HIV

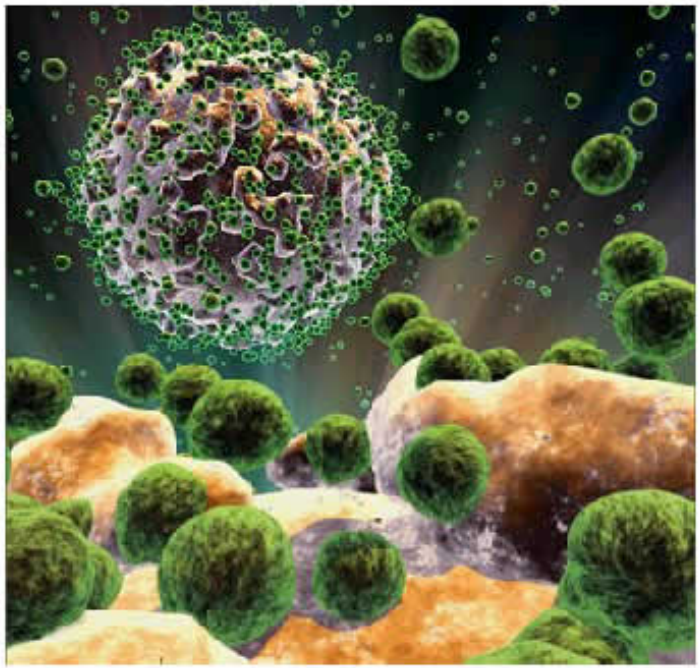
(Human Immunodeficiency Virus)

&

AIDS

Acquired Immune Deficiency Syndrome

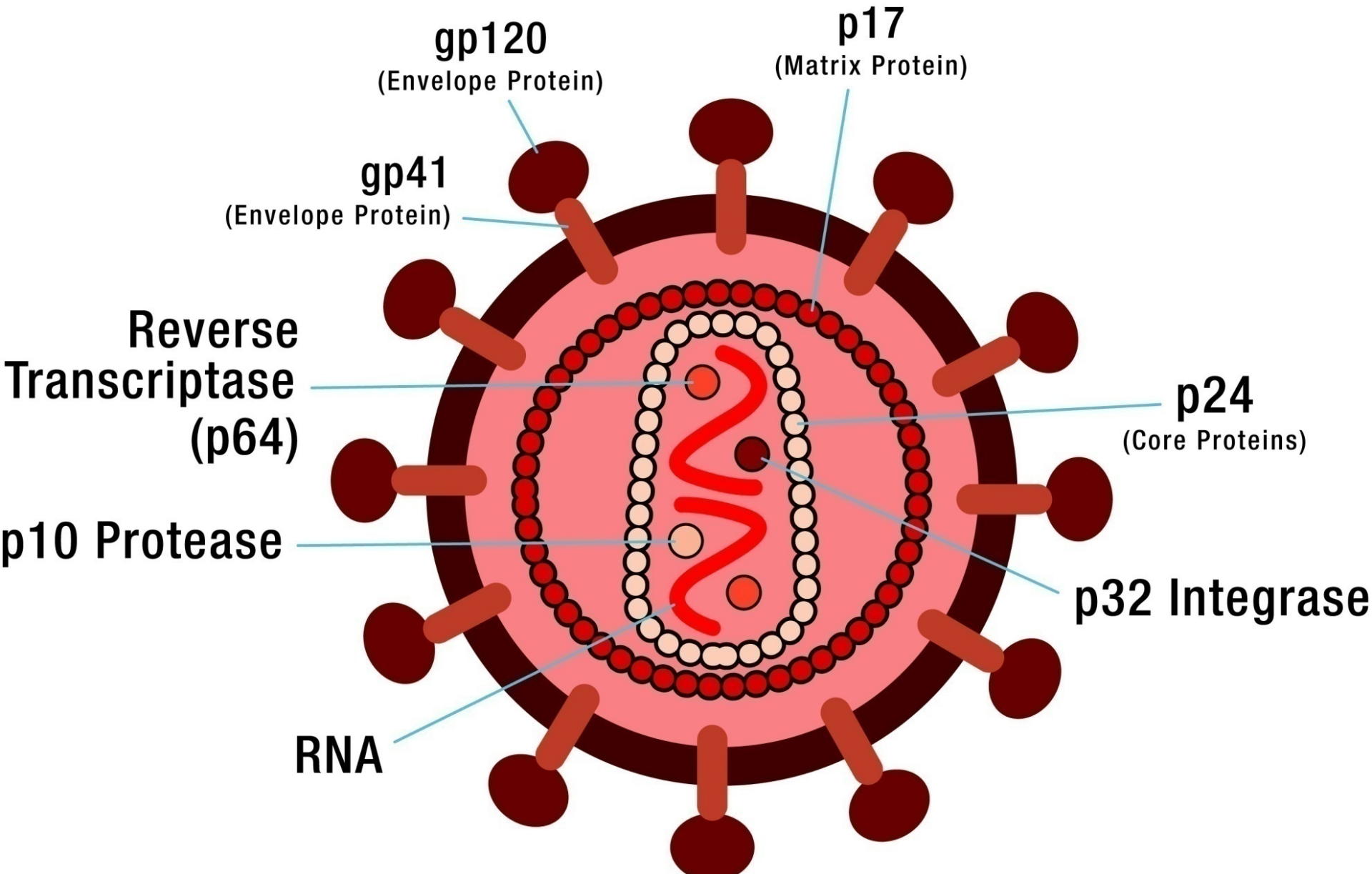
Immunology Unit
Department of
Pathology
King Saud
University



Objectives

- To know the modes of transmission of HIV
- To understand HIV interactions with CD4 positive helper lymphocytes
- To understand the mechanisms involved in immunodeficiency associated with HIV
- To know the course of immunological events from the time of infection with HIV until the development of AIDS

STRUCTURE OF HIV CELL



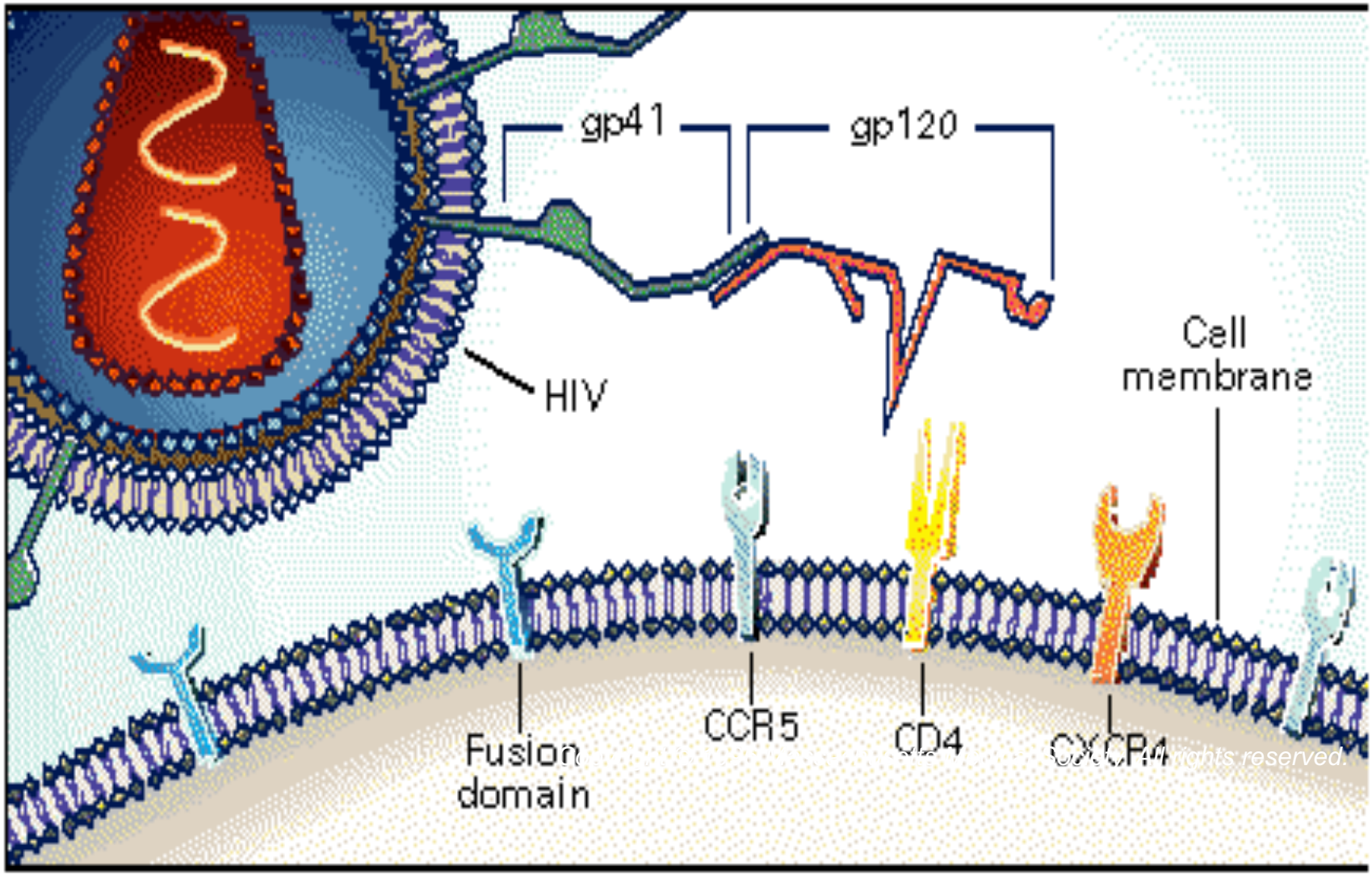
Transmission

- Modes of infection
  - Sexual transmission at genital or colonic mucosa
  - Blood transfusion
  - Mother to infant
  - Accidental occupational exposure

How HIV Enters Cells

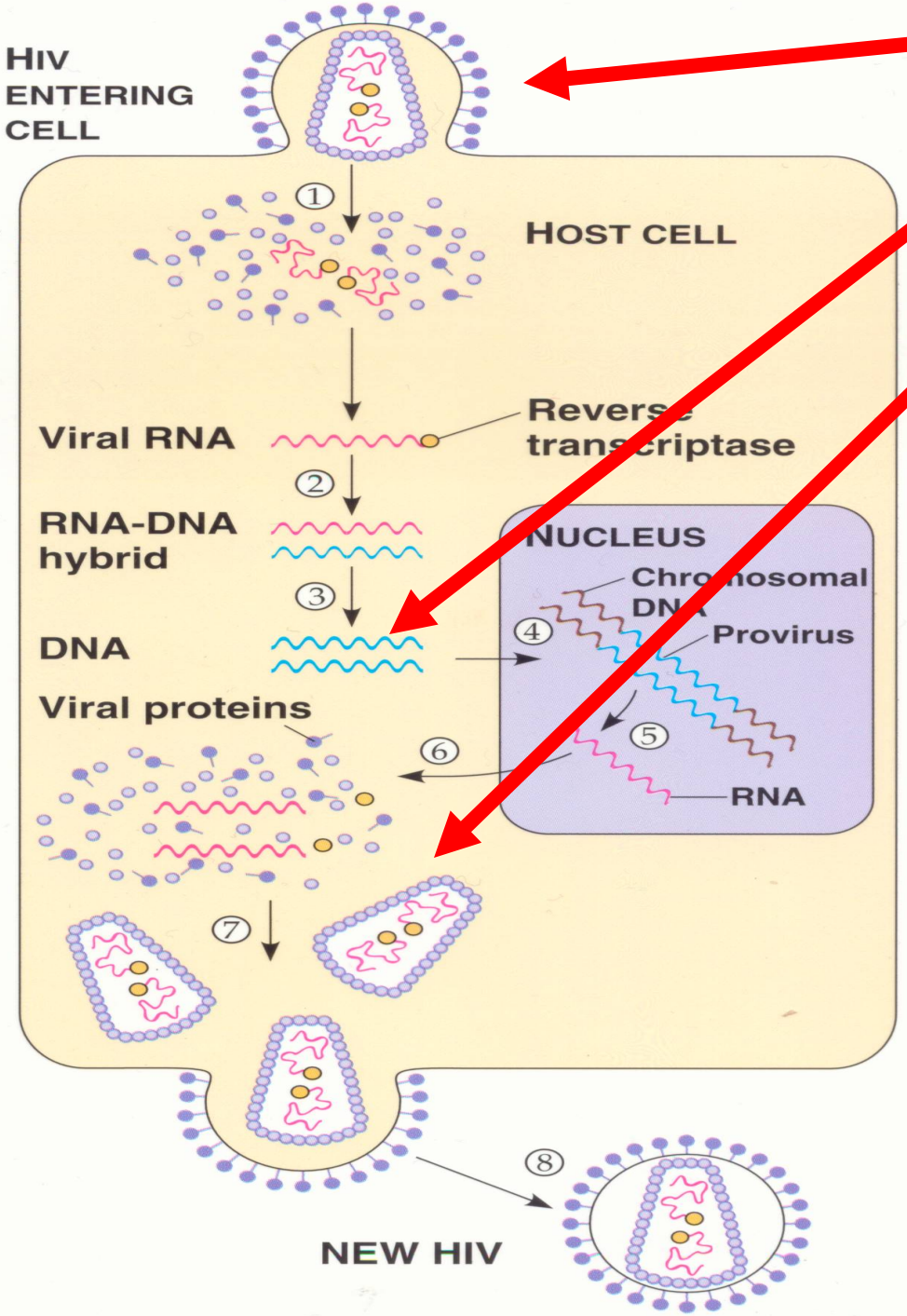
- gp120 env protein binds to CD4 molecule
  - CD4 found on T-cells macrophages, and microglial cells
  - Binding to CD4 is not sufficient for entry
- gp120 env protein binds to co-receptor
  - Chemokine receptors:
  - CCR5 and CXCR4 receptors
- Binding of virus to cell surface results in fusion of viral envelope with cell membrane
- Viral core is released into cell cytoplasm

HIV and Cellular Receptors



Viral-host Dynamics

- About 10^{10} (10 billion) virions are produced daily
- Average life-span of an HIV virion in plasma is ~6 hours
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days
- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells, unlike other retroviruses



1. HIV (retrovirus) enters cell
2. Reverse Transcriptase makes DNA copy of RNA
3. Viral DNA forms provirus with host DNA

Viral DNA makes mRNA

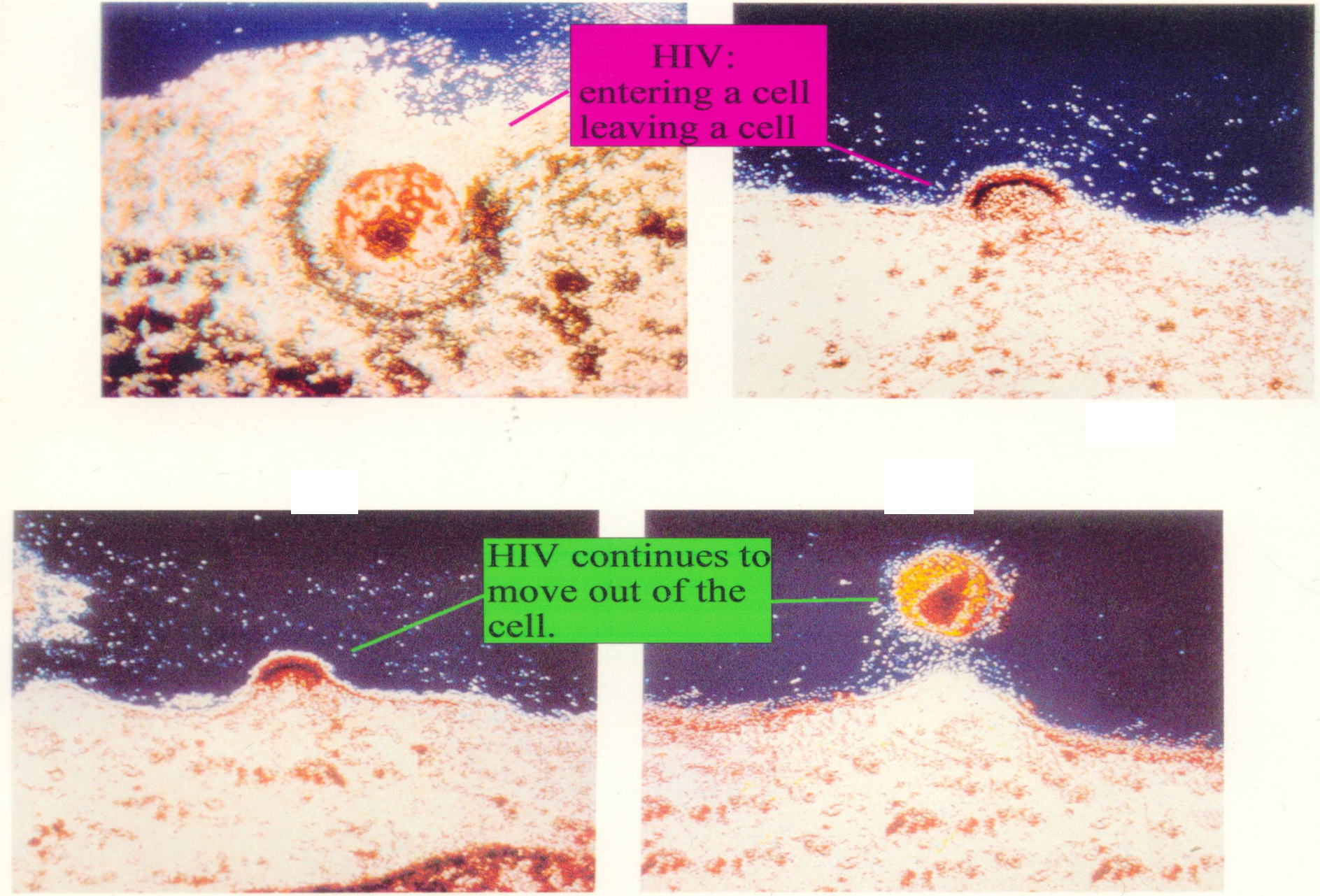
mRNA makes HIV proteins

HIV proteins become HIV capsid

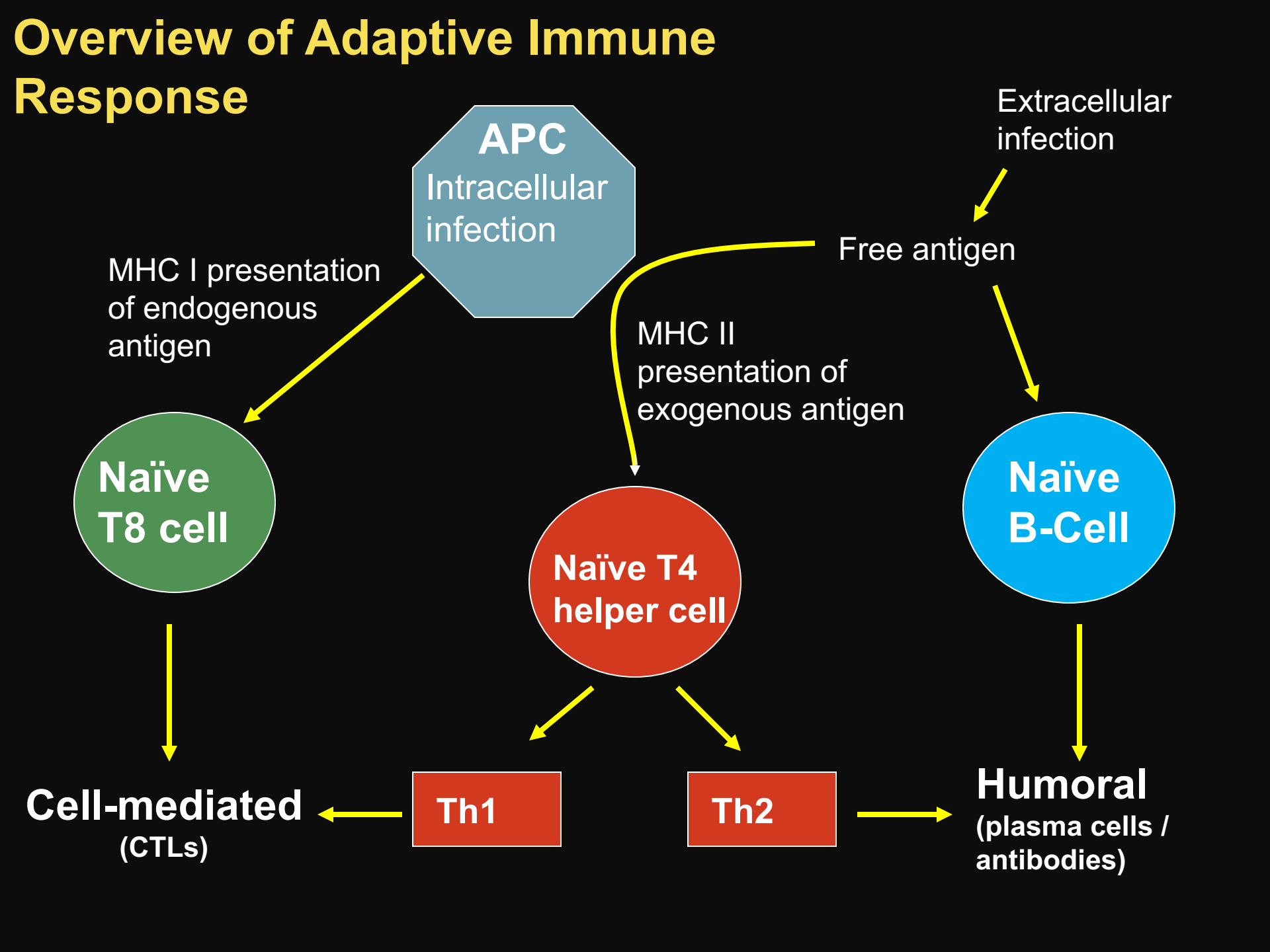
mRNA is collected inside of HIV capsid forming new HIV

New HIV leaves cell and wraps itself in host membrane (envelope)

HIV entering and leaving a human cell



Overview of Adaptive Immune Response



General Principles of Viral-host Interactions

- Host: mounts HIV-specific immune responses
  - Cellular (cell-mediated) - most important
  - Humoral (antibody-mediated)

- Virus: subverts the immune system
  - Infects CD4 cells that control normal immune responses
  - Integrates into host DNA
  - High rate of mutation
  - Hides in tissue not readily accessible to immune system

Cellular Immune Responses to HIV

- CD8 Cytotoxic T lymphocyte (CTL)
  - Derived from naïve T8 cells, which recognize viral antigens in context of MHC class I presentation
  - Directly destroy infected cell
  - Activity augmented by Th1 response

Cellular Immune Responses to HIV

- CD4 Helper T Lymphocyte (Th)
  - Plays an important role in cell-mediated response
  - Recognizes viral antigens by an antigen presenting cell (APC)
    - Utilizes major histocompatibility complex (MHC) class II
  - Differentiated according to the type of “help”
    - Th1 - activate Tc (CD8) lymphocytes, promoting cell-mediated immunity
    - Th2 - activate B lymphocytes, promoting antibody mediated immunity

Humoral Immune Response to HIV

- Neutralization
  - Antibodies bind to surface of virus to prevent attachment to target cell
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Fc portion of antibody binds to NK cell
  - Stimulates NK cell to destroy infected cell

Cells Infected by HIV

- Numerous organ systems are infected by HIV:
  - Brain: macrophages and glial cells
  - Lymph nodes and thymus: lymphocytes and dendritic cells
  - Blood, semen, vaginal fluids: macrophages
  - Bone marrow: lymphocytes
  - Skin: langerhans cells
  - Colon, duodenum, rectum: chromaffin cells
  - Lung: alveolar macrophages

General Principles of Immune Dysfunction in HIV

- All elements of immune system are affected
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue
  - Impaired ability to mount immune response to new antigen
  - Impaired ability to maintain memory responses
  - Susceptibility to opportunistic infections

Mechanisms of CD4 Depletion and Dysfunction

- Direct
  - Elimination of HIV-infected cells by virus-specific immune responses
  - Loss of plasma membrane integrity because of viral budding
- Indirect
  - Syncytium formation
  - Apoptosis
  - Autoimmunity

Syncytium Formation

- Observed in HIV infection, most commonly in the brain
- Uninfected cells may then bind to infected cells due to viral gp 120
- This results in fusion of the cell membranes and subsequent syncytium formation.
- These syncytia are highly unstable and die quickly

Role of Cellular Activation in Pathogenesis of HIV

- HIV induces immune activation
  - Which may seem paradoxical because HIV ultimately results in severe immunosuppression
- Activated T-cells support HIV replication
  - Intercurrent infections are associated with transient increases in viremia
  - Accounts for why TB worsens underlying HIV disease

Role of Cytokine Dysregulation in Pathogenesis of HIV

- HIV is associated with increased expression of pro-inflammatory cytokines
  - TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
- HIV results in disruption and loss of immunoregulatory cytokines
  - IL-2, IL-12
  - Necessary for modulating effective cell-mediated immune responses (CTLs and NK cells)

Primary Infection

- 70-80% symptomatic, 3-12 weeks after exposure
- Fever, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis
- Surge in viral RNA copies to >1 million
- Fall in CD4 count to 300-400
- Recovery in 7-14 days

Seroconversion

- Median 8 weeks after infection
- Level of viral load post sero-conversion correlates with risk of progression of disease

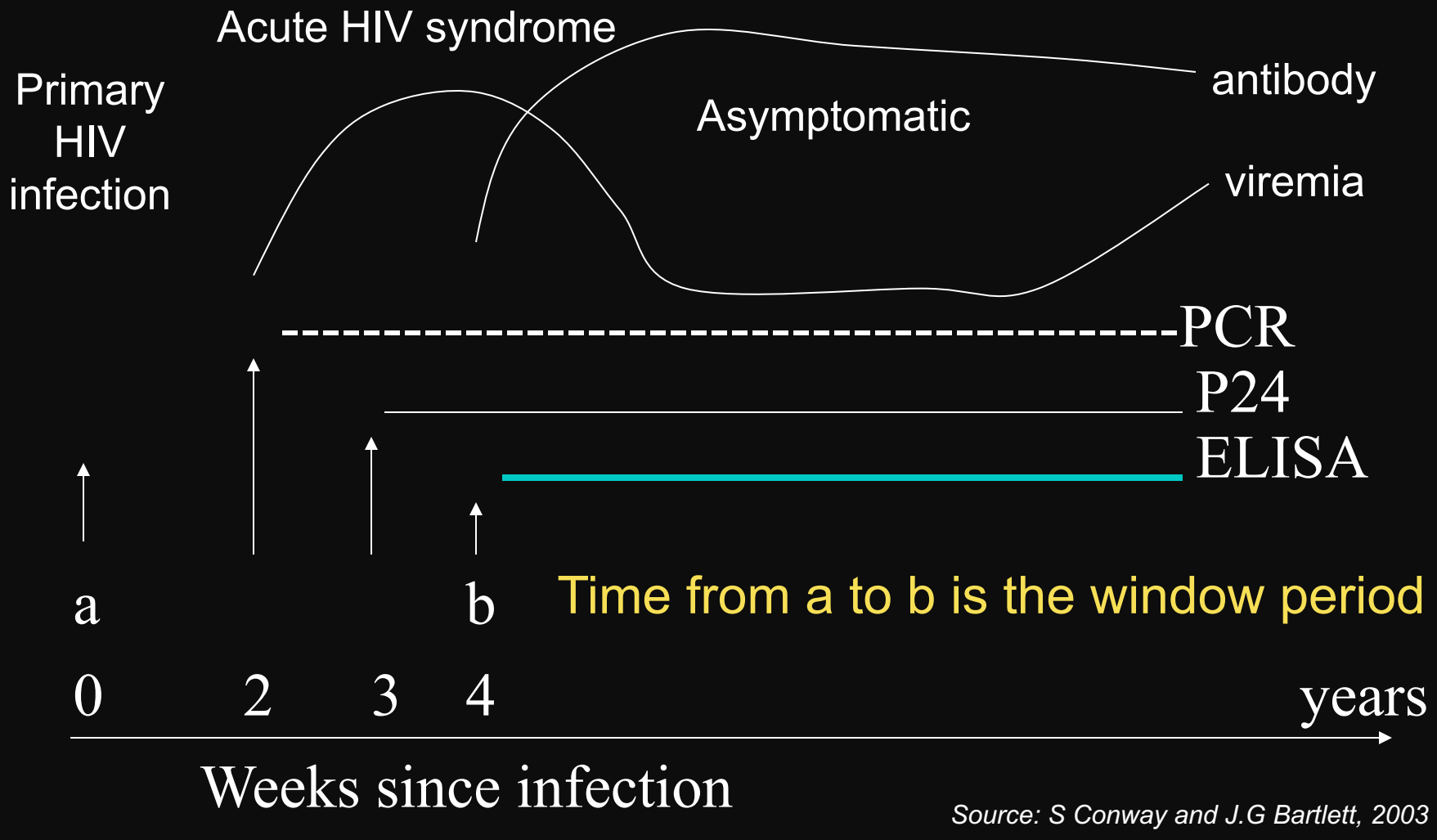
- Asymptomatic Phase
- Remain well with no evidence of HIV disease except for generalized lymphadenopathy
- Fall of CD4 count by about 50-150 cells per year

CD4 T-cell Count and Progression to AIDS

- Gradual reduction in number of circulating CD4 cells is inversely correlated with the viral load

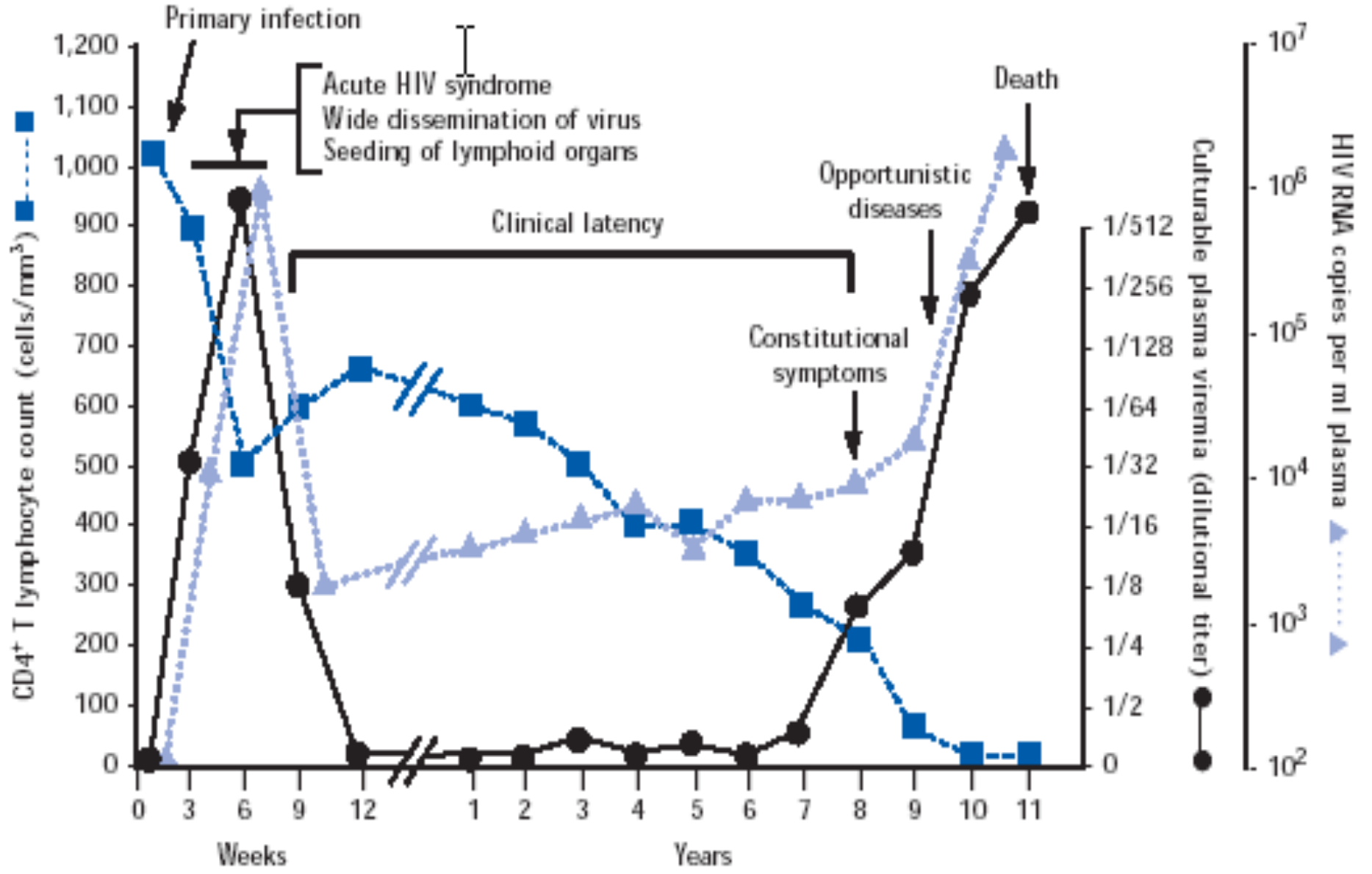
- Any depletion in numbers of CD4 cells renders the body susceptible to opportunistic infections

Window Period: Untreated Clinical Course



Source: S Conway and J.G Bartlett, 2003

Natural History of HIV



Laboratory Markers of HIV Infection

- Viral load
  - Marker of HIV replication rate
- CD4 count
  - Marker of immunologic damage

Diagnosis

- Antibody test, ELISA
- Western blot
- HIV RNA viral load

Management

- Treatment recommended when symptomatic or CD4 count below 200
- Earlier if high viral load, rapidly falling CD4 count, hepatitis C co-infection

  - Antiviral therapy
    - Reverse transcriptase inhibitors
    - Protease inhibitors
    - Fusion inhibitors

Take Home Message

- Infection with HIV usually occurs by sexual transmission, blood transfusion, mother to infant or accidental exposure
- HIV targets the immune system and primarily infects CD4 positive lymphocytes
- Immunodeficiency associated with HIV infections is mainly due to reduction in CD4 positive helper lymphocyte numbers
- Increased viral load, significant reduction in CD4 lymphocytes and opportunistic infections are the hallmarks of progression to AIDS

Thank you