Secondary Immunodeficiency & Immunology of HIV infection

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Secondary Immunodeficiencies

- Acquired defect in one or more components of the immune system that manifests clinically as increased susceptibility to infections
- Increased susceptibility to common infectious agents & opportunistic infections
- Symptoms vary depending on degree of immunosuppression & inherent host susceptibility factors
- Withdrawal of the external condition causing immunodeficiency can result in restoration of immune function

Predisposing factors	Specific factors
Premature and newborn infants	Physiological immunodeficiency due to immaturity of the immune system
Hereditary and metabolic diseases	Chromosome abnormalities (e.g. Down syndrome), uraemia, DM, malnutrition, vitamin and mineral deficiency, protein-loosing enteropathies, NS, SCD
Immunosuppressive agents	Radiation, immunosuppressive drugs, corticosteroids
Infectious	Congenital infections (rubella), viruses (measles, varicella, HIV, CMV, EBV), acute bacterial disease, severe mycobacterial or fungal disease
Infiltrative and haematological	Histiocytosis, sarcoidosis, lymphoma, leukaemia, myeloma, aplastic anaemia
Surgery and trauma	Burns, splenectomy
Miscellaneous	SLE, chronic active hepatitis, alcoholic cirrhosis, ageing

Acquired Hypogammaglobulinaemia

- Young adults
- Low but detectable levels of total immunoglobulin
- Normal T cell numbers and function in most cases
- Rx – immunoglobulin therapy
- No evidence of genetic transmission, unlike CVID

Agent-Induced Immunodeficiency

- Exposure to any of a number of environmental agents that induce an immunosuppressed state
  - Corticosteroids - inhibition of T cell activation, B cell maturation & cytokine synthesis; lymphopaenia
  - Immunosuppressive & cytotoxic drugs (AZA, MTX, 6-MP, cyclophosphamide), Radiotherapy - bone marrow suppression
  - Cyclosporine - inhibits T cell signalling
  - Biologics e.g. rituximab

Extremes of age

- The very young and the very old
- Neonates, especially premature babies can be very susceptible to infection,
- Degree of prematurity linked to the degree of immune dysfunction
- All the basic immune components are in place in a full-term healthy newborn, but the complete range of innate and adaptive immune functions take some time to mature

Malnutrition

- Affects both innate and adaptive immunity
- Low protein-calorie diets (hypoproteinemia) associated with depressed T-cell number & function; deleterious B cell effects may take longer to appear
- Micronutrient insufficiency (zinc, ascorbic acid) also contributes to immunodeficiency
- Vitamin D deficiency linked to an inhibition in the ability of macrophages to act against intracellular pathogens e.g. *M.tuberculosis*

Medical states

- Splenectomy
  - Antibody deficiency & susceptibility to infections with encapsulated bacteria, malaria, salmonellosis
- Poor nutrition; surgery/trauma/ICU
- Protein-loosing states
- Renal disease

Immunology of HIV Infection

HIV/AIDS

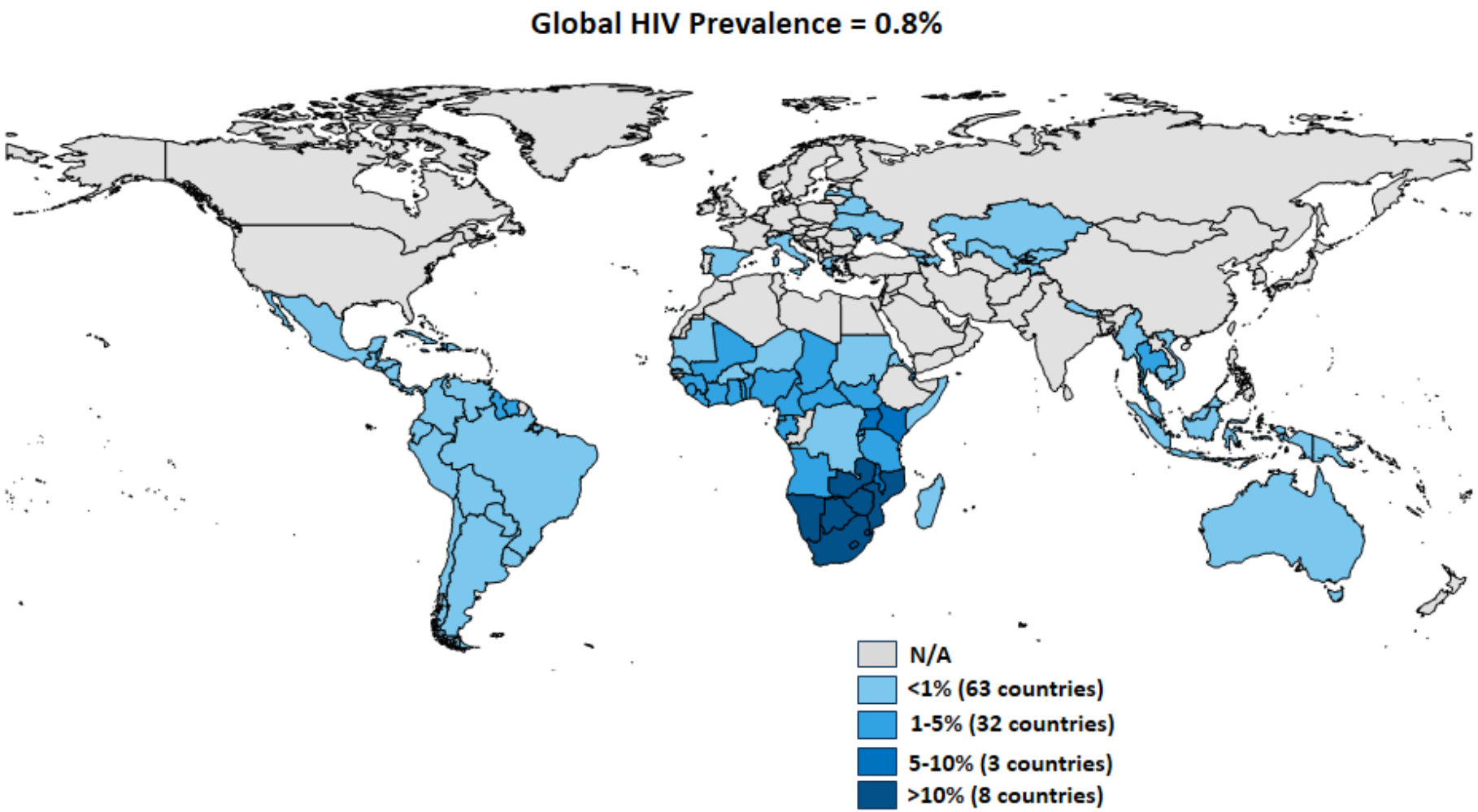
- HIV causes AIDS
- AIDS first recognized as opportunistic infections in a cluster of individuals on both coasts of the US in June 1981
- Displayed unusual infections e.g. PJP, previously limited to individuals taking immunosuppressive drugs; KS, a rare skin tumour, etc.
- Evaluation revealed a deficiency in cell-mediated immune responses and a significant decrease in the $CD4^+$ T cell subpopulation (T_H cells)

HIV/AIDS

- Majority of the patients were homosexual males
- Others thought to be at risk at that time:
  - Promiscuous heterosexual individuals of either sex and their partners
  - Recipients of blood & blood products prior to 1985
  - Infants born to HIV-infected mothers

Figure 1

Adult HIV Prevalence, 2015



NOTES: Data are estimates. Prevalence includes adults ages 15-49.
SOURCES: Kaiser Family Foundation, based on UNAIDS, AIDSinfo, Accessed June 2016

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HIV/AIDS Epidemic

- Approximately 36.7 million people living with HIV at the end of 2016; 2.1 million were children (<15 yr old)
- 1.8 million new infections
- 1 million AIDS-related deaths
- 35 million deaths since the start of the epidemic

UNAIDS Data 2017

HIV/AIDS Epidemic

- Kenya - 4th largest epidemic (2016)
  - 1.6 million people living with HIV
  - 5.4% adult HIV prevalence
  - 62,000 new infections
  - 36,000 people died from AIDS-related deaths (64,000 in 2010)
  - 64% adults with HIV on ART, 65% children

UNAIDS Data 2017

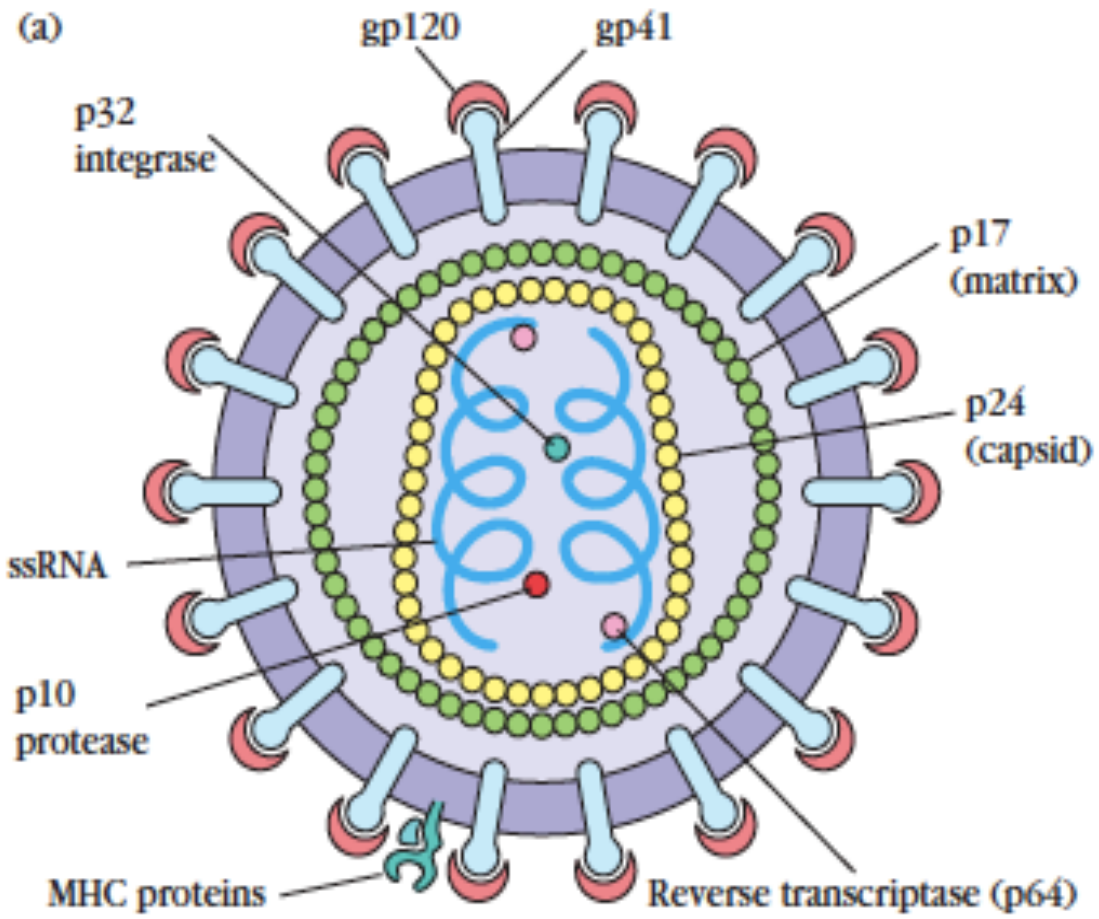
Human Immunodeficiency Virus-1 (HIV-1)

- Retrovirus of the lentivirus genus (displays long incubation periods)
- Characterized by Luc Montagnier in Paris & Robert Gallo in Bethesda, Maryland, USA (1983)
- RNA virus; reverse-transcribed to DNA when the virus enters a cells, by the virally coded reverse transcriptase enzyme
- This copy of DNA is called a provirus; it's integrated into the cell genome and replicated along with the cell DNA
- When the provirus is expressed to form new virions (viral particles), the cell lyses

HIV-1

- Alternatively, the provirus may remain latent in the cell until some regulatory signal starts the expression process
- HIV-2 isolated from AIDS sufferers in Africa about 5 years after the discovery of HIV-1
- HIV-2 prevalence limited mostly to West Africa; disease progresses much more slowly

Structure of HIV



B. M. Peterlin and P. A> Luciw, 1988, AIDS

- Lipid envelope derives from the host cell; contains some host cell membrane proteins e.g. MHC I & II
- Env studded by 2 viral glycoproteins, gp120 & gp41 which are important for the infection process
- Within the env is the viral matrix p17 and the core/nucleocapsid (p24)
- Genome consists of 2 copies of ssRNA, associated with 2 molecules of RT (p64), a protease (p10) and and integrase (p32) – viral enzymes

Transmission

- Intimate contact with body fluids
  - Sexual contact (75%)
    - Unprotected vaginal and anal intercourse
  - Receipt of infected blood or blood products
    - Transfusions, contaminated needles & syringes
  - Perinatal transmission HIV-infected mothers to their infants
    - During labour and delivery (in utero)
    - Breast milk

Spread

- Direct infection of activated but resting memory $CD4^+$ T cells present within vaginal mucosa is the likely primary initial source in the FGT (the most studied location)
- Dendritic cells take up the virus (may not become infected) & transport intact infectious virus to T cells
- Free virus can also squeeze between epithelial cells or gain access through microabrasions
- Whether free of cell-associated, the virus migrates through the submucosa to the draining lymph node, where the adaptive immune response can be initiated (& further spread)

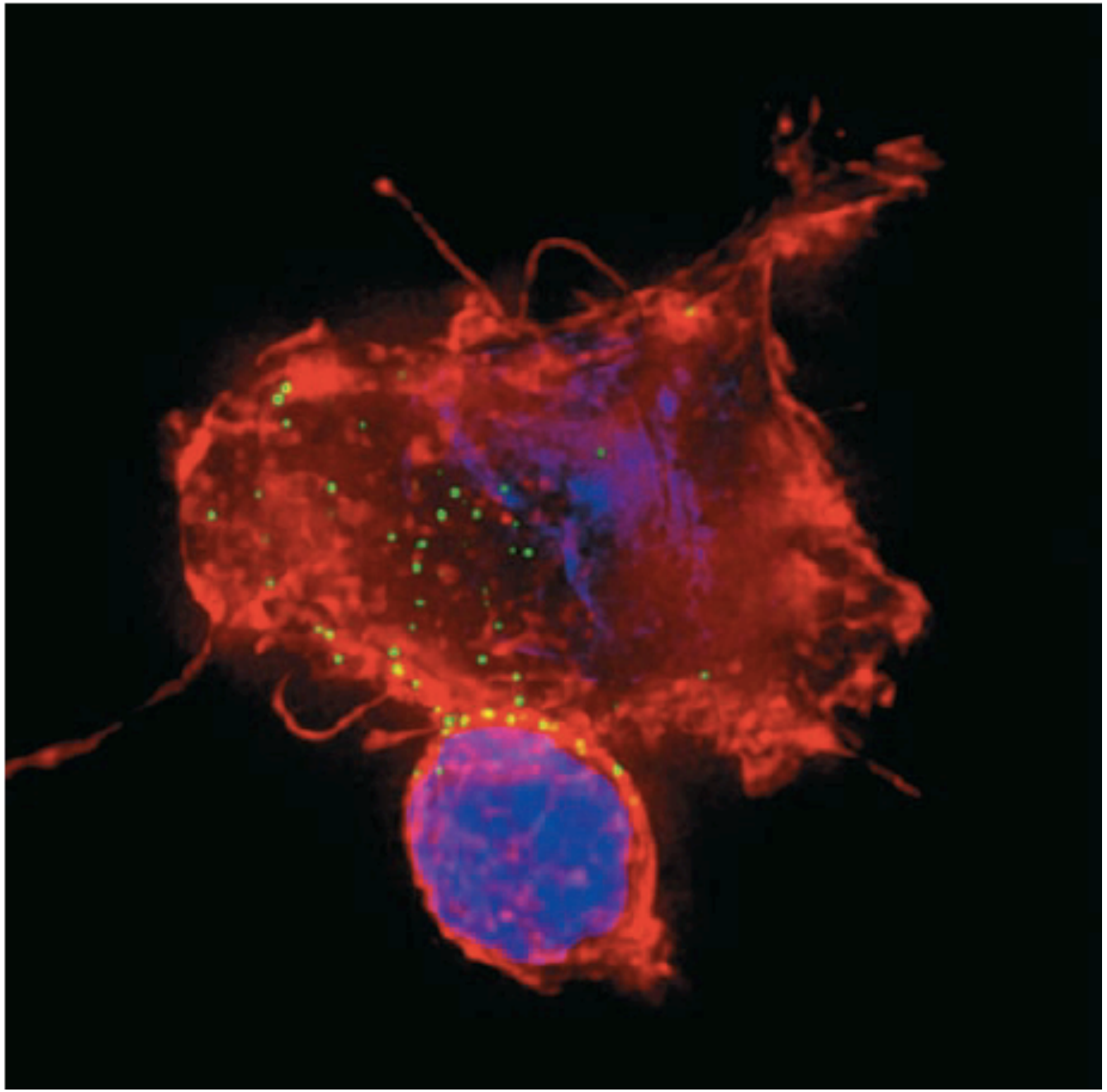


FIGURE 18-11 Interaction between dendritic cell and T cell, indicating passage of HIV-1 (green dots) between the cells. Note that particles cluster at the interface between the large dendritic cell and the smaller T cell. *[Courtesy of Thomas J. Hope, Northwestern University.]*

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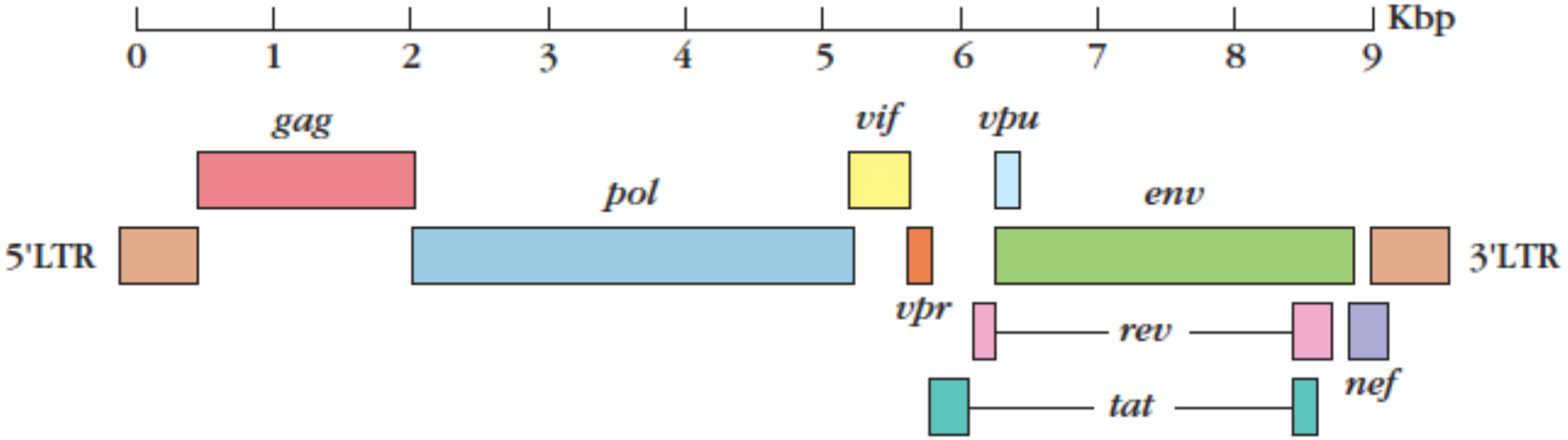
HIV Genome



- Structural genes: *gag, pol, env*
- Regulatory genes/accessory: *tat, rev, nef, vpu, vpr,vif*

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Gene	Protein product	Function of encoded proteins
gag	53-kDa precursor	*Nucleocapsid proteins*
	↓	
	p17	Forms outer core-protein layer (matrix)
	p24	Forms inner core-protein layer (capsid)
	p9	Is component of nucleoid core
	p7	Binds directly to genomic RNA
env	160-kDa precursor	*Envelope glycoproteins*
	↓	
	gp41	Is transmembrane protein associated with gp120 and required for fusion
	gp120	Protrudes from envelope and binds CD4
pol	Precursor	*Enzymes*
	↓	
	p64	Has reverse transcriptase and RNase activity
	p51	Has reverse transcriptase activity
	p10	Is protease that cleaves *gag* precursor
	p32	Is integrase

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Gene	Protein product	Function of encoded proteins
		Regulatory proteins
tat	p14	Strongly activates transcription of proviral DNA
rev	p19	Allows export of unspliced and singly spliced mRNAs from nucleus
		Auxiliary proteins
nef	p27	Down-regulates host-cell class I MHC and CD4
vpu	p16	Is required for efficient viral assembly and budding. Promotes extracellular release of viral particles, degrades CD4 in ER
vif	p23	Promotes maturation and infectivity of viral particle
vpr	p15	Promotes nuclear localization of preintegration complex, inhibits cell division

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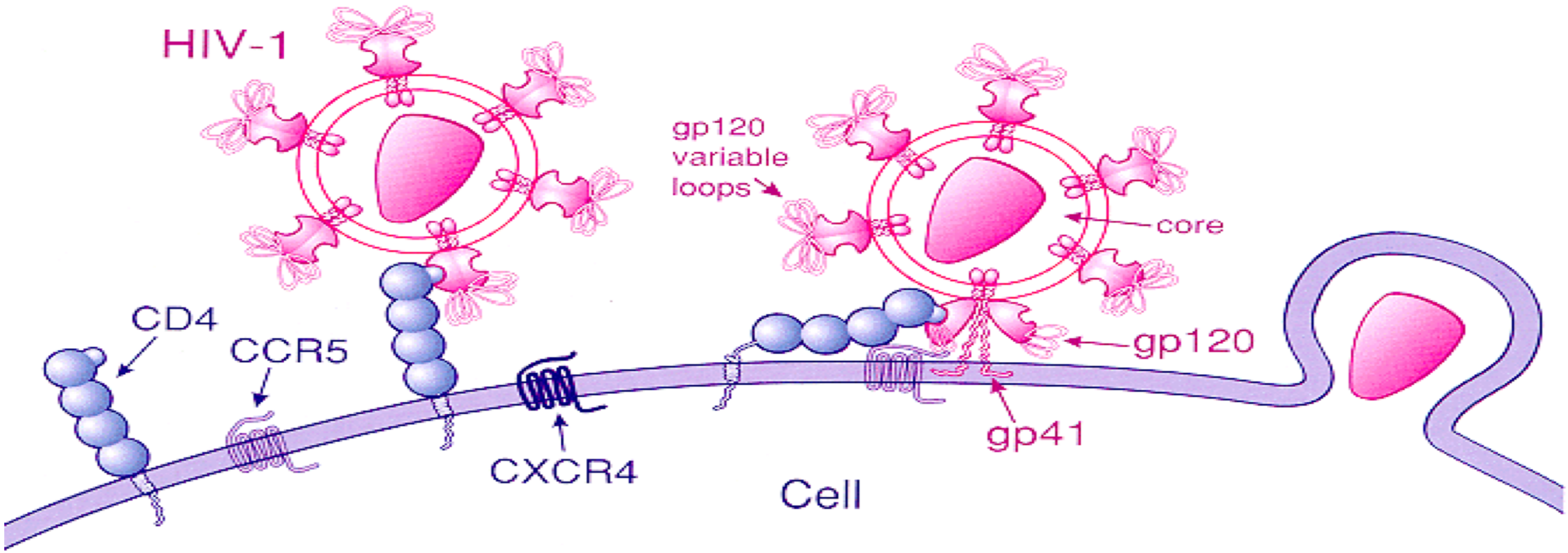
HIV-1 Life Cycle

- Infects cells that carry the CD4 antigen – T_H cells, monocytes, macrophages
  - High-affinity interaction between gp120 & CD4
  - Expression of a co-receptor required for viral entry – CCR5 or CXCR4 (chemokine receptors)
    - Infection of a T cell assisted by CXCR4, while CCR5 is the preferred coreceptor for viral entry into monocytes and macrophages
- RNA genome of the virus reverse transcribed & a complementary DNA (cDNA) copy integrates into the host genome

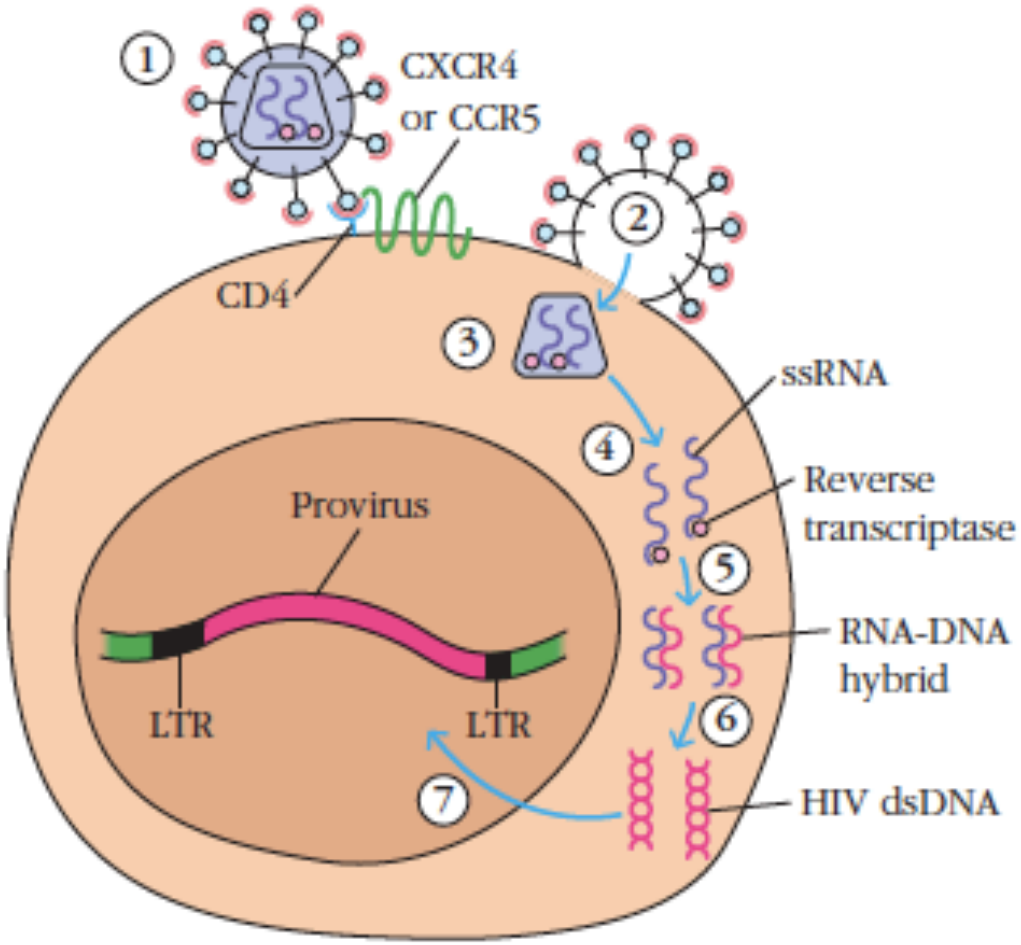
HIV-1 Life Cycle

- The integrated provirus is transcribed
- The various viral RNA messages are spliced & translated into proteins
- These initial viral proteins are cleaved by the virally encoded protease into forms that make up the nuclear capsid in a mature infectious viral particle
- Viral expression leads to newly formed virions that bud from the surface of the infected cell, often causing cell lysis
- HIV-1 can also become latent or remain unexpressed for long periods of time in an infected cell



Viral Attachment

(a) Infection of target cell



1. HIV gp120 binds to CD4 on target cell.
2. HIV gp41 binds to a chemokine receptor (CXCR4 or CCR5) and fuses with the target cell membrane.
3. Nucleocapsid containing viral genome and enzymes enters cells.
4. Viral genome and enzymes are released following removal of core proteins.
5. Viral reverse transcriptase catalyzes reverse transcription of ssRNA, forming RNA-DNA hybrids.
6. Original RNA template is partially degraded by ribonuclease H, followed by synthesis of second DNA strand to yield HIV dsDNA.
7. The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the viral integrase enzyme.

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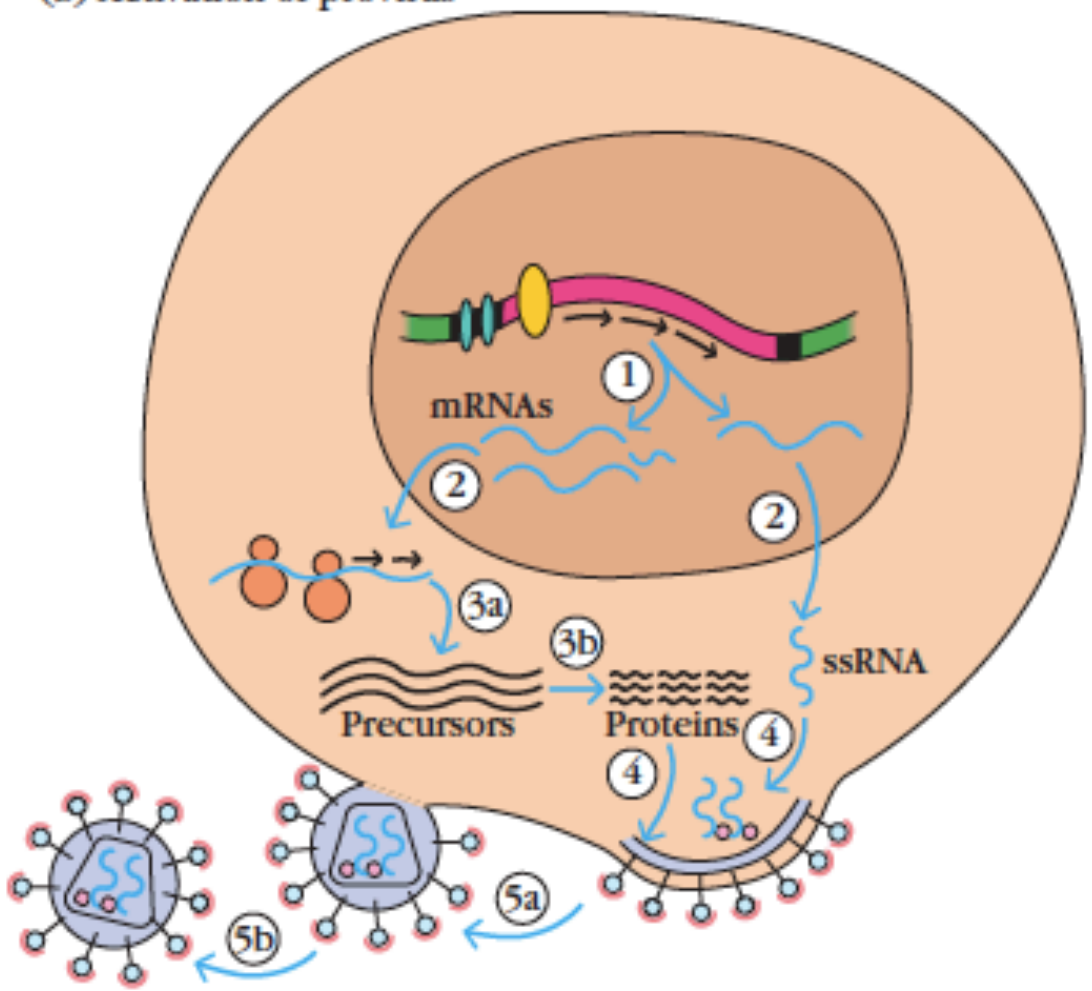
(b) Activation of provirus



1. Transcription factors stimulate transcription of proviral DNA into genomic ssRNA and, after processing, several mRNAs.
2. Viral RNA is exported to cytoplasm.
3a. Host-cell ribosomes catalyze synthesis of viral precursor proteins.
3b. Viral protease cleaves precursors into viral proteins.
4. HIV ssRNA and proteins assemble beneath the host-cell membrane, into which gp41 and gp120 are inserted.
5a. The membrane buds out, forming the viral envelope.
5b. Released viral particles complete maturation; incorporated precursor proteins are cleaved by viral protease present in viral particles.

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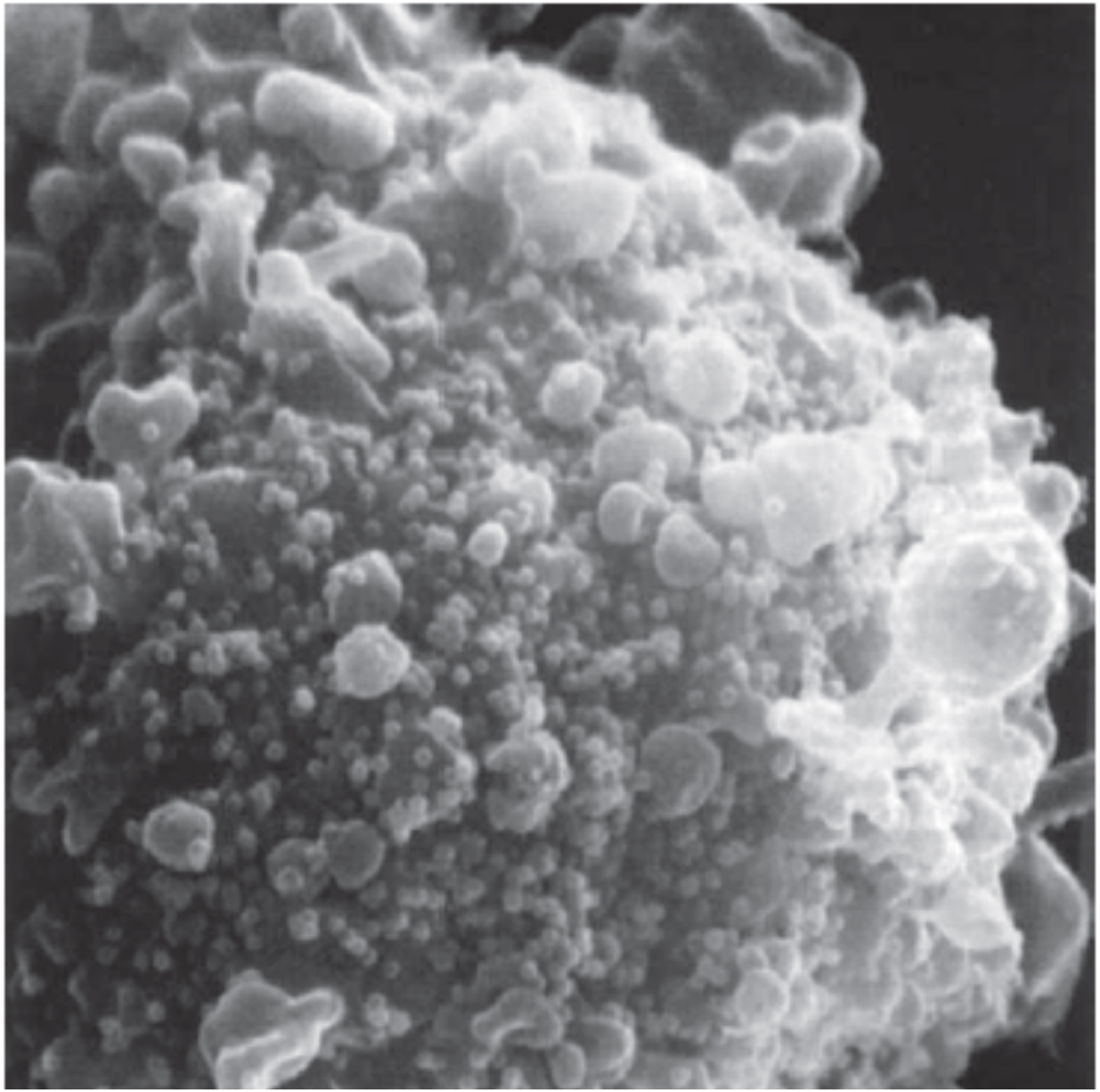

FIGURE 18-14 Once the HIV provirus has been activated, buds representing newly formed viral particles can be observed on the surface of an infected T cell. The extensive cell damage resulting from budding and release of virions leads to the death of infected cells. *[Courtesy of R. C. Gallo, 1988, HIV—The cause of AIDS: An overview on its biology, mechanisms of disease induction, and our attempts to control it.* Journal of Acquired Immune Deficiency Syndromes *1:521.]*

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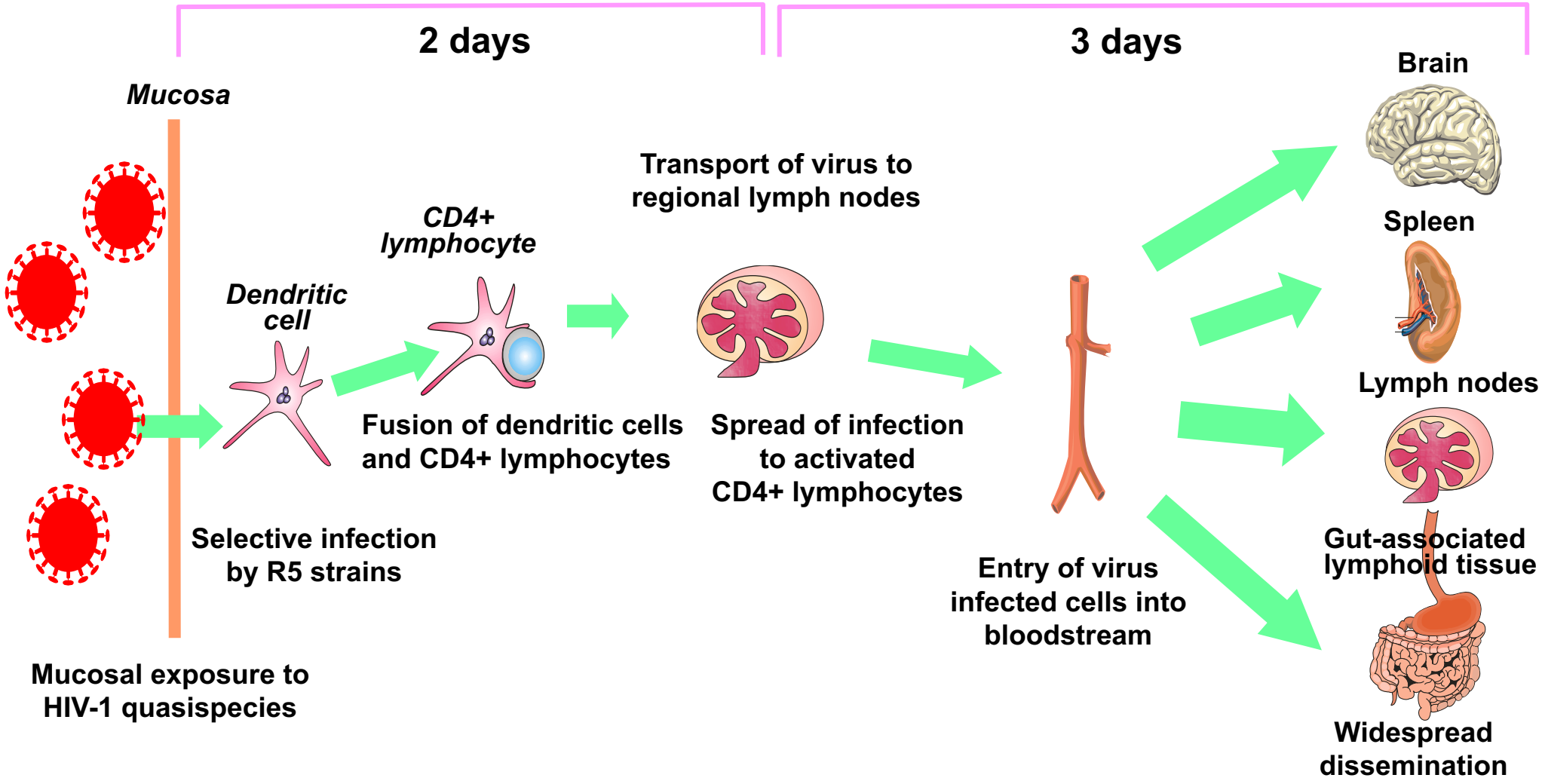
Pathophysiology and Clinical Course

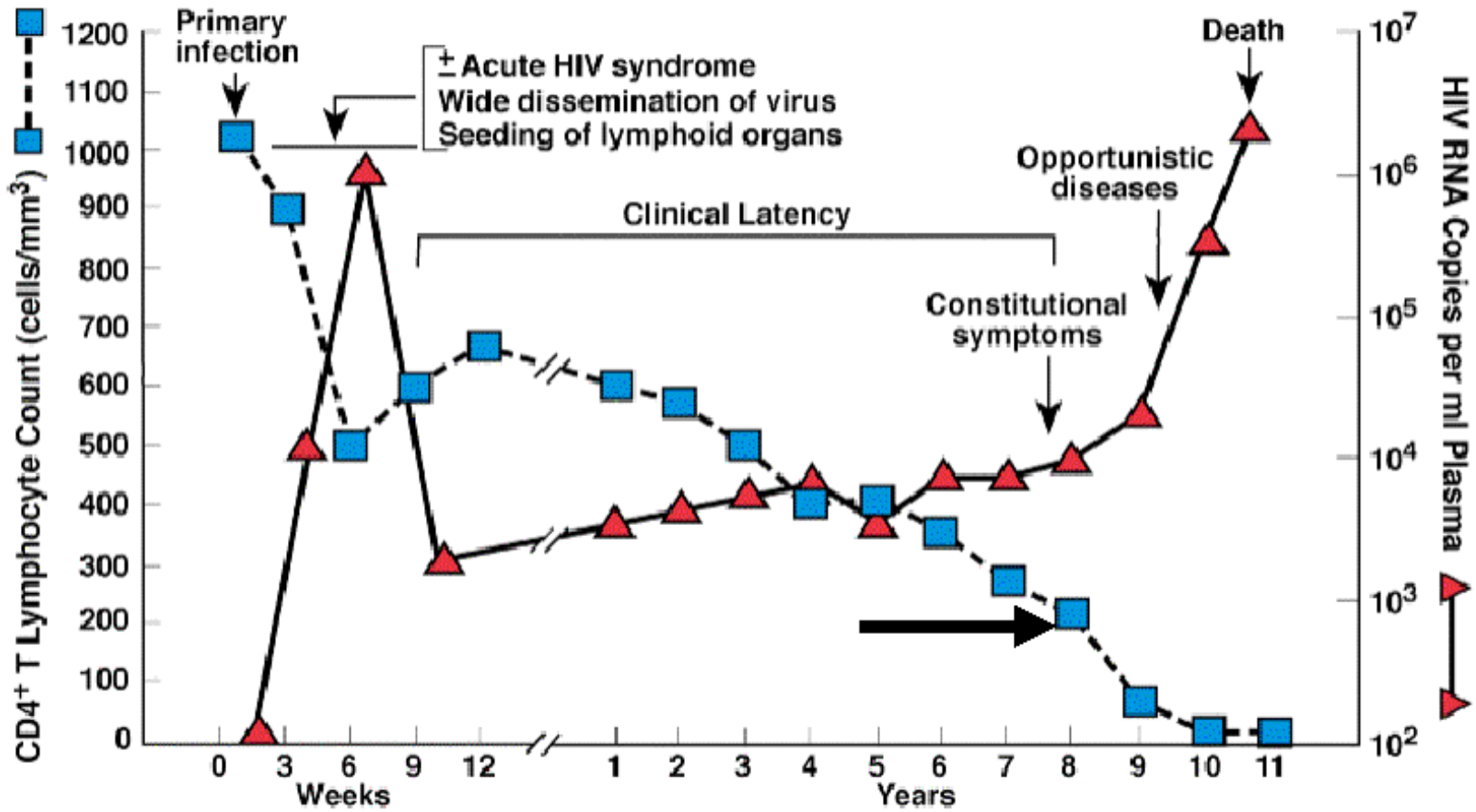
- Gradual impairment of immune function & progression to AIDS
- Isolation of HIV-1 & its growth in culture allowed purification of viral proteins & development of tests for detection infection
- ELISA - detection of Abs against HIV-1 proteins e.g. *gag* p24, one of the most immunogenic HIV proteins
- Antibodies appear in serum of infected individuals within 6 - 12 weeks after exposure, but can take up to 6 months to appear - seroconversion

Dissemination of HIV



Kahn et al., NEJM 1998; 339(1): 34

Typical Course of HIV Infection



Modified From: Fauci, A.S., et al, *Ann. Intern. Med.*, 124:654, 1996

Phases of HIV infection

- 3 phases which occur over 8 to 12 years
- **Acute/primary infection phase**
  - No detectable anti-HIV-1 antibodies
  - Flu-like symptoms (fever, lymphadenopathy, myalgia, malaise, headache) approximately 2 to 4 weeks after exposure
  - High rate of viral replication; viral load (number of virions) can be quite high in blood and other body fluids
  - Decreasing amount of $CD4^+$ T cells
  - After a few weeks the immune system catches up controlling viral replication where it remains for several years

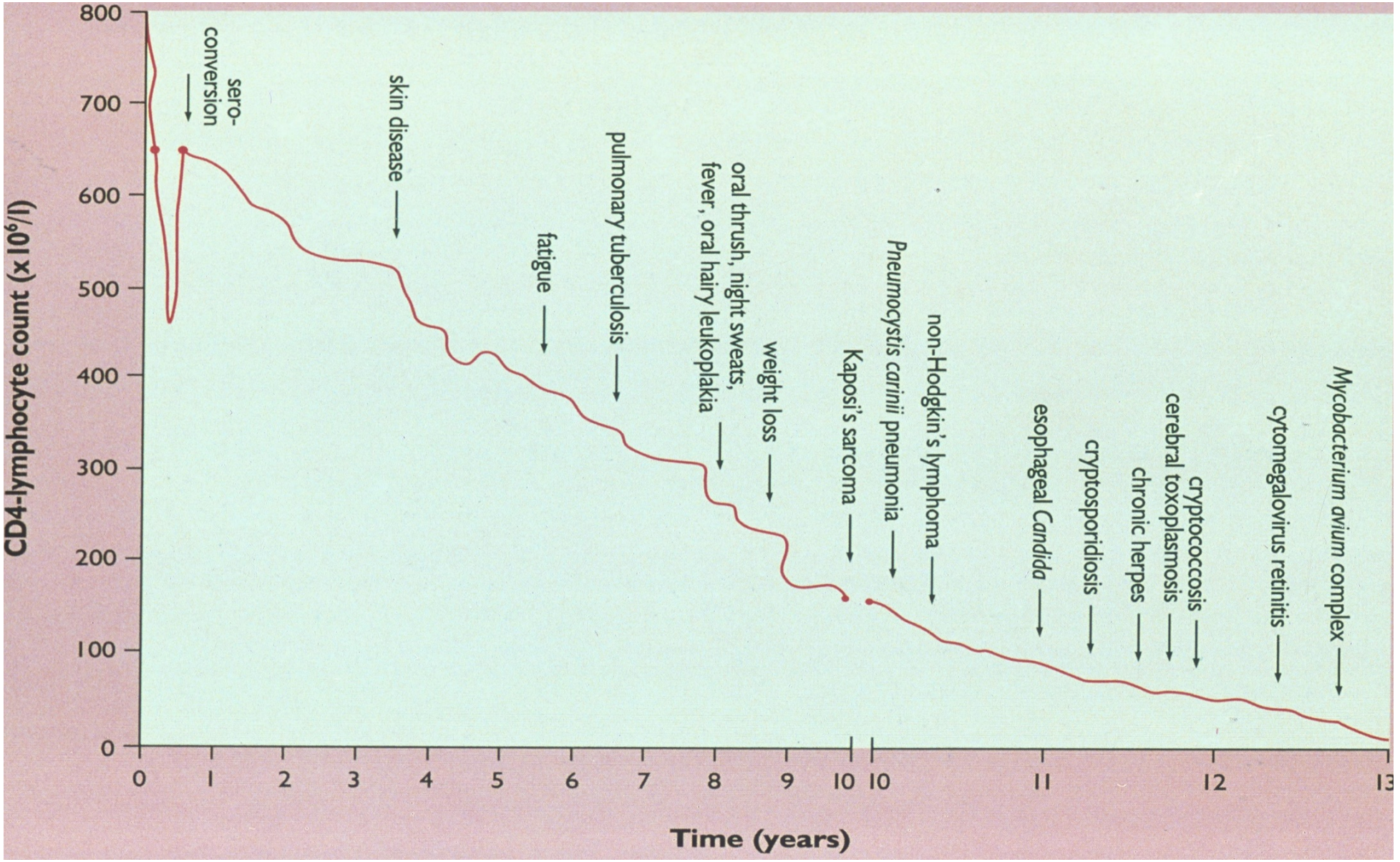
Phases of HIV infection

- **Chronic asymptomatic phase/Latency**
  - No signs or symptoms of illness
  - This phase lasts 10 years on average
  - Gradual decline in $CD4^+$ T cells
  - Driven by an immune response involving antibodies & cytotoxic $CD8^+$ T cells that keep viral replication in check & drive down the viral load
  - Viral load can be measured by PCR assays for viral RNA

Phases of HIV infection

- **AIDS**
  - Acquired Immunodeficiency Syndrome – profound deficiency in T cell immunity
  - Greatly diminished numbers of $CD4^+$ T cells (<200 cells/µl of blood)
  - Opportunistic infections – *C.albicans*, PJP, TB etc
  - Without ART this phase can lead to death within 2 to 3 years

HIV, CD4 Decline, Complications

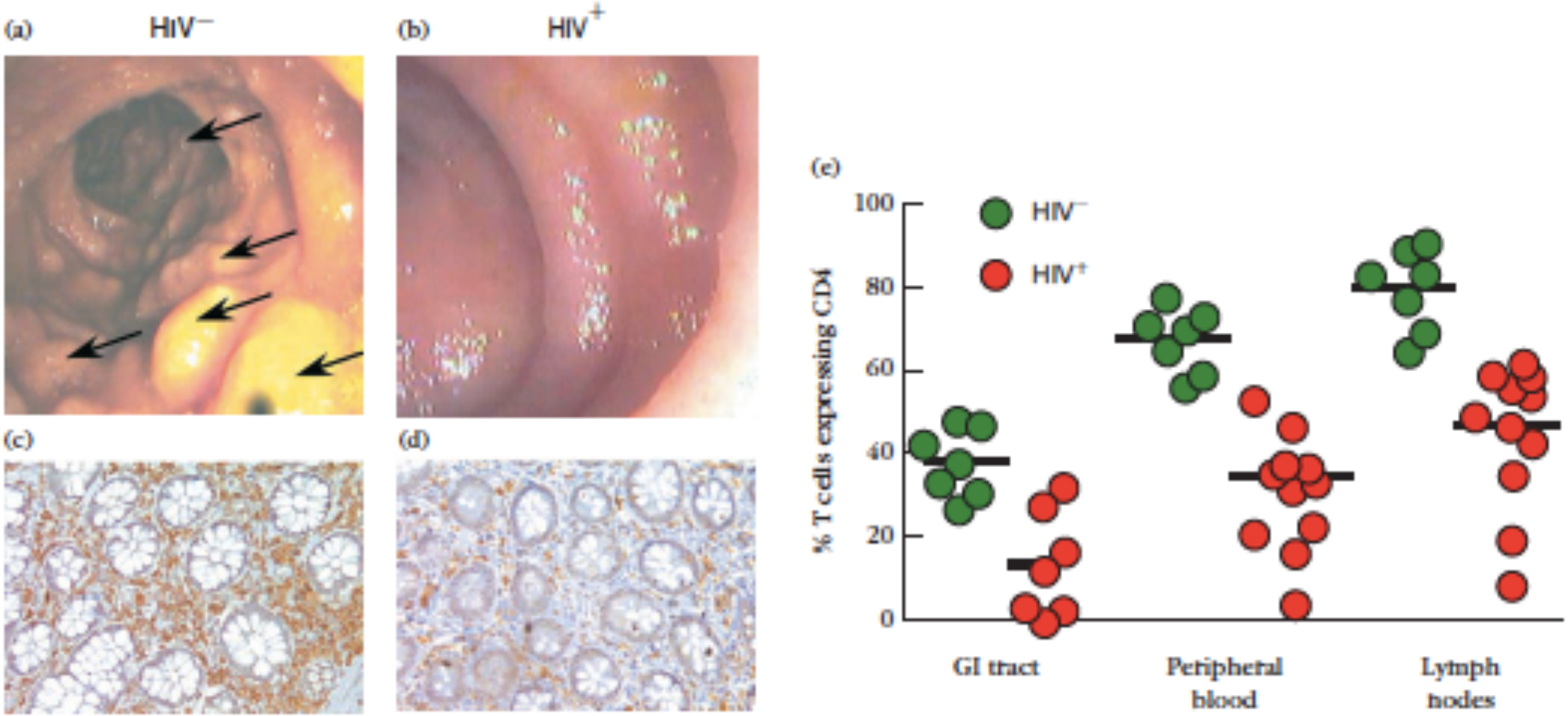


Mechanism of Progression to AIDS

- Understanding how the immune system holds HIV-1 in check during the asymptomatic phase could aid in the design of effective therapeutic & preventive strategies
- Long-term nonprogressors (infected individuals who remain asymptomatic for very long periods without treatment) are the subject of intense study
- Also high-risk populations who remain seronegative despite known & repeated exposure e.g. CSWs
  - Discovery of CCR5 deletion
  - Presence of strong $CD8^+$ T cell responses
  - HLA-associated influences on disease susceptibility

Mechanism of progression to AIDS

- Plasma viral loads remain fairly stable throughout the period of chronic HIV infection
- LN biopsies show high levels of infected cells at all stages of infection, with effacement, long before plasma viral load increases above the steady-state level
- Lymphoid tissue in the GI tract also depleted – thought to be the main site of HIV-1 replication and $CD4^+$ T cell depletion

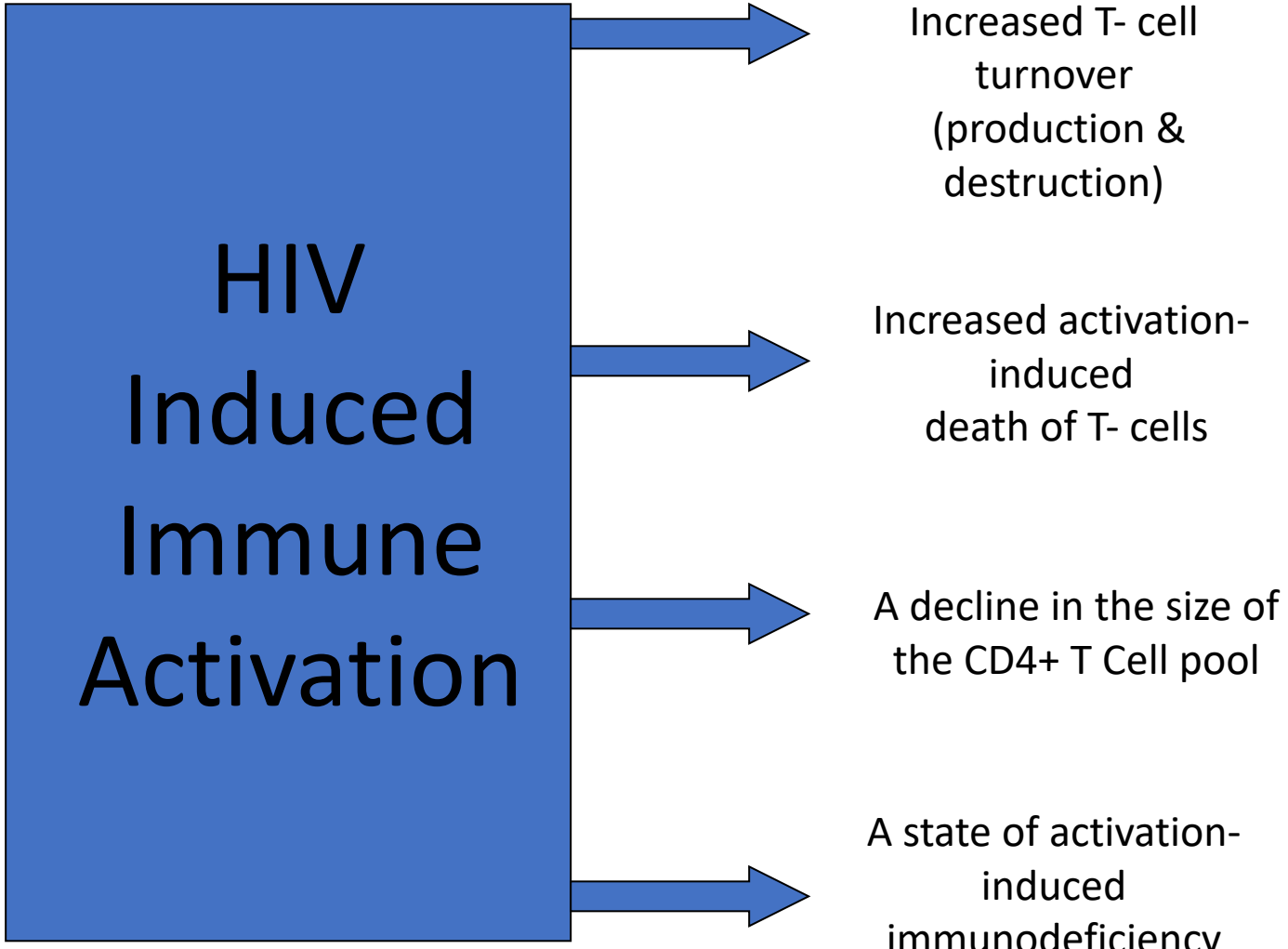


1. J. M. Brenchley *et al*, 2004, *CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract*. Journal of Experimental Medicine 200:749
2. Kuby Immunology, 7th edition

Immunological Abnormalities in HIV/AIDS

- Progressive depletion of $CD4^+$ T cells
- Impaired T-cell immunity (even when $CD4^+$ T cells are present in normal numbers)
- Impaired mononuclear macrophage function
- Impaired production of specific antibody despite a polyclonal increase in serum immunoglobulins that lack antibody functions

HIV infection leads to a state of generalized immune activation



$CD4^+$ T Cell Depletion

- Direct viral infection & destruction
  - Half-life of an actively infected $CD4^+$ T cell is less than 1.5 days
- Smaller numbers of $CD4^+$ T cells become infected but do not actively replicate virus; these latently infected cells persist for long periods
- $CD4^+$ T cell count (and viral load) are the primary focus of follow-up testing in HIV-infected individuals

Other Immunologic Consequences

- Decrease or absence of delayed type hypersensitivity
- Decreased serum immunoglobulins (especially IgG & IgA)
- Impaired cellular responses to antigens
  - The HIV-infected individual loses the ability to mount T-cell responses in a predictable sequence
    - Responses to specific recall antigens (e.g. influenza virus) are lost first
    - Then response to alloantigens declines
    - Finally mitogenic responses to stimuli disappear
- Innate responses also impacted, including NK & dendritic cell functions

TABLE 18-4 Immunologic abnormalities associated with HIV infection

Stage of infection	Typical abnormalities observed
	LYMPH NODE STRUCTURE
Early	Infection and destruction of dendritic cells; some structural disruption, especially to gastrointestinal tract-associated lymphoid tissues
Late	Extensive damage and tissue necrosis; loss of follicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells
	T HELPER (T_H) CELLS
Early	Depletion of $CD4^+$ T cells, especially in the gut (T_H17 main targets); loss of in vitro proliferative response to specific antigen
Late	Further decrease in T_H-cell numbers and corresponding helper activities; no response to T-cell mitogens or alloantigens

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TABLE 18-4 Immunologic abnormalities associated with HIV infection

Stage of infection	Typical abnormalities observed
	ANTIBODY PRODUCTION
Early	Enhanced nonspecific IgG and IgA production but reduced IgM synthesis
Late	No proliferation of B cells specific for HIV-1: no detectable anti-HIV antibodies in some patients; increased numbers of B cells with low CD21 expression and enhanced Ig secretion
	CYTOKINE PRODUCTION
Early	Increased levels of some cytokines
Late	Shift in cytokine production from T_H1 subset to T_H2 subset
	DELAYED-TYPE HYPERSENSITIVITY
Early	Highly significant reduction in proliferative capacity of T_H1 cells and reduction in skin-test reactivity
Late	Elimination of DTH response; complete absence of skin-test reactivity
	T CYTOTOXIC (T_C) CELLS
Early	Normal reactivity
Late	Reduction but not elimination of CTL activity due to impaired ability to generate CTLs from T_C cells

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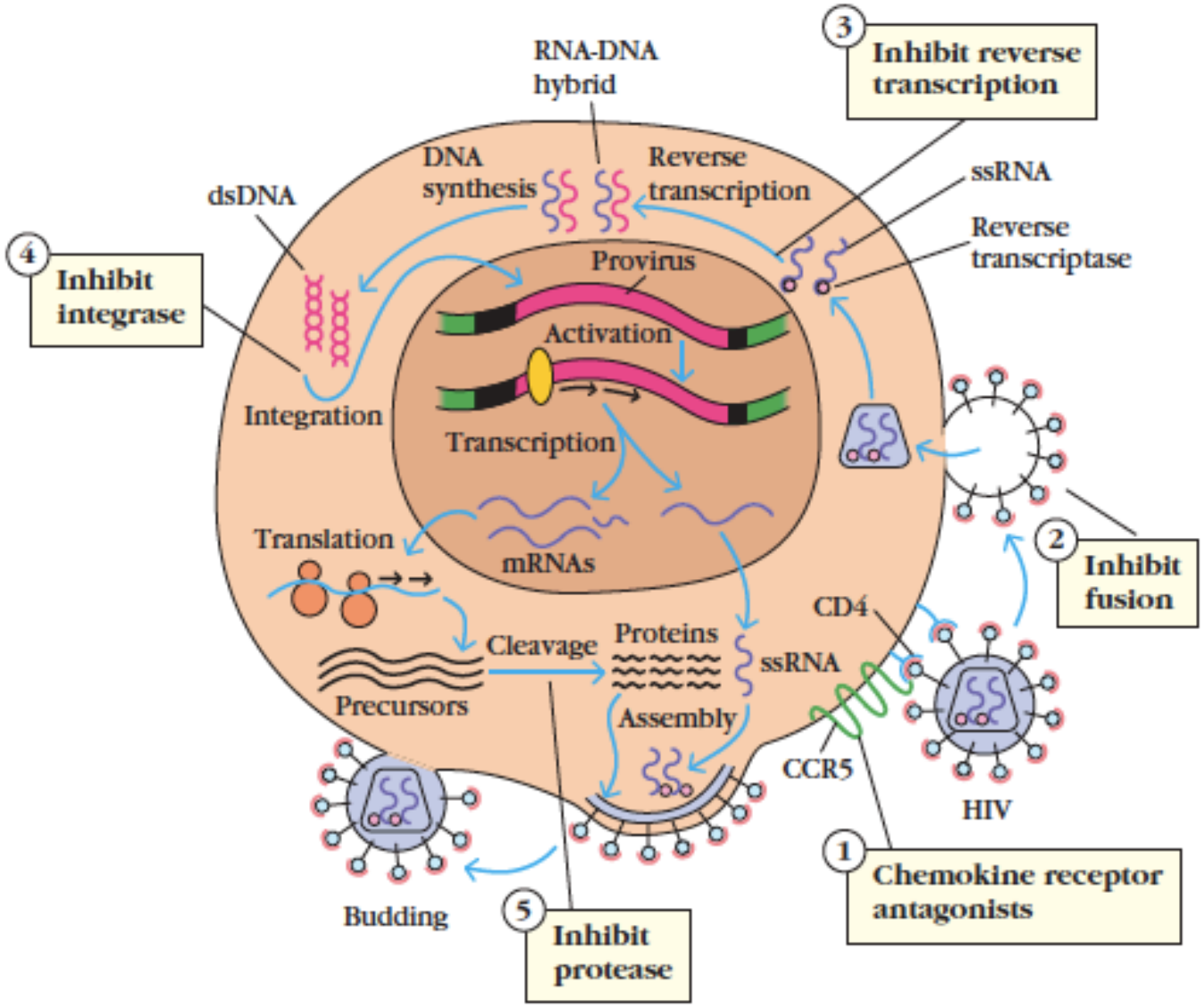
Therapeutic targets to inhibit HIV replication



Antiretroviral Therapy

- HAART/cART – use of 3 or more anti-HIV drugs from different classes, to overcome the ability of the virus to rapidly produce drug resistant mutants
- In many cases, cART has lowered plasma viral loads to undetectable levels
- Virus may persist in sites that are not readily penetrated by ART, e.g. brain, thereby making it difficult to eradicate all virus from an infected individual and cure AIDS

A vaccine may be the only way to stop the HIV/AIDS epidemic

- Prevent infection and/or progression to disease
- Challenges to vaccine development
  - Rapid mutation of HIV-1 (many variants)
  - Neutralizing antibodies do not necessarily inhibit viral spread
  - Limited animal models