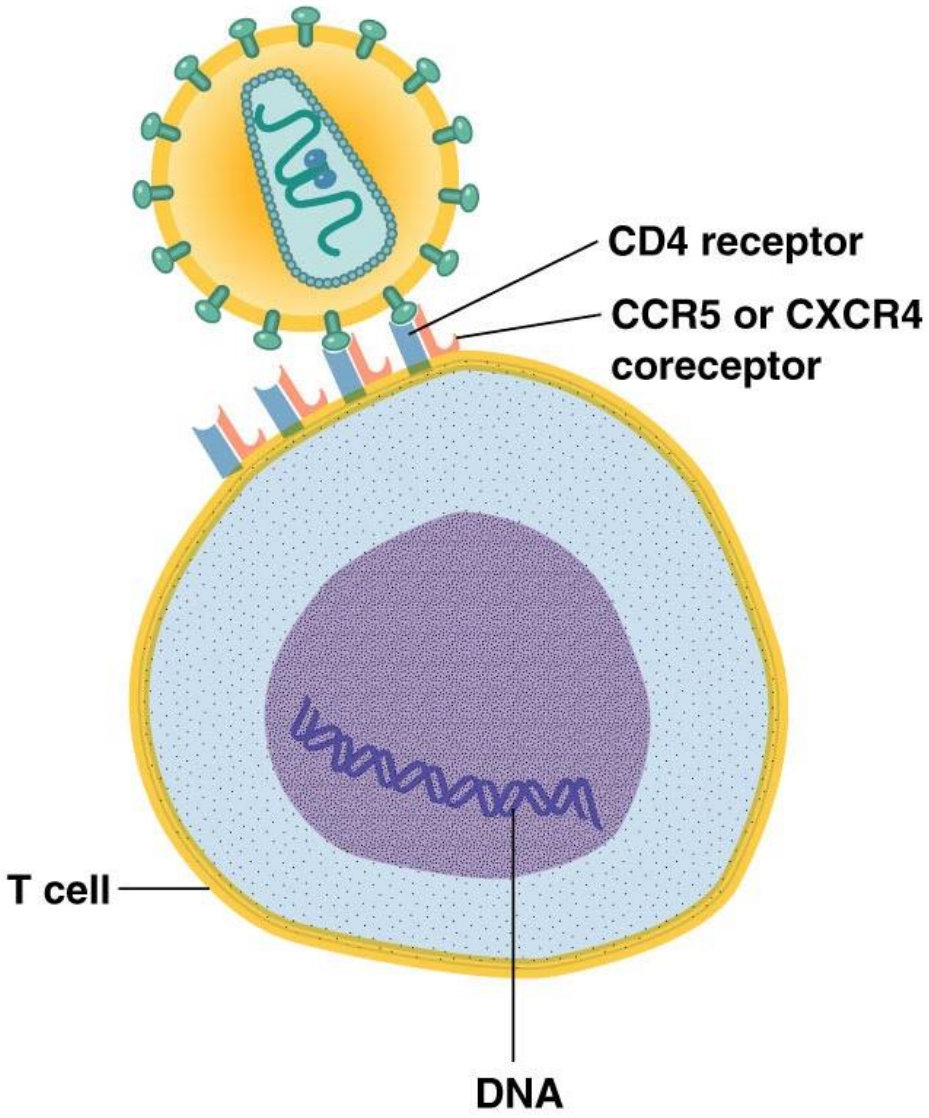
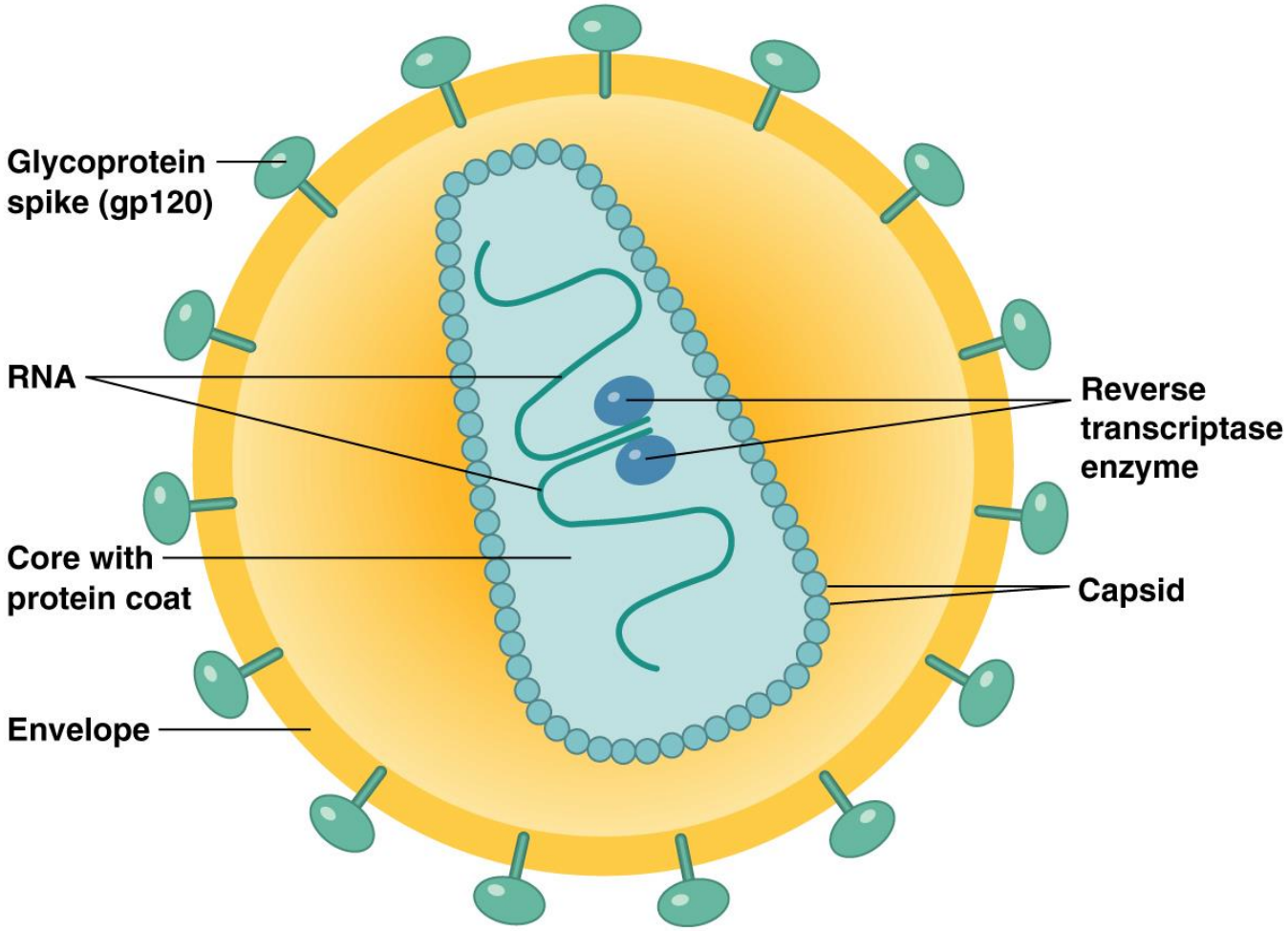


Figure 19.12b

HIV

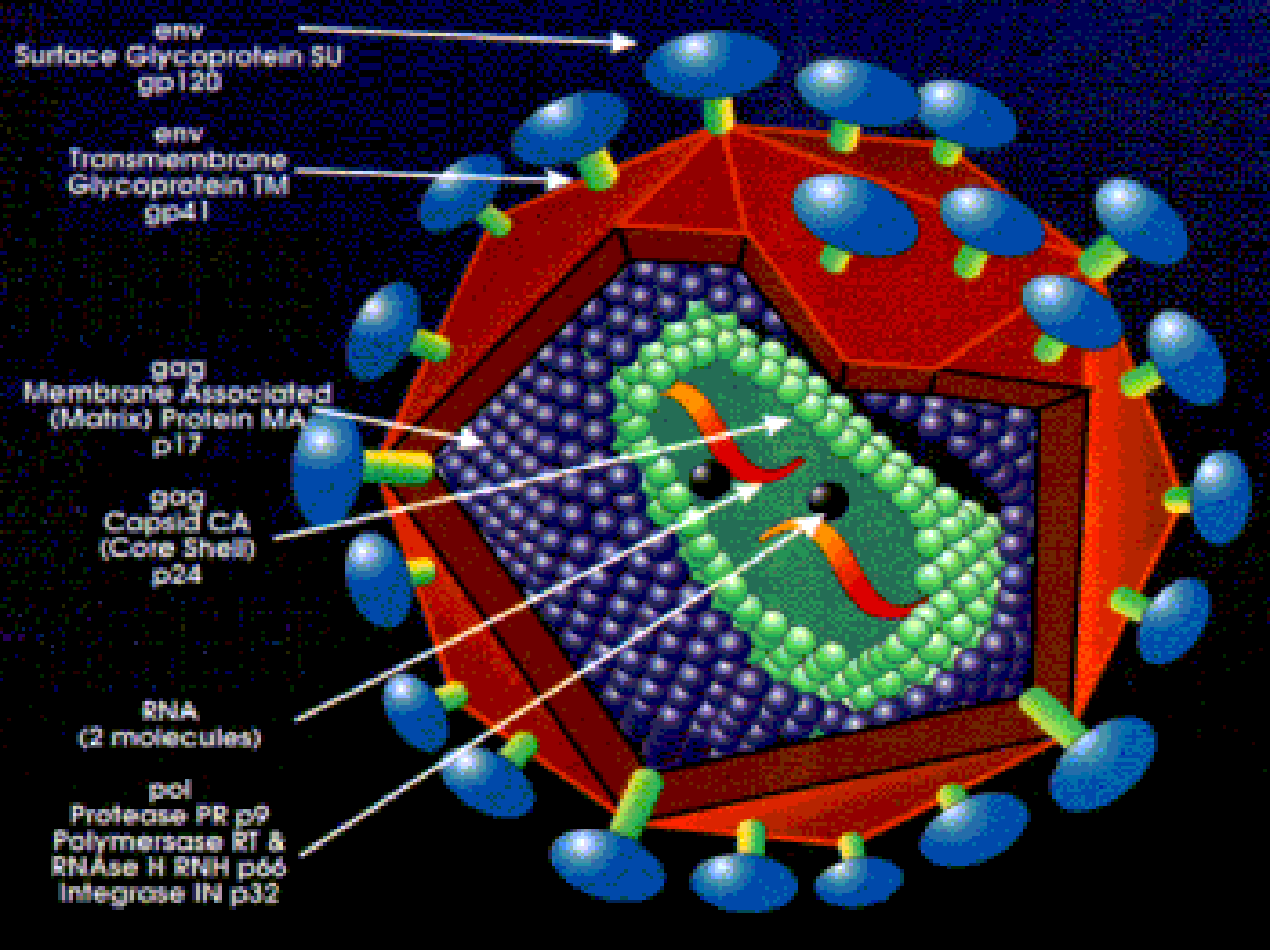
- RNA virus - Retroviridae
- can produce DNA
- 80-120 nm
- + strand; can integrate to host chromosome
- attack only T_H cells
- receptor sites: CCR5 and CxCR4

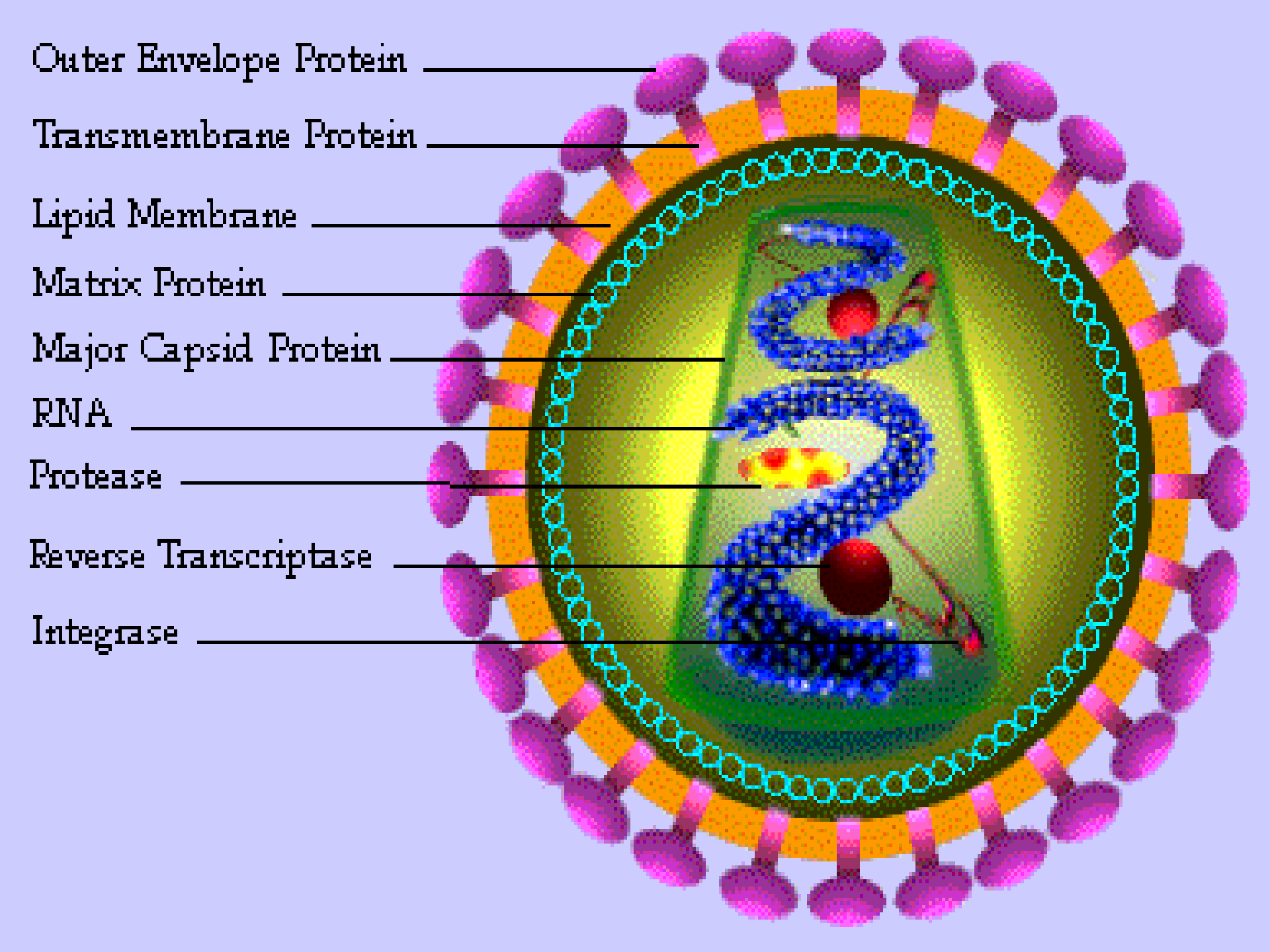
Acquired Immunodeficiency Syndrome (AIDS)

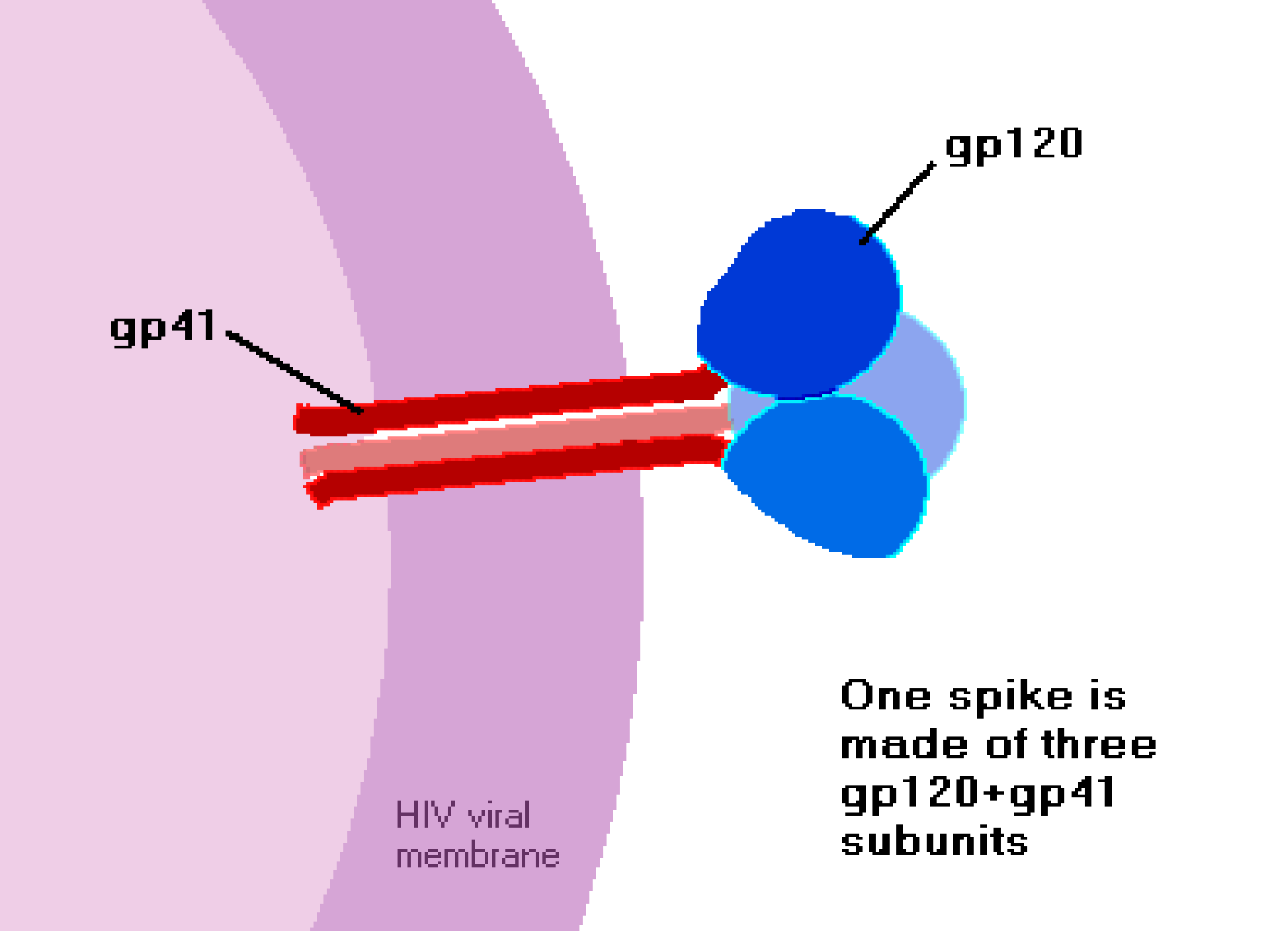


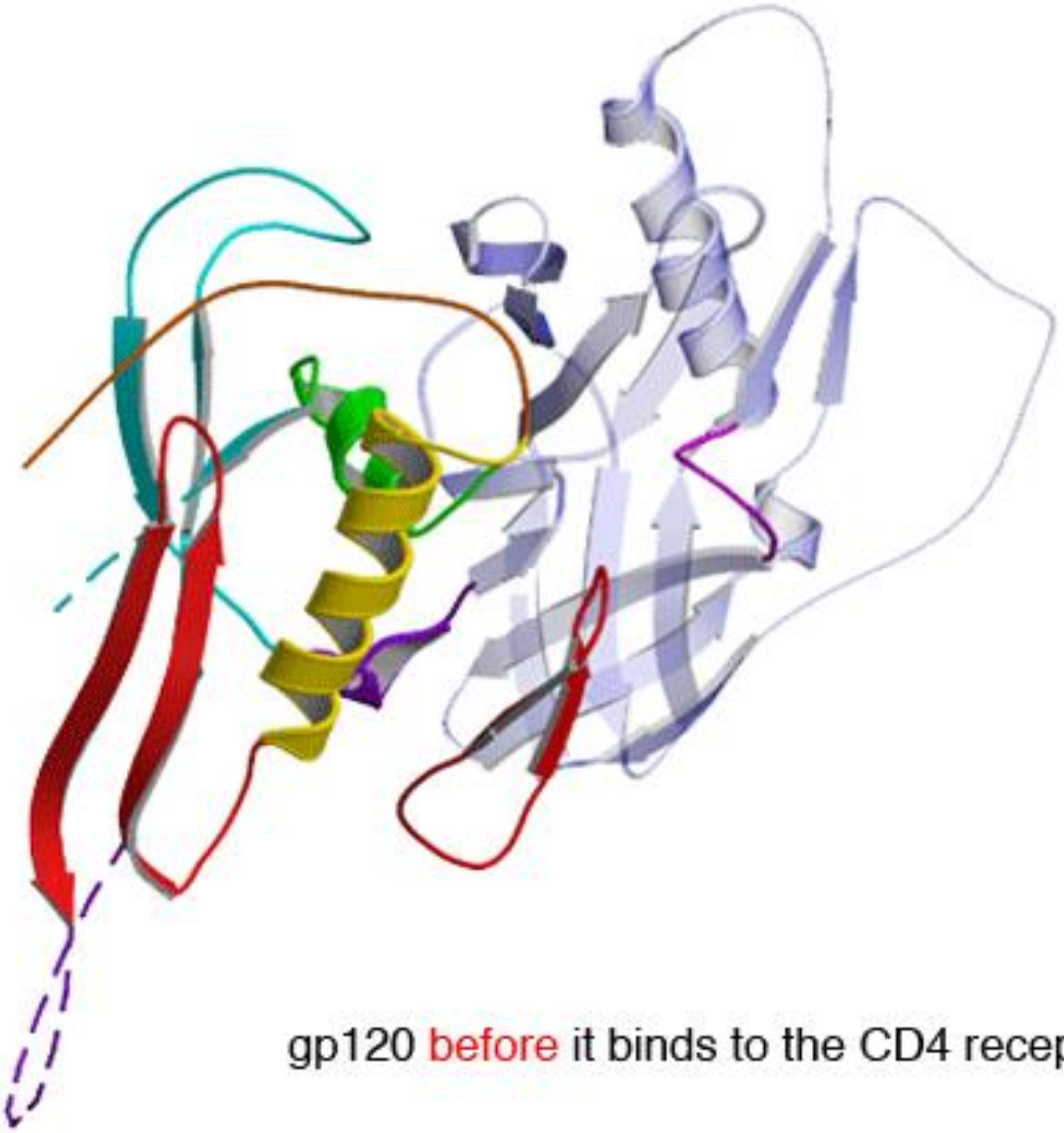
(a) Structure of HIV.

Figure 19.12a


env
Surface Glycoprotein SU
gp120
env
Transmembrane
Glycoprotein TM
gp41
gag
Membrane Associated
(Matrix) Protein MA
p17
gag
Capsid CA
(Core Shell)
p24
RNA
(2 molecules)
pol
Protease PR p9
Polymerase RT &
RNAse H RNH p66
Integrase IN p32

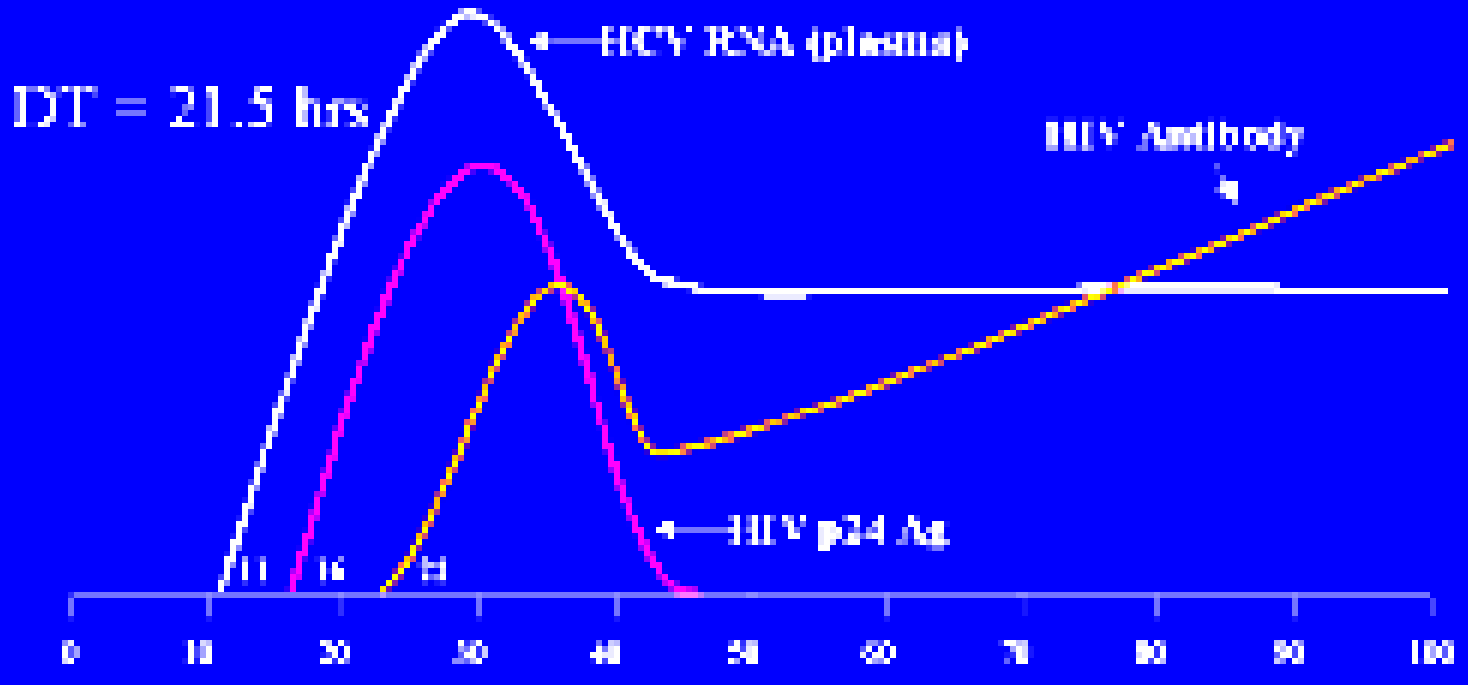

Outer Envelope Protein
Transmembrane Protein
Lipid Membrane
Matrix Protein
Major Capsid Protein
RNA
Protease
Reverse Transcriptase
Integrase


gp120
gp41
HIV viral membrane
One spike is made of three gp120+gp41 subunits



gp120 before it binds to the CD4 receptor

HIV markers during early infection



Theoretical Infectivity	**Day 0**	
HIV RNA	**Day 11**	5 Days
HIV p24 Ag	**Day 16**	6 Days
HIV Antibody	**Day 22**	

HIV Genome

- gag – synthesis of core and capsid protein of the virus
- pol – polymerase, RT, production of DNA, endonuclease and protease
- env – spike CHON (gp160)
- tax, rex – transactivation of the virus
- tat – transactivation of the virus; upregulation of HIV replication

- rev – regulate expression of the virus
- art, trs – upregulase, depresses nef
- nef (F, 3’, orf, B) – down regulates viral expression
- vif (Q, sor, A) – helps initiates replication
- vpr, vpx – unknown function
- LTR – long terminal repeats

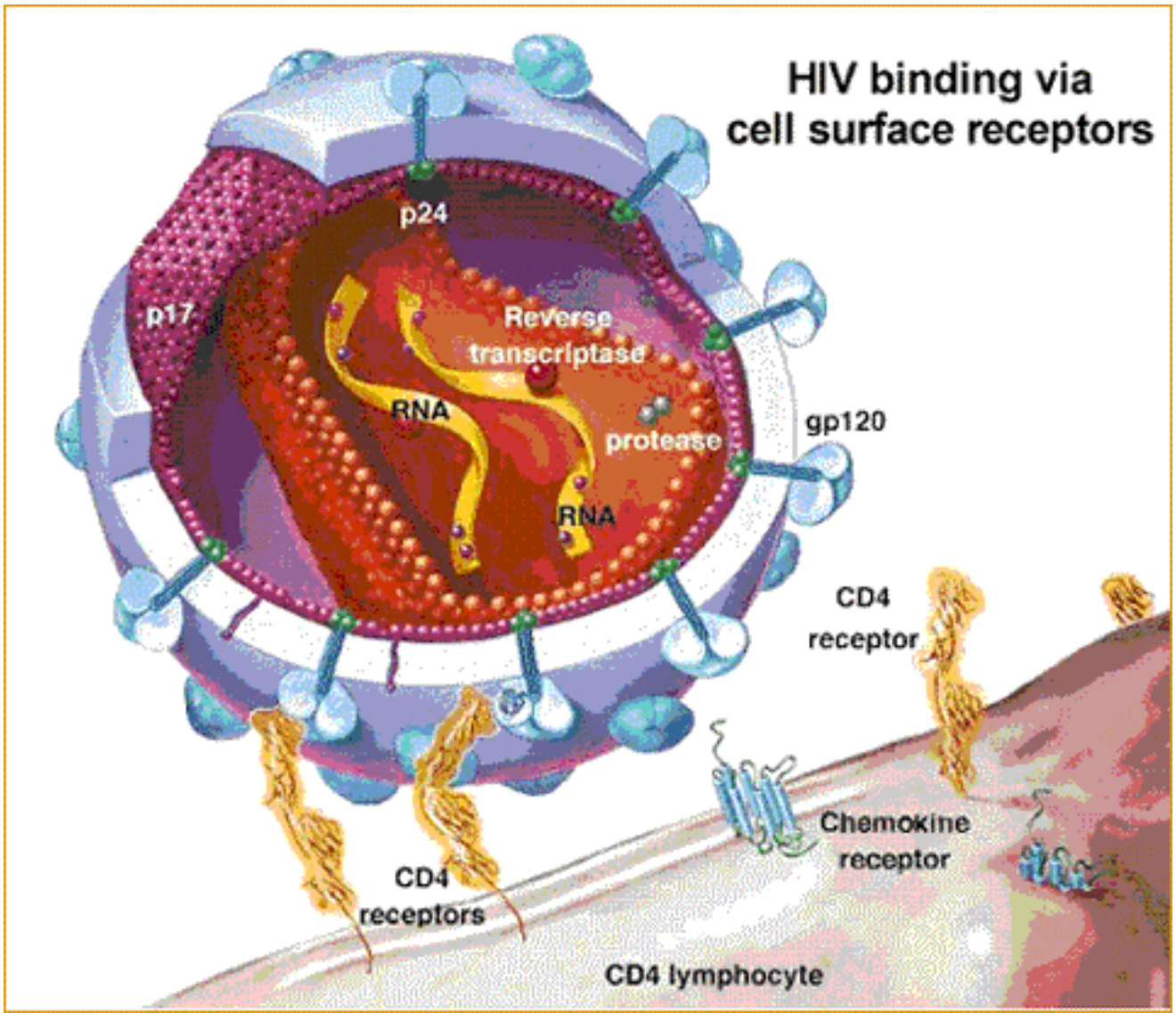
CD4

PARTICLES OF HIV (*blue spheres*), the virus that causes AIDS, bud from an infected white blood cell before moving on to infect other cells. The immune system controls such spread at first but is eventually outmaneuvered by the virus.

Chemokine Receptors

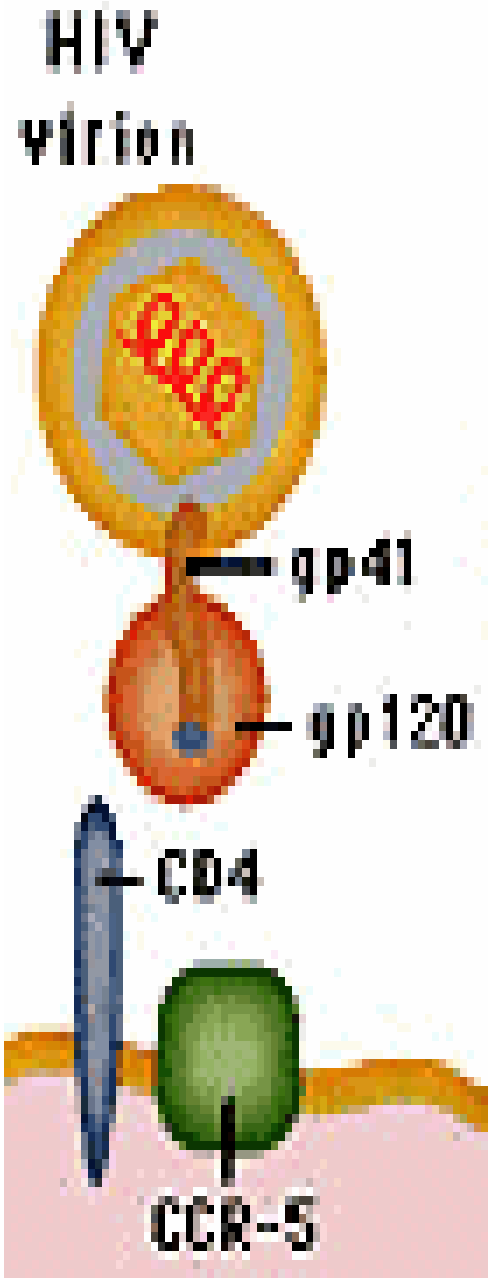
- Members of the large family of seven transmembrane domain G protein-coupled receptor
- Function in immune and inflammatory response

Entry of HIV-1 nd HIV 2



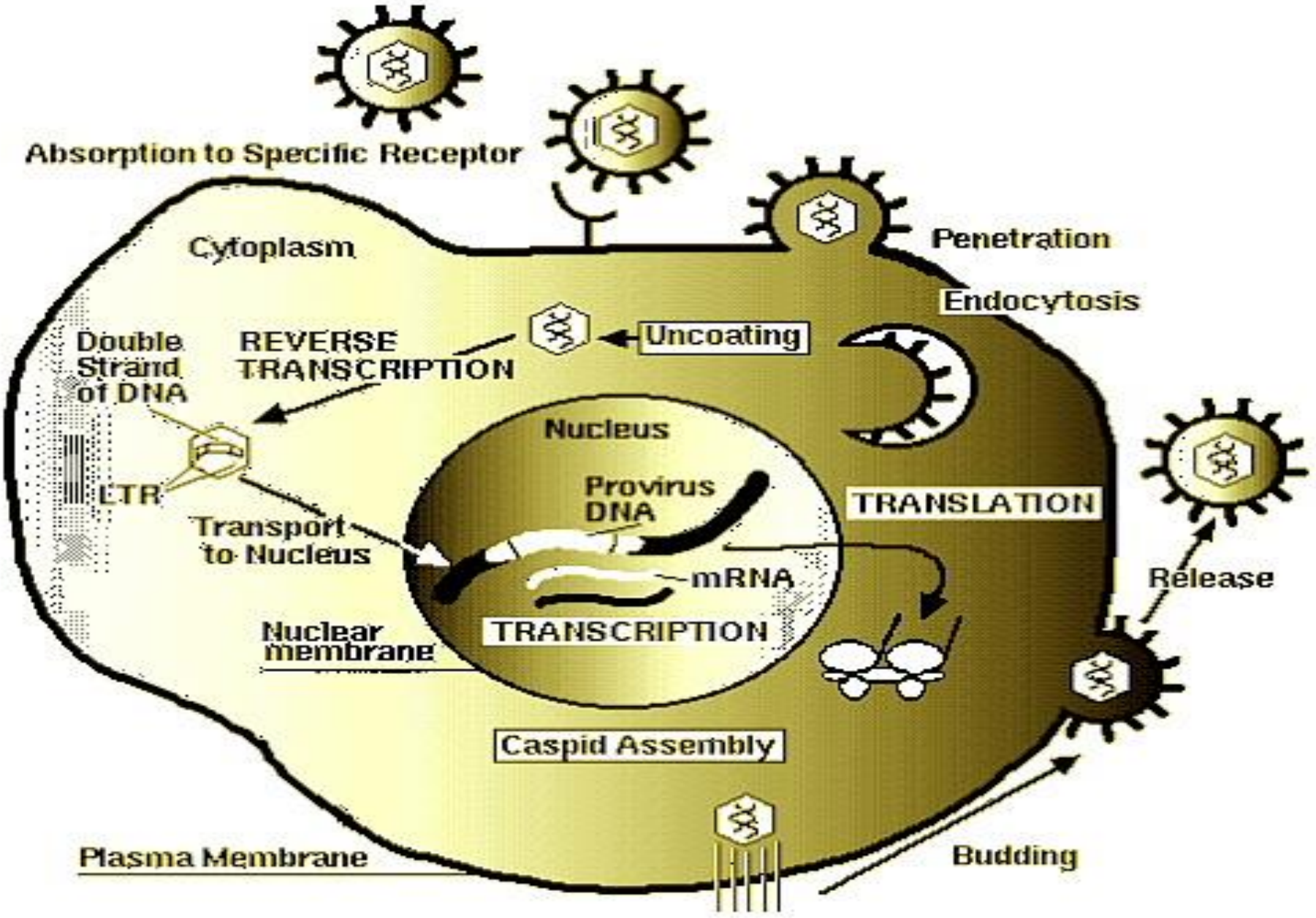
CCR5

- Co-factor for the entry of R5 tropic strains of HIV
- Receptor for the CC chemokines RANTES, MIP-1α, MIP1-β and MCP-3
- Expressed in peripheral blood-derived dendritic cells, subsets of Th1 lymphocytes and $CD34^{+}$ hematopoietic stem cell
- Together with CD4, important for the transmission of HIV and establishment of infection

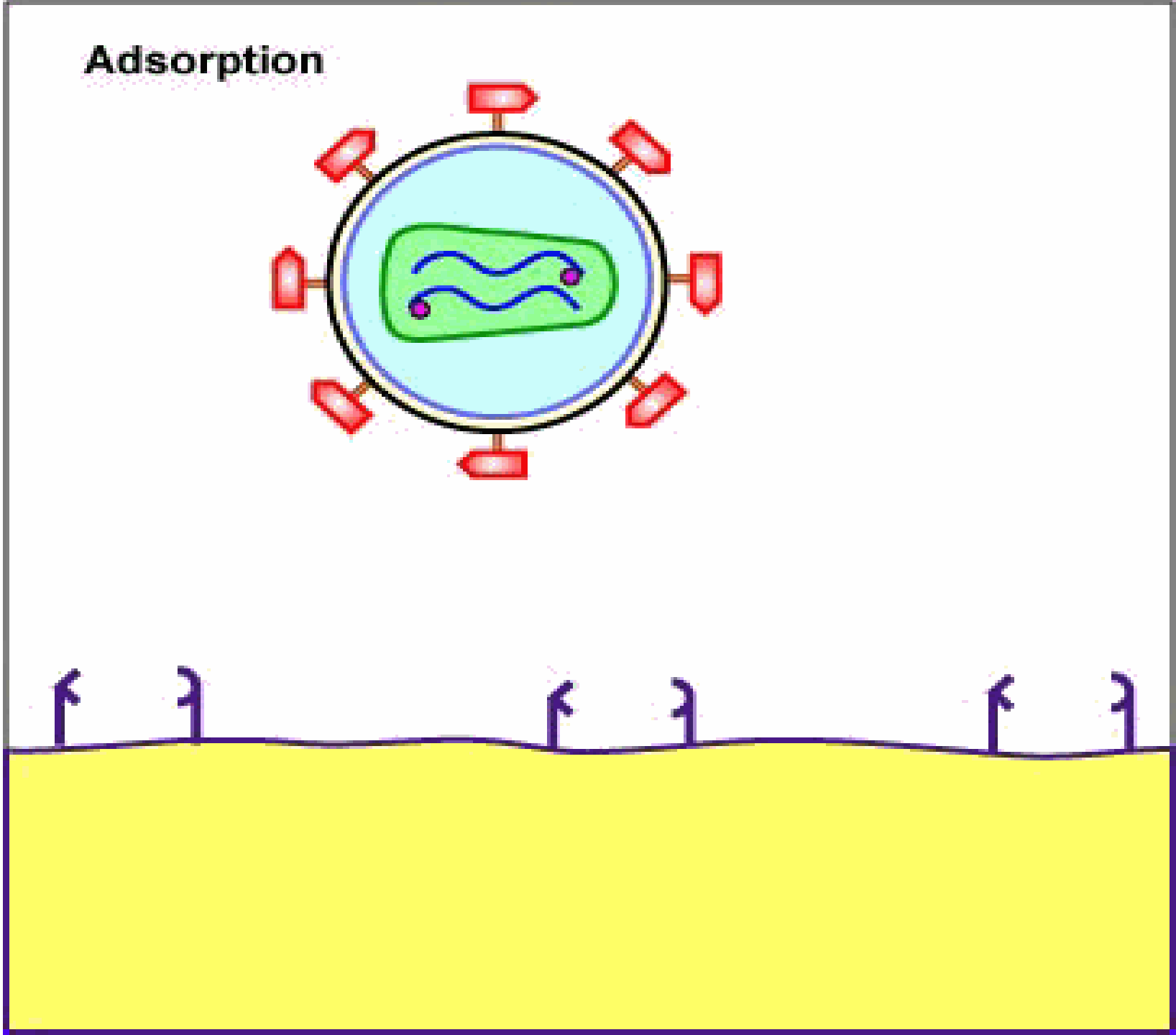


Life Cycle

1. Viral attachment
2. Viral penetration and fusion
3. Uncoating
4. Reverse transcription
5. Nuclear entry
6. Integration and RNA transcription
7. Protein synthesis and protease cleavage
8. Viral assembly and budding


Absorption to Specific Receptor
Cytoplasm
Penetration
Endocytosis
Uncoating
Double Strand of DNA
REVERSE TRANSCRIPTION
LTR
Transport to Nucleus
Nucleus
Provirus DNA
TRANSLATION
mRNA
TRANSCRIPTION
Nuclear membrane
Release
Caspid Assembly
Plasma Membrane
Budding

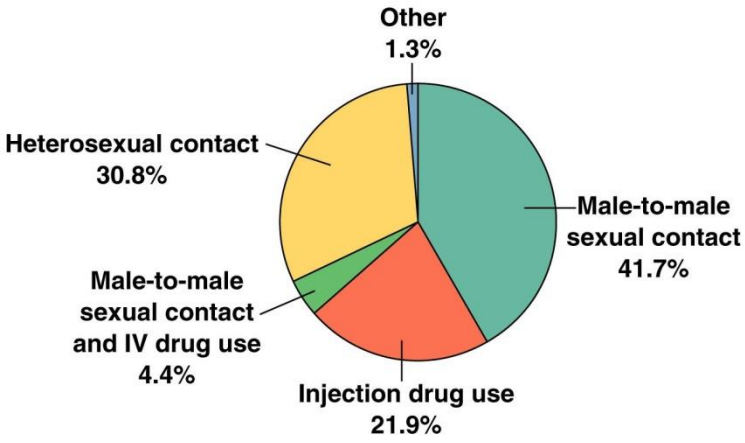
Life Cycle



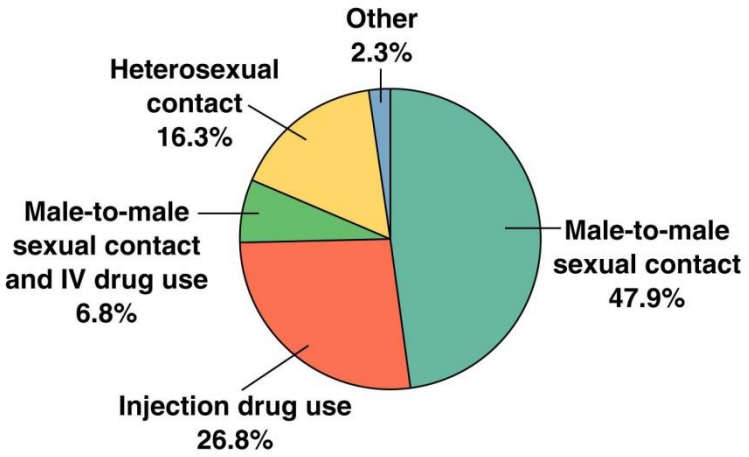
HIV Transmission

- HIV survives 6 hours outside a cell
- HIV survives less than 1.5 days inside a cell
- Infected body fluids transmit HIV via
  - Sexual contact
  - Breast milk
  - Transplacental infection of fetus
  - Blood-contaminated needles
  - Organ transplants
  - Artificial insemination
  - Blood transfusion

Modes of HIV Transmission



Estimated AIDS cases by transmission mode in 2003



Estimated total AIDS cases by transmission mode through 2003

Figure 19.17

AIDS Worldwide

- United States, Canada, western Europe, Australia, northern Africa, and South America
  - Injecting drug use and male-to-male sexual contact.
- Sub-Saharan Africa
  - Heterosexual contact.
- Eastern Europe, Middles East, and Asia
  - Injecting drug use, heterosexual contact.

AIDS Worldwide

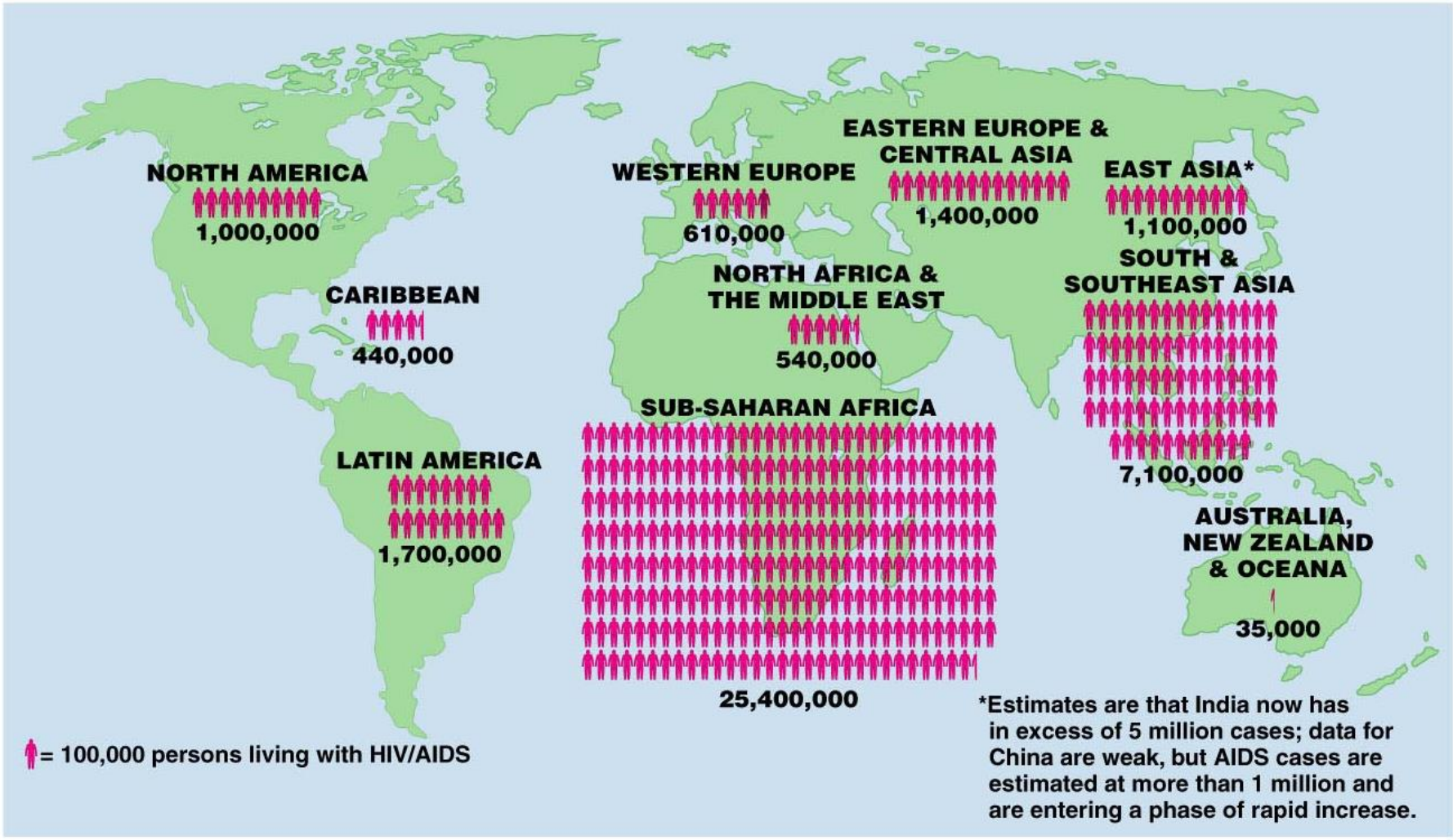


Figure 19.16

Clades

- HIV-1 is the most common. It has 11 clades:
  - 90% of U.S. infections caused by clade B.
  - Clade C predominates in sub-Saharan African.
  - Clades B, C, and E are in south and southeast Asia.
- HIV-2 is seen in western Africa.

Immune Abnormalities resulting to HIV infections

CD4	Dec. proliferative response Dec lymphokine production
Monocytes	Dec. CD8 activity against target cells Dec T_{DH} response Dec. chemotaxis Dec. Il-1 production Dec. microbicidal activity
NK	Dec. cytotoxic activity
B cells	Dec. ag-specific humoral response Uncontrolled production of abs

Mechanism of immune suppression (Direct)

- cytocidal effect on CD4
- functional defects on infected CD4
- impaired ag presentation of monokine production by macrophage

(Indirect)

- generation of T_s or factor
- inverse CD4/CD8 ratio
- induction of autoimmune phenomena
- cytotoxic cell activity against viral or self proteins
- decrease humoral immune response

How come HIV escapes the wrath of our immune system?

- infection of lymphocytes and macrophages
- inactivation of CD4, incapacitating the system
- ag drift of gp 120
- heavy glycosylation of gp120
- latency

The Stages of HIV Infection

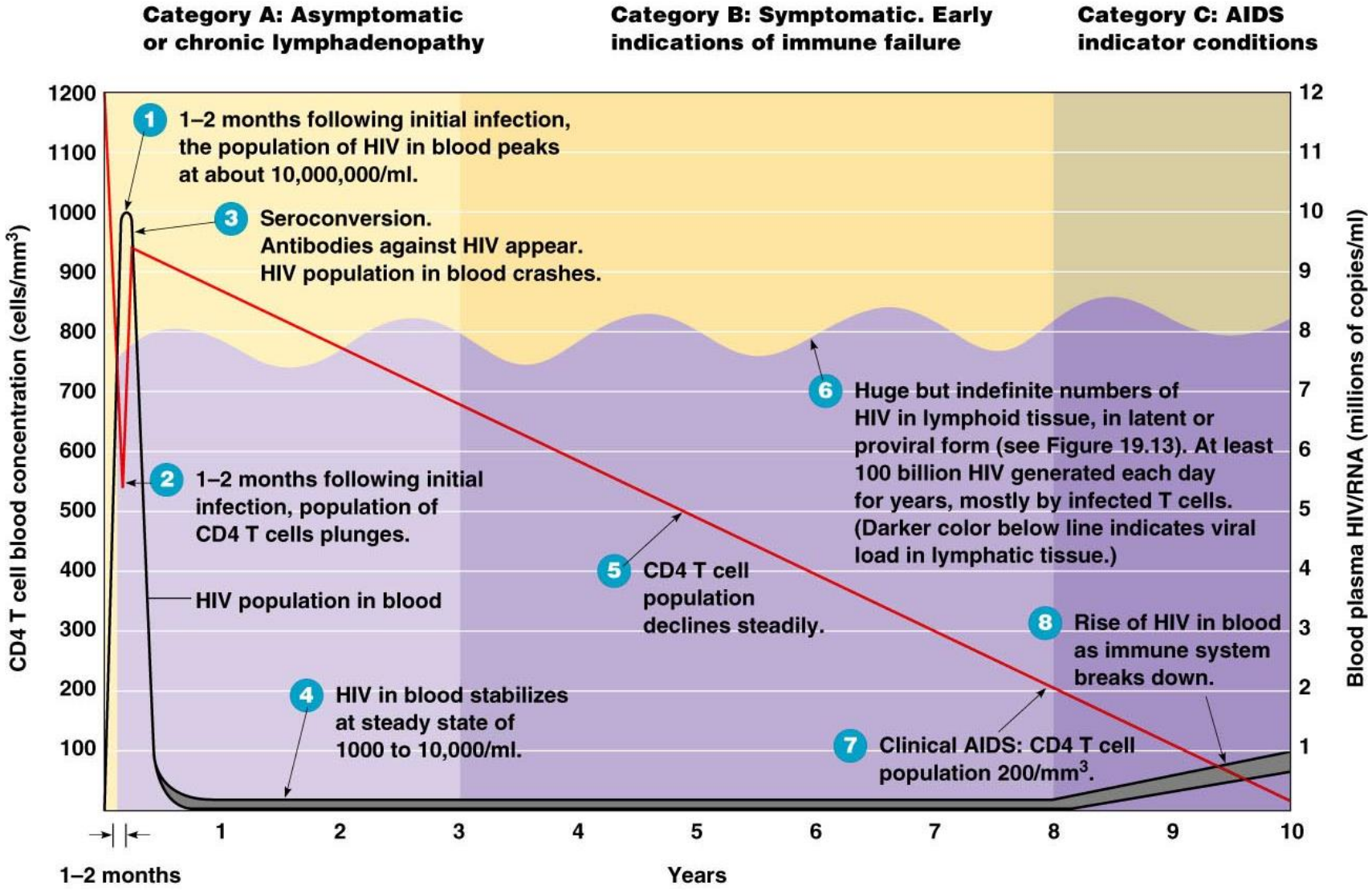
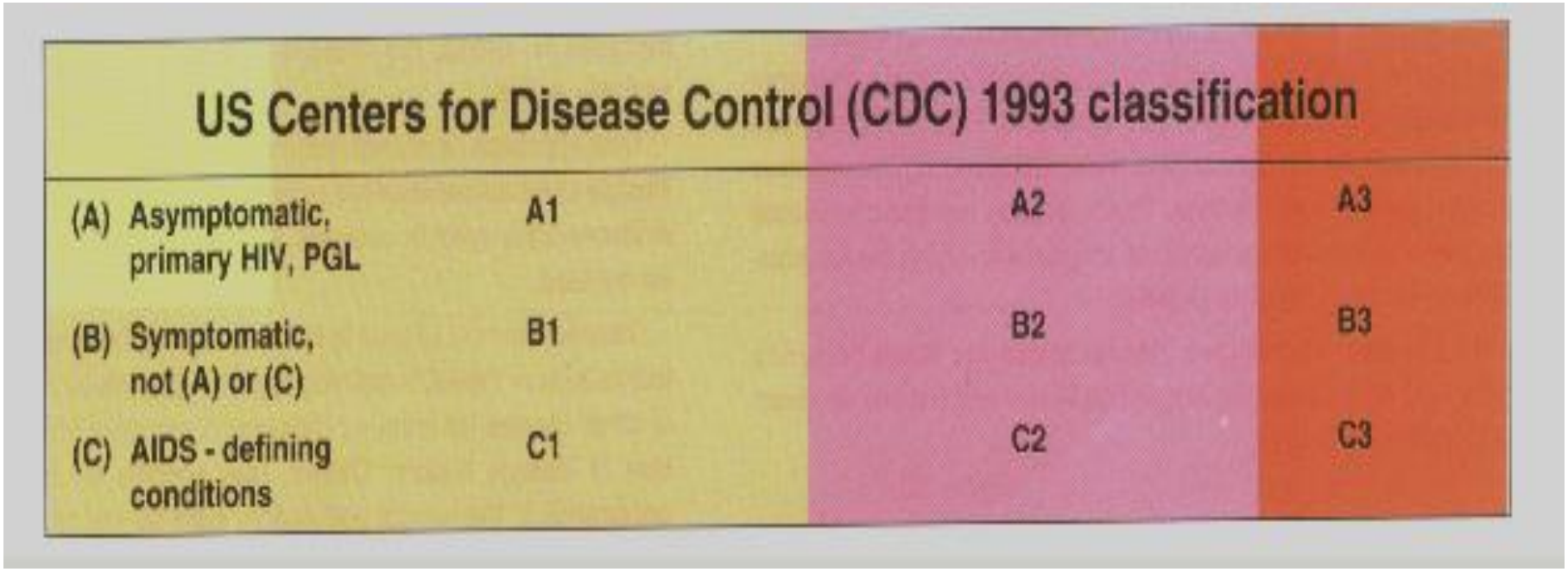


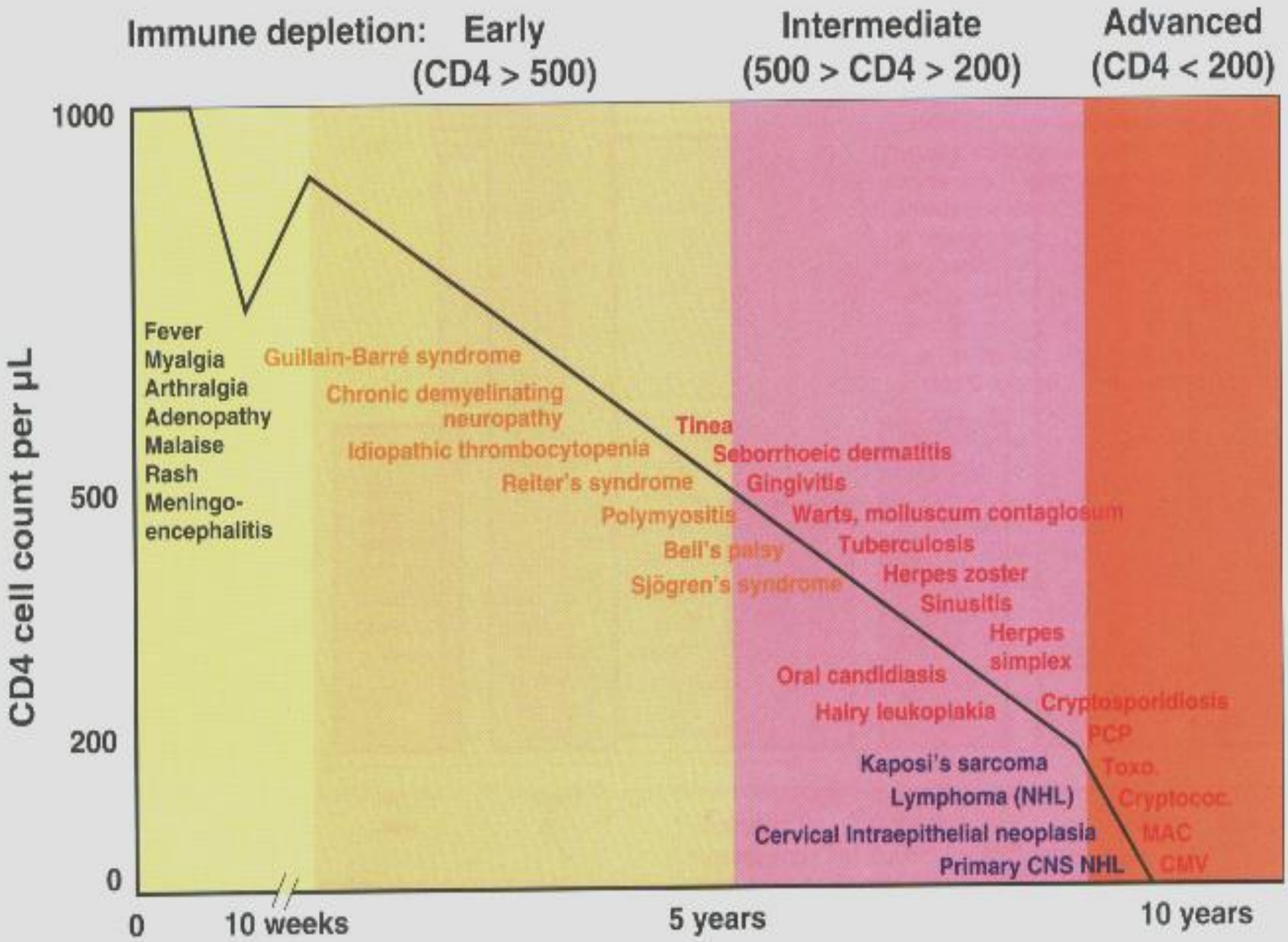
Figure 19.15

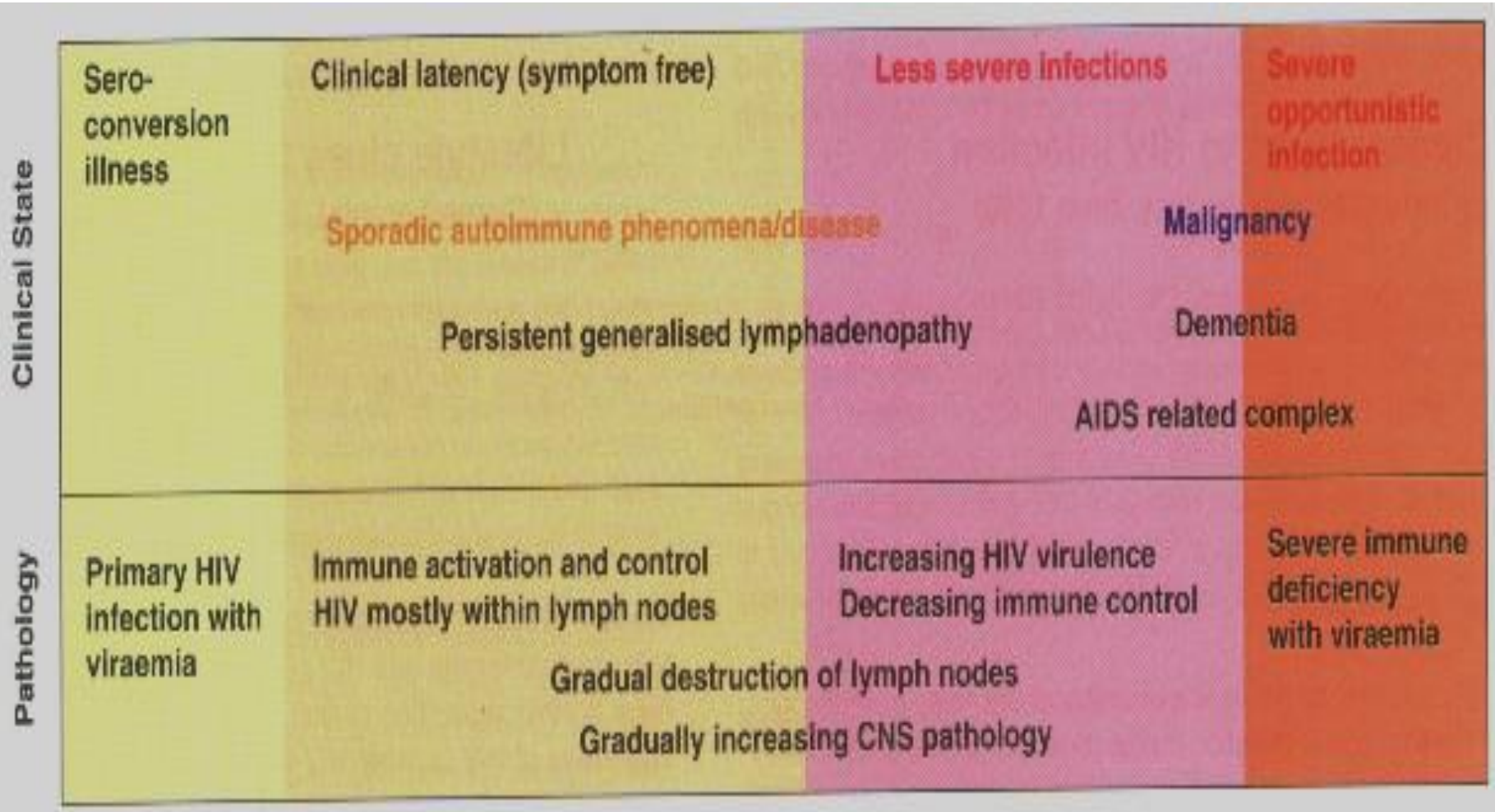
CDC – 3 major categories

- Category A
- Category B
- Category C



US Centers for Disease Control (CDC) 1993 classification			
(A) Asymptomatic, primary HIV, PGL	A1	A2	A3
(B) Symptomatic, not (A) or (C)	B1	B2	B3
(C) AIDS - defining conditions	C1	C2	C3


Immune depletion: Early (CD4 > 500)
Intermediate (500 > CD4 > 200)
Advanced (CD4 < 200)
CD4 cell count per µL
1000
500
200
0
Fever
Myalgia
Arthralgia
Adenopathy
Malaise
Rash
Meningo-encephalitis
Guillain-Barré syndrome
Chronic demyelinating neuropathy
Idiopathic thrombocytopenia
Reiter's syndrome
Polymyositis
Bell's palsy
Sjögren's syndrome
Tinea
Seborrhoeic dermatitis
Gingivitis
Warts, molluscum contagiosum
Tuberculosis
Herpes zoster
Sinusitis
Herpes simplex
Oral candidiasis
Hairy leukoplakia
Cryptosporidiosis
PCP
Toxo.
Cryptococ.
MAC
CMV
Kaposi's sarcoma
Lymphoma (NHL)
Cervical intraepithelial neoplasia
Primary CNS NHL
0
10 weeks
5 years
10 years


Clinical State
Sero-conversion illness
Clinical latency (symptom free)
Less severe infections
Severe opportunistic infection
Sporadic autoimmune phenomena/disease
Malignancy
Persistent generalised lymphadenopathy
Dementia
AIDS related complex
Pathology
Primary HIV infection with viraemia
Immune activation and control
HIV mostly within lymph nodes
Increasing HIV virulence
Decreasing immune control
Severe immune deficiency with viraemia
Gradual destruction of lymph nodes
Gradually increasing CNS pathology

Laboratory test abnormality

Haematology

Low haemoglobin level

Thrombocytopenia

Leukopenia

Presence of atypical "reactive" lymphocytes

Lymphocytosis

Lymphopenia

Immunology

Elevated immunoglobulins (IgG, IgA and, to a lesser extent, IgM)

Abnormal T cell subsets

Cutaneous anergy on delayed type hypersensitivity skin testing

Biochemistry

Elevated total protein with hypergammaglobulinaemia

Abnormal levels of liver enzymes: elevated alkaline phosphatase, elevated transaminases

Arterial hypoxaemia with or without radiological abnormality

Anatomical pathology

Kaposi's sarcoma

Lymphoma

Follicular hyperplasia

Histological evidence of opportunistic infection

Forensic examination in suicide

Opportunistic Infections in AIDS

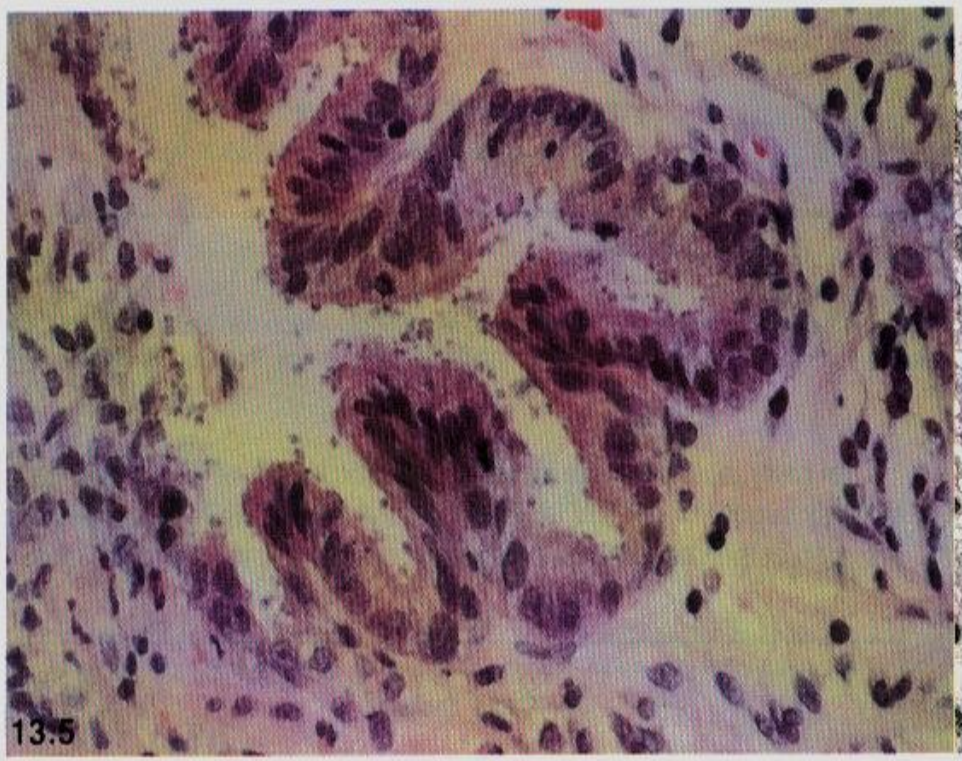
Some Common Diseases Associated with AIDS

TABLE 19.5 Some Common Diseases Associated with AIDS

Pathogen or Disease	Disease Description
Protozoa	
Cryptosporidium hominis	Persistent diarrhea
Toxoplasma gondii	Encephalitis
Isospora belli	Gastroenteritis
Viruses	
Cytomegalovirus	Fever, encephalitis, blindness
Herpes simplex virus	Vesicles of skin and mucous membranes
Varicella-zoster virus	Shingles
Bacteria	
Mycobacterium tuberculosis	Tuberculosis
M. avium-intracellulare	May infect many organs; gastroenteritis and other highly variable symptoms
Fungi	
Pneumocystis jiroveci	Life-threatening pneumonia
Histoplasma capsulatum	Disseminated infection
Cryptococcus neoformans	Disseminated, but especially meningitis
Candida albicans	Overgrowth on oral and vaginal mucous membranes (category B stage of HIV infection)
C. albicans	Overgrowth in esophagus, lungs (category C stage of HIV infection)
Cancers or Precancerous Conditions	
Kaposi's sarcoma	Cancer of skin and blood vessels (caused by human herpesvirus 8)
Hairy leukoplakia	Whitish patches on mucous membranes; commonly considered precancerous
Cervical dysplasia	Abnormal cervical growth

Table 19.5

Cryptosporidium parvum



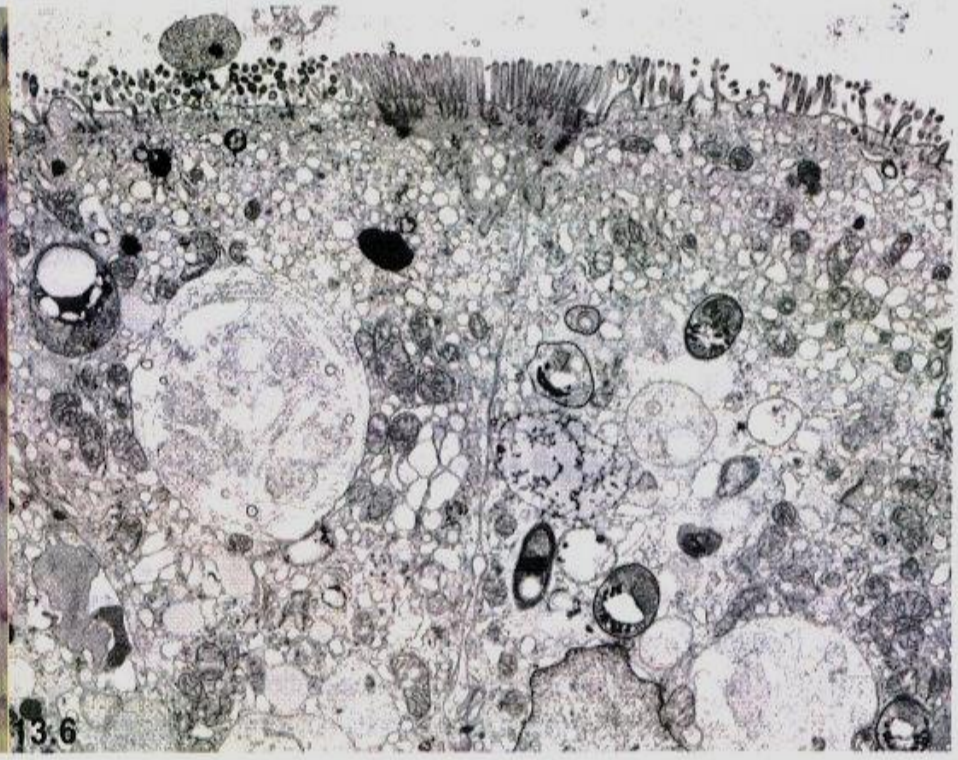


Figure 13.5: Photomicrograph of duodenal cryptosporidiosis. Numerous parasites attached to enterocytes. Cryptosporidiosis causes secretory diarrhoea and is an AIDS-defining illness. Figure 13.6: Electron-micrograph of microsporidia in enterocytes. Seen clearly in large organelles on electron microscopy, this parasite may also be seen on stool microscopy.

Toxoplasma gondii

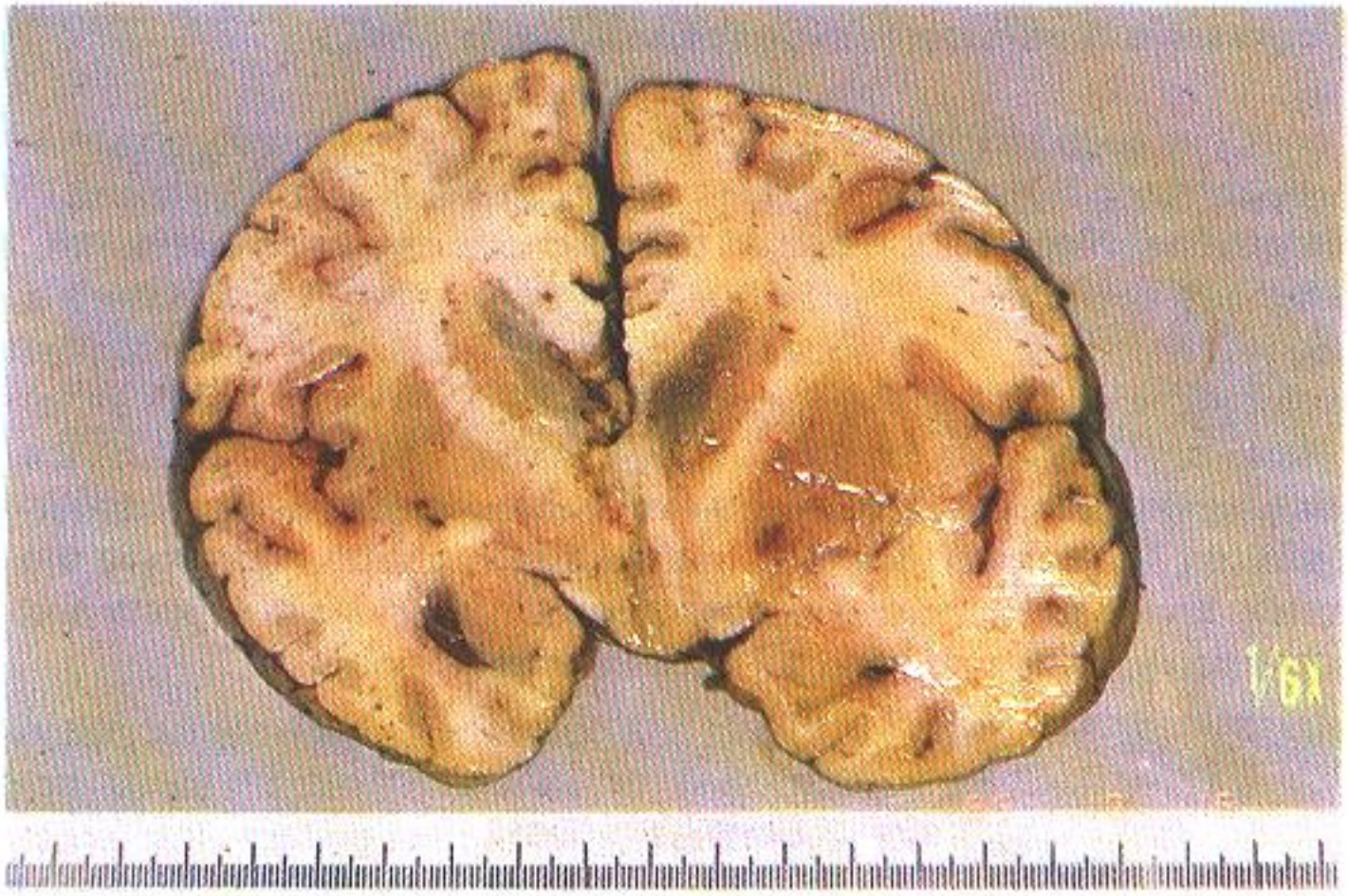


Figure 8.4: Cerebral toxoplasmosis diagnosed after the death of the patient. A treatable opportunistic infection, not diagnosed before death because the patient's HIV status was unknown.

Isospora belli

Cytomegalovirus

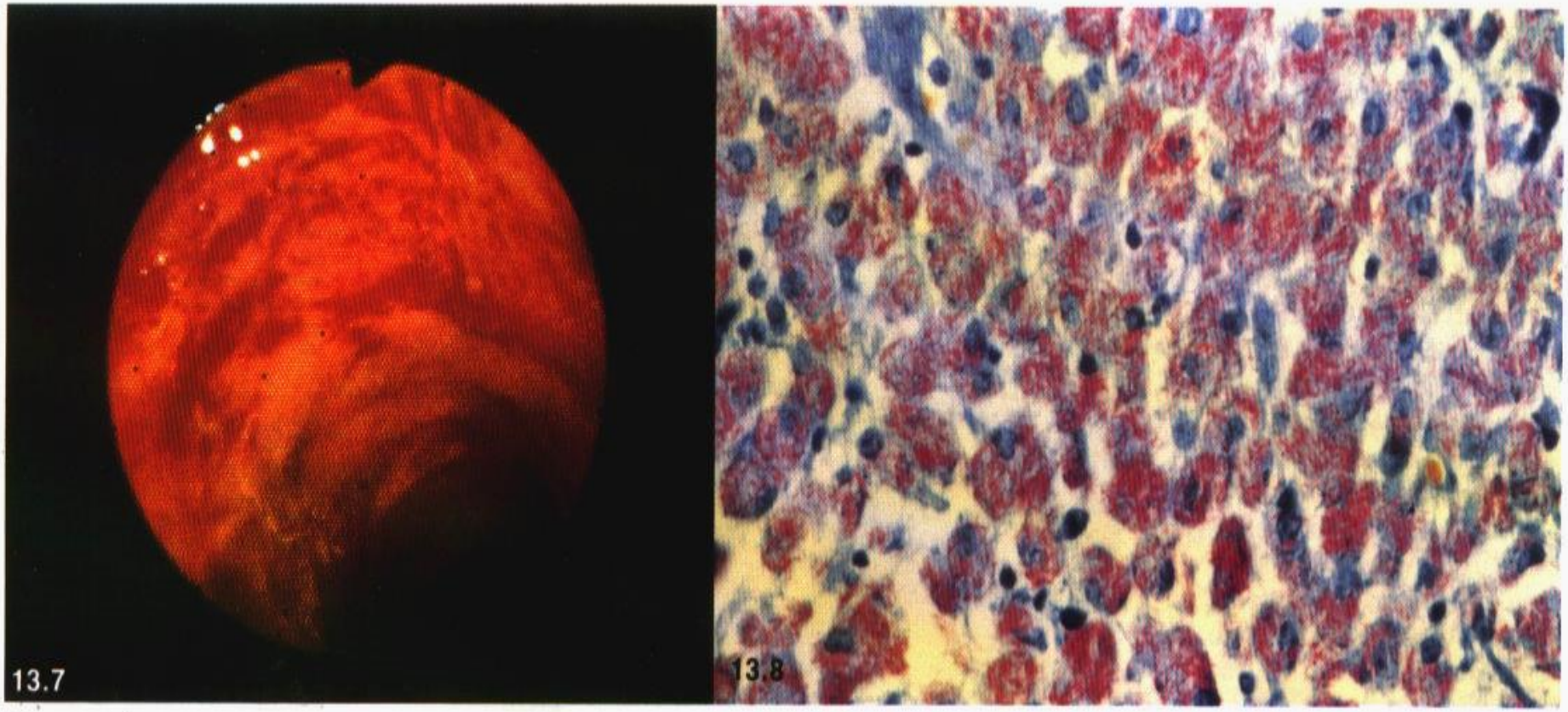


Figure 13.7: Sigmoidoscopy showing cytomegalovirus colitis, a haemorrhagic colitis that is usually visible in the rectum or sigmoid colon. Figure 13.8: Duodenal biopsy with Mycobacterium avium, *showing sheets of acid-fast bacilli in intestinal mucosa. These cause malabsorptive diarrhoea.*

HSV

Figure 14.2: Disseminated varicella-zoster — herpetiform cluster of vesicles. The haemorrhagic component indicates atypical zoster. Rapid diagnosis can be achieved with Tzanck smear or by immunofluorescent test with monoclonal antibodies.

Molluscum contagiosum

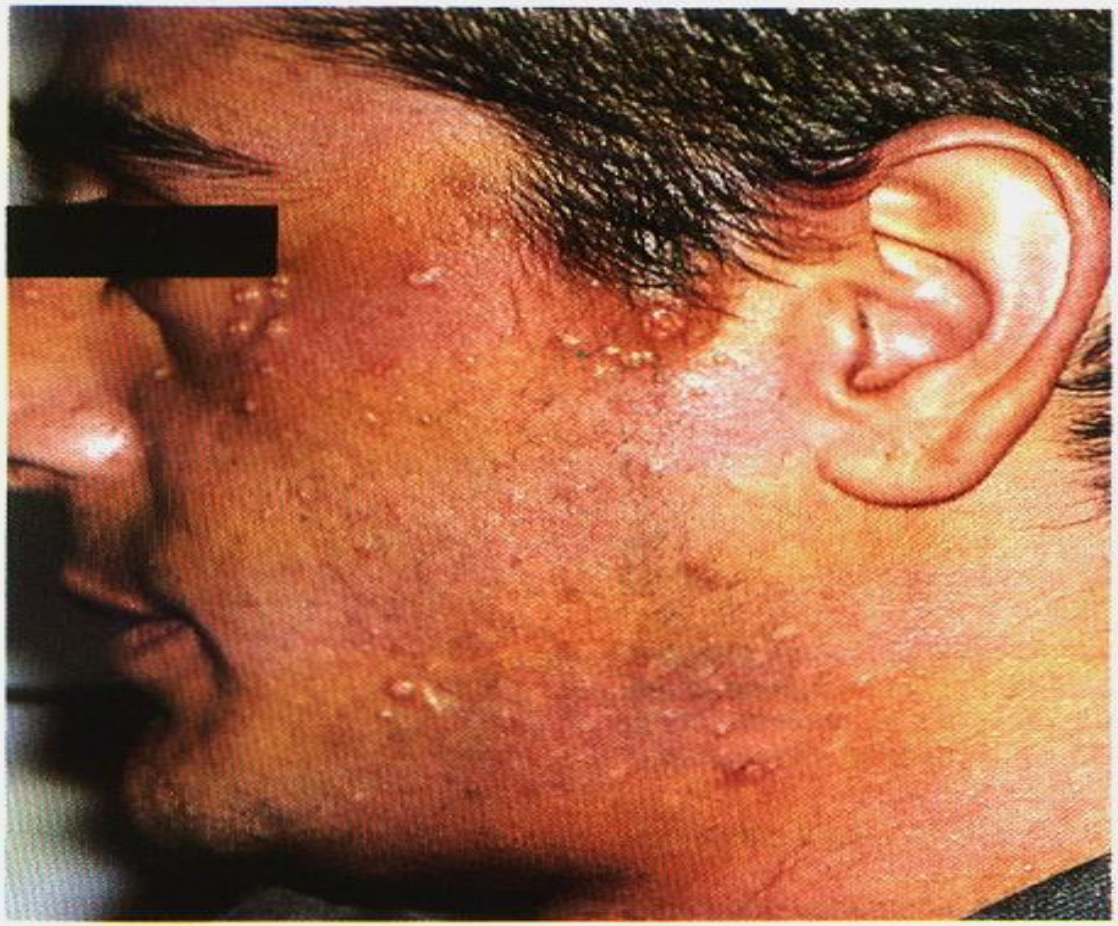


Figure 14.3: Molluscum contagiosum. Typically facial or anogenital in location in HIV patients, with multiple florid lesions. Compare the similarity with Figure 14.5.

VZV

Figure 15.3: Zoster in a patient with HIV infection. Photograph reproduced with the permission of Professor J Mills, Macfarlane Burnet Centre for Medical Research.

Mycobacterium

Figure 14.4: Atypical mycobacterial infection — indolent lesion, innocuous appearance with lack of pustules or crusting; diagnosis made on biopsy. Consider performing a biopsy if surrounding tissue is palpably thickened.

Pneumocystis carinii

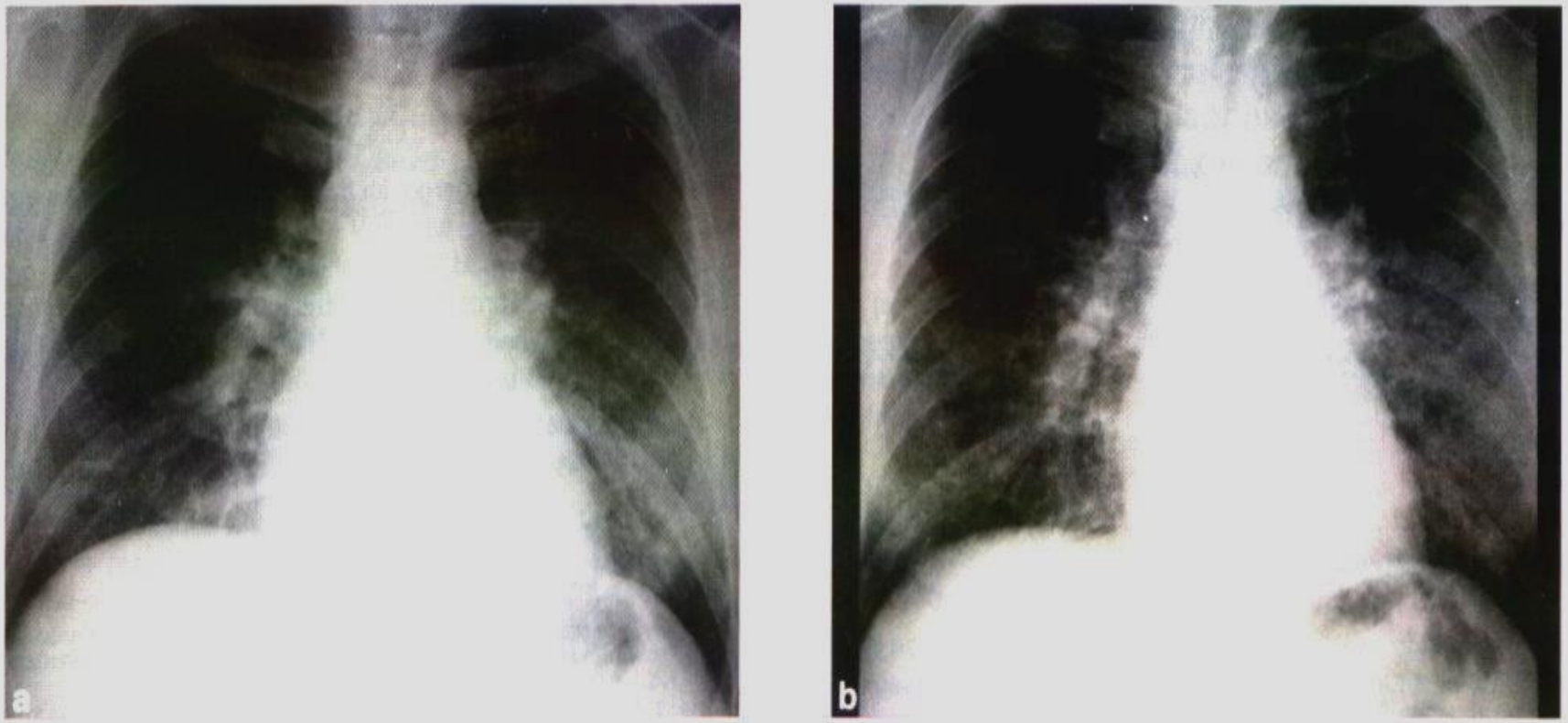


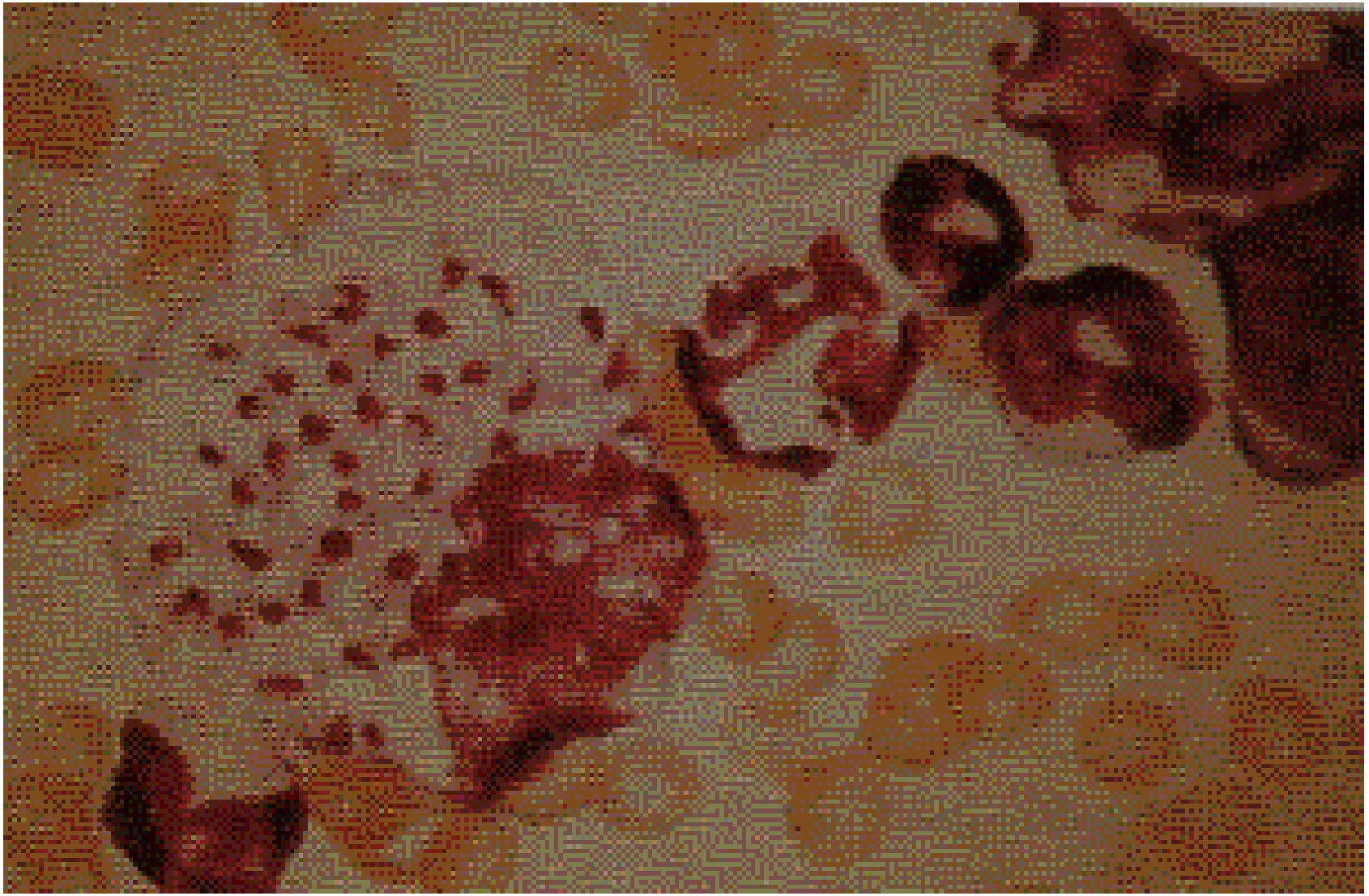
Figure 7.1: Pneumocystis carinii *pneumonia, (***a***) initially diagnosed as pulmonary oedema because HIV infection was unidentified; (***b***) six days later, showing progression of disease due to lack of appropriate therapy.*

Comment: Failure to consider HIV infection despite adequate clinical clues endangered the patient's life and wasted expensive resources.

Table 7.1: *Pneumocystis carinii* pneumonia

- Common in HIV medicine
- Most common AIDS-defining illness in the undiagnosed HIV infected patient
- Significant morbidity and mortality
- Insidious, non-specific onset
- Routine investigations often unhelpful
- Effective, readily available therapy
- Preventable (prophylaxis starts when CD4 cell count is below 250/μL)

Histoplasma capsulatum



Cryptococcus neoformans

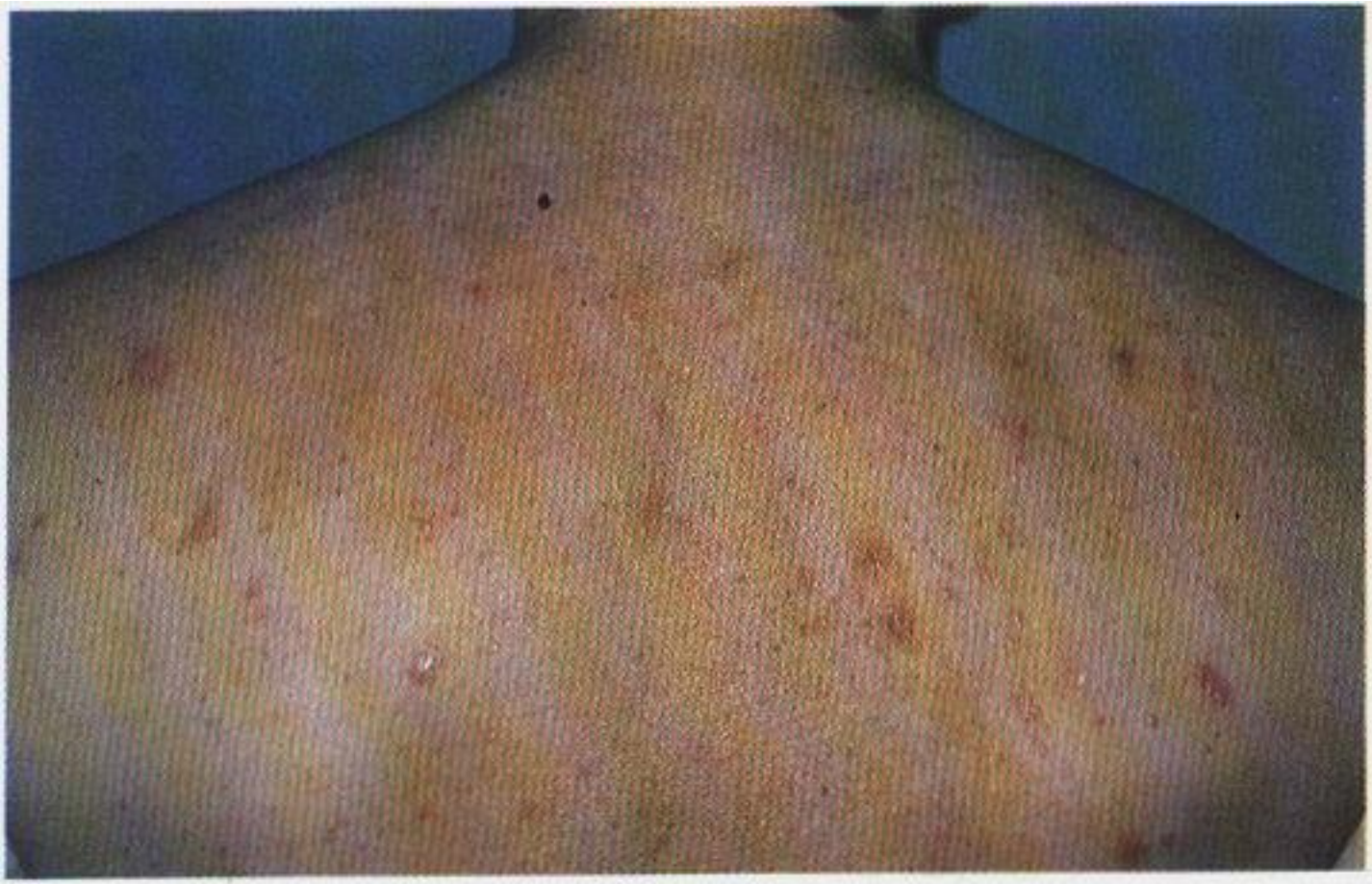


Figure 14.5: Cryptococcosis — may simulate molluscum contagiosum.

C. albicans

Figure 9.1: Oral candidiasis — discrete colony. Figure 9.2: Oral candidiasis — extensive colonisation under a removable partial denture. There is no evidence of candidiasis when the denture is in place. Figure 9.3: Angular cheilitis, without visible colonisation by Candida. *Figure 9.4: Acute necrotising ulcerative gingivitis around mandibular incisor teeth.*

Kaposis sarcoma

Figure 10.10: Kaposi's sarcoma involving the bulbar conjunctiva.

Kaposis sarcoma

Oral Hairy Leukoplakia

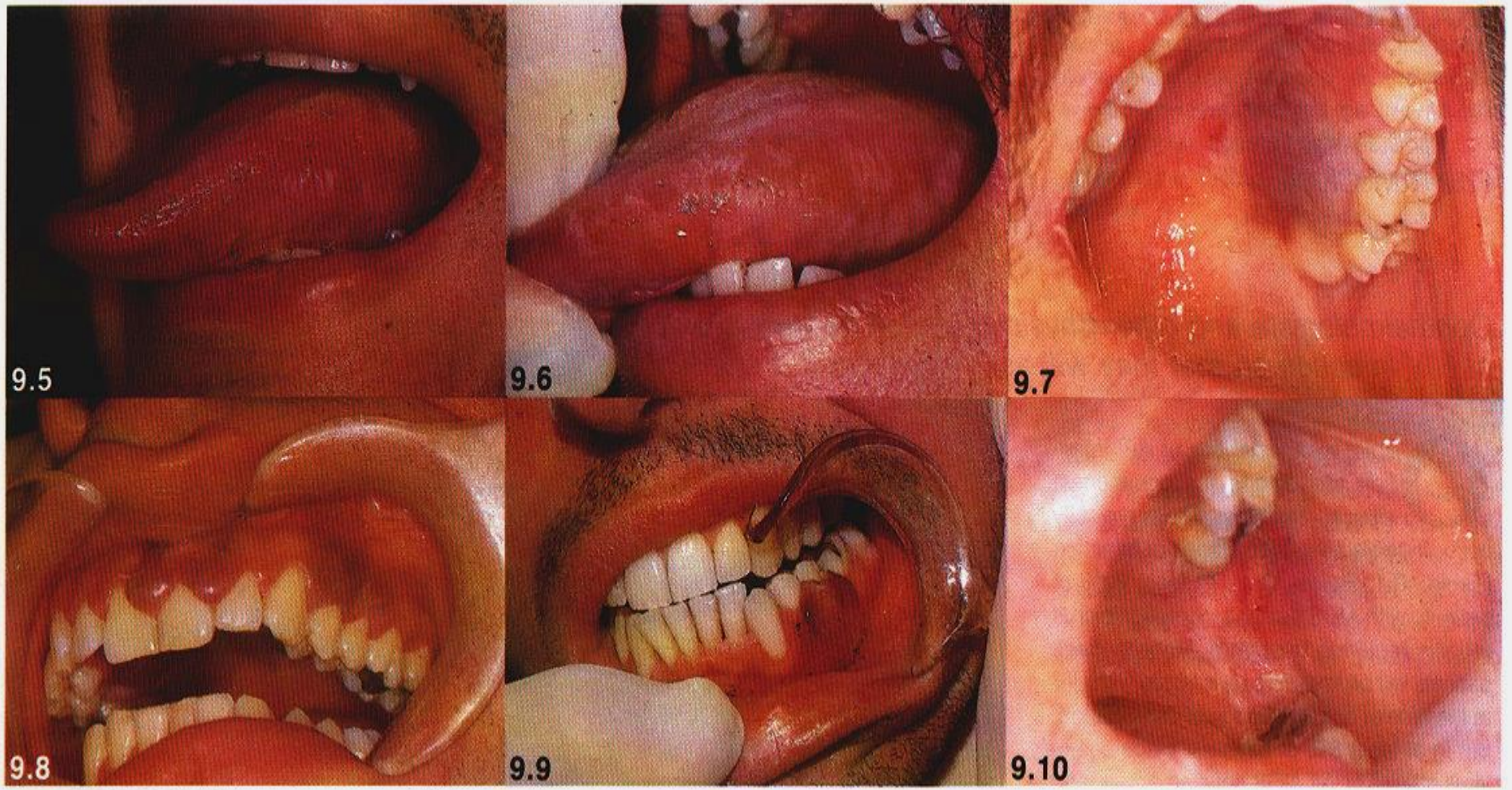


Figure 9.5: Oral hairy leukoplakia — discrete patch on the side of the tongue. Figure 9.6: Oral hairy leukoplakia — extensive, covering the side of the tongue. Figure 9.7: Kaposi's sarcoma on palate. Figure 9.8: Kaposi's sarcoma on gingiva. Figure 9.9: B cell lymphoma on gingival margin of mandibular premolar teeth. Figure 9.10: Cytomegalovirus oral ulcer of the cheek.

Keratoderma

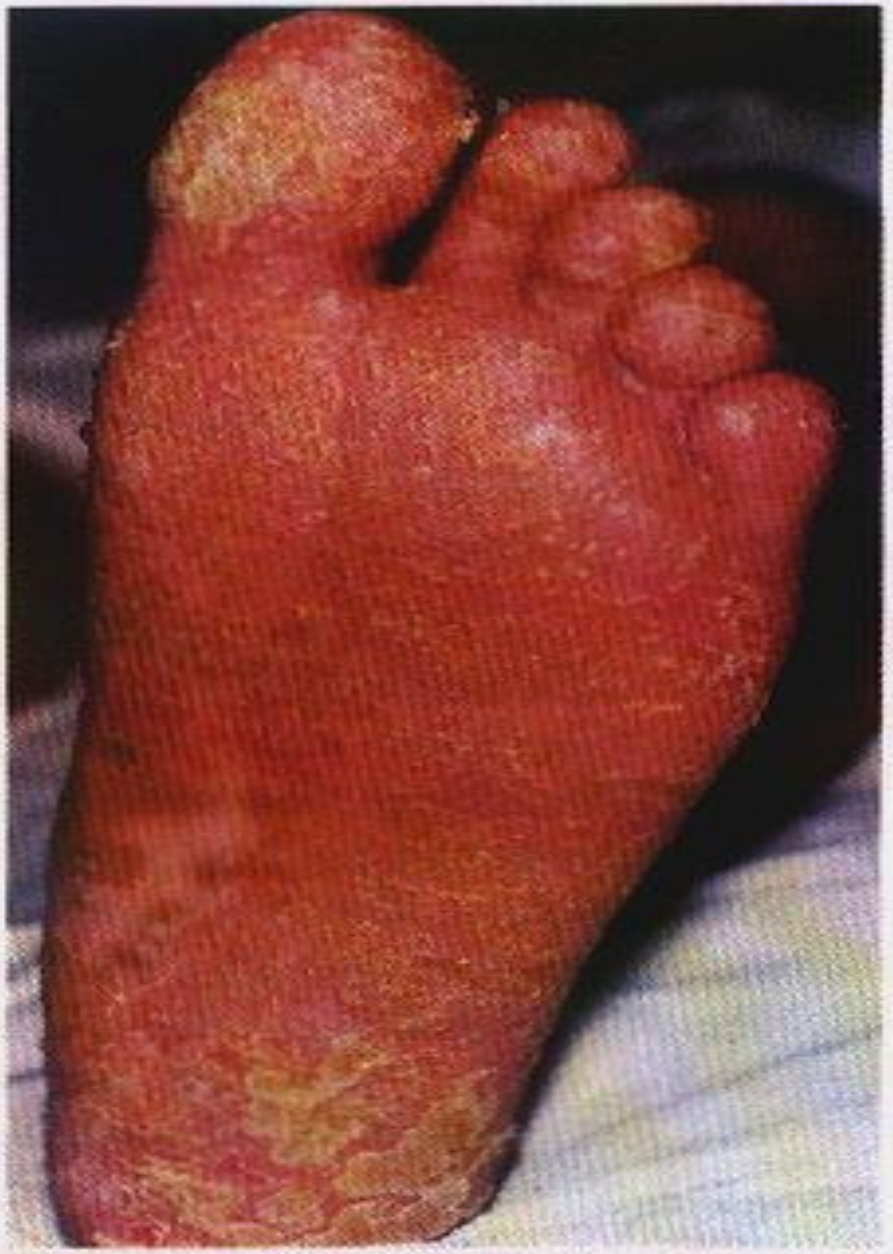


Figure 11.1: Keratoderma blennorrhagica and sausage digits.

Diagnostic Methods

- Seroconversion takes up to three months.
- HIV antibodies detected by ELISA.
- HIV antigens detected by Western blotting.
- Plasma viral load is determined by PCR or nucleic acid hybridization.

Laboratory Diagnosis

- Serology
  1. ELISA
  2. Latex agglutination
  3. IFA
  4. Western Blot analysis
- p24 antigen
- cultures
- CD4/CD8 ratio

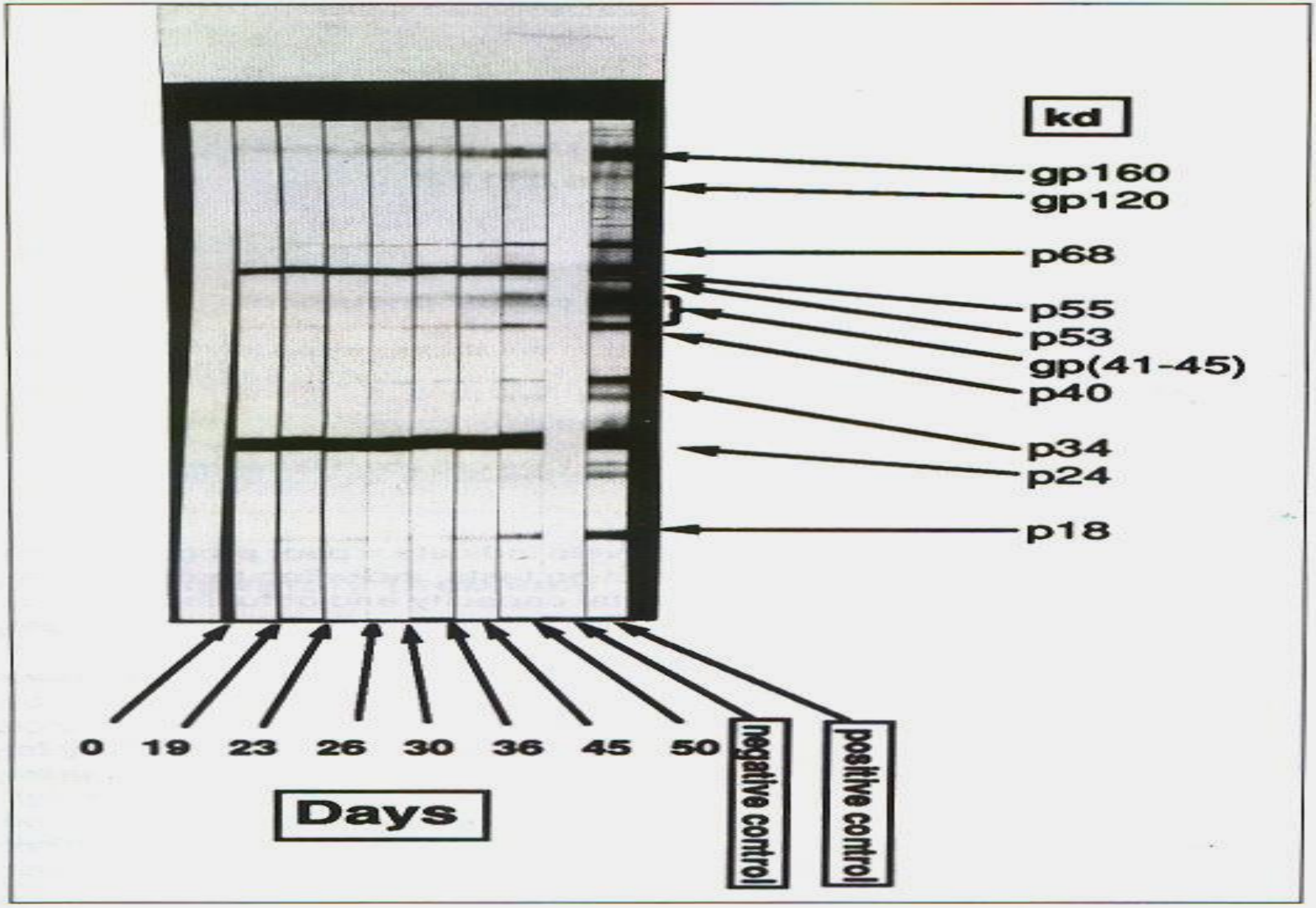


Figure 6.3: Western immunoblots of a patient progressing from seronegative to positive. Bands corresponding to p24 and p55 viral proteins typically are detected early in seroconversion, followed by glycoprotein bands (gp120; gp41) of the viral envelope.

Prevention of AIDS

- Use of condoms and sterile needles.
- Health care workers use Universal Precautions
  - Wear gloves, gowns, masks, and goggles.
  - Do not recap needles.
  - Risk of infection from infected needlestick injury is 0.3%.

Vaccine Difficulties

- Mutations
- Clades
- Antibody-binding sites “hidden”
- Infected cells not susceptible to CTLs
- Proviruses
- Latent viruses

Chemotherapy

- Nucleotide reverse transcriptase inhibitors.
- Non-nucleoside reverse transcriptase inhibitors.
- Protease inhibitors.
- Fusion inhibitors

Highly Active Antiretroviral Therapy (HAART)

- Combinations of nucleoside reverse transcriptase inhibitors plus
  - Non-nucleoside reverse transcriptase inhibitor or
  - Protease inhibitor