Infectious Diseases

Lesson 15

HIV Infection

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Learning objectives

- To know the main features of the HIV epidemic
- To develop enough skills to properly evaluate a patient who presents with the diagnostic possibility of HIV infection
- To know the principles of the management and follow-up of acute and chronic HIV infection

Contents

- Impact of the HIV and AIDS epidemic
- Pathogenesis and progression
- Diagnosis
- HIV-quiz
- Acute infection
- Chronic infection
- Patient's follow-up
- Conclusions
- Further reading

Impact of the HIV and AIDS epidemic

Brief history of the epidemic

- 1980s
  - First cases of AIDS reported
  - HIV discovered
  - First antiretroviral (zidovudine) available
- 1990s
  - Effective treatment (HAART)
  - HIV viral load test widely available
- 2000 through now
  - Refinement of treatment
  - Third World tragedy

Origin of HIV

- Mutations of **simian immunodeficiency virus** (SIV), from chimpanzees or other monkeys

- Transmission during monkey hunting ?

- HIV present in blood sample of patient died in 1959

- It is estimated that HIV …

  - o Originated in Africa in 1930s
  - o Reached developed countries at about 1970

Persons living with HIV in 2013

North America and Western and Central Europe
2.3 million
[2.0 million – 3.0 million]

Eastern Europe & Central Asia
1.1 million
[980 000– 1.3 million]

Caribbean
250 000
[230 000 – 280 000]

Middle East & North Africa
230 000
[160 000 – 330 000]

Asia and the Pacific
4.8 million
[4.1 million – 5.5 million]

Latin America
1.6 million
[1.4 million – 2.1 million]

Sub-Saharan Africa
24.7 million
[23.5 million – 26.1 million]

Total: 35.0 million [33.2 million – 37.2 million]

Source: UNAIDS

UNAIDS

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UNAIDS

Children (<15 years) estimated to be living with HIV in 2013

Eastern Europe & Central Asia
14 000
[13 000 – 14 000]

North America and Western and Central Europe
2800
[2300 – 3600]

Middle East & North Africa
16 000
[11 000 – 22 000]

Caribbean
17 000
[14 000 – 20 000]

Asia and the Pacific
210 000
[190 000– 270 000]

Latin America
35 000
[27 000 – 54 000]

Sub-Saharan Africa
2.9 million
[2.6 million – 3.2 million]

Total: 3.2 million [2.9 million – 3.5 million]

UNAIDS

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UNAIDS

Estimated number of adults and children newly infected with HIV in 2013

Eastern Europe & Central Asia
110 000
[86 000 – 130 000]

North America and Western and Central Europe
88 000
[44 000 – 160 000]

Middle East & North Africa
25 000
[14 000 – 41 000]

Caribbean
12 000
[9400 – 14 000]

Asia and the Pacific
350 000
[250 000 – 510 000]

Latin America
94 000
[71 000 – 170 000]

Sub-Saharan Africa
1.5 million
[1.3 million – 1.6 million]

Total: 2.1 million [1.9 million – 2.4 million]

Source: UNAIDS

UNAIDS

Estimated number of adults and children newly infected with HIV in 2013

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Total: 2.1 million [1.9 million – 2.4 million]

Source: UNAIDS

UNAIDS

Impact of the HIV pandemic in some countries of Africa

Life expectancy in years graph showing World, Botswana, South Africa, Kenya, Swaziland, Uganda, Zimbabwe, and Sub-Saharan Africa from 1960 to 2010.
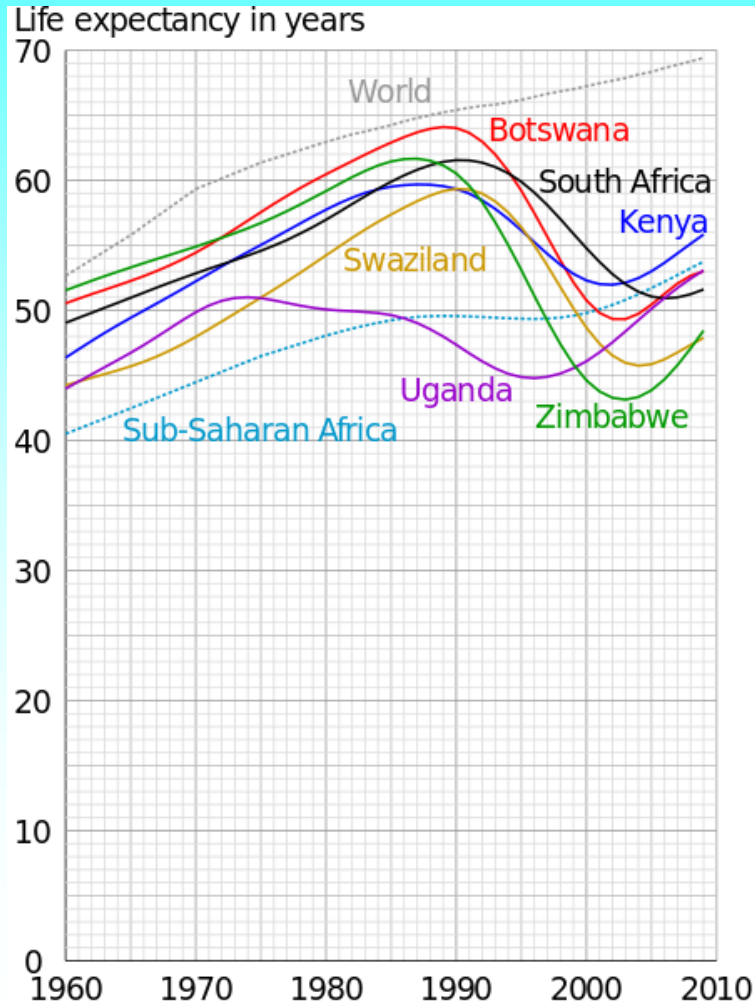
Graphs of **life expectancy** at birth for some sub-Saharan countries showing the **fall in the 1990s primarily due to the AIDS pandemic**. Data from The World Bank.

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Impact of the HIV epidemic in the UK and in Spain

	UK	Spain
Persons now living with HIV	95,000	**140,000**
Percentage of male	70	**75**
Main route of infection	Sexual	**Parenteral**
Death toll so far	20,000	**50,000**

HIV transmission

- Sexual
  - **Anal** and **vaginal** intercourse (the most important)
  - Oro-genital sex
- Parenteral
  - **Blood** and **blood derivatives** (the most efficient)
  - **Drug addiction**
- Vertical, during …
  - Pregnancy and delivery
  - Maternal lactation
- Occupational

HIV transmission

- Sexual
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Pathogenesis and progression

Characteristics of HIV

- Retrovirus, lentivirus genus
- Two species: **HIV-1** and HIV-2
- HIV-1: phylogenetic groups: **M**, N and O
- M: subtypes A to J

- Coreceptor tropism:
  - CXCR4 → syncytia
  - CCR5 → no syncytia

HIV life cycle
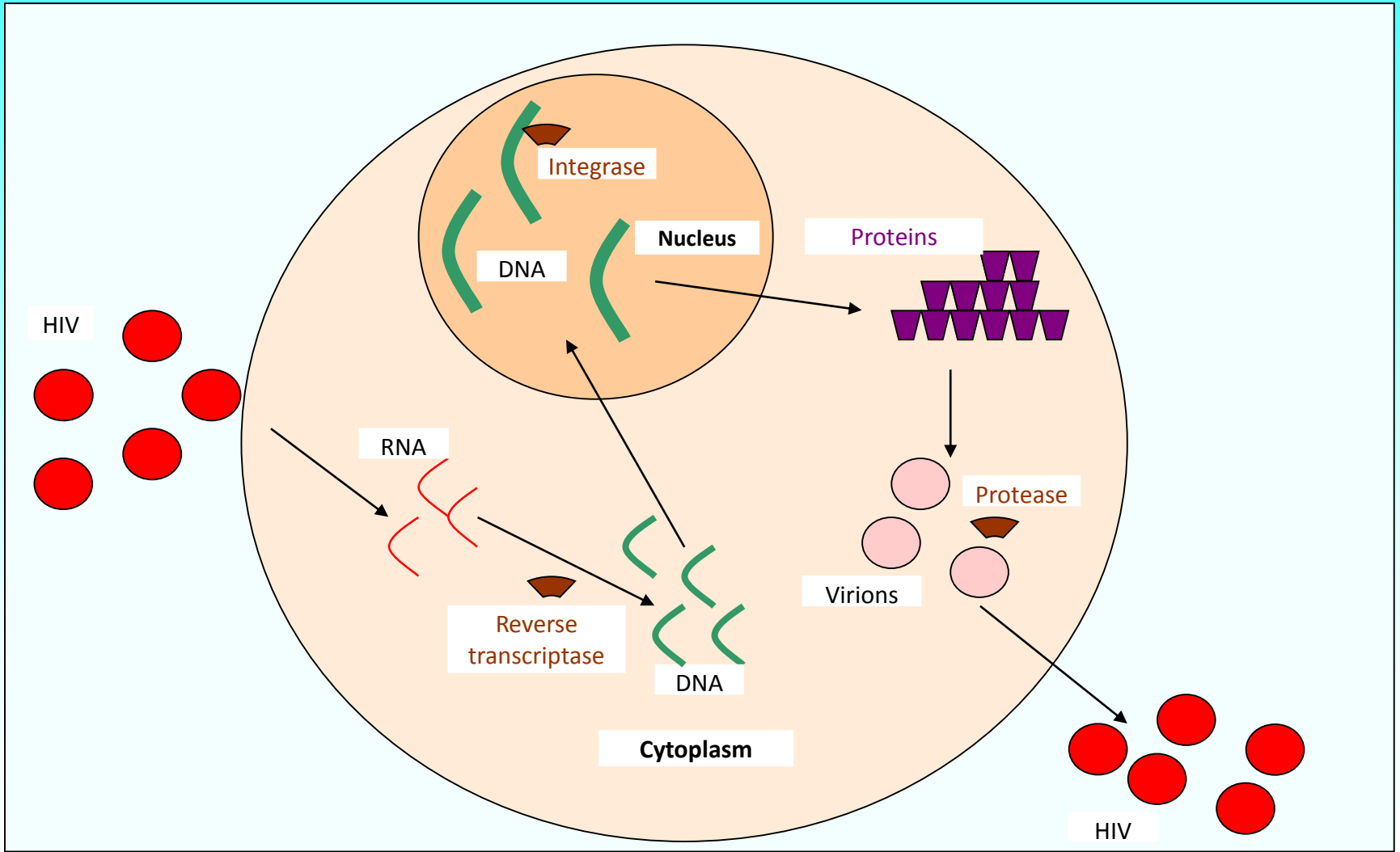
HIV life cycle
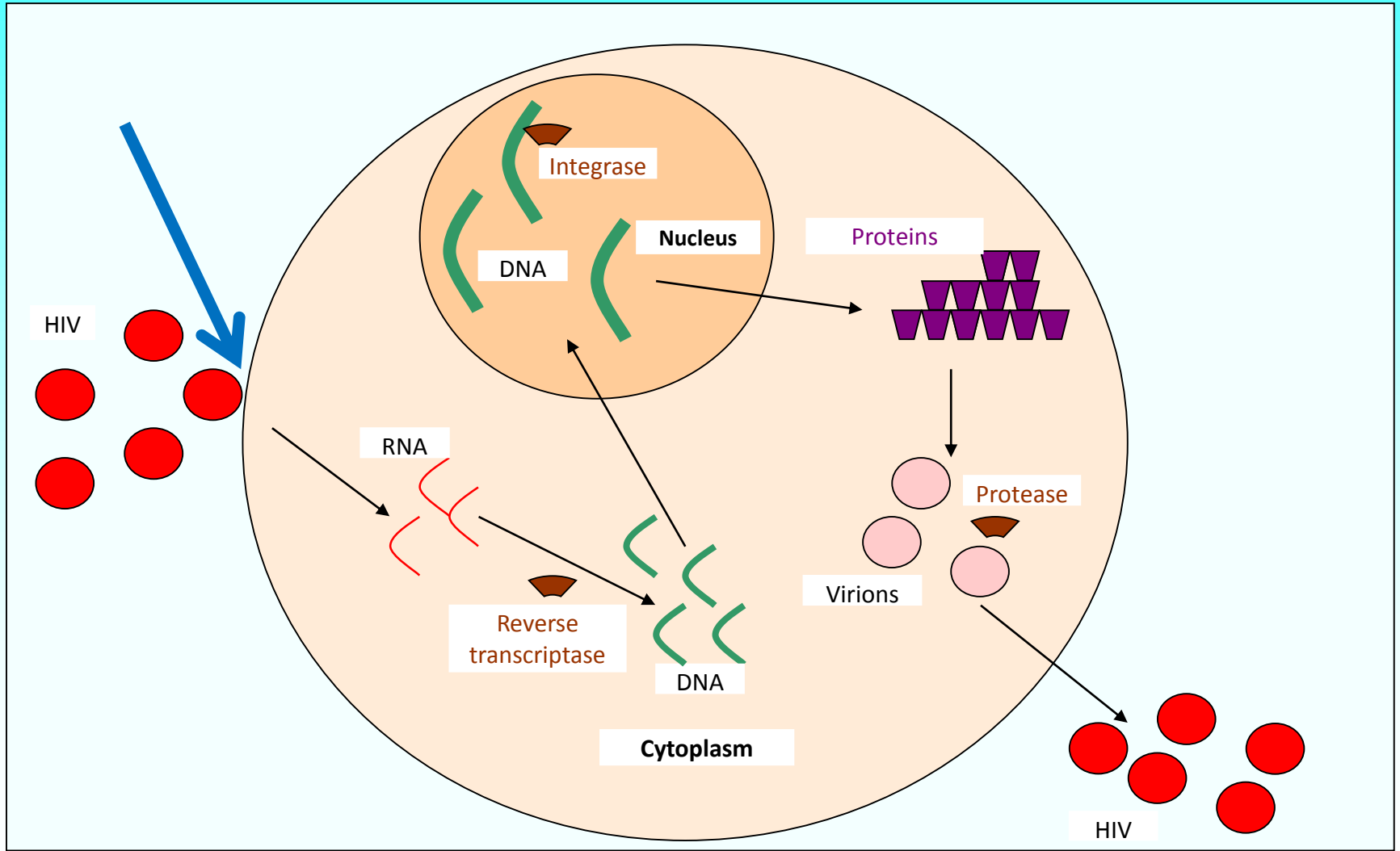
HIV life cycle

Integrase

Nucleus

DNA

Proteins

HIV

RNA

DNA

Reverse transcriptase

Virions

Protease

Cytoplasm

HIV
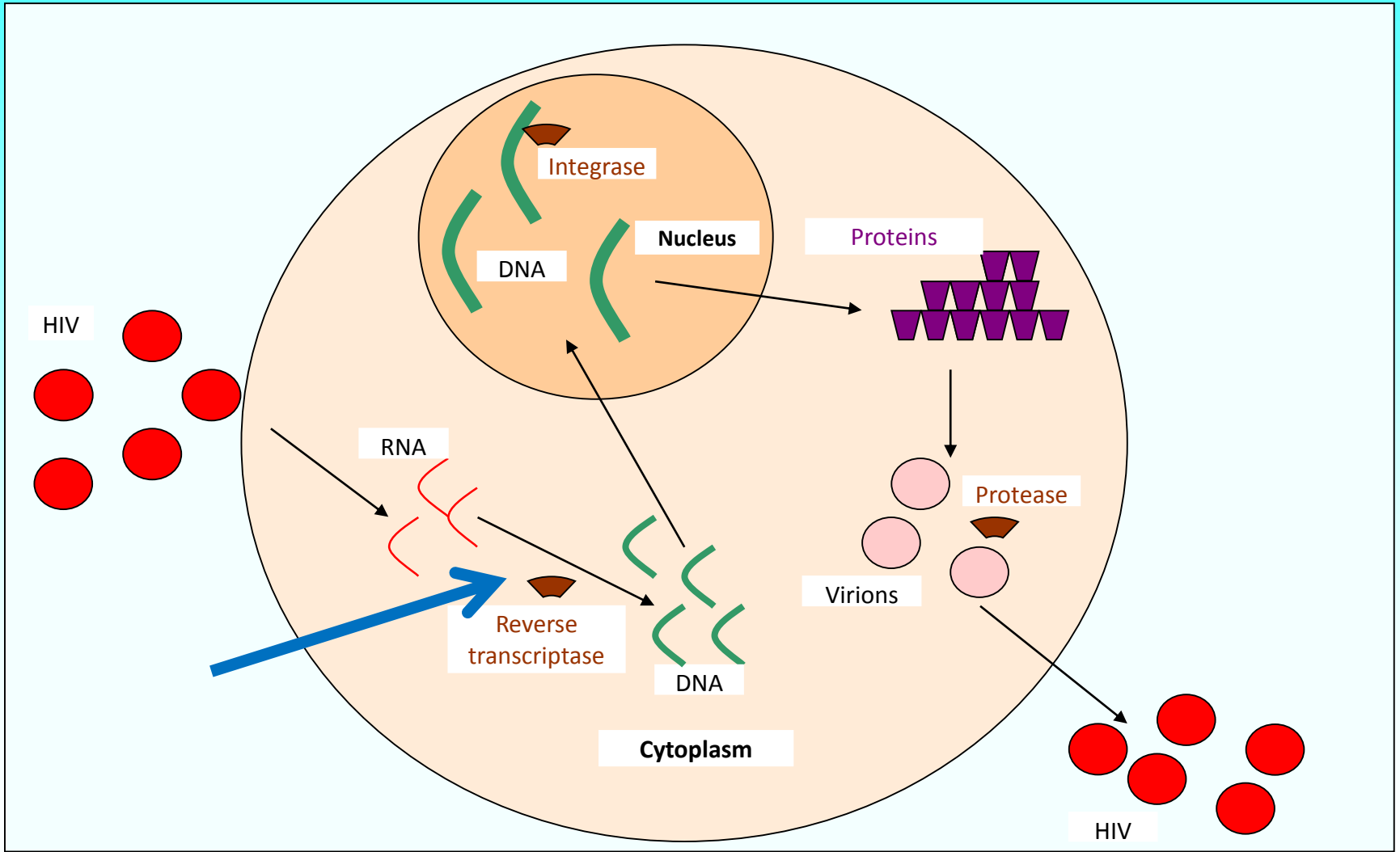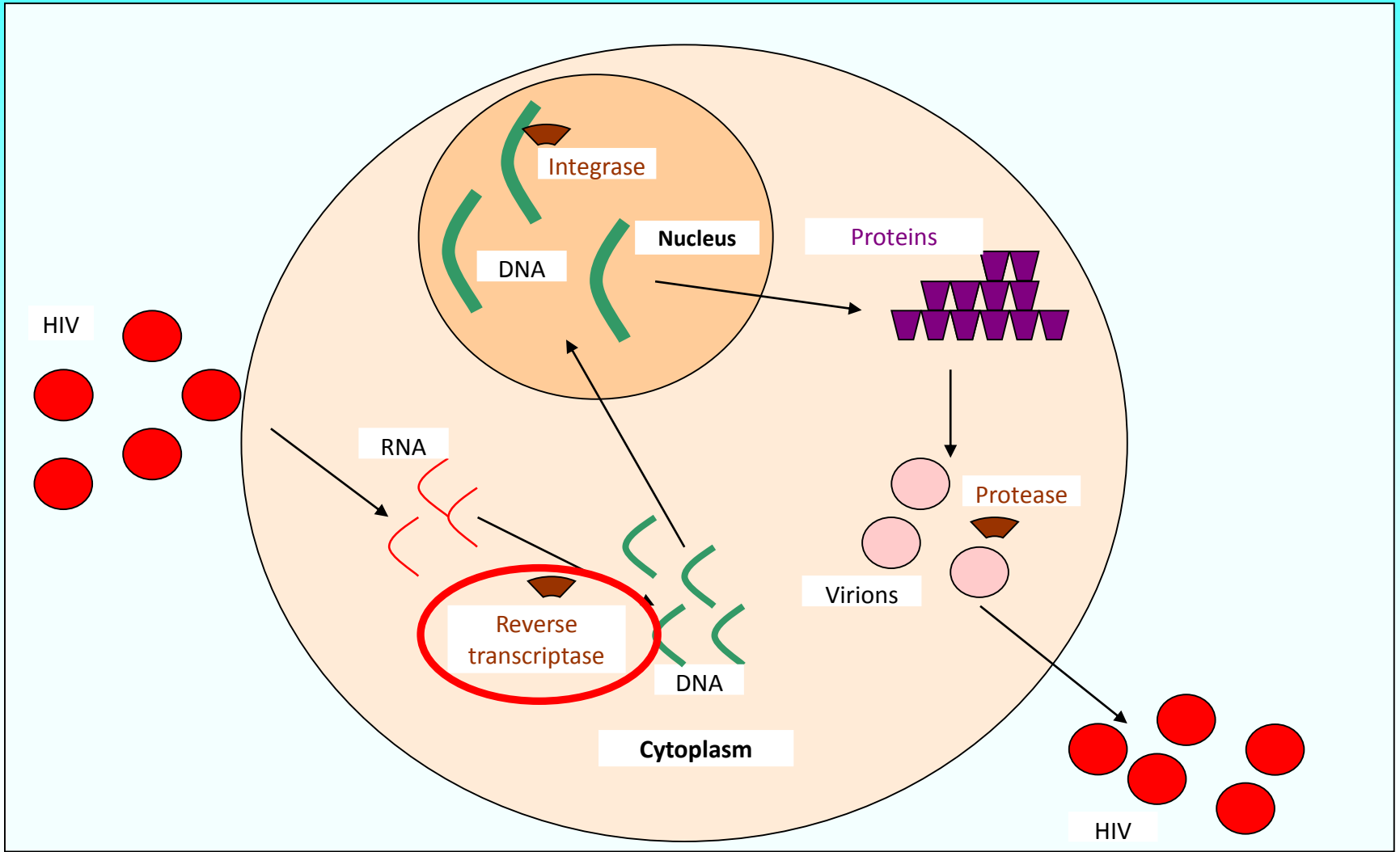
HIV life cycle
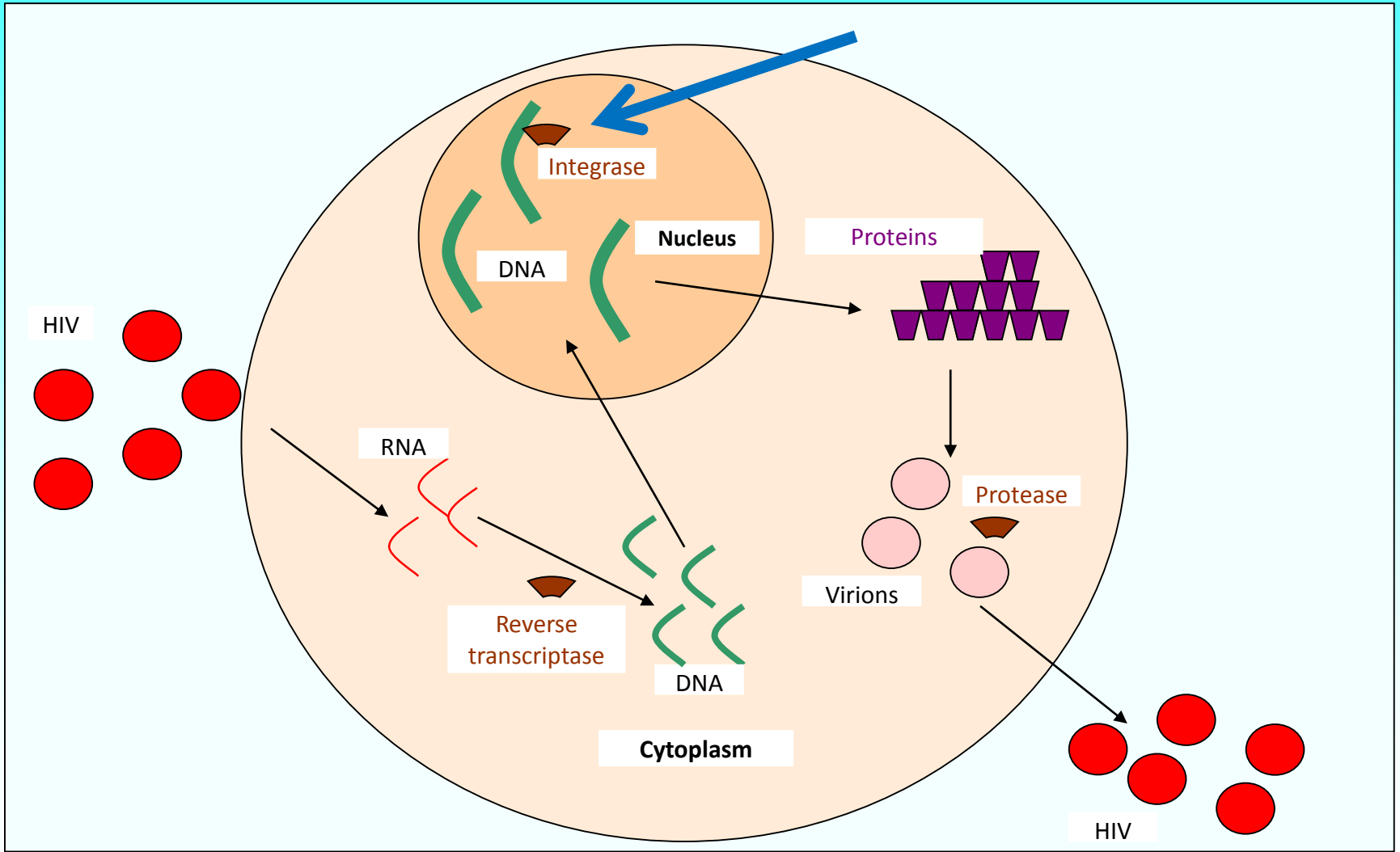
HIV life cycle
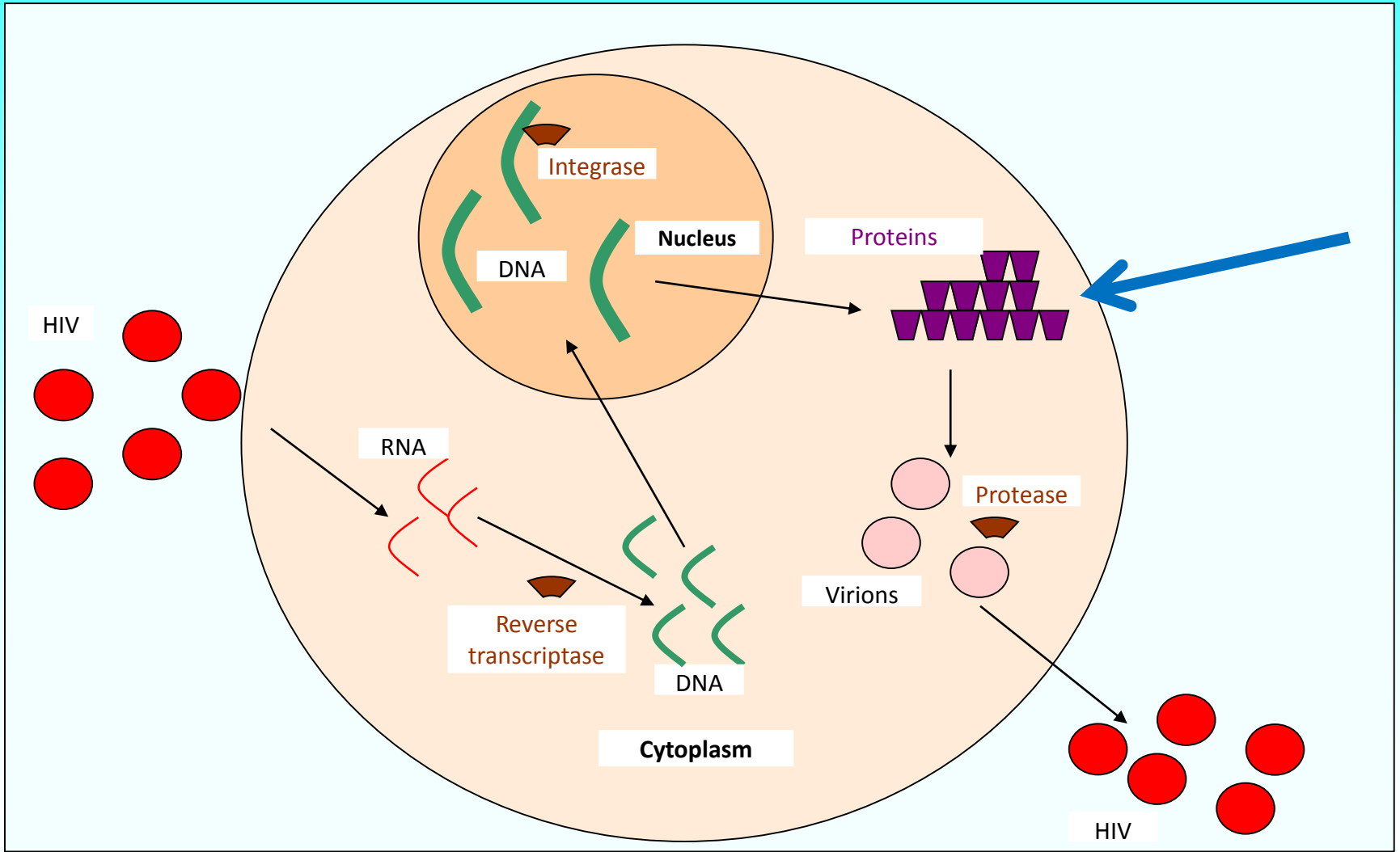
HIV life cycle
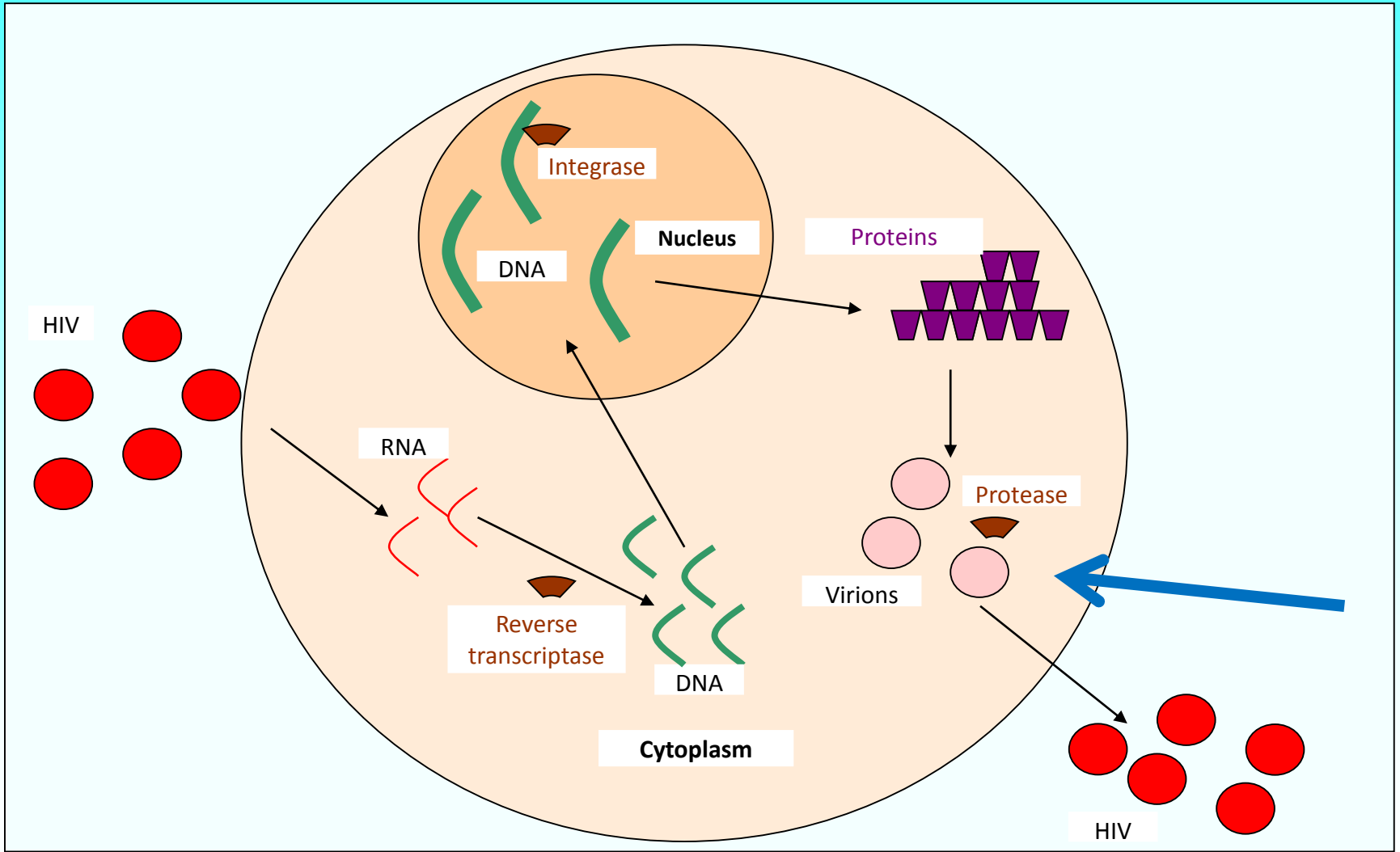
HIV life cycle
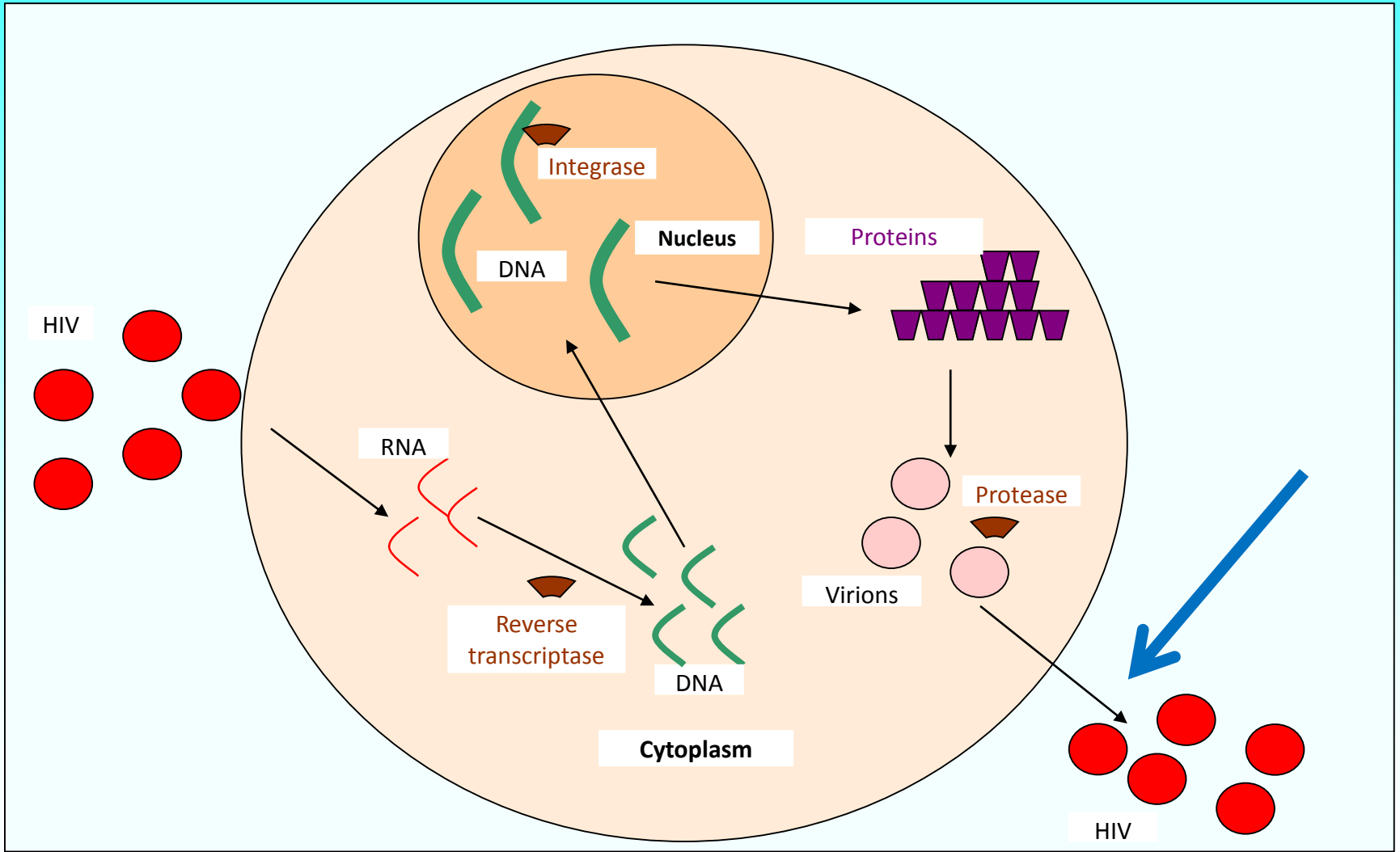
HIV life cycle

HIV life cycle

Characteristics of HIV

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Characteristics of HIV

Lipid bilayer

Envelope proteins (gp120)

RNA (viral genome)

Capsule protein (p24)

Reverse transcriptase
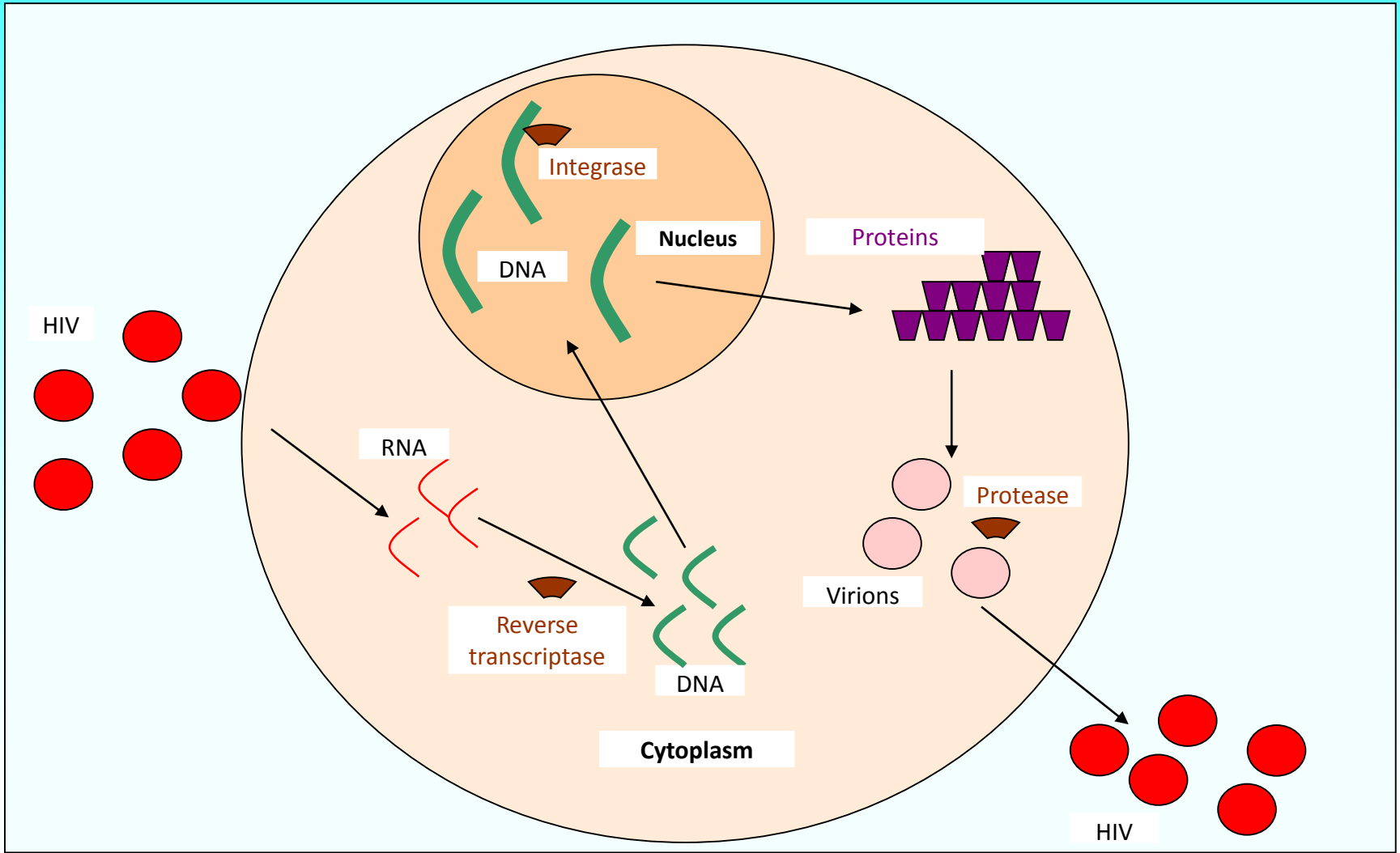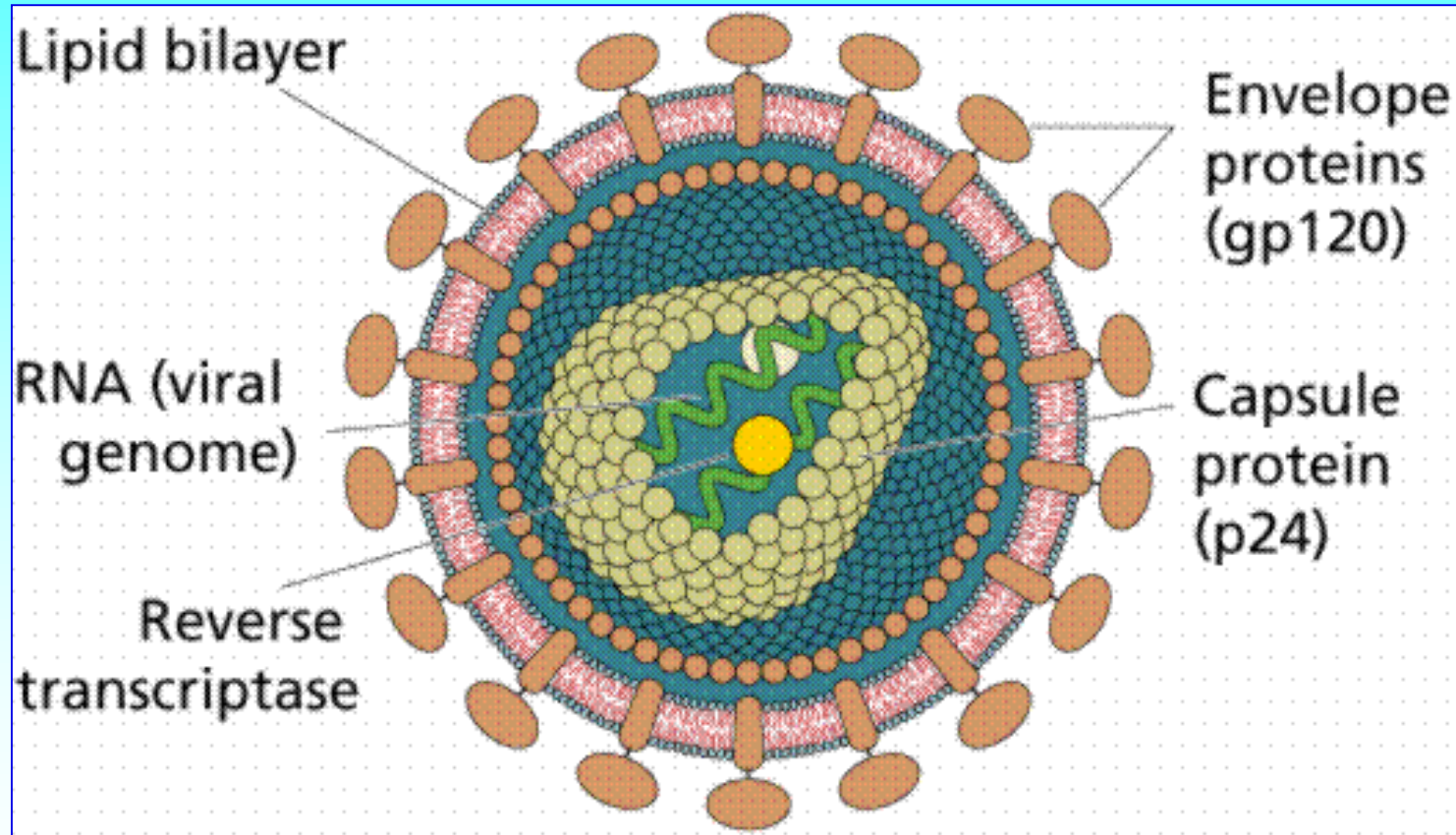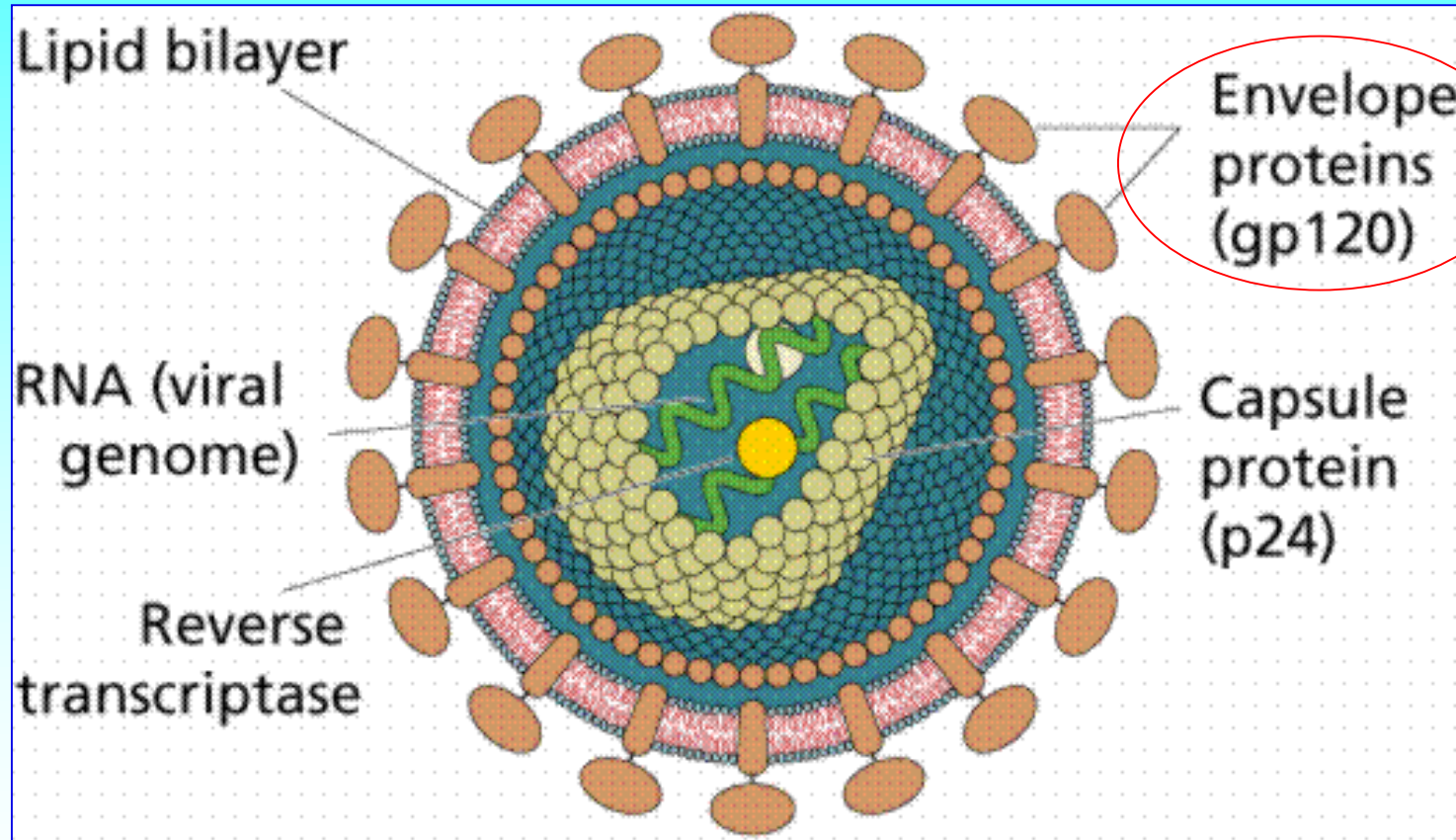
Cellular receptors and coreceptors of HIV
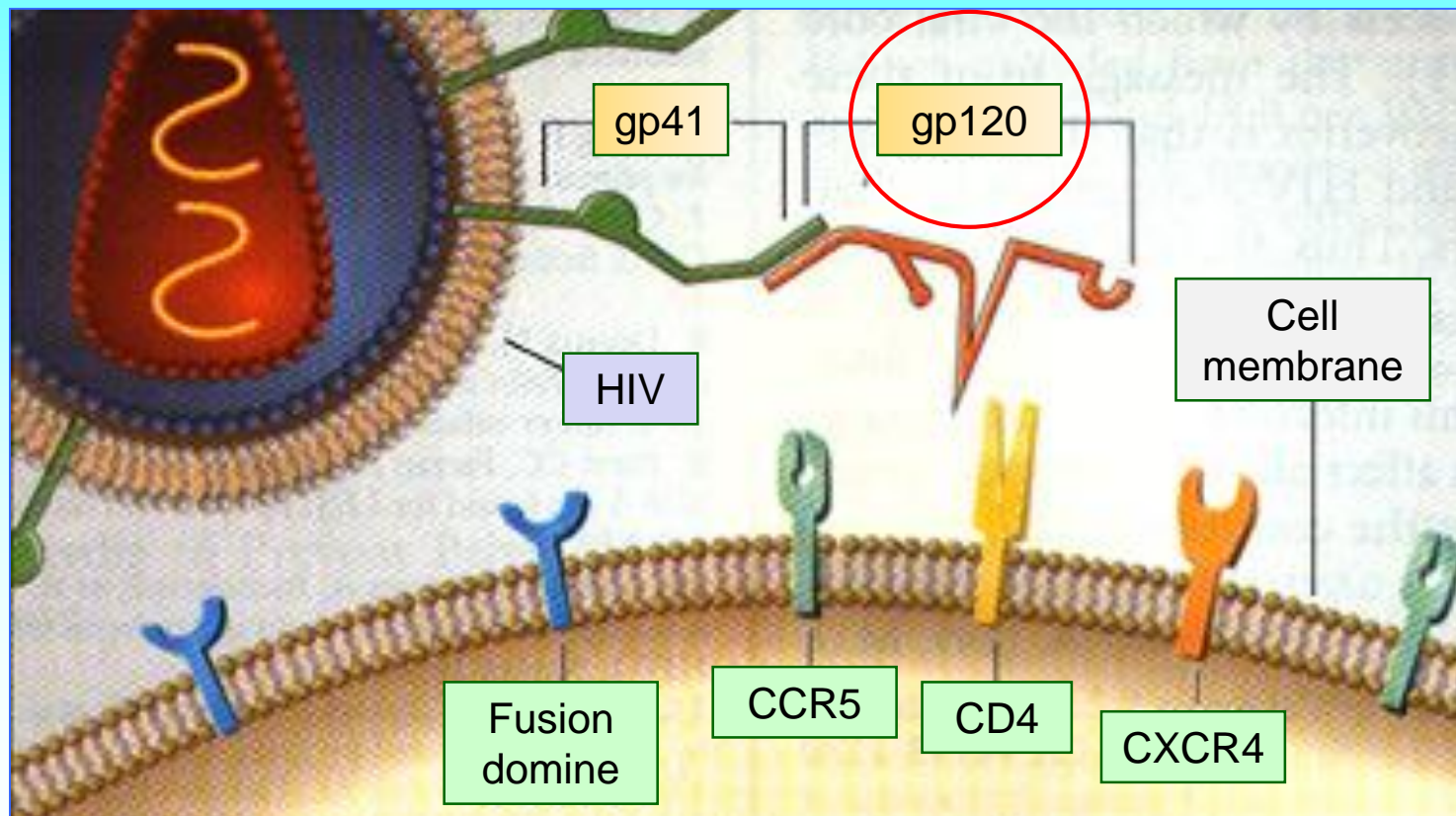
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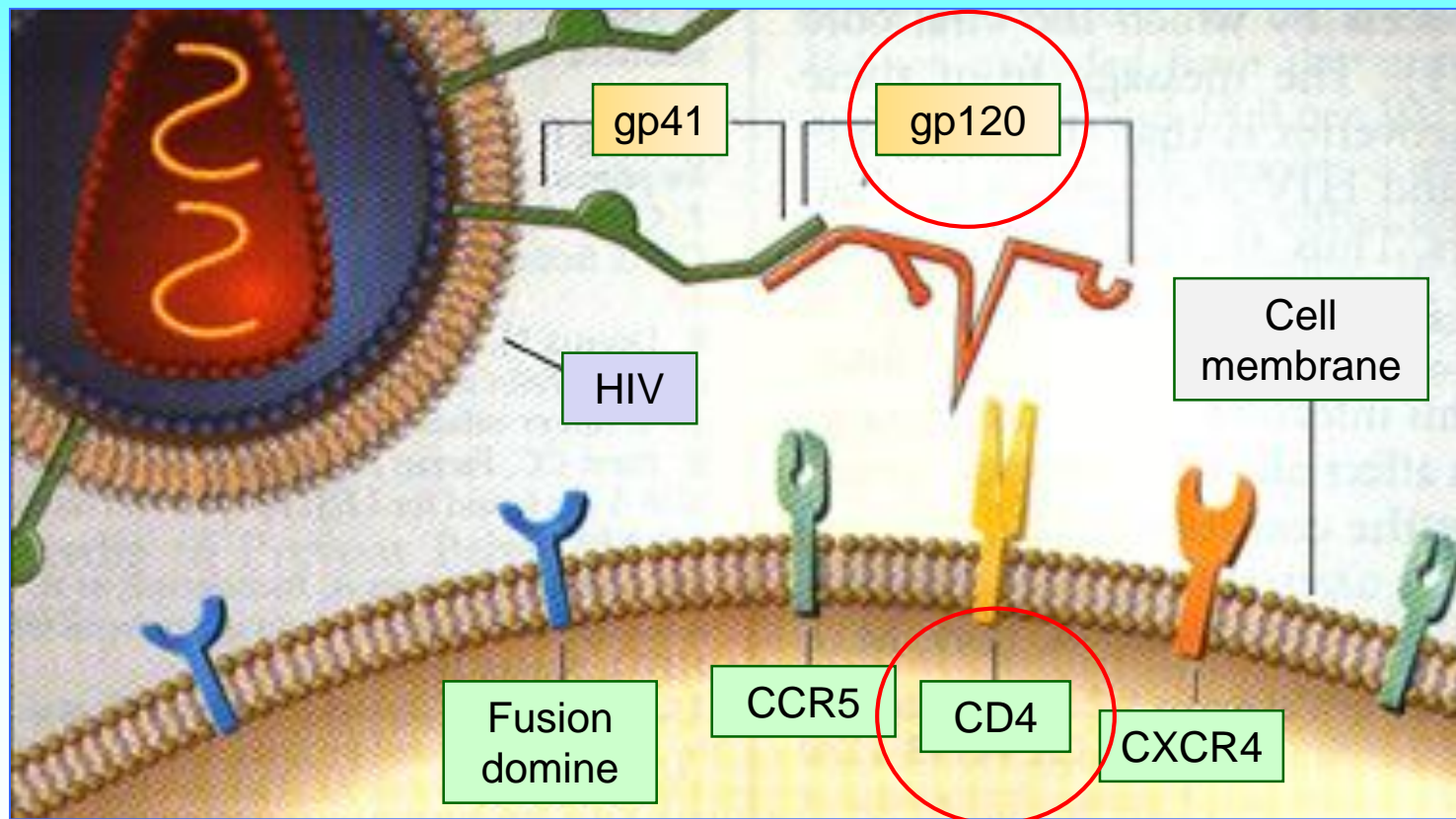
Introducing CD4 count

- Subset of helper T lymphocytes that are targeted by HIV
- Surrogate **marker for immune function**
- Normal range 450 - 1500 cells/μL
- Acute HIV infection: transiently reduce CD4 count, then partial recovery takes place
- Chronic infection: loss ~ 80 cells / year
- Significant risk of AIDS-defining diagnosis when CD4 < 200

Introducing viral load, HIV RNA

- Copies of virus in blood, per mL
- Undetectable (< 20) to several million of copies
- **Prognosis** of HIV-infection directly related to initial set point of plasma viral load
- Excellent indicator of **response to treatment**

Clinical progression of untreated HIV infection

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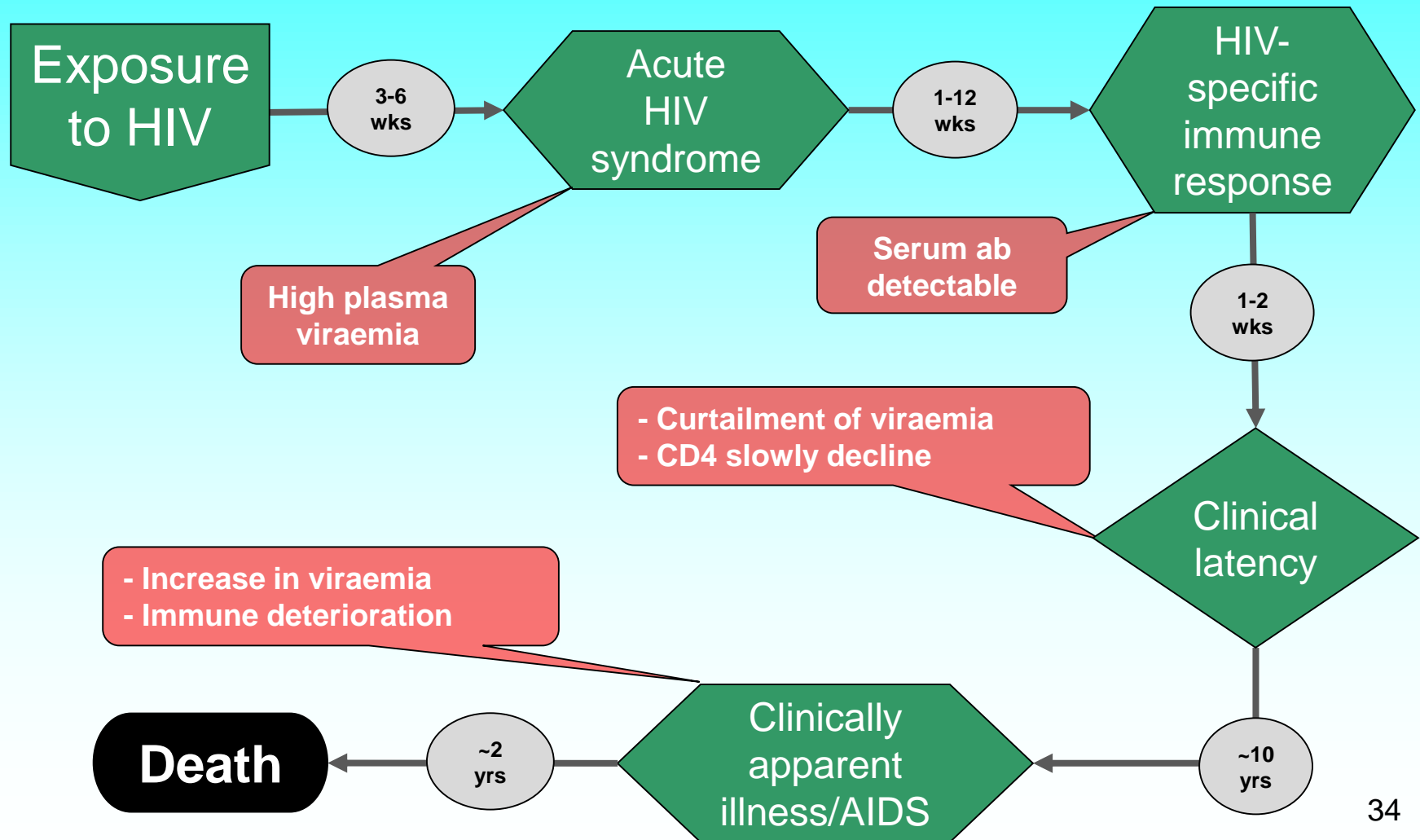
Natural history of HIV infection
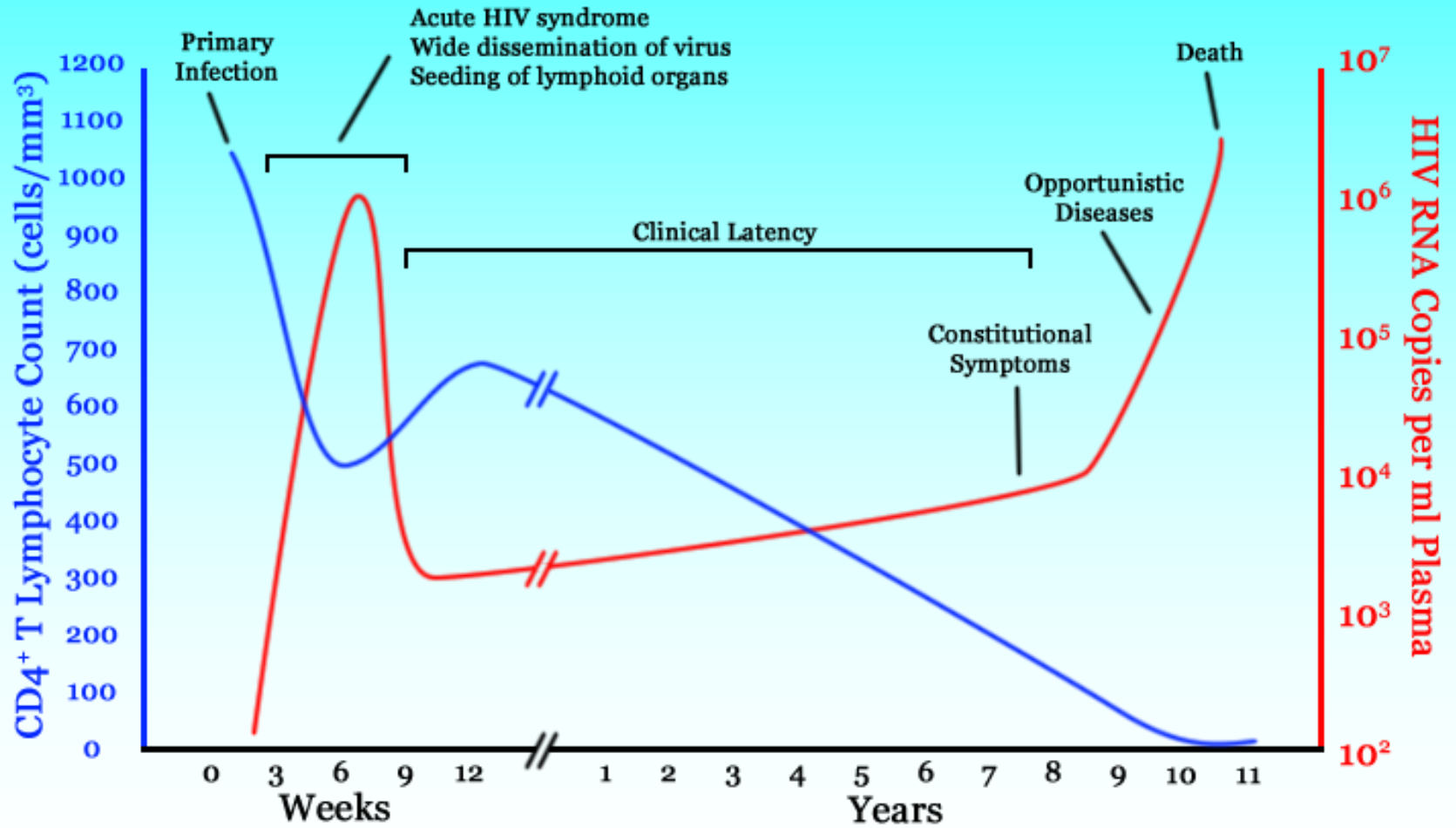
Clinical progression of untreated HIV infection

- Infection to AIDS ~ 7 years
  - Approximately 10% of adults will progress to AIDS within the first 2 - 3 years
  - 5 -10% have stable CD4 counts and no symptoms after 10 years
  - Large variation from patient to patient
- Infection to death ~ 10 years

Determinants of progression of HIV infection

- Characteristics of the **virus**:
  - Types and subtypes
  - Syncytia formation → ↑ progression
- **Host** factors
  - Age, coinfections
  - Some polymorphisms → ↓ progression
  - Coreceptors CCR5-Δ32 and CCR2-64I → ↓ progression
- Mixed: response of cytotoxic (CD8) T lymphocytes after initial infection

Diagnosis

HIV-antibody detection

Immunoenzymatic analysis

Western blot

Sensibility and specificity, both almost 100 %

False positive HIV test result

- Autoimmune diseases

- Recent vaccinations

- Multiple pregnancies

- Infections such as syphilis, hepatitis B, malaria or tuberculosis

- Multiple myeloma

- Chronic renal failure

- Laboratory technical problem

False negative HIV test result

- **Window period**: first few weeks after infection, up to 3 months? → HIV-RNA detectable in many of those cases
- HIV groups O or N infection
- Agammaglobulinemia
- Laboratory technical problem

Whom to test

- Ideally, every person
- Especially important:
  - Pregnant women
  - Persons with illnesses associated with HIV
  - Persons possibly exposed to infection:
    - Sexually active men or women, who are not in a long term mutually monogamous relationship
    - Those seeking STD evaluation or treatment

HIV testing

- Should be considered routine

- Formal pre-test counsel NOT required

- Requirements:
  - None in special
  - Arrange for a way to deliver results, as with any other test
  - If positive, referral pathways should be clear

New born

- Antibody tests not useful in neonate: maternal antibodies transmitted transplacentally
- HIV RNA
  - 1 - 3 days
  - 4 - 6 weeks
  - 8 - 12 weeks
- HIV antibodies, after 18 months

HIV quiz

How many persons you estimate are living with HIV in the Valencian Community at this time?

A 10

B 100

C 1.000

D 10.000

E 100.000

Which of the following data indicate the most advanced HIV-disease of all five?

A   100 CD4 cells per µL and 1,000 HIV-RNA copies per ml

B   150 CD4 cells per µL and 10,000 HIV-RNA copies per ml

C   200 CD4 cells per µL and 50,000 HIV-RNA copies per ml

D   250 CD4 cells per µL and 100,000 HIV-RNA copies per ml

E   300 CD4 cells per µL and 1,000,000 HIV-RNA copies per ml

Acute infection

General concepts

- Equivalent names
  - Primary HIV infection
  - Acute HIV syndrome
  - Acute retroviral syndrome
- Asymptomatic in 1/3 of cases approximately
- Symptoms typically begin 1 to 4 weeks after exposure

Clinical features

- Fever, generally low-grade
- Weakness
- Lethargy
- Headache
- Myalgia, arthralgia, diffuse pain
- Pharyngitis
- Lymphadenopathies
- Skin rash
- Generally 7 to 14 days duration

Primary HIV-infection rash:

- Mostly affects the upper part of the body: chest, face, and palms of the hands
- Typically is flat or barely raised and consists of small reddish dots or spots
- Generally is non-itching

Analyses abnormalities

- Lymphocytopenia / lymphocytosis
- Thrombocytopenia
- Increased liver enzymes
- Other non-specific alterations
- High HIV RNA, > 100,000 copies per mL
- Low CD4 cell count

Natural history of HIV infection

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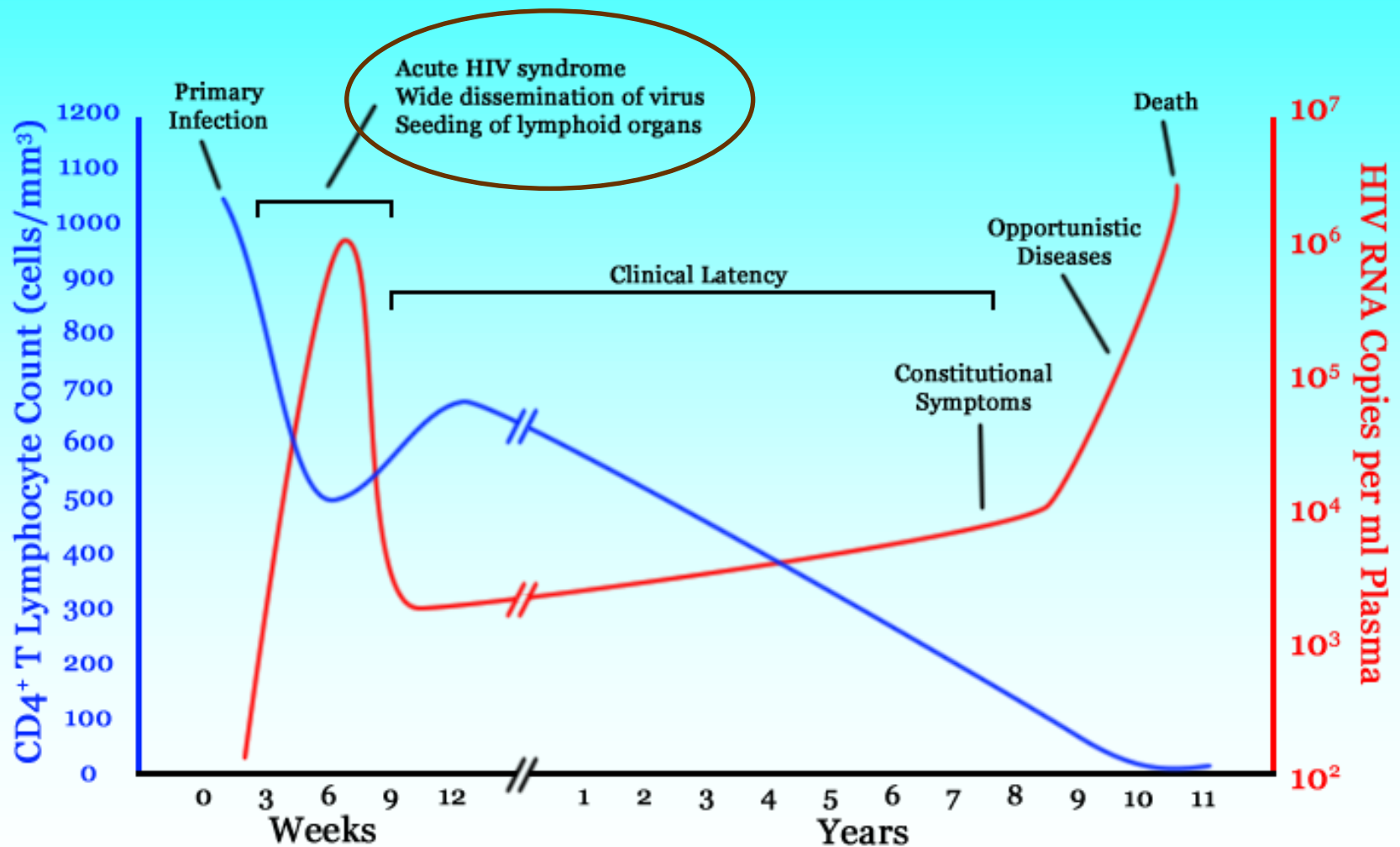
Differential diagnosis

- Infectious mononucleosis
- Strep throat
- Influenza
- "Viral illness"
- Secondary syphilis
- Acute viral hepatitis
- Parvovirus B19 infection
- Rubella
- Drug reaction

Diagnosis

- **Difficult ! - Need to think about it !**
- HIV antibody - (+ > 20 days after infection)
- HIV RNA detectable
- Earliest HIV marker: pro-viral DNA

Treatment

- Recommended by most experts
- Same treatment as for chronic disease: combinations of antiretrovirals, generally of three drugs, examples:
  - Emtricitabine + tenofovir + efavirenz (Atripla ®)
  - Lamivudine + abacavir + dolutegravir
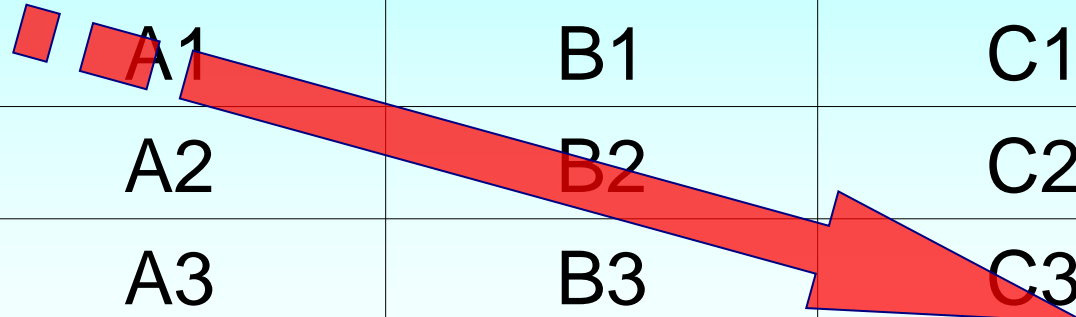
Chronic infection

1993 CDC HIV infection classification

Clinical features → CD4/μL ↓	A No symptoms, adenopathies	B Minor symptoms	C AIDS defining illnesses
≥500	A1	B1	C1
200-499	A2	B2	C2
<200	A3	B3	C3

1993 CDC HIV infection classification

Clinical features → CD4/μL ↓	A No symptoms, adenopathies	B Minor symptoms	C AIDS defining illnesses
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≥500	**A1**	B1	C1
200-499	A2	**B2**	C2
<200	A3	B3	**C3**

CDC stage A

- Patient **asymptomatic**
- After development of an HIV-specific immune response 1-3 months post infection
- Presence of **antibodies** for HIV, but they indicate **INFECTION** rather than PROTECTION
- Marked decline in plasma viremia, generally remains low

CDC stage A (cont'd)

- **CD4** count
  - may return to normal or stabilize at a somewhat lower level
  - decline slowly over years
- HIV **replication continues** in lymph nodes (resulting in **persistent generalized lymphadenopathy**) and other tissue compartments
- Take years

CDC stage B, main illnesses

- Bacillary angiomatosis
- Candidiasis: oropharyngeal, vulvovaginal
- Hairy leukoplakia, oral
- Herpes zoster (shingles)
- Pelvic inflammatory disease (PID)
- Cervical dysplasia, cervical carcinoma in situ
- Idiopathic thrombocytopenic purpura

Bacillary angiomatosis, caused by *Bartonella quintana* and *Bartonella henselae*

Oral **candidiasis** (thrush)

Oral hairy leukoplakia, caused
by Epstein-Barr virus

Herpes zoster

CDC stage B, main illnesses

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- Hairy leukoplakia, oral
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CDC Stage C, main illnesses (AIDS defining conditions)

- *Pneumocystis jiroveci (carinii)* pneumonia
- Cerebral toxoplasmosis
- Esophageal candidiasis
- Cytomegalovirus retinitis
- Tuberculosis
- Progressive multifocal leukoencephalopathy
- Kaposi's sarcoma
- Carcinoma of the cervix
- Non-Hodgkin's lymphoma
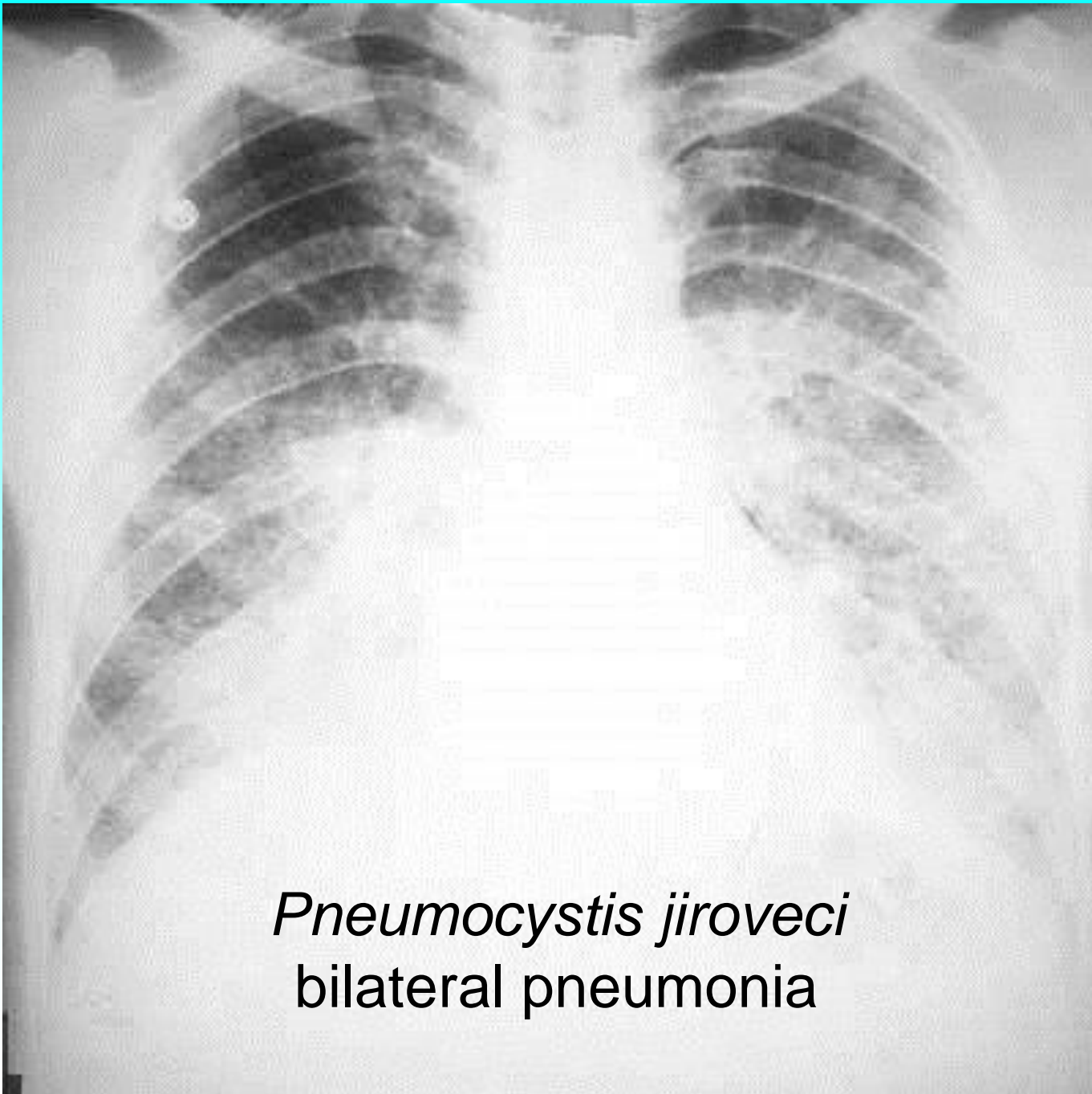
Pneumocystis jiroveci
bilateral pneumonia
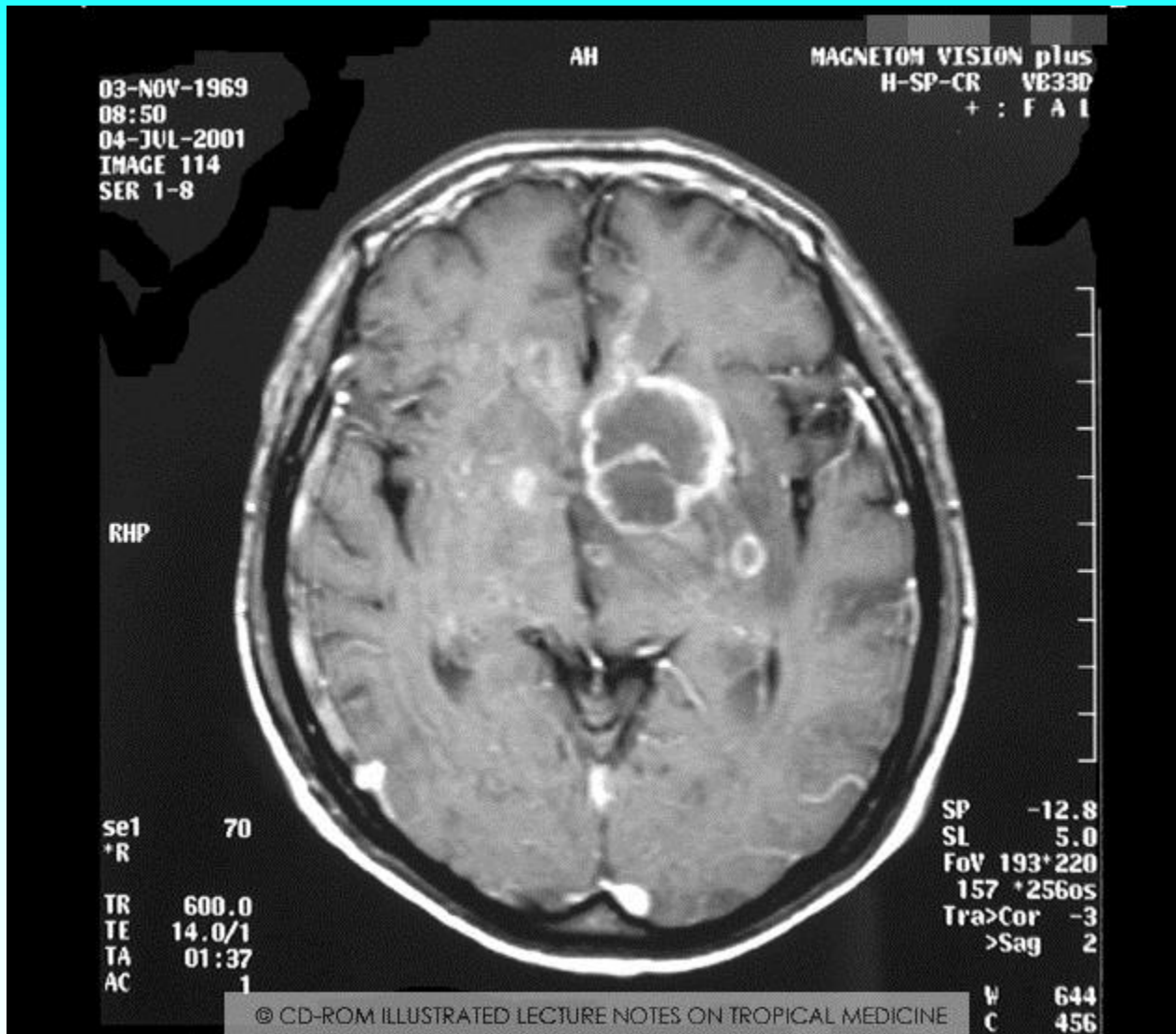
Cerebral toxoplasmosis
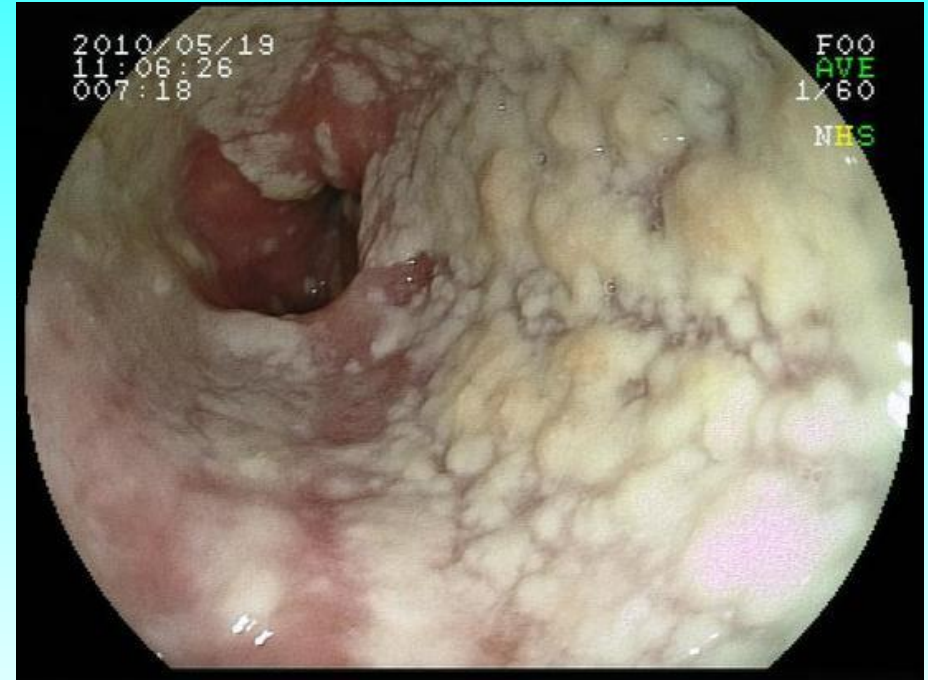
Esophageal candidiasis
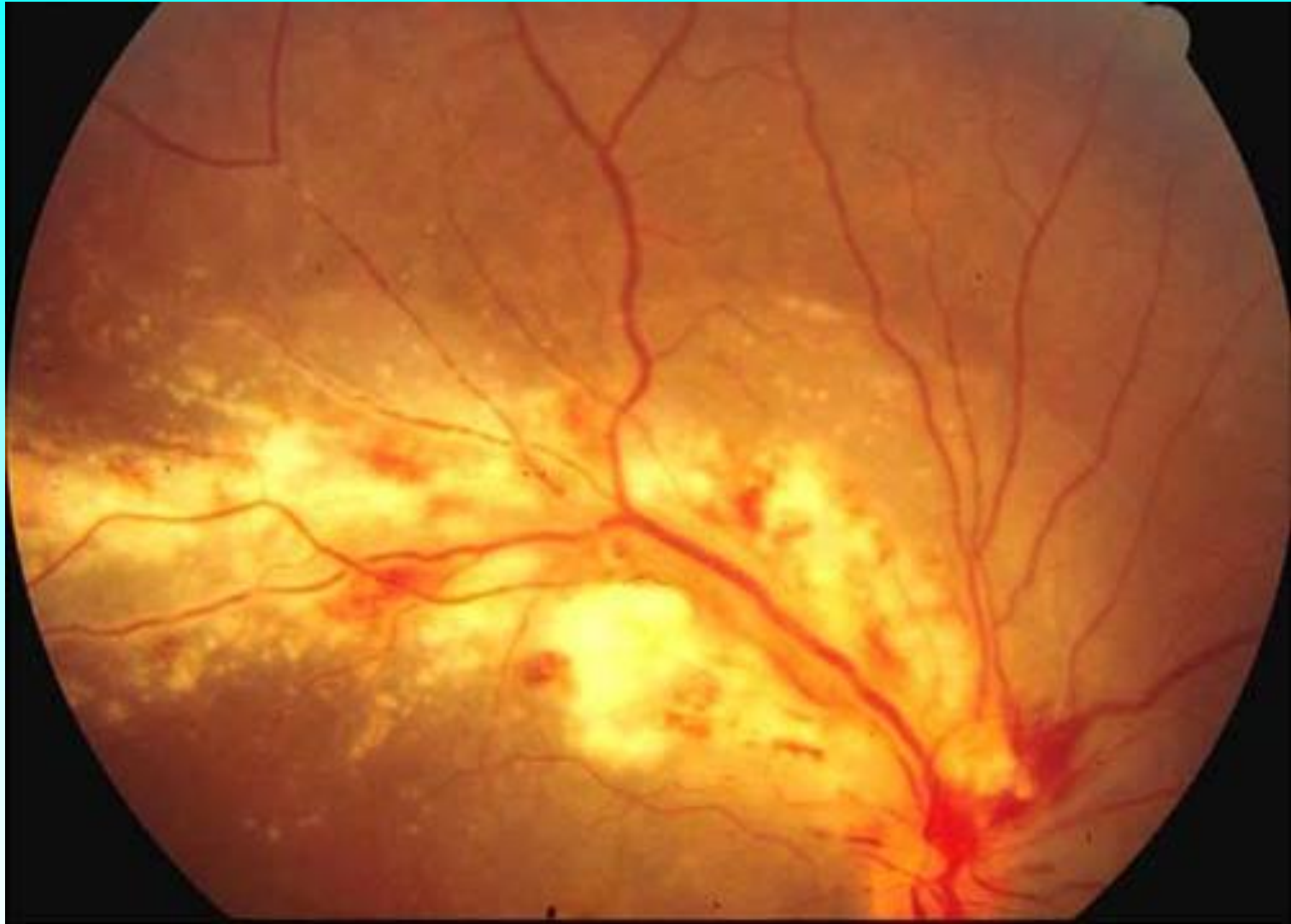
Cytomegalovirus retinitis
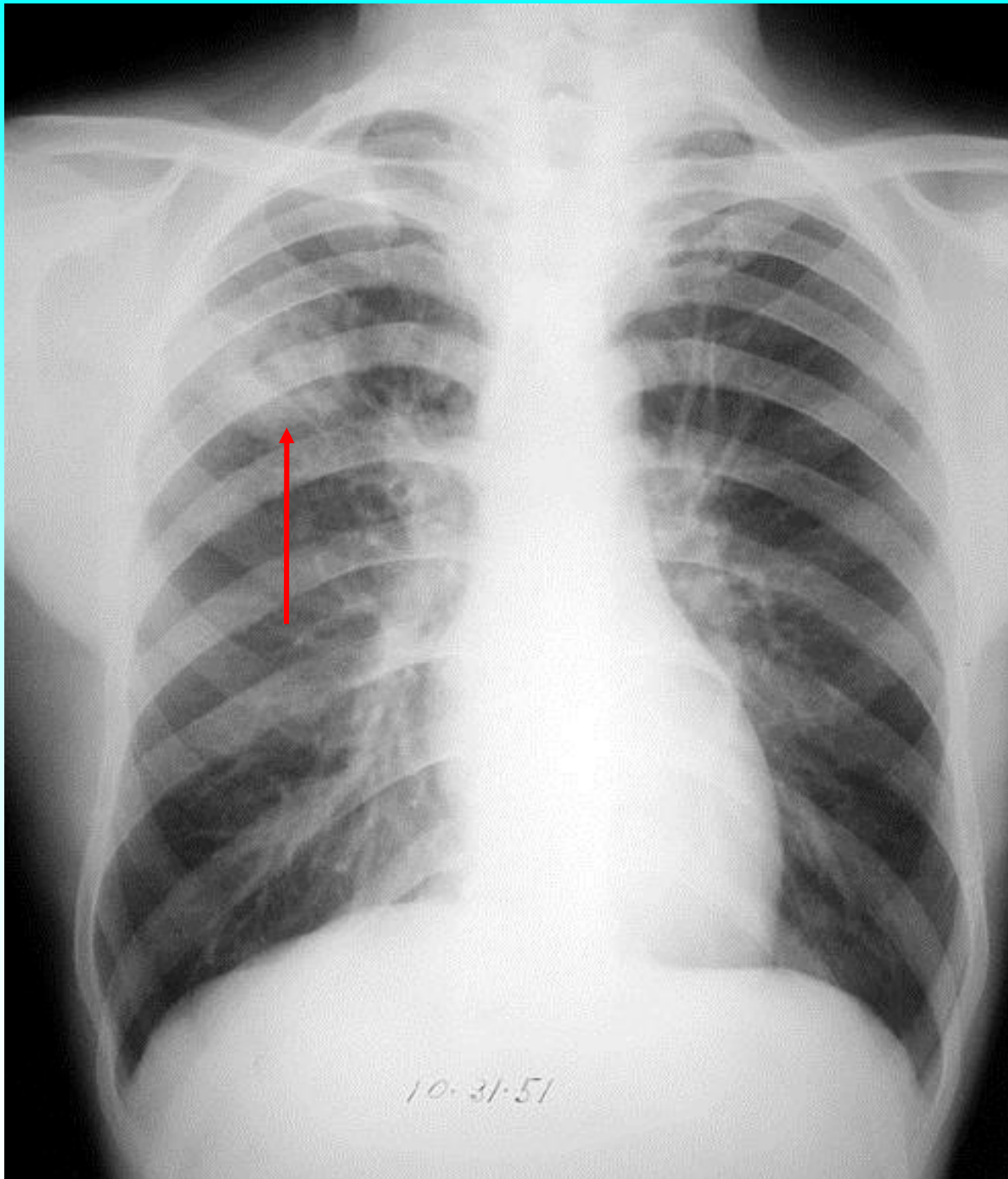
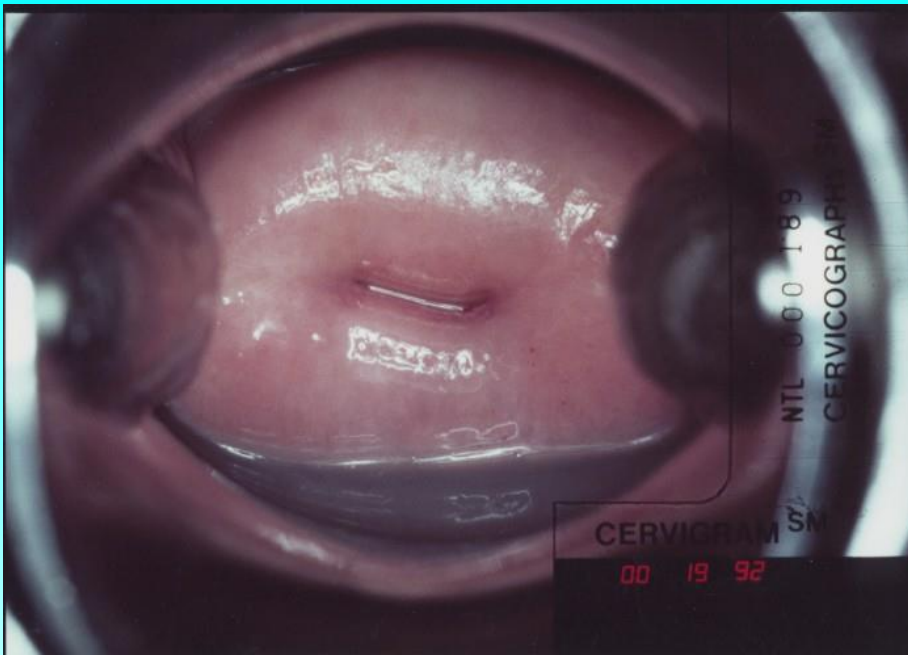Pulmonary tuberculosis
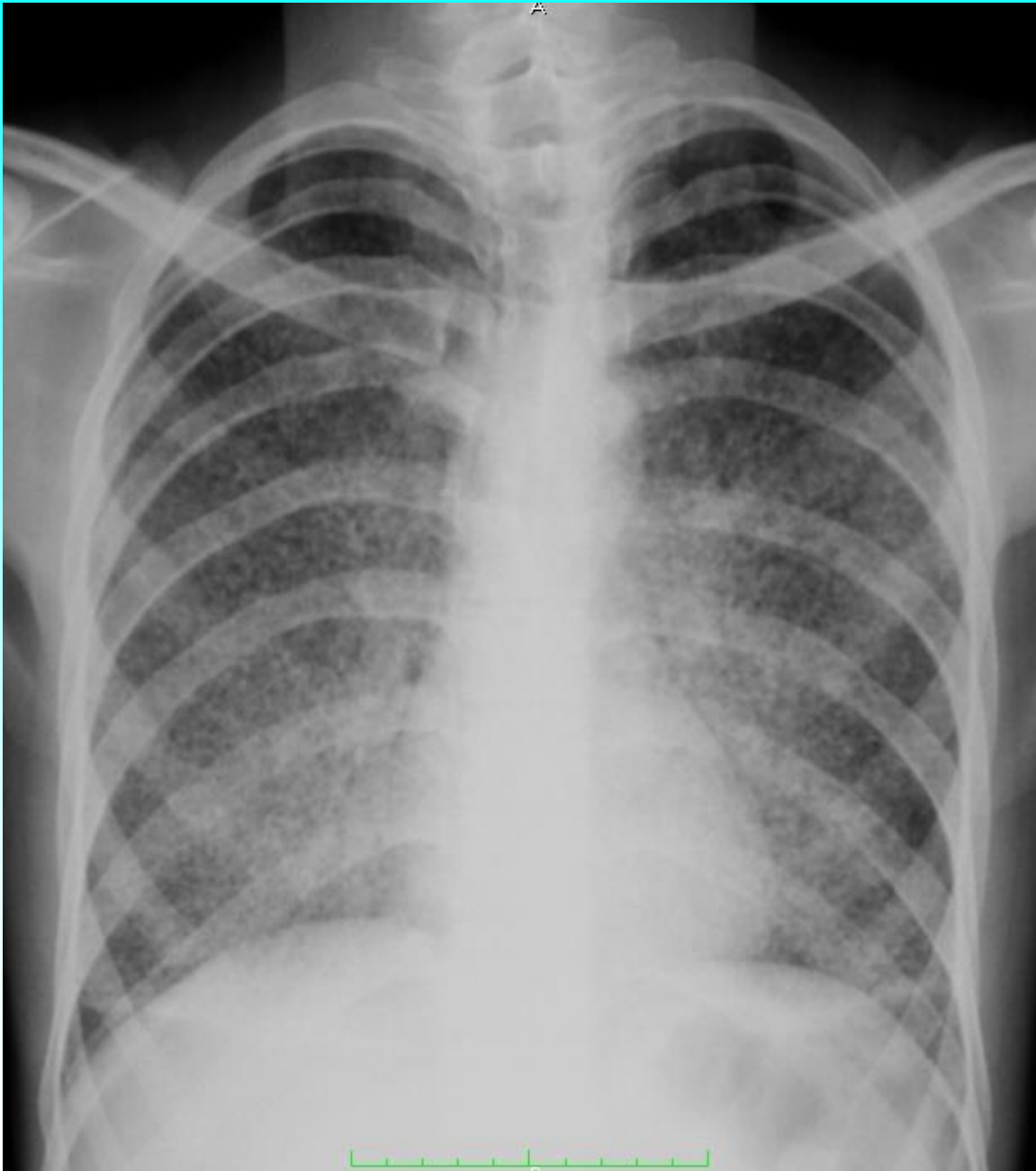
Miliary tuberculosis
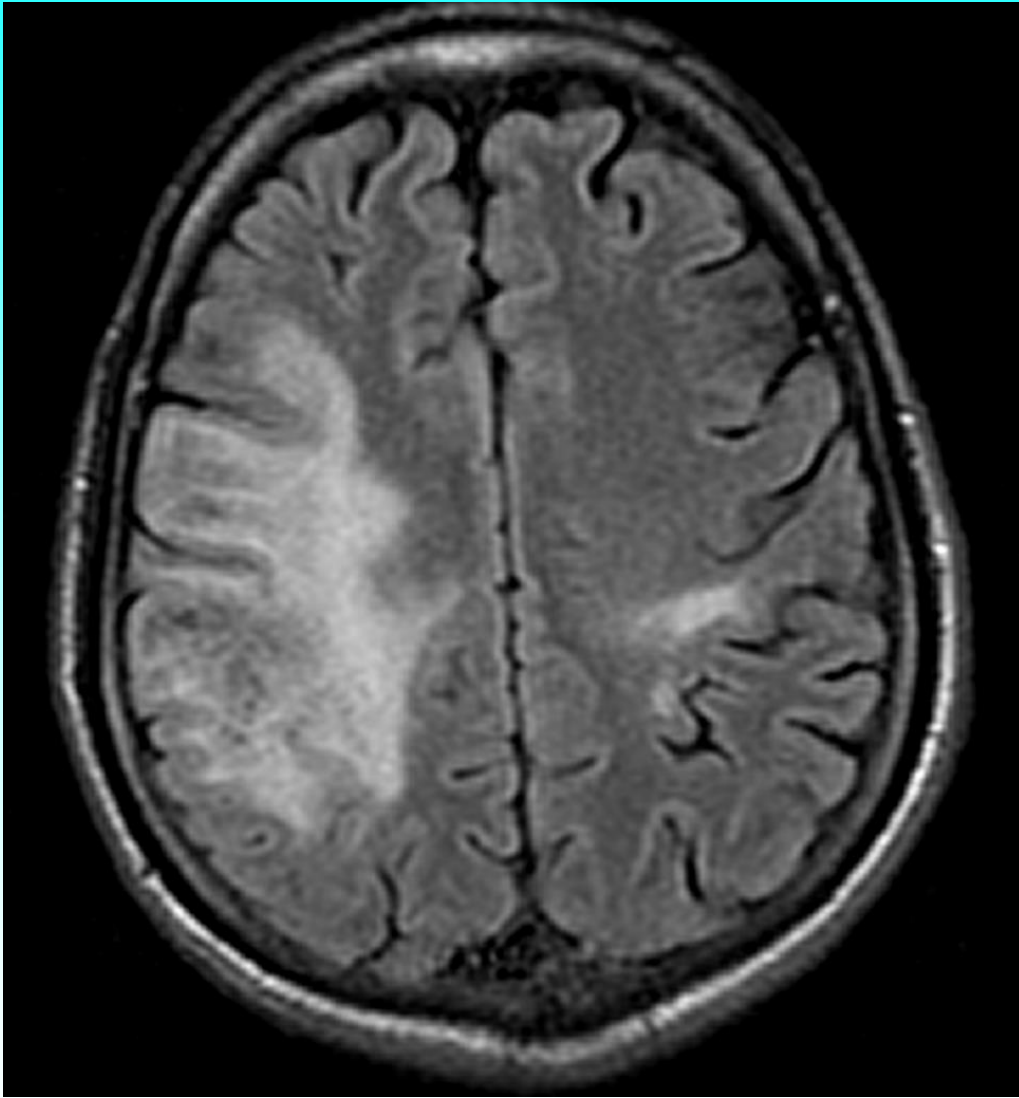
Progressive multifocal
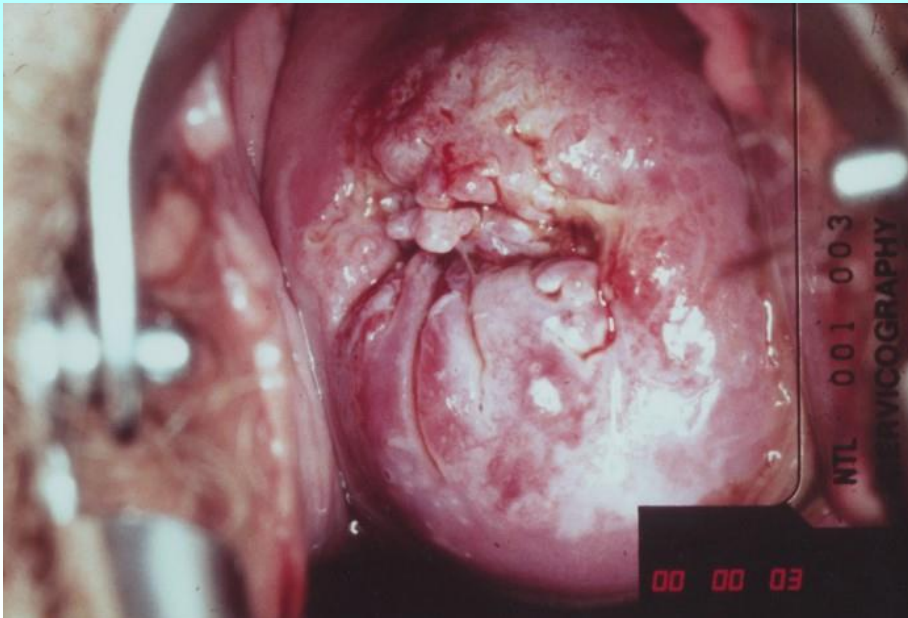leukoencephalopathy,
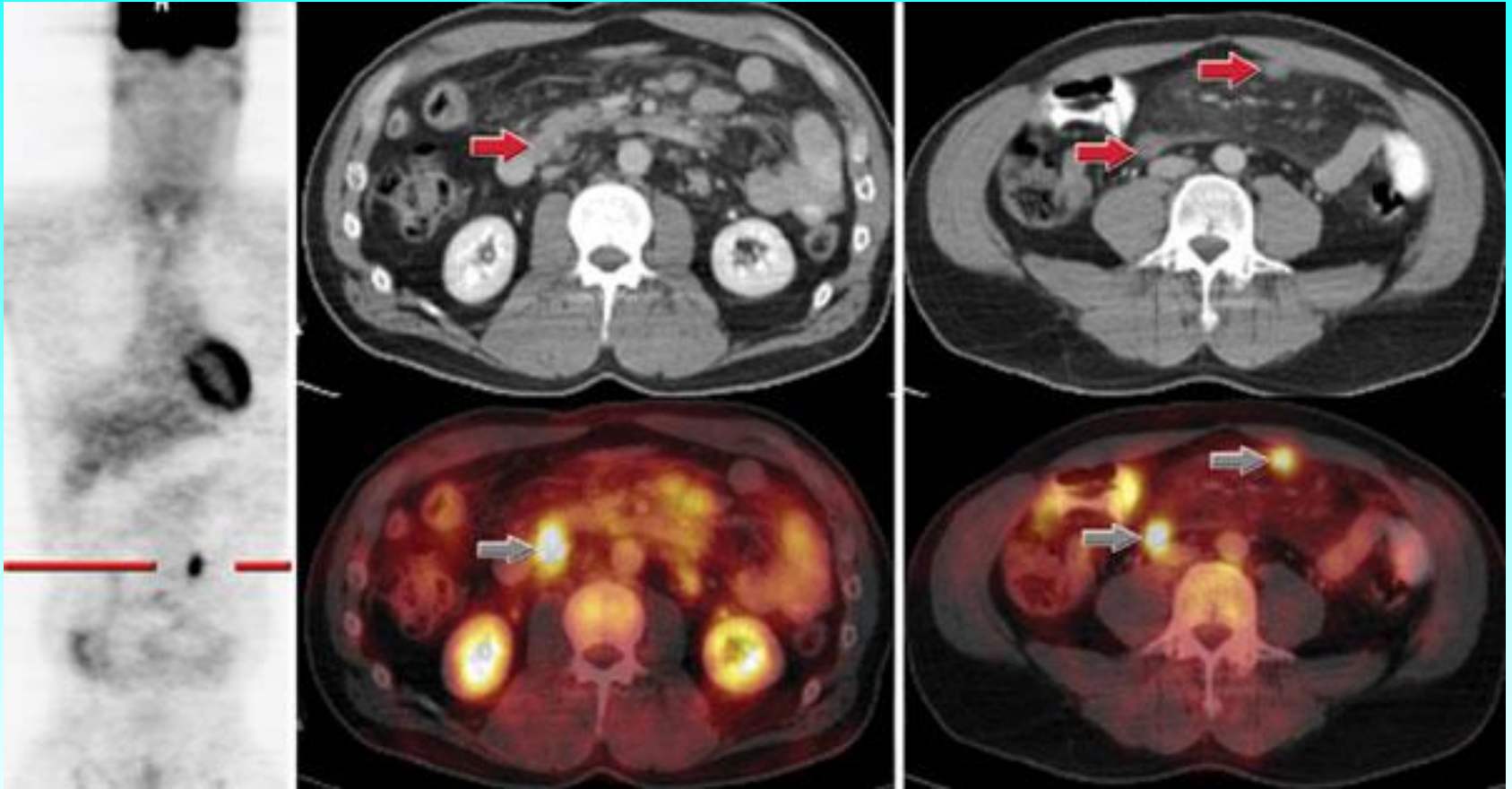caused by JC virus a
polyomavirus

Kaposi's sarcoma

Normal

Carcinoma of the cervix

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma

Patients' follow-up

Initial evaluation

- Fist visit
  - Anamnesis and physical exam
  - Blood analyses and other tests
- Second visit
  - HIV infection stage, prognosis
  - Check if there are any coinfections
  - If needed …
    - Vaccinations
   - Opportunistic infections prophylaxis
    - Antiretroviral treatment

Initiation of treatment

- Indications
  - **CD4 lymphocytes < 350 per μL**
  - **Prevention of vertical transmission**
  - Antecedent of AIDS defining illnesses
  - Hepatitis B infection, renal failure, cardiovascular diseases, etc.
  - All HIV-infected patients, as a general rule
- Take into account …
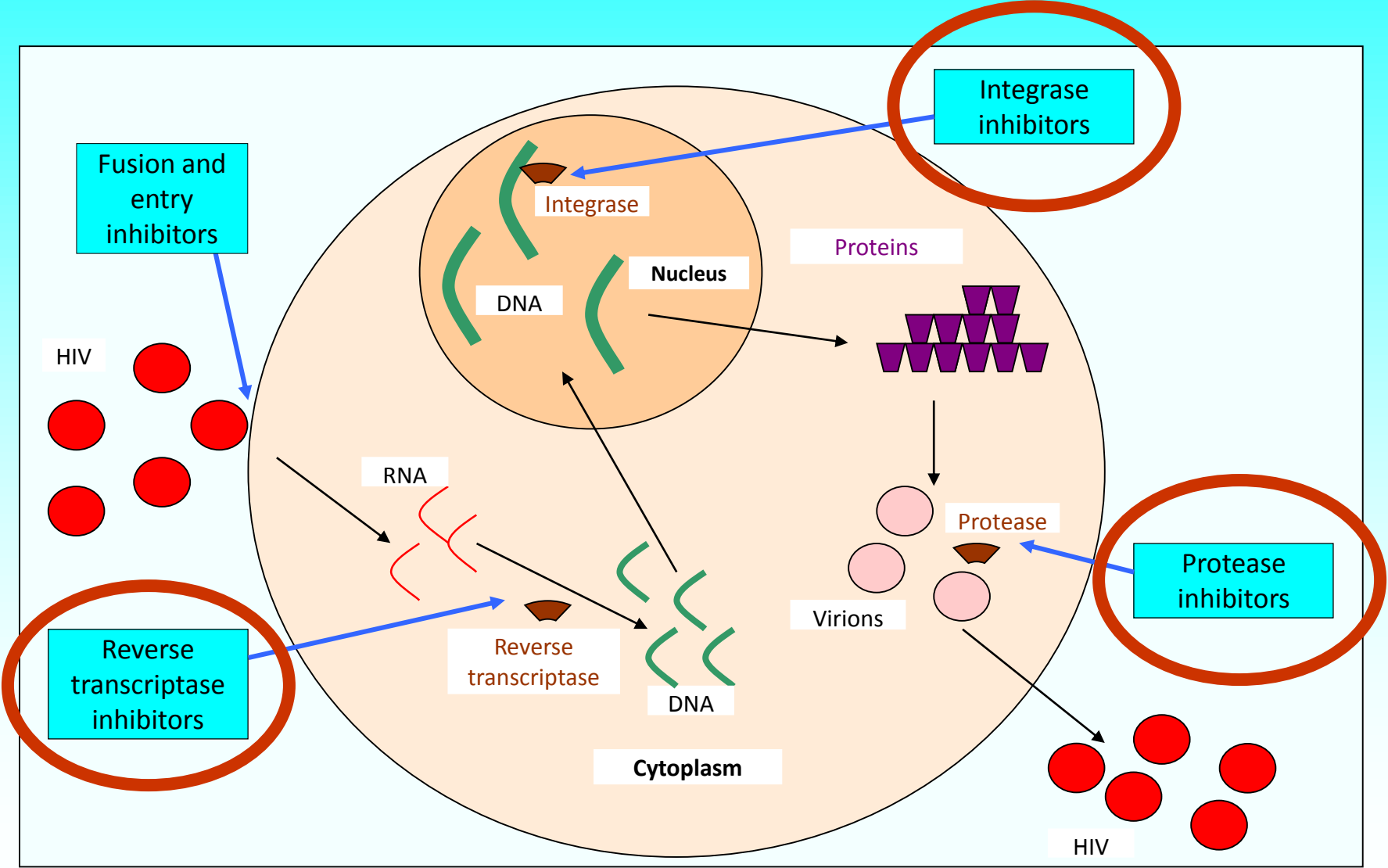 - Attitude of patient
  - Personal and social circumstances

Groups of antiretroviral drugs

- **Reverse transcriptase inhibitors:**
  - **Nucleoside and nucleotide analogues**
  - **Non-nucleoside analogues**
- **Protease inhibitors**
- **Integrase inhibitors**
- Coreceptor antagonists
- Fusion inhibitors

Mode of action of antiretrovirals
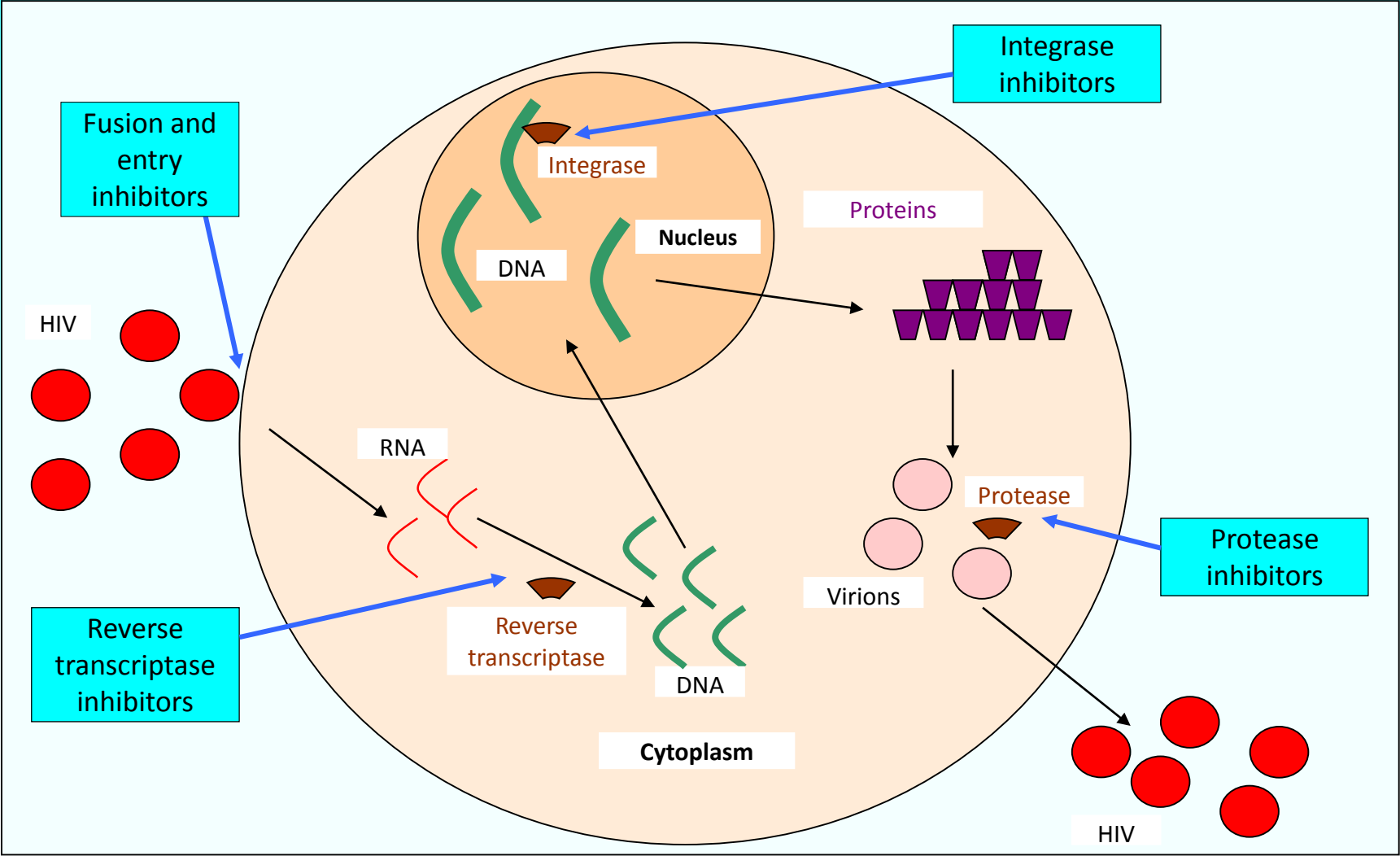
Mode of action of antiretrovirals

Commonly used combinations of antiretroviral treatment

- Emtricitabine [a] + tenofovir [a] + efavirenz [b]
- Emtricitabine [a] + tenofovir [a] + atazanavir [c] + ritonavir [d]
- Emtricitabine [a] + tenofovir [a] + elvitegravir [e] + cobicistat [d]
- Lamivudine [a] + abacavir [a] + dolutegravir [e]

[a] Nucleoside or nucleotide analogue

[b] Non-nucleoside analogue

[c] Protease inhibitor

[d] Booster

[e] Integrase inhibitor

Response to antiretroviral treatment

- **Eradication** of HIV is **not feasible** with present treatments
- **Objective**: to maintain **HIV RNA undetectable**, which may be impeded by:
  - **Suboptimal adherence**
  - Drug interactions
  - Gastrointestinal malabsorption
  - HIV resistance

Resistance tests

- Types of tests
  - **Genotypic**
  - Phenotypic
- Indications
  - Before starting first treatment
  - Suboptimal response to treatment
  - HIV RNA > 1000 copies per mL after initial adequate response
- Limited clinical usefulness

Continued follow-up

- Every 3 to 6 months
- Clinical changes
- General analyses
- HIV RNA
- CD4 lymphocyte count
- Control of **coinfections** as needed
- **Cardiovascular risk factors** evaluation and control

Conclusions

You have learnt …

- How to diagnose HIV-infection, including peculiar clinical contexts
- The significance of laboratory tests in the follow-up of HIV-infection
- The clinical features of HIV-infection in the different stages of the disease

Further reading

References

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Last updated on November 13, 2014. Available at: http://www.aidsinfo.nih.gov.

- Günthard HF, Aberg JA, Eron JJ et al and International Antiviral Society-USA Panel. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA 2014: 410-25.

Preparing your exam

Just these slides

Thank you for your attention

Study a lot !!!, this subject and all other subjects

I wish you a gook luck in your exams