

Acquired immunodeficiency syndrome

- Human immunodeficiency virus (HIV) causes a progressive acquired immunodeficiency.
- Failure of immune defense permits opportunistic infections, selected neoplasms, and neurologic disease.
- The clinical phenotype reflects viral replication, loss of CD4⁺ T cells, and incomplete immune control.

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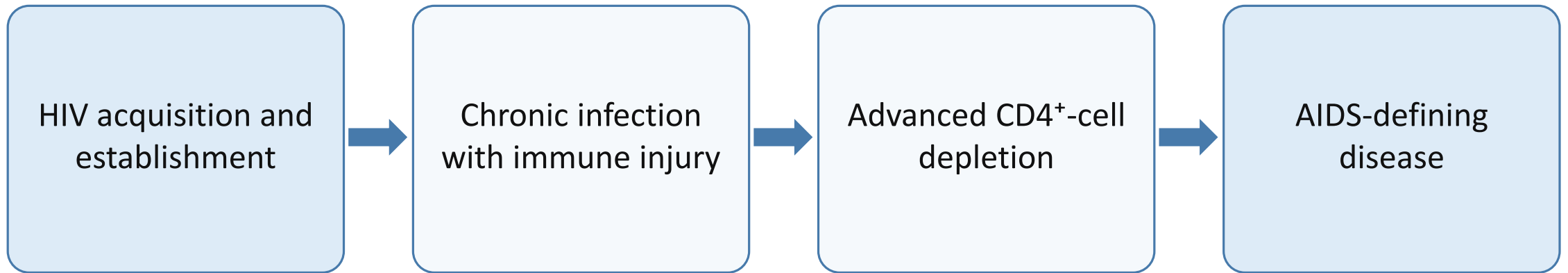
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Learning objectives

- Explain major HIV exposure routes and determinants of transmission.
- Identify HIV structural components and the steps of infection.
- Connect cellular immune injury with clinical progression, pathology, and opportunistic disease.
- Distinguish the effect of antiretroviral therapy from eradication of the viral reservoir.

HIV infection and AIDS are not synonymous



Untreated HIV may progress to AIDS; Effective therapy profoundly alters the course.

The hallmark is defective cell-mediated immunity

- Progressive loss of CD4⁺ helper T cells undermines immune coordination.
- Surviving T cells also have functional abnormalities.
- Macrophages, dendritic cells, and B-cell responses are affected.
- Immunodeficiency is broader than a low circulating CD4⁺ count alone.

Three major consequences of immunodeficiency

Domain	Biologic explanation	Representative manifestation
Infection	Poor control of opportunistic and latent microbes	Pneumocystis pneumonia; cryptococcosis
Neoplasia	Reduced immune surveillance of oncogenic viruses	Kaposi sarcoma; B-cell lymphoma
Nervous system	HIV-related neuroinflammation and secondary disease	HIV-associated neurocognitive disorder

Organ involvement can be direct, indirect, or opportunistic.

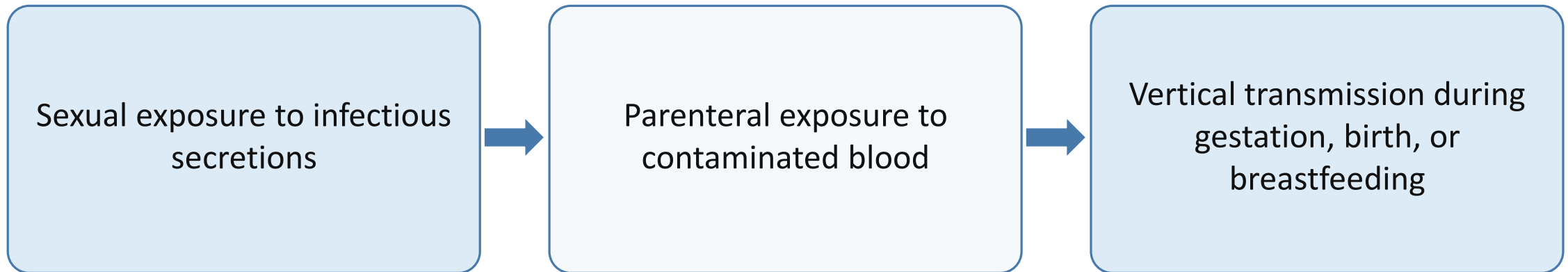
AIDS is a major global disease burden

- A very large worldwide population living with HIV.
- 's 2021 reference period, the distribution was especially concentrated in Africa.
- Population estimates are time-dependent and must not be treated as current surveillance figures.

Antiretroviral therapy reshapes the epidemic

- ART suppresses replication, limits progression, and reduces mortality.
- Effective therapy also decreases transmission, including vertical transmission.
- Persistent HIV infection and inequitable access remain important public-health challenges.

Three principal modes of HIV transmission



Transmission requires a biologically plausible exposure to HIV-containing material.

Sexual transmission: Mucosal acquisition

- Sexual transmission is the predominant route worldwide discussion.
- Virus may cross damaged mucosa or interact with susceptible mucosal immune cells.
- CD4⁺ T cells and dendritic cells help establish the infection at entry sites.

Other sexually transmitted infections amplify risk

- Ulcerative sexually transmitted disease can compromise mucosal barriers.
- Inflammation recruits activated susceptible target cells into mucosal tissue.
- Syphilis, chancroid, herpes, gonorrhea, and chlamydia are cited as cofactors.

Blood-borne transmission requires direct inoculation

- Sharing needles and syringes can transfer HIV-infected blood.
- Contaminated transfused blood or blood products and organs can transmit HIV.
- Improved donor screening and safer blood products dramatically reduced transfusion-associated infection.

Transmission pathways versus nonroutes

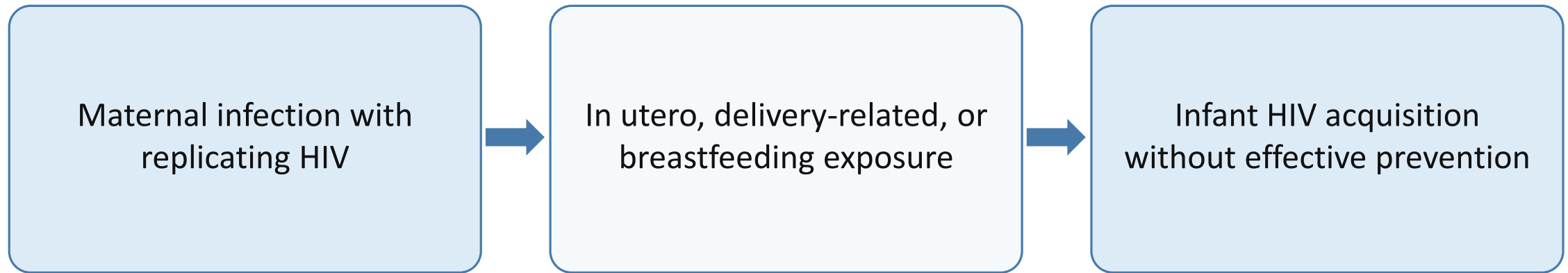
Exposure pathway	Transmission interpretation
Blood or infectious sexual secretions contacting susceptible tissue	Biologically plausible transmission route
Needlestick exposure to infected blood	Recognized occupational route; uncommon
Casual household, school, or workplace contact	Does not transmit HIV
Insect bites	Not a meaningful mode of HIV transmission

Avoid stigmatizing nontransmission contact.

Vertical transmission has distinct windows

- In utero: Transplacental infection before delivery.
- Intrapartum: Exposure during delivery.
- Postpartum: Exposure through breast milk.
- Maternal viral burden and immune impairment influence risk in untreated infection.

Maternal HIV and pediatric infection



Major reductions in vertical transmission with maternal ART.

Occupational infection: Rare but consequential

- Percutaneous injuries and contact of infected blood with nonintact skin can transmit HIV.
- Transmission is much less efficient than many other blood-borne viral infections.
- Prompt antiretroviral post-exposure intervention.

Exposure categories are not personal identities

- Risk is determined by exposure routes and infectiousness, not by membership of a social group.
- Regional patterns of sexual and parenteral transmission differ.
- Historical United States case proportions are time-specific, not timeless risk estimates.

HIV-1 and HIV-2: Related lentiviruses

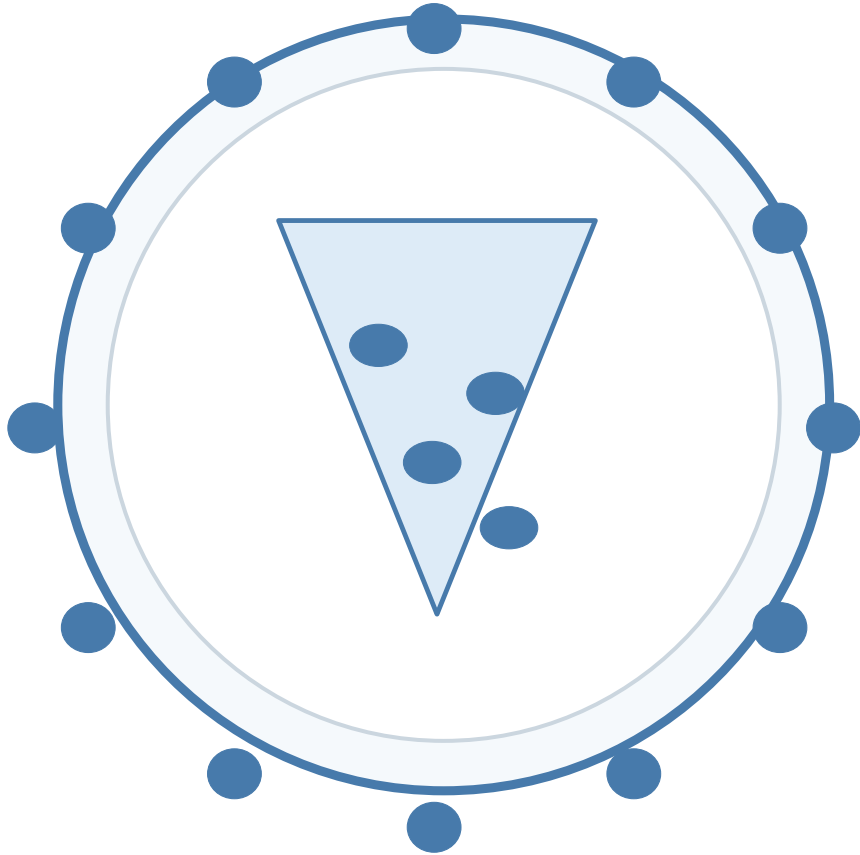
Feature	HIV-1	HIV-2
Phylogeny	Human lentivirus	Related human lentivirus
Geography in Robbins	Most common in US, Europe, central Africa	Prominent in western Africa and India
Clinical result	Can produce AIDS	Can produce a similar disease

The subsequent molecular discussion primarily concerns HIV-1.

HIV is an enveloped RNA retrovirus

- HIV belongs to the lentivirus family.
- The core contains two RNA copies plus viral reverse transcriptase, integrase, and protease.
- A host-derived lipid envelope carries gp120 and gp41, which mediate cell entry.

Anatomy of the HIV-1 virion



Gp120 / gp41: Attachment and fusion

Lipid envelope: Host-cell derived

P17 matrix beneath envelope

P24 protein forms capsid

RNA genome + viral enzymes

Structural proteins and enzymes

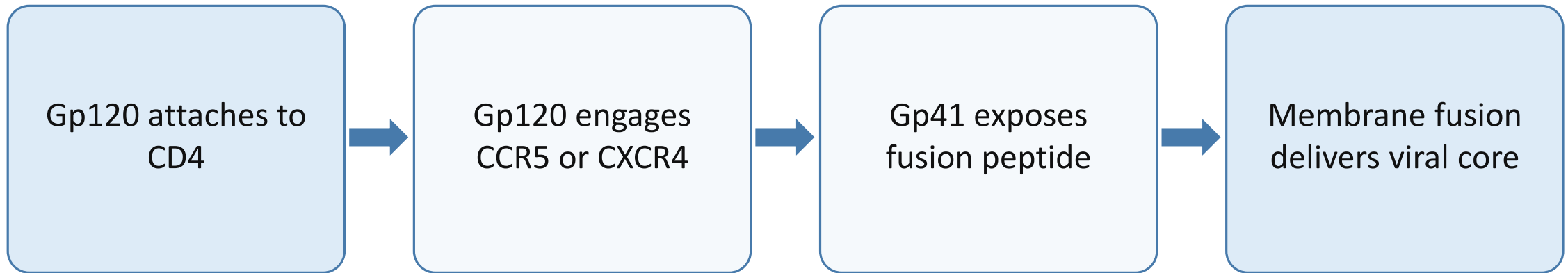
Component	Principal role
gp120	Binds CD4 and chemokine coreceptor
gp41	Mediates envelope fusion
p24	Major capsid protein
p17	Matrix beneath lipid envelope
Reverse transcriptase / integrase / protease	DNA synthesis / integration / virion maturation

These functions explain major mechanistic therapeutic targets.

HIV genome: Canonical and accessory functions

- Long terminal repeats contain sequences regulating viral gene transcription.
- Gag and pol encode precursors of structural and enzymatic proteins.
- Env encodes envelope glycoproteins.
- Regulatory and accessory genes include tat, rev, vif, nef, vpr, and vpu.

Cell entry requires two receptor interactions



CD4 binding alone is insufficient for productive viral entry.

Chemokine coreceptors and viral tropism

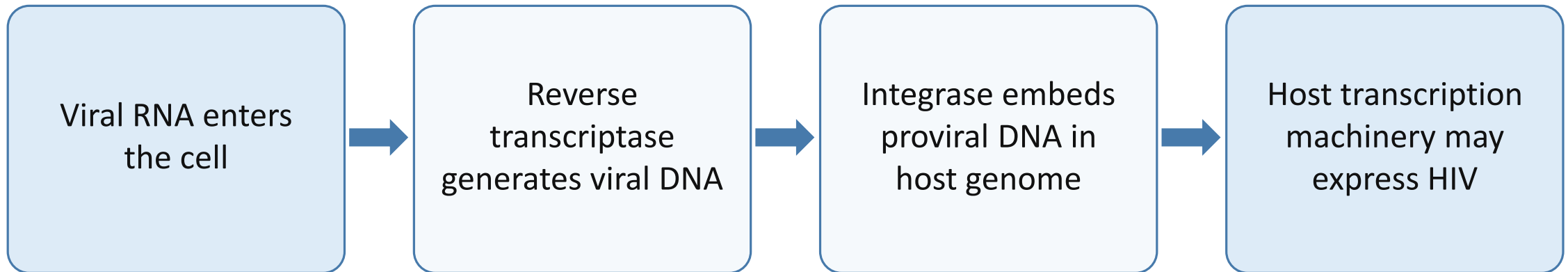
Viral phenotype	Coreceptor	Typical preference
R5 / M-tropic	CCR5	Monocyte–macrophage lineage; common early
X4 / T-tropic	CXCR4	T cells; may expand during progression
Dual tropic	CCR5 and CXCR4	Can use either coreceptor

Tropism describes receptor usage, not an absolute cell restriction.

Host CCR5 variation illustrates receptor dependence

- Some inherited CCR5 variants impair infection by CCR5-dependent HIV strains.
- Resistance to R5 HIV is not equivalent to protection from every possible HIV isolate.
- Host genetic susceptibility is one component of a much broader host–virus interaction.

From viral RNA to integrated provirus

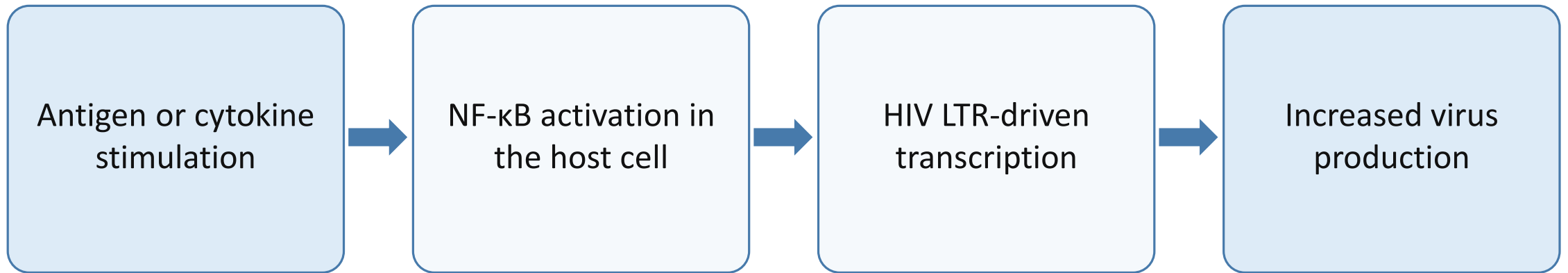


Integration creates a durable molecular basis for persistence.

Latency and productive infection are distinct

- Integrated proviral DNA may persist without substantial viral gene expression.
- Cell activation can induce transcription and productive replication.
- Productive infection generates virions and can injure or destroy infected T cells.

Physiologic T-cell activation can activate HIV

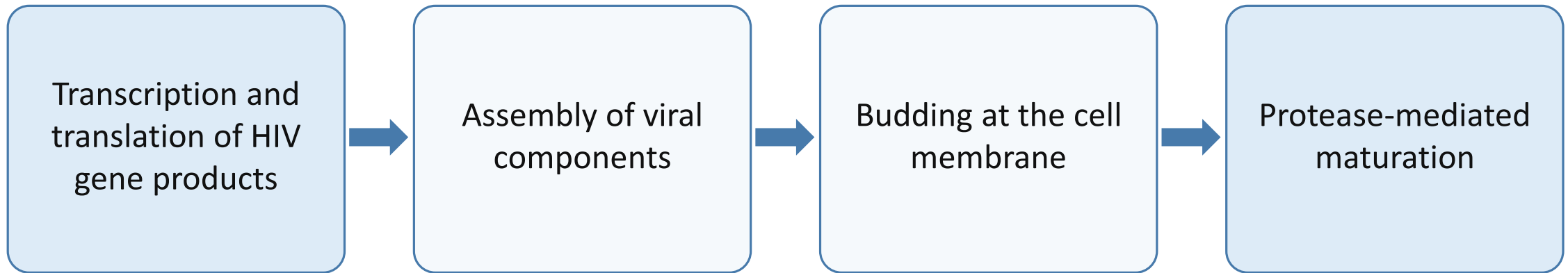


HIV exploits signaling normally used for immune responses.

New infections can accelerate existing HIV replication

- Intercurrent microbial infections stimulate inflammatory cytokine production.
- T-cell and macrophage activation promotes HIV transcription.
- Greater replication can fuel further immune cell loss and infection susceptibility.

Viral production creates mature virions



The role of protease is viral-protein processing; Drugs can interrupt this step.

Therapeutic targets map to viral biology

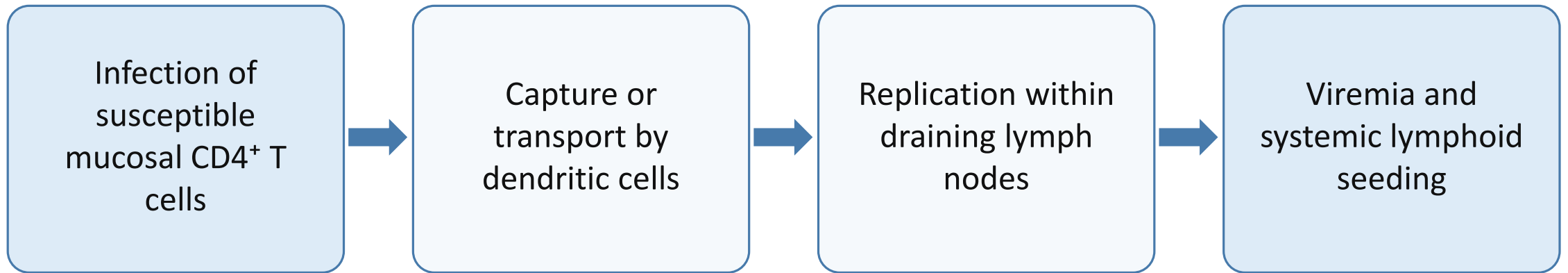
Viral process	Molecular target / general class
Entry / fusion	CD4–coreceptor interaction or fusion processes
Reverse transcription	Reverse transcriptase inhibitors
Integration	Integrase inhibitors
Protein processing	Protease inhibitors

This is a mechanistic framework, not a current prescribing protocol.

The immune system is the principal viral target

- CD4⁺ T lymphocytes are the major targets of HIV-associated immune failure.
- Macrophages and dendritic cells also participate in infection and viral persistence.
- The CNS is affected through infection of cells in the monocyte–macrophage lineage.

Early dissemination begins at mucosal sites



The earliest major tissue reservoir can lie outside peripheral blood.

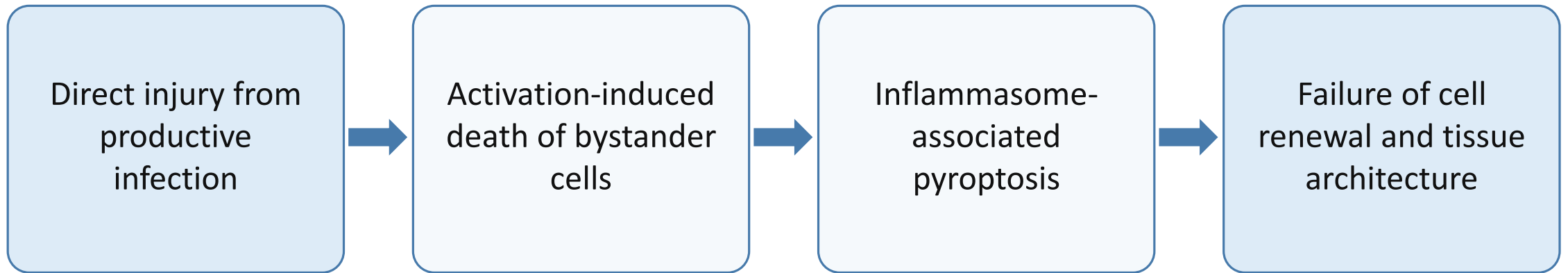
Mucosal memory T cells are especially vulnerable

- Mucosal tissues contain a large compartment of memory CD4⁺ T cells.
- Early HIV infection produces prominent loss of these susceptible cells.
- This early tissue depletion may be underrepresented by circulating-cell measurements.

Secondary lymphoid tissues sustain infection

- Lymph nodes and spleen contain infected lymphocytes and virions.
- Follicular dendritic cells can retain antibody-coated, infectious virions.
- Ongoing replication in organized lymphoid tissue persists during clinical latency.

Pathways to CD4⁺ T-cell depletion



Several mechanisms act together; Virus-induced cell death is central.

Direct cytopathic injury is a major mechanism

- Active viral production is associated with death of infected CD4⁺ T cells.
- Memory cells within tissues are particularly susceptible.
- Compensatory T-cell replacement can initially conceal extensive turnover.

Bystander damage amplifies T-cell loss

- Chronic immune activation can drive apoptosis of uninfected T cells.
- Abortive infection may activate the inflammasome and pyroptotic cell death.
- Cellular inflammatory products can recruit further susceptible cells.

Lymphoid architectural damage compounds deficiency

- Progressive disease disrupts germinal centers and follicular dendritic-cell networks.
- Loss of organized tissue impairs immune-cell interactions and antigen responses.
- Advanced lymphoid depletion accompanies severe systemic immunodeficiency.

Functional abnormalities extend beyond T-cell number

Compartment	Immunologic abnormality	Consequence
T cells	Reduced Th1 responses and helper activity	Poor defense against intracellular microbes
B cells	Polyclonal activation but weak new responses	Impaired antibody protection
Macrophages	Impaired chemotaxis, phagocytosis, antigen presentation	Weakened innate and adaptive coordination

Qualitative defects help explain complex infection patterns.

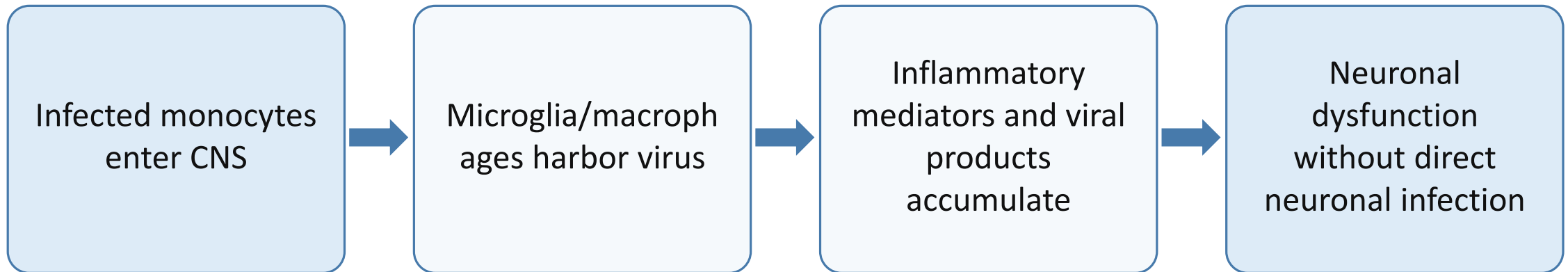
B-cell hyperactivation coexists with poor immunity

- HIV-associated stimulation produces enlarged germinal centers and hypergammaglobulinemia.
- Despite activation, effective responses to new antigens can be compromised.
- Defective T-cell help and B-cell dysfunction contribute to impaired opsonization.

Macrophages provide persistent cellular niches

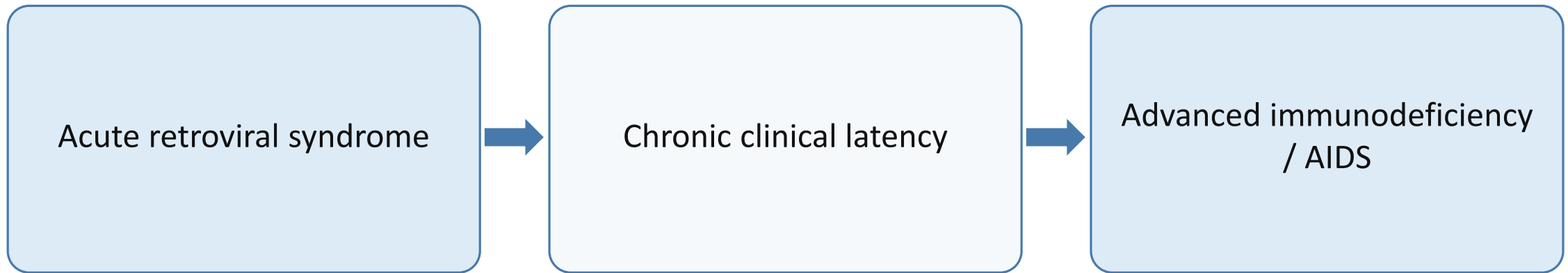
- Macrophages can remain viable despite carrying substantial viral material.
- Infected macrophages in tissues outnumber infected circulating monocytes.
- Monocyte-lineage cells may distribute virus to organs, including brain.

HIV-related neurologic injury: Proposed mechanism



Indirect neurotoxicity as a major explanation; Mechanisms remain incompletely resolved.

Untreated clinical course has three broad phases



Clinical latency does not mean virologic inactivity.

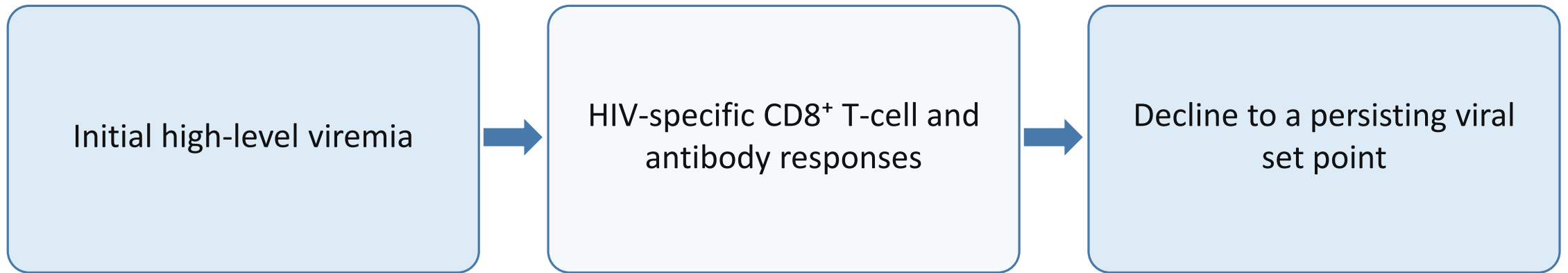
Acute infection: Systemic viral dissemination

- HIV replication initially increases rapidly within lymphoid tissue.
- Viremia distributes infection to lymphoid and other tissues.
- Immune responses subsequently reduce, but do not eliminate, replication.

Acute retroviral syndrome is nonspecific

- Reported features include fever, sore throat, myalgia, fatigue, and weight loss.
- Some patients develop rash, cervical adenopathy, diarrhea, or vomiting.
- Clinical overlap with other acute viral illnesses means symptoms alone are not diagnostic.

Partial antiviral control after acute infection



Immune control reduces viremia but does not sterilize infection.

The viral set point has prognostic meaning

- Steady-state plasma HIV RNA reflects a host–virus equilibrium after primary infection.
- Higher set points are associated with faster CD4⁺ decline and progression.
- Individual trajectories vary, and ART changes the untreated natural history.

Clinical latency masks ongoing pathology

- Many individuals have few clinical symptoms during the chronic phase.
- Lymphoid infection, replication, and CD4⁺ depletion nevertheless continue.
- Persistent generalized lymphadenopathy can be a clinical manifestation.

Progression to AIDS marks loss of immune containment

- Viral replication becomes more difficult for host immunity to control.
- CD4⁺ depletion crosses thresholds associated with serious opportunistic disease.
- Severe infections, neoplasms, and neurologic syndromes dominate the presentation.

Historical CDC CD4⁺ categories

CD4 ⁺ cells/ μ L	Category in Robbins discussion
≥ 500	Category 1
200–499	Category 2
< 200	Category 3: most severe depletion

Historical surveillance framework; Not a substitute for current guidelines.

Viral load and CD4⁺ counts answer different questions

- Plasma HIV RNA quantifies circulating viral burden and response to suppression.
- CD4⁺ count reflects the degree of helper T-cell depletion and infection vulnerability.
- Interpretation requires clinical context and antiretroviral-treatment status.

Advanced AIDS produces multisystem disease

- Presentations may combine prolonged fever, weight loss, diarrhea, and generalized adenopathy.
- Severe infections arise from microbes otherwise contained by healthy immunity.
- Neoplasms and neurologic disorders may be presenting or concurrent diseases.

Why opportunistic infections emerge

- Latent microbes can reactivate when cellular immunity fails.
- Low-virulence environmental organisms become invasive in susceptible hosts.
- The dominant pathogens differ by geography, exposure history, and degree of immunosuppression.

Pneumocystis pneumonia: Impaired cellular defense

- *Pneumocystis jirovecii* is an important fungal opportunist in untreated AIDS.
- Pneumonia may present with respiratory impairment in advanced immunodeficiency.
- Its incidence declined markedly in populations responding to ART.

Mucosal candidiasis can signal immune decline

- Oral, esophageal, and genital candidiasis occur with impaired immune defense.
- Oral thrush may herald advancing immunologic dysfunction.
- Deeply invasive candidiasis is less characteristic without additional risk factors.

Cytomegalovirus: Severe organ disease

- CMV can produce retinitis, esophagitis, colitis, or disseminated infection.
- Retinitis is associated with profound CD4⁺ depletion.
- Effective ART reduced the incidence of severe CMV disease.

Typical and atypical mycobacterial infections

Organism group	Typical clinical pattern in HIV
Mycobacterium tuberculosis	May reactivate or be acquired; pulmonary and disseminated forms
Mycobacterium avium complex	Disseminated infection particularly in advanced immunosuppression

Severely impaired T-cell immunity can blunt granulomatous responses.

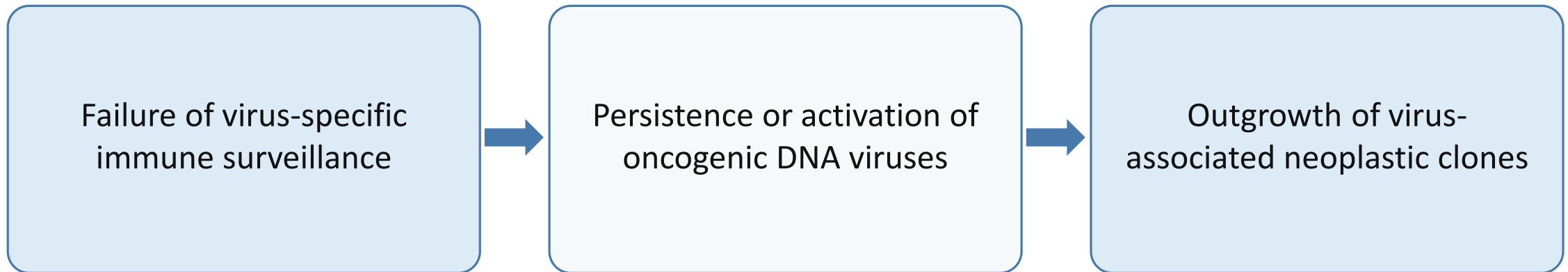
Central nervous system opportunists

- *Cryptococcus neoformans* is associated with opportunistic meningitis.
- *Toxoplasma gondii* can cause encephalitis with focal CNS lesions.
- JC virus causes progressive multifocal leukoencephalopathy.

Enteric infection and persistent diarrhea

- Cryptosporidium and Cystoisospora may produce profuse watery diarrhea.
- Other intestinal microorganisms, including enteric bacteria, can contribute.
- Consequences include significant fluid loss and nutritional compromise.

Why certain cancers increase in AIDS



Different tumors involve different viruses and additional transformation events.

Kaposi sarcoma is HHV-8 associated

- Kaposi sarcoma is a vascular/spindle-cell neoplasm linked to HHV-8 (KSHV).
- AIDS-related disease may involve skin, mucosa, lymph nodes, lung, and gastrointestinal tract.
- Reduced HHV-8 control and local growth/angiogenic signals contribute to pathogenesis.

Kaposi sarcoma: Specific morphologic clues

- The lesion contains spindle-shaped cells and slit-like vascular spaces.
- Inflammatory cells accompany proliferating spindle cells.
- Histologic findings require correlation with context; Morphology alone is not a marker of HIV infection.

B-cell lymphomas are enriched in HIV infection

- Immunodeficiency permits emergence of aggressive B-cell lymphomas.
- Some arise through EBV/HHV-8-associated viral oncogenesis.
- Others may relate to chronic germinal-center B-cell proliferation and oncogenic rearrangements.

Oncogenic viruses and HIV-associated tumors

Oncogenic virus	Illustrative HIV-associated lesion
HHV-8 (KSHV)	Kaposi sarcoma; primary effusion lymphoma
Epstein–Barr virus	Selected B-cell lymphomas; often HIV-associated Hodgkin lymphoma
High-risk human papillomavirus	Cervical and anal squamous malignancies

These relationships are not interchangeable diagnostic criteria.

HPV-associated squamous neoplasia is clinically important

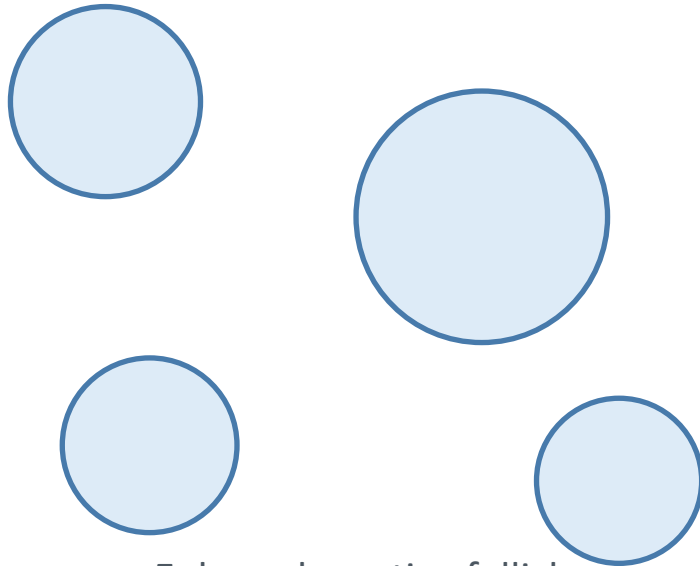
- Reduced immune surveillance allows persistence of high-risk HPV.
- HIV-associated cervical and anal squamous lesions may be more frequent.
- Evaluation and prevention depend on appropriate specialty-specific protocols.

HIV-related neurologic disease is multifactorial

- HIV-associated neurocognitive disorder can occur without a dominant opportunistic lesion.
- Neurologic symptoms may also reflect CNS infection or lymphoma.
- Neuropathology must discriminate direct inflammatory consequences from secondary pathology.

Lymph-node morphology evolves with infection

Early infection: Reactive follicles



Enlarged reactive follicles

Advanced disease: Lymphoid involution



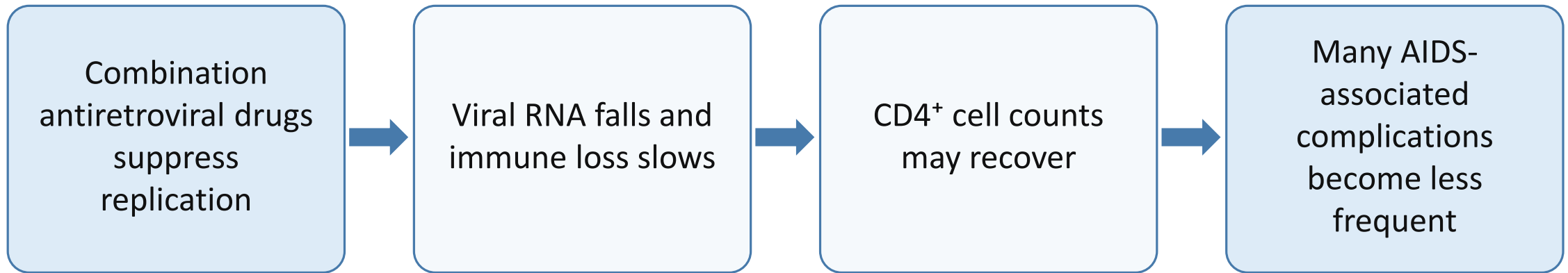
Depleted follicles and disrupted network

Native schematic of lymph-node architecture — not histology

Advanced AIDS may suppress typical inflammation

- Profound CD4⁺ deficiency can reduce formation of well-organized granulomas.
- Opportunistic microbes may be numerous despite a sparse inflammatory infiltrate.
- Special stains may be needed when microorganisms are not evident on routine sections.

Successful ART interrupts the pathogenic cascade



Suppression is not eradication of integrated provirus.

Effective treatment does not erase proviral persistence

- Infected cellular reservoirs can maintain integrated HIV DNA.
- Stopping therapy may allow clinically important viral rebound.
- Long-term HIV management therefore differs from a sterilizing cure.

Immune reconstitution can unmask inflammation

- Immune reconstitution inflammatory syndrome can follow initiation of ART in advanced disease.
- Clinical deterioration may occur despite falling viral load and rising CD4⁺ count.
- This paradox to an excessive response to persisting microbial antigens.

Long-treated patients have broader morbidity

- Effective ART has reduced classic opportunistic AIDS outcomes.
- Cardiovascular, renal, hepatic, and neoplastic disease remain consequential.
- Persistent inflammation, immune alterations, and treatment toxicities may contribute.

Clinicopathologic interpretation: Three questions

Question	What to evaluate
Is there substantial immune impairment?	CD4 ⁺ status, infection history, treatment context
What lesion explains current symptoms?	Site-specific infection, neoplasia, or inflammatory process
What evidence identifies the lesion?	Morphology, organism studies, and relevant confirmatory testing

Do not diagnose AIDS from nonspecific lymph-node morphology alone.

Clinical problem: Acute mononucleosis-like illness

- A patient develops fever, sore throat, myalgias, rash, and adenopathy after a possible exposure.
- The syndrome is compatible with acute HIV infection but is nonspecific.
- Ask: Why may early immune response coexist with appreciable viral dissemination?

Case interpretation: Early dissemination

- Infected mucosal and lymphoid cells amplify HIV before complete antiviral control.
- Viremia accompanies systemic symptoms and tissue seeding.
- An immune response lowers the viral burden without clearing integrated viral DNA.

Clinical problem: Progressive immune failure

- An untreated patient with profound CD4⁺ depletion develops pneumonia, oral candidiasis, and focal neurologic symptoms.
- Consider simultaneous opportunistic conditions rather than a single unifying organism.
- Ask: What immune defect connects pulmonary, mucosal, and CNS susceptibility?

Case interpretation: Cell-mediated immune failure

- Deficient CD4⁺ T-cell responses compromise defense against fungi and intracellular microbes.
- Different organ systems may be affected by distinct opportunistic pathogens.
- A focused diagnostic assessment should identify the specific cause in each site.

Core mechanisms to retain

- HIV uses CD4 plus a chemokine coreceptor for entry and integrates into host DNA.
- Replication and immune activation drive CD4⁺ T-cell death and progressive tissue damage.
- Late immune failure produces characteristic patterns of infection, malignancy, and neurologic illness.
- ART markedly alters outcomes but leaves persistent viral reservoirs.

Selected source and scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease, 11th edition (2026), chapter 6.
- AIDS: epidemiology and HIV properties (p. 219–220).
- Pathogenesis, natural history, clinical features, morphology, and treatment effects (p. 220–230).
- Clinical guidelines and current surveillance estimates were not added to this source-restricted deck.