HIV infection

HIV

Human **I**mmunodeficiency **V**irus

How HIV Affects Immune System

- HIV attaches to cells of the immune system through special surface markers called CD4 receptors
- The following immune cells have CD4 receptors
  - T-Lymphocytes – CD4+ Cells
  - Macrophages
  - Monocytes
  - Dendritic cells

Effect of HIV on the Immune System

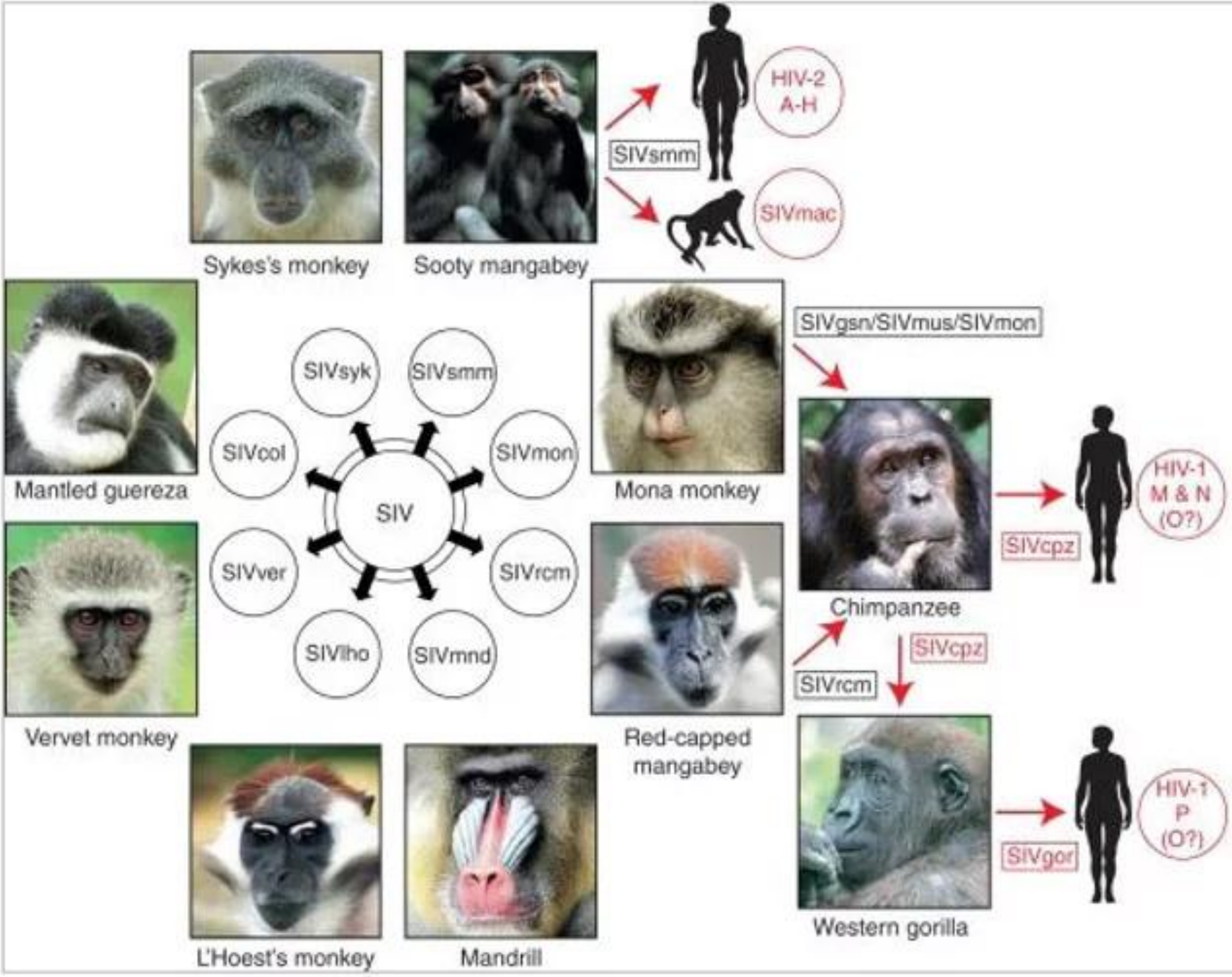
- The hallmark of HIV/AIDS is a profound immunodeficiency as a result depletion of CD4+ T lymphocytes.

- The CD4+ T cell depletion is two fold
  - Reduction in numbers
  - Impairment in function

- Individuals with HIV infection are susceptible to many infections especially at later stages of HIV infection

Comparison of HIV species

Species	Virulence	Infectivity	Prevalence	Inferred origin
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Africa	Sooty Mangabey


Sykes's monkey
Sooty mangabey
SIVsmm
HIV-2
A-H
SIVmac
Mantled guereza
SIVsyk
SIVsmm
SIVcol
SIVmon
SIV
SIVver
SIVrcm
SIVlho
SIVmnd
Mona monkey
SIVgsn/SIVmus/SIVmon
Chimpanzee
SIVcpz
HIV-1
M & N
(O?)
Vervet monkey
Red-capped
mangabey
SIVrcm
SIVcpz
Western gorilla
SIVgor
HIV-1
P
(O?)
L'Hoest's monkey
Mandrill

Summary of the global HIV epidemic (2018)

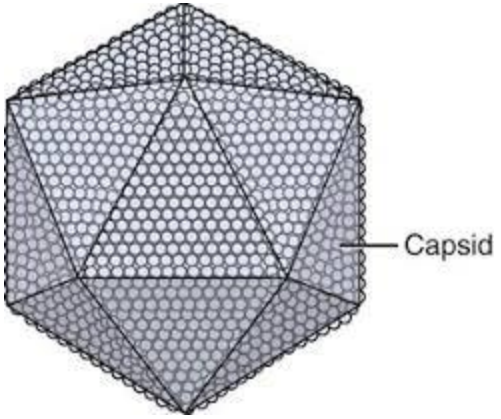
	People living with HIV in 2018	People newly infected with HIV in 2018	HIV-related deaths 2018
Total	37.9 million [32.7 million – 44.0 million]	1.7 million [1.4 million – 2.3 million]	770 000 [570 000 – 1.1 million]
Adults	36.2 million [31.3 million – 42.0 million]	1.6 million [1.2 million – 2.1 million]	670 000 [500 000 – 920 000]
Women	18.8 million [16.4 million – 21.7 million]	–	–
Men	17.4 million [14.8 million – 20.5 million]	–	–
Children (<15 years)	1.7 million [1.3 million – 2.2 million]	160 000 [110 000 – 260 000]	100 000 [64 000 – 160 000]

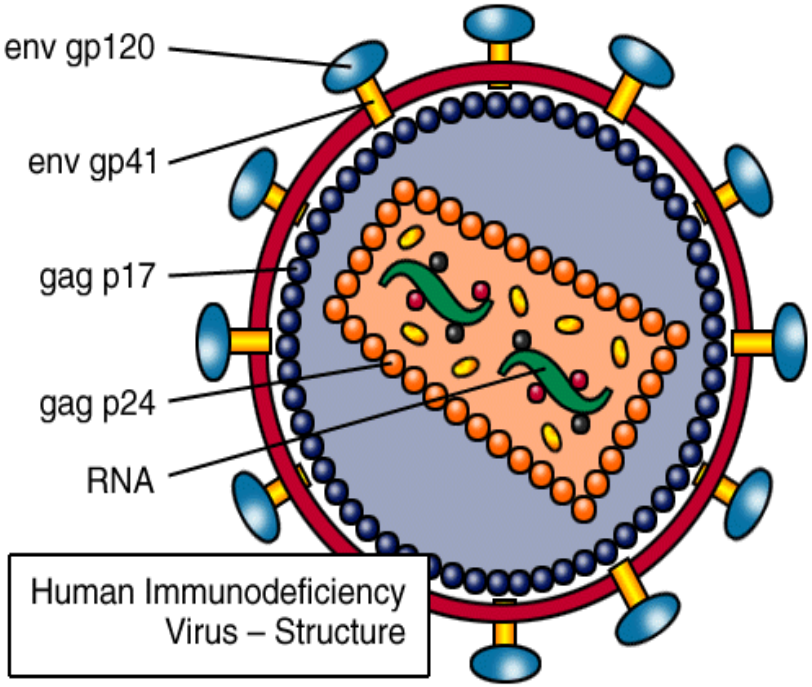
Source: UNAIDS/WHO estimates

World Health Organization

HIV

- RNA virus,
- Envelope gp120 & gp41
- Icosahedral symmetry
- Nucleocapsid
  - Outer matrix protein (p17)
  - Major capsid protein (p24)
  - Nuclear protein (p7)
- Diploid RNA with several copies of reverse transcriptase





HIV life cycle

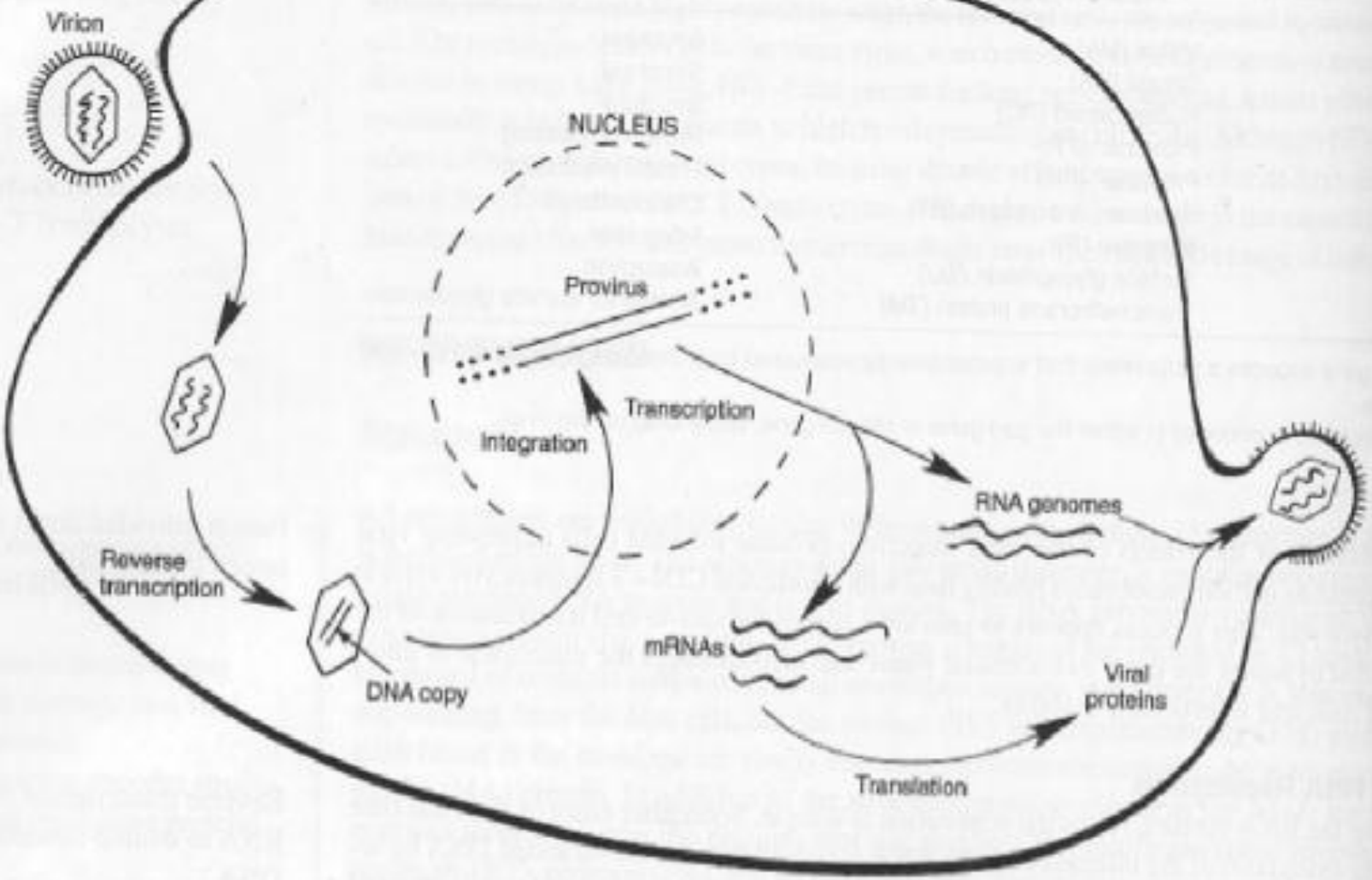
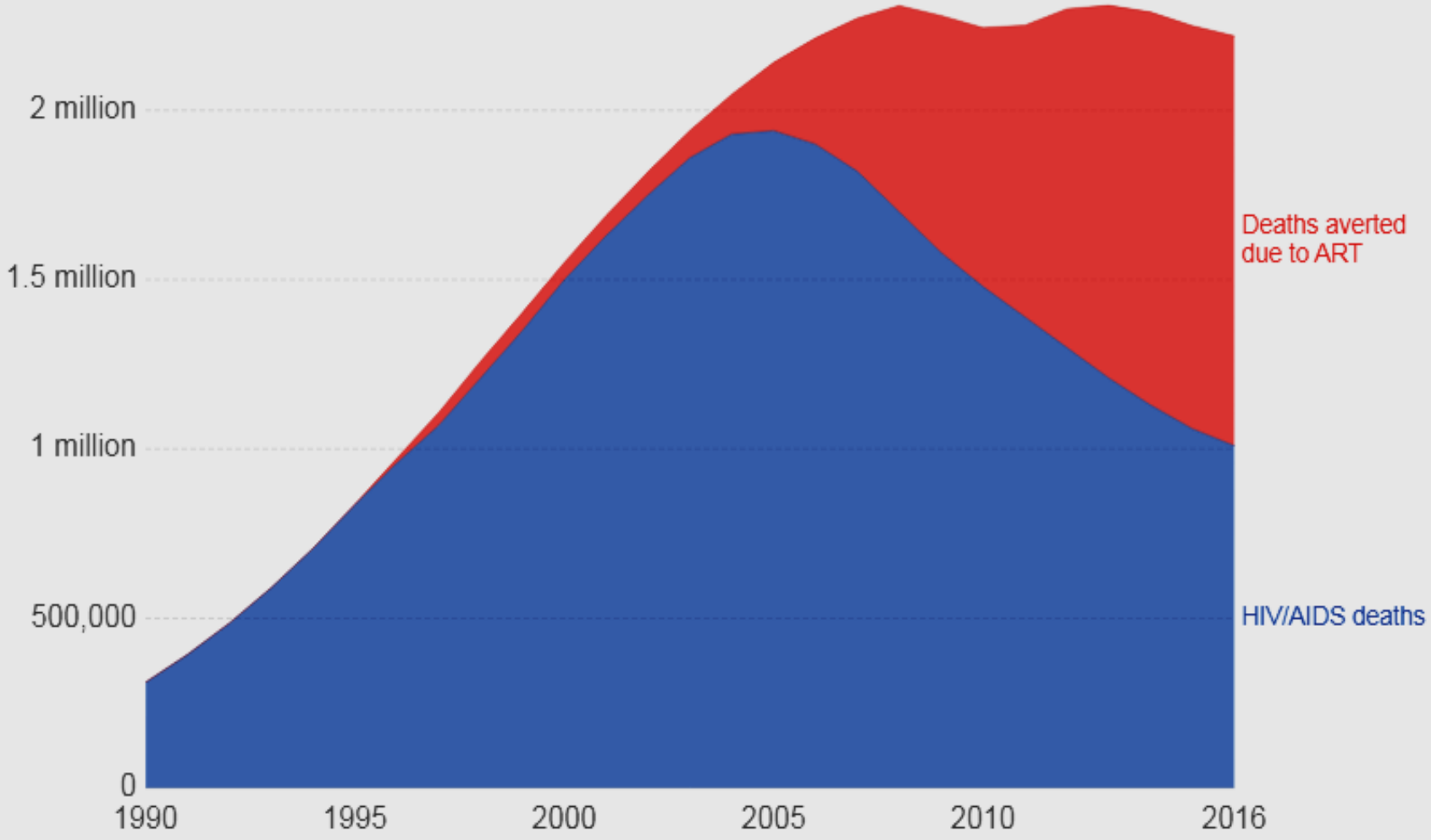


Figure 41–2. Retroviral life cycle.

HIV/AIDS deaths and deaths averted due to antiretroviral therapy (ART), World

Our World in Data

Annual number of deaths from HIV/AIDS and the estimated number which have been averted as a result of antiretroviral therapy (ART).

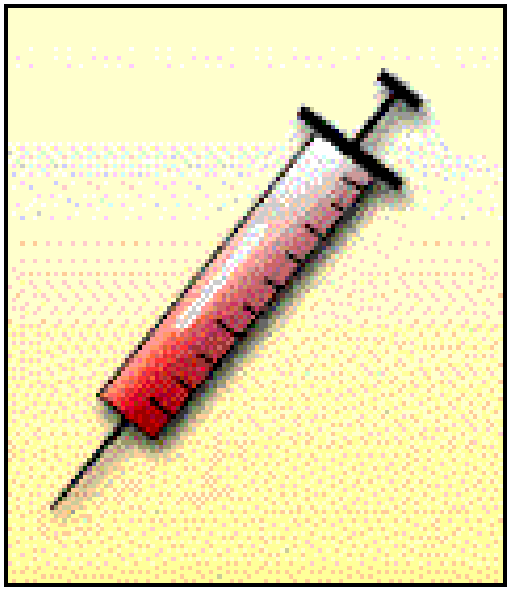


Source: UNAIDS
OurWorldInData.org/hiv-aids • CC BY

Unprotected sexual intercourse with an infected partner

Vertical transmission
(from mother to child)

- **in utero**
- **during delivery**
- **breastmilk**



Injection drug use
(rare: infected blood/blood products)

HIV INFECTION

HIV is not transmitted by

- **Coughing, sneezing**
- **Water, food.**
- **Public baths**
- **Handshakes.**
- **Work or school contact**
- **Using telephones**
- **Sharing cups, glasses, plates, or other utensils**

Natural History of HIV Infection

- Virus can be transmitted during **each** stage
- **Primary HIV Infection**

- **Seroconversion**
  - Infection with HIV, antibodies develop
- **Asymptomatic**
  - No signs of HIV, immune system controls virus production
- **Symptomatic**
  - Physical signs of HIV infection, some immune suppression
- **AIDS**
  - Opportunistic infections, end-stage disease

Acquired **I**mmuno**D**eficiency **S**yndrome

A = not inherited

I = immune system

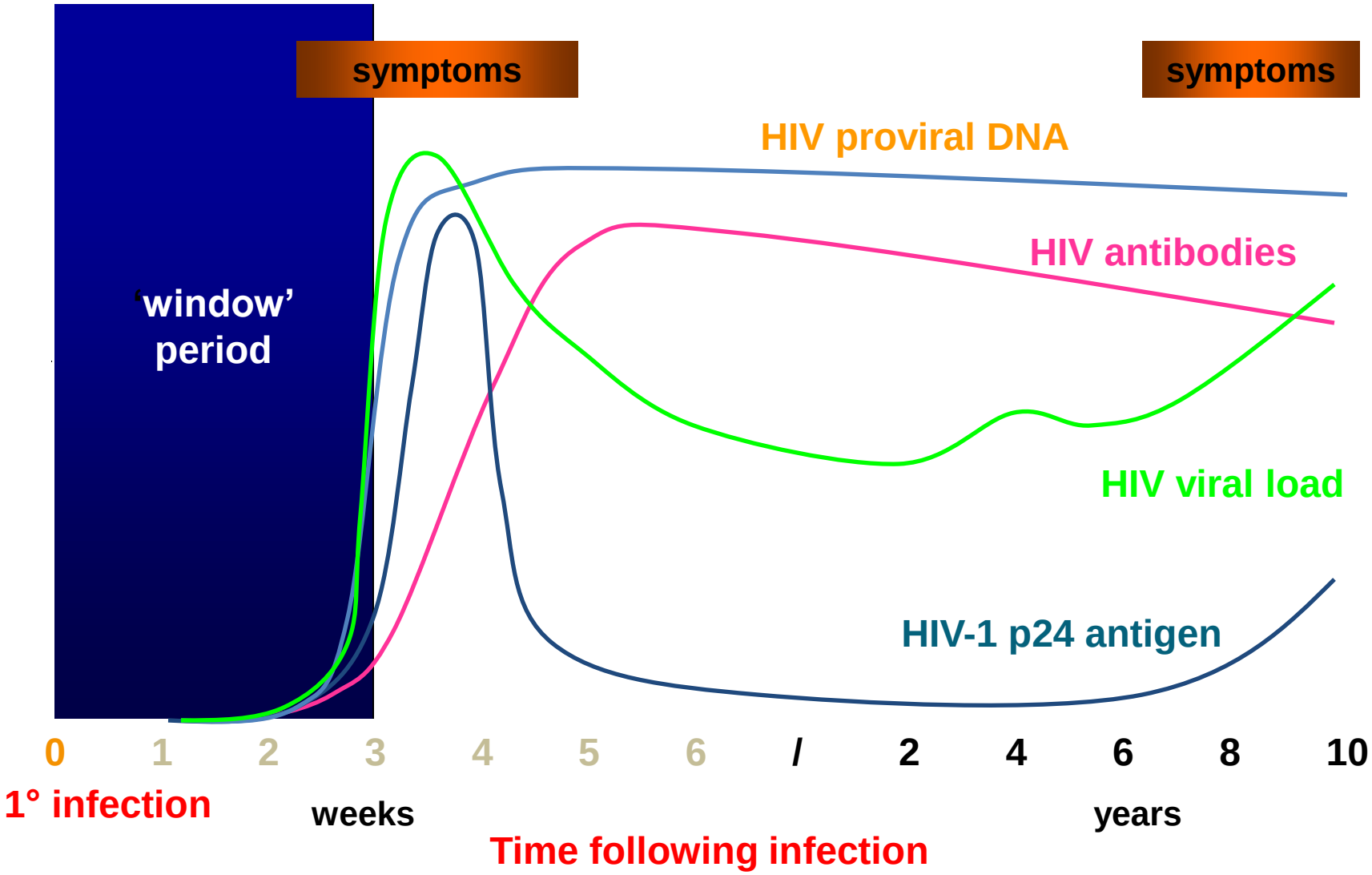
D = deficiency – inability to protect against illness

S = **s**yndrome, a group of symptoms or illnesses that occur as a result of HIV infection

Host immune response during HIV infection

- **Primary HIV Infection**
  - On exposure, there is a 2-4 week period of intense viral replication and widespread dissemination of virus characterized by
    - High plasma viral load (RNA)
    - Rapid decline in CD4 count
    - In some cases an acute illness occurs
      - Lasts from 1-2 weeks, but it is rarely diagnosed
      - Symptoms if present resemble those of other viral illnesses; requires high index of suspicion
    - Symptom resolution with reduction in plasma viremia due to development of an immune response and antibodies to the virus

‘typical’ primary HIV-1 infection

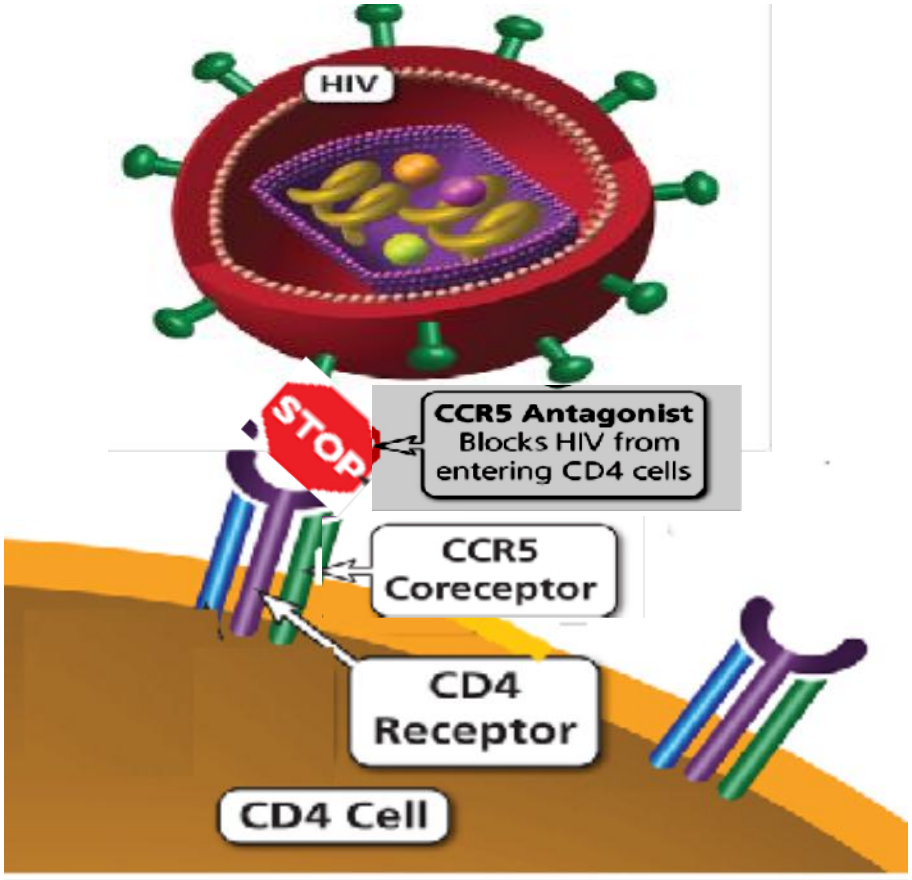


Asymptomatic Disease (Latency)

- Patients then enter a stage of asymptomatic disease phase lasting on average 2-10 years (clinical latency)

- Characterized by gradual decline in CD4 count
  - Rate depends on viral load

- Long term non-progressors
  - Rare
  - >>10-15 year survival without ART
  - CD4>500; low viral load
  - Host genetic/immunological or viral factors may be involved

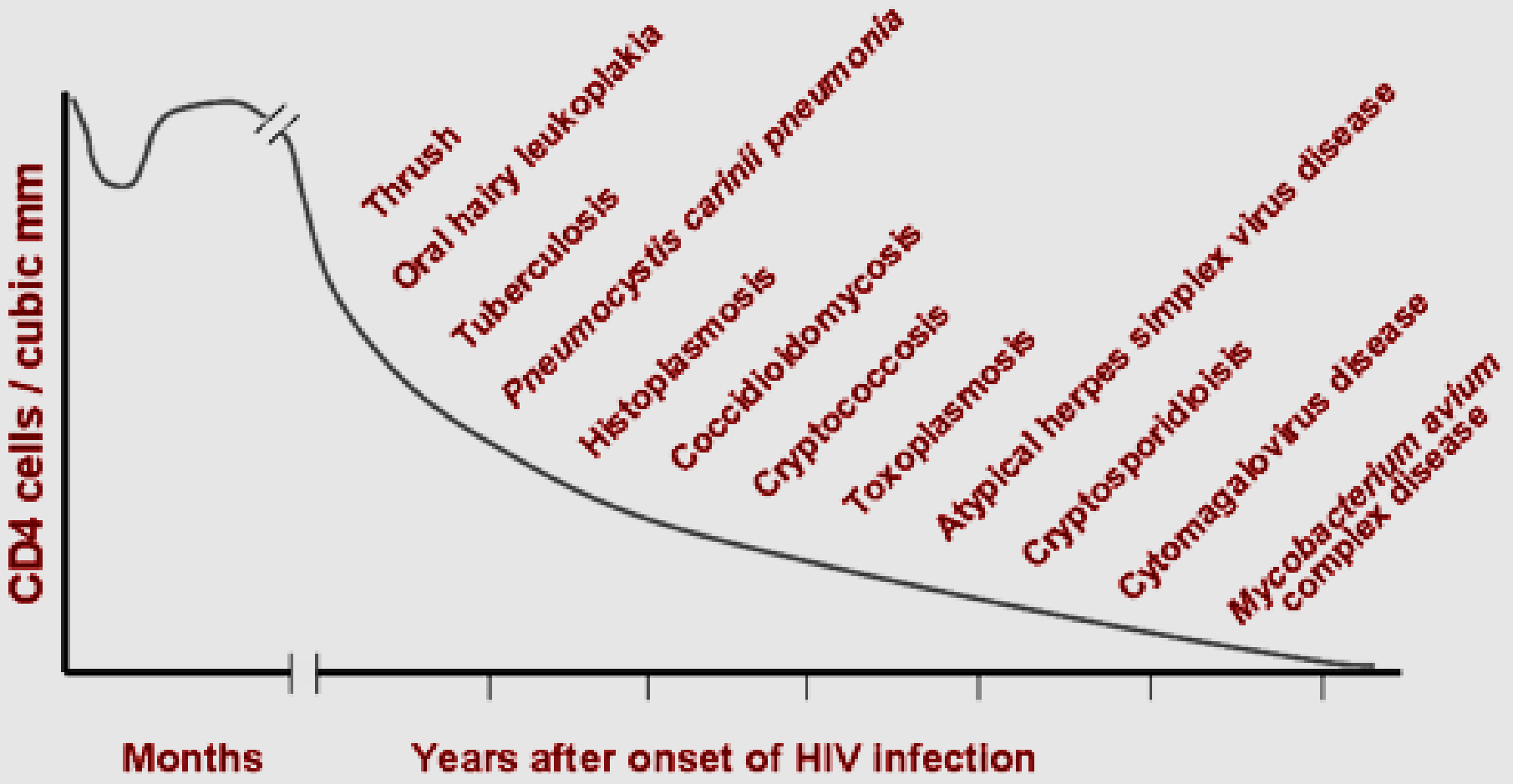


The CC chemokine receptor 5 (CCR5) is used by the human immunodeficiency virus (HIV) to infect cells. Rx Strategies target human CCR5

Symptomatic Disease and AIDS

- Viral load continues to rise causing
  - Increased demands on immune system as production of CD4 cells cannot match destruction
  - Increased susceptibility to common infections (URTI, pneumonia, skin etc)
  - Late-stage disease is characterized by a CD4 count <200cells/mm^3 and the development of opportunistic infections, selected tumors, wasting, and neurological complications).

Natural History of HIV-1 Infection



Complications of AIDS

As CD4 count declines the complications may occur

CD4 COUNT	COMPLICATION
200-500	Bacterial pneumonia, pulmonary TB .Herpes zoster ,oropharyngeal candidasis.
<200	Pneumocystis pneumonia ,extra pulmonary TB ,disseminated fungal infection ,wasting syndrome,CNS manifestations.
<100	Disseminated herpes simplex, toxoplasmosis, esophageal candidasis.
<50	Disseminated CMV , Mycobacterium avium complex(MAC),CNS lymphoma, Kaposi sarcoma.

Oral (thrush) candidiasis

Sore white patches may accompynied with dysphagia(candidal esophagitis

- **Hairy leukoplakia is a white patch on the side of the tongue with a corrugated or hairy appearance. occurs usually in persons who are immunocompromised, especially those with human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS).and EBV infection.**

Pneumocystis jiroveci pneumonia

- diffuse ground-glass opacity (GGO), which reflects the accumulation of intra-alveolar fibrin, debris, and organisms., The term ground-glass refers to parenchymal opacification, which does not obscure the underlying pulmonary architecture. This usually occurs in a bilateral, symmetrical, predominantly perihilar distribution and may be geographic or mosaic in appearance, with areas of normal lung adjacent to areas of affected lung

WHO clinical staging of HIV disease in adults (1/4)

Clinical stage 1	**Asymptomatic** **Persistent generalized lymphadenopathy**
Clinical stage 2	Moderate unexplained weight loss (under 10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) **Herpes zoster** **Angular cheilitis** **Recurrent oral ulceration** **Papular pruritic eruptions** **Seborrhoeic dermatitis** Fungal nail infections

WHO clinical staging of HIV disease in adults and adolescents (2/4)

Clinical stage 3	**Unexplained severe weight loss (over 10% of presumed or measured body weight)** **Unexplained chronic diarrhoea for longer than one month** **Unexplained persistent fever (intermittent or constant for longer than one month)** **Persistent oral candidiasis** **Oral hairy leukoplakia** **Pulmonary tuberculosis** **Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)** **Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis** **Unexplained anaemia (below 8 g/dl), neutropenia**

WHO clinical staging of HIV disease in adults and adolescents (3/4)

Clinical stage 4	HIV wasting syndrome *Pneumocystis* jiroveci pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Extrapulmonary tuberculosis Kaposi sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy

WHO clinical staging of HIV disease in adults and adolescents (4/4)

Clinical stage 4	Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacteria infection Progressive multifocal leukoencephalopathy Chronic cryptosporidiosis Chronic isosporiasis Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis) Recurrent septicaemia (including non-typhoidal *Salmonella*) Lymphoma (cerebral or B cell non-Hodgkin) Invasive cervical carcinoma Atypical disseminated leishmaniasis Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Natural History of HIV Infection

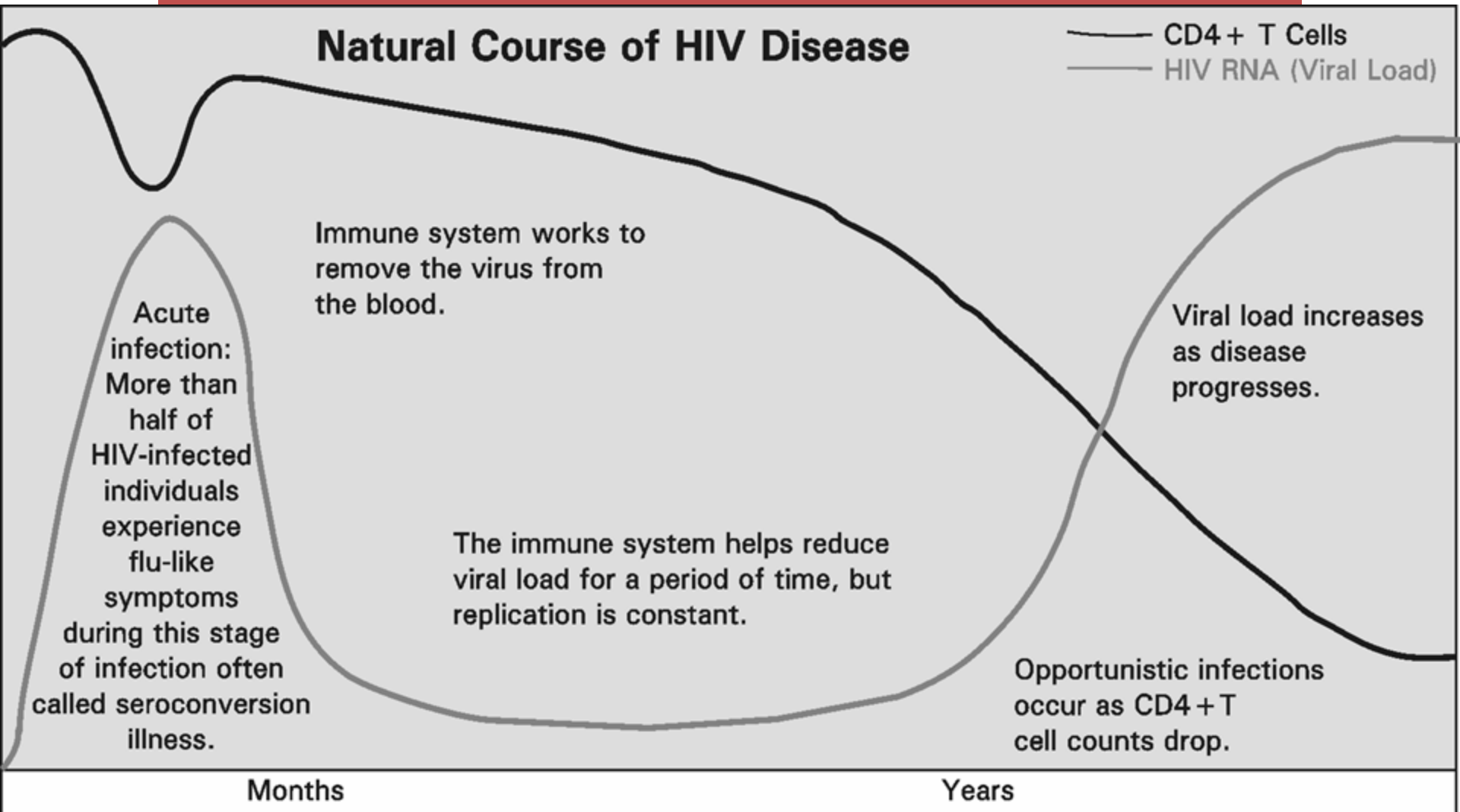


Figure1. The natural progression of HIV disease. Without intervention, viral load will continue to increase as CD4+T cell counts decline.

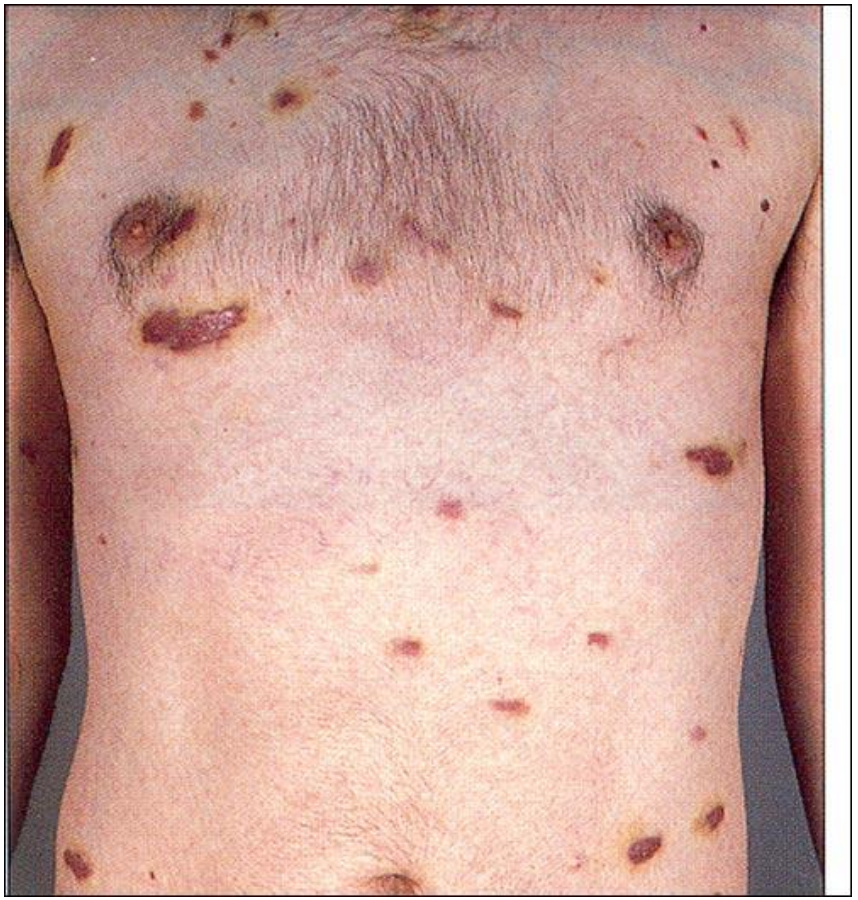
Natural History of HIV Infection

- **Immune suppression**
  - **HIV attacks CD4 cells, that protect body from illness Over time, the body's ability to fight common infections is lost**
  - **Opportunistic infections occur**

Oral Candidiasis (thrush)

Kaposi's sarcoma (KS)

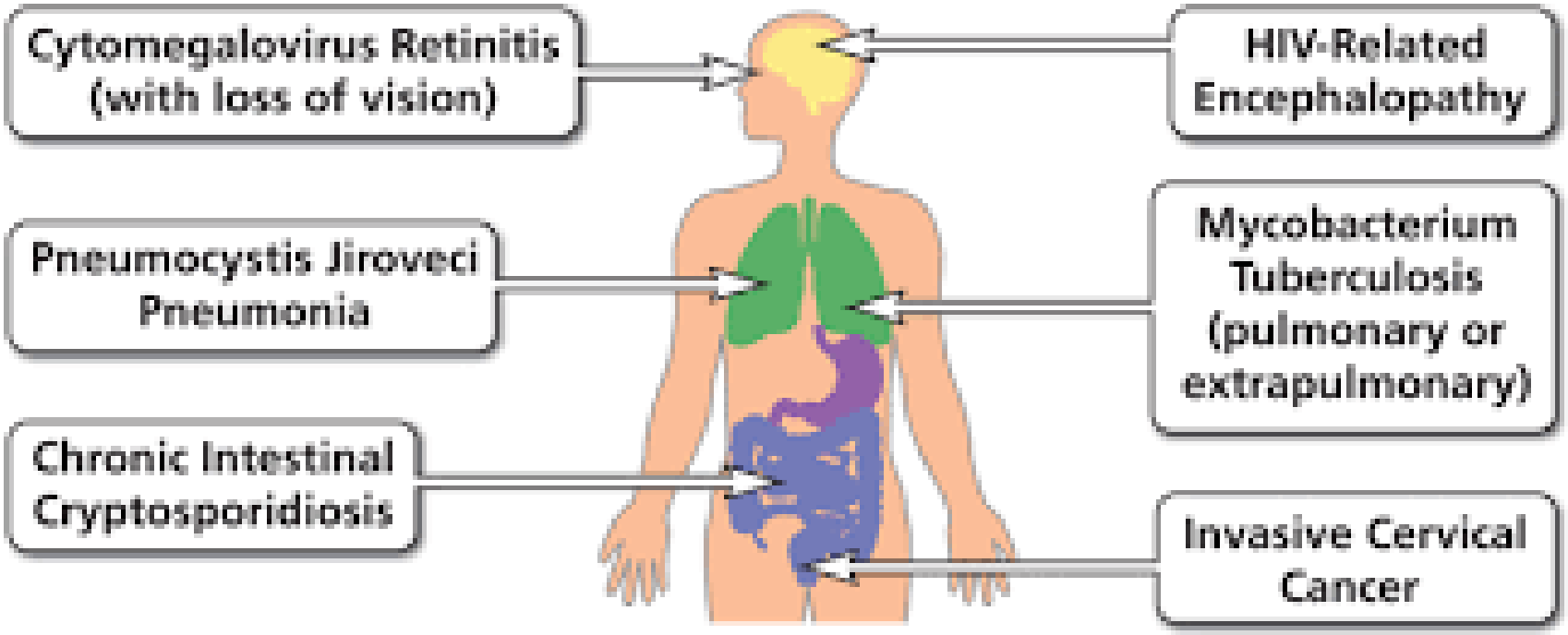
- Kaposi's sarcoma (shown) is a rare cancer of the blood vessels that is associated with HIV. It manifests as bluish-red oval-shaped patches that may eventually become thickened. Lesions may appear singly or in clusters.



AIDS surveillance case definitions

CD4 cell categories	Clinical categories		
	A- Asymptomatic, PGL or acute HIV infection	B*- Symptomatic (not A or C)	C- AIDS indicator condition (1987)
>500/mm3 (29 percent)	A1	B1	C1
200-499/mm3 (14-28 percent)	A2	B2	C2
<200/mm3 (<14 percent)	A3	B3	C3

Examples of AIDS-Defining Conditions



AIDS

- AIDS (AIDS indicator condition according to the 1987 CDC criteria and revised 1993 CDC criteria that include a CD4 cell count below 200/mm3 regardless of the presence or absence of symptoms).
- WHO clinical Stage 3/4

- Advanced HIV infection characterized by a CD4 cell count below 50/mm3.

Blood Detection Tests

HIV enzyme-linked immunosorbent assay (ELISA)	**Screening test for HIV Sensitivity > 99.9%**
Western blot	Confirmatory test Speicificity > 99.9% (when combined with ELIZA)
HIV rapid antibody test	Screening test for HIV Simple to perform
Absolute CD4 lymphocyte count	Predictor of HIV progression Risk of opportunistic infections and AIDS when <200
HIV viral load tests	Best test for diagnosis of acute HIV infection Correlates with disease progression and response to HAART(highly active antiretroviral therapy)

managment

Goals

- Improved quality of life.
- Reduction of HIV-related morbidity and mortality .
- Restoration and/or preservation of immunologic function.
- Maximal and durable suppression of viral load.
- Prevention of vertical transmission.
- Prevention of transmission to sexual partners.

Baseline evaluation

- Complete H&P
- Laboratory testing:
  - HIV antibody
  - CD4 cell count
  - Plasma HIV RNA
  - Resistance test (genotype)
  - CBC, chemistry profile, BUN, Cr, transaminase
  - Fasting glucose and lipids

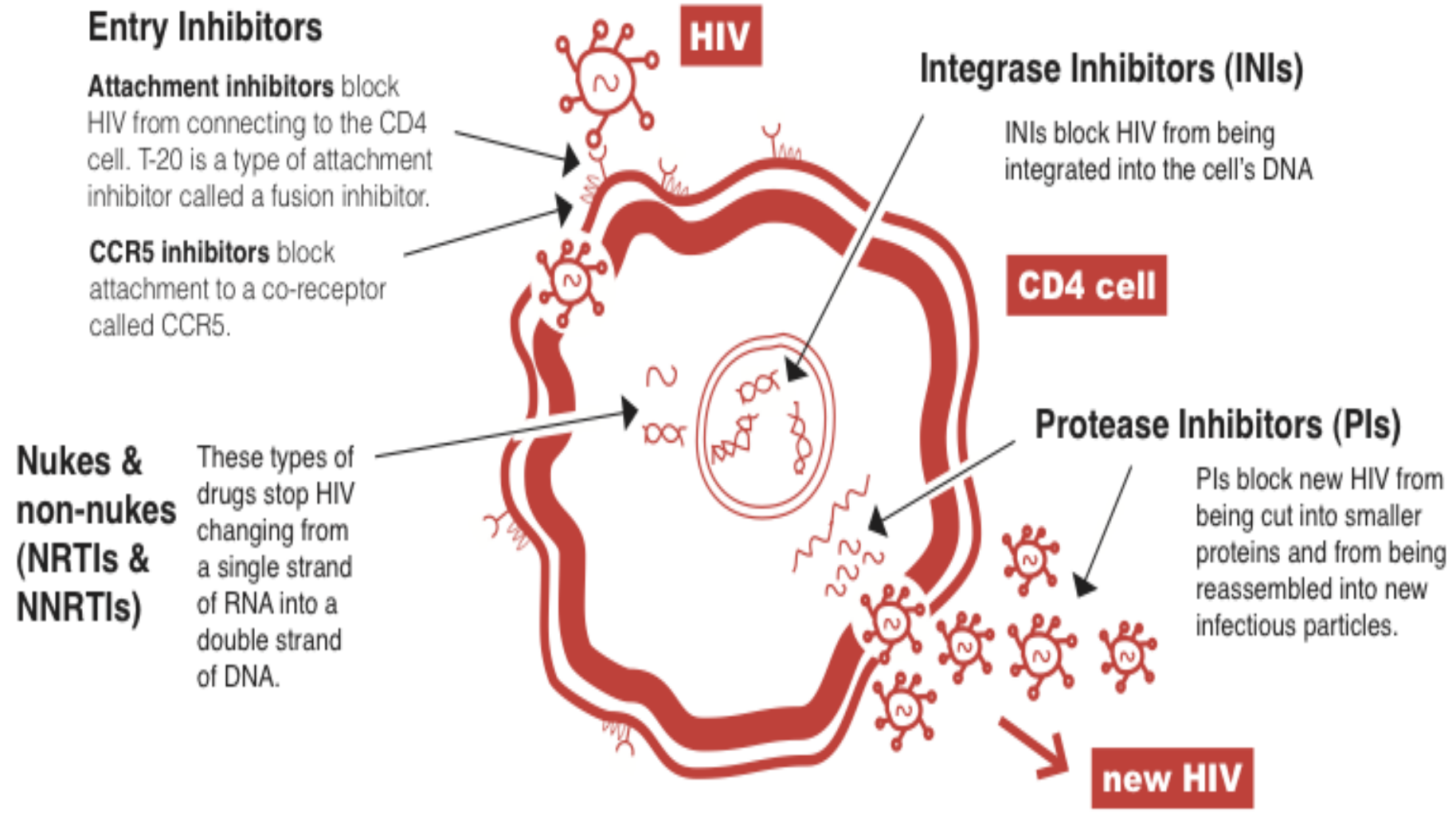
- Chest X ray . Tuberculin skin test.
- Hepatitis A, B, C serology.
- RPR or VDRLA rapid plasma reagin (RPR) test is a blood test used to screen for syphilis,
- Testing for chlamydia and gonorrhea
- Toxoplasma IgG.
- Gynecologic exam with Pap smear
- Ophthalmology exam (CD4 cell count <100 cells/μL)

When to Start ART

Current recommendation:

ART for all patients regardless of CD4 counts

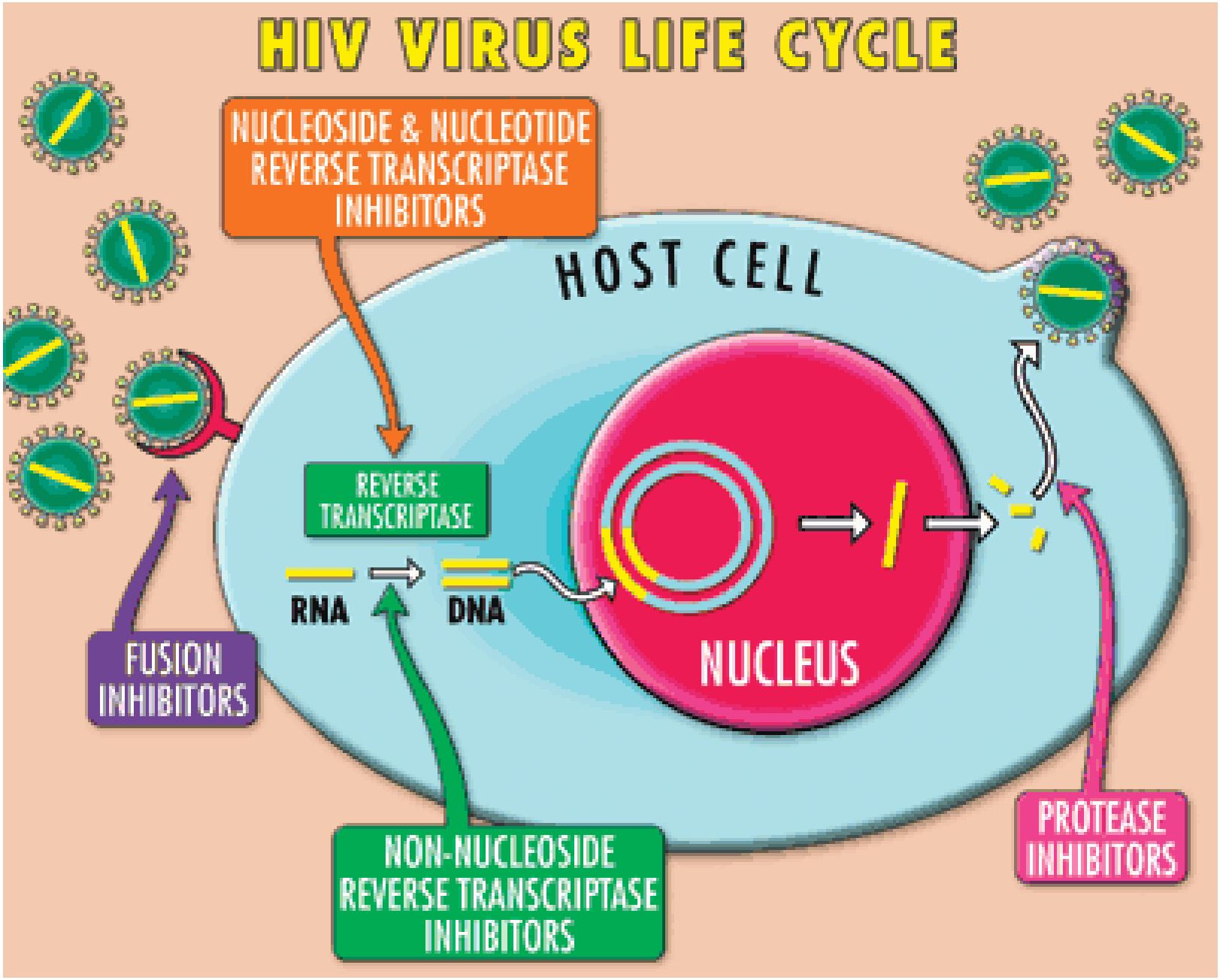
How HIV drugs work



Classes of drugs

Antiretroviral (ARV) drugs are broadly classified by the phase of the retrovirus life-cycle that the drug inhibits.

- Reverse-transcriptase inhibitor(RTI)
- Protease inhibitors (PIs)
- Integrase inhibitors
- Entry inhibitors (or fusion inhibitors)


HIV VIRUS LIFE CYCLE
NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
HOST CELL
REVERSE TRANSCRIPTASE
RNA
DNA
NUCLEUS
FUSION INHIBITORS
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
PROTEASE INHIBITORS

Antiretroviral Drugs

Reverse Transcriptase Inhibitors(13)

Nucleoside analogues

- zidovudine (AZT, ZDV)
- didanosine (ddI)
- zalcitabine (ddC)
- stavudine (d4T)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)

Nucleotide analogue

- tenofovir (TFV)

Non-nucleoside analogues

- nevirapine (NVP)
- delavirdine (DLV)
- efavirenz (EFV)
- etravirine (ETV)
- rilpivirine (RPV)

Integrase Inhibitor (2)

- raltegravir (RAL)
- elvitegravir (ELV)

Fusion Inhibitor

- fuzeon (T20)

Entry Inhibitor (CCR5)

- maraviroc (MVC)

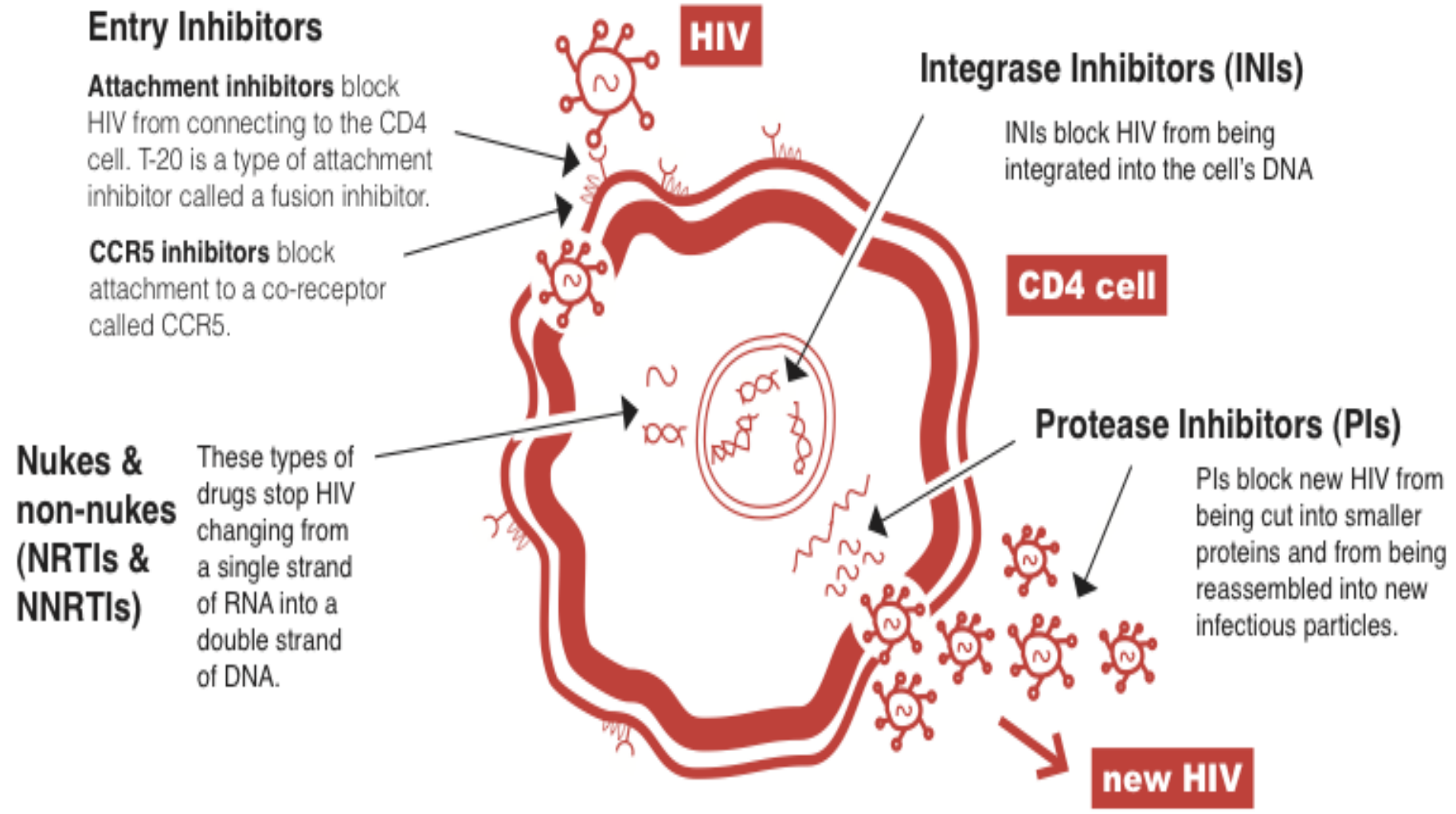
Protease Inhibitors (10)

- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- amprenavir (APV)
- lopinavir/r (LPV/r)
- fosamprenavir (FPV)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)
- dolutegravir (DTG)

FOLLOW UP

- CD4 counts every 3–6 months
- Viral load tests every 3–6 months and 1 month following a change in therapy
- PPD and INH for those with positive PPD and normal chest radiograph
- RPR or VDRL for syphilis
- Toxoplasma IgG serology and CMV IgG serology
- Pneumococcal vaccine and Influenza vaccine in season
- Hepatitis B vaccine for those who are HBsAb-negative
- *Haemophilus influenzae* type b vaccination
- Papanicolaou smears every 6 months for women

hiv


Entry Inhibitors
Attachment inhibitors block HIV from connecting to the CD4 cell. T-20 is a type of attachment inhibitor called a fusion inhibitor.
CCR5 inhibitors block attachment to a co-receptor called CCR5.
HIV
Integrase Inhibitors (INIs)
INIs block HIV from being integrated into the cell's DNA
CD4 cell
Nukes & non-nukes (NRTIs & NNRTIs)
These types of drugs stop HIV changing from a single strand of RNA into a double strand of DNA.
Protease Inhibitors (PIs)
PIs block new HIV from being cut into smaller proteins and from being reassembled into new infectious particles.
new HIV

- Thank u