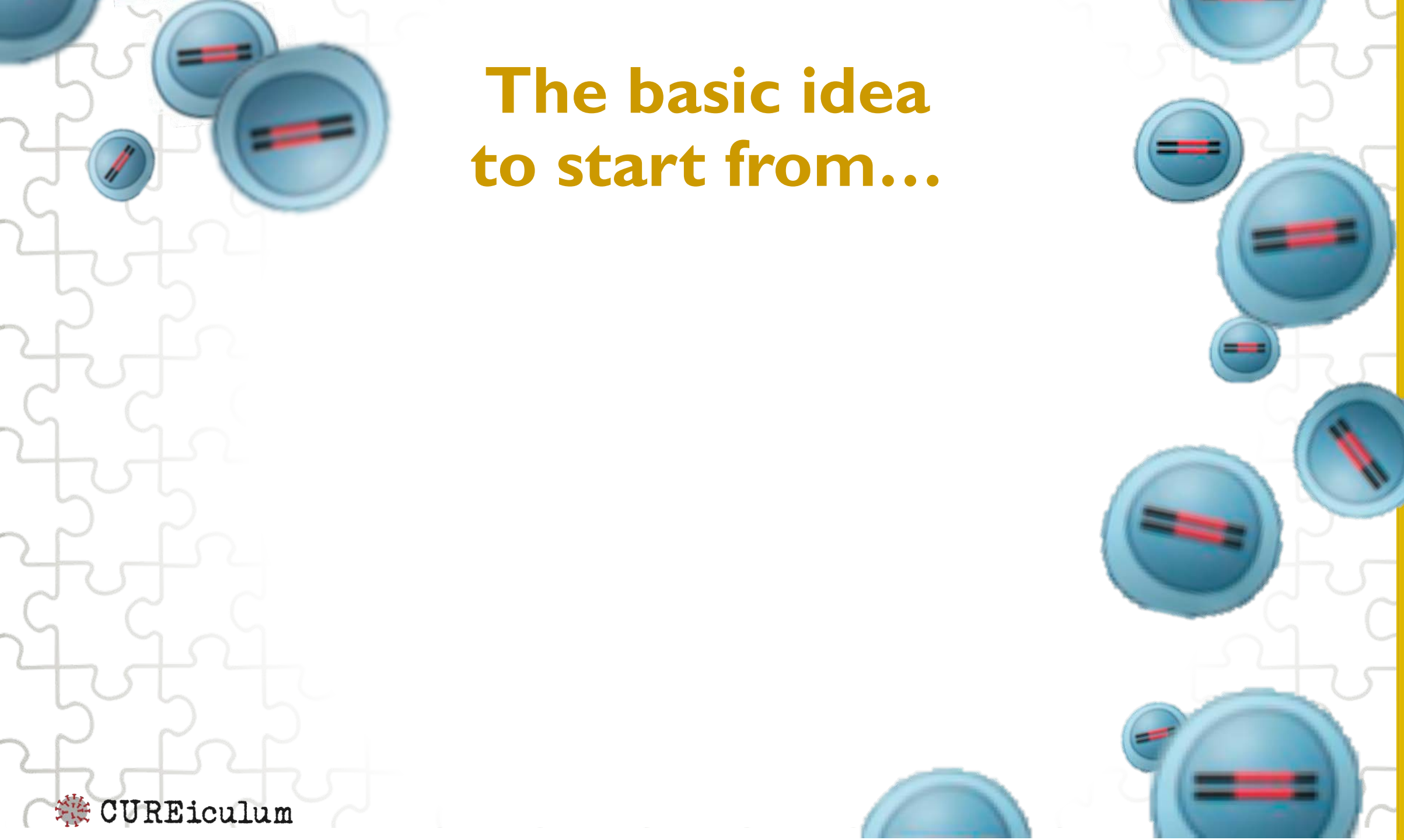
HIV Persistence

What We Know about How HIV Persists in Your Body Despite Taking Antiretroviral Therapy

CUREiculum

This research training curriculum is a collaborative project aimed at making the science of HIV cure-related research accessible to the community and the HIV research field.

The basic idea to start from…



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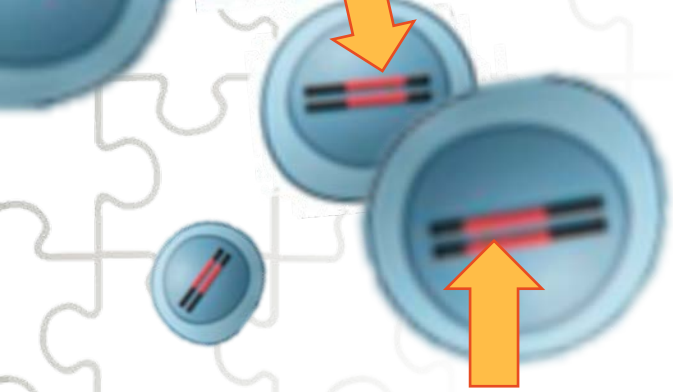

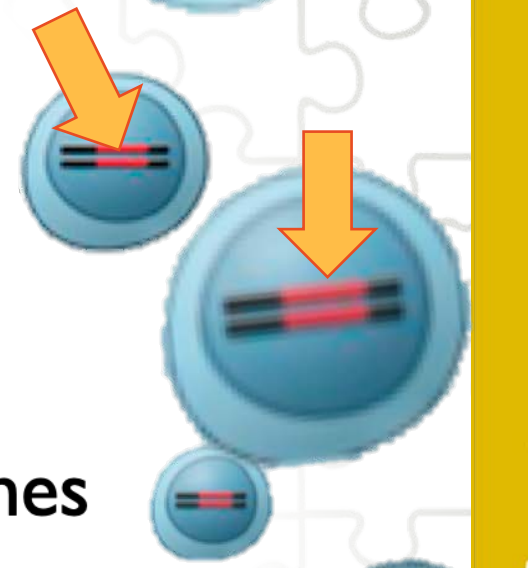

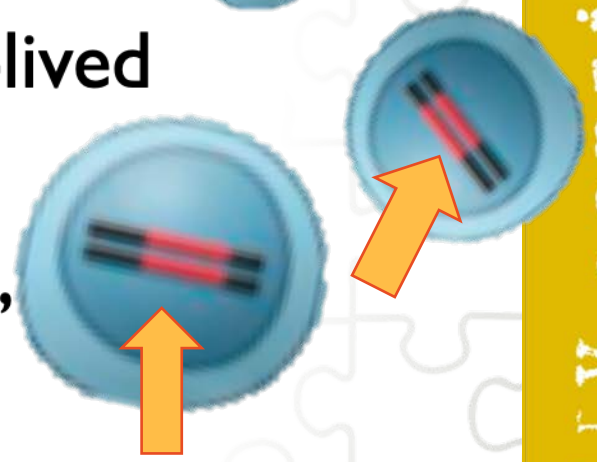

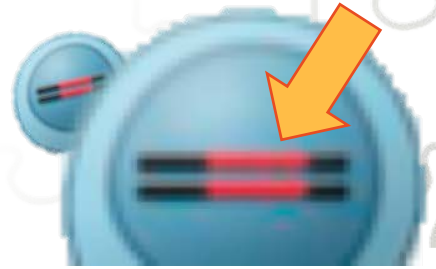

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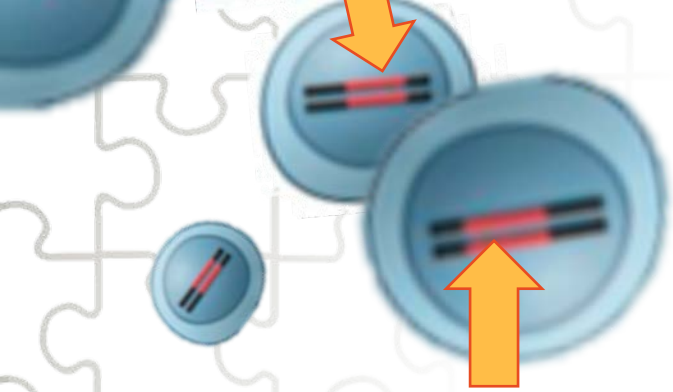

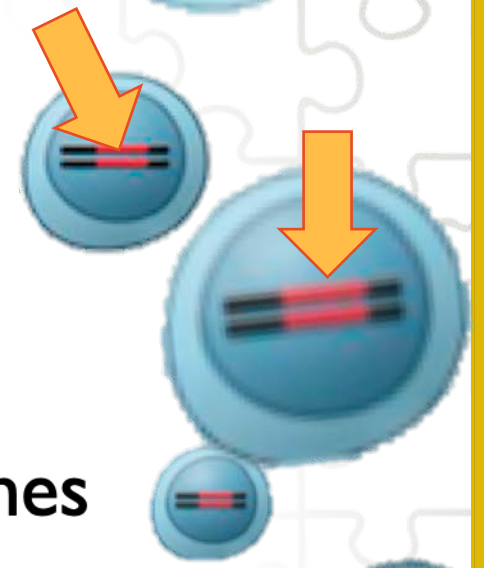

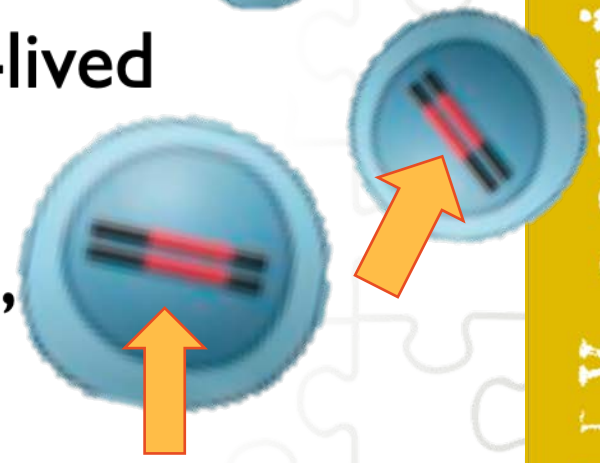

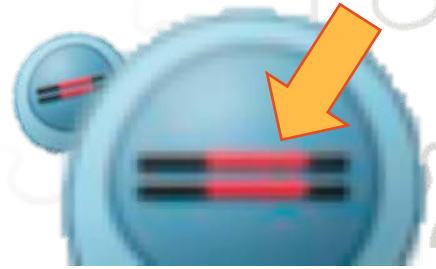

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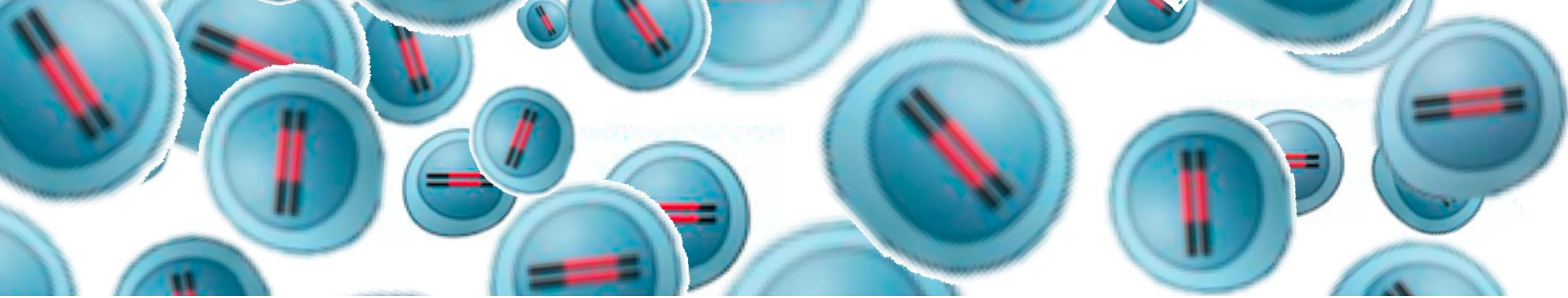
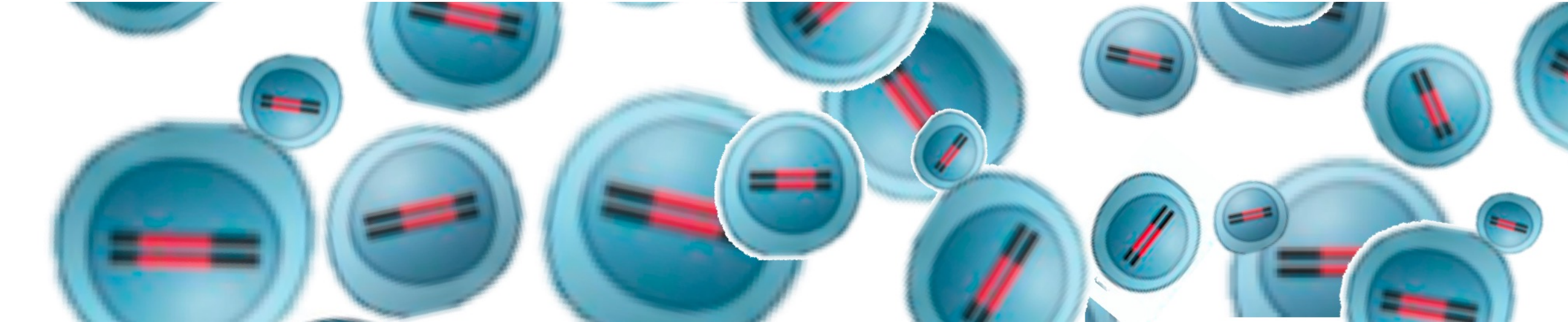
- HIV that persists despite ART is referred to as…



…the *HIV reservoir*



HIV viral load and the hidden reservoir

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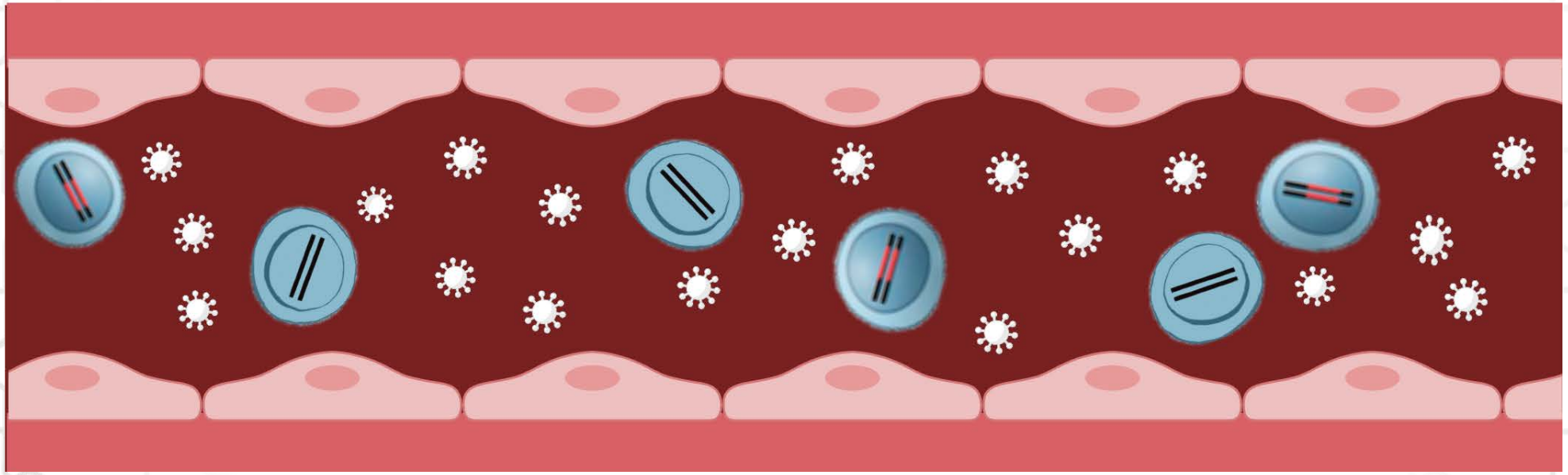
When HIV is replicating in the body, copies of the virus are floating freely in the bloodstream and can damage the immune system.



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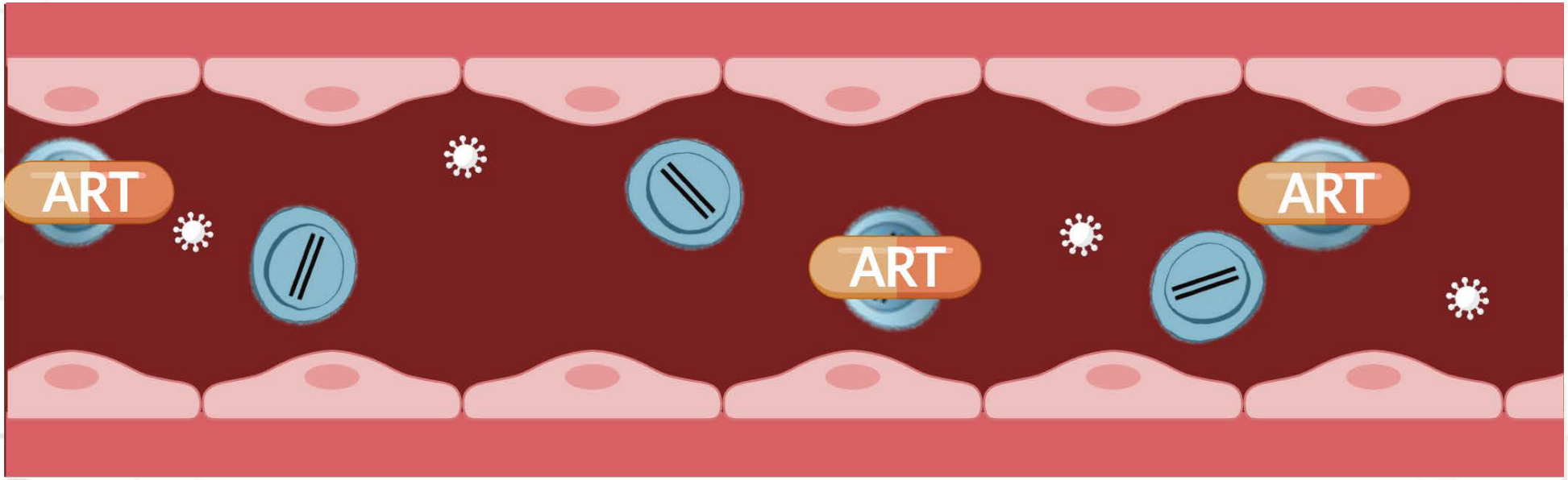
Antiretroviral therapy (ART) blocks the virus from replicating, preventing damage to the immune system



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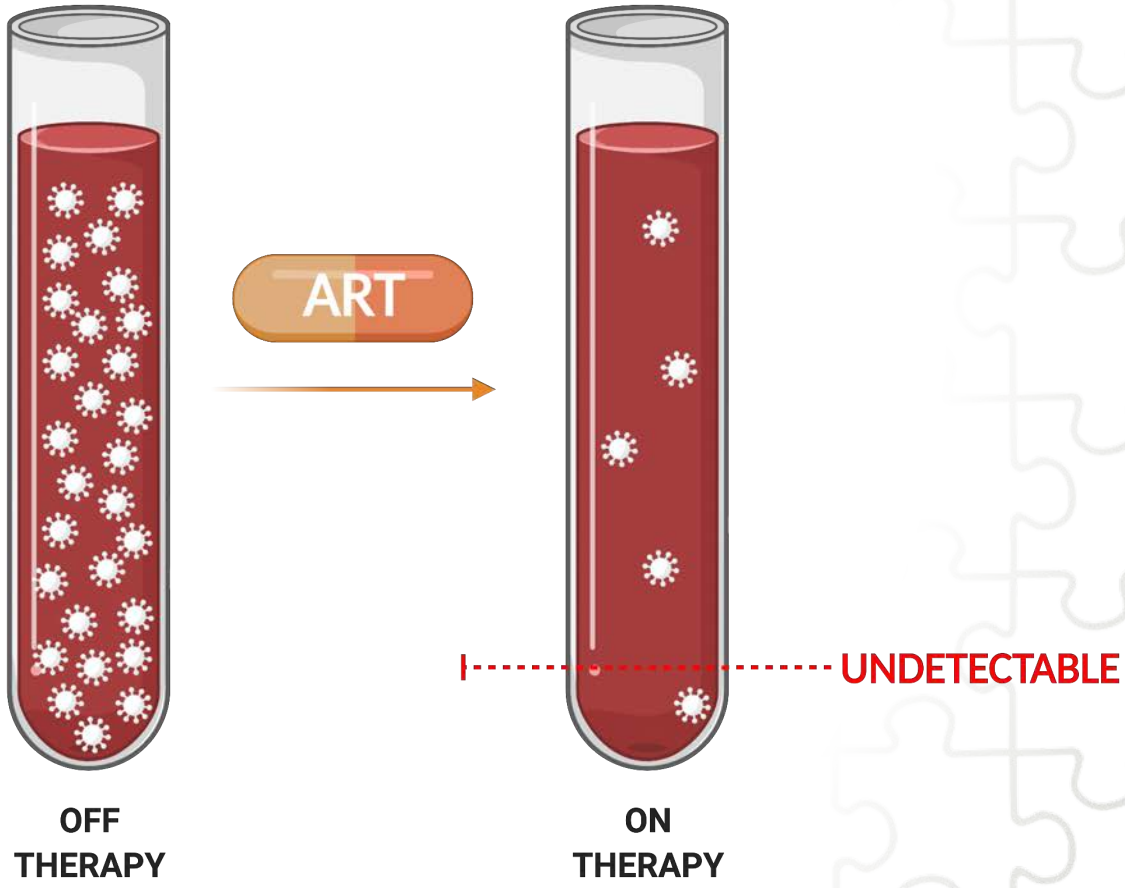
In people on ART, the number of HIV copies that can be measured in a blood sample by the viral load test typically declines to levels too low to detect ("undetectable").



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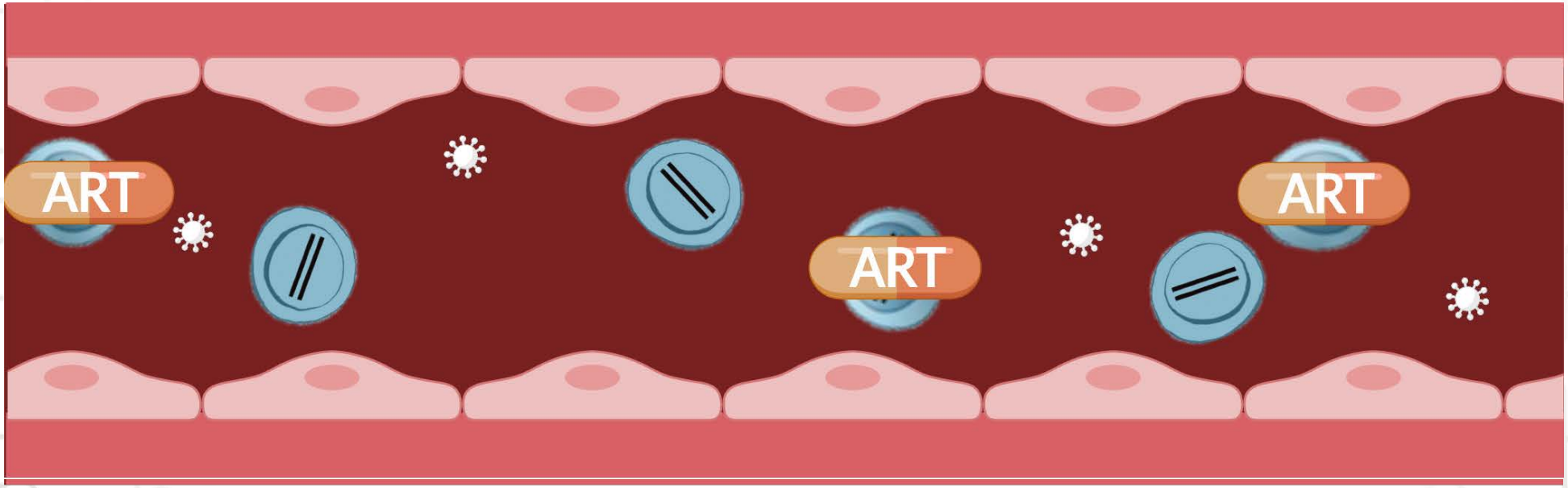
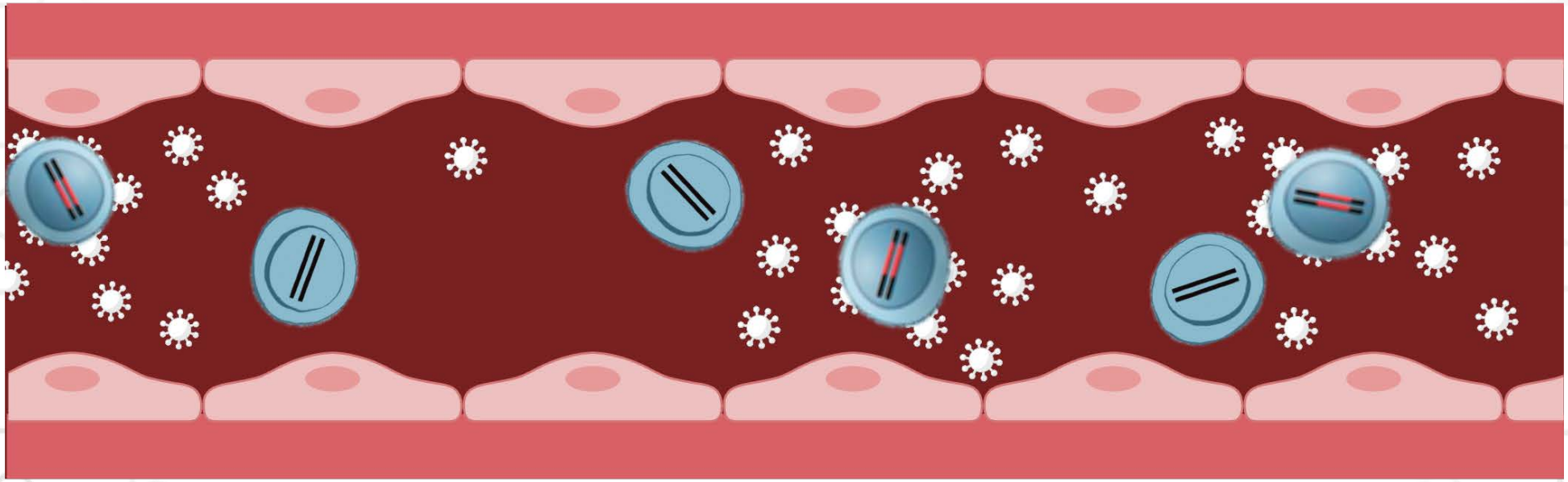
But even if viral load is undetectable, HIV usually remains present inside some cells (the persistent HIV reservoir).



HIV viral load and the hidden reservoir

Unfortunately, if ART is stopped, HIV replication almost always restarts from this reservoir and HIV copies become detectable again by the viral load test



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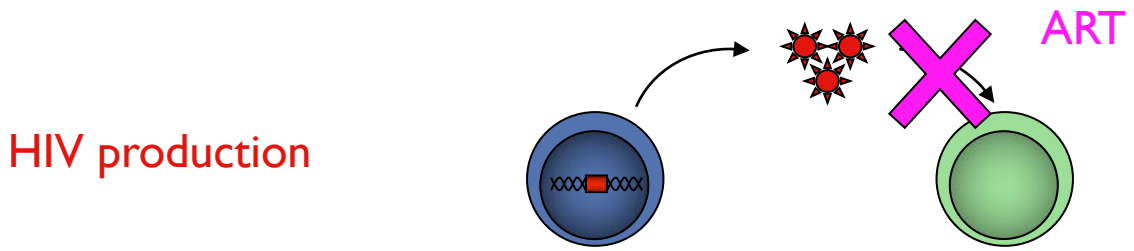

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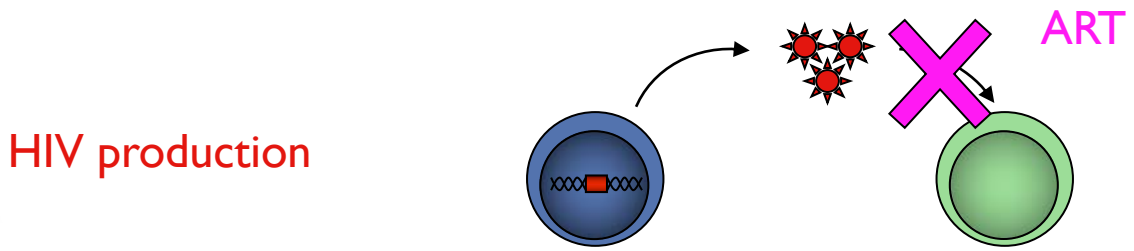
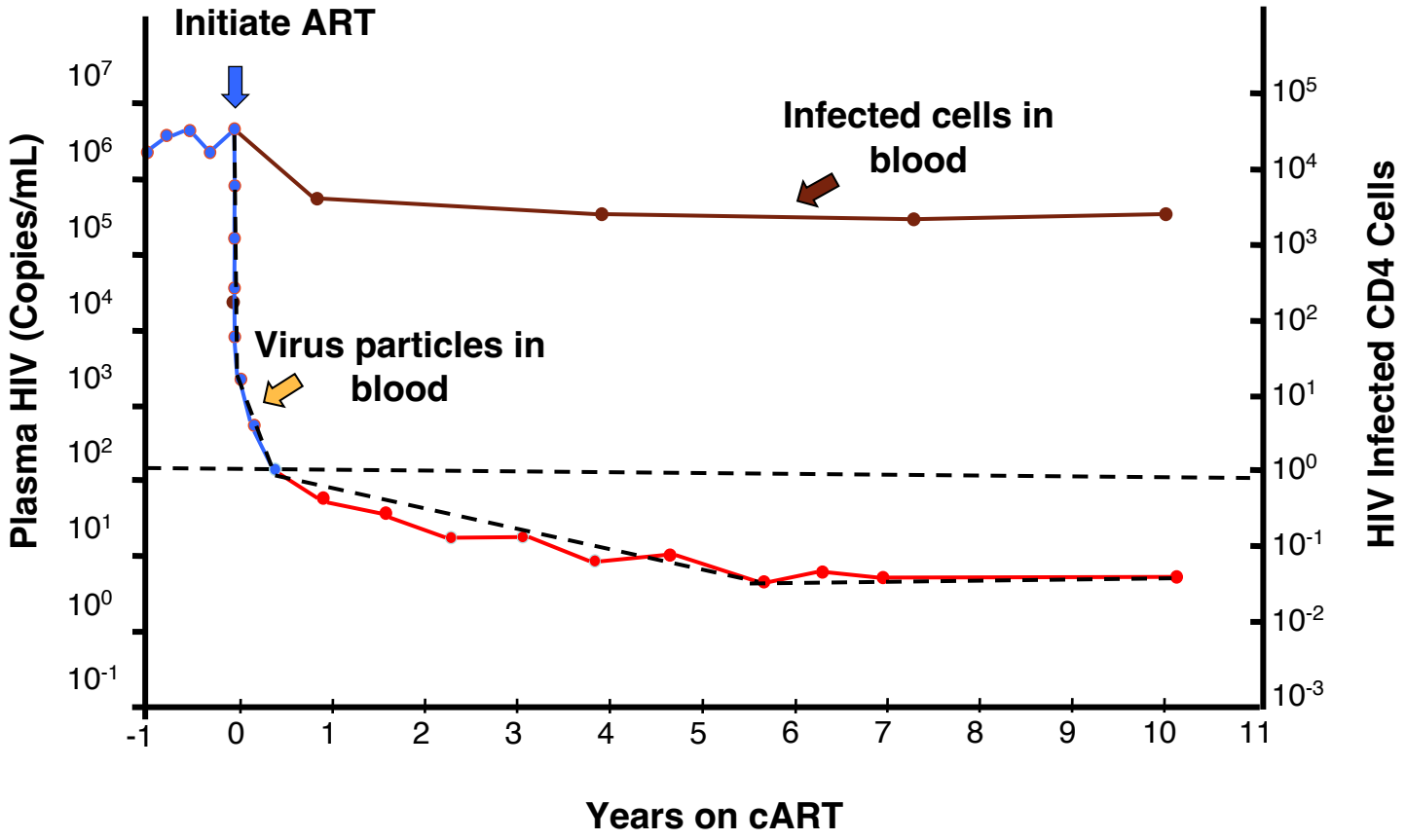


- If ART is stopped, HIV copies can emerge from these long-lived infected cells, infect other cells and replicate, causing a rebound in viral load

ART doesn't cure HIV infection



The number of HIV RNA copies (viral load) declines rapidly after ART is started, but the number of HIV-infected cells containing the virus's genetic blueprint in the form of DNA declines very slowly

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- **HIV exploits this feature** of the immune system to persist. in the body, by infecting and hiding out in long-lived memory CD4+ T cells

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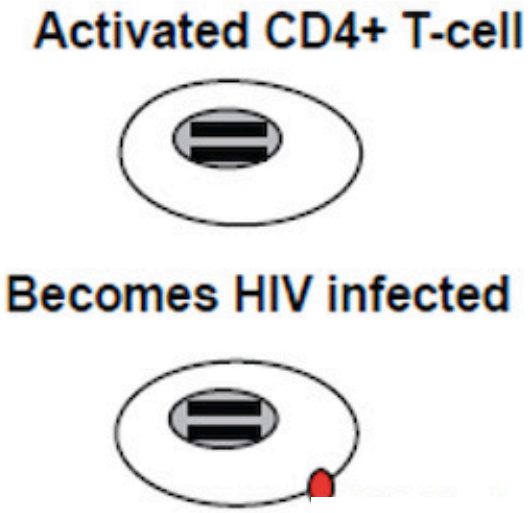

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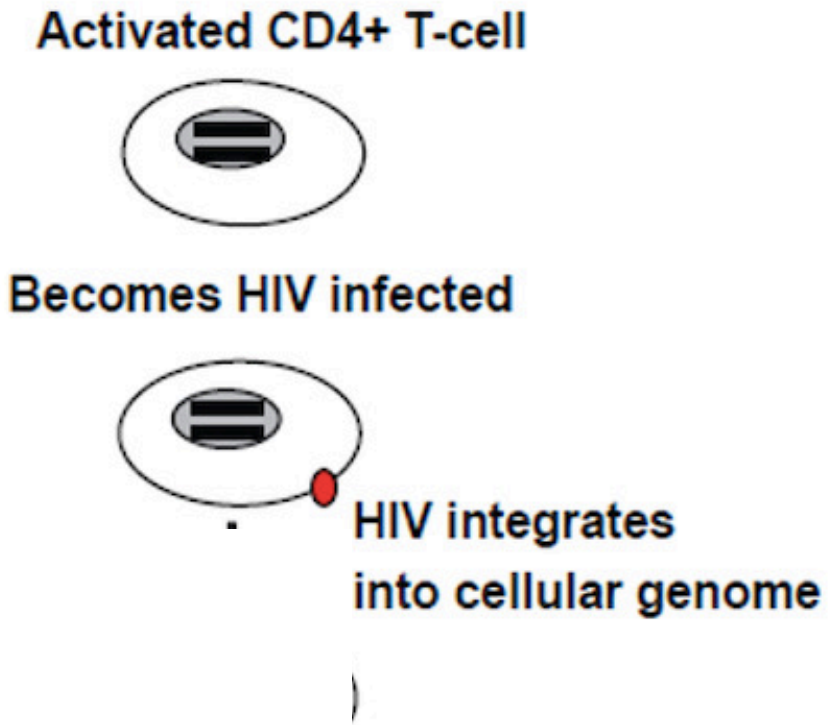

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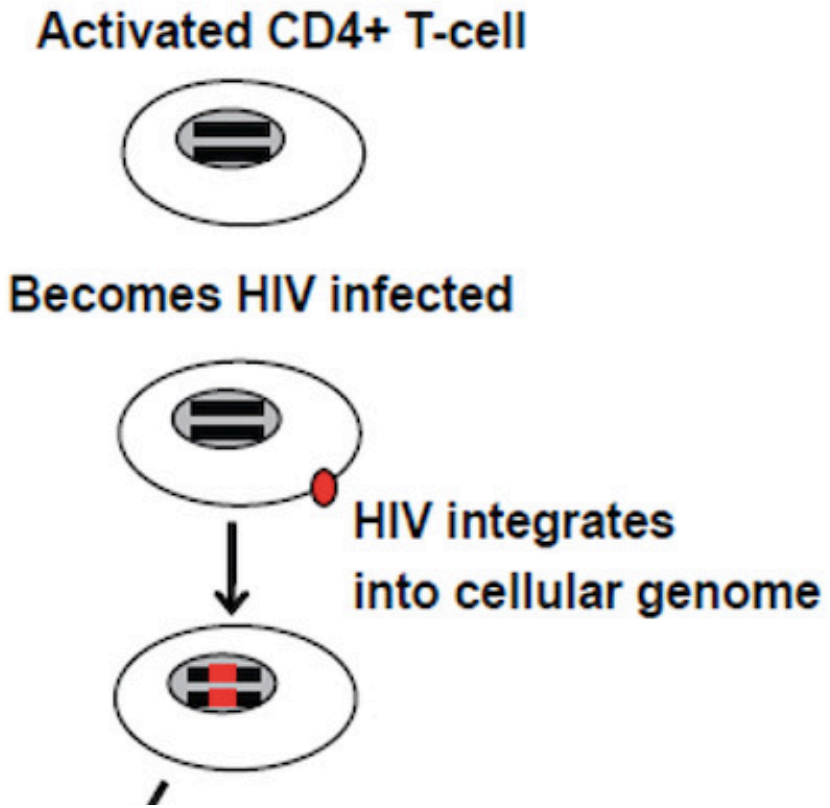

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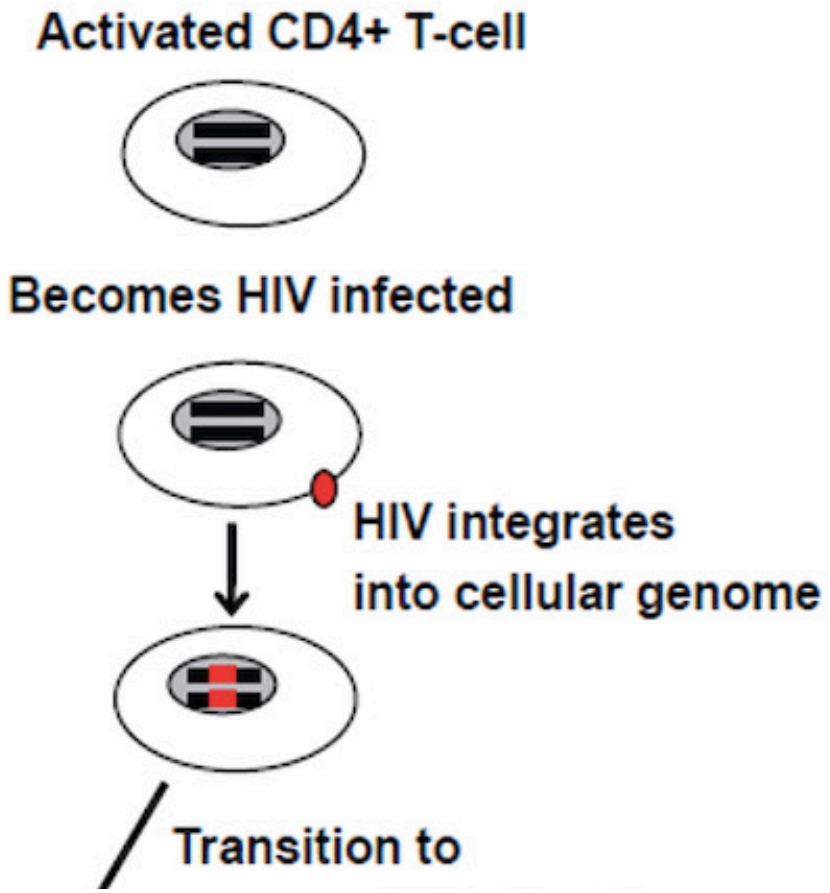

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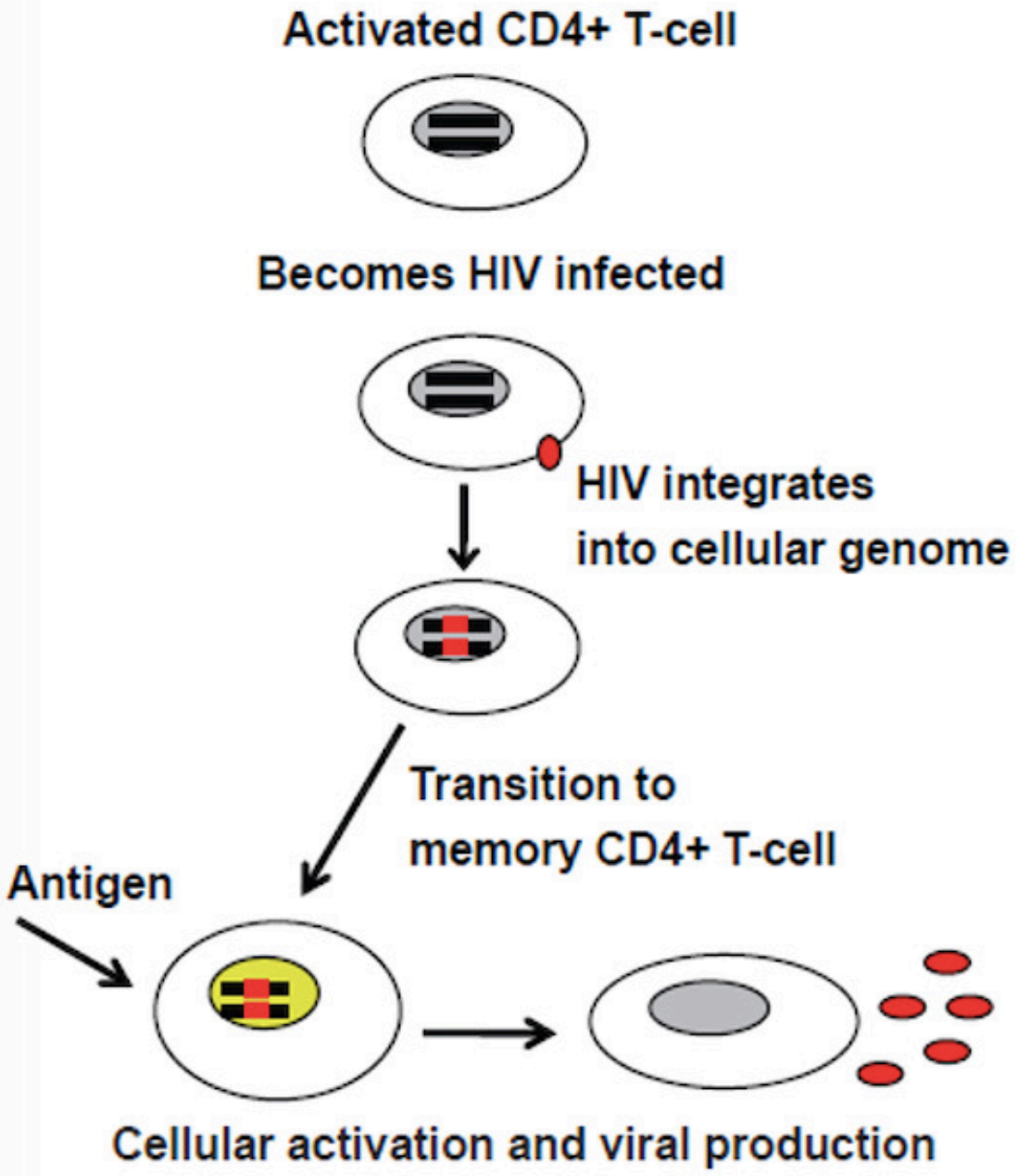

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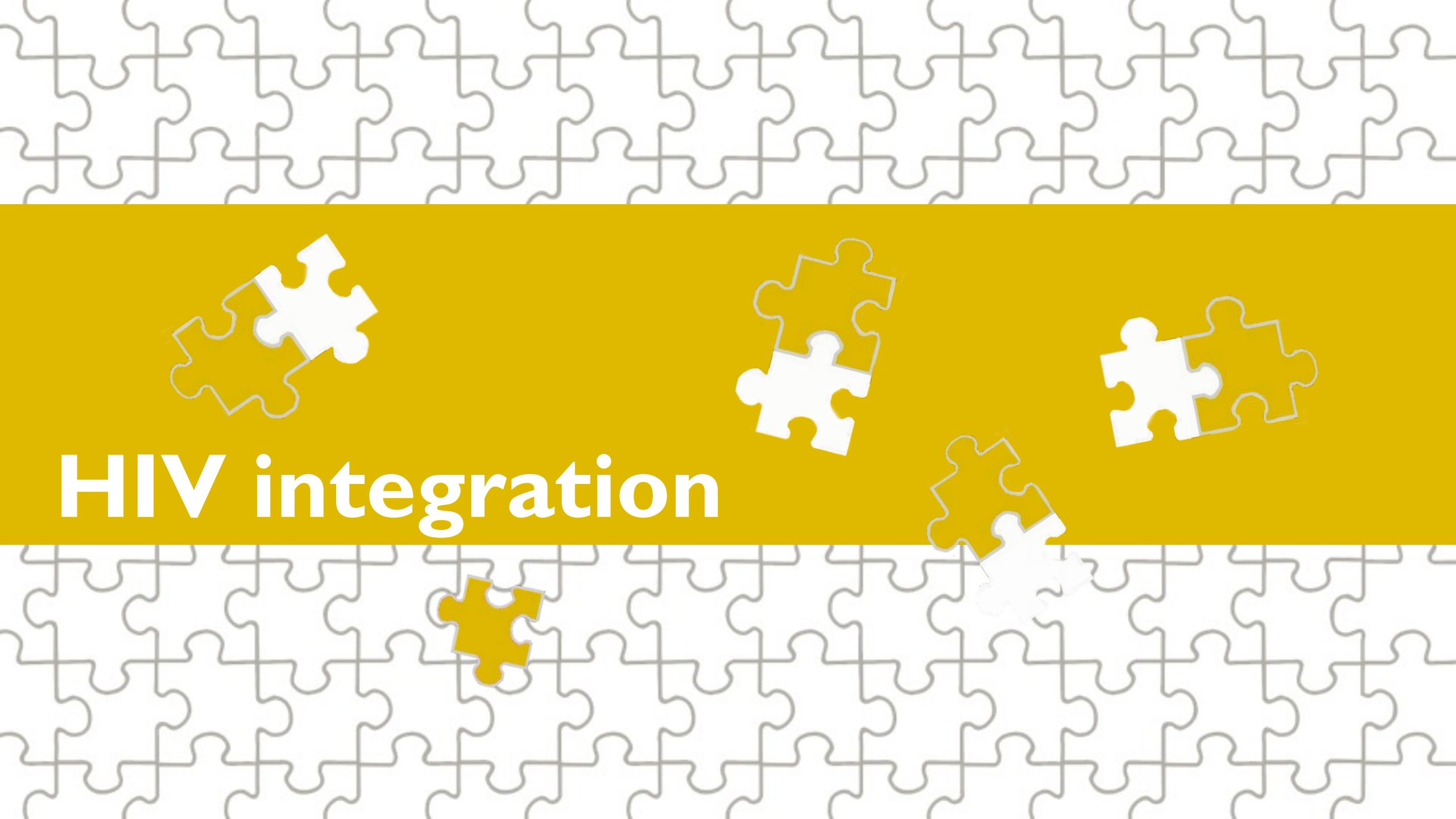
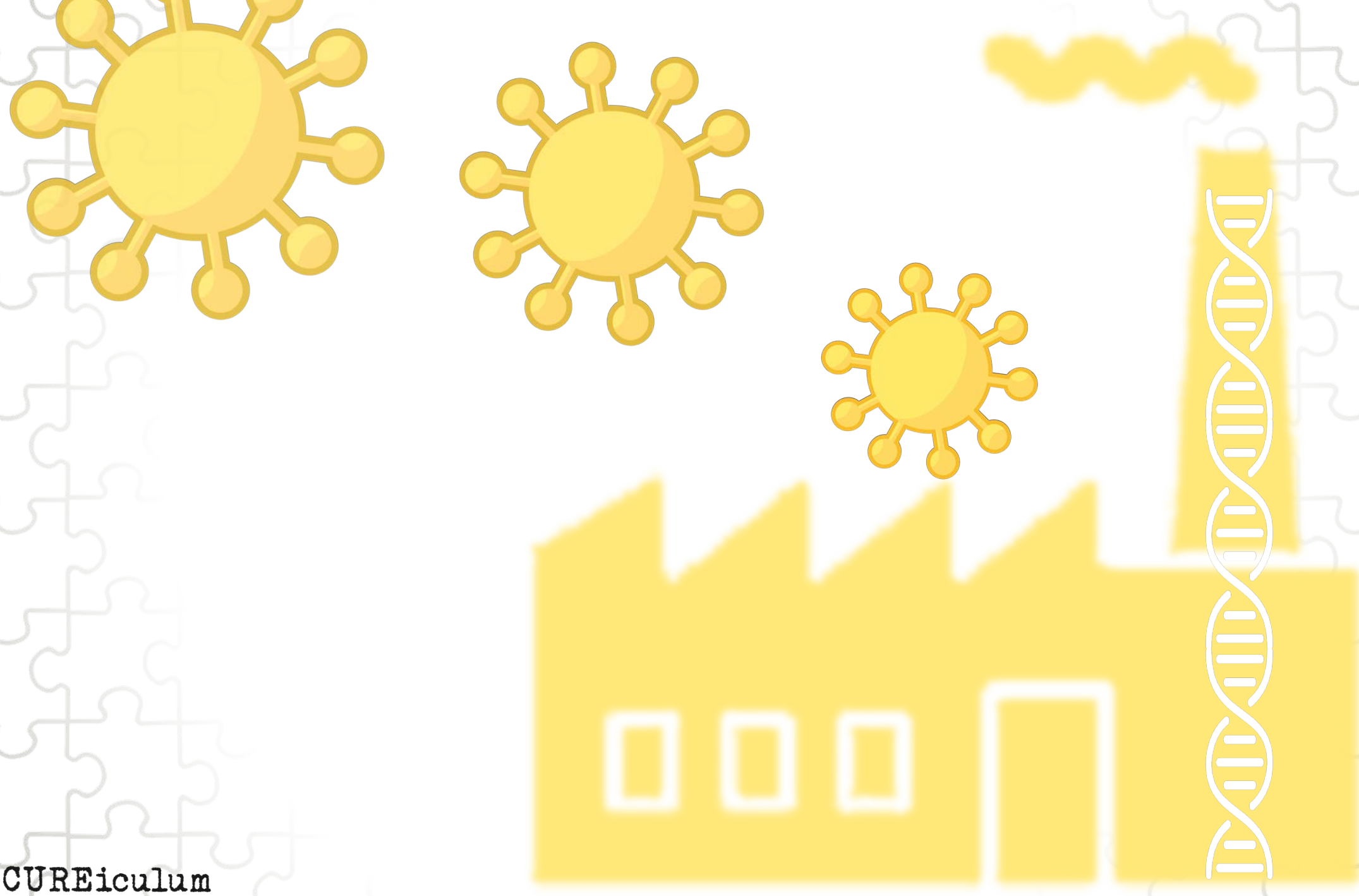
HIV integration





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    - HIV's genetic code integrates into the genome of CD4+ T cells, hijacking the factory to make HIV proteins

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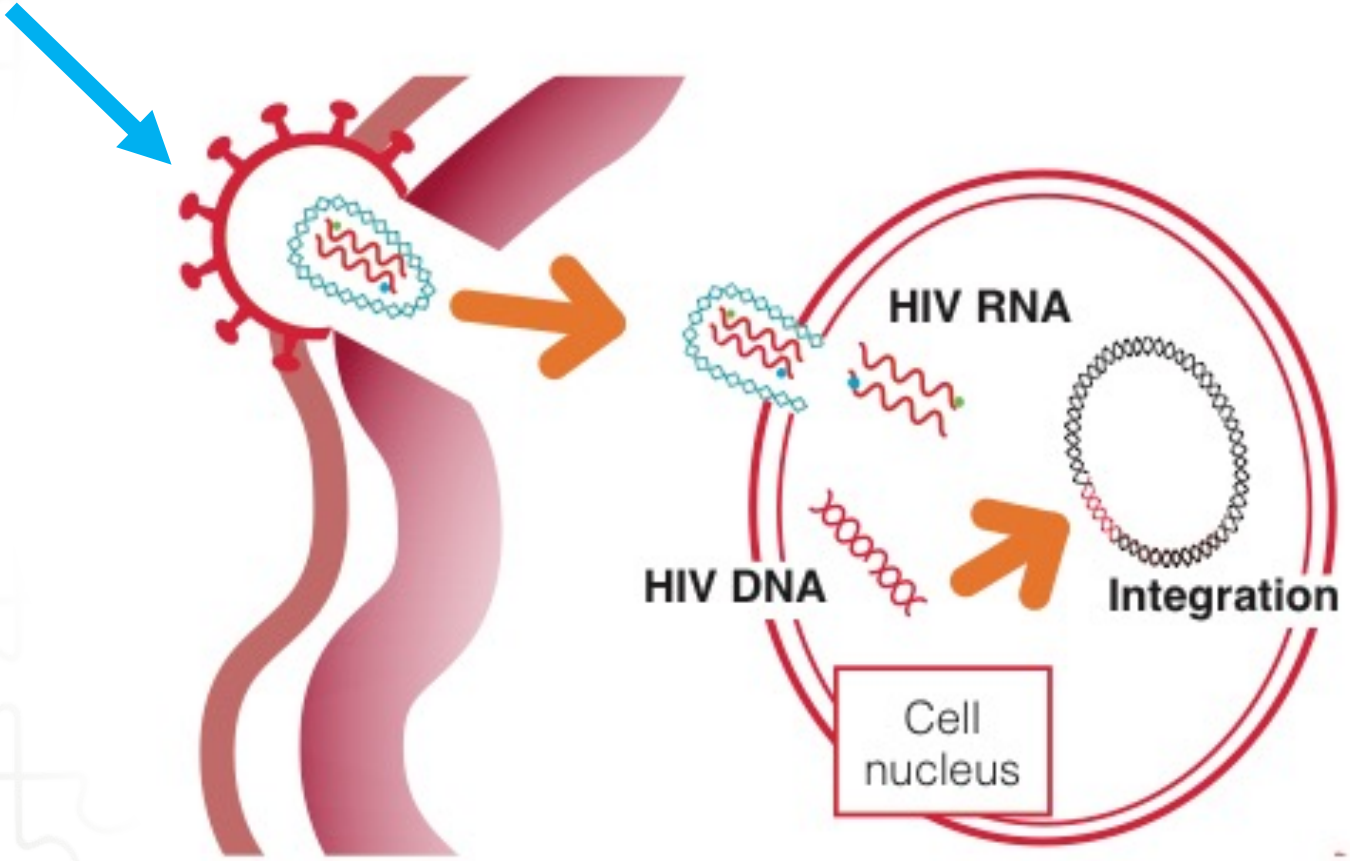

Image credit: HIV i-Base

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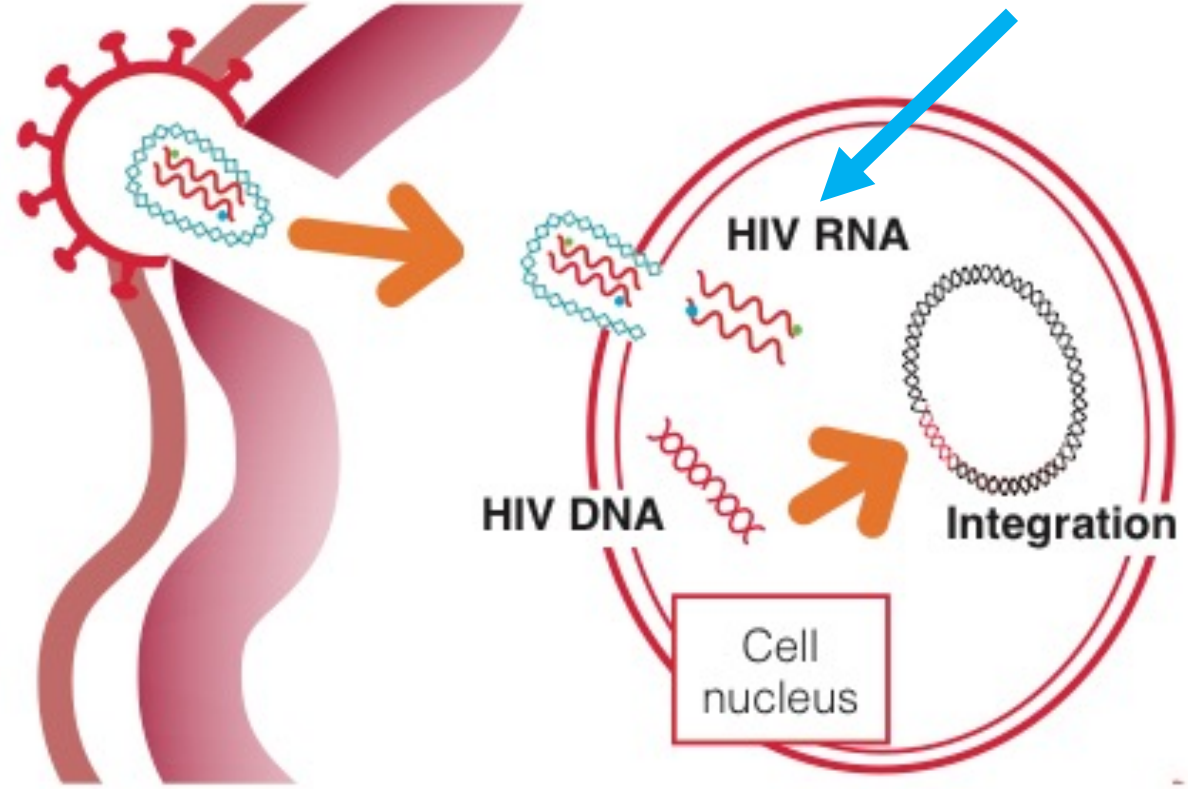
HIV first binds to cell and inserts virus's genetic material in the form of RNA



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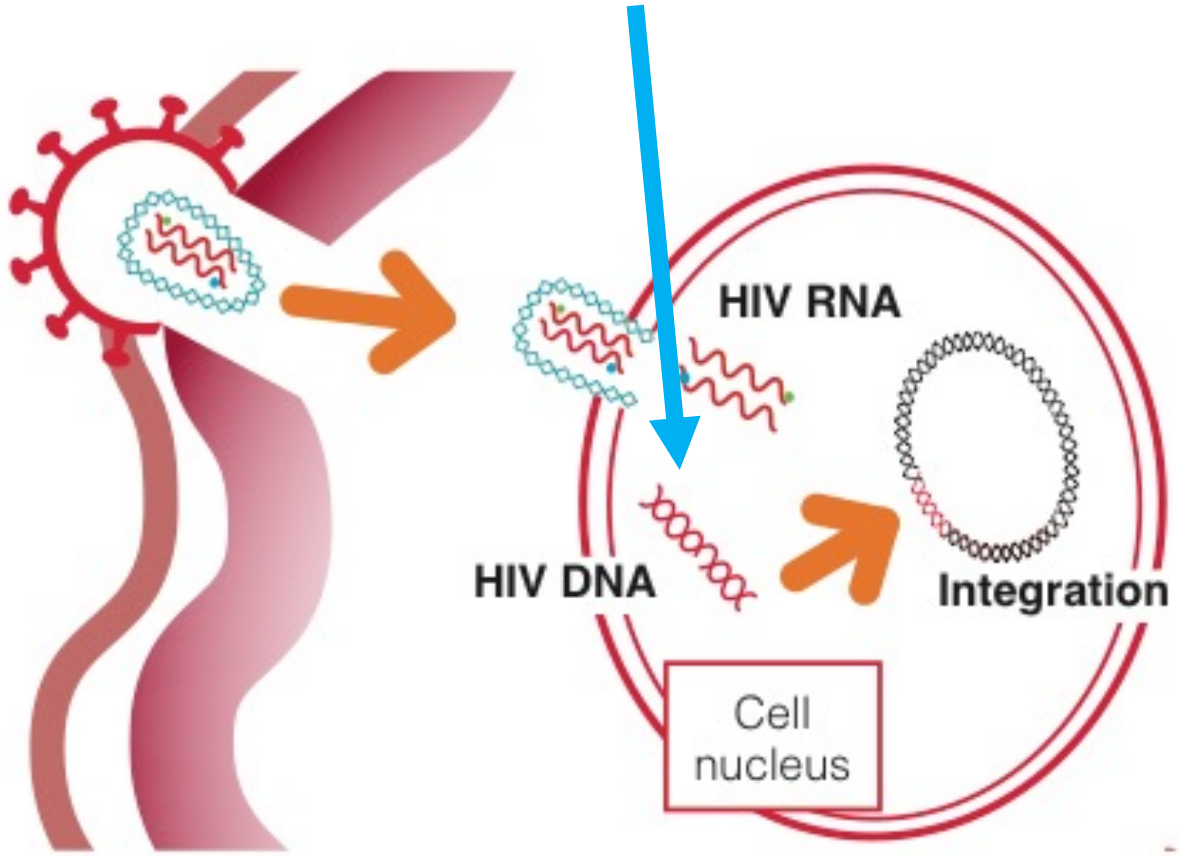

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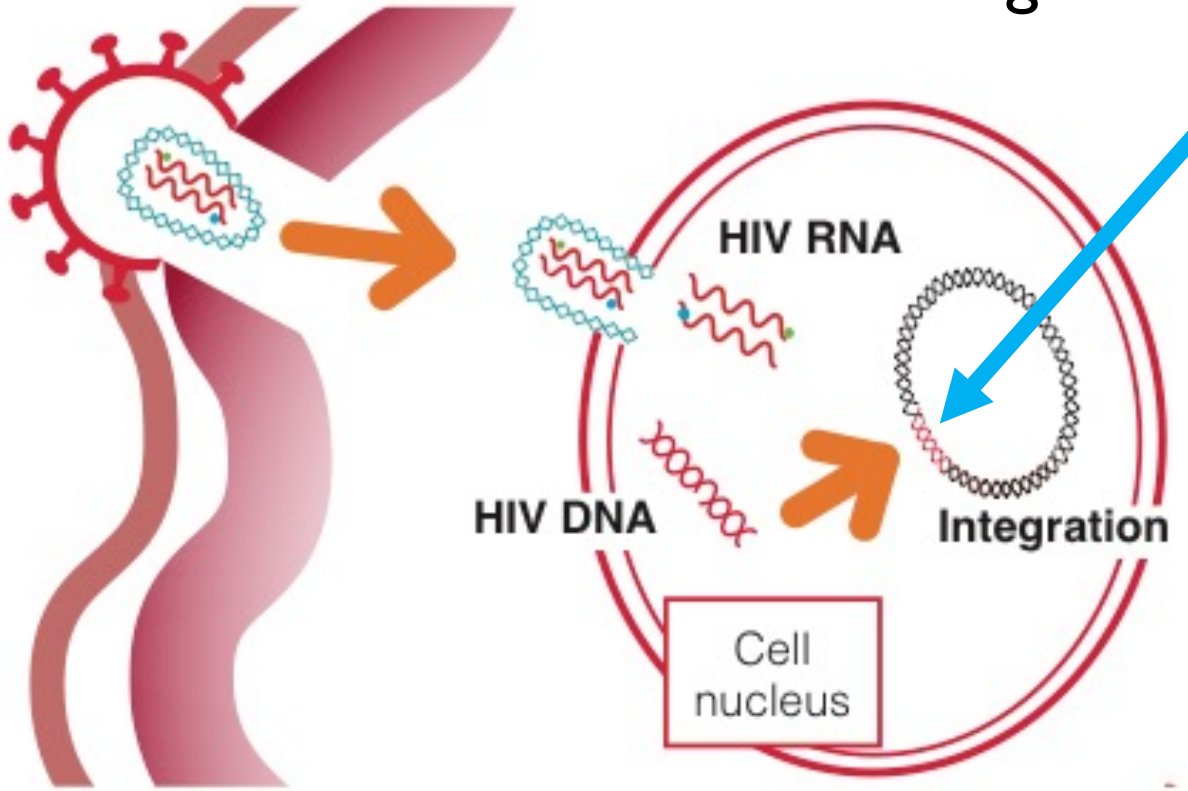

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- Not all HIV integrations are successful – some cells contain only partial, defective copies of HIV DNA *(this makes measuring the amount of intact HIV challenging)*
- The **exact location** in the CD4+ T cell genome where HIV integrates varies, and influences whether the virus can hijack the cell's genetic machinery to make more HIV copies

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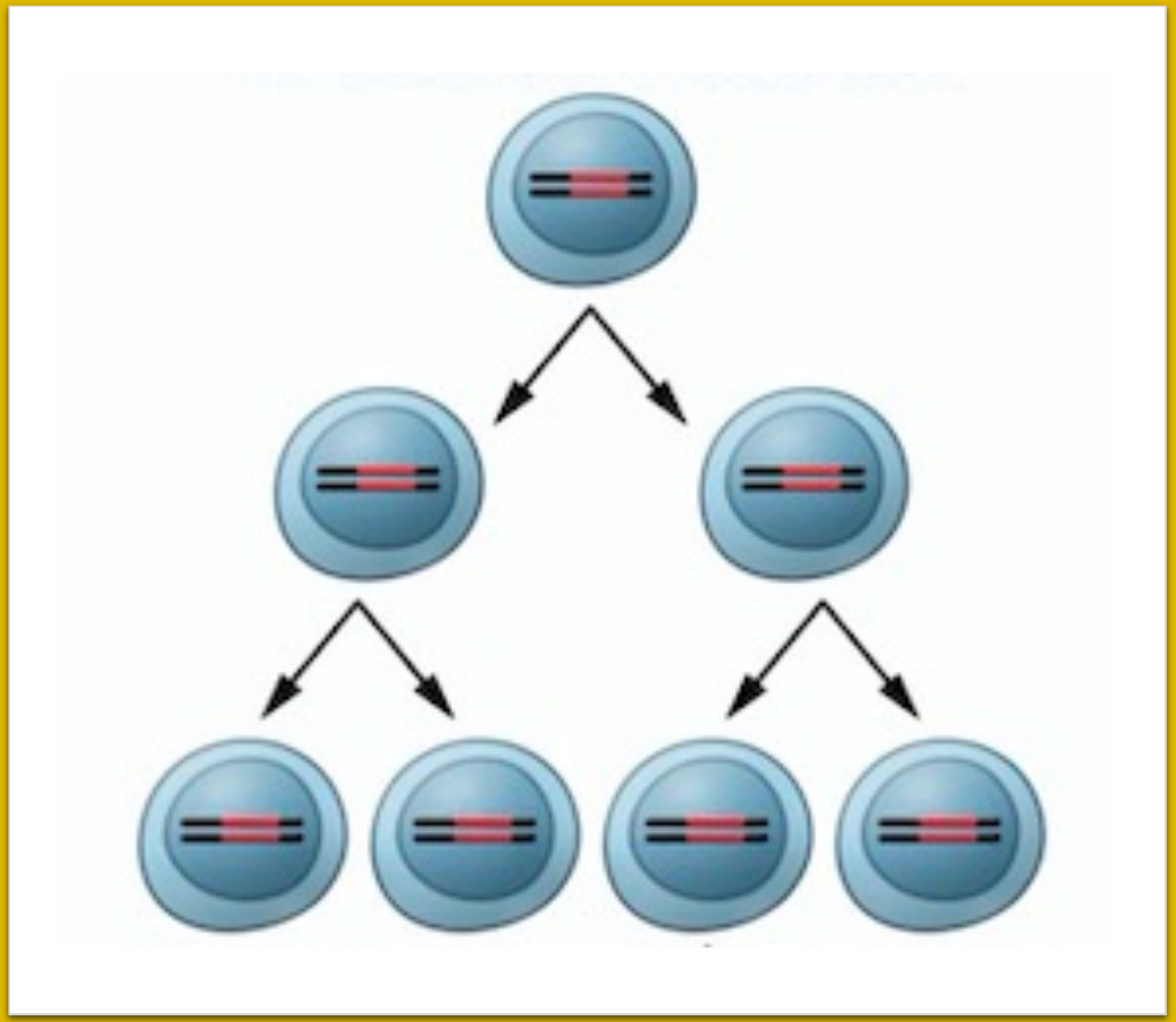
- Memory CD4+ T cells can copy themselves in a process called **"homeostatic proliferation"** (a process used by the immune system to maintain numbers of memory CD4+ T cells)



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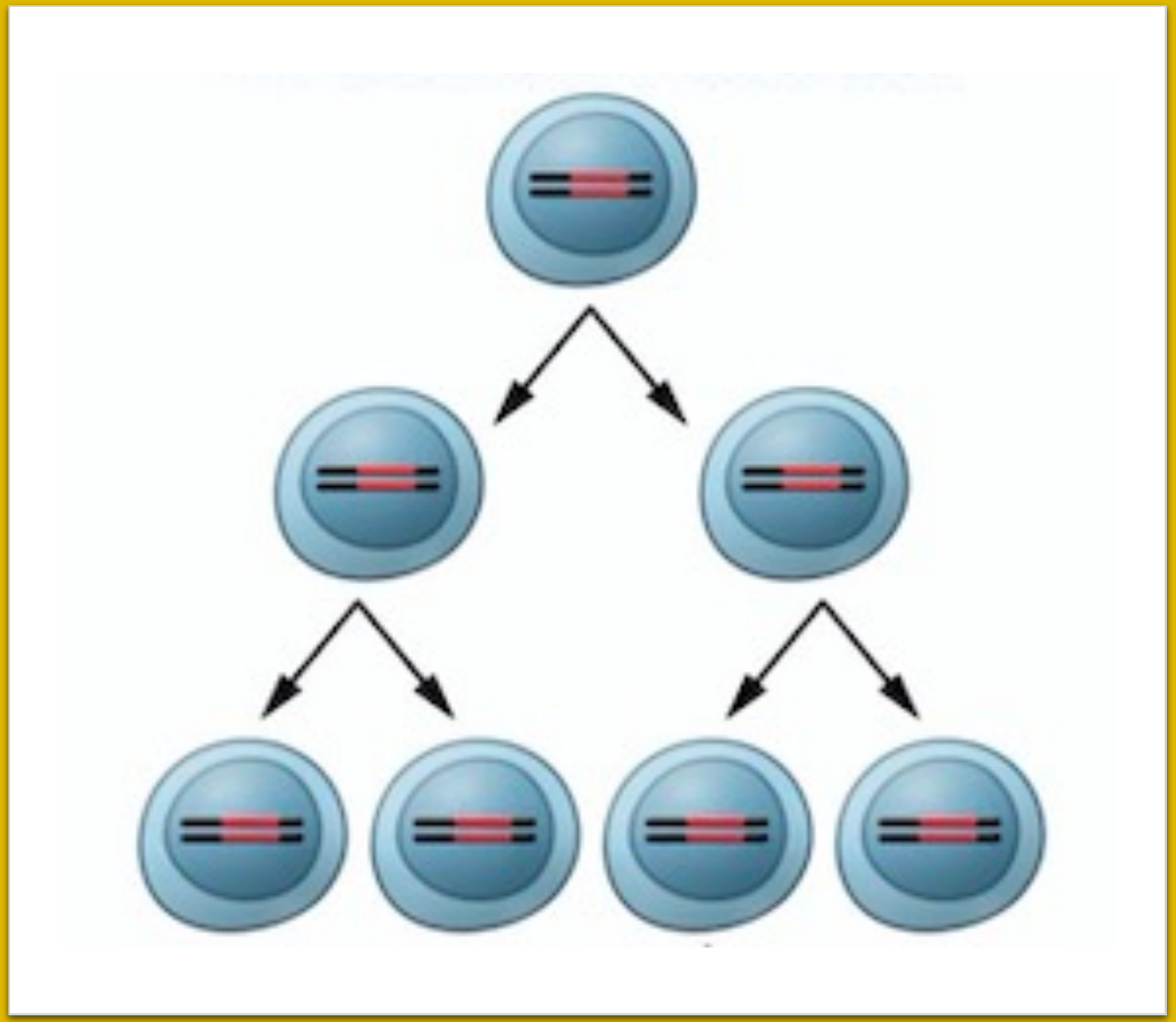
- If HIV is integrated into the CD4+ T cell's genome *(the red bands in the image)*, the genetic blueprint for the virus gets copied along with the cell



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- The parts of a pathogen that trigger an immune response are called **antigens**, so this is referred to as antigen-specific CD4+ T cell proliferation
- As with homeostatic proliferation, if HIV is integrated into the cell's genome, the genetic blueprint for the virus gets copied along with the CD4+ T cell

HOW do HIV-infected CD4+ T cells persist?

- HIV integration into certain places in the genome of a memory CD4+ T cell may allow the virus to influence the proliferation and survival of the cell
- Researchers have reported that the proliferation and survival of a minority of HIV-infected memory CD4+ T cells (~2%) in people on ART may be driven by this mechanism

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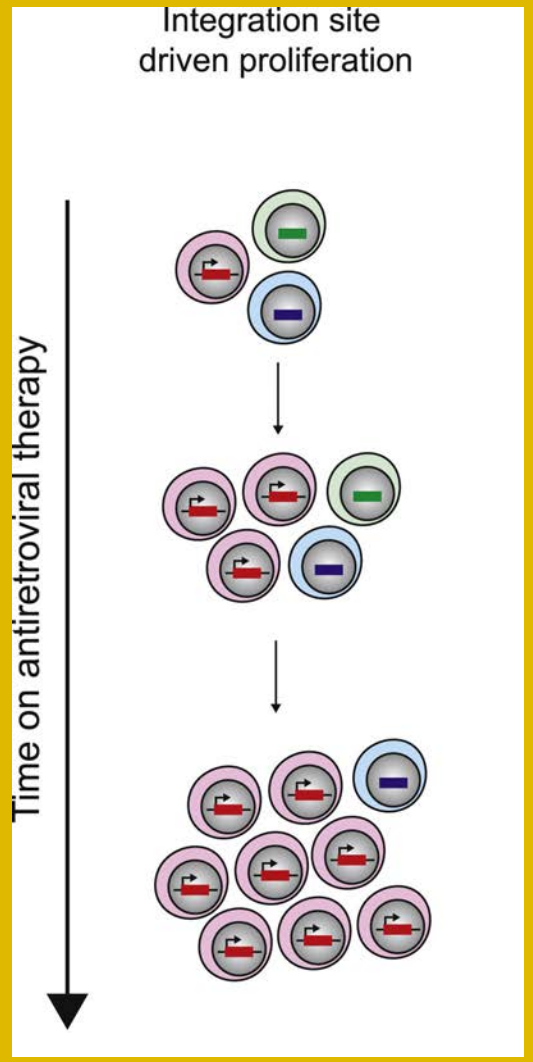

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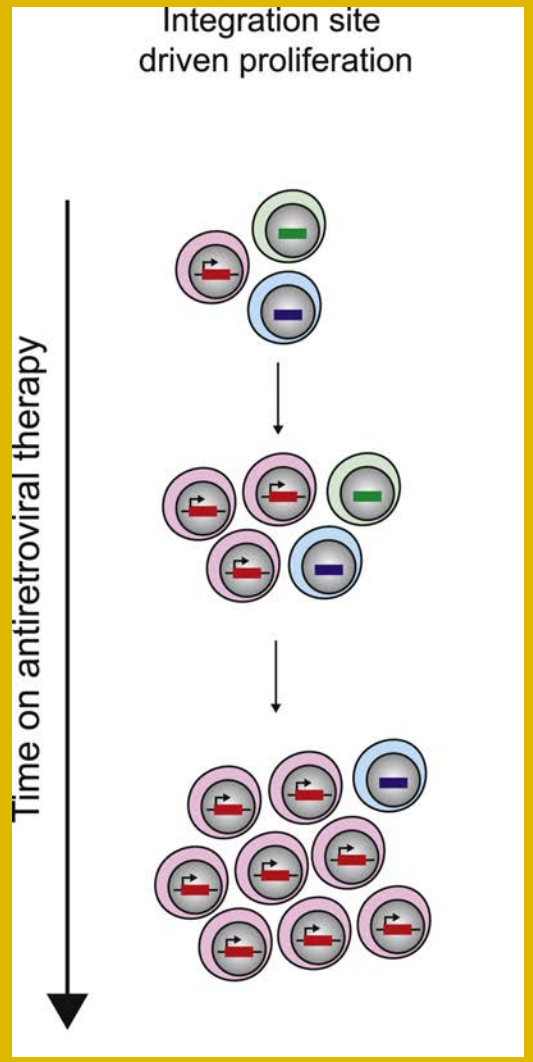
Homeostatic: maintaining the body's total count of memory cells



CUREiculum

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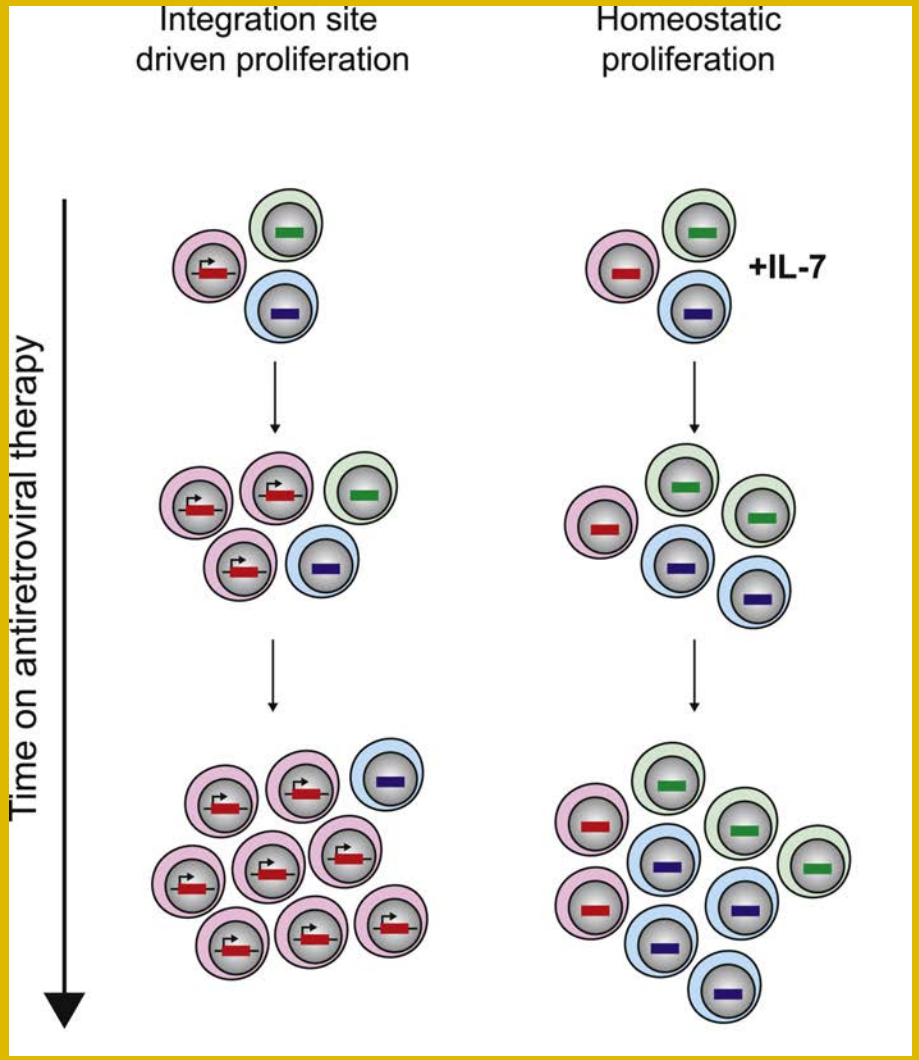

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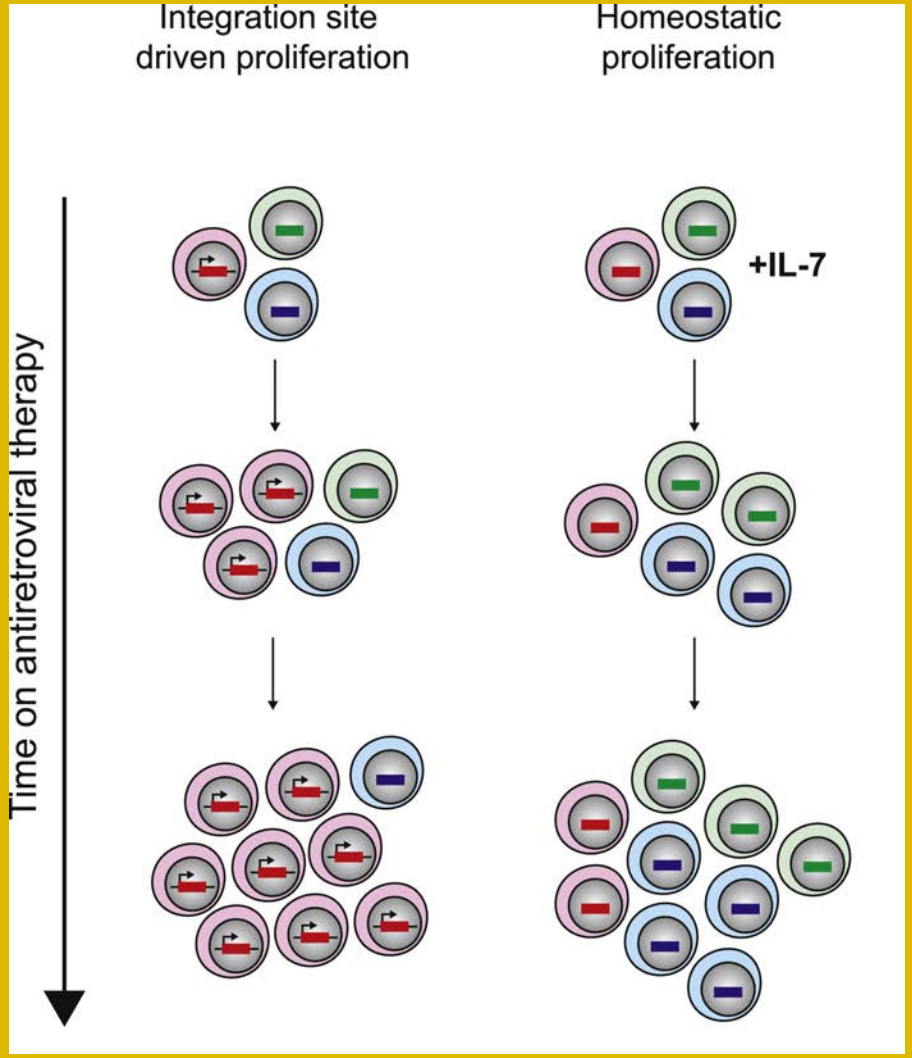

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CUREiculum

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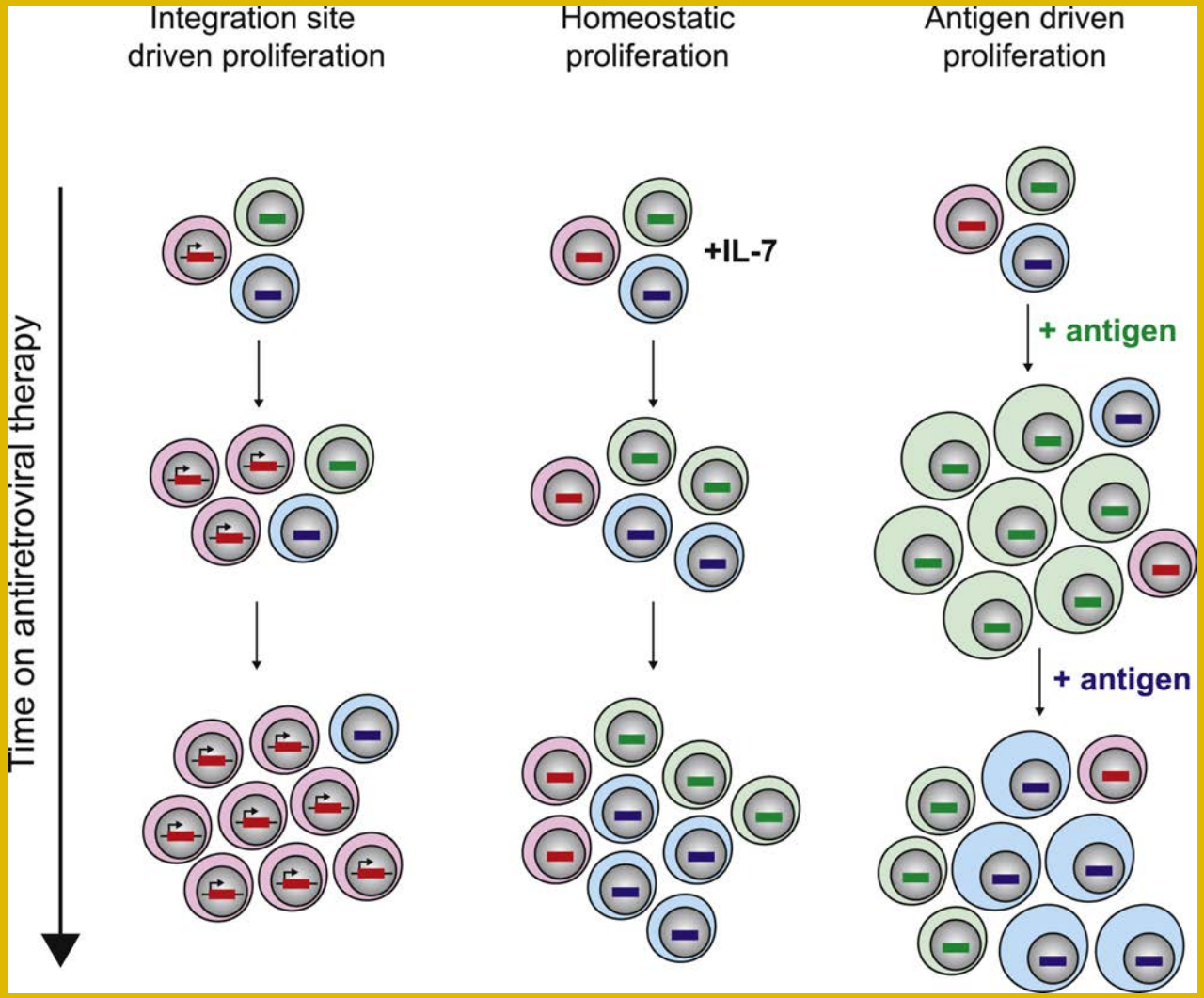
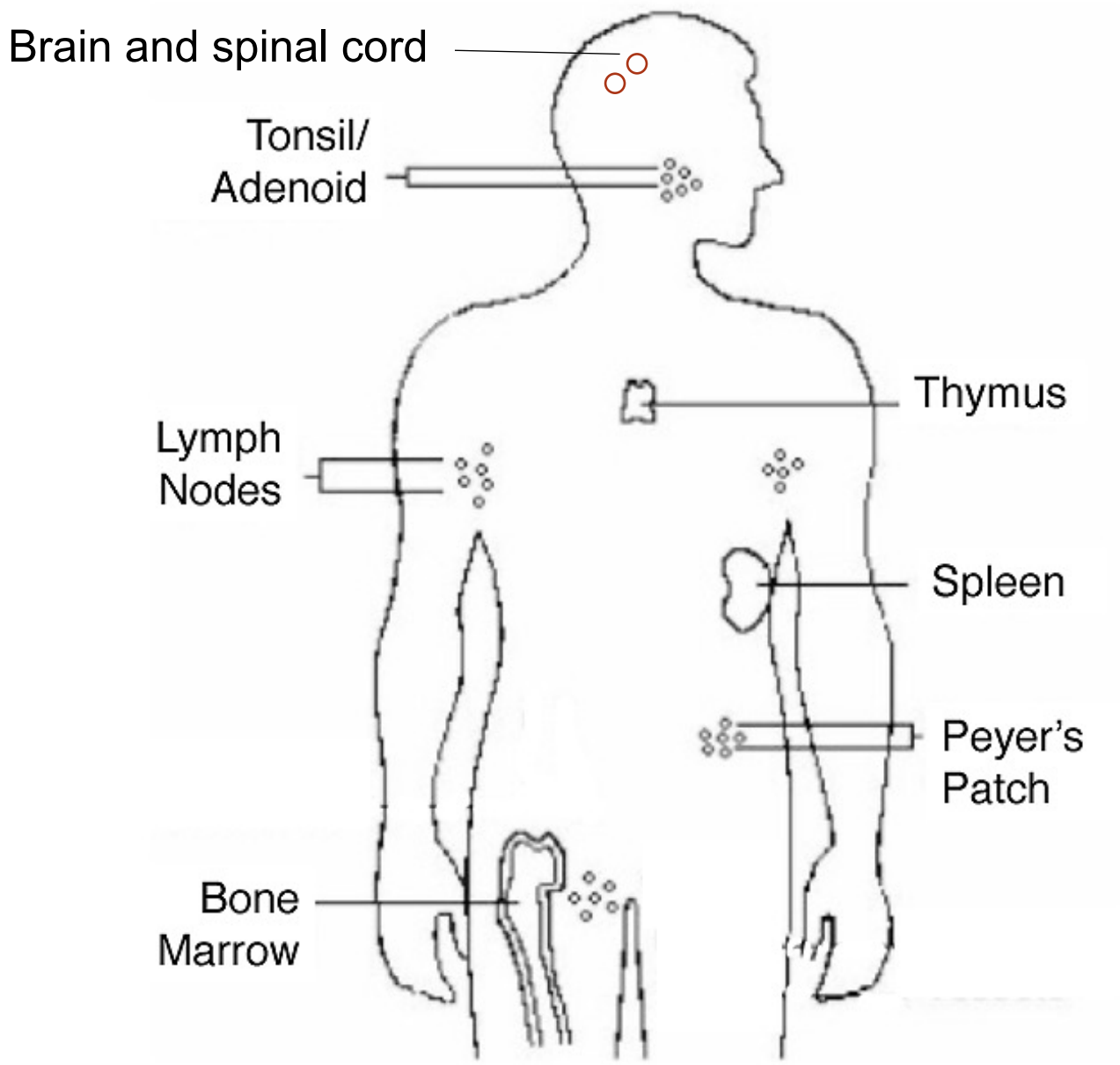


Cell Host Microbe. 2020 Apr 8;27(4):519-530. doi: 10.1016/j.chom.2020.03.014.

Where do HIV-infected CD4+ T cells persist?

Where do HIV-infected CD4+ T cells persist?

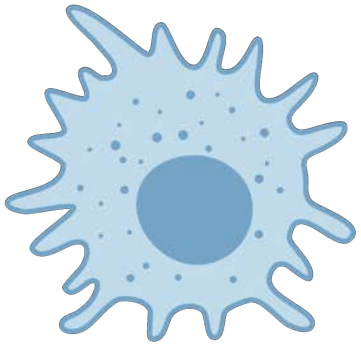
- Multiple potential sites of HIV persistence
- Lymph nodes and gut-associated lymphoid tissue (GALT) are the major sites



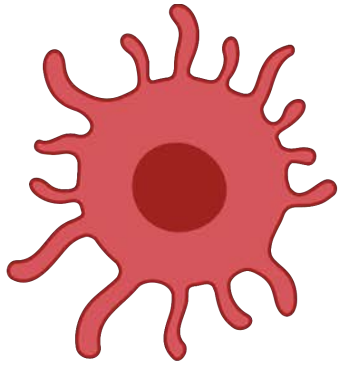
Other cells targeted by HIV?

- CD4+ T cells are not the only type of immune cell that HIV can infect
- HIV can also be found in immune cells called **monocytes**, **macrophages** and **dendritic cells**
- There is debate among scientists about whether HIV can persist long-term in these cells when people are on ART

monocyte



macrophage



dendritic cell

Other cells targeted by HIV?

- The **latest evidence** is that the source of viral load rebound after ART interruption is HIV emerging from infected CD4+ T cells
- Most scientists consider **HIV-infected CD4+ T cells** to be the major site of HIV persistence in people on ART
- For this reason, a primary goal in cure research is eliminating, reducing, or controlling the HIV reservoir in CD4+ T cells

Measuring HIV persistence

Measuring HIV persistence

- Scientists constantly working to identify better ways of measuring the amount of HIV that persists despite ART
- Efforts are particularly focused on HIV that is intact and capable of replicating if ART is stopped

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Examples of HIV reservoir tests

- **HIV DNA:** measures the amount of HIV genetic material, but can't show whether it represents intact or defective virus
- **Quantitative virus outgrowth assay (QVOA):** estimates the amount of HIV present in a sample that is capable of replicating in a lab dish
- **Intact proviral DNA assay (IPDA):** measures the amount of virus genetic material that appears intact and likely able to replicate

CONCLUSION

- The ability of HIV to persist in the body represents a challenge for efforts to cure HIV infection
- Multiple approaches being pursued to try to reduce, eliminate or control persistent HIV without the need for ongoing treatment
- See other CUREiculum modules for additional information

ACKNOWLEDGMENTS

AIDS treatment ATAC activists coalition

AIDS ACTION BALTIMORE

MARTIN DELANEY COLLABORATORIES COMMUNITY ADVISORY BOARD

TAG Treatment Action Group

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Their caring support of the CUREiculum 2.0. will make a difference in the lives of thousands. of people living with HIV

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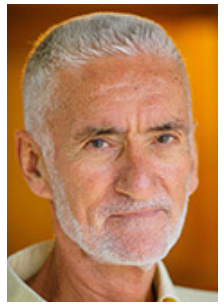

Biomedical Review

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