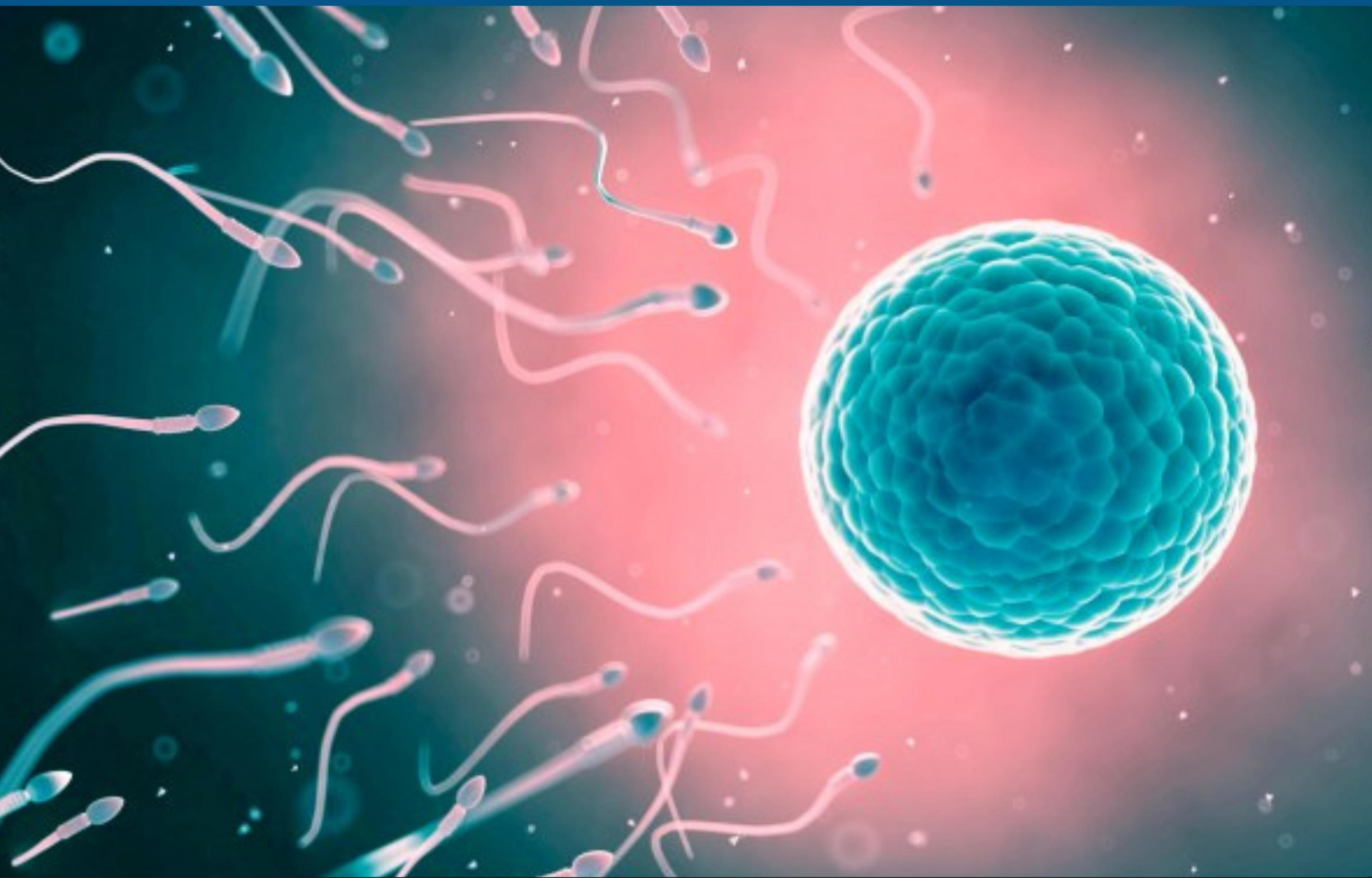


SEXUAL AND REPRODUCTIVE HEALTH

TAILORED FOR MEDICAL STUDENTS, USMLE, PLAB, PA & NURSING



4th EDITION



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162 PAGES

MORE ON HIV

MORE ON HIV

The Origins of HIV:

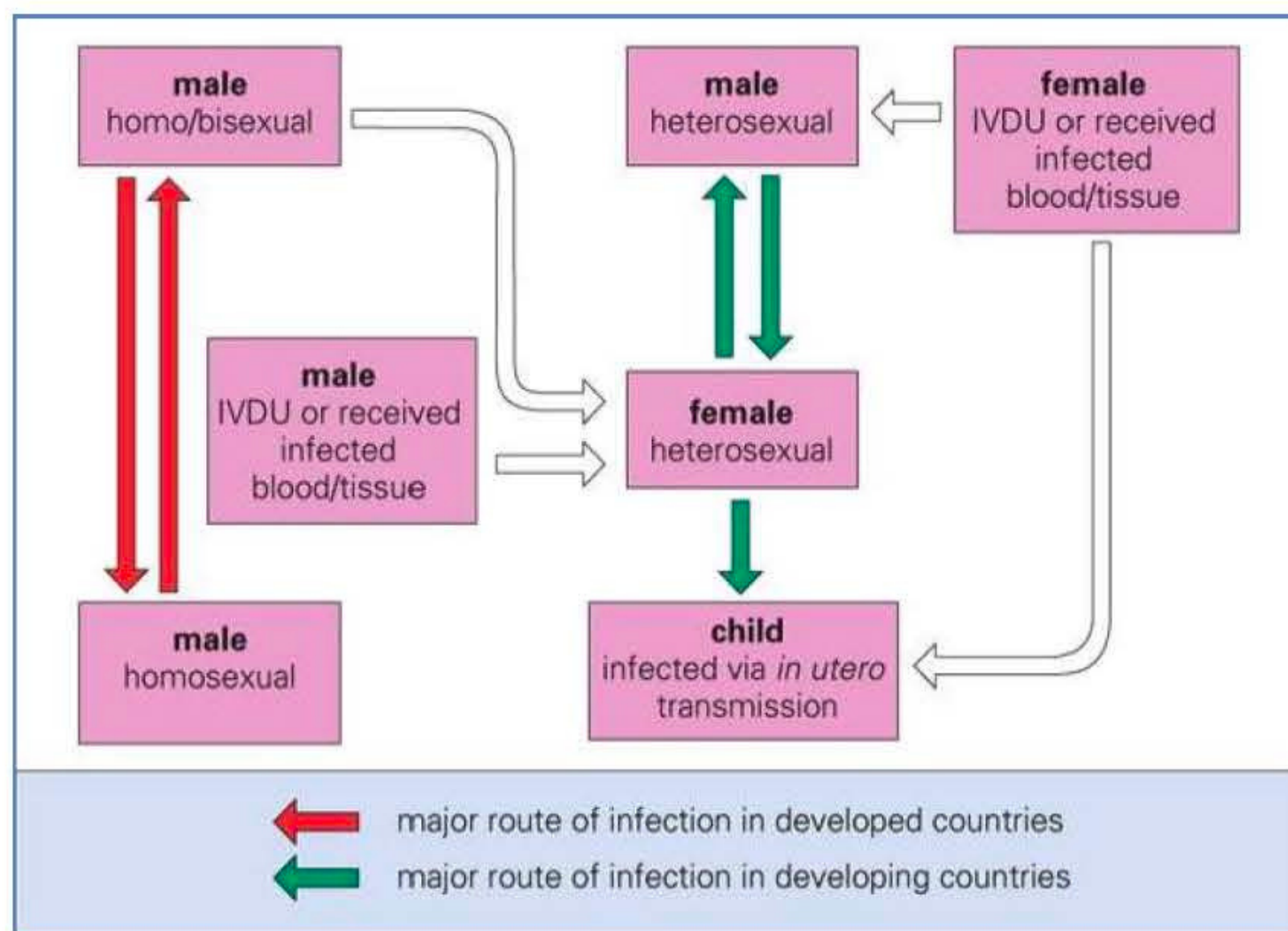
- **HIV-1 and HIV-2 have sequence homology with corresponding viruses in African primates:**
 - ∴ It is Likely that HIV originated in African Primates → Crossed over to Humans.
- **Possibility of Further Transmissions:**
 - The original virus still exists in African Primates (& Is *STILL EVOLVING*)
 - ∴ Further transmission of similar viruses to Humans is Very Possible.
 - (If it has done it once, it will do it again)

Epidemiology of HIV:

- **Sub-Saharan = Most Affected:**
 - 2/3 of all HIV cases
 - (24.7 million people in 2006.)
 - **75%** of all AIDS-Related Deaths occurred in sub-Saharan Africa
- **Developing Countries:**
 - High Prevalence
- **Developed Countries:**
 - Low Prevalence – (But Incidence is Increasing)
- **(HIV-2):**
 - Less virulent infection
 - Perinatal transmission is less common
 - Most common in West Africa

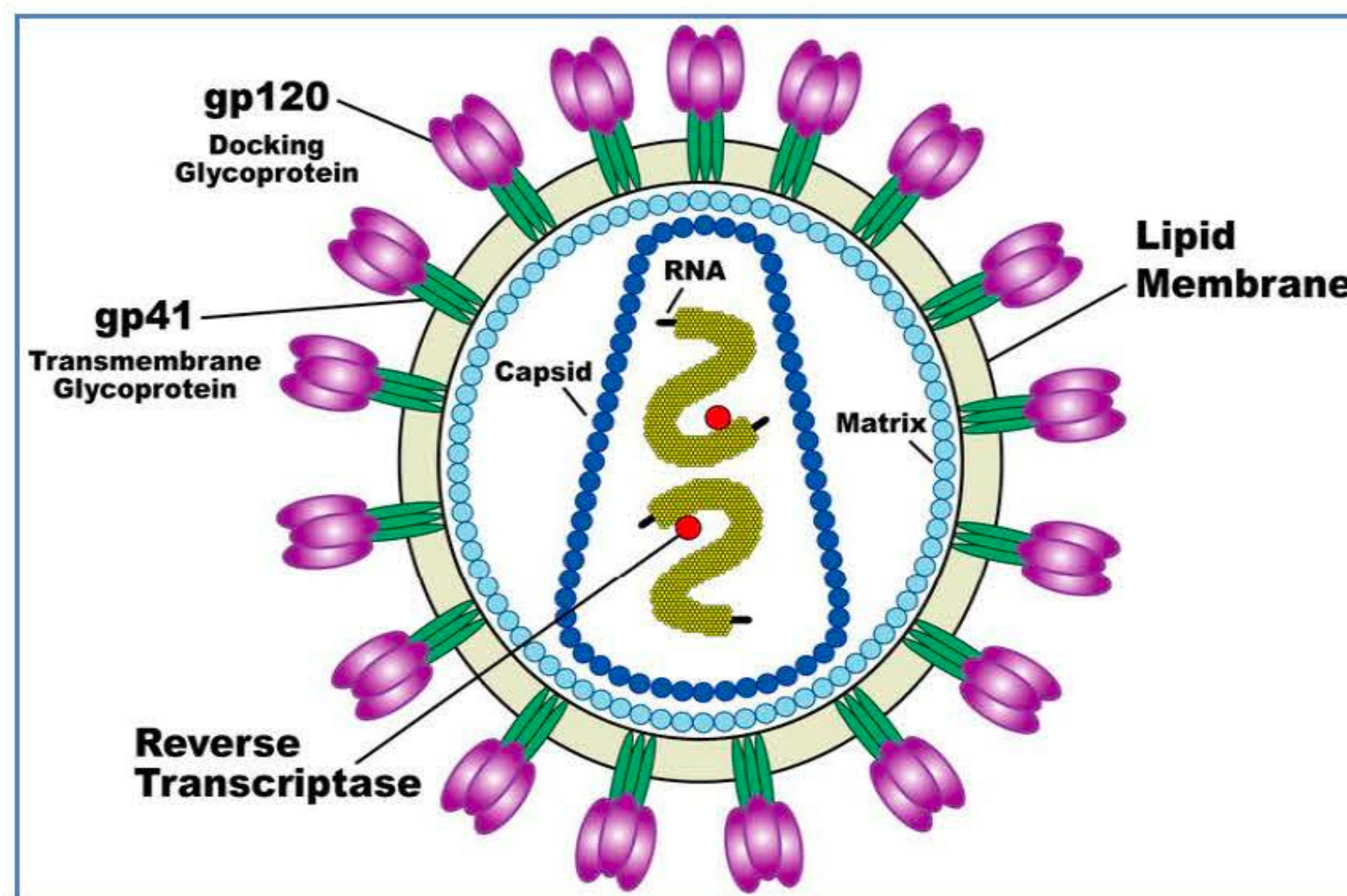
Transmission:

- **Sexual Transmission:**
 - 75% of transmission worldwide
 - **Risk Factors that Increase Chance of Sexual Transmission:**
 - **Trauma/Inflammation** - (The Virus must attach to CD4 receptors; Therefore presence of inflammatory cells @ Site of Inoculation vastly increases risk of transmission)
 - **Sexually Transmitted Diseases** (Eg: Gonorrhoea, Chlamydia, trichomoniasis or vaginosis) – Because they lead to Inflammation in the Genital Region.
 - **Higher risk with Anal Sex rather than Vaginal or Oral Sex:**
 - Vagina is Stratified Squamous (Greater Barrier Protection)
 - Rectum is Simple Columnar (Less Barrier) + Anal Sex commonly causes bleeding.
 - **Developing Countries:**
 - Males→Females Transmission (heterosexual transmission)
 - Vertical Mother→Child transmission.
 - IV Drug use
 - Blood Transfusion
 - **Developed Countries:**
 - Male→Male Transmission (Homosexuality)
 - IV Drug use
- **Parenteral Transmission (Blood Transfusion/IV-Needle Sharing):**
 - Depends on Titre in the Blood & the Amount of Blood Transferred. (Determines the number of Infectious Doses Contained)
- **Perinatal:**
 - Transplacental infection is becoming one of the most important routes of transmission
 - Breastmilk.
- **Note: Transmission is Surprisingly Difficult:**
 - Risk of Percutaneous Exposure is ≈ 0.3%
 - Risk of Mucous Membranous Exposure ≈ 0.09%
 - **Factors = Amount of Blood & Titre of Virus.**



Structure of the HIV Virion & Contents:

- Dicosahedral capsid
- **2x Separate Strands of ssRNA**
- **Envelope with Glycoproteins (Incl. Gp120 – important for adhesion & entry to CD4 T-Cells)**
- **Contains Reverse Transcriptase Enzymes:**
 - Necessary for Reverse Transcription of ssRNA genome into DNA to Integrate into host Genome.
- Gag ,Pol, Env – Open Reading Frames in Genome



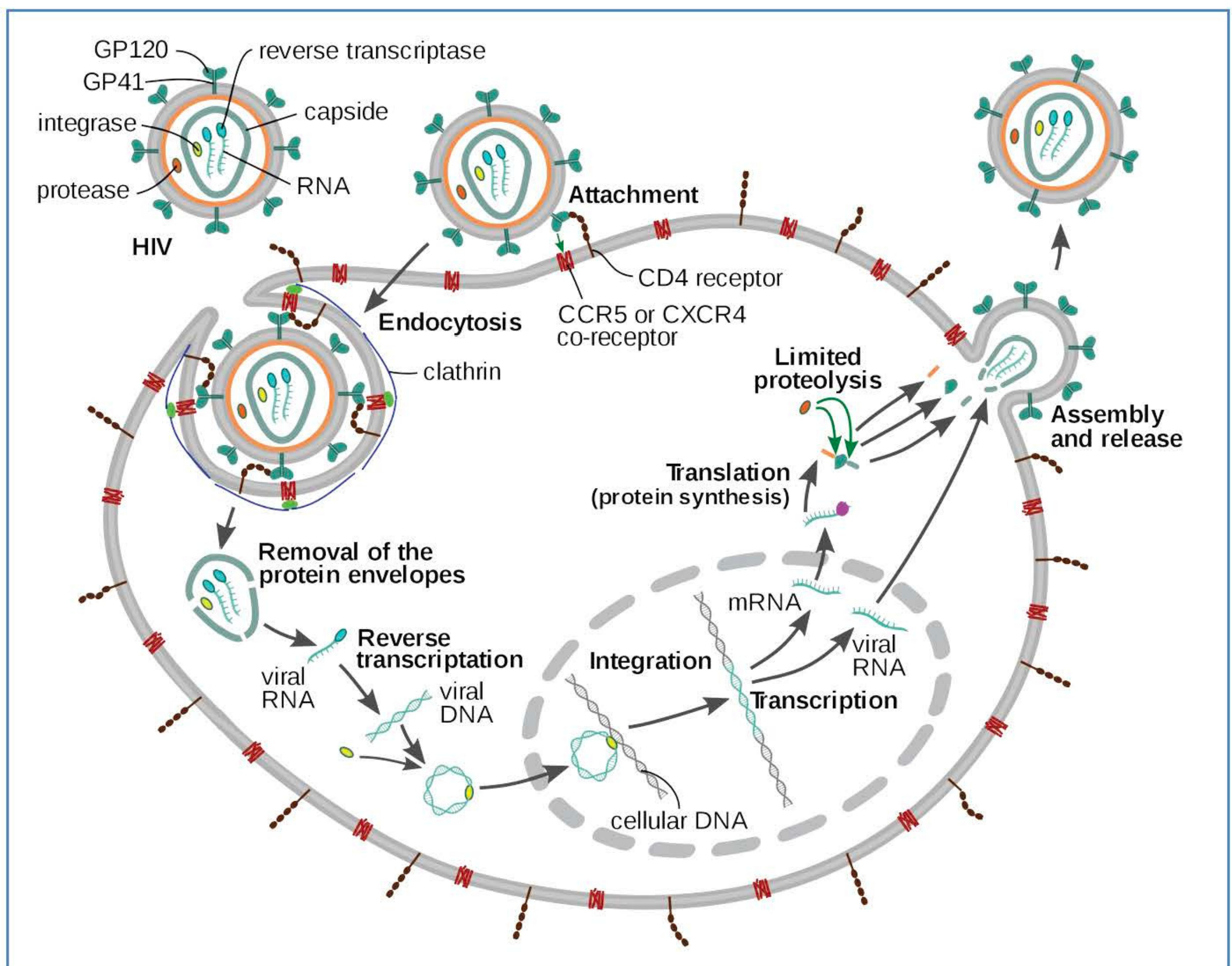
<https://www.cgl.ucsf.edu/chimera/data/hiv09/hiv-demo.html>

Reverse Transcriptase Enzyme:

- **Necessary for DNA Production from the Positive-ssRNA in the Virus.**
 - Reverse Transcription of Positive-ssRNA genome into DNA to Integrate into host Genome.
 - → Produces ssDNA from ssRNA
 - Then → Produces dsDNA from ssDNA
- **Note: Highly Error-Prone → High Mutation Rate → Production of QUASISPECIES:**
 - Quasispecies = Mutant/Recombinant Viral Genomes
 - Quasispecies are constantly subject to Genetic Variation, Competition & Selection.
 - → Assists virus to persist in the host. (Overwhelms the Immune Response)

Process of HIV Infection (@ The Cellular Level):

- **GP120** on Virus Binds to CD4 Receptors
- **Fusion of Viral Envelope** with Cell Membrane → Uptake into cell.
- **Reverse Transcriptase:**
 - → Produces ssDNA from ssRNA
 - Then → Produces dsDNA from ssDNA
- **dsDNA → Migrates to the Nucleus → Integrates into Host Genome:**
 - ∴ HIV Uses host DNA-Replication for Reproduction.
 - Is Transparent to the Immune System.
 - Virus replicates with DNA Replication or Cellular Protein Synthesis.
 - Can also be *transported* by migrating cells into other areas of the body – Eg: Crossing the BBB.
- **Genes Transcribed & Translated** → Viral proteins
- **Assembly**
- **Budding** → Released



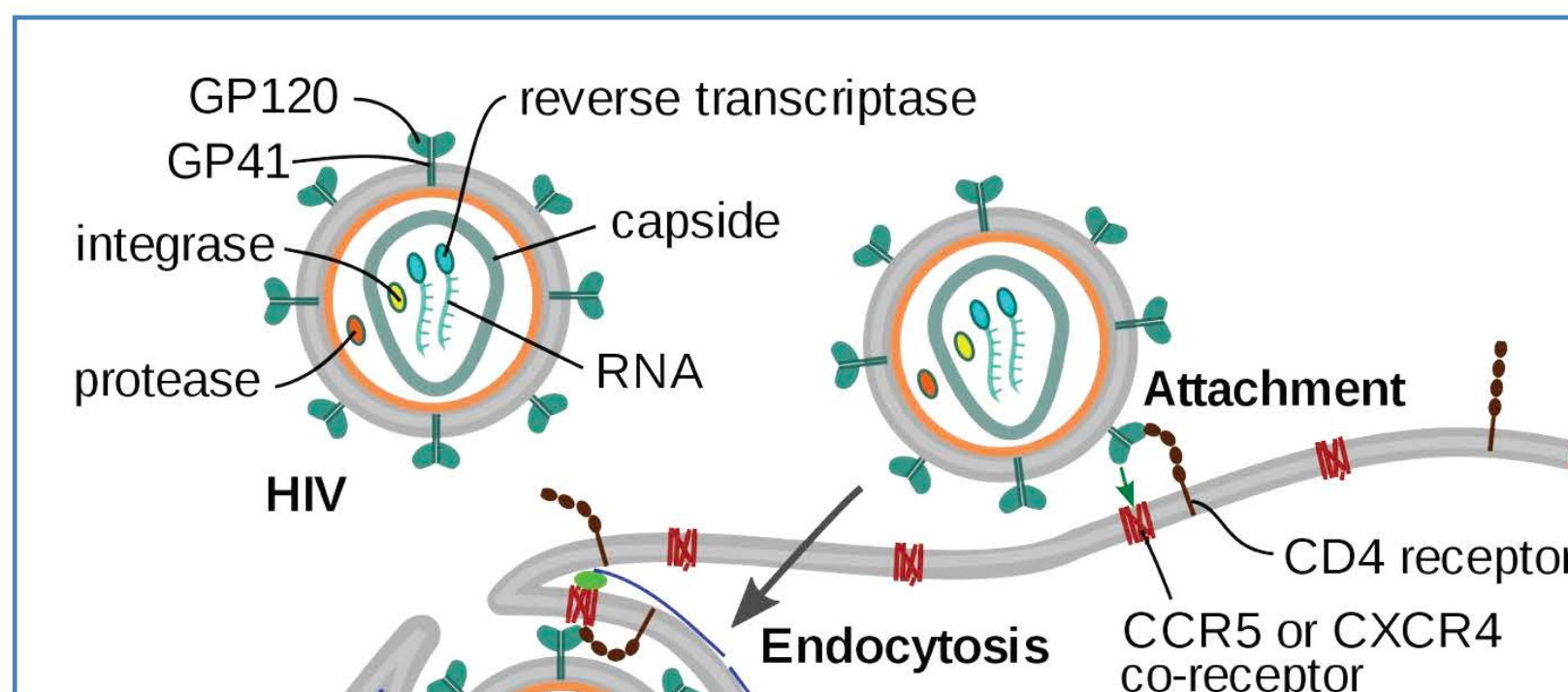
Jmarchn, CC BY-SA 3.0 <<https://creativecommons.org/licenses/by-sa/3.0/>>, via Wikimedia Commons

Susceptible Cells

- ****T-Helper Cells**
- **But Also:**
 - **B lymphocytes**
 - **Macrophages/Monocytes**
 - **Dendritic cells**
 - **Microglia (In CNS)**

Major HIV Receptors:

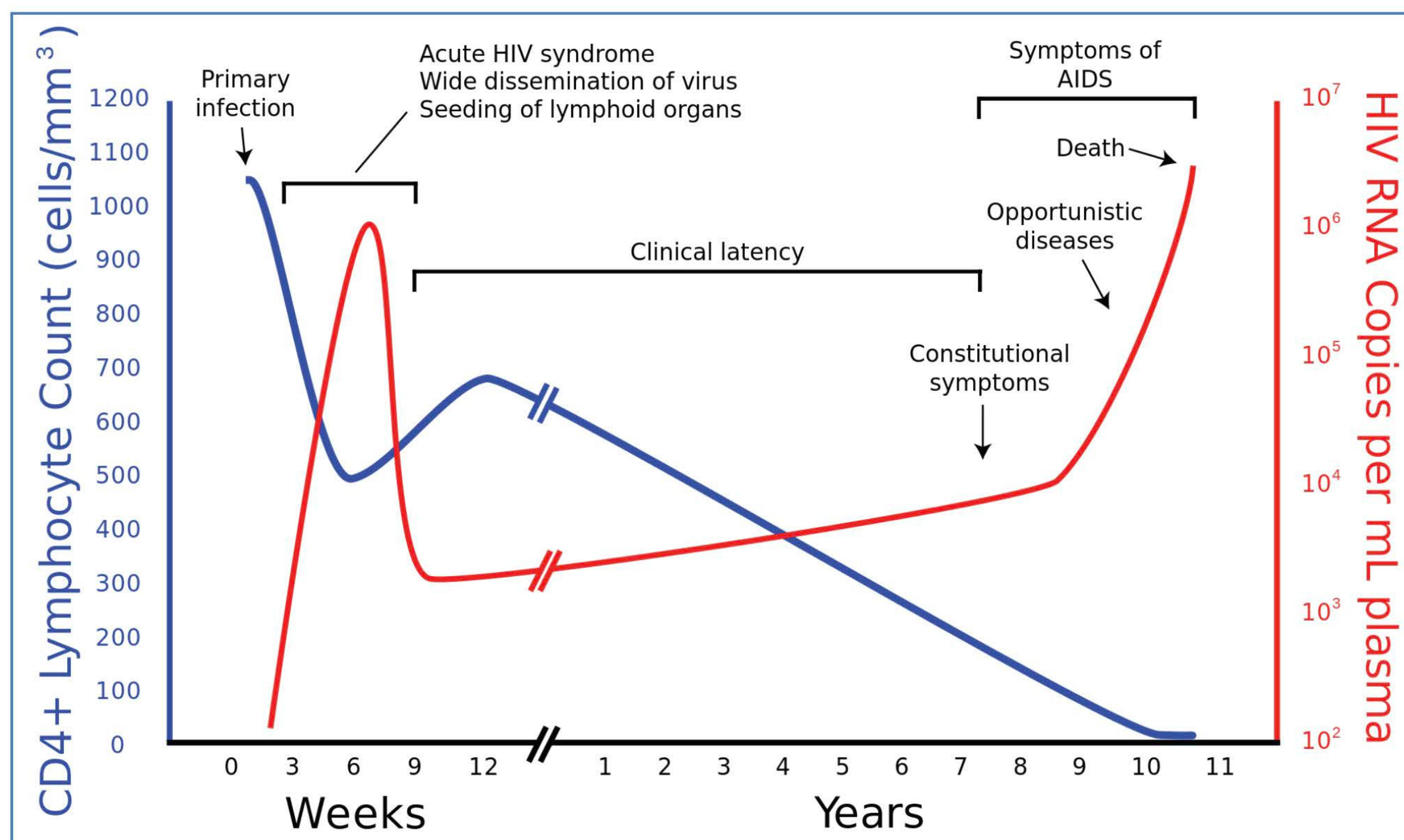
- 1: The CD4 molecule – (on CD4-Th-cells)
- 2: Chemokine Receptors - (act as Co-Receptors for the HIV):
 - T-cell Tropic strains: use the CXCR-4 chemokine receptor
 - Preferentially Infect T-Cells
 - Macrophage-Tropic strains: use the CCR-5 chemokine receptor
 - Preferentially Infect Macrophages
 - (Note: Macrophages can readily cross the BBB → Infect Glial Cells → Produce cytokines → wipe out the neurons → AIDS Dementia)



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Typical timescale of HIV infection

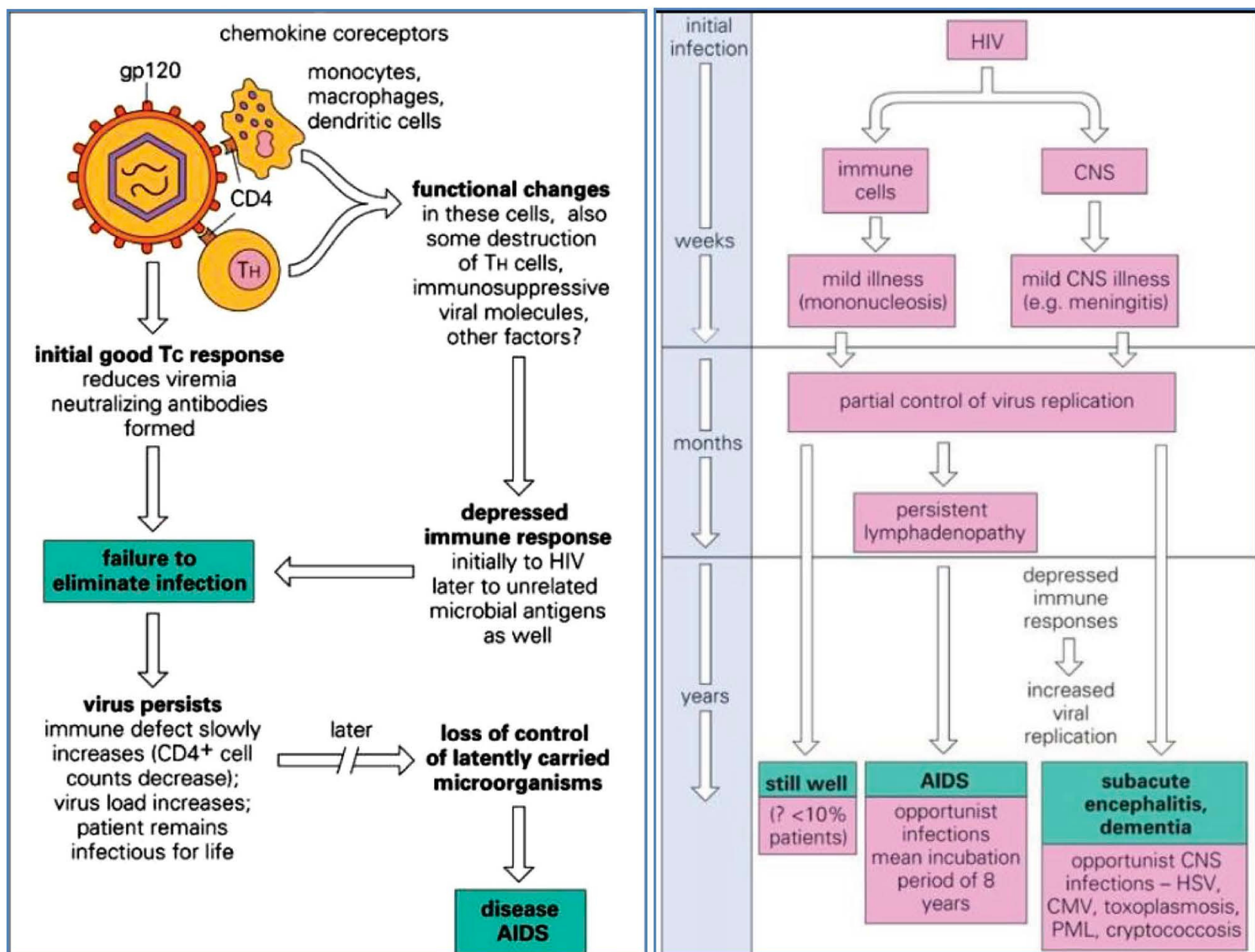
- 1-2 months:
 - Acute infection
 - Following the acute infection, Antibody titres rise (**Detectable after 2.5mths**)
- 2-4 Years:
 - Asymptomatic infection
- 8 years:
 - Symptomatic infection
- 10-12 years:
 - Advanced infection (If no intervention)



https://www.wikidoc.org/index.php/HIV_AIDS_natural_history,_complications,_and_prognosis

Pathogenesis of AIDS:

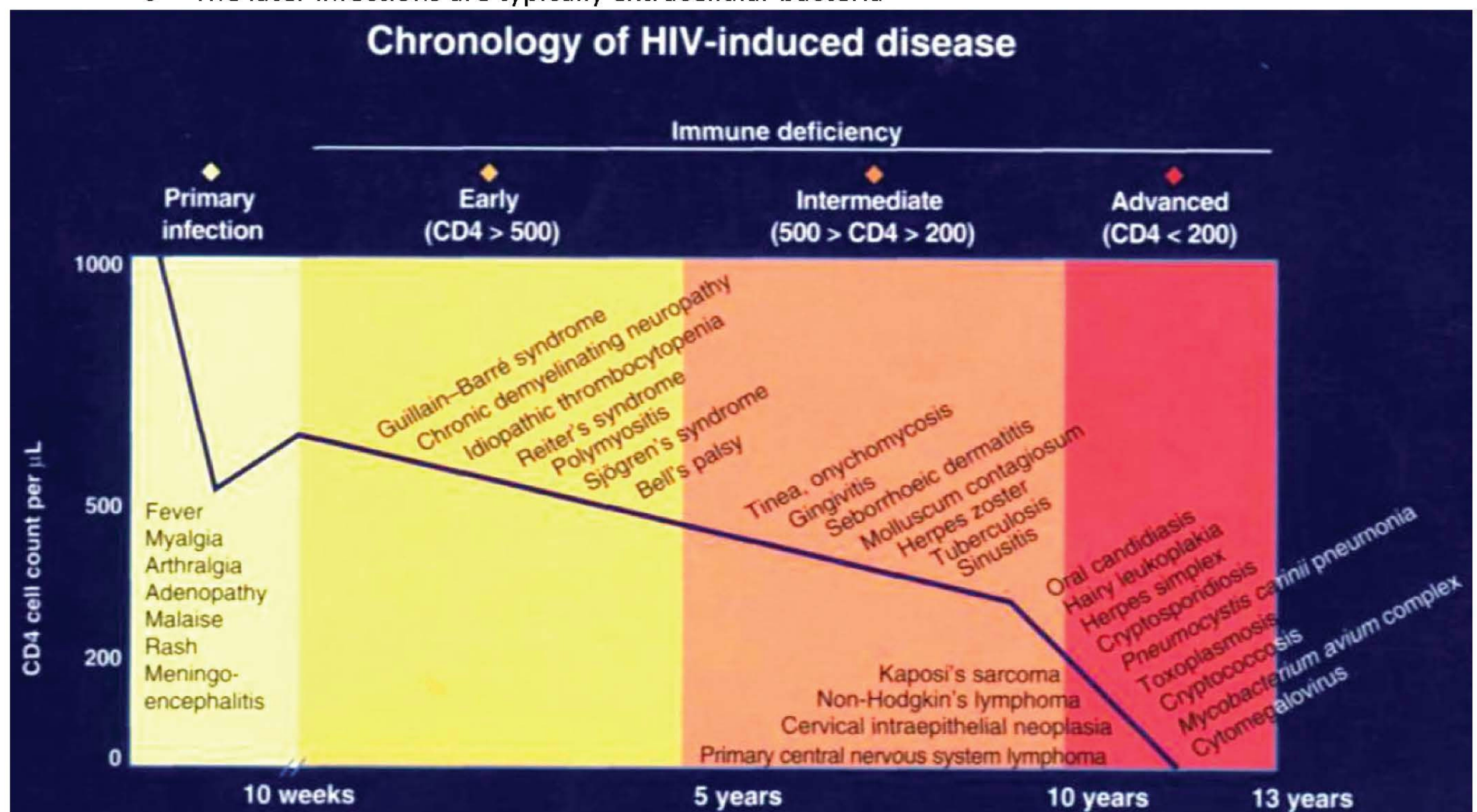
- **1: Acute Infection:** (High Risk of Transmission)
 - **Symptoms:**
 - Flu-Like Symptoms
 - Maculopapular Rash (AKA: Immuno-Thrombocytopenic Purpura)
 - **Characterised by:**
 - High plasma Viremia (red line, top)
 - Massive Depletion of CD4/CCR5 Low CD4 **Memory Cells** in the **Mucosal Associated Lymphoid Tissues (MALT)**. (green line, bottom)
 - Loss of Memory Cells requires constant immune activation → Hyperactive immune system
 - During this period, many Quasispecies will be made (due to high polymerase error rate & Rapid CD4-Cell Turnover)
 - Absence of HIV-1 specific antibodies (orange line, bottom).
 - **Viremia drops as cytotoxic CD8+ T Lymphocytes (CTL) develop:**
 - (blue line, bottom)
 - An individual **Viral-Load Set Point** is reached during chronic infection.
 - (**Viral set points** differ greatly among individuals (eg, red dotted line, top) and predict disease progression.)
 - **Note: Takes weeks-months for antibodies to rise.**
- **2: Chronic (Asymptomatic) Infection:**
 - Ineffective cell mediated immune responses lead to the chronic stage of the infection
 - There is Chronic Immune Activation → CD4+ T-cell Depletion (Driven into Apoptosis)
 - Viral diversity increases throughout the disease (closed circles, top).
 - As CD4-T-Cells are Depleted, Viral Titre Rises.
 - Eventually, the virus produces more quasispecies, than the amount of specific CD8-T-cells the body can produce.
- **3: AIDS (Symptomatic):** (High Risk of Transmission)
 - The *Terminal* Stage of the Disease.
 - There are too many HIV Quasispecies for the CD8-Tc-Cells & Antibodies to deal with.
 - **How HIV Causes Immunosuppression:**
 - **CD4 Depletion Via:**
 - Direct CD4-T-Cell Lysis
 - Cytotoxic T-Cells kill CD4-T-Cell
 - Apoptosis of CD4-T-Cell
 - Infected CD4-T-Cells can fuse together → form 'Syncytia' → Removed by Spleen.
 - (Ie: Predominantly via the Immune Response, not the Virus)
 - **CD4 Depletion → Immunosuppression By:**
 - ↓IFN γ Production
 - ↓Antibody Production
 - ↓Antibody Isotype Switching
 - ↓Macrophage Activation
 - ↓CD8-T-Cell Activation
 - →→**Loss of the Adaptive Immune System → Opportunistic Infections.**
 - **HIV can lead to Death of Neurons (AIDs Dementia). How?:**
 - Infected Macrophages can cross the BBB → Infect Glial Cells (Esp. Astrocytes)→ Glia Produce TNF cytokines → Kill Neurons → AIDS Dementia
- **(Note: CD4:CD8 ratios can be a good marker for disease progression)**



Unattributable

Opportunistic Infections & Tumours in AIDS:

- Loss of CD4 Cells → ↓ production of IFN γ → ↑ Intracellular Viral/Bacterial Infections.
- What do the common opportunistic infections associated with AIDS have in common?
 - Infections where IFN γ (from Th-Cells) is really important to protection are the first infections seen (i.e.: Those with intracellular viruses/bacteria).
 - The later infections are typically extracellular bacteria



OPPORTUNIST INFECTIONS AND TUMORS IN AIDS

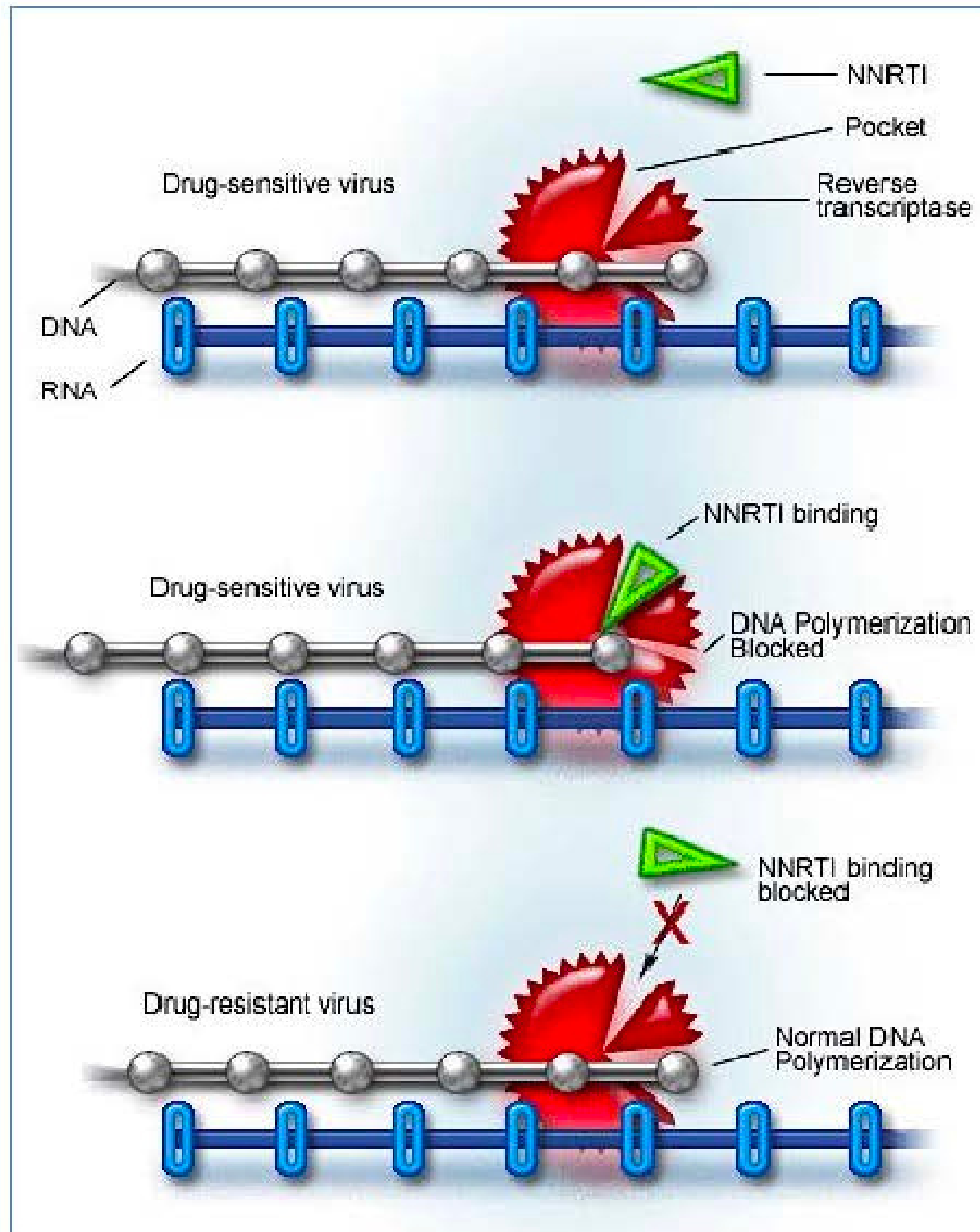
viruses	disseminated CMV (including retina, brain, peripheral nervous system, gastrointestinal tract) HSV (lungs, gastrointestinal tract, CNS, skin) JC virus (brain – PML) EBV (hairy leukoplakia, primary cerebral lymphoma)
bacteria*	mycobacteria (e.g. <i>Mycoplasma avium</i> , <i>M. tuberculosis</i> – disseminated, extrapulmonary) <i>Salmonella</i> (recurrent, disseminated) septicemia
protozoa	<i>Toxoplasma gondii</i> (disseminated, including CNS) <i>Cryptosporidium</i> (chronic diarrhea) <i>Isospora</i> (with diarrhea, persisting more than one month)
fungi	<i>Pneumocystis jiroveci</i> (pneumonia) <i>Candida albicans</i> (esophagitis, lung infection) <i>Cryptococcus neoformans</i> (CNS) histoplasmosis (disseminated, extrapulmonary) <i>Coccidioides</i> (disseminated, extrapulmonary)
tumors	Kaposi's sarcoma** B cell lymphoma (e.g. in brain, some are EBV induced)
other	wasting disease (cause unknown) HIV encephalopathy

*also pyogenic bacteria (e.g. *Haemophilus*, *Streptococcus*, *Pneumococcus*) causing septicemia, pneumonia, meningitis, osteomyelitis, arthritis, abscesses etc.; multiple or recurrent infections, especially in children

**associated with HHV8, an independently-transmitted agent; 300-times as frequent in AIDS as in other immunodeficiencies

HIV Drug Options:

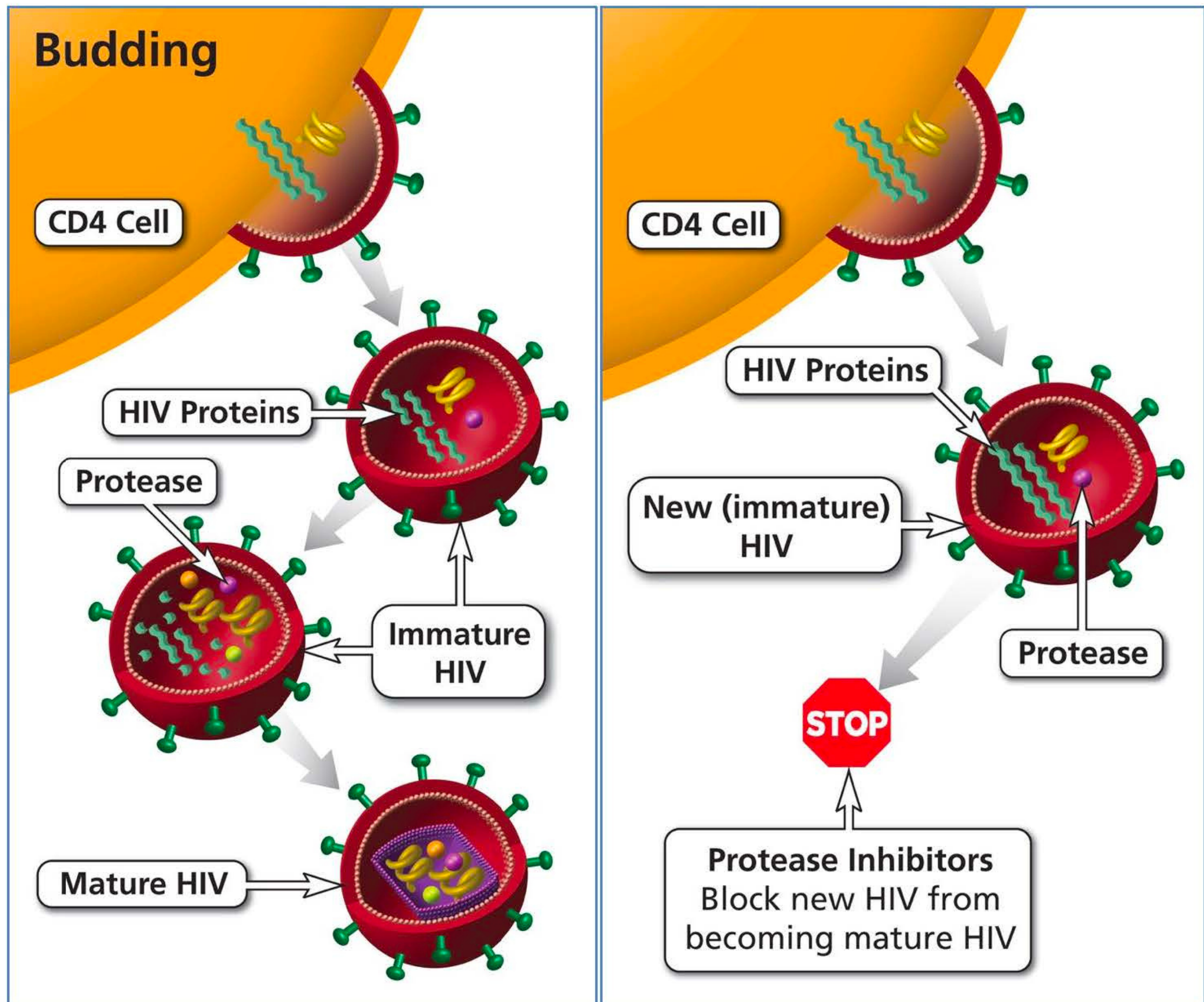
- **Fusion Inhibitors:**
 - **Eg: CCR5 Inhibitors:**
 - Prevent HIV from fusing with the Cellular Membrane
- **Reverse Transcriptase Inhibitors (RTI's)**
 - **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)** – (Blocks addition of purines/pyrimidines to DNA)
 - Zidovudine (azidothymidine, AZT)
 - Didanosine (dideoxyinosine, ddi)
 - Zalcitabine (dideoxycytidine, ddC)
 - Lamivudine (3TC) (complementary resistance spectrum to AZT)
 - → **Prevents Extension of the Chain of DNA Synthesis.**



Adapted from François Clavel, M.D., et al.² *N Engl J Med.* 2004;350(10):1023-1035.

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):**
 - Targets the Non-Nucleoside-Binding Site of the HIV's Reverse Transcriptase → Inhibits RT Activity.

- **Protease inhibitors** – (Next generation of drugs):
 - Prevents cleavage of Inactive Poly-Proteins into Active Viral Proteins.
 - → Assembly of ineffective (Non-Infective) viruses.



<https://clinicalinfo.hiv.gov/en/glossary/protease-inhibitor-pi>

SEXUAL DYSFUNCTIONS & TREATMENT:

SEXUAL DYSFUNCTIONS & TREATMENT:

Both Women & Men:

- **Hypoactive Sexual Desire Disorder:**

- Characterised as a marked lack of sexual fantasies/desire for some period of time.
- Considered a *Disorder* if it causes distress/interpersonal difficulties and not be accounted for by another medical disorder (depression/drugs/other).
- **Treatment:** Psychological 'Couple' Therapy (Relationship/Communication/Sexual Counselling)



- **Sexual Aversion:**

- Characterised as active avoidance of sexual encounters.
- (More common in women – Theorized to be due to being the 'receptive' partner → Makes them vulnerable to physical/sexual abuse and they may have less perceived control over sexual experiences.)
- **Treatment:** Counselling



- **Dyspareunia:**

- Painful sexual intercourse, due to medical or psychological causes.
- Women – If she's a virgin, her 1st time can be painful.
 - - Or if the couple aren't physically size-compatible.
 - - Or if there is insufficient lubricant production
 - - STD
- Man – If he has phimosis (Tight foreskin)
 - - STD
- **Treatment:** Depends on the cause – self-explanatory.



Women-Specific:

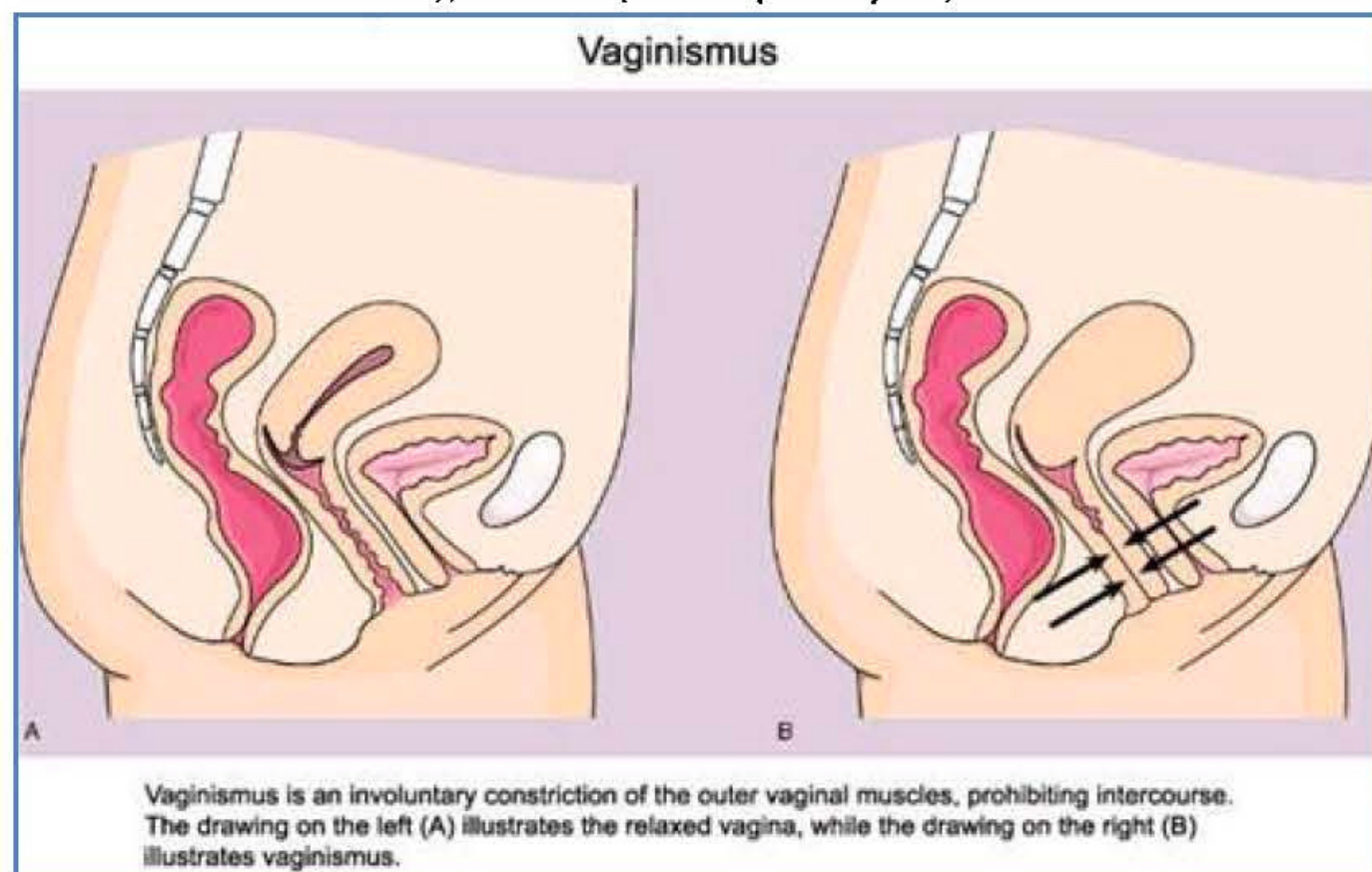
- **Female Sexual Arousal Disorder:**

- Characterised by the inability to attain/maintain an adequate **Lubrication-Swelling** response during sexual activity.
- **Causes** – Stress, Fatigue, Gender Mis-Identity, Childhood Sexual Abuse, others....
- **Treatment:** Exogenous Lubricant, Couple Counselling, Drug 'Bremelanotide' to ↑Libido.



- **Vaginismus:**

- **Vaginal Spasm** – painful & often prolonged contraction of the vagina in response to touching of the Vulva or Vagina.
- Is the result of a conditioned reflex of the **Pubococcygeus Muscle** → contracts in response to any form of penetration.
- Affects a woman's ability to engage in any form of Vaginal Penetration.
- **Some Causes** – Fear of Painful Sex, Belief that sex is wrong/shameful, traumatic sexual experiences.
- **Treatment:**
 - Psychological – Address the psychological aspects.
 - Physical – Sensate Focus Exercises, Self-administered Vaginal Dilators (Gradually increasing in size), Botox (Local paralytic)



- **Female Orgasmic Disorder:**

- Characterised by a Significant Delay/Total Absence of Orgasm during sexual activity.
- **Cause** – Can result from Trauma, but can also be acquired through Relationship Problems.
- **Treatment** – Research suggests that women can increase orgasm capacity through masturbatory training & "Exploring themselves", and de-stigmatizing sex.



Men-Specific:

- **Male Erectile Disorder:**

- 25% of all men over 40yrs.
- Inability to develop/maintain an erection of the penis.
- **Causes** – Decreased Blood-Flow to the Penis due to:
 - Damage to Nervi Erigentes,
 - Diabetes
 - Depression
- **Treatment**- Viagra (sildenafil) / Cialis (tadalafil)



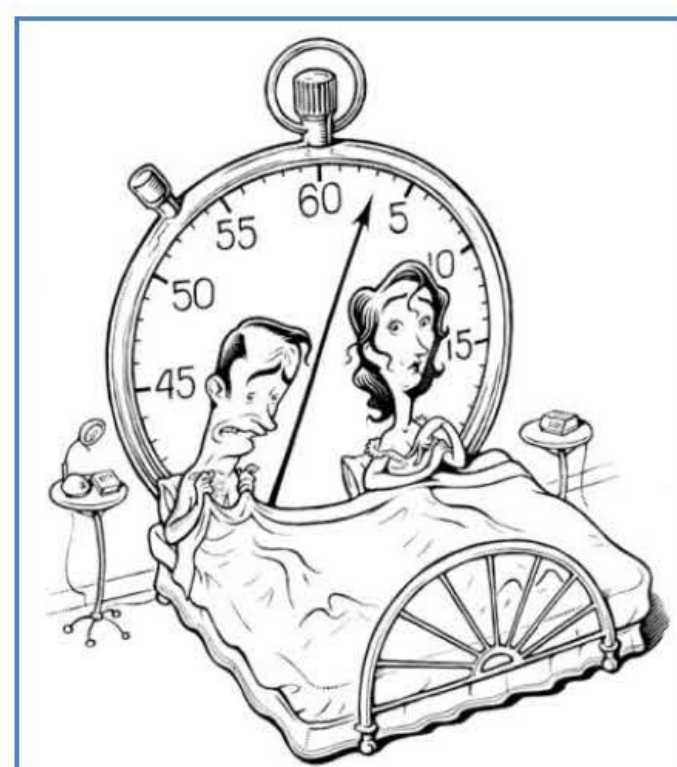
- **Male Orgasmic Disorder:**

- Persistent/recurrent inability to achieve orgasm despite lengthy sexual contact/intercourse.
- **Cause** – (Rarely physical) Acquired – traumatic sexual experience, strict religious upbringing, hostility over control, lack of trust.
- **Treatment** – Counselling & Psychotherapy → ↓performance anxiety, ↑Arousal.



- **Premature Ejaculation:**

- A condition where a man ejaculates earlier than he or his partner would like him to.
- Defined by *Masters & Johnson* as when the man ejaculates before his partner achieves orgasm more than 50% of the time.
- **Cause** – Psychological, Environmental & Physical Factors.
 - Depression, Stress, Unrealistic Expectations, Sexual Repression, Lack of confidence, poor emotional intimacy.
 - Neurological.
- **Treatment** – Topical Lignocaine Sprays, Mental Desensitisation to sex, Low-Dose Tricyclic Antidepressants to prolong serotonergic stimulation.



Tips for Clinicians When Talking about Sexual Dysfunction:

- Communication:

- Be comfortable talking about sex
- Be empathetic, non-judgemental & understanding
- Reassure the individual
- Never assume anything
- Start with general, non-threatening questions:
 - Are you sexually active at present?
 - Do you have any sexual concerns/worries that I might be able to help you with?
- Generalise:
 - “Many people in your situation have sexual worries”
 - “It’s not just you”
- Normalise:
 - “It’s normal for people who take this medication...What worries have you had?”
- Basic Screening Questions:
 - When was the last time you had any sexual activity?
 - Have you engaged in sex with just men/women or both?
 - How many people have you had sex with in the past year?
 - How are things going for you sexually?
 - Any questions/concerns about sex at the present time?

- Examinations:

- Sexual History
- Genitourinary
- General Physical (Identify systemic illnesses/signs of abuse)
- Neurologic & Vascular Exam
- Laboratory Testing (Haem/Biochem/Endocrine)
- **Women:**
 - Pap Smear
 - Vaginal Culture
 - Hormones
- **Men:**
 - Hormones