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GLOBAL EDUCATION

HIV: Discovery and Early Findings

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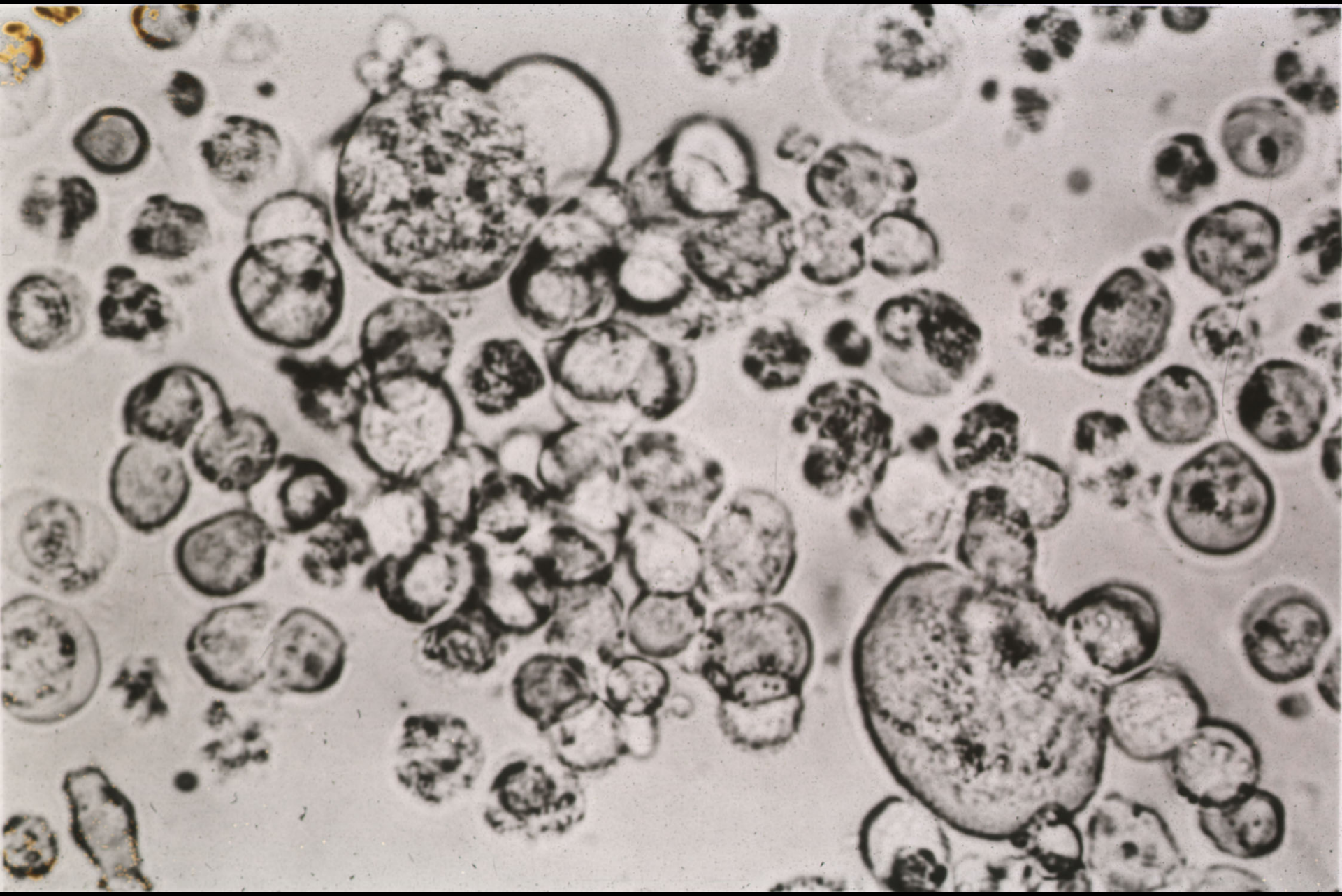
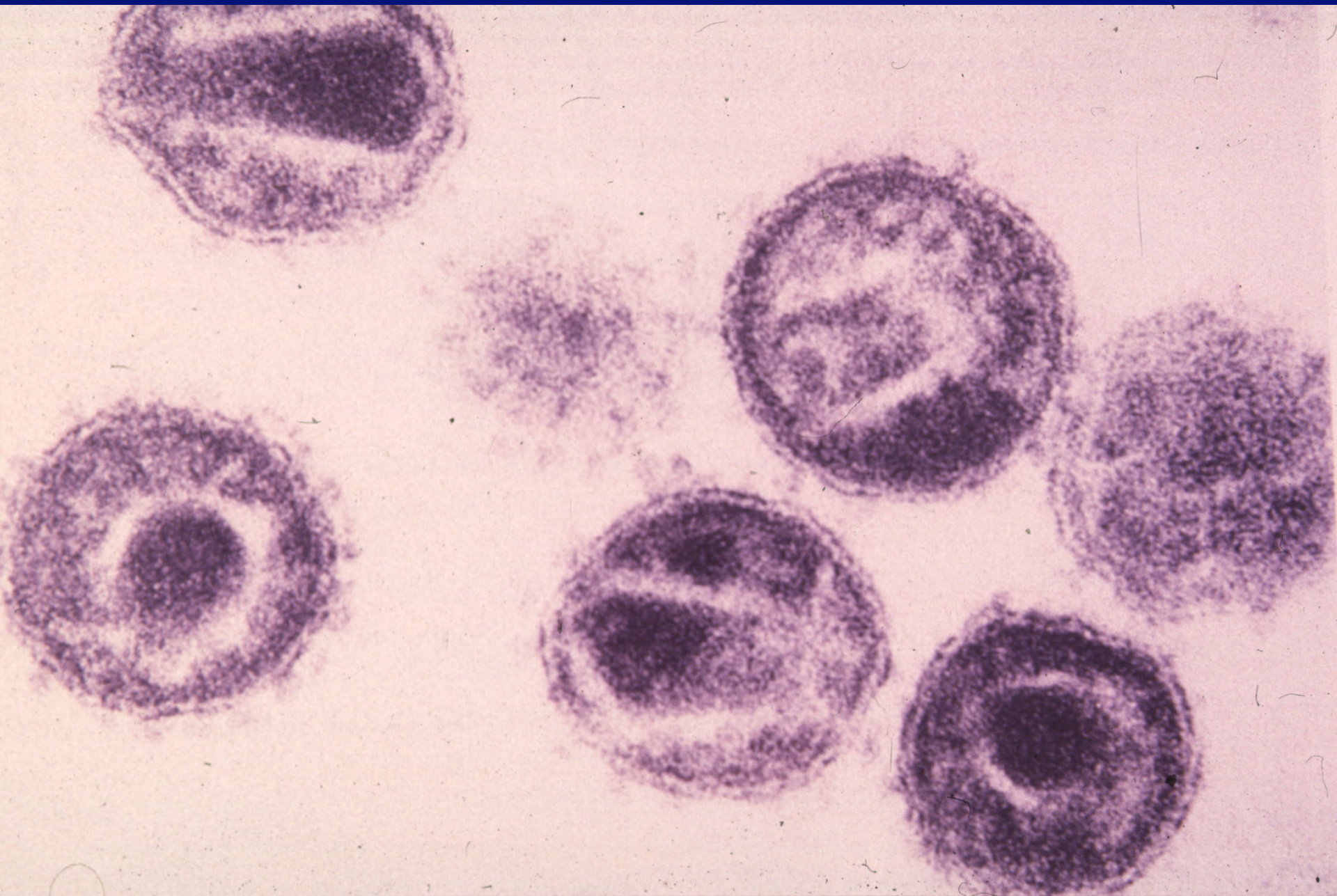
University of California
San Francisco

How Does HIV Differ from Other Epidemic Pathogens?

- **Directly attacks the immune system**
- **Involves virus incorporation into the cellular genome**
- **Establishes a chronic infection before becoming pathogenic**
- **Involves an agent that frequently changes or modulates itself within the host.**
- **Can recruit other cells by direct infection or cell:cell transfer**



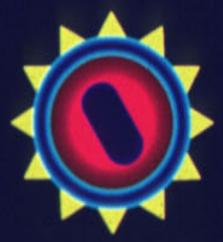
AIDS-Associated Retrovirus (ARV)



LAV / HTLV III / ARV

ARV = HIV-1$_{SF}$

Components of HIV Infection



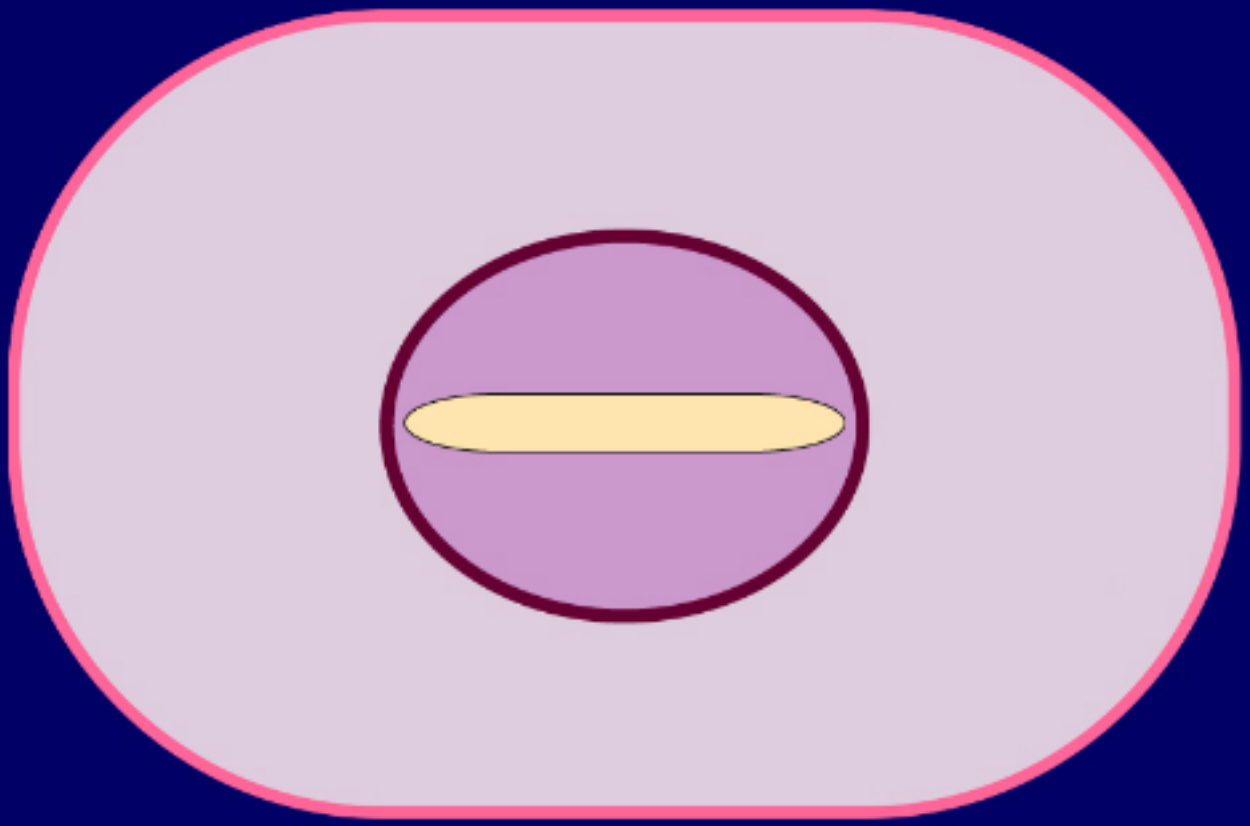
VIRUS

CELLS

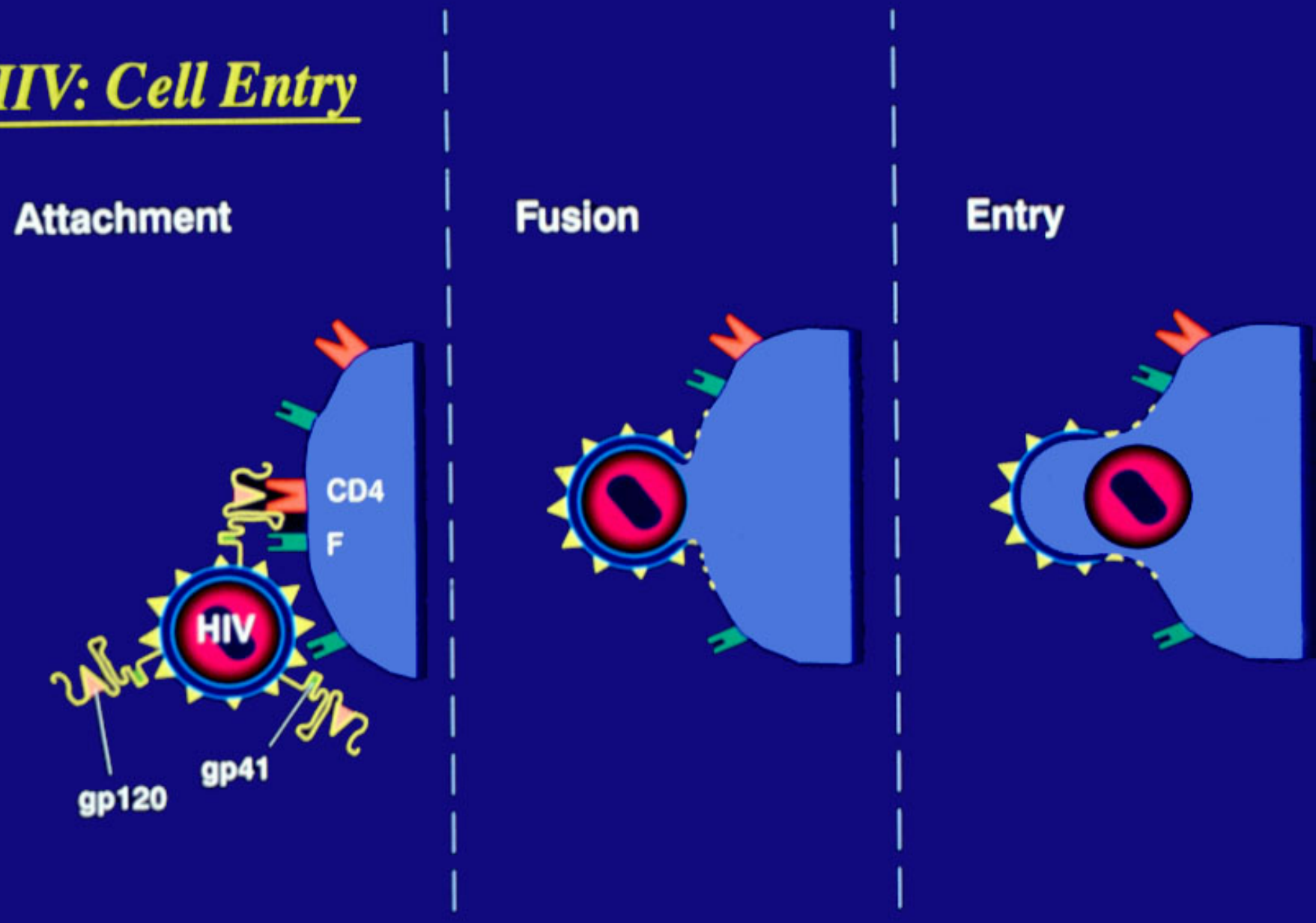
HOST

HIV Pathogenesis

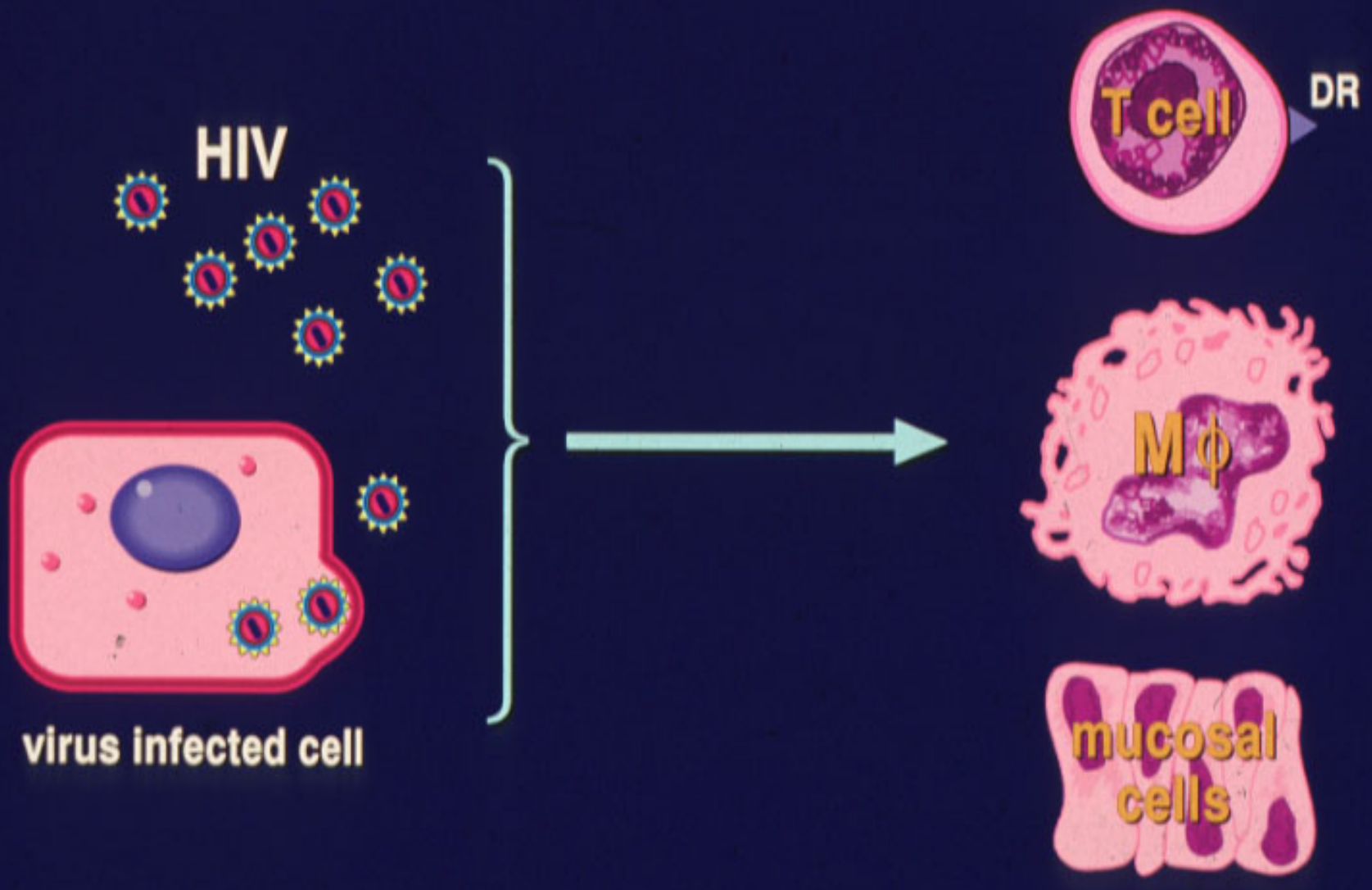
Virus : Host Interactions

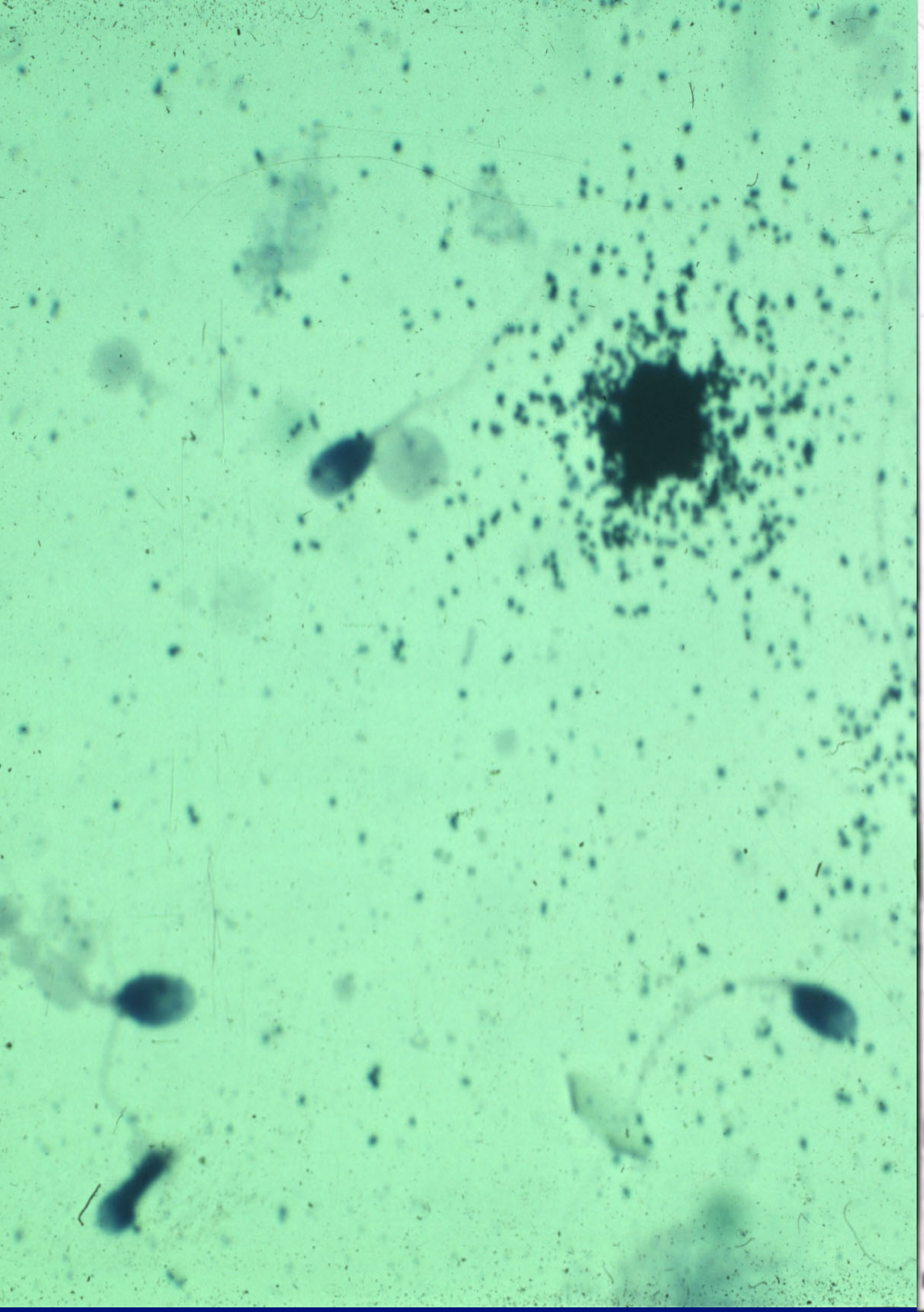


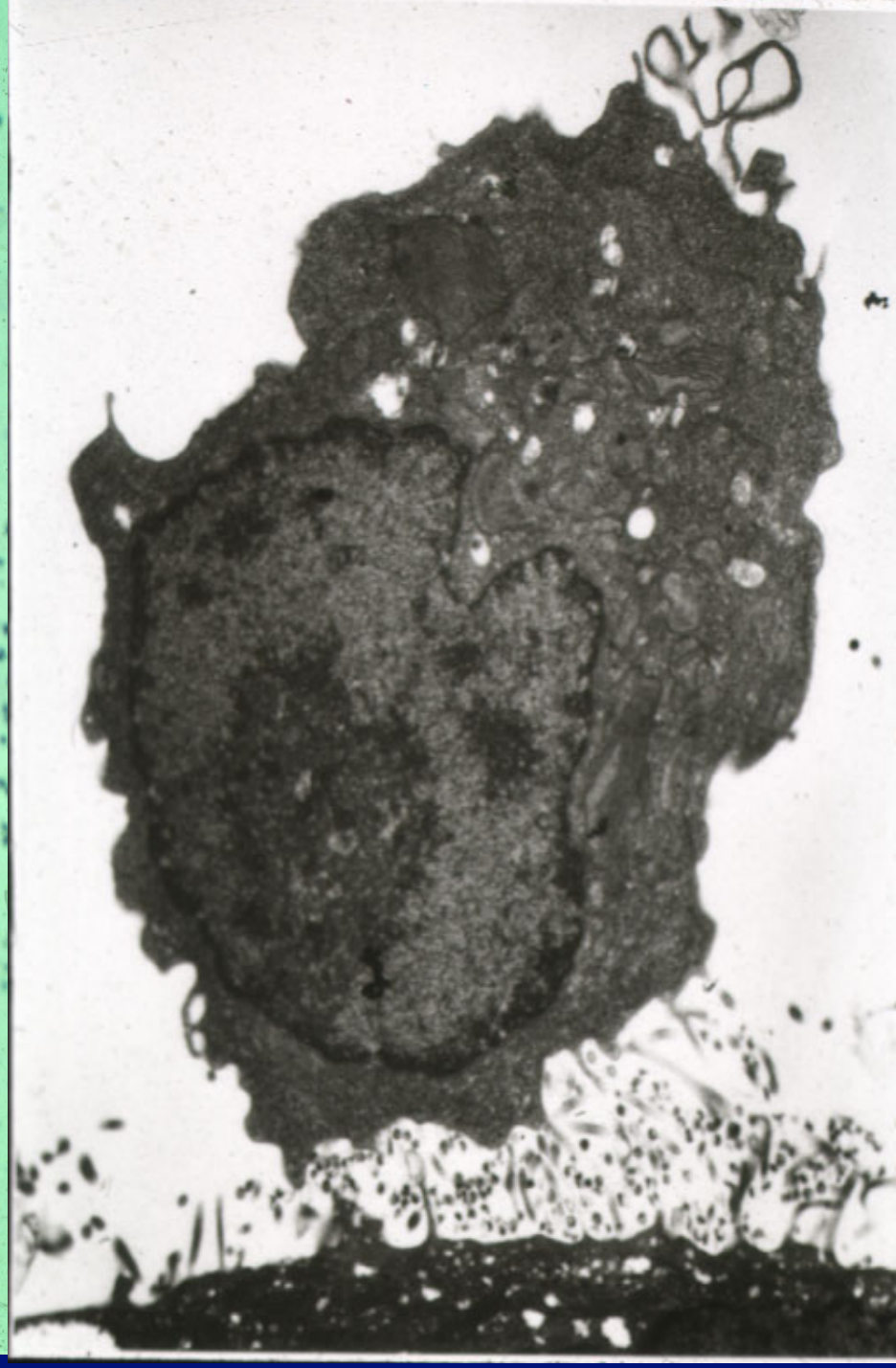
HIV: Cell Entry



Initial HIV Infection







Human Cells Susceptible to HIV

Hematopoietic

- T lymphocytes
- B lymphocytes
- Macrophages
- NK cells
- Megakaryocytes
- Dendritic cells
- Promyelocytes
- Stem Cells
- Thymic epithelium
- Follicular dendritic cells
- Bone marrow endothelial cells

Skin

- Langerhans cells
- Fibroblasts

Brain

- Capillary endothelial cells
- Astrocytes
- Macrophages (microglia)
- Oligodendrocytes
- Choroid plexus
- Ganglia cells
- Neuroblastoma cells
- Glioma cell lines
- Neurons (?)

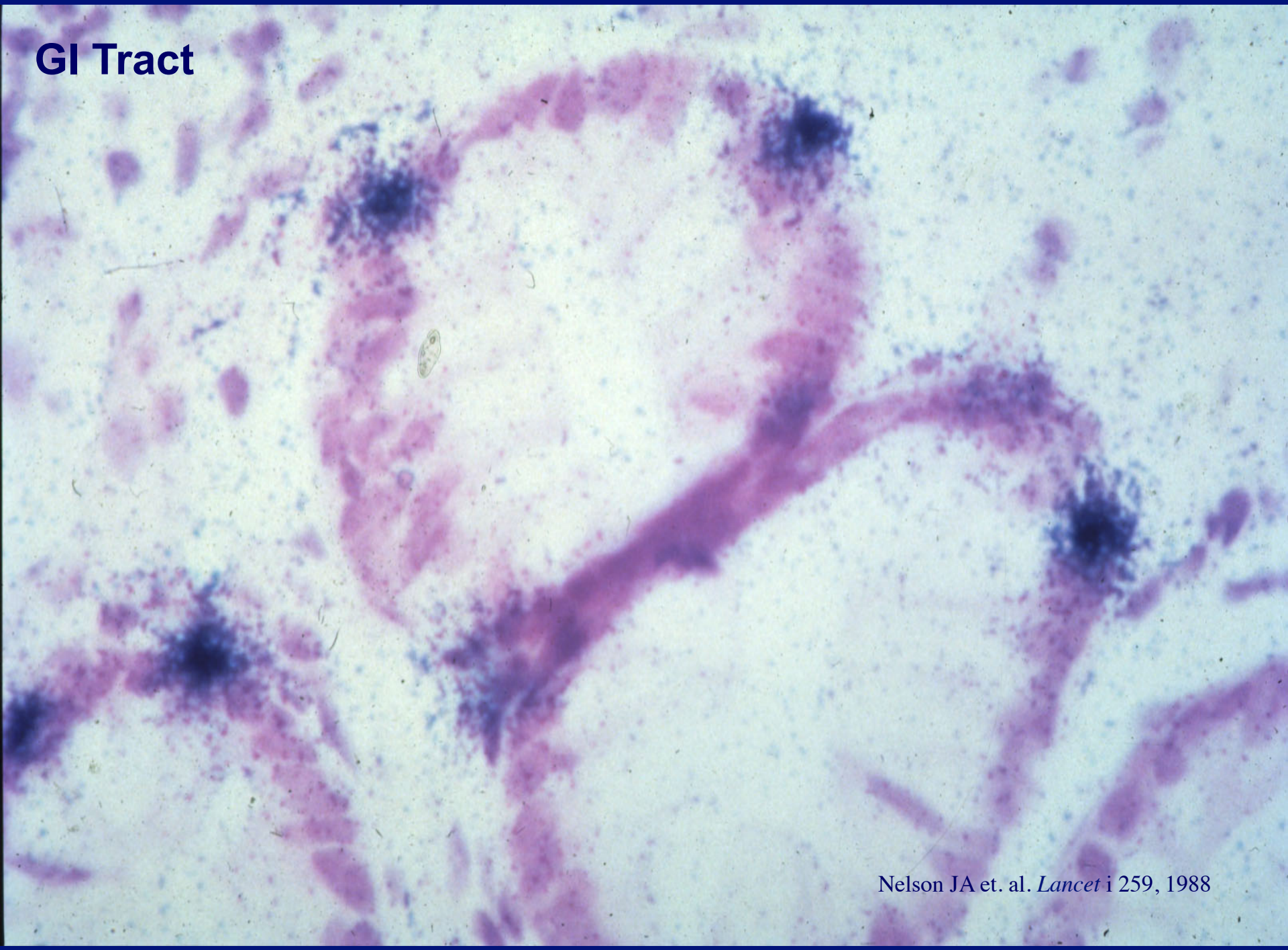
Bowel

- Columnar and goblet cells
- Enterochromaffin cells
- Colon carcinoma cells

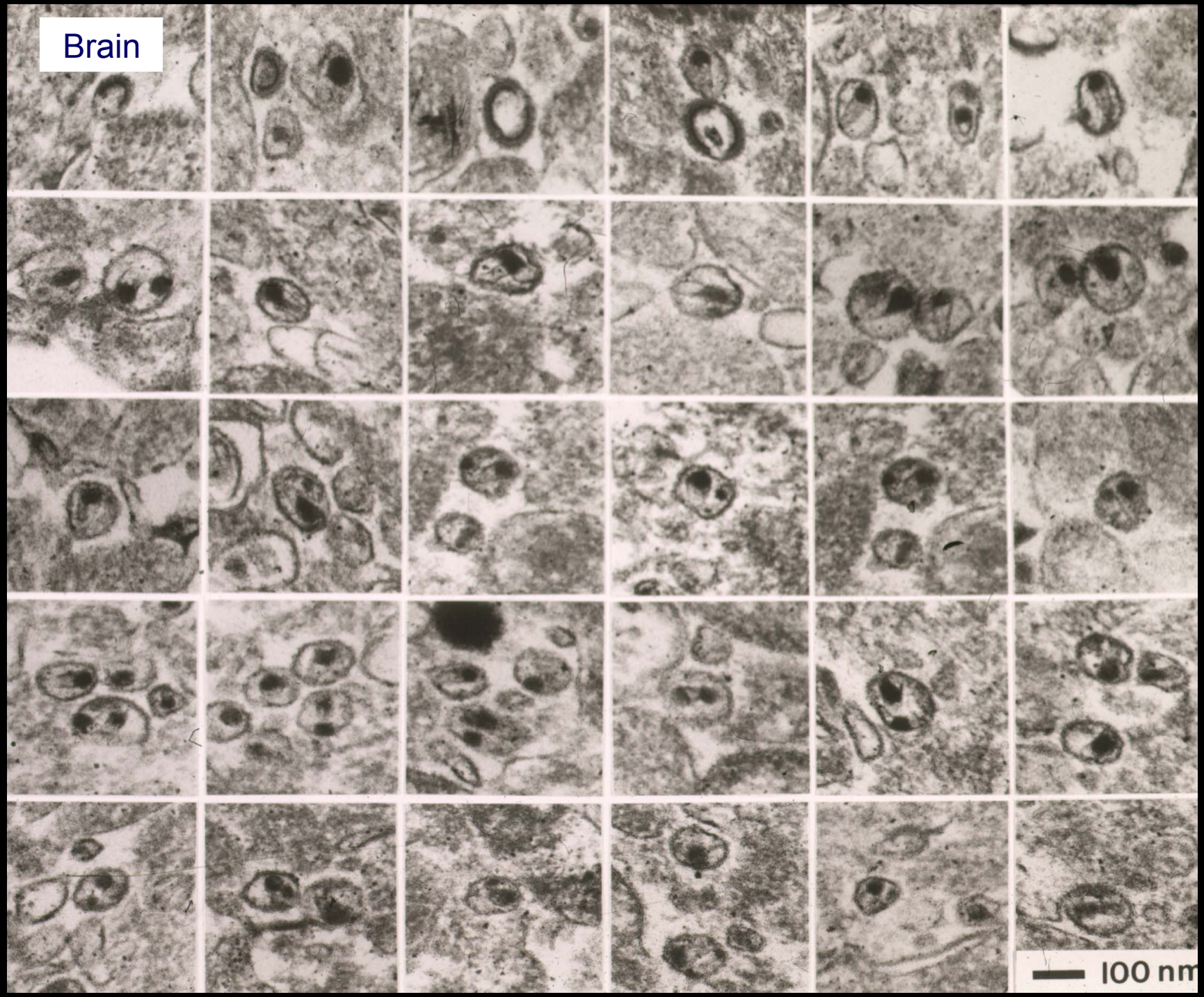
Other

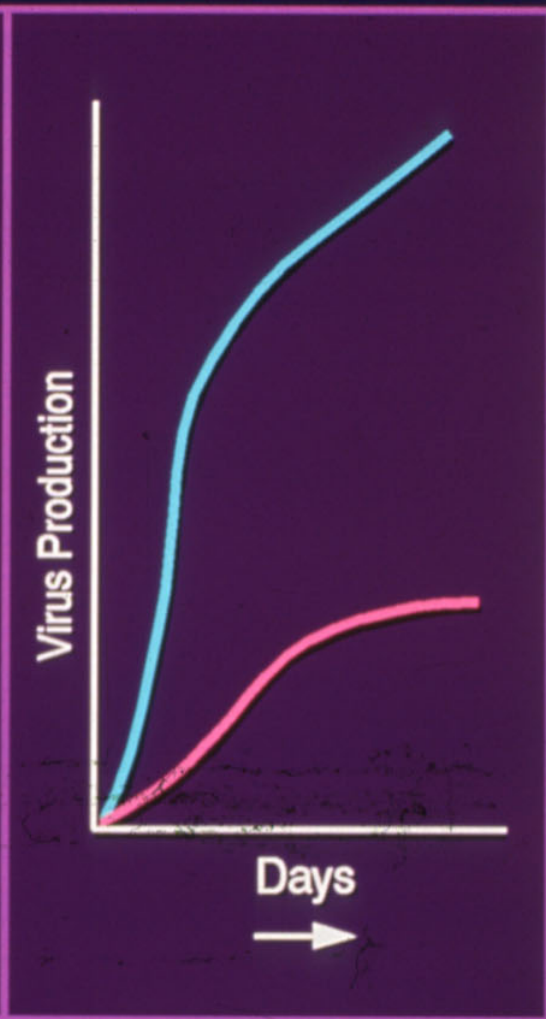
- Myocardium
- Renal tublar cells
- Synovial membrane
- Hepatocytes
- Hepatic sinusoid endothelium
- Hepatic carcinoma cells
- Kupffer cells
- Dental pulp figroblasts
- Pulmonary figroblasts
- Fetal adrenal cells
- Retinal cells
- Cervix-derived epithelial cells
- Cervix (epithelium ?)
- Prostate
- Testes
- Osteosarcoma cells
- Rhabdomyosarcoma cells
- Fetal chorionic villi
- Trophoblast cells

GI Tract



Nelson JA et. al. *Lancet* i 259, 1988


Brain
100 nm



Host Range **Replication** **Cell Killing**

Biologic Causes for the Spread of HIV/AIDS

Infected individuals remain healthy for many years

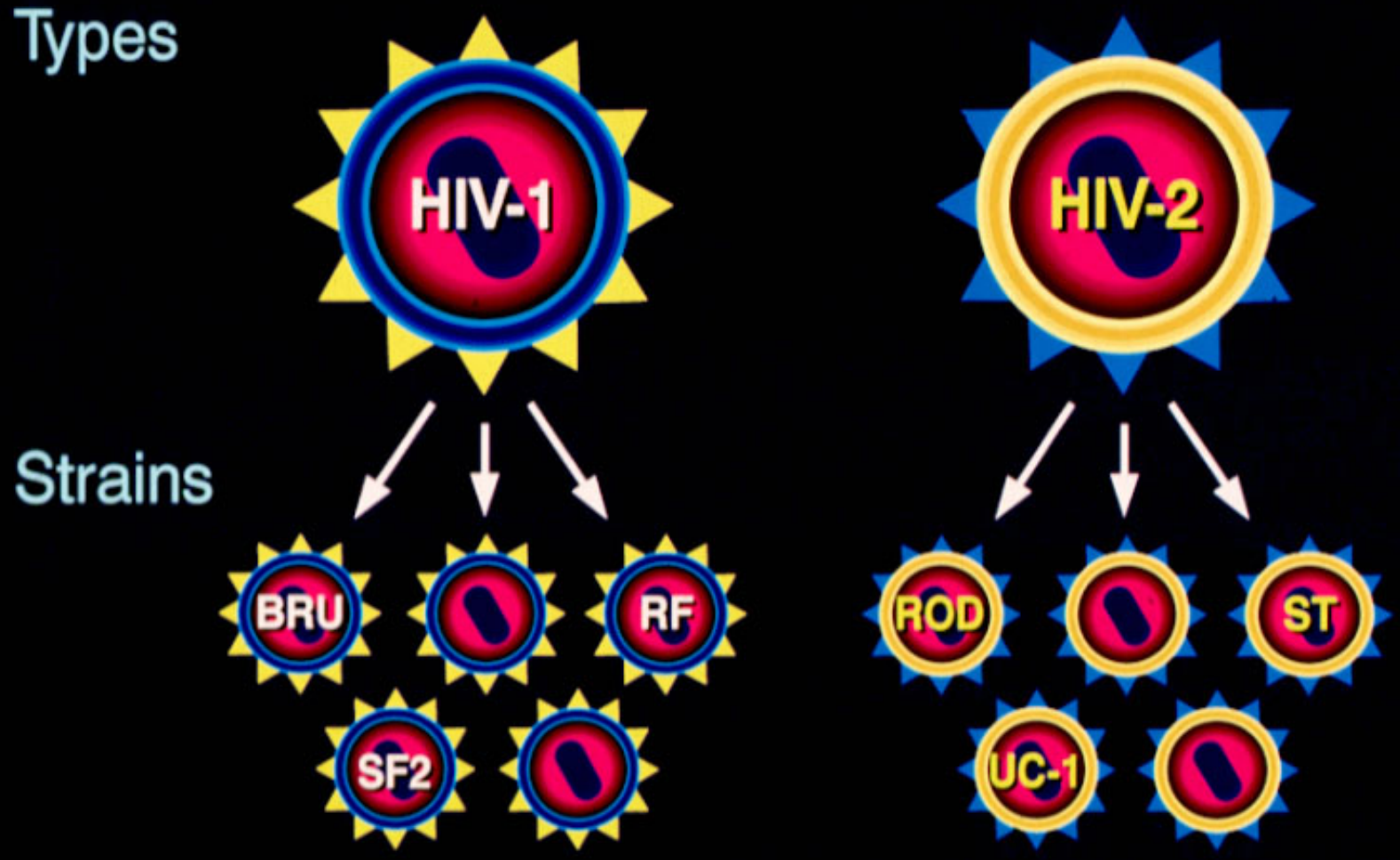
Virus can be transmitted by an infected cell

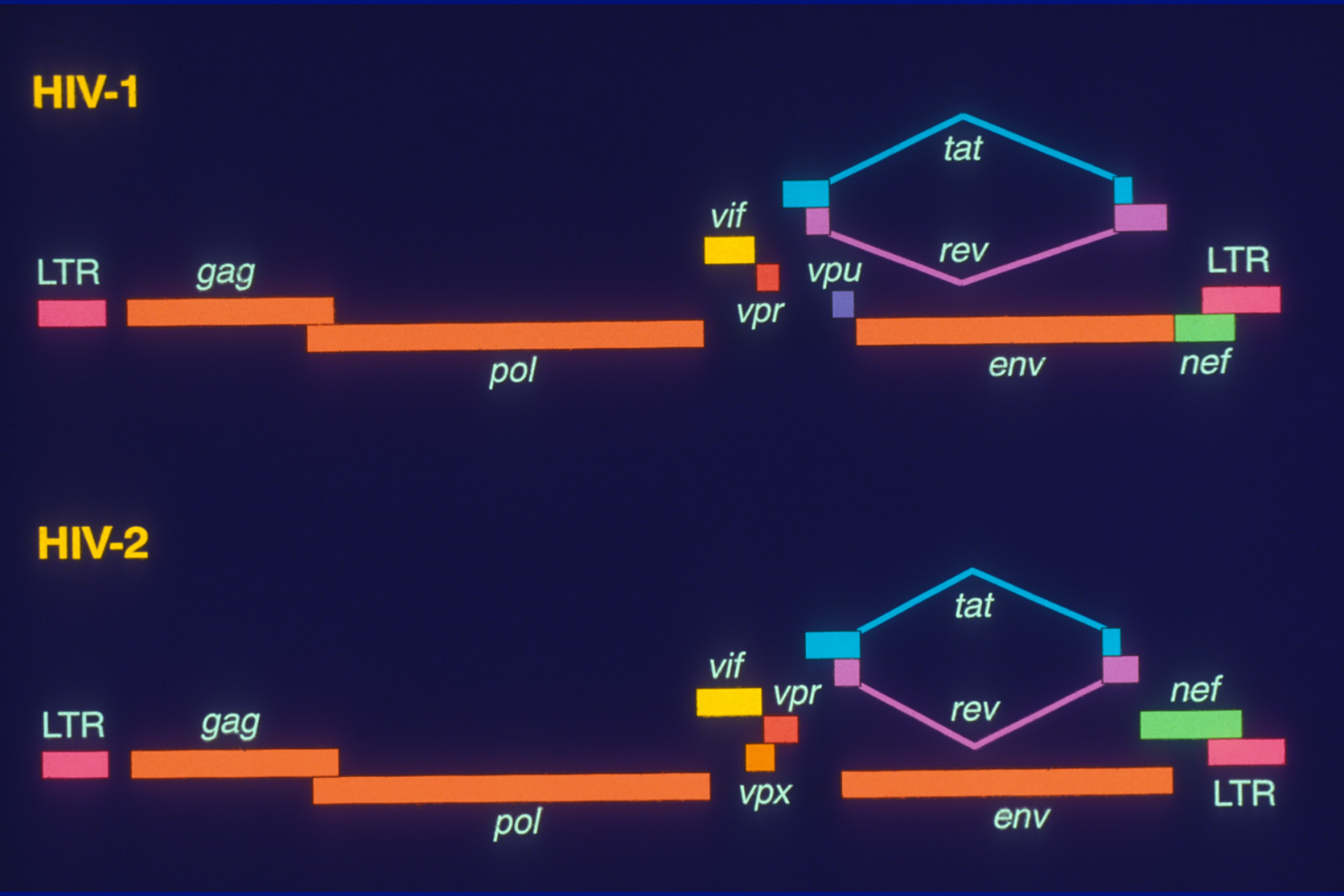
Virus is spread by sexual transmission

Virus mutates at a rapid rate

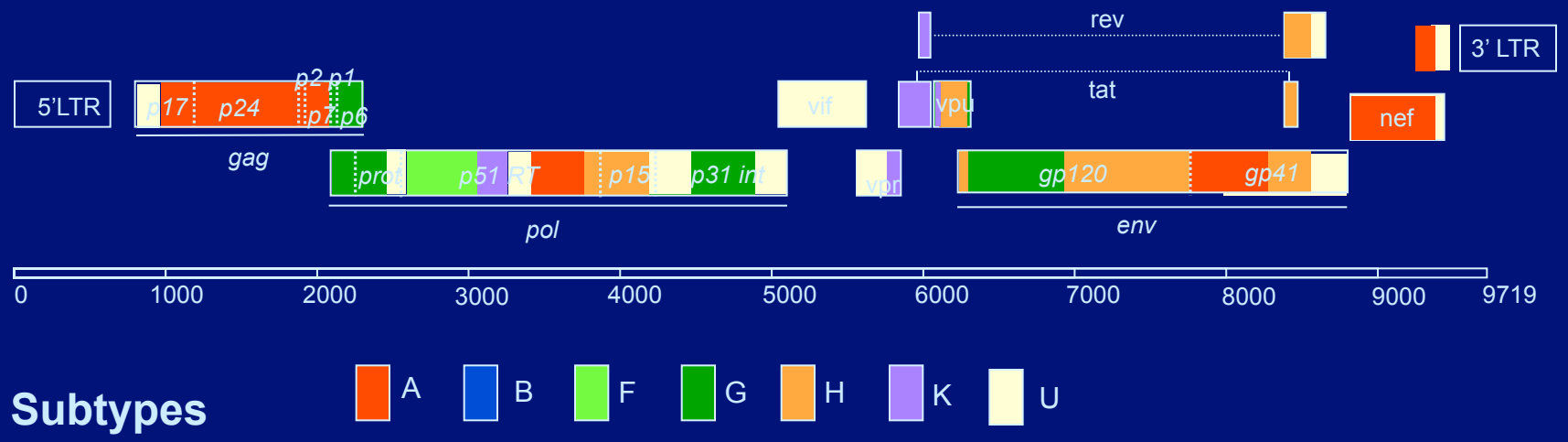
Virus can become resistant to immune response

The AIDS Viruses




HIV-1
tat
vif
rev
LTR
gag
vpu
LTR
vpr
pol
env
nef
HIV-2
tat
vif
vpr
nef
rev
LTR
gag
vpx
pol
env
LTR

Multi-clade Recombinant HIV-1

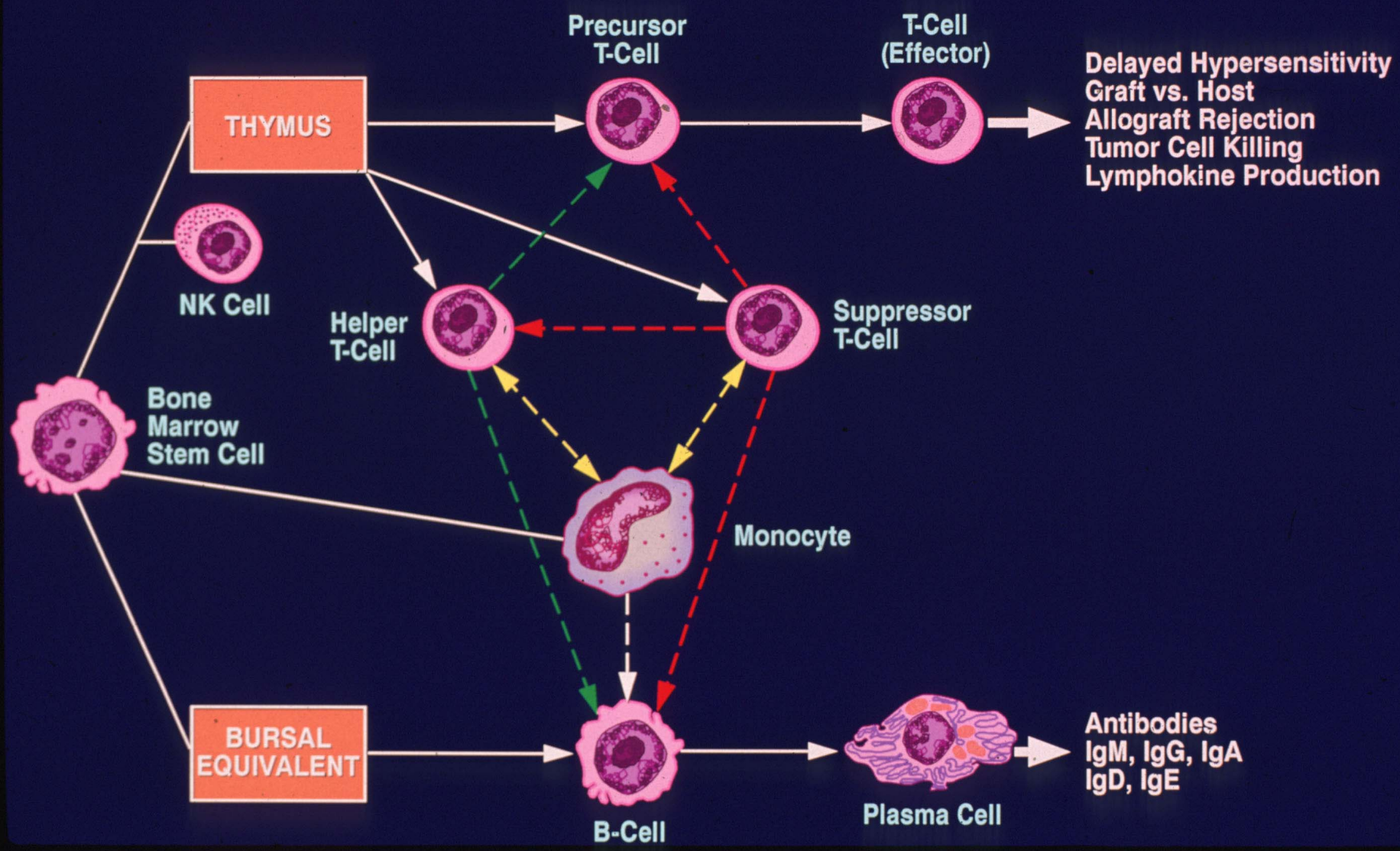


Provided by R. Najera

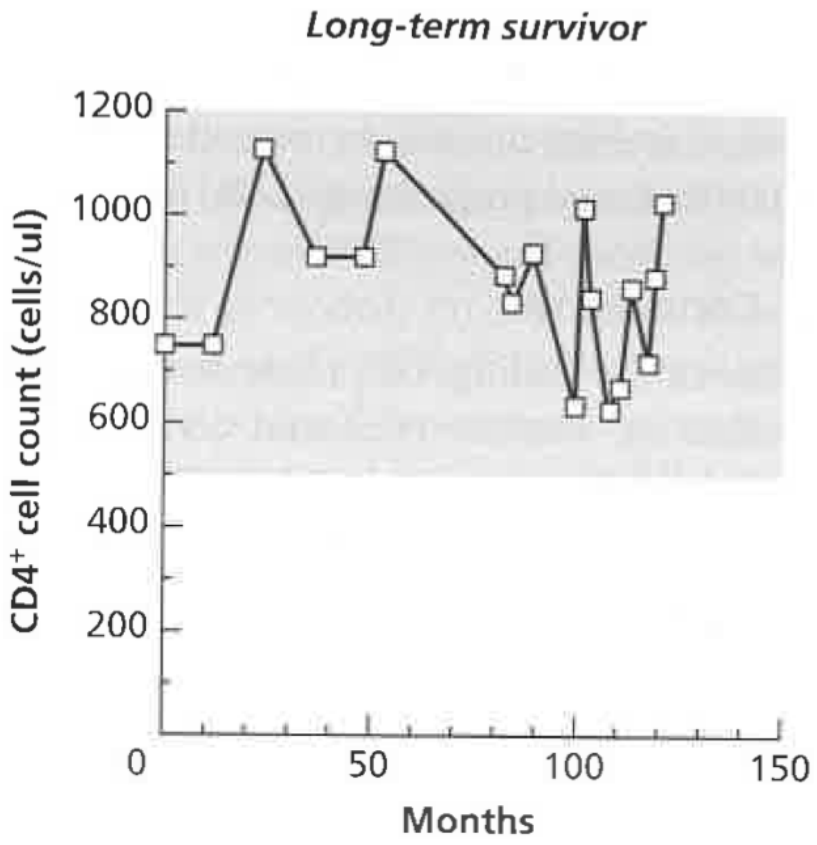
HIV Pathogenesis

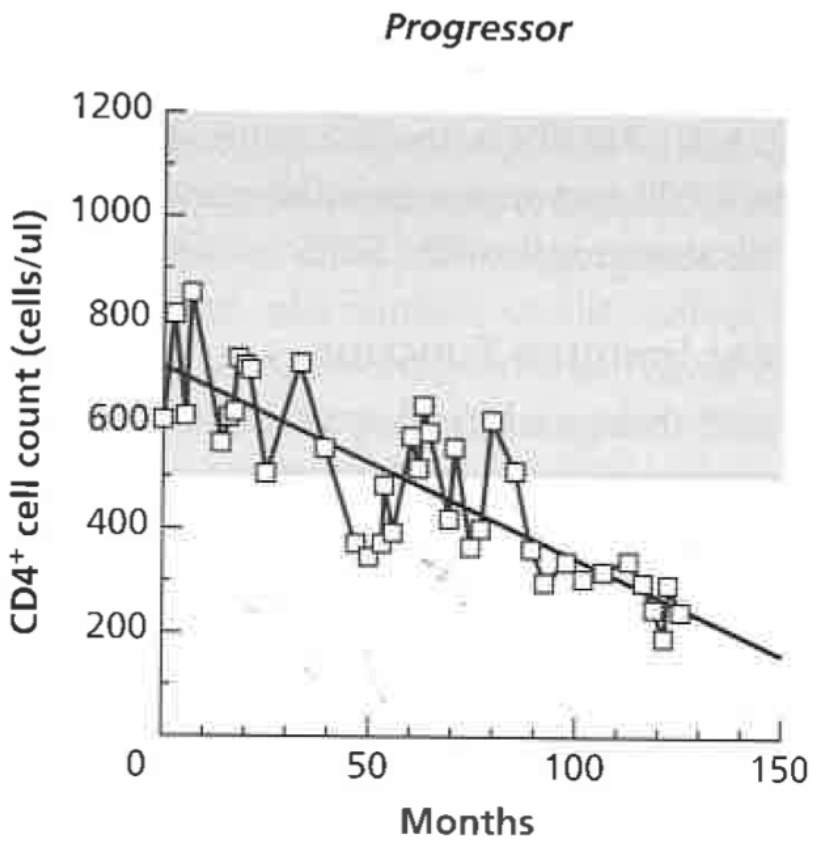
Virus : Host Interactions

Major Cells in the Immune System



Loss of CD4+ Lymphocytes in HIV Infection

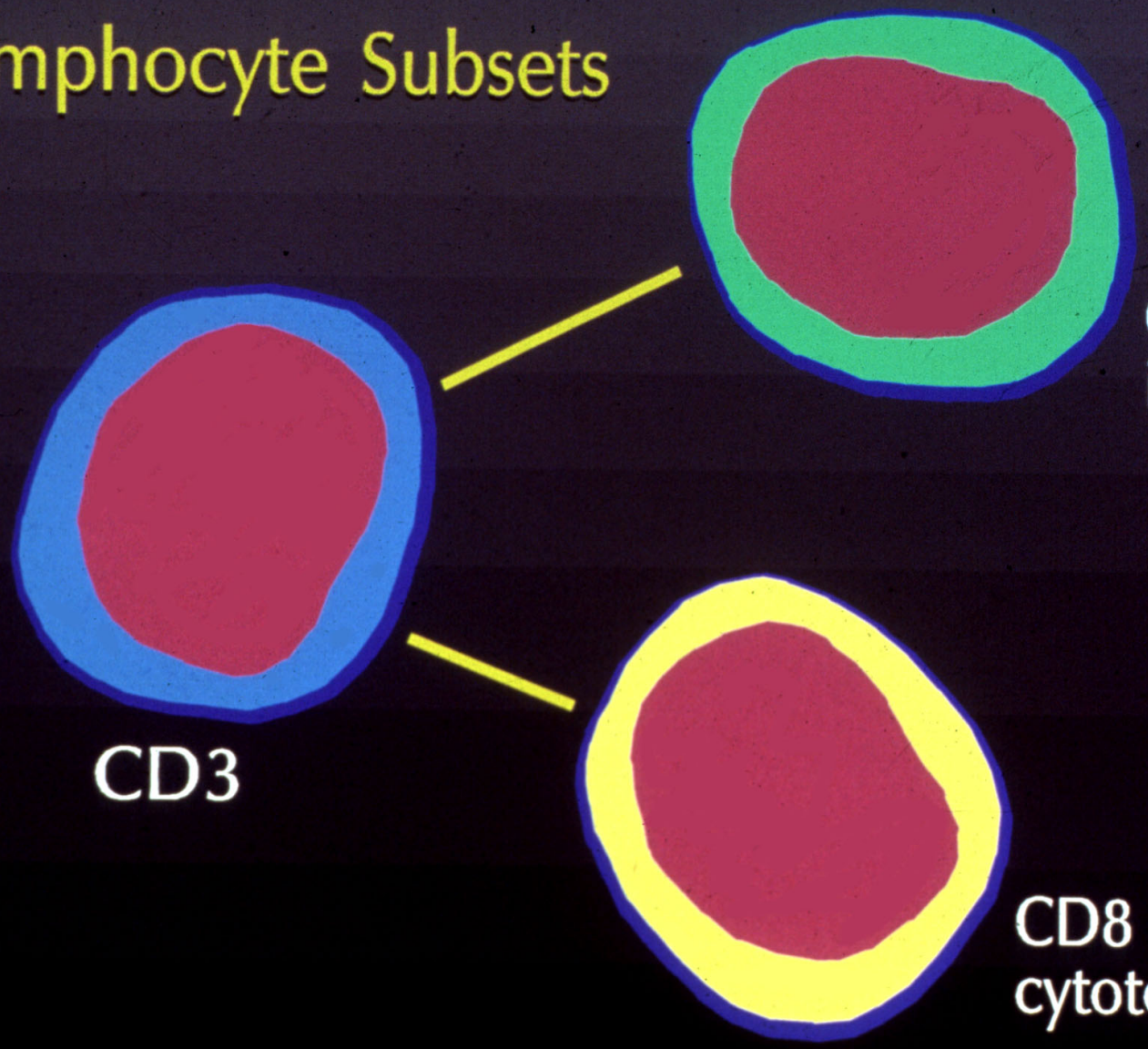




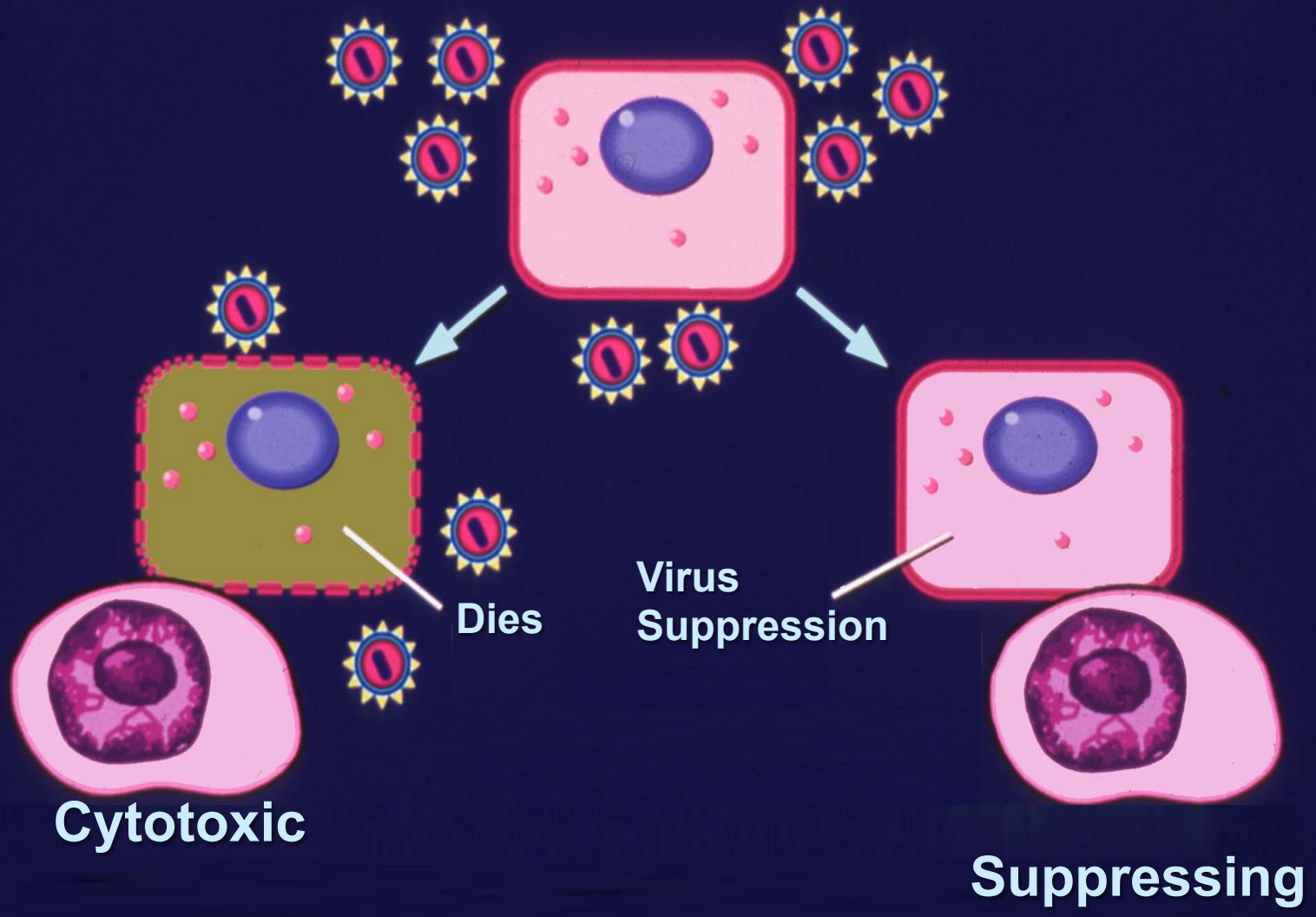
HIV Isolation from Peripheral Blood of a Clinically Healthy Infected Man

Date	Virus Isolation	Date	Virus Isolation	Date	Virus Isolation
10/84	+	2/94	–	8/05	–
11/84	+	8/94	–	2/06	–
1/85	+	2/95	–	8/06	–
2/85	+	8/95	–	2/07	–
4/85	–	2/96	–	8/07	–
8/85	–	8/96	–	2/08	–
11/85	–	2/97	–	8/08	–
2/86	–	8/97	–	2/09	–
8/86	–	2/98	–	8/09	–
2/87	–	8/98	–	2/10	–
8/87	–	2/99	–	8/10	–
2/88	–	8/99	–	2/11	–
8/88	–	2/00	–	8/11	–
2/89	–	8/00	–	2/12	–
8/89	–	2/01	–	8/12	–
2/90	–	8/01	–	2/13	–
8/90	–	2/02	–	8/13	–
2/91	–	8/02	–		
8/91	–	2/03	–		
2/92	–	8/03	–		
8/92	–	2/04	–		
2/93	–	8/04	–		
8/93	–	2/05	–		

Lymphocyte Subsets



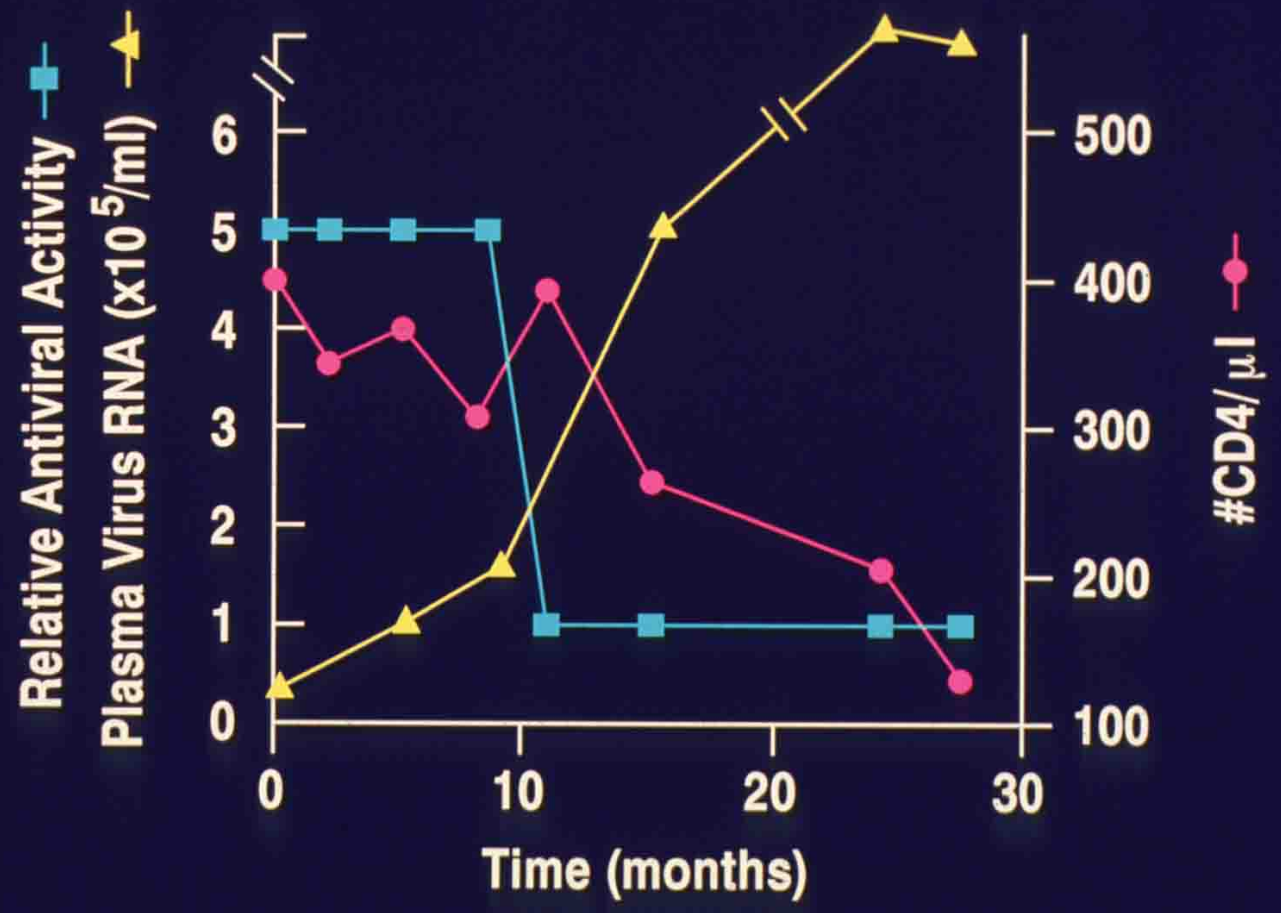
CD8+ Cell Antiviral Activity



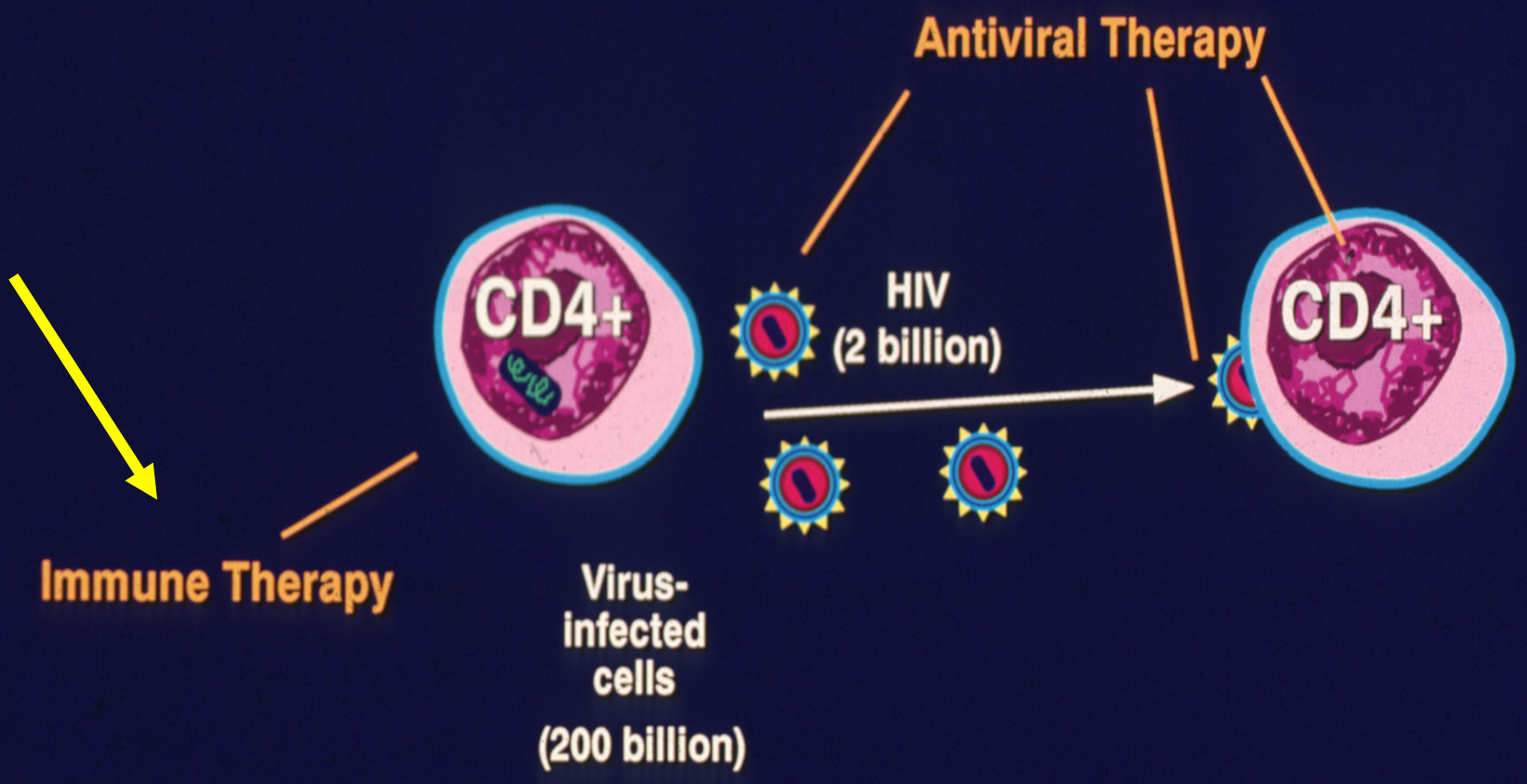
Major Characteristics of Long-Term Survivors of HIV Infection

- **Clinically asymptomatic for ≥ 10 years; no antiviral therapy**
- **Normal CD4+ cell number**
- **Low virus load (measured by plasma viremia; infected PBMC)**
- **Low immune activation; normal T-reg function**
- **Elite Controllers: Undetectable plasma virus for 2-10 years**

CD8+ Cell Anti-HIV Activity in a Healthy Individual Over Time



Approaches at Controlling HIV Infection



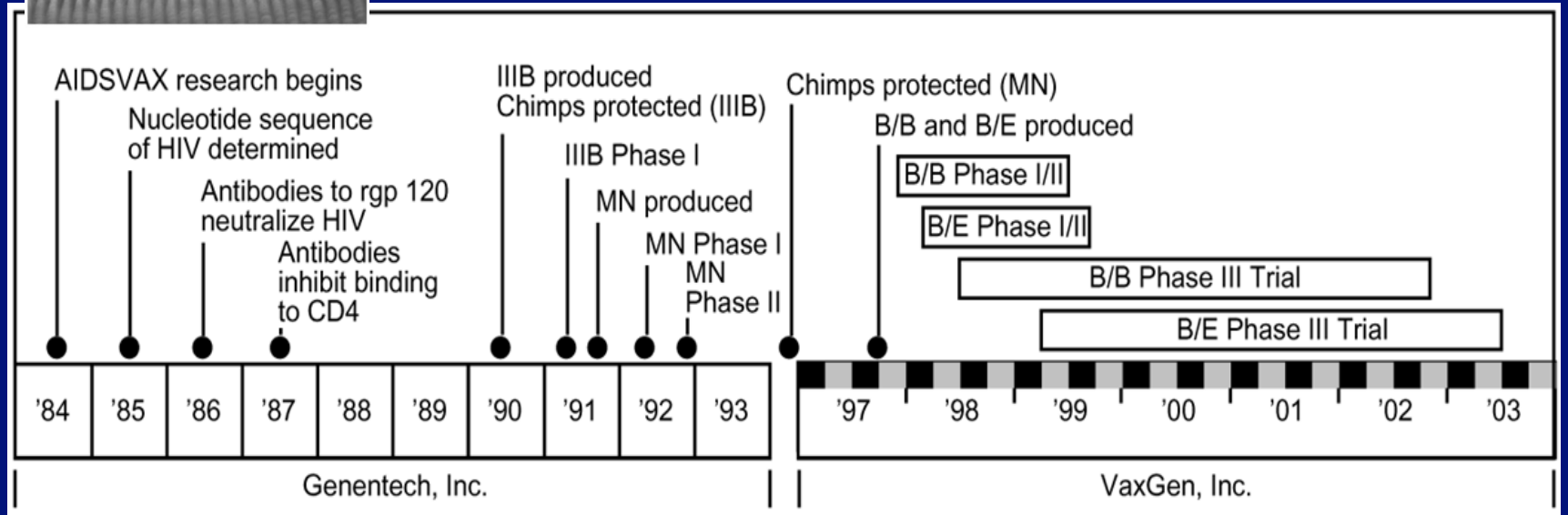
The Ideal HIV Vaccine

- **Induces:**
  - **Early innate response that can curtail the infection**
  - **Cellular and humoral immune responses against virus-infected cells as well as HIV; not autoimmune activities**
  - **Antibodies that neutralize HIV; not enhancing antibodies**
  - **Local immunity at all entry sites for HIV**
- **Safe with long-lasting effects**

Challenges of Developing an HIV Vaccine

- **HIV integrates into the cellular genome**
- **Infected cells transmit the infection**
- **Cell to cell transfer of infection takes place**
- **Numerous HIV variants: virus replication leads to mutations**
- **Virus compromises immune function**

Timeline for Phase III Vaccine Trials held in Canada, Puerto Rico, the Netherlands, and the United States



Francis DP et. al. *AIDS*, 17, 147, 2003

Future Considerations

- **Role of emerging recombinant viruses in HIV transmission, drug/immune resistance, and disease.**
- **Role of immune therapy in controlling HIV as seen in long- term survivors.**
- **Develop an effective vaccine that prevents infection by all HIV-1 and HIV-2 isolates.**
- **Can we bring about a cure involving elimination of HIV from the body or continual control of the virus as seen in elite controllers?**