

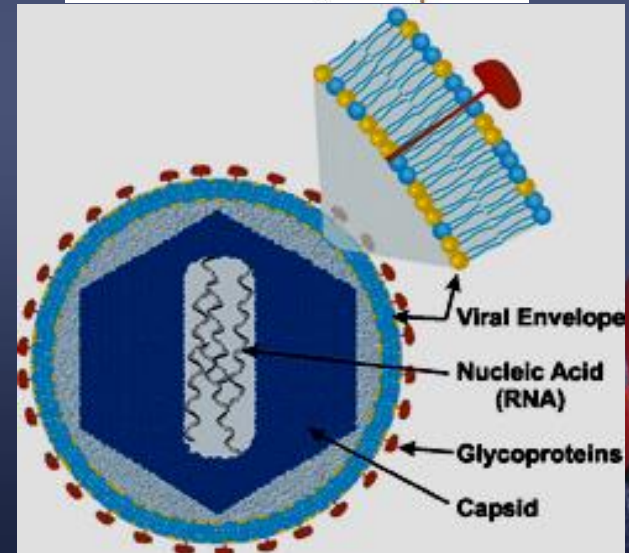
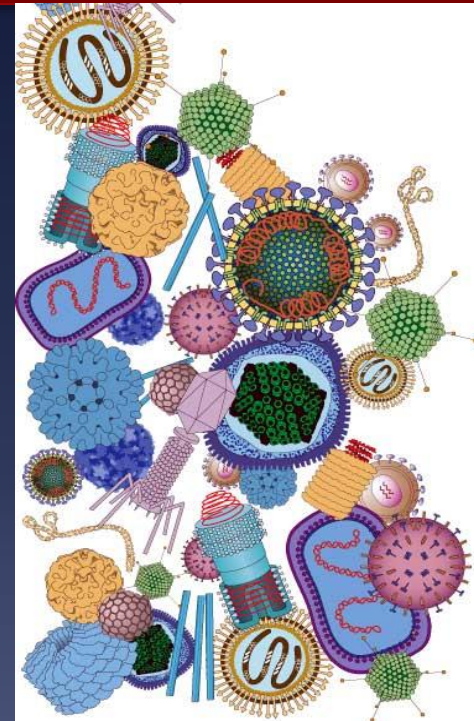
Lecture 21: The Biology of HIV



What are Viruses?

A virus particle, or **virion**, consists of the following:

- ❑ **Nucleic acid** - Genetic instructions, either **DNA** or **RNA**, either single-stranded or double-stranded
- ❑ **Coat of protein** - Surrounds the DNA or RNA to protect it
- ❑ **Lipid membrane** - Surrounds the protein coat (found only in some viruses, including influenza; **enveloped** viruses as opposed to **naked** viruses)



What Type of Virus is HIV?

- ❑ Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family)
- ❑ Lentiviruses are transmitted as enveloped RNA viruses
- ❑ Upon target cell entry, viral RNA is converted to dsDNA by a virally encoded reverse transcriptase present in the virus particle



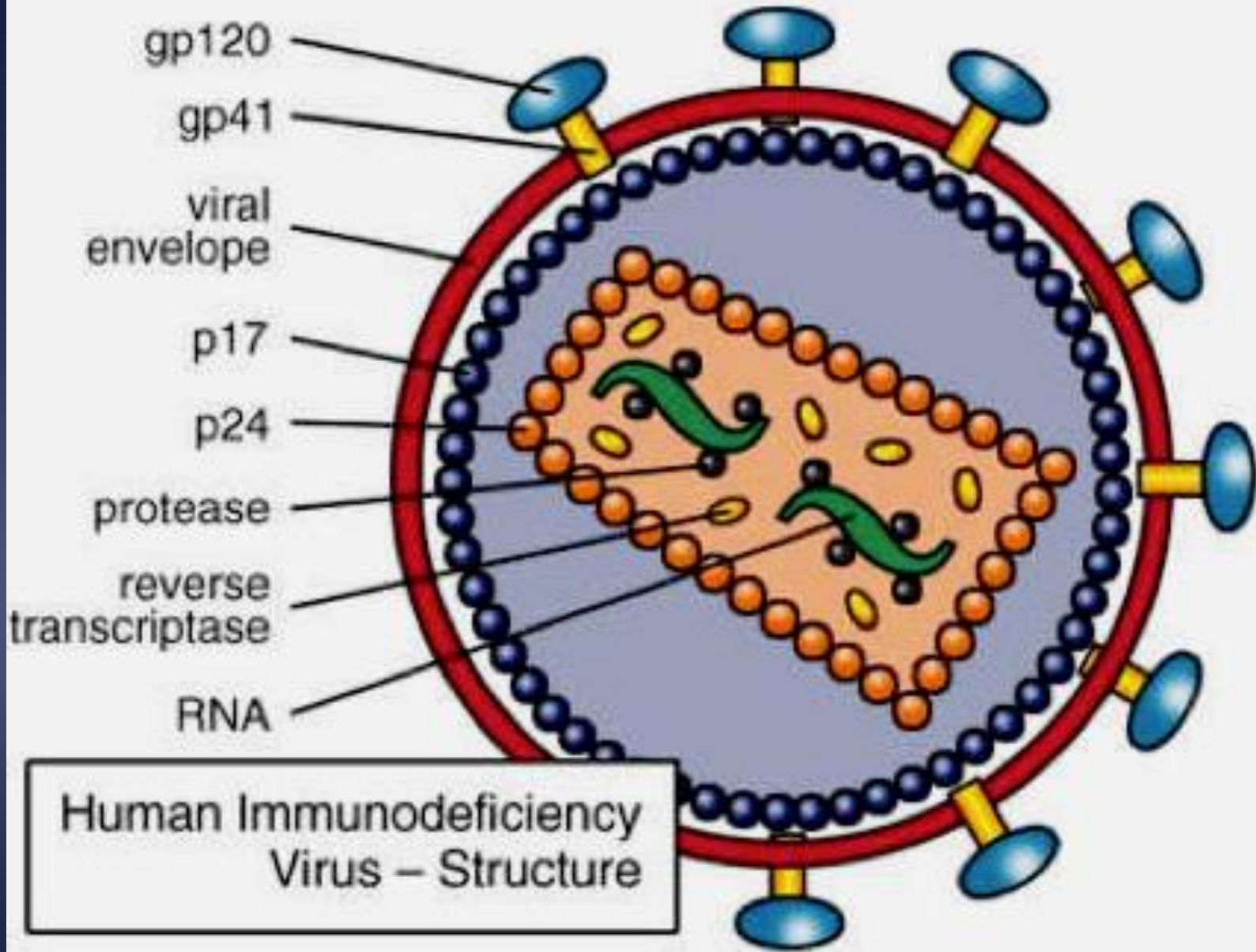
A microscopic view of a cell infected with HIV [CREDIT: csend.hu]

What Does HIV look like?

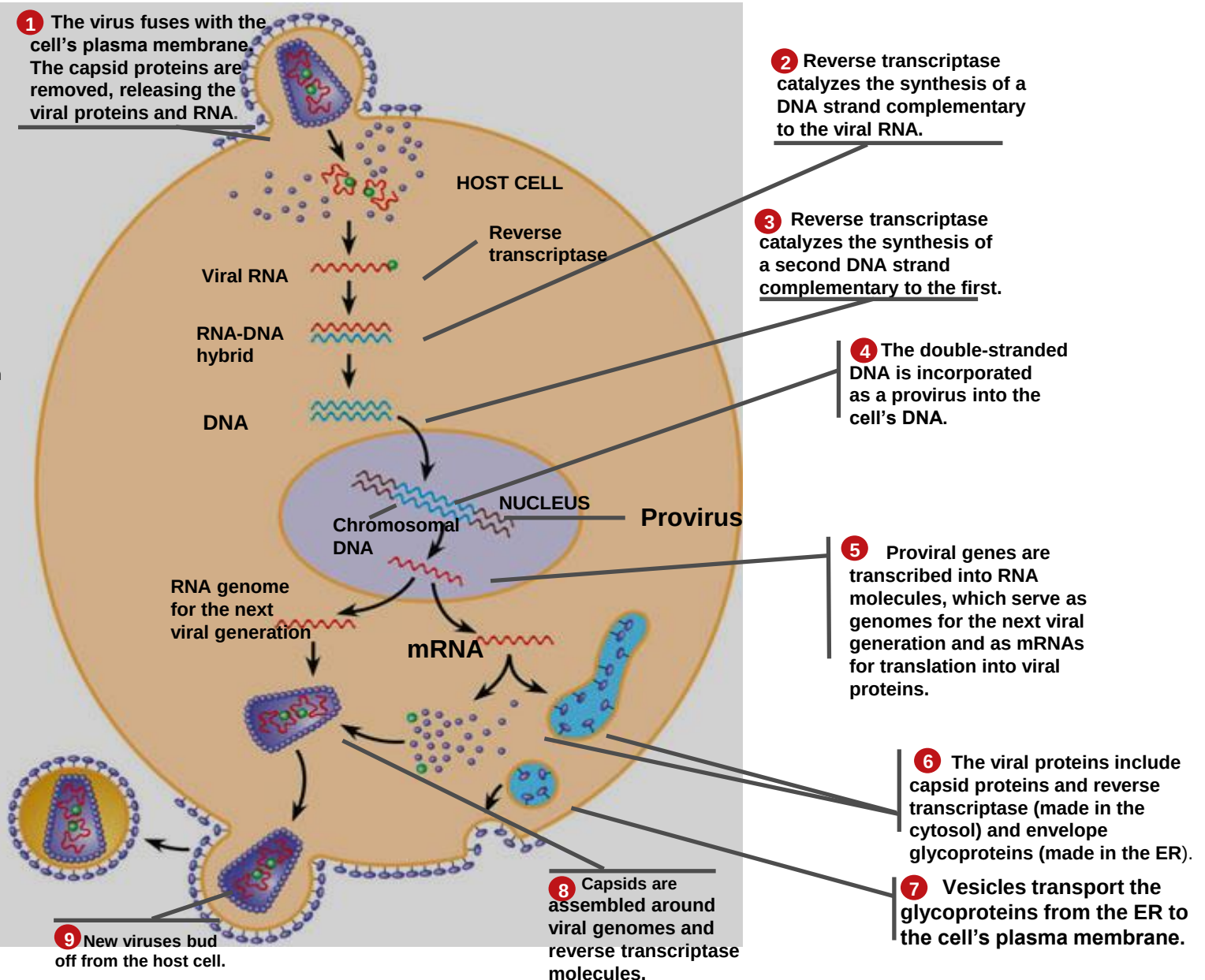
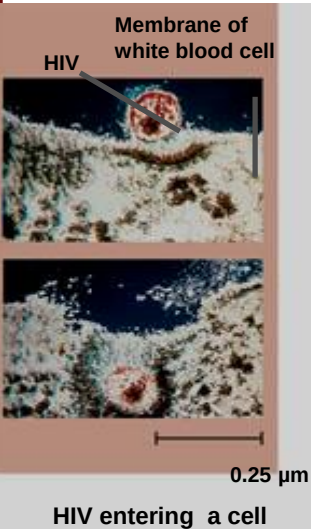
- ❑ An HIV particle is around 100-150 billionths of a meter in diameter. That's about the same as:
 - 0.1 microns
 - 4 millionths of an inch
 - one twentieth of the length of an E. coli bacterium
 - one seventieth of the diameter of a human CD4+ white blood cell.



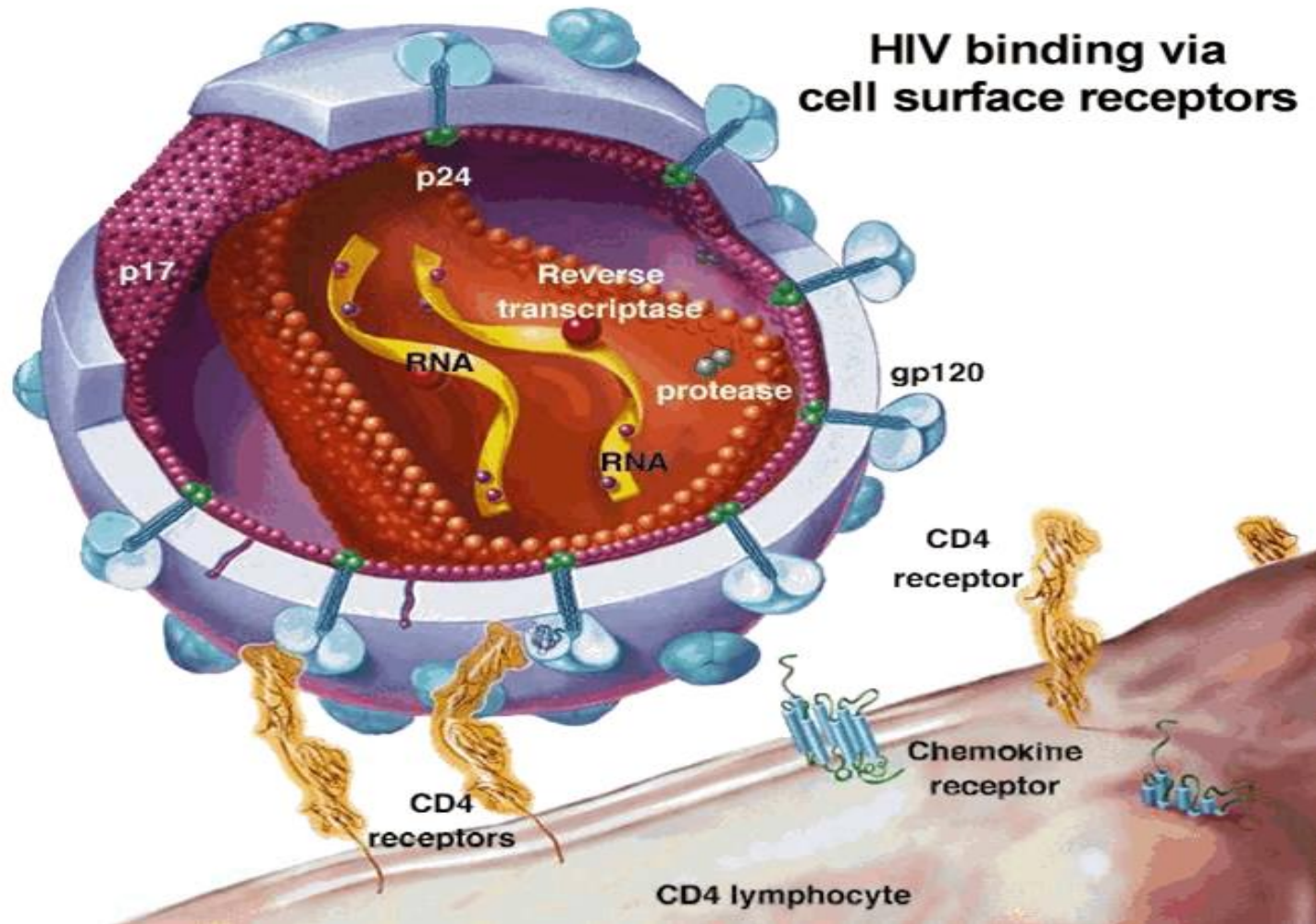
Major Viral Components



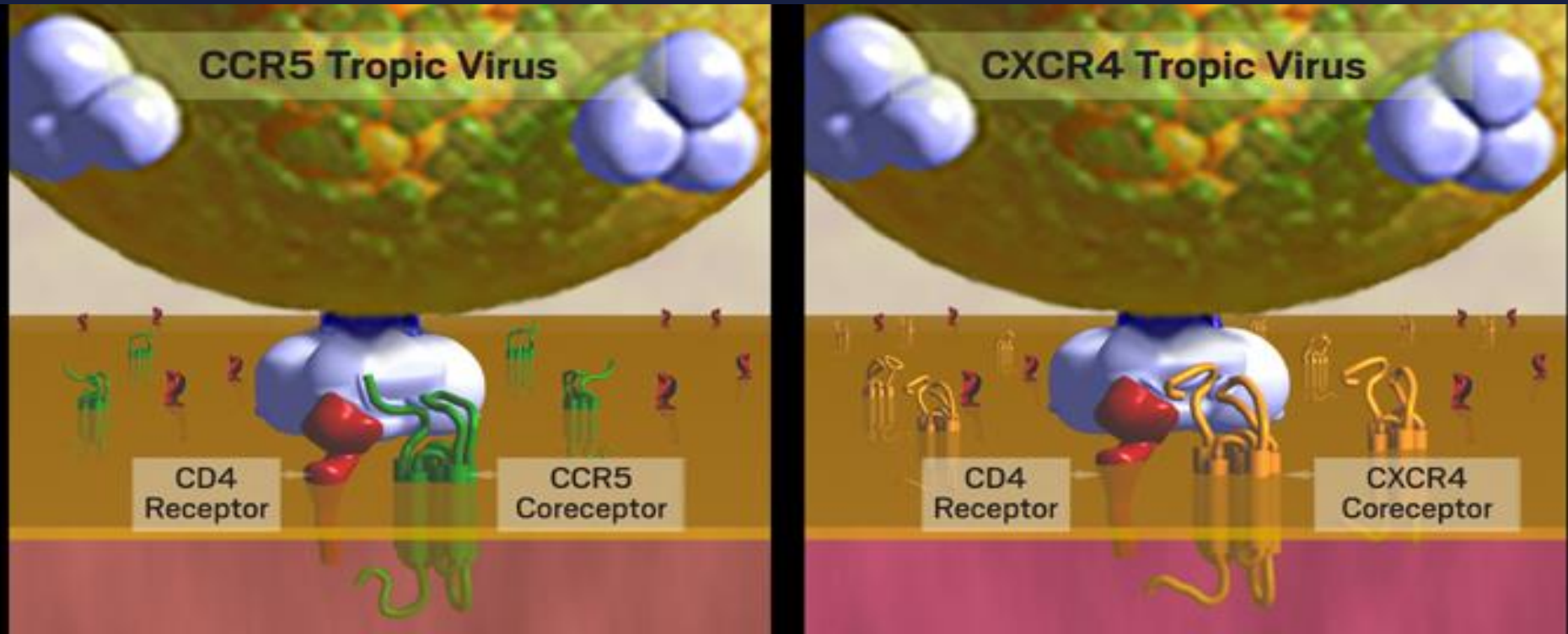
The reproductive cycle of HIV, a retrovirus



Binding of HIV to CD4 T-cell



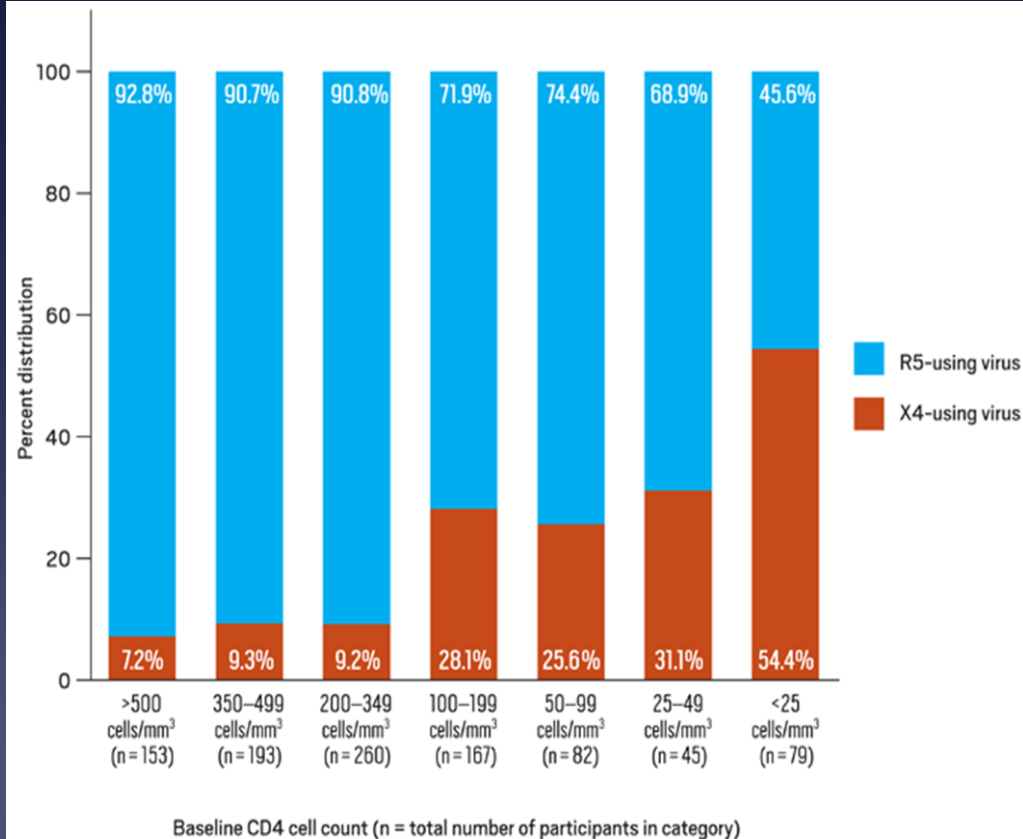
Dynamics of Cell Entry



- Up to 90% of newly transmitted HIV uses CCR5 (M-tropic)
- R5 viruses are more often transmitted sexually
- CXCR4-tropic virus emerges in ~50-60% of infected individuals within 5yrs
- X4-tropic (T-tropic virus) associated with pronounced depletion of CD4 T cells

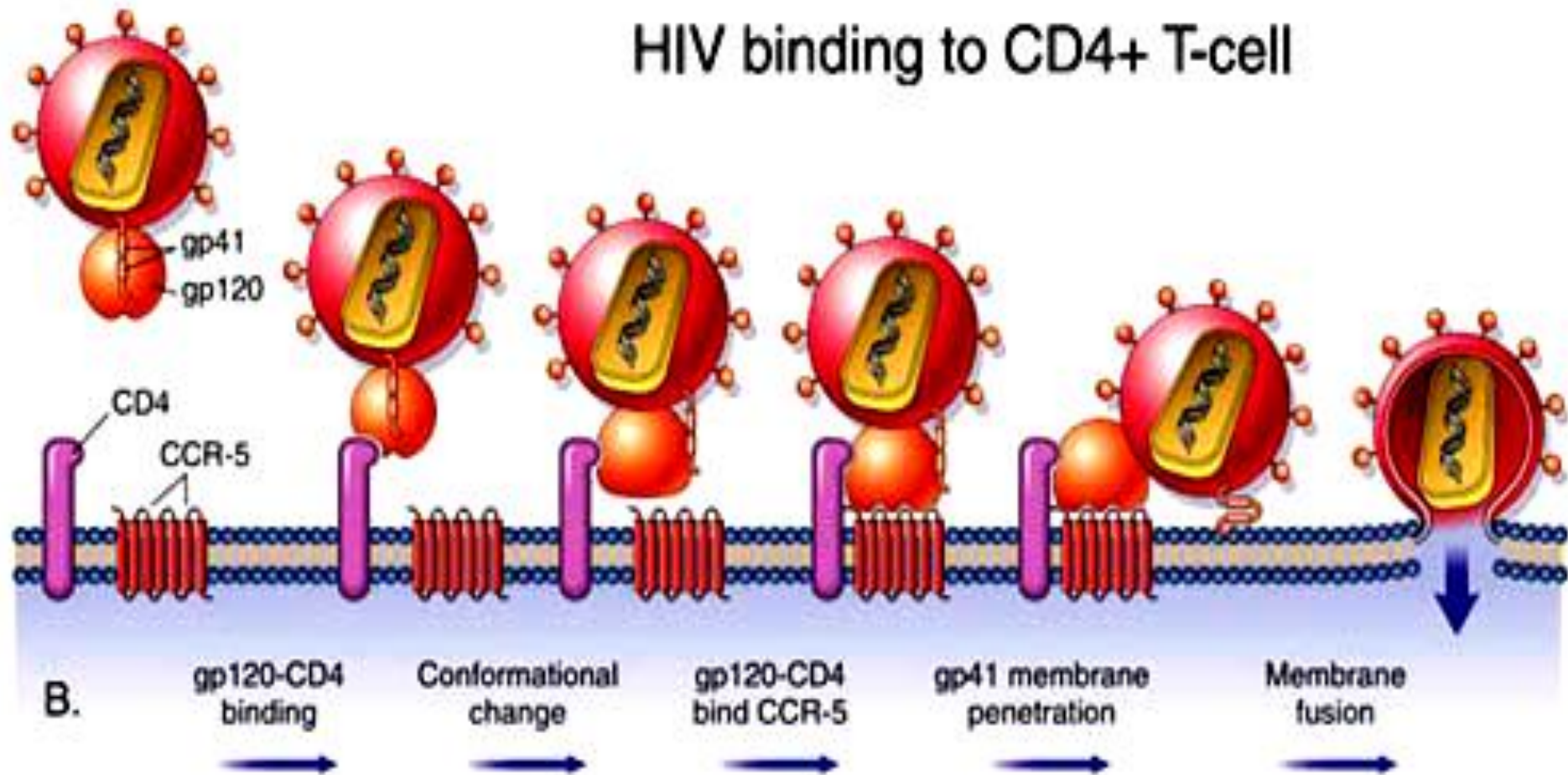
Understanding HIV Tropism

- ❑ Lower CD4 counts and higher viral load is seen with dual or mixed tropic virus compared to pure R5 or X4.
- ❑ X4- virus correlates with syncytia formation
- ❑ X4 – virus associated with more rapid progression to AIDS

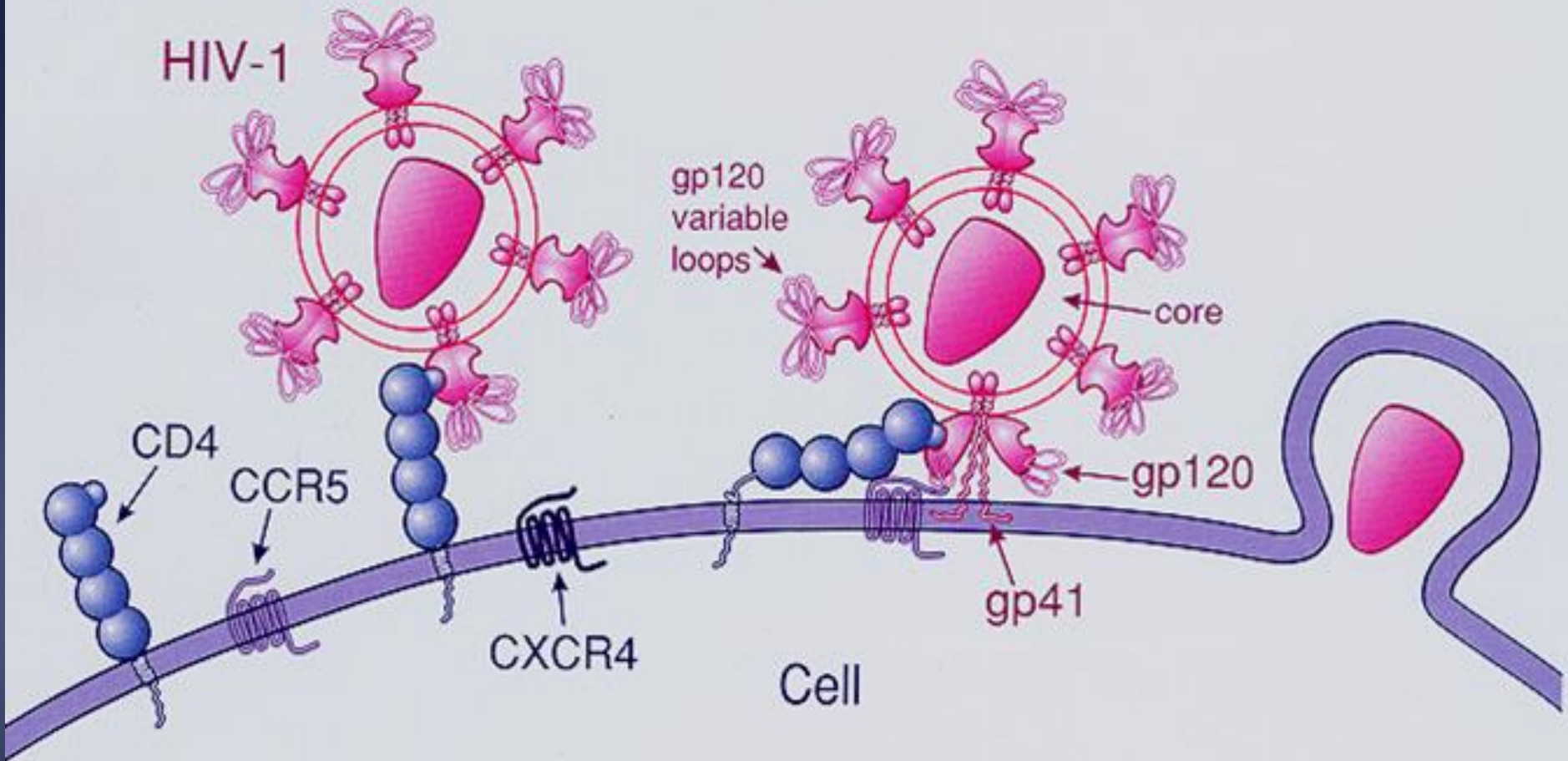


- ❑ CXCR4 is expressed on nearly all CD4 T cells whereas only 15-30% express CCR5. Therefore, X4 virus has a wider range of susceptible target cells

Sequential Binding of HIV to CD4+ Cells

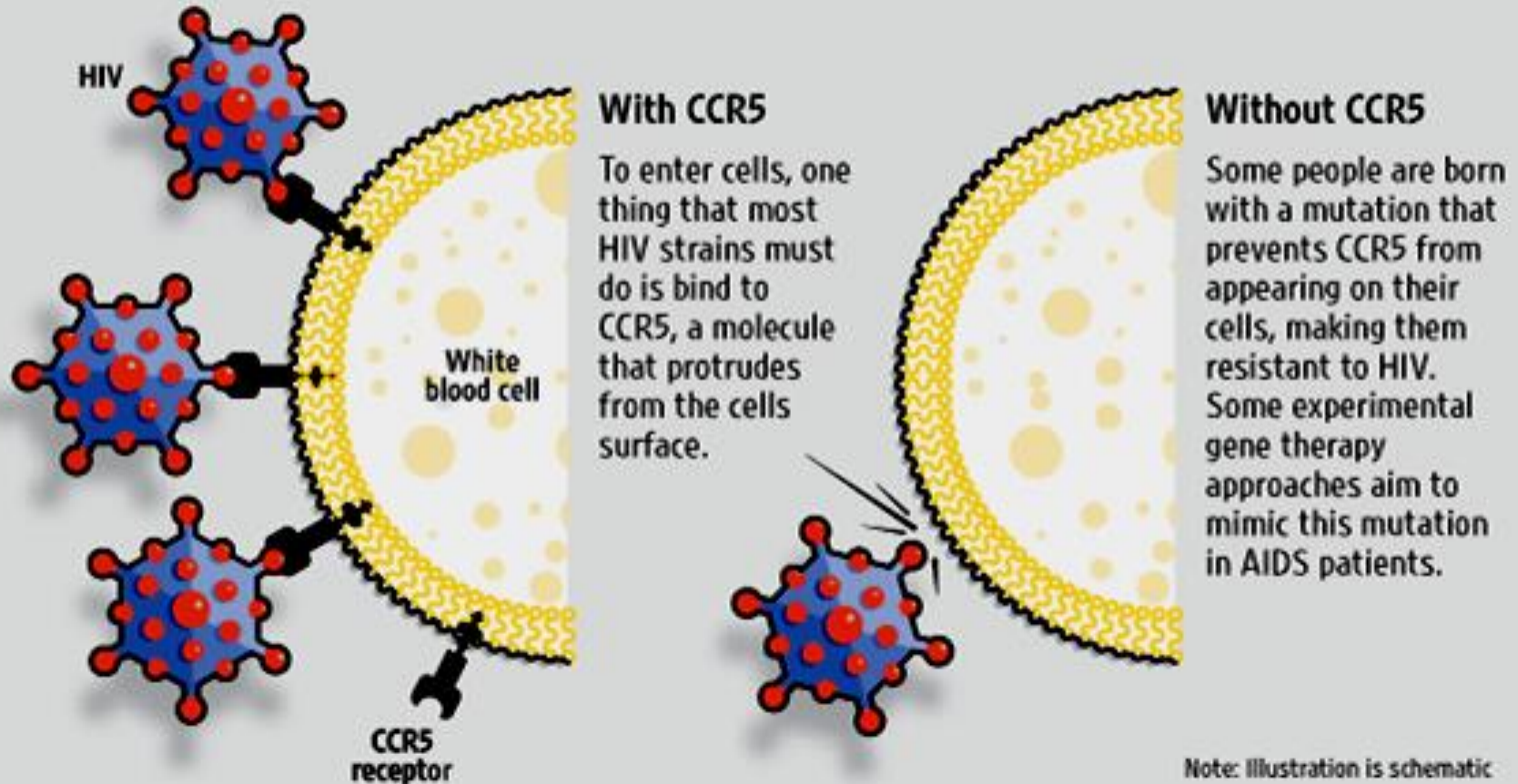


HIV Receptors Entry and Replication



CCR5 Delta-32 mutation & Resistance to HIV

Barring the Door | How a mutation can protect against HIV



- ❑ ~1% of Europeans, and even more in northern Europe, inherit the CCR5 mutation from both parents, making them resistant to HIV infection
- ❑ 10 to 15% of Europeans carry a mutation from 1 parent making it more difficult, but not impossible for them to become infected ("elite controllers"- maintain very low viral load without ART)
- ❑ People of African, Asian and South American descent almost never carry it

"Berlin Patient" Still HIV-free 4 Years after Bone Marrow Transplant

- ❑ Timothy Ray Brown, a 40-year-old man received 2 bone marrow transplants for acute myeloid leukemia
- ❑ Donor had a double or homozygous CCR5-delta32 mutation
- ❑ The patient was 'conditioned' by intensive chemotherapy and radiation prior to transplantation
- ❑ Successful reconstitution of CD4⁺ T cells in blood and gut without any trace of HIV
- ❑ The last direct evidence of HIV was detectable on day 60 after transplantation.

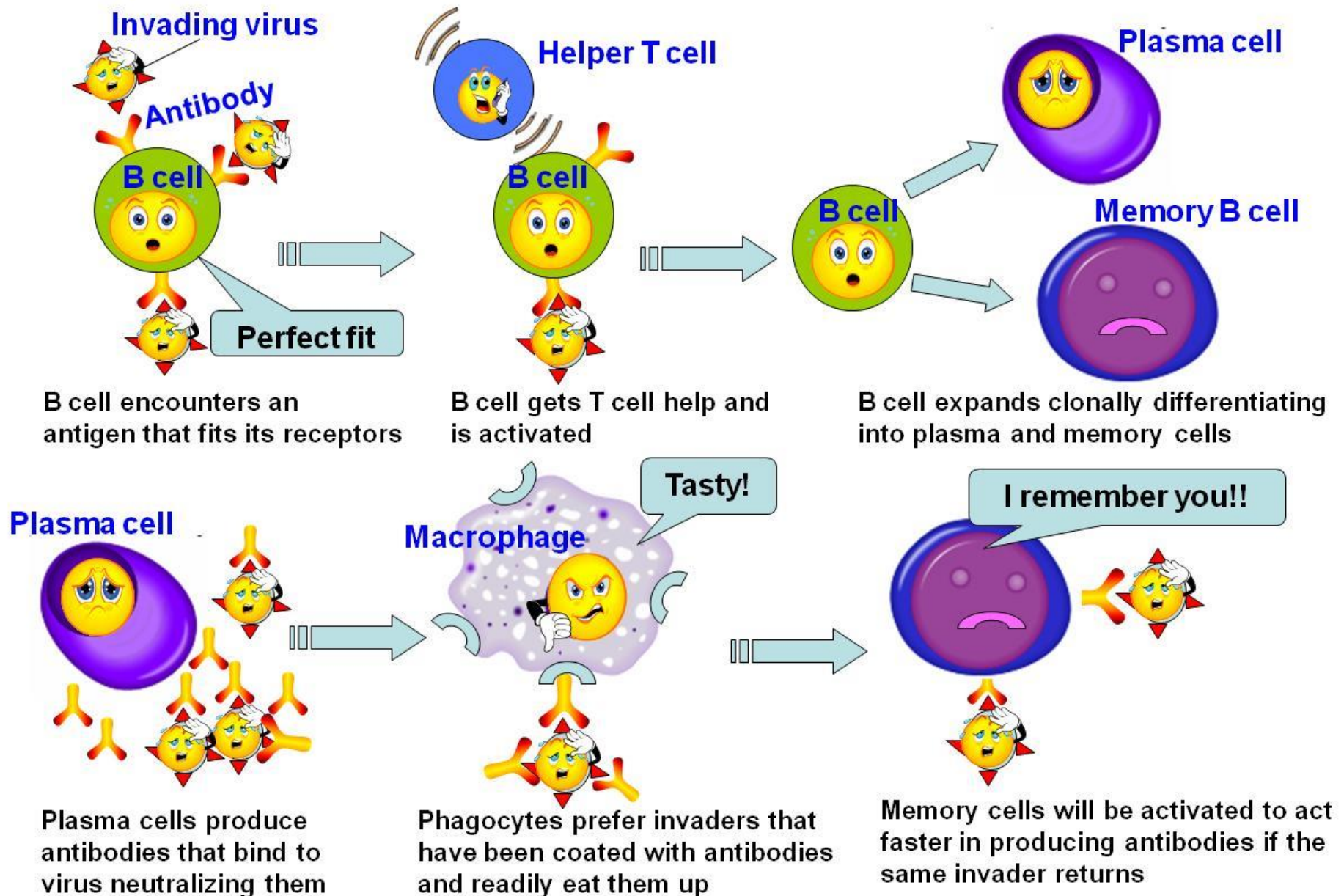


Doctor Gero Huetter of Berlin's University Hospital 'Charite,' speaks to the press about the miraculous recovery of his patient.

This is currently the only case of HIV that has been cured in the world



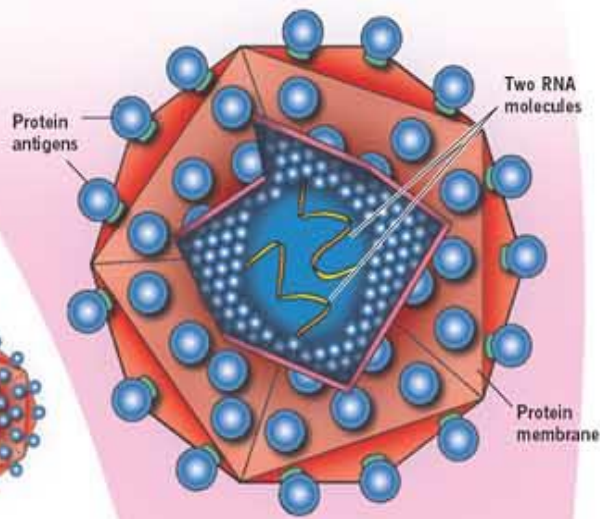
HIV and The Immune System



Fighting HIV

HIV attacks

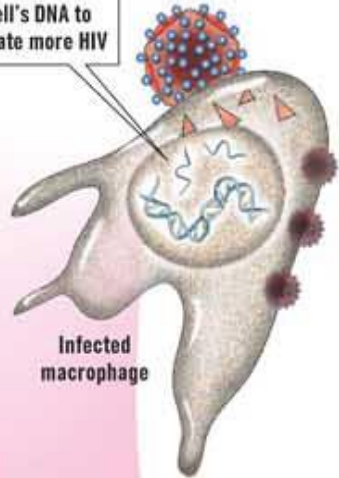
As the human immunodeficiency virus (HIV) travels through the blood, it reproduces by burrowing into cells and combining its RNA with the cell's DNA to create copies of itself.



HIV retrovirus

RNA material combines with cell's DNA to create more HIV

New HIV virus buds out of cell



Infected macrophage

Losing the battle

The major weakness in the body's immune system is the CD4 "helper" T-cell. By binding with CD4 cells, HIV can kill them and stop production of antibodies, leaving the immune system weakened and vulnerable to opportunistic disease.

Doctors gauge the health of the immune system by counting CD4 cells. A healthy, HIV-negative adult has between 600 and 1,200 CD4 cells per cubic millimeter of blood. If the count falls below 350, the immune system has become weakened.

Body battles back

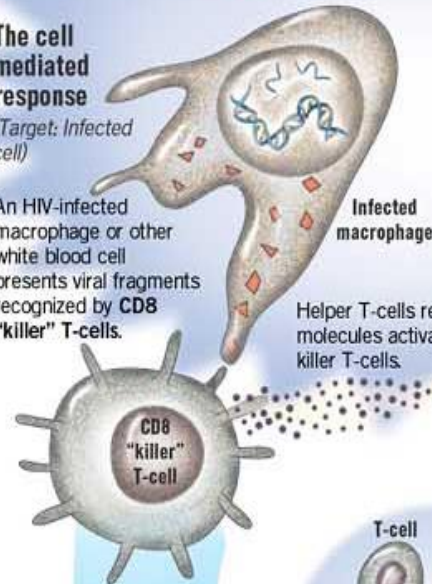
The immune system responds in two ways. In the **humoral response**, B-cells produce **antibodies** that attach to the virus and mark it for destruction by other white blood cells called **macrophages**.

In the second defense, called the **cellular response**, specialized white blood cells called **T-cells** either help to make antibodies or kill cells already infected with HIV.

The cell mediated response

(Target: Infected cell)

An HIV-infected macrophage or other white blood cell presents viral fragments recognized by CD8 "killer" T-cells.



Infected macrophage

Helper T-cells release molecules activating killer T-cells.

Killer T-cells are prompted by helper T-cells to destroy more HIV-infected cells.

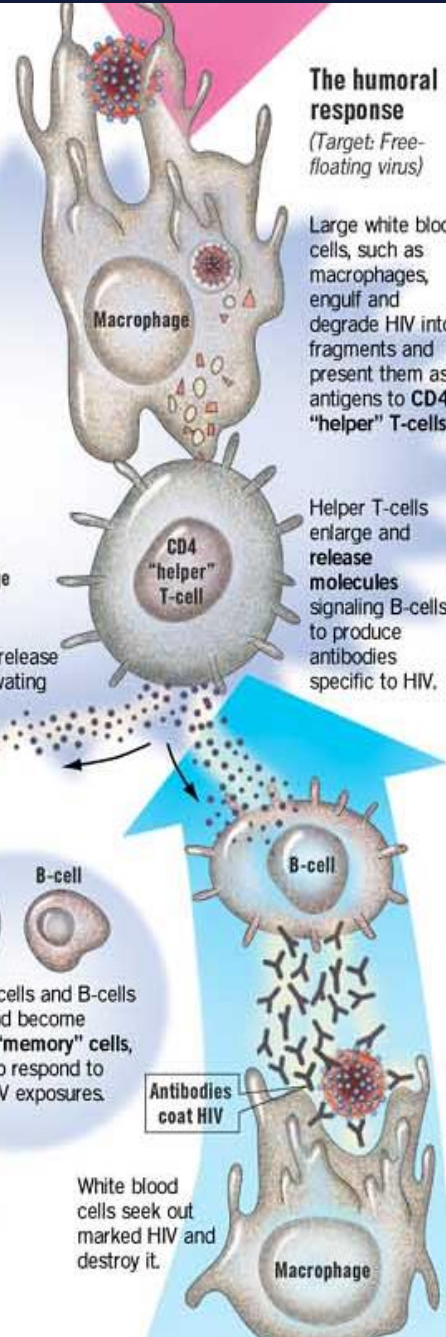


The humoral response

(Target: Free-floating virus)

Large white blood cells, such as macrophages, engulf and degrade HIV into fragments and present them as antigens to CD4 "helper" T-cells.

Helper T-cells enlarge and release molecules signaling B-cells to produce antibodies specific to HIV.



Antibodies coat HIV

White blood cells seek out marked HIV and destroy it.

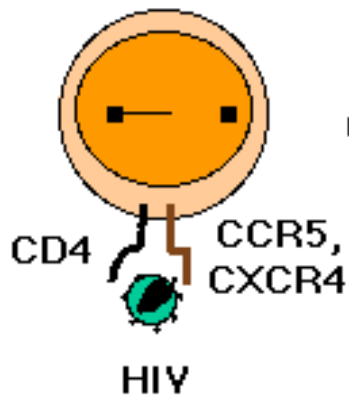
Macrophage

Macrophage

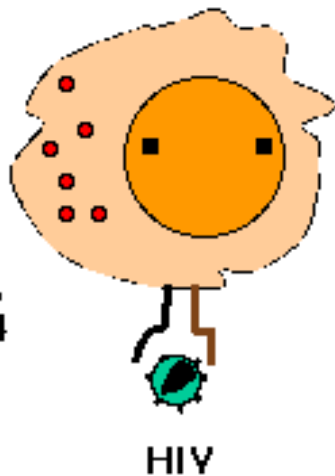
Cell Types Infected by HIV

HIV uses the same receptors to infect blood cells

T-lymphocyte



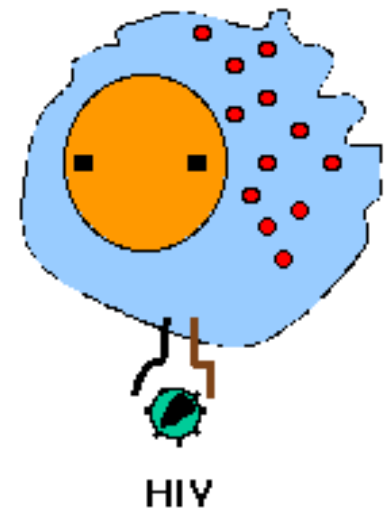
NKT cell



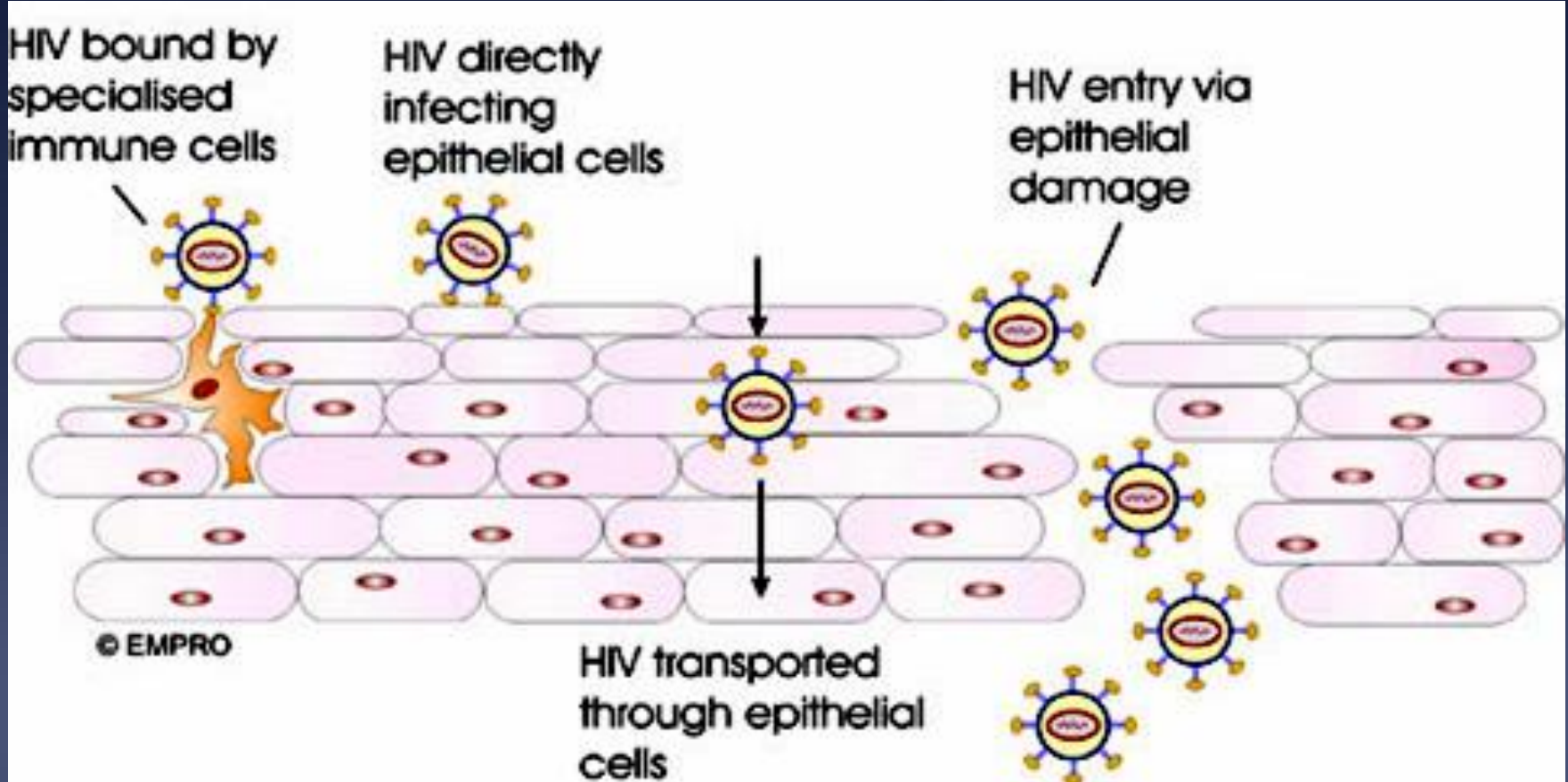
Macrophage



**NK cell
(CD4+)**



HIV and the Epithelium

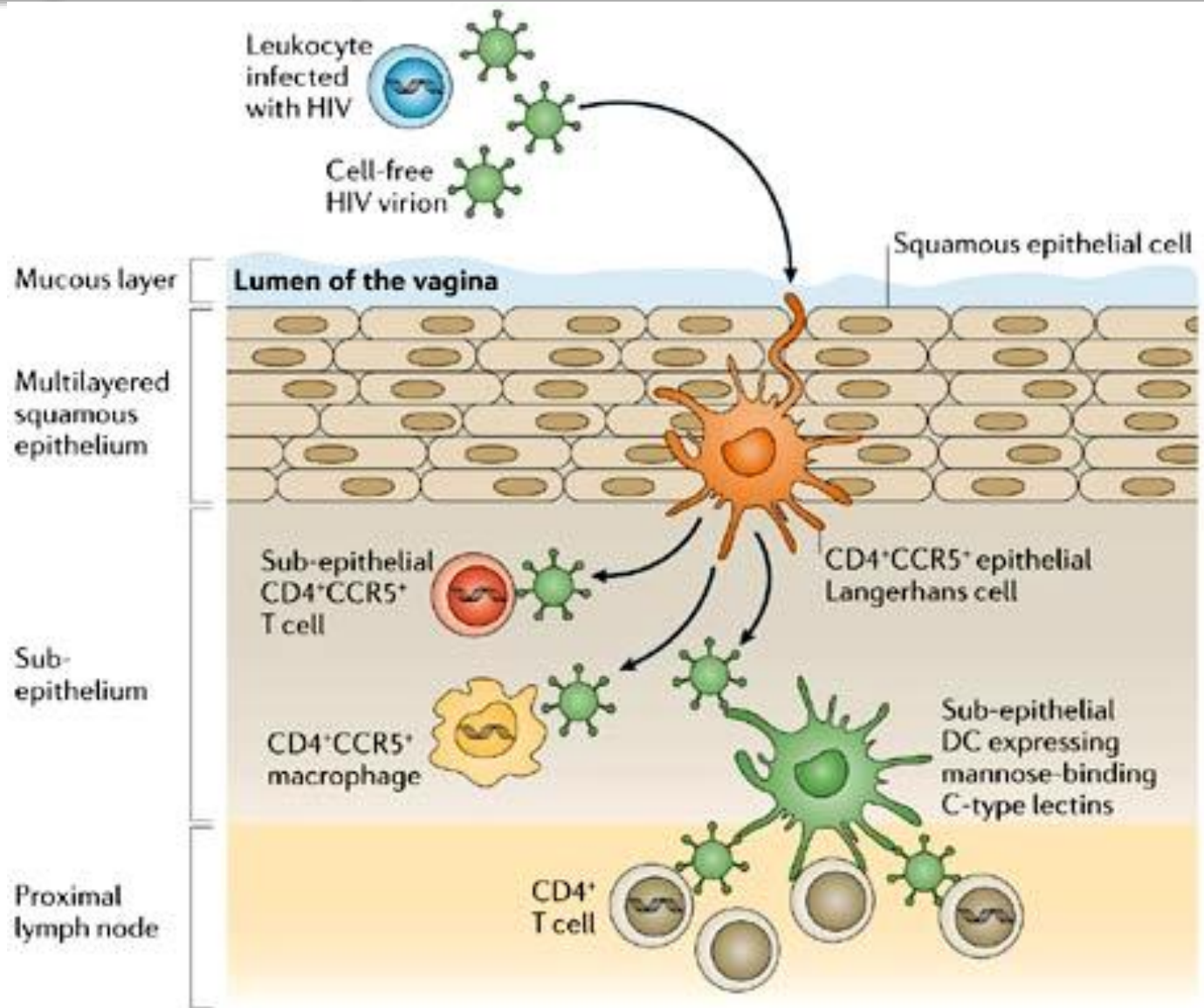


❑ Free and cell associated HIV may be able to cross these columnar and stratified epithelial cell layers in a number of ways. These include:

- ❑ Free HIV directly infecting the epithelial cells
- ❑ Free HIV being transported through the epithelial cell
- ❑ Cell-associated HIV passing between the epithelial cells
- ❑ Free HIV being bound by specialized immune cells in the epithelial layer
- ❑ Free HIV gaining access to underlying tissue and cells by the effects of physical damage to the epithelial layer

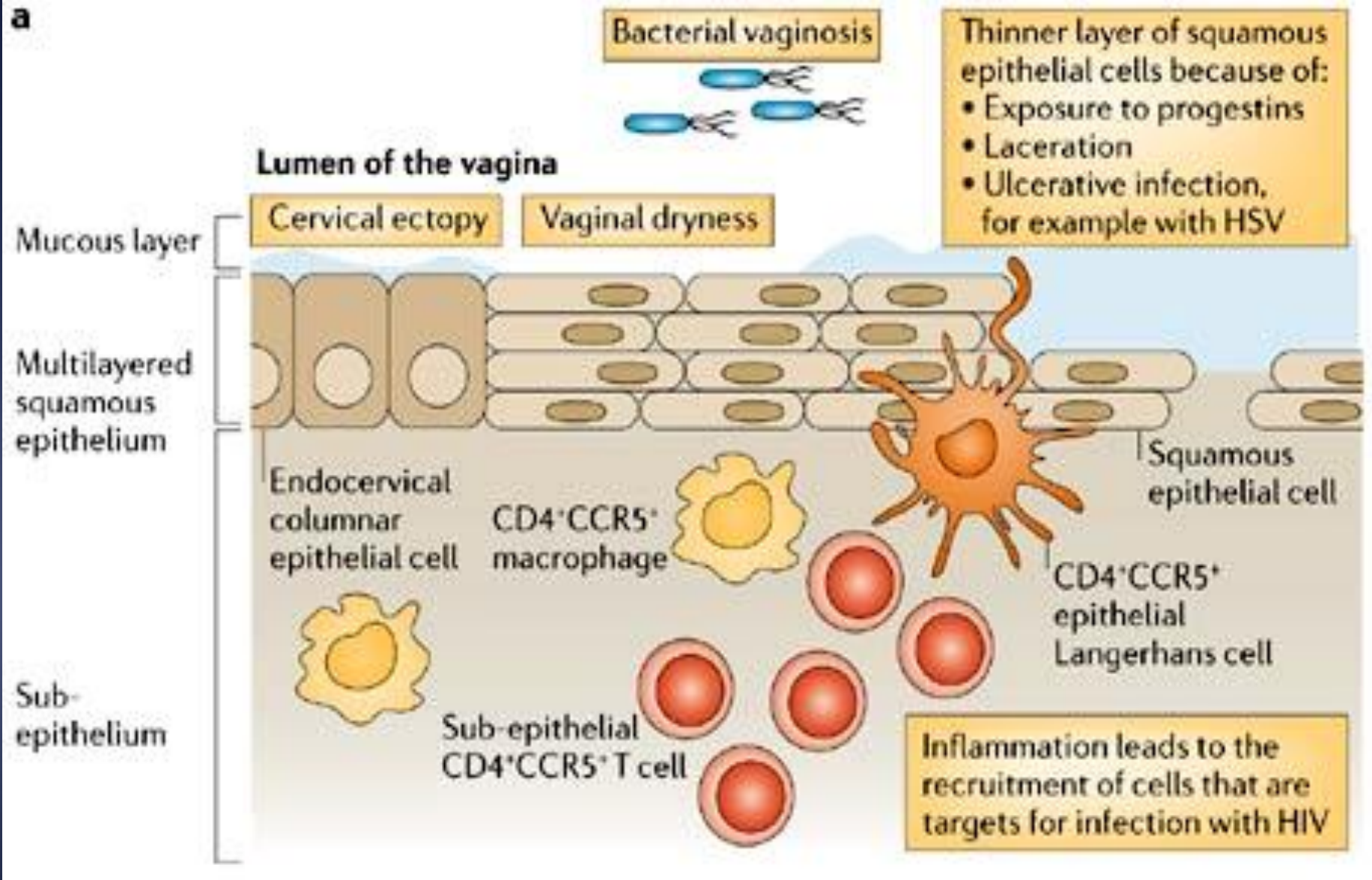


Vaginal Acquisition of HIV infection

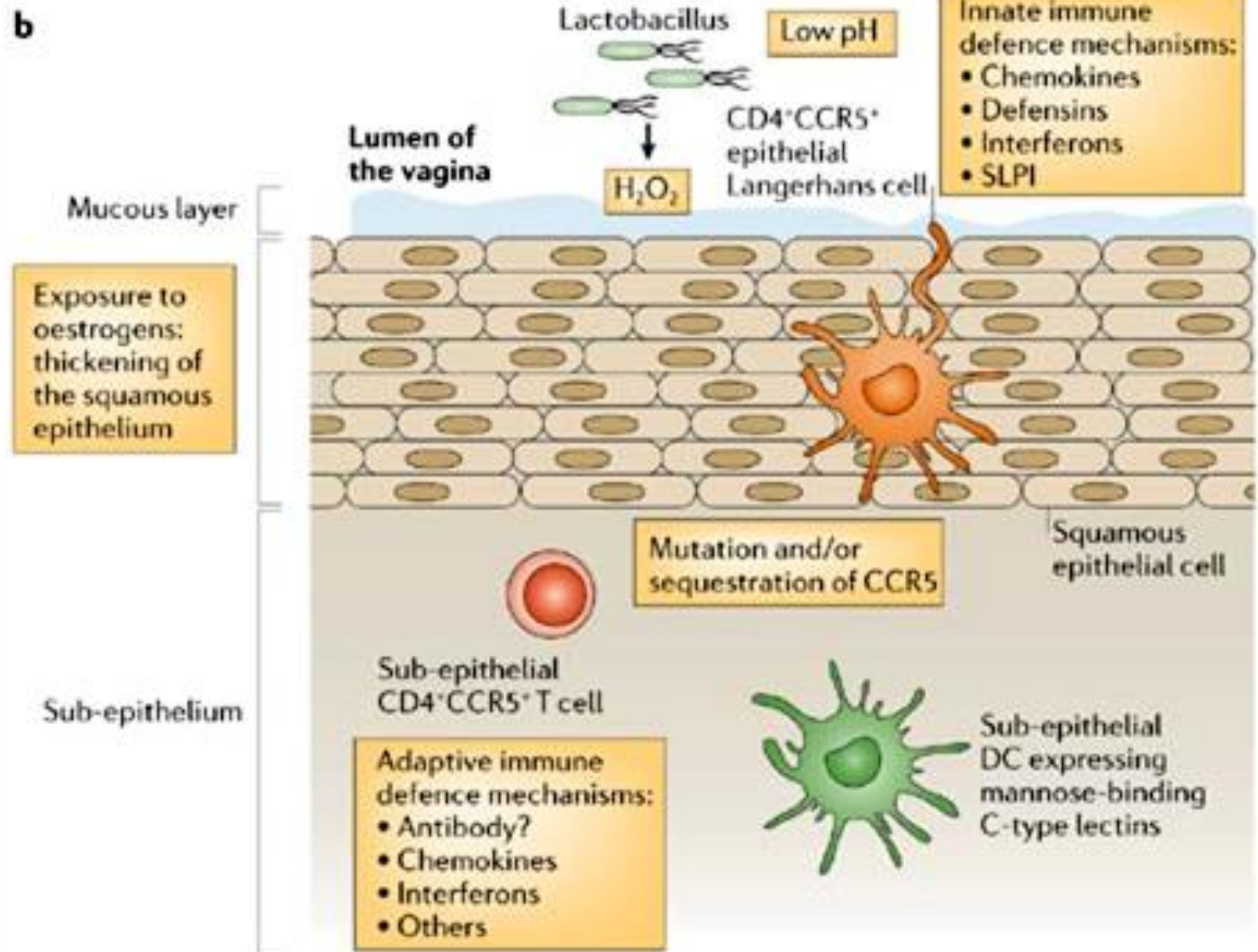


Factors that can increase the risk of HIV infection

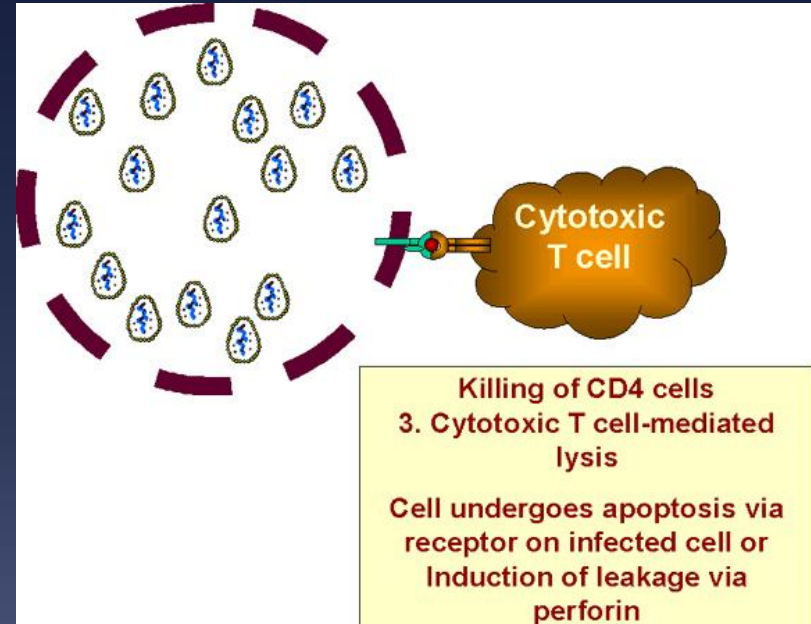
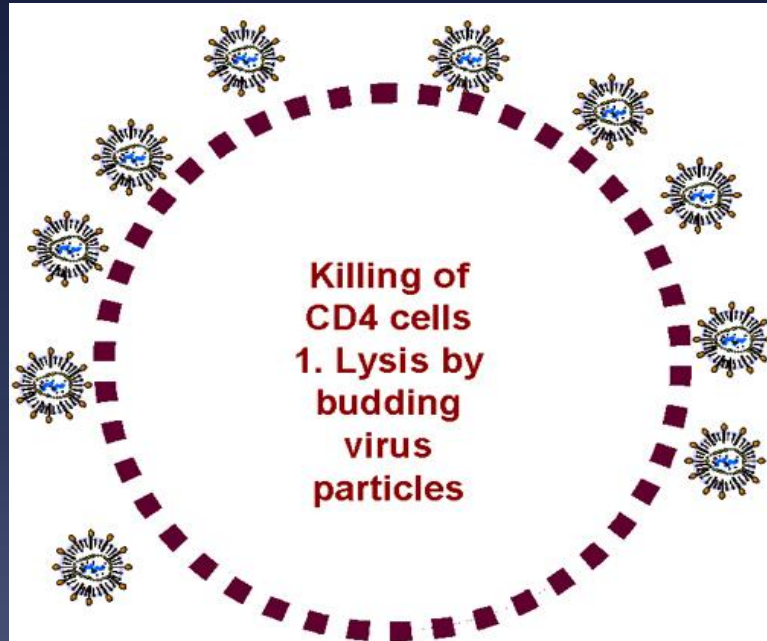
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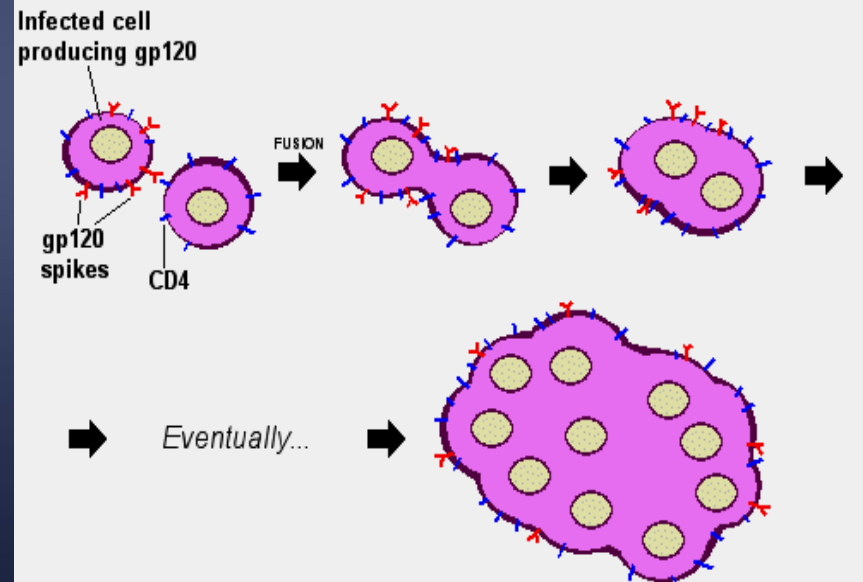
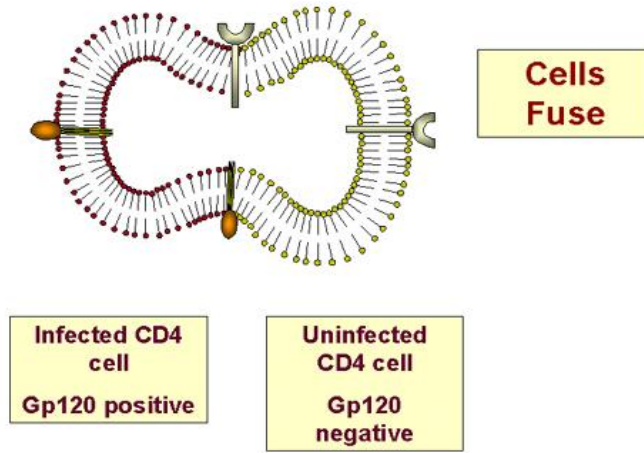
Factors That can Decrease Risk of HIV Infection



Possible Mechanisms for the Loss of CD4 cells After HIV infection



Killing of CD4 cells 2. Syncytium Formation



HIV Induced Syncytia

