HIV and AIDS

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HIV : HUMAN IMMUNODEFICIENCY VIRUS

- VIRUS that target immune cells leading over time to IMMUNODEFICIENCY
- Which will lead to AIDS :

AQUIRED IMMUNODEFICIENCY SYNDROME

- that increase risk of infections and tumors

-People with HIV can take medicines to control the virus, keep their immune system strong, and stay healthy for many years before developing AIDS

HIV-1 vs HIV-2

- Two types of HIV (two viruses) cause infection:-

HIV-1: Causes majority of infections worldwide

HIV-2: causes a similar illness to HIV-1 but progresses more slowly and less transmissible, is restricted mainly to western Africa .

- Both are sexually transmitted.
- Both can cause AIDS.

Epidemiology

- 38 million are living with HIV , 1.7 million new infections and 690 000 AIDS related deaths.
- The global epidemiology of HIV has been changed by expanding access to combination antiretroviral therapy (ART), which reached 25.4 million people in 2019 , the annual number of AIDS –related deaths has more than halved since the peak in 2004.
- Regions have differences in HIV prevalence, incidence and dominant modes of transmission , HIV has had a devastating impact in sub-Saharan Africa , particularly in Southern Africa, where average life expectancy of general population fell to below 40 years before the introduction of ART .

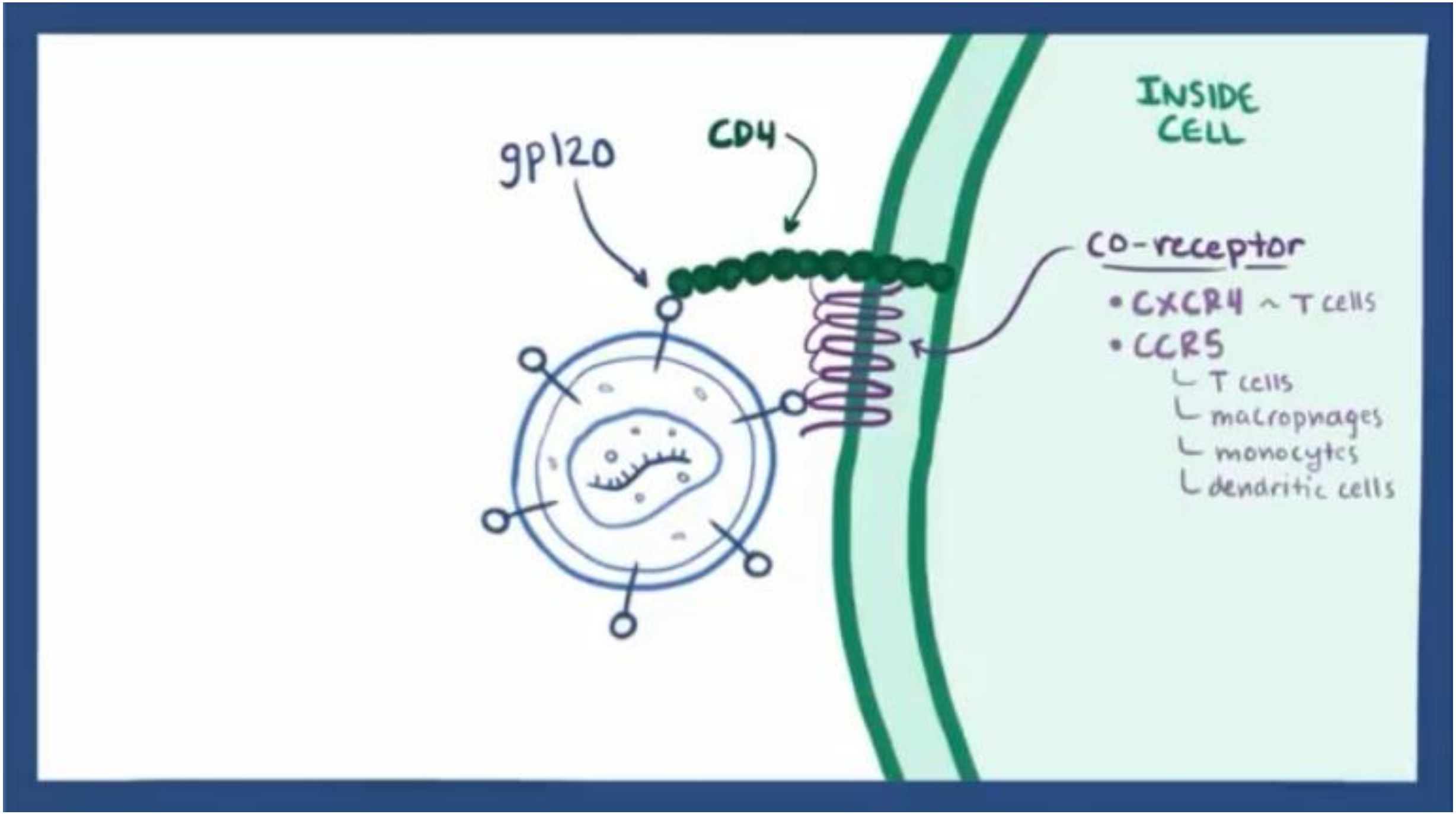
14.1 Regional HIV prevalence in 2019, incidence trend and dominant mode of transmission

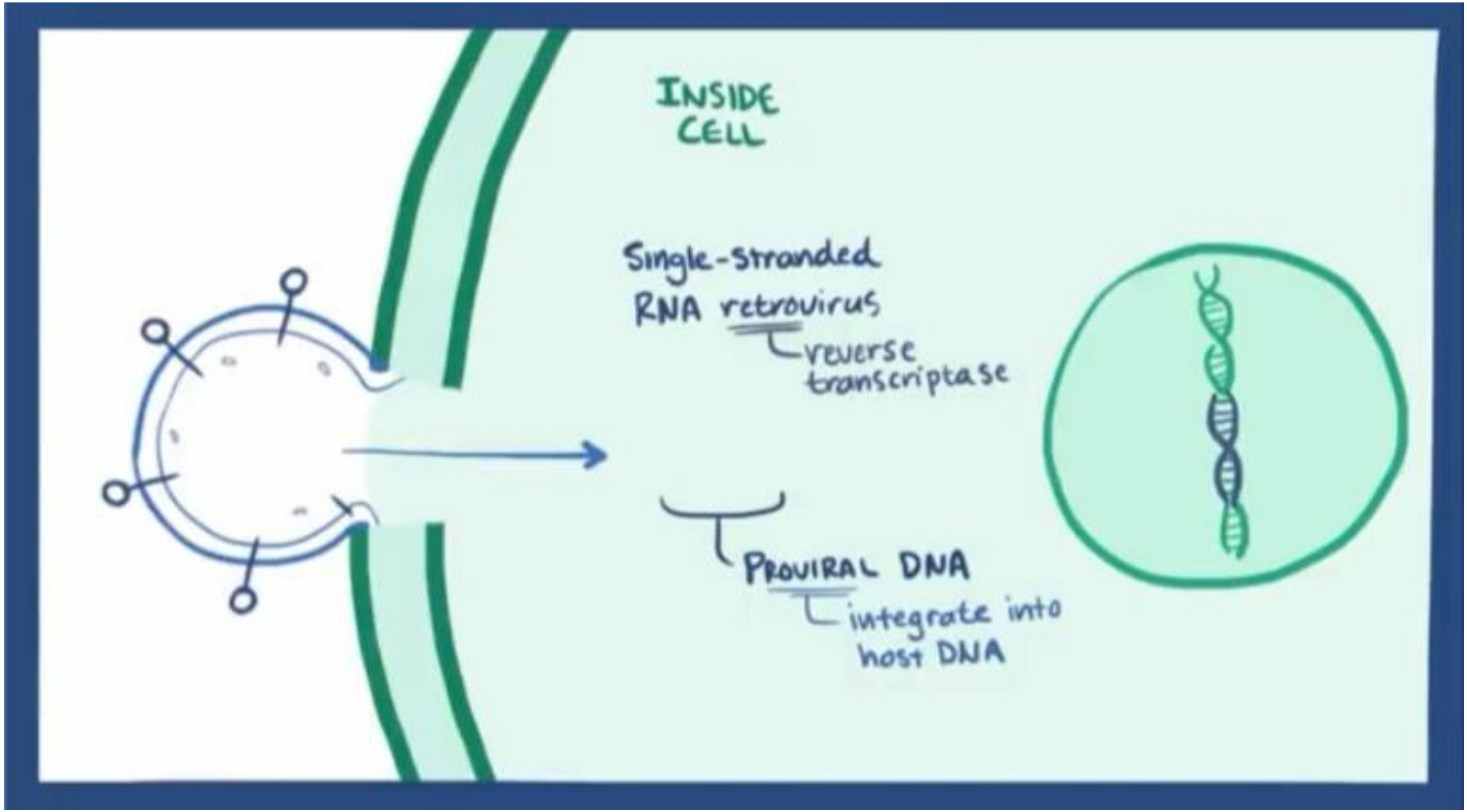
Region	People living with HIV (millions)	HIV incidence trend (2010–2019)	Dominant transmission
Sub-Saharan Africa	25.6	Decreasing	Heterosexual
Asia and Pacific	5.8	Decreasing	MSM, heterosexual
Latin America and Caribbean	2.4	Increasing	MSM, heterosexual
Western and Central Europe, and North America	2.2	Stable	MSM, IDU
Eastern Europe and Central Asia	1.7	Increasing	IDU, MSM
Middle East and North Africa	0.24	Increasing	IDU, MSM

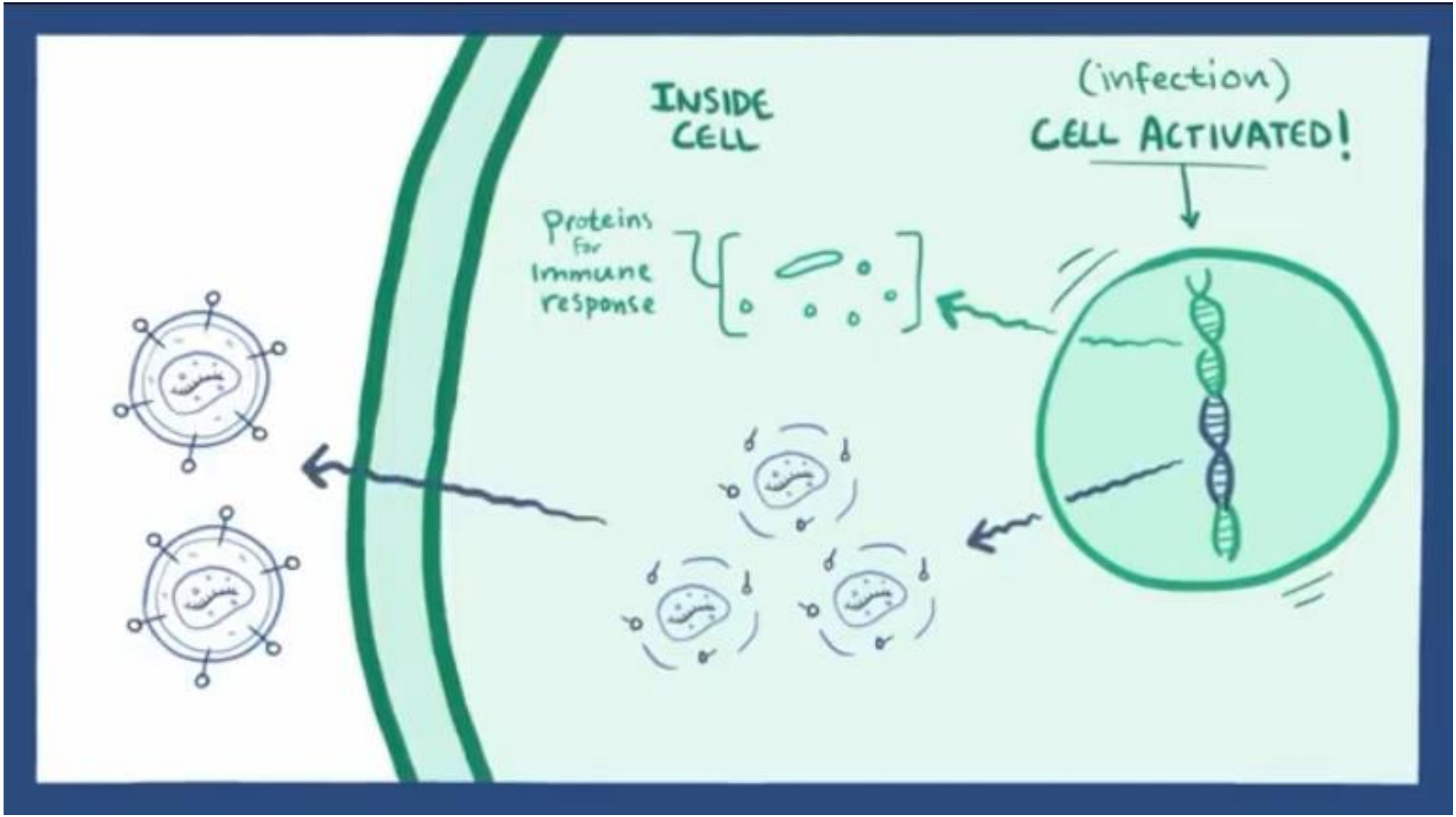
(IDU = injection drug-users; MSM = men who have sex with men)

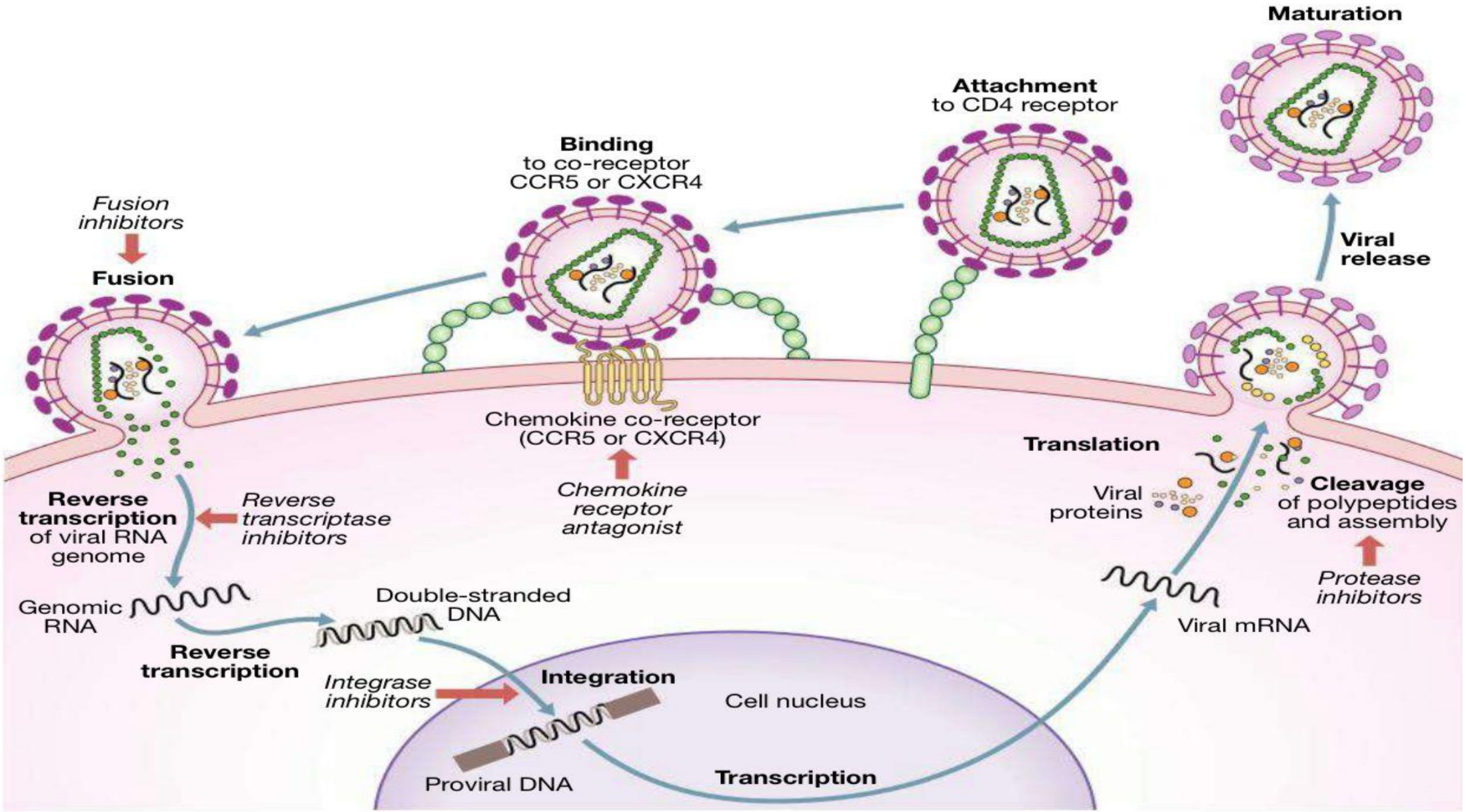
Transmission

NOTE:-HIV can transmit through saliva only if there is mucosal breakage


gp120
CD4
INSIDE CELL
co-receptor
• CXCR4 ~ T cells
• CCR5
└ T cells
└ macrophages
└ monocytes
└ dendritic cells


INSIDE CELL
Single-stranded RNA retrovirus
reverse transcriptase
PROVIRAL DNA
integrate into host DNA


INSIDE CELL
(infection)
CELL ACTIVATED!
Proteins for immune response



Life cycle of HIV. Red arrows indicate sites of action of antiretroviral drugs.

Clinical Manifestations of HIV

- ***Primary HIV infection : (Flu-Like)***

Primary infection is symptomatic in more than 50% of cases
(Diagnosis is often missed – Comes with general symptoms)

Incubation period – Usually from 2-4 weeks after exposure.

Duration – Up to 2 weeks

The level of HIV in blood very high – High risk of TRANSMISSION.

Clinical manifestation resemble those of Mononucleosis But the presence of Maculopapular rash or Mucosal Ulceration strongly suggest Primary HIV Infection !

In infectious mononucleosis, Rash generally occurs only if we give aminopenicillins !

14.7 Clinical features of primary infection

- Fever
- Maculopapular rash
- Pharyngitis
- Lymphadenopathy
- Myalgia/arthralgia
- Diarrhoea
- Headache
- Oral and genital ulceration
- Meningo-encephalitis
- Bell's palsy

In Labs – Transient Lymphopenia (Mainly CD4 Lymphocytes) which may result in OPPOTUNISTIC INFECTIONS, Also Thrombocytopenia and moderate elevation of liver enzymes are common.

- ***Asymptomatic Infection : (Feeling Fine)***

Prolonged period of Clinical Latency follows primary infection – ASYMPTOMATIC !

Seropositive, BUT Asymptomatic.

Longest Stage – 4 to 8 years duration

Usually patient present with Generalized Lymphadenopathy with nodes typically < 2 cm diameter.

Destruction of nodes architecture as disease advances, So Lymph nodes regress.

Why Asymptomatic ? Viremia peaks during primary infection and then DROPS as the immune response develops, to reach PLATEAU about 3 months later.

** The levels of viremia is a predictor of the rate of decline in CD4 counts – Highly variable (Explained by genetic factors)*

- ***Minor HIV-associated Disorders : (Falling Count)***

Impairment of Cellular Immunity, Symptomatic and Opportunistic infections incidence increase at this stage.

At this stage, CD4 count > 200 cells/mm !

Occurs in most patients before they develop AIDS.

Lasts about 1 to 3 years duration.

Careful examination should be done as ORAL CANDIDIASIS and ORAL HAIRY LEUCOPLAKIA are common conditions that requires initiating prophylaxis against opportunistic infection ! Irrespective to the CD4 count.

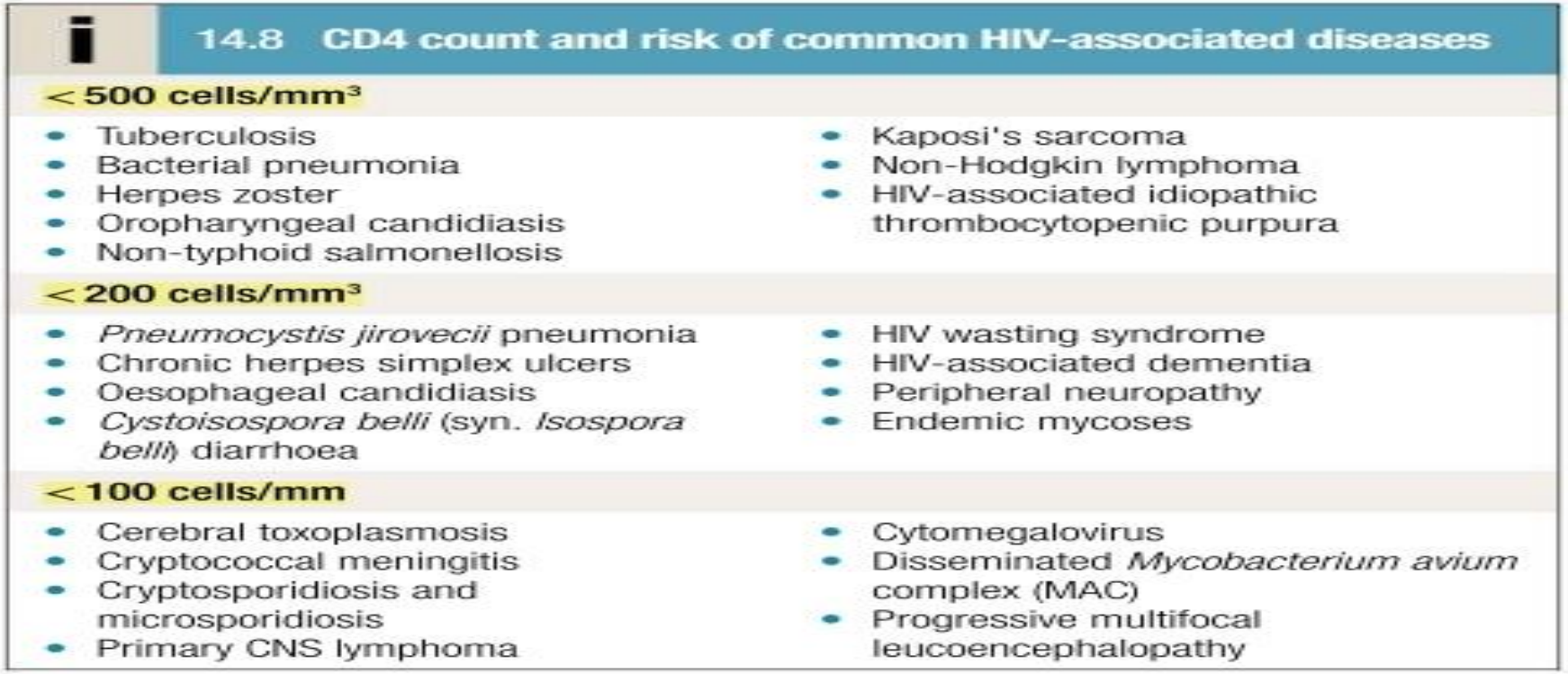
- ***Acquired Immunodeficiency Syndrome : (Final Crisis)***

Development of specified opportunistic infections, Cancers and sever manifestation of HIV itself.

Patient with CD4 count < 200 cell/mm are considered to have AIDs !

Examples :

Candidiasis of oesophagus, trachea and bronchi
TB (extra-pulmonary)
Pneumocystis pneumonia
Toxoplasmosis
HIV Encephalopathy, HIV Wasting Syndrome
CMV disease, Herpes simplex chronic (> 1 month)



14.8 CD4 count and risk of common HIV-associated diseases

< 500 cells/mm³

- Tuberculosis
- Bacterial pneumonia
- Herpes zoster
- Oropharyngeal candidiasis
- Non-typhoid salmonellosis
- Kaposi's sarcoma
- Non-Hodgkin lymphoma
- HIV-associated idiopathic thrombocytopenic purpura

< 200 cells/mm³

- *Pneumocystis jirovecii* pneumonia
- Chronic herpes simplex ulcers
- Oesophageal candidiasis
- *Cystoisospora belli* (syn. *Isospora belli*) diarrhoea
- HIV wasting syndrome
- HIV-associated dementia
- Peripheral neuropathy
- Endemic mycoses

< 100 cells/mm

- Cerebral toxoplasmosis
- Cryptococcal meningitis
- Cryptosporidiosis and microsporidiosis
- Primary CNS lymphoma
- Cytomegalovirus
- Disseminated *Mycobacterium avium* complex (MAC)
- Progressive multifocal leucoencephalopathy

AIDs associated malignancies :

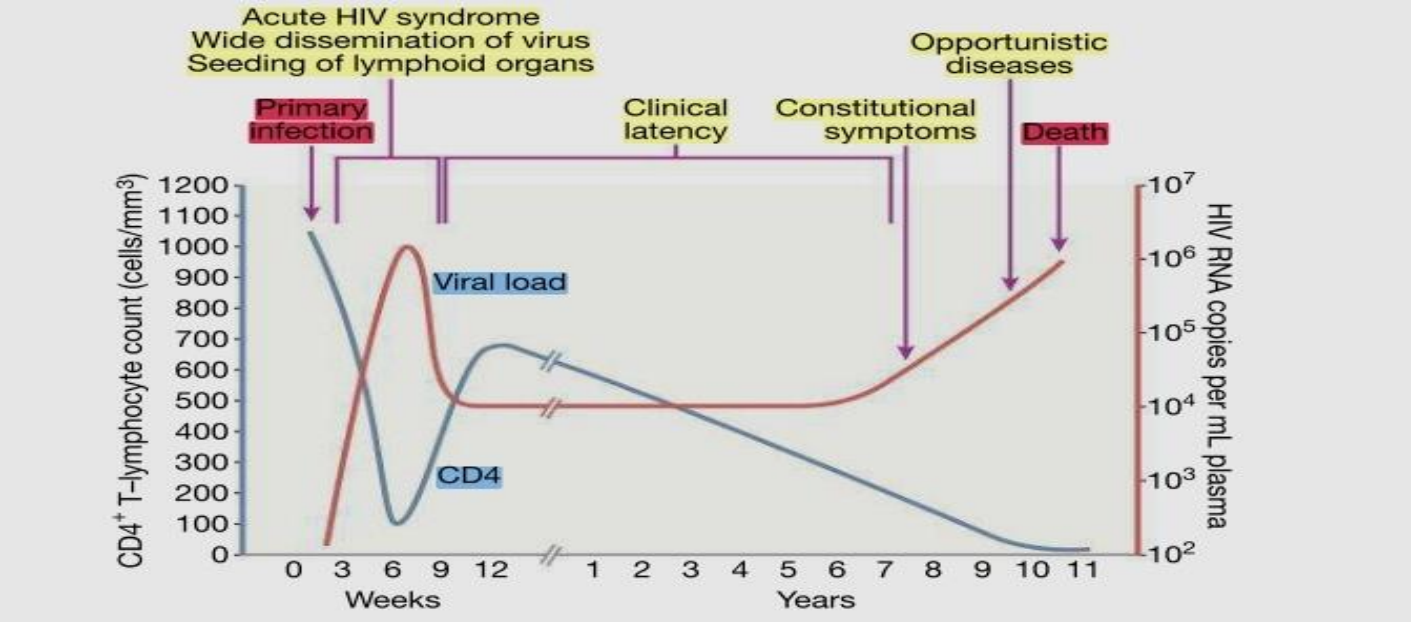
***Kaposi sarcoma* – HHV8**

***Cervical carcinoma* – Human papillomavirus**

***Non-Hodgkin lymphoma* – EPV**

***Primary CNS lymphoma* EPV**

* *CD4 count – Indicates the degree of immunosuppression and help determine the prognosis ! (Measured by flow cytometry)*
* *Viremia – May predict the rate of disease progression and provide indication of treatment ! (Measured by quantitative PCR of HIV RNA)*



- ***HIV Staging Classification : (2 Classifications, WHO and CDC)***

i HIV clinical staging classifications

World Health Organization (WHO) clinical stage (used in low- and middle-income countries)	Centers for Disease Control (CDC) clinical categories (used in high-income countries)
Stage 1 Asymptomatic Persistent generalised lymphadenopathy	**Category A** Primary HIV infection Asymptomatic Persistent generalised lymphadenopathy
Stage 2 Unexplained moderate weight loss (< 10% of body weight) Recurrent upper respiratory tract infections Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections	**Category B** Bacillary angiomatosis Candidiasis, oropharyngeal (thrush) Candidiasis, vulvovaginal; persistent, frequent or poorly responsive to therapy Cervical dysplasia (moderate or severe)/cervical carcinoma in situ Constitutional symptoms, such as fever (38.5°C) or diarrhoea lasting > 1 month Oral hairy leucoplakia Herpes zoster, involving two distinct episodes or more than one dermatome Idiopathic thrombocytopenic purpura Listeriosis Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess Peripheral neuropathy
Stage 3 Unexplained severe weight loss (> 10% of body weight) Unexplained chronic diarrhoea for > 1 month Unexplained persistent fever (> 37.5°C for > 1 month) Persistent oral candidiasis Oral hairy leucoplakia Pulmonary tuberculosis Severe bacterial infections Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 80 g/L), neutropenia (< 0.5 × 10^9/L) and/or chronic thrombocytopenia (< 50 × 10^9/L)	
Stage 4 Candidiasis of oesophagus, trachea, bronchi or lungs Cervical carcinoma – invasive Cryptococcosis – extrapulmonary Cryptosporidiosis, chronic (> 1 month) Cytomegalovirus disease (outside liver, spleen and nodes) Herpes simplex chronic (> 1 month) ulcers or visceral HIV encephalopathy HIV wasting syndrome Cystoisosporiasis (formerly known as isosporiasis), chronic (> 1 month) Kaposi's sarcoma Lymphoma (cerebral or B-cell non-Hodgkin) Mycobacterial infection, non-tuberculous, extrapulmonary or disseminated Mycosis – disseminated endemic (e.g. coccidioidomycosis, talaromycosis (formerly penicilliosis), histoplasmosis) *Pneumocystis* pneumonia Pneumonia, recurrent bacterial Progressive multifocal leukoencephalopathy Toxoplasmosis – cerebral Tuberculosis – extrapulmonary (CDC includes pulmonary) Sepsis, recurrent (including non-typhoidal *Salmonella*) (CDC only includes *Salmonella*) Symptomatic HIV-associated nephropathy* Symptomatic HIV-associated cardiomyopathy* Leishmaniasis, atypical disseminated*	**Category C**

*These conditions are in WHO stage 4 but not in CDC category C.

DIAGNOSIS

PCR

- PCR RNA test the viral load in the blood . This test is used before antibody is formed .
- Can be performed in days after the exposure .
- The used type in testing donated blood .
- Usually patients with acute HIV have very high viremia

P24 test

- Test for protein 24 , the major HIV protein .
- Done after 2-3 weeks of the infection until p 24 is produce , but need to be before the antibody is formed as well .
- Less costly .
- Less sensitive .

Seroconversion

- HIV Antibody test .
- Done after 3 - 7 weeks of exposure .

- Because of the interval between contracting HIV and the start of seroconversion, a negative test result does not necessarily mean that a person does not have the virus , false positive .

ELISA

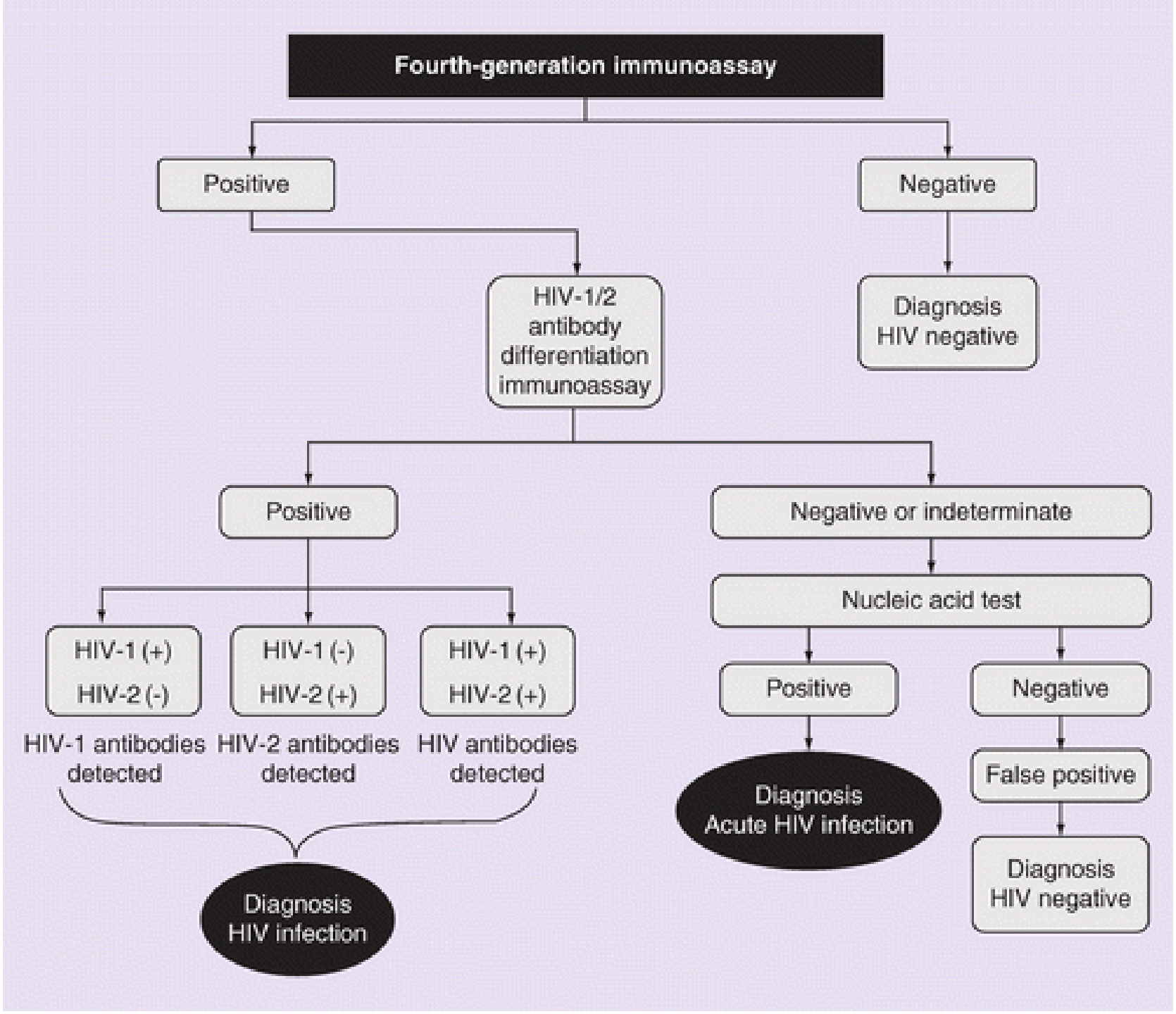
- An antigen/antibody lab test .
- can usually detect HIV 1 - 12 weeks after exposure.
- High sensitivity and high specificity . (negative ELISA exclude HIV)

DIAGNOSIS OF AIDS :

- CD4 TCells count is below 200 .
- CD4 Tcells percentage to the total lymphocytes is below 14 % .
- AIDS defining illness :

AIDS-defining illnesses

- Candidiasis of the esophagus, bronchi, trachea, or lungs [(but NOT the mouth (thrush)]
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than one month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcer(s) (more than 1 month in duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (more than 1 month in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jiroveci pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV


Fourth-generation immunoassay
Positive
Negative
HIV-1/2 antibody differentiation immunoassay
Diagnosis HIV negative
Positive
Negative or indeterminate
HIV-1 (+) HIV-2 (-)
HIV-1 (-) HIV-2 (+)
HIV-1 (+) HIV-2 (+)
Nucleic acid test
Positive
Negative
HIV-1 antibodies detected
HIV-2 antibodies detected
HIV antibodies detected
Diagnosis Acute HIV infection
False positive
Diagnosis HIV infection
Diagnosis HIV negative

Treatment

Immunization

- Vaccination with live organisms is contraindicated in patients with severe immune suppression .
- CD4 count should be considered .
- All patients should be given a conjugate pneumococcal vaccine and annual influenza vaccination.
- Hepatitis B vaccination should be given to those who are not immune.
- Additional vaccines may be recommended.

Antiretroviral therapy

- ART has transformed HIV from a progressive illness with a fatal outcome into a chronic manageable disease with a near-normal life expectancy.
- The goals of ART are to:

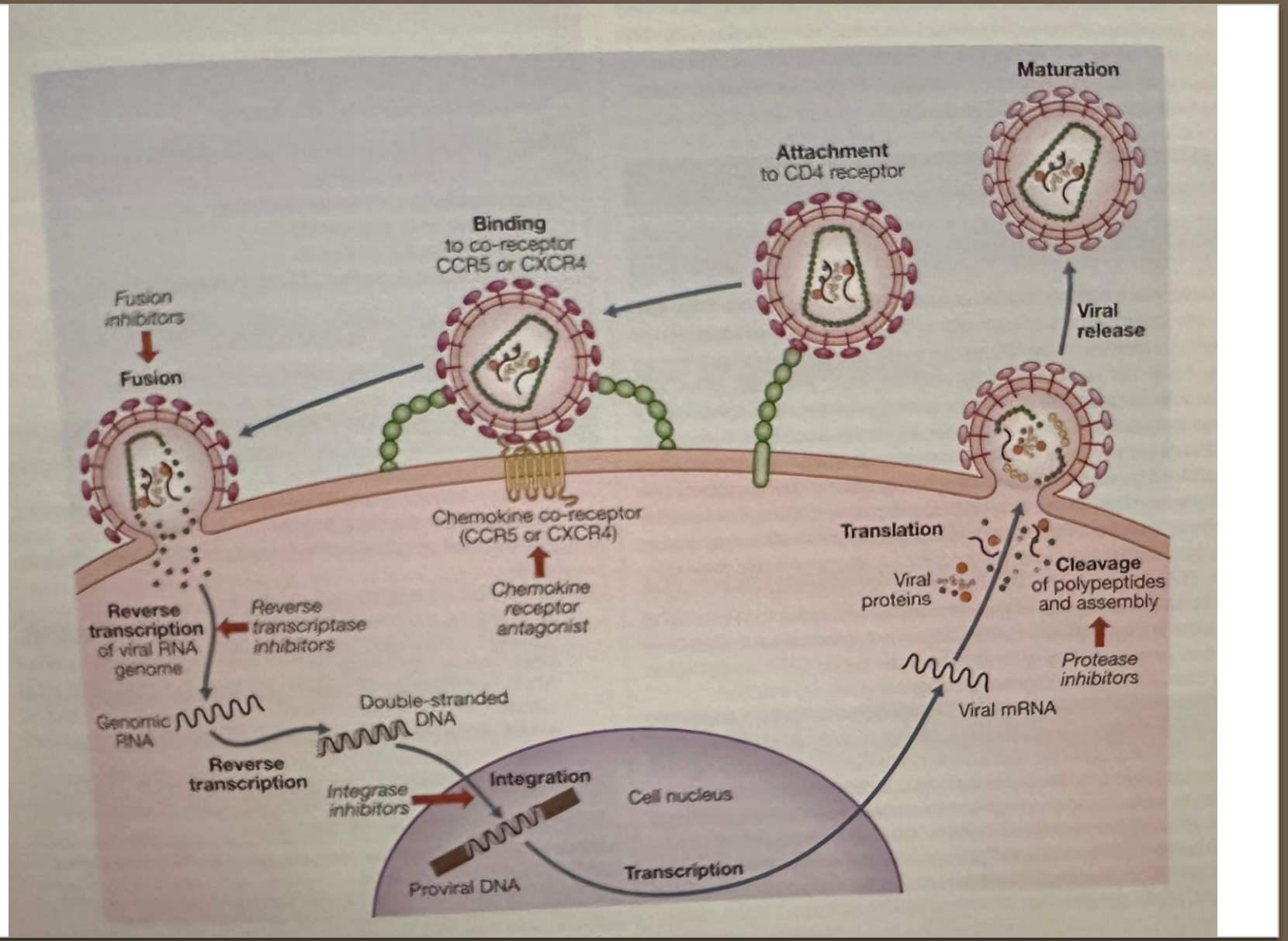
1. Reduce the viral load to an undetectable level for as long as possible.
2. Improve the CD4 count to over 200cells/mm^3.
3. Improve the quantity and quality of life without unacceptable drug toxicity.
4. Reduce HIV transmission.

14.16 Currently preferred antiretroviral drugs

Classes	Drugs
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir, emtricitabine, lamivudine, tenofovir
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz*, rilpivirine (only if viral load < 100 000)
Protease inhibitors (PIs)	Atazanavir*, darunavir, lopinavir*
Integrase inhibitors	Dolutegravir, bictegravir

*These drugs are no longer recommended as first-line options due to their toxicity.

The standard combination ART regimens are two NRTIs together with an NNRTIs, protease inhibitor (PI) or integrase inhibitor.


Maturation
Attachment
to CD4 receptor
Binding
to co-receptor
CCR5 or CXCR4
Fusion
inhibitors
Fusion
Viral
release
Chemokine co-receptor
(CCR5 or CXCR4)
Chemokine
receptor
antagonist
Translation
Viral
proteins
Cleavage
of polypeptides
and assembly
Protease
inhibitors
Reverse
transcription
of viral RNA
genome
Reverse
transcriptase
inhibitors
Genomic
RNA
Double-stranded
DNA
Reverse
transcription
Integrase
inhibitors
Integration
Cell nucleus
Viral mRNA
Proviral DNA
Transcription

- Start ART in all people with confirmed HIV infection, irrespective of CD4 count or clinical status.
- Early initiation of ART, compared with the previous strategy of deferring ART until CD4 threshold or clinical disease occurs, has been shown to reduce morbidity and mortality.

Indications for Initiation of Antiretroviral Therapy for HIV

Clinical Category	CD4 count	Viral Load	Recommendation
Symptomatic (AIDS, severe Sx)	Any value	Any value	Treat
Asymptomatic, AIDS	< 200/mm^3	Any value	Treat
Asymptomatic	> 200/mm^3 but < 350	Any value	Treatment should generally be offered
Asymptomatic	> 350/mm^3	>30,000 bDNA or >55,000 PCR	Some experts would recommend initiating treatment
Asymptomatic	> 350/mm^3	<30,000 bDNA or <55,000 PCR	Many experts would defer therapy and observe

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, February 5, 2001, Table 6.

CBB/2002

ART in pregnancy

- All pregnant women should have HIV testing at an early stage in pregnancy.
- All pregnant women who are ART-naïve should start ART as soon as possible.
- Caesarean section is associated with lower risk of mother-to-child transmission than vaginal delivery, but the mode of delivery doesn’t affect transmission risk if the viral load is suppressed be ART.
- HIV is also transmitted by breastfeeding

Prevention

Pre-exposure prophylaxis	Post-exposure prophylaxis
Daily tenofovir plus emtricitabine has been shown to reduce the risk of HIV acquisition in people who are at ongoing high risk and it's well tolerated.	• The first dose should be given as soon as possible. Tenofovir together with emtricitabine is the most widely used dual NRTI combination together with either a PI or integrase inhibitor depending on ART exposure in the source patient. • HIV antibody testing should be performed 3 months after exposure.

THANK YOU !