

Pathogenesis of HIV Infection and AIDS

From viral entry to multisystem immune dysfunction

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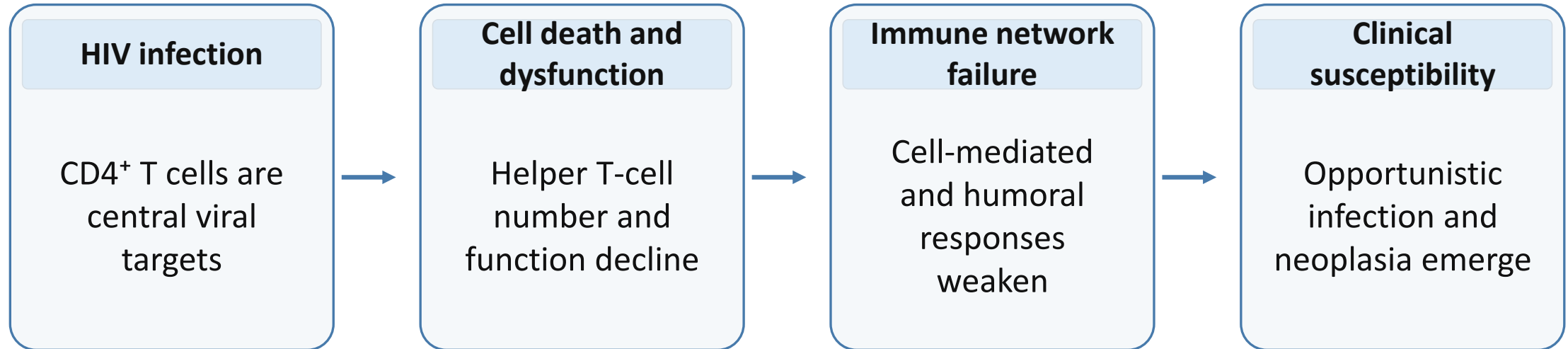
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Learning objectives

- Explain HIV entry through CD4 and chemokine coreceptors.
- Trace reverse transcription, integration, latency, and productive replication.
- Differentiate the mechanisms of CD4⁺ T-cell depletion.
- Explain the reservoir and immune effects of infected myeloid and lymphoid cells.
- Connect B-cell and CNS abnormalities to HIV pathogenesis.

CD4⁺ T-cell injury drives AIDS immunodeficiency



AIDS is chiefly an acquired defect in helper T-cell–dependent immunity; Infection of non–T cells adds further injury.

HIV acts within several interacting cellular compartments

CD4⁺ T cells

Principal cells depleted by productive infection.

Macrophages

Longer-lived infected cells with impaired host-defense functions.

Dendritic cells

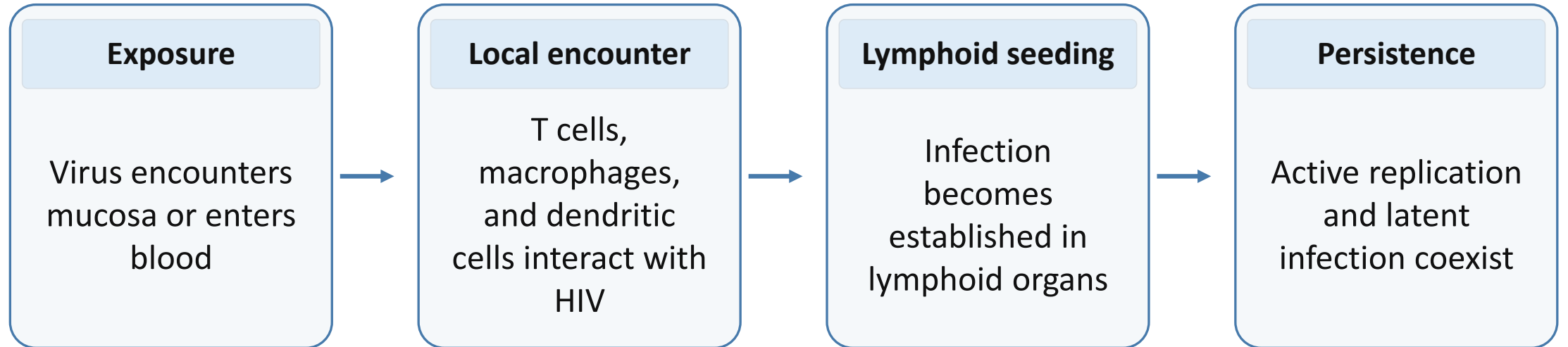
Capture or transfer virus and support dissemination.

CNS myeloid cells

Microglia and infiltrating macrophages link HIV to neurologic damage.

The disease cannot be understood solely from circulating CD4⁺ T-cell counts.

Mucosal entry establishes infection in lymphoid tissue



Lymphoid tissues are sites of viral amplification, immune-cell injury, and persistence.

Latent and productive infection have distinct fates

Latent infection

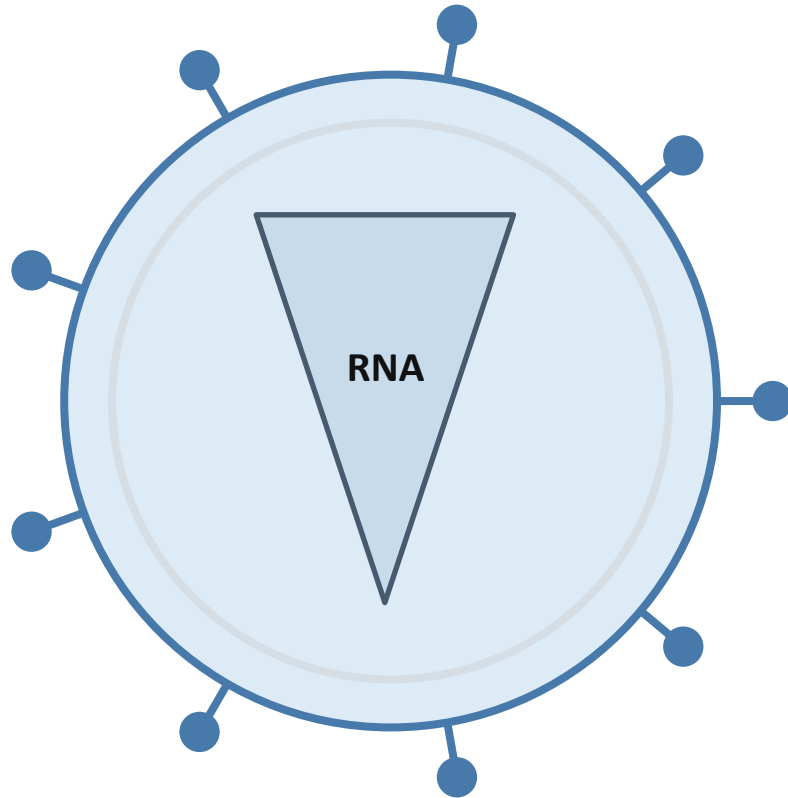
- Integrated proviral DNA is transcriptionally silent.
- Infected cells may survive for months or years.
- Cells serve as a persistent viral reservoir.

Productive infection

- Proviral RNA and viral proteins are expressed.
- New virions assemble and leave the cell.
- Extensive budding often accompanies cell injury and death.

The latent reservoir and ongoing productive infection are biologically different obstacles.

The HIV virion contains an enveloped RNA core



Gp120

Surface glycoprotein; Binds CD4 and coreceptors

Gp41

Transmembrane glycoprotein; Drives fusion

P17 matrix / p24 capsid

Structural layers surrounding the genome

RNA and enzymes

RNA genome, reverse transcriptase, integrase, protease

Gp120 and gp41 divide entry functions

Gp120: Attachment

- External envelope glycoprotein.
- Binds CD4, then CCR5 or CXCR4.
- Coreceptor recognition follows CD4-induced conformational change.

Gp41: Fusion

- Transmembrane envelope glycoprotein.
- Exposes a hydrophobic fusion peptide.
- Drives fusion of viral and host membranes.

Attachment and membrane fusion are separate, sequential entry steps.

The HIV genome links genes to pathogenic functions

Genome regions shown as functional groups, not to physical scale

LTR	Gag	Pol	Vif	Vpr	Tat	Rev	Vpu	Env	Nef	LTR
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

Gag

Matrix, capsid, and nucleocapsid

Pol

Reverse transcriptase, integrase,
protease

Env

Gp120 binding and gp41 fusion

Tat

Enhances viral transcription

Vif

Counteracts APOBEC3G

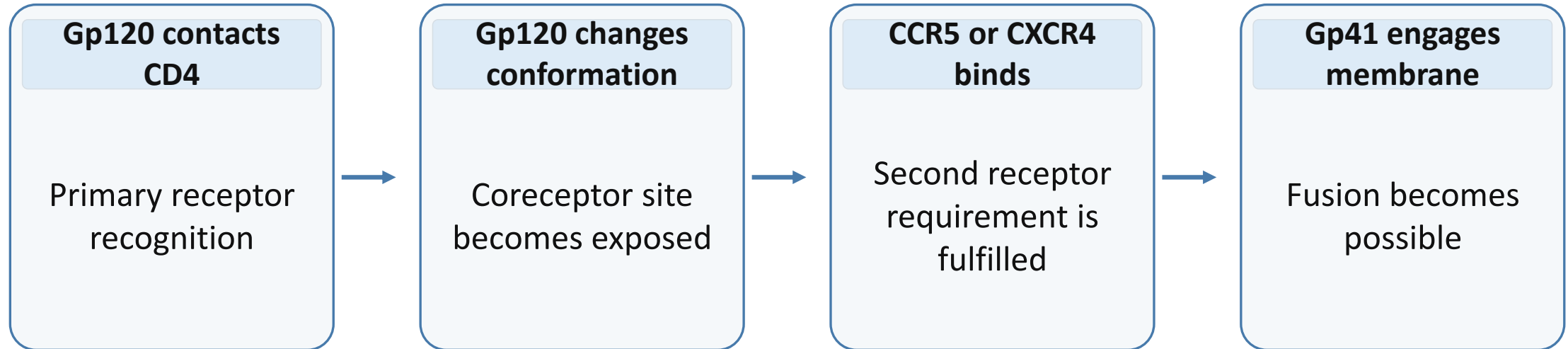
Vpr

Supports nuclear targeting in
macrophages

Viral proteins have distinct roles in the life cycle

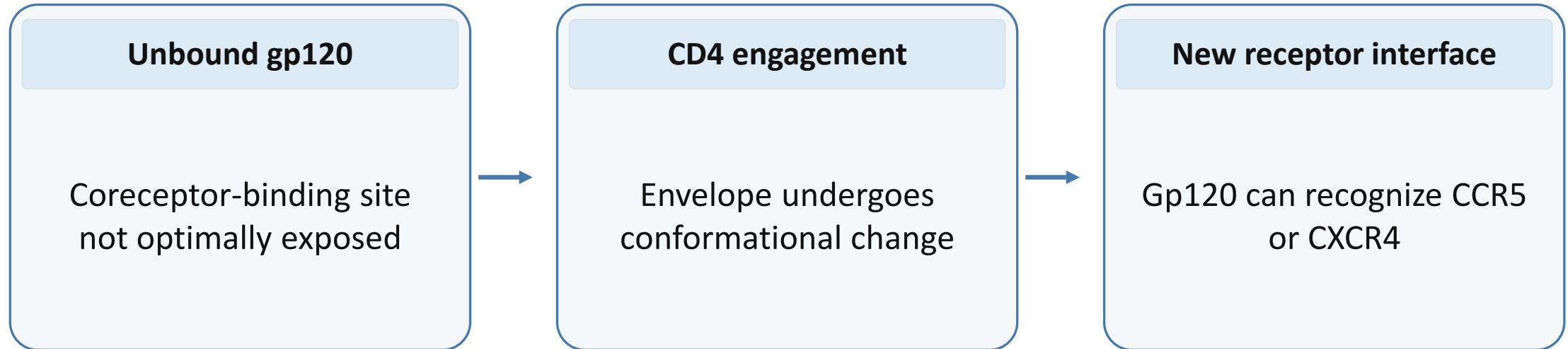
Protein / region	Principal function in the source	Pathogenetic implication
gp120 / gp41	CD4–coreceptor binding / membrane fusion	Cell tropism and entry
Reverse transcriptase	RNA → proviral DNA	Enables DNA phase
Integrase	Proviral genome insertion	Persistence / latency
Vif	Counteracts APOBEC3G	Promotes productive replication
Vpr	Macrophage nuclear targeting	Replication in nondividing cells

CD4 binding alone does not permit cellular entry



Coreceptor recognition is necessary in addition to CD4 attachment.

Gp120–CD4 binding exposes a coreceptor site



The order matters: Coreceptor binding follows CD4-triggered structural rearrangement.

Coreceptor use defines the R5 and X4 phenotypes

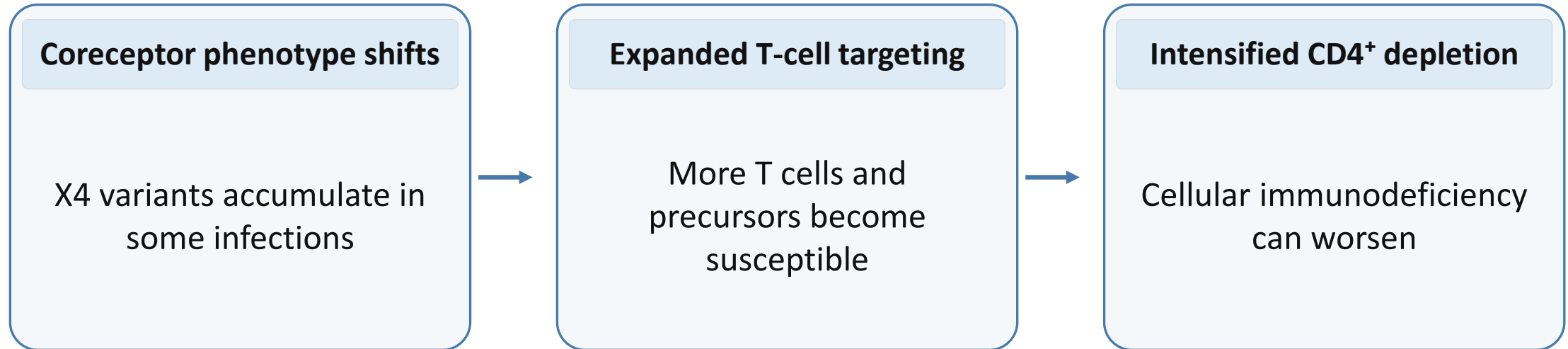
Viral phenotype	Coreceptor	Predominant tropism
R5	CCR5	Monocyte / macrophage lineage (M-tropic)
X4	CXCR4	T-cell lineage (T-tropic)
R5X4	Both	Dual coreceptor usage

The phenotypes describe receptor use and associated cell preference, not separate HIV species.

R5 strains predominate in many early infections

- R5 (M-tropic) virus as dominant early in most infections.
- CCR5 availability permits infection of susceptible mucosal and myeloid targets.
- R5 predominance at transmission helps link mucosal infection to systemic establishment.
- This is a population-level tendency, not an absolute rule for every individual.

X4 emergence is associated with greater T-cell injury



The source describes the X4 phenotype as particularly damaging to the T-cell compartment.

T-cell and macrophage tropism are not identical

Activated / memory T cells

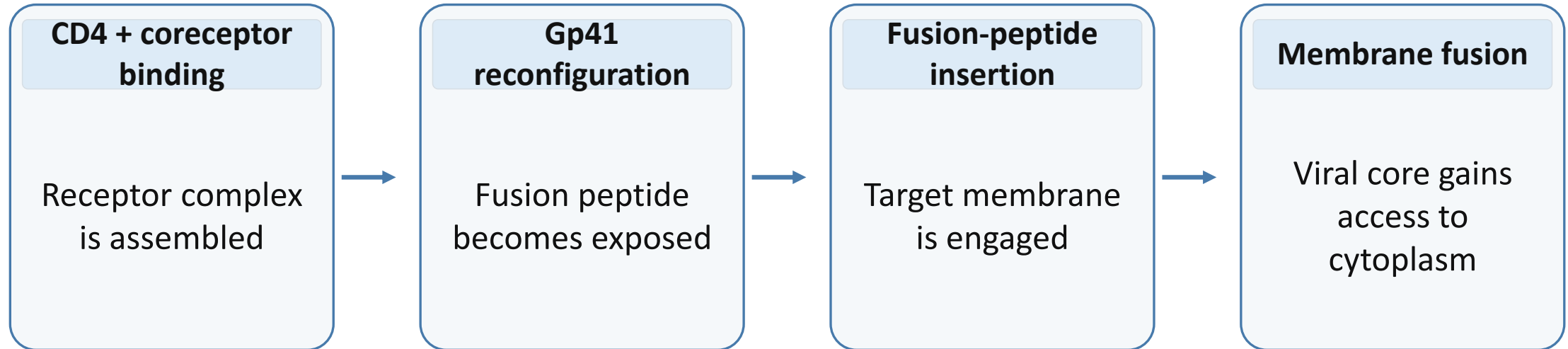
- Express CD4 with suitable coreceptors.
- Especially susceptible to productive replication.
- Frequent cytopathic loss after extensive budding.

Macrophages

- Express lower levels of CD4 with coreceptors.
- Can support infection without cell division.
- Relatively resistant to HIV cytopathic effects.

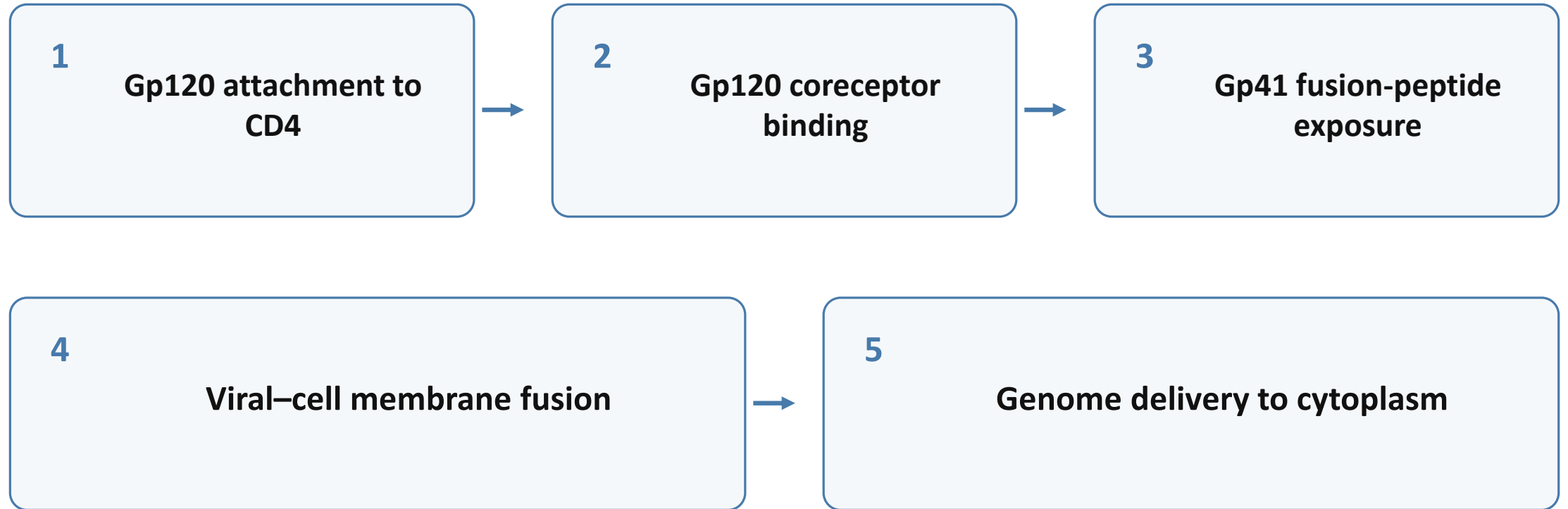
Tropism shapes both the cellular distribution of infection and the fate of infected cells.

Gp41 fusion allows the HIV core to enter



The envelope is not simply endocytosed as an inert particle; It actively mediates membrane fusion.

Entry sequence: A mechanistic checkpoint map



Every step occurs before reverse transcription and proviral integration.

Chemokine occupancy may limit HIV entry

- CCR5 and CXCR4 are physiological chemokine receptors.
- Chemokine binding can sterically interfere with HIV attachment to coreceptors.
- Tissue chemokine concentrations therefore may influence infection efficiency.
- This mechanism highlights why coreceptor interactions are biologically consequential.

CCR5 genotype modifies vulnerability to R5 infection

Two protective CCR5 alleles

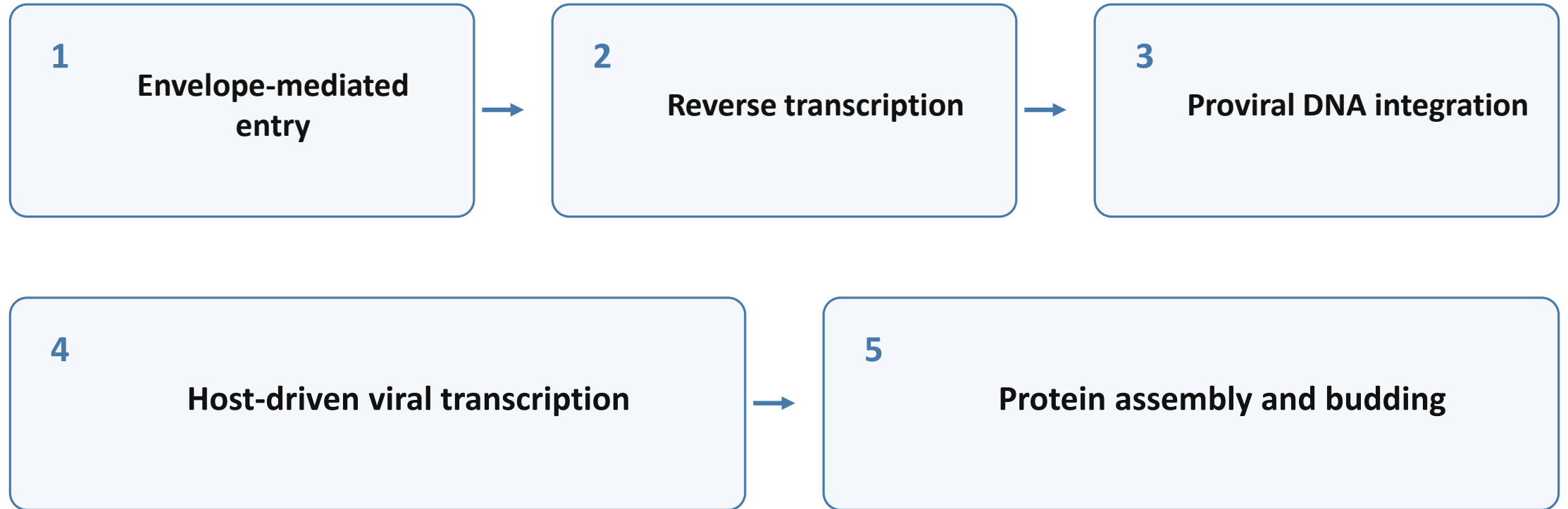
- Strong resistance to infection by R5 HIV isolates is described.
- Protection is coreceptor-specific; It is not universal protection from all HIV phenotypes.

One protective CCR5 allele

- Does not prevent AIDS after infection.
- The source describes a tendency toward delayed disease onset.

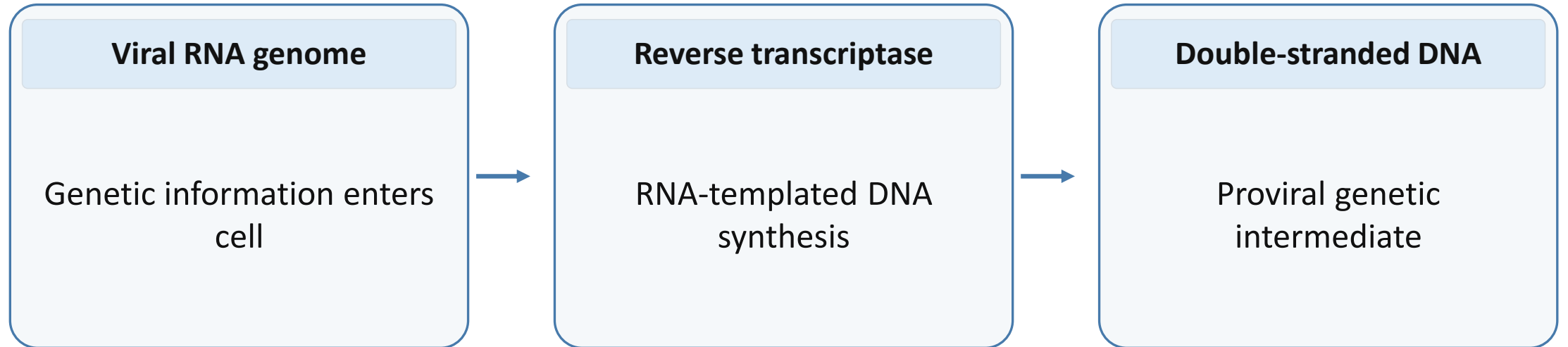
The source's ancestry-specific percentages are not needed to establish the receptor mechanism.

HIV replication traverses RNA and DNA phases



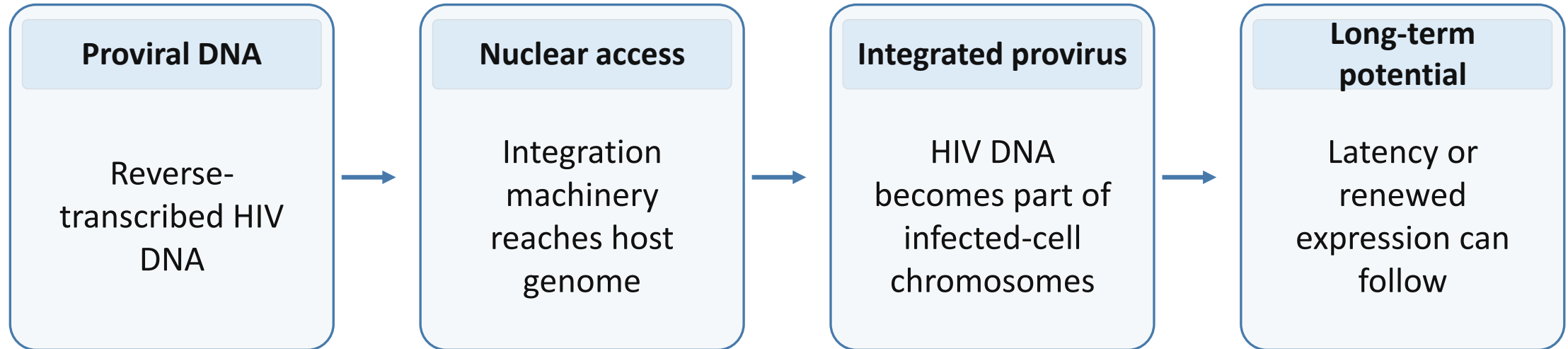
Persistence depends on the DNA intermediate; Productive infection requires subsequent viral gene expression.

Reverse transcriptase synthesizes proviral DNA



Reverse transcription is the molecular transition that makes integration into host DNA possible.

Integration converts HIV into a long-lived genomic infection



An integrated provirus may persist without production of infectious virions.

Latency is transcriptional silence—not viral absence

Silent provirus

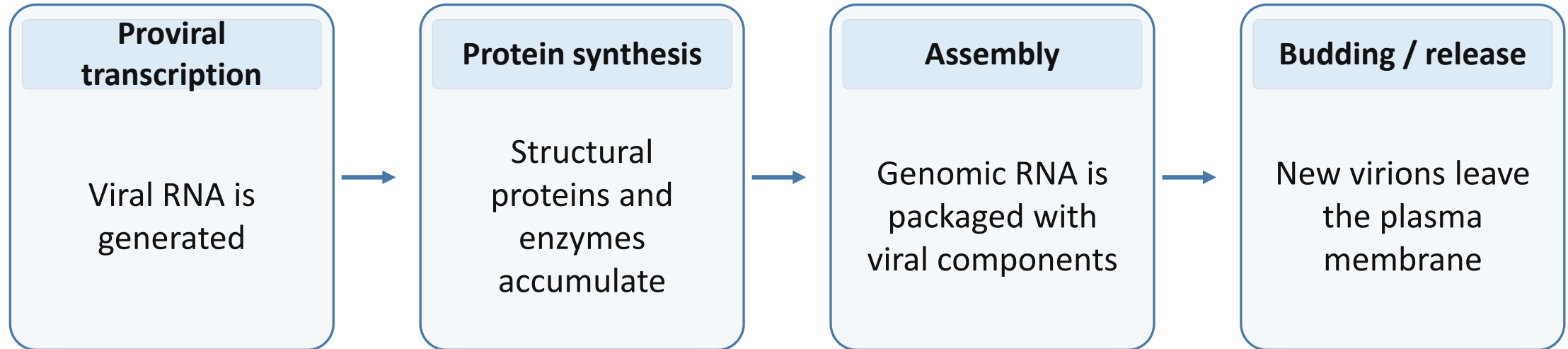
- HIV DNA is integrated.
- Little or no viral gene expression.
- No ongoing virion production required for persistence.

Activated provirus

- Cell activation induces transcription.
- Viral RNA and proteins accumulate.
- Production of virions can injure the cell.

A cell can contain HIV genetic material while producing no detectable infectious virus.

Virus assembly and budding complete productive infection



The textbook associates sustained productive budding in CD4⁺ T cells with cytopathic injury.

Gag and Pol processing supports virion function

Precursor / gene	Products highlighted in Robbins	Role
Gag polyprotein	p17 matrix, p24 capsid, p7 nucleocapsid, p6	Structural organization and RNA packaging
Pol polyprotein	Reverse transcriptase, integrase, protease	DNA synthesis, integration, maturation
Env precursor gp160	gp120 and gp41	Receptor binding and membrane fusion

Protease-dependent processing converts polyproteins into functional components.

T-cell activation changes replication permissiveness

Naive / resting T cells

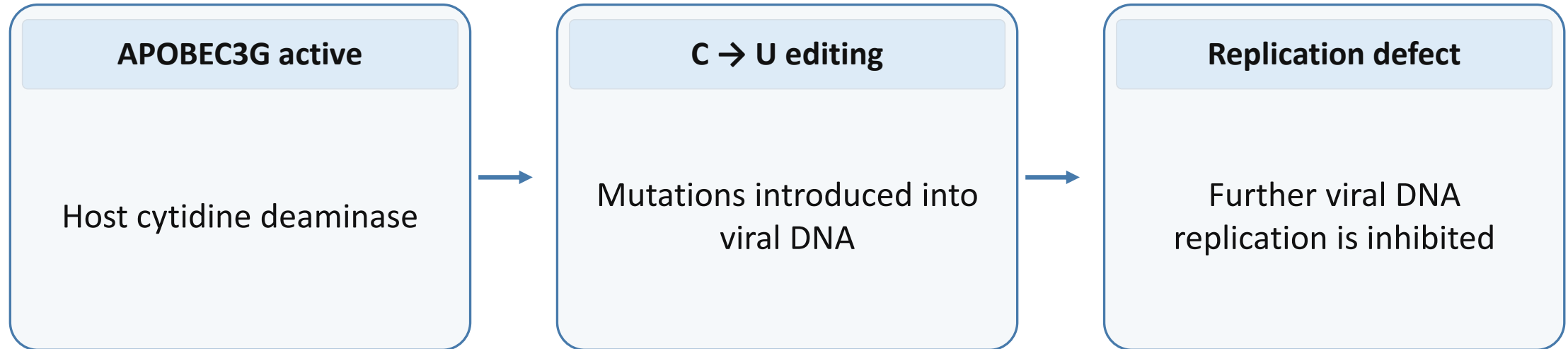
- Relatively inefficient productive infection.
- Active APOBEC3G can restrict viral DNA.
- Less favorable environment for viral gene expression.

Activated / memory T cells

- Greater permissiveness to productive infection.
- APOBEC3G restriction can be reduced.
- Activation-associated transcription factors favor viral RNA expression.

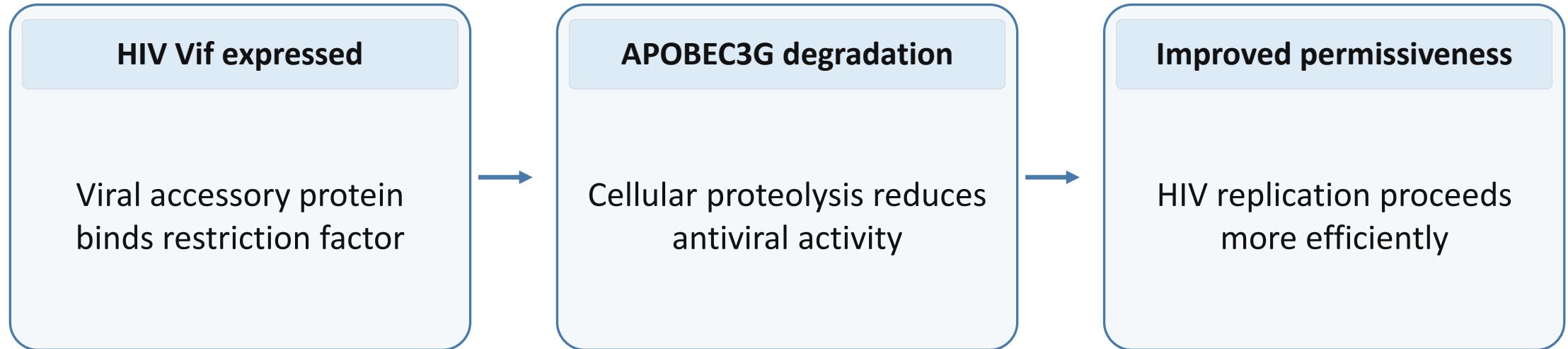
Susceptibility depends on cellular activation state, not simply CD4 expression.

APOBEC3G is a cellular antiviral restriction factor



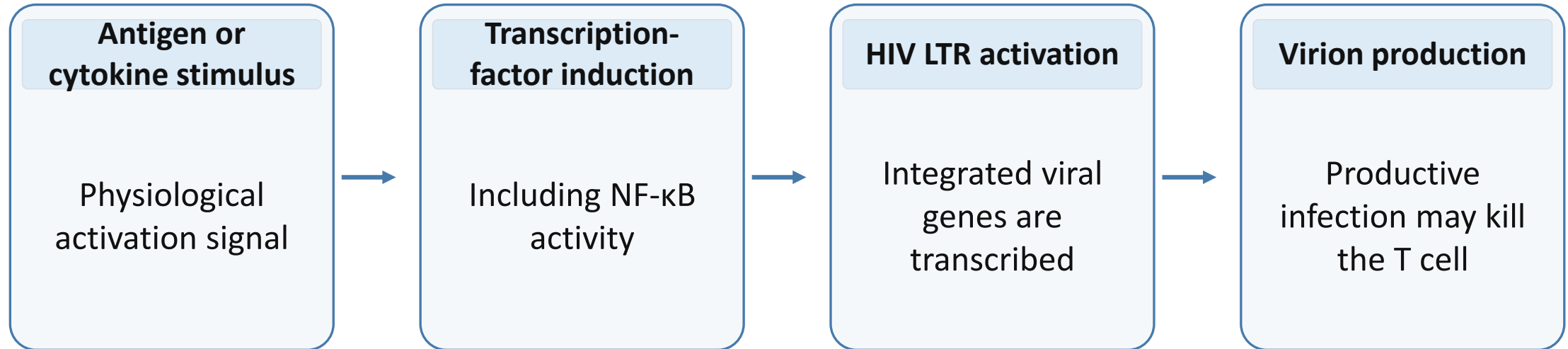
This intrinsic defense is particularly relevant to restriction in resting T cells.

Vif antagonizes APOBEC3G-mediated restriction



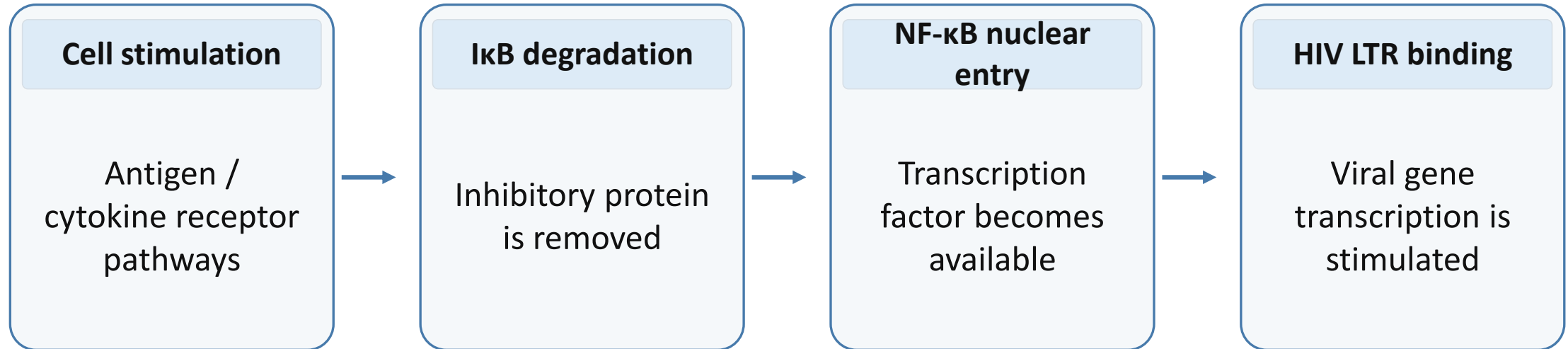
Host restriction and viral countermeasure operate on the same viral replication barrier.

Activation of latently infected T cells can revive HIV



Normal immune activation can unintentionally trigger HIV expression.

NF- κ B links inflammation to viral transcription



The HIV promoter uses a transcription factor normally mobilized for immune responses.

The long terminal repeat responds to host activation

Two long terminal repeats flank the HIV genetic region

5' LTR

HIV gene region / integrated provirus

3' LTR

NF- κ B and other host factors

Bind control sequences in HIV LTR

Tat protein

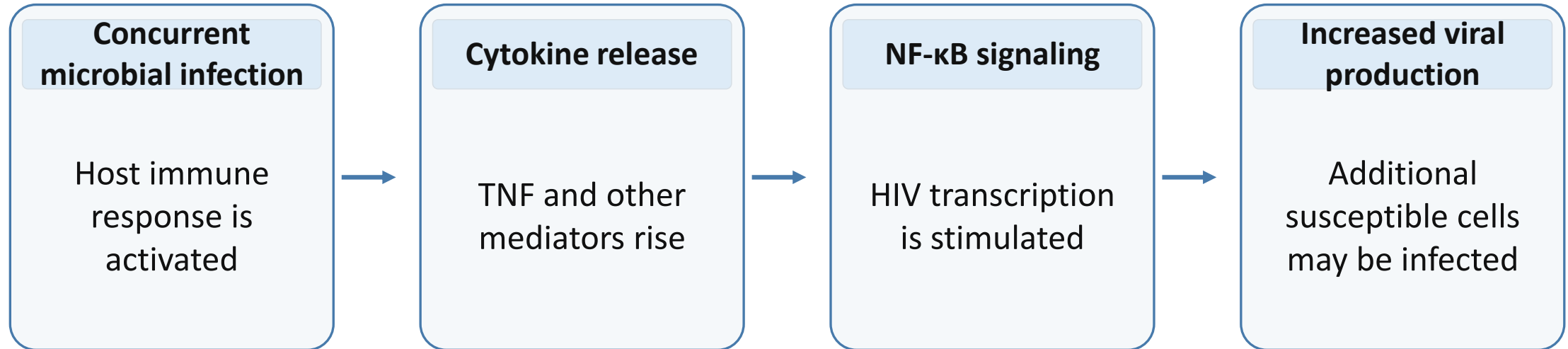
Enhances elongation of HIV transcription

Cell activation

Makes the host transcriptional environment permissive

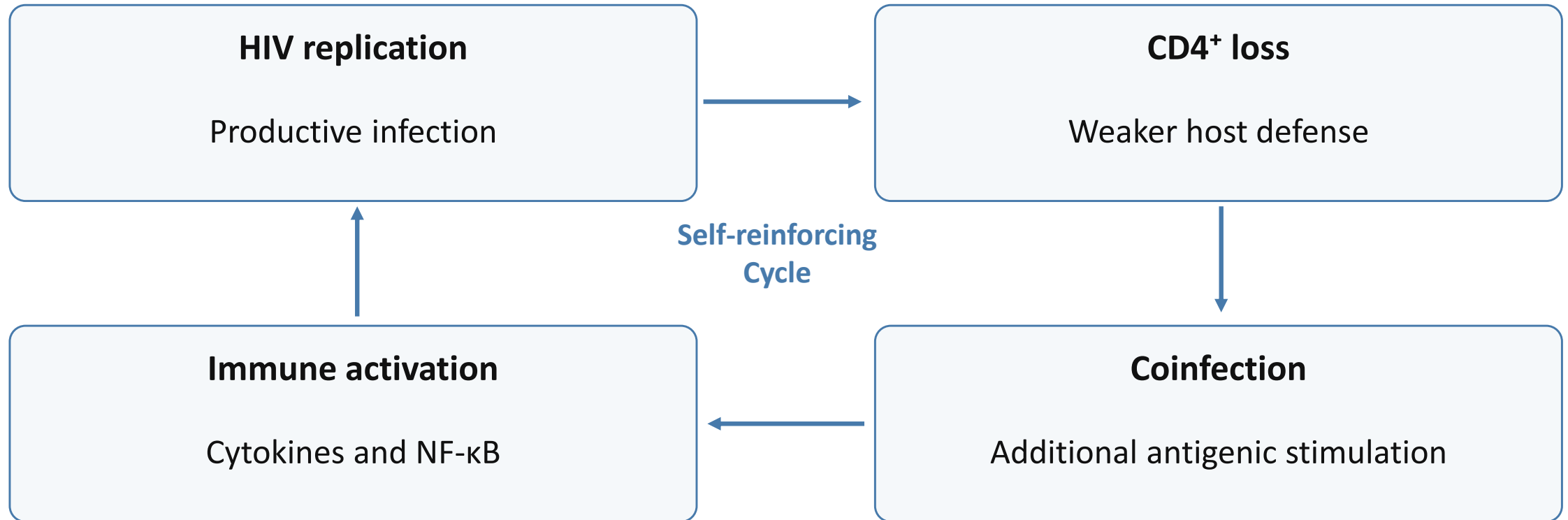
A physiological immune-activation signal can become a viral transcription signal.

Other infections can increase HIV replication



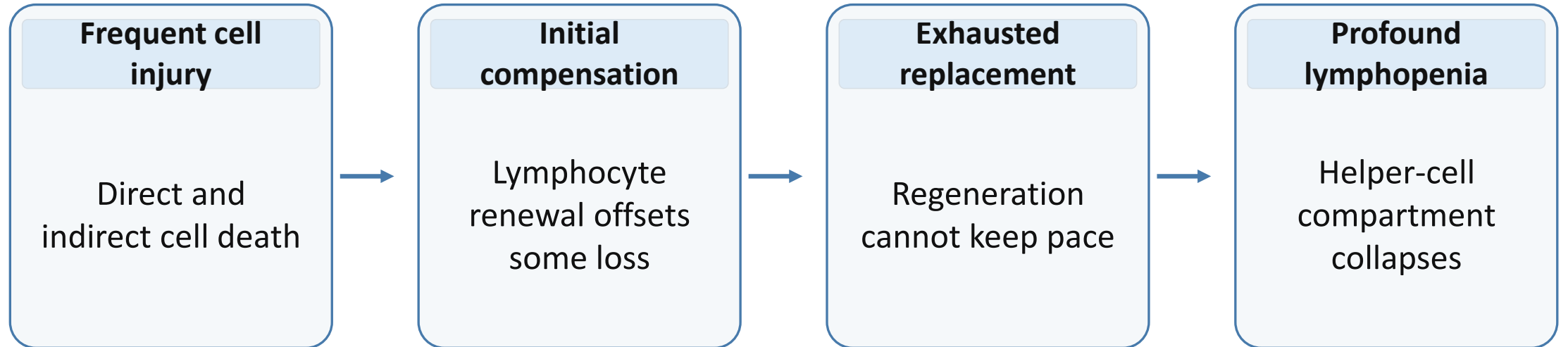
A response intended to eliminate other microbes may create opportunities for HIV amplification.

Inflammation and HIV reinforce one another



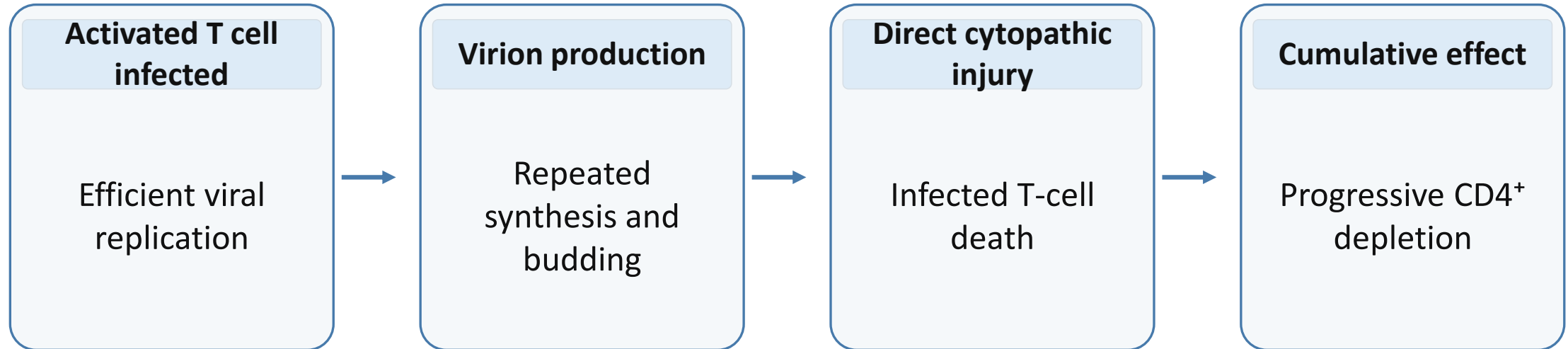
This self-amplifying loop links immune deficiency with persistent immune activation.

CD4⁺ depletion begins when loss exceeds replacement



A deceptively slow fall in blood CD4⁺ counts can mask substantial tissue turnover.

Productive HIV infection directly damages CD4⁺ T cells



Direct viral cytopathicity as a major mechanism of infected-cell loss.

Most infected cells are not visible in peripheral blood

Blood compartment

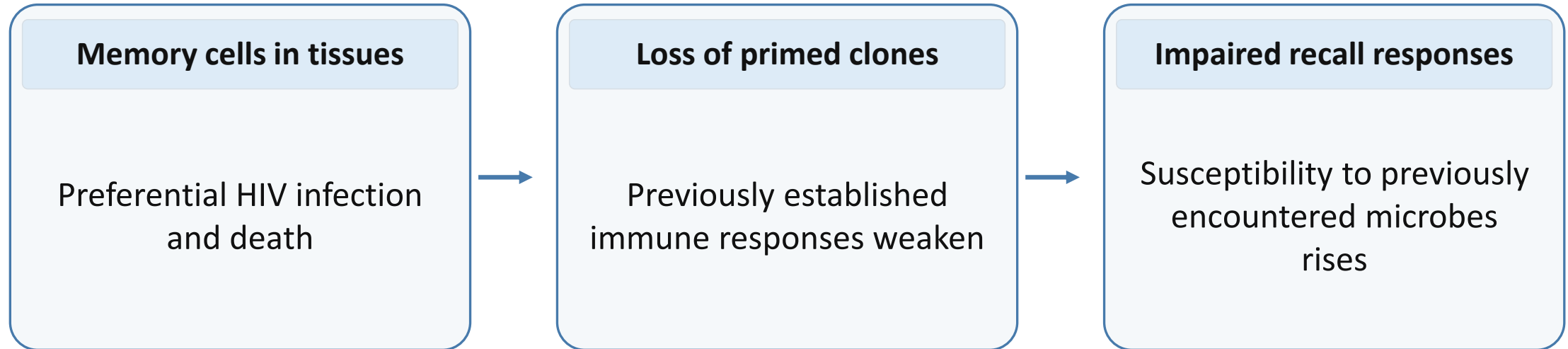
- Only a small fraction of infected cells may circulate.
- Peripheral measurements can underestimate infected tissue burden.

Tissue compartment

- Secondary lymphoid organs and mucosa contain many infected cells.
- Tissue death is central to cumulative CD4⁺ loss.

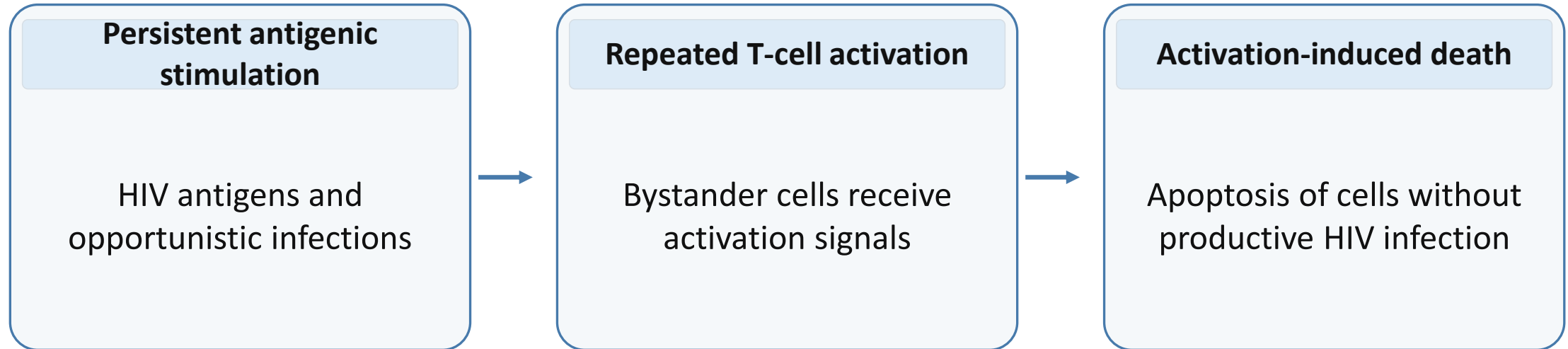
Blood and tissue distributions should not be treated as interchangeable.

Memory CD4⁺ T-cell loss impairs recall immunity



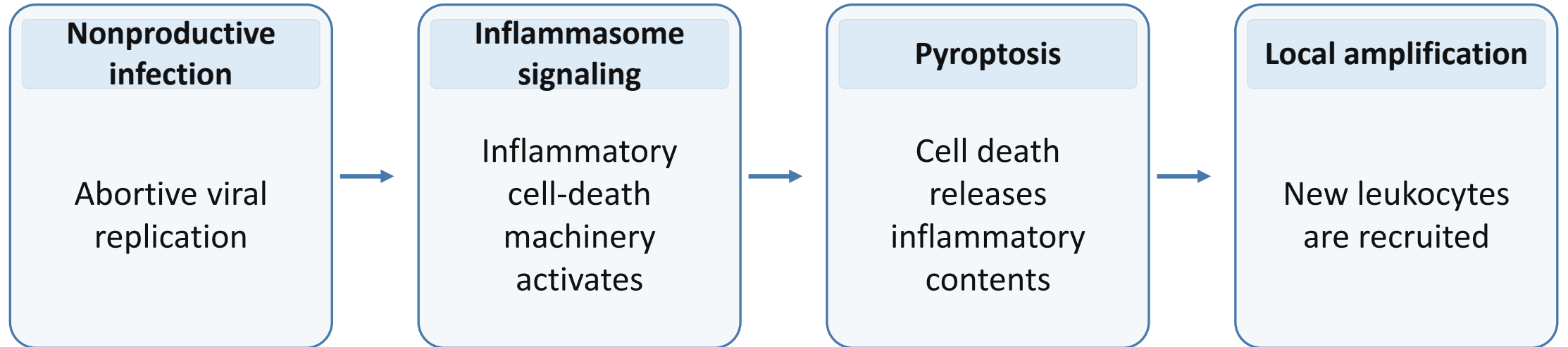
HIV depletes immune memory as well as total helper T-cell numbers.

Activation-induced apoptosis removes uninfected cells



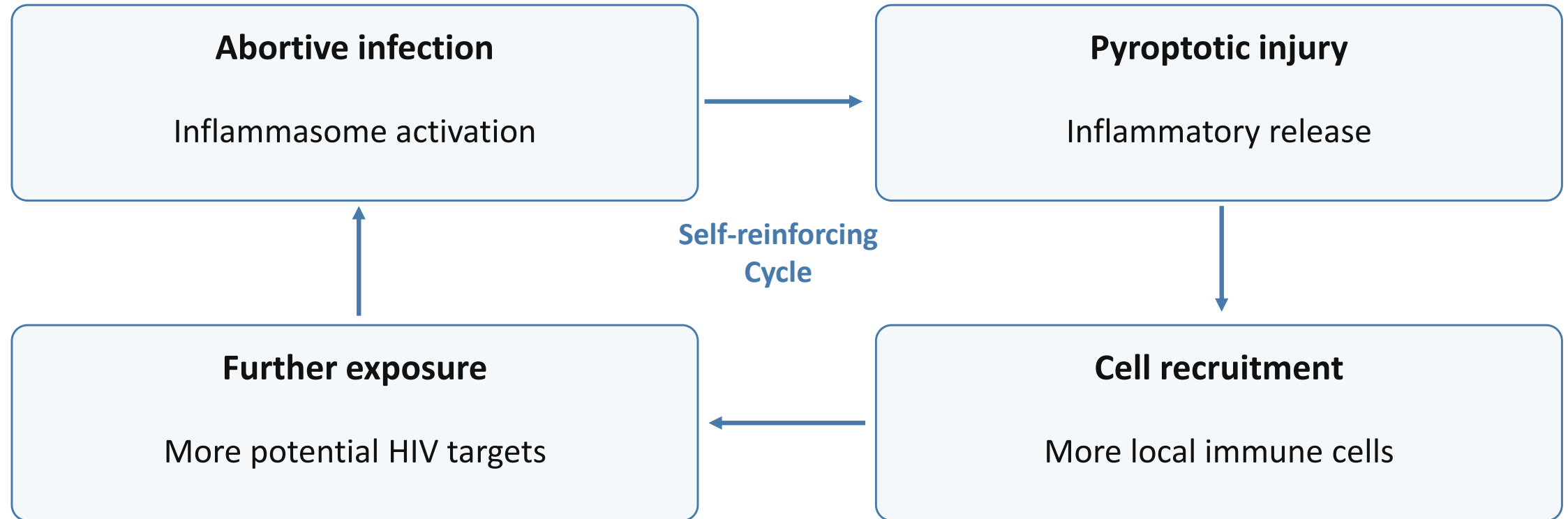
The number of dying T cells can exceed the number infected at a given time.

Abortive HIV infection can elicit pyroptosis



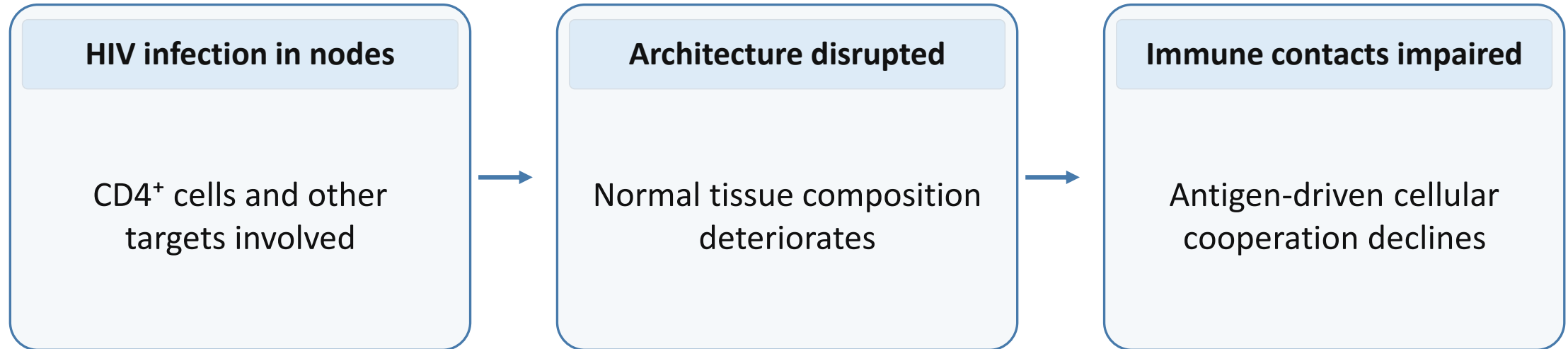
Pyroptosis can connect nonproductive infection to collateral inflammation.

Pyroptosis may recruit more susceptible target cells



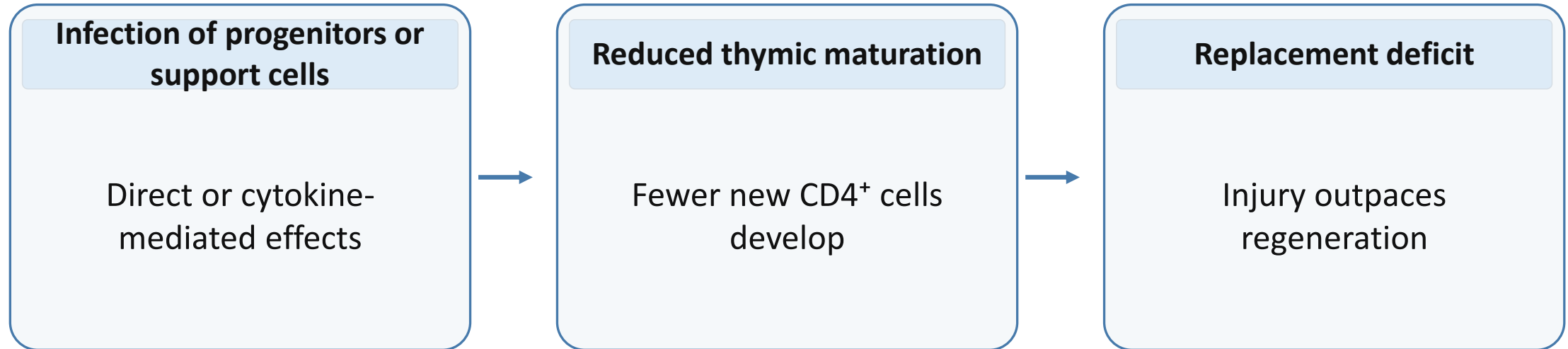
The source presents this as a potential contributor to the spread of infection.

Damage to lymphoid organs weakens cellular interactions



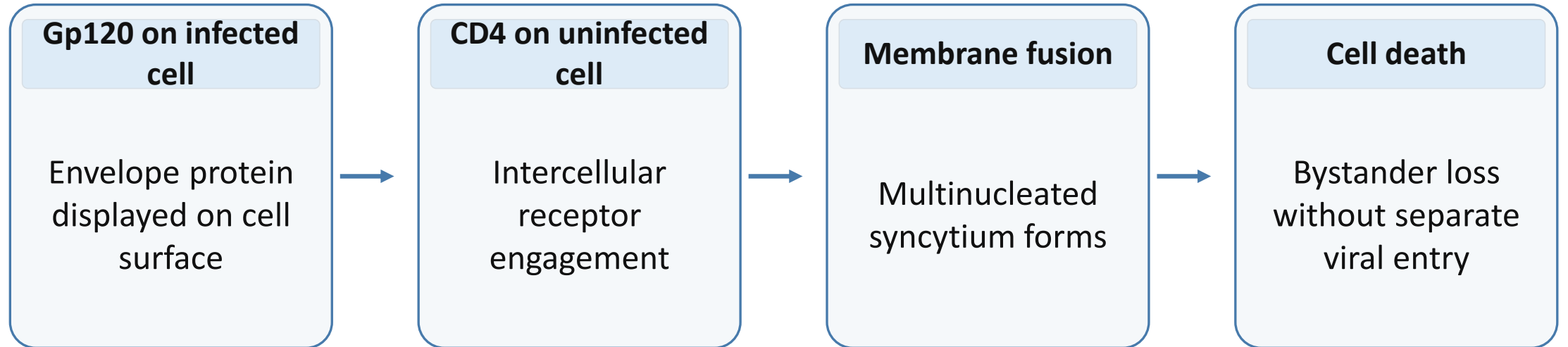
Loss of lymphoid organization compounds the reduction in immune-cell numbers.

Impaired T-cell maturation can compound depletion



Precursor and support-cell injury as possible additional mechanisms.

Syncytia allow injury to spread between adjacent cells



The source associates this mechanism particularly with X4 T-tropic strains in culture.

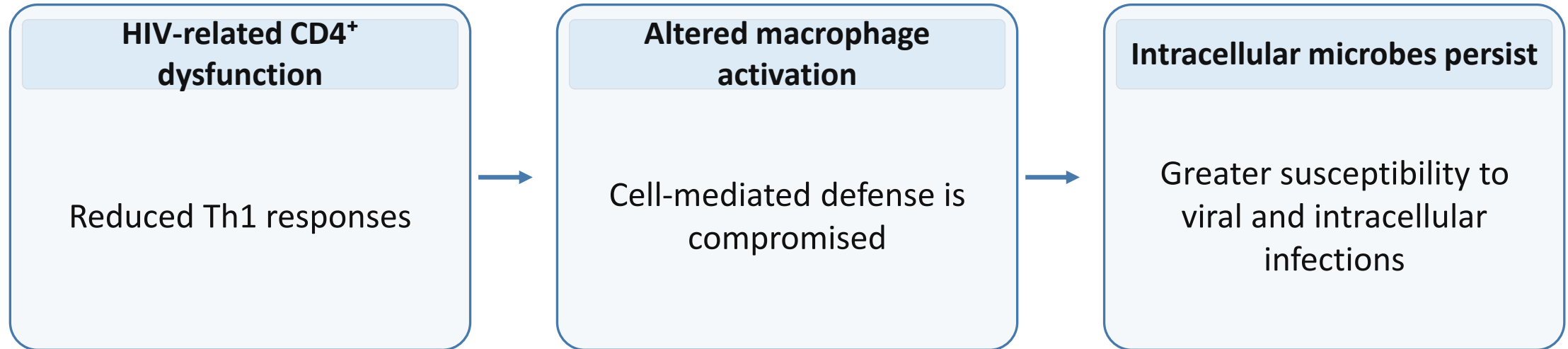
CD4⁺ T cells are depleted by parallel mechanisms

Mechanism	Direct cellular event	Distinct contribution
Productive infection	Viral cytopathic death	Loss of infected T cells
Activation-induced apoptosis	Death of uninfected activated cells	Bystander cell loss
Abortive infection	Inflammasome-associated pyroptosis	Inflammation and recruitment
Lymphoid / thymic injury	Disorganized organs; impaired precursors	Reduced immune maintenance
Syncytium formation	Fusion of infected and uninfected cells	Collateral cell death

Surviving CD4⁺ T cells may also function poorly

- Antigen-driven proliferation is diminished even before advanced symptomatic disease.
- Th1-type responses are reduced and intracellular signaling may be defective.
- Both qualitative dysfunction and numerical CD4⁺ loss contribute to immune deficiency.
- The reduction of T-cell help compromises other leukocyte compartments.

Reduced Th1 help compromises intracellular defense



Mechanism—not simply low lymphocyte numbers—explains the pattern of opportunistic infections.

Loss of CD4 help propagates across immune compartments

CD8⁺ responses

Reduced coordination of cellular antiviral responses.

B-cell responses

Defective help for effective new antibody formation.

Macrophage function

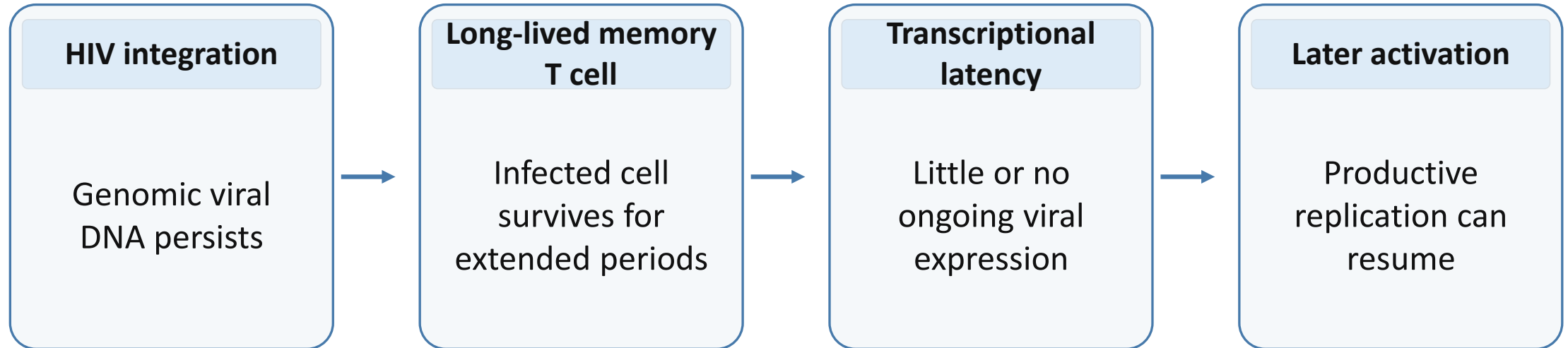
Altered signals and direct myeloid infection impair defense.

Lymphoid organization

Loss of tissue integrity disrupts multicellular immunity.

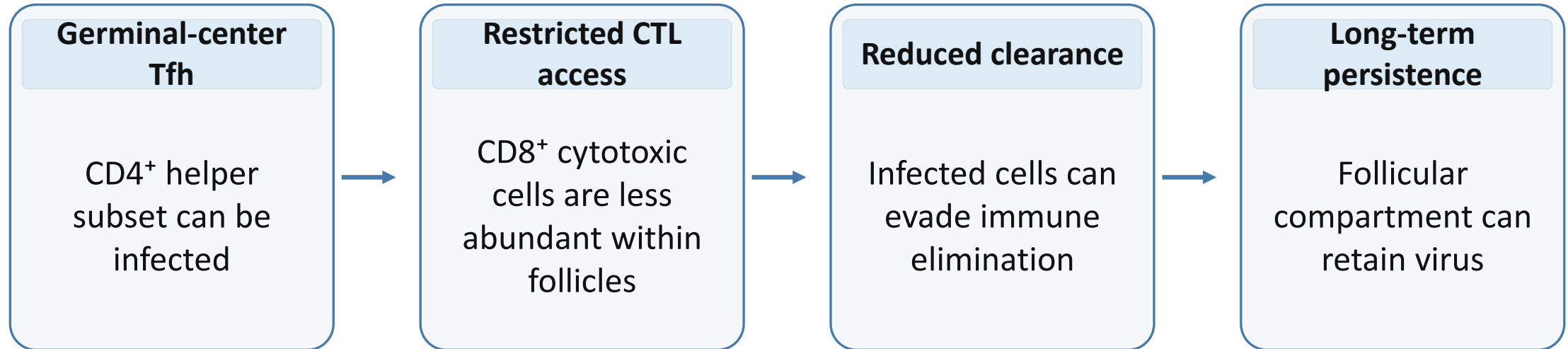
CD4⁺ lymphocytes act as immune-system coordinators rather than isolated effector cells.

Long-lived memory cells sustain latent proviruses



Persistence of an integrated provirus explains why suppression of circulating virus does not erase infection.

Follicular helper T cells form a reservoir niche



Anatomical positioning affects the efficiency of immune elimination.

The major viral reservoirs use different mechanisms

Site / cell	How HIV persists	Why elimination is difficult
Memory CD4 ⁺ T cell	Integrated, transcriptionally silent provirus	Long-lived cells with minimal viral expression
T follicular helper cell	Infected cells within germinal centers	Relatively limited CD8 ⁺ CTL access
Macrophage	Infected, cytopathically resistant cells	Cell survival and viral retention
Follicular dendritic cell	Intact virus held on surface processes	Captured virions can remain infectious

Macrophages permit HIV replication without division

Typical dividing T-cell environment

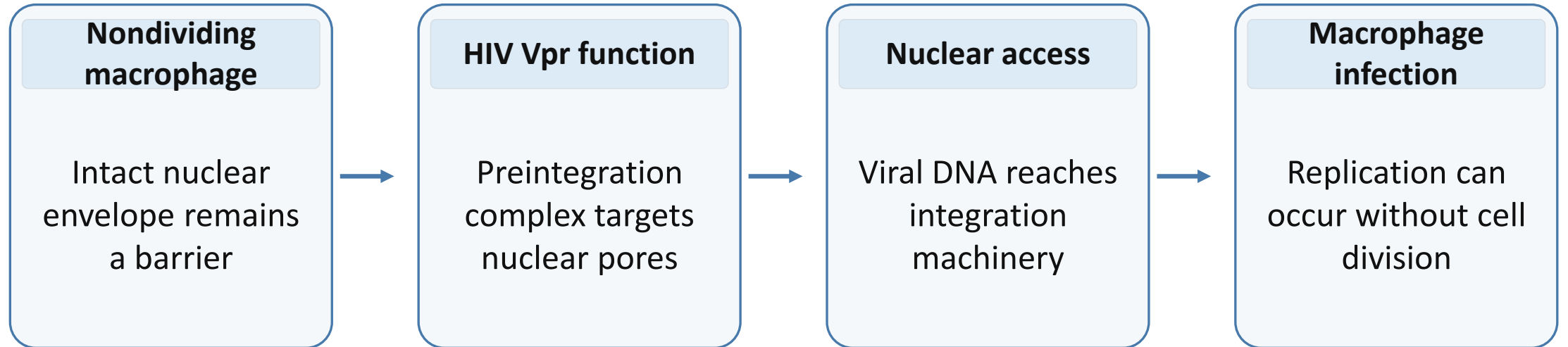
- Activated cells are highly permissive.
- Productive replication frequently leads to cell death.

Terminally differentiated macrophage

- Cell division is not necessary for HIV replication.
- Vpr is linked to nuclear import of the viral preintegration complex.

HIV-1 has an unusual capacity to establish infection in nondividing myeloid cells.

Vpr facilitates nuclear entry in macrophages



Vpr provides a mechanistic explanation for HIV replication in differentiated macrophages.

Infected macrophages survive longer than many T cells

CD4⁺ T lymphocytes

- Productive infection often cytopathic.
- Rapid loss reduces longevity of infected cells.

Tissue macrophages

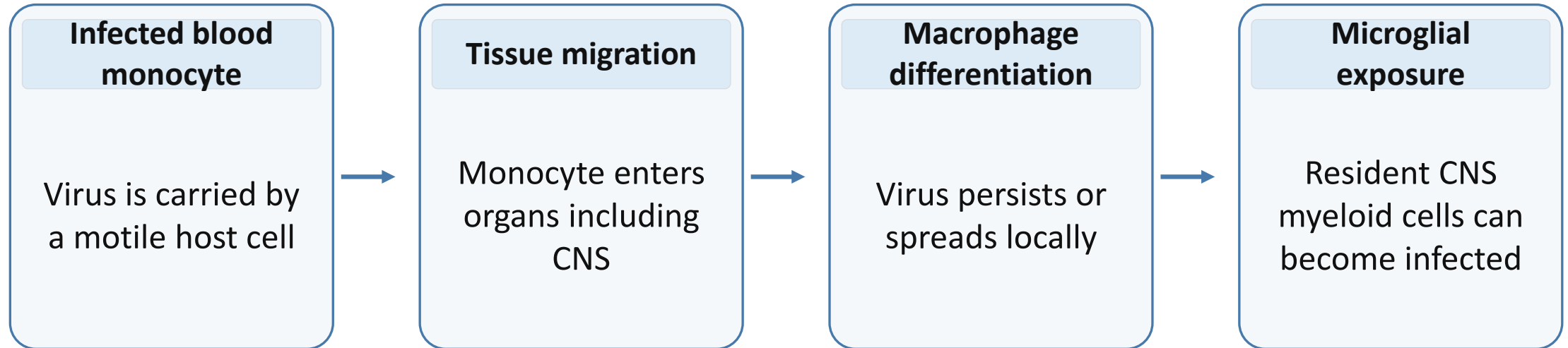
- Often contain many virions in intracellular vesicles.
- Release relatively small quantities of virus.
- Resist cytopathic effects; Can serve as reservoirs.

Different infected-cell survival patterns diversify HIV persistence.

HIV alters macrophage antimicrobial functions

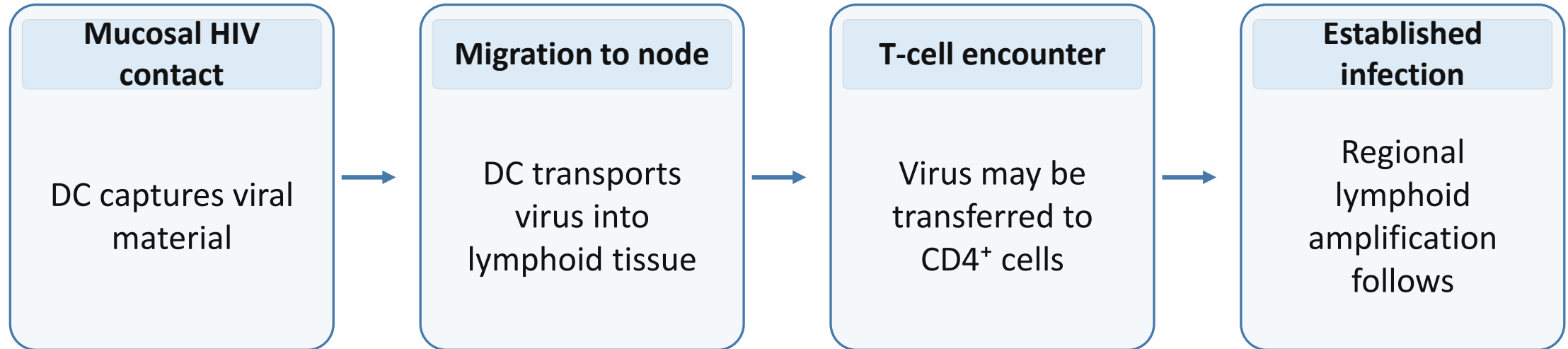
Macrophage function	Abnormality described in AIDS	Host-defense consequence
Chemotaxis	Reduced	Impaired movement to sites of infection
Phagocytic / microbicidal activity	Reduced	Less effective microorganism clearance
Antigen presentation	Lower class II HLA; poor T-cell presentation	Weaker T-cell activation
Cytokine secretion	IL-1 reduced; TNF dysregulated	Distorted inflammatory coordination

Monocytes can move HIV into distal tissues



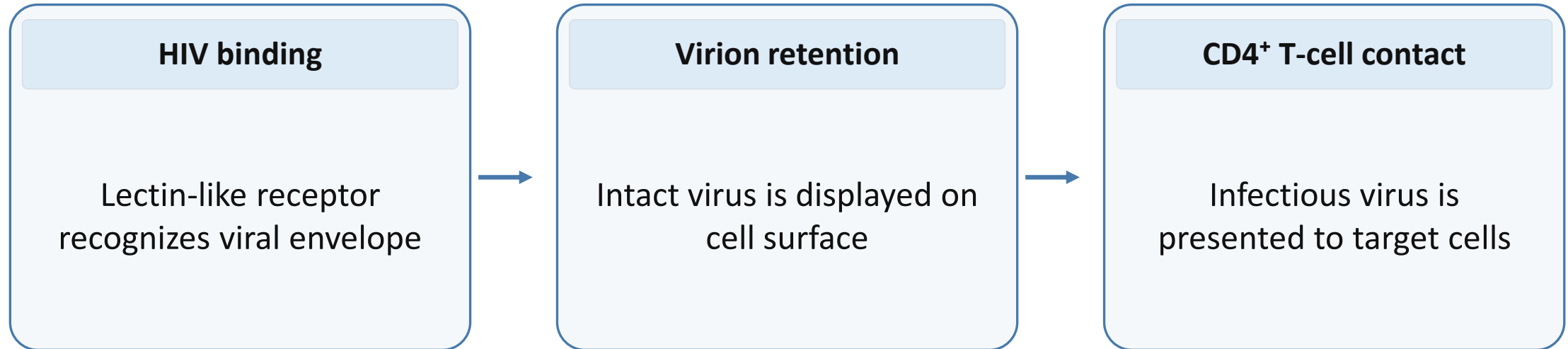
Cell-associated trafficking adds a dissemination route beyond free virions.

Mucosal dendritic cells can convey HIV to lymph nodes



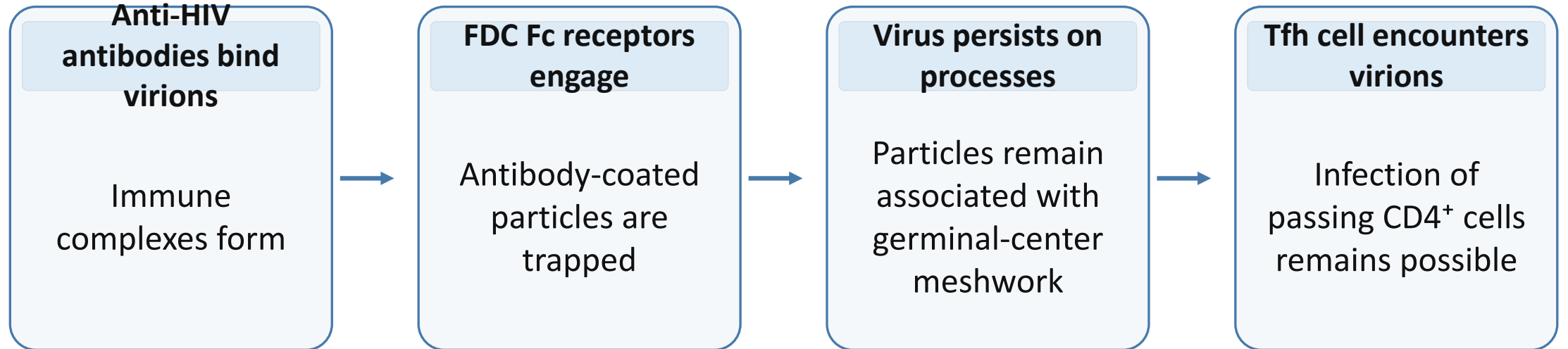
Dendritic cells can promote dissemination even when capture is not equivalent to productive infection.

Dendritic-cell receptors can retain infectious HIV



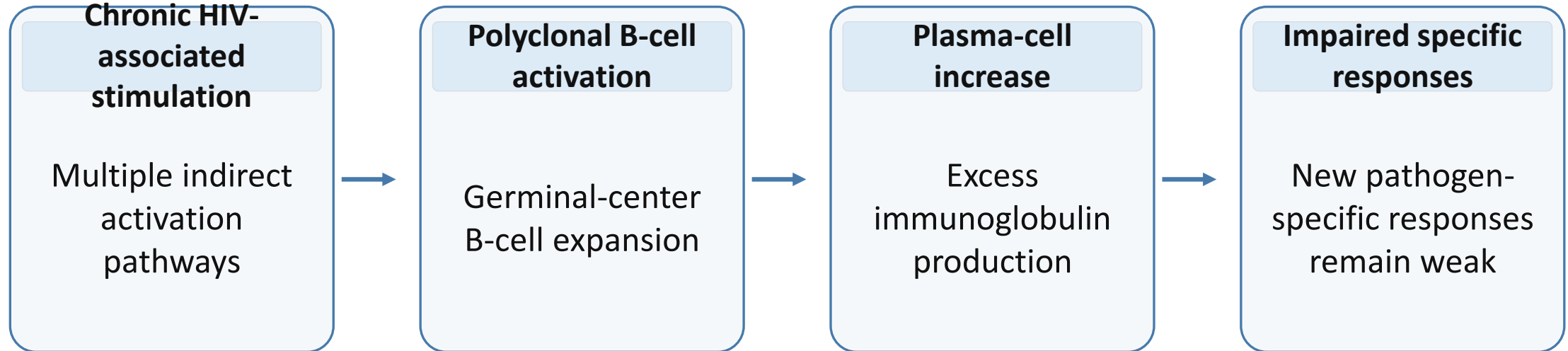
DC-mediated transfer distinguishes viral capture from intracellular replication.

Follicular dendritic cells retain virions externally



Most FDC-associated particles are surface-bound rather than evidence of productive FDC infection.

HIV perturbs B cells without directly infecting them



The source separates B-cell activation from effective humoral immunity.

Several pathways may drive polyclonal B-cell activation

EBV reactivation

EBV can polyclonally stimulate B cells.

Viral gp41

The source proposes B-cell growth and differentiation effects.

IL-6

Infected macrophage-derived IL-6 may promote B-cell proliferation.

Multifactorial activation

The source proposes several contributors rather than a single established cause.

These mechanisms are presented by the source as contributors, not exclusive alternatives.

High immunoglobulin levels do not ensure protection

Polyclonal stimulation

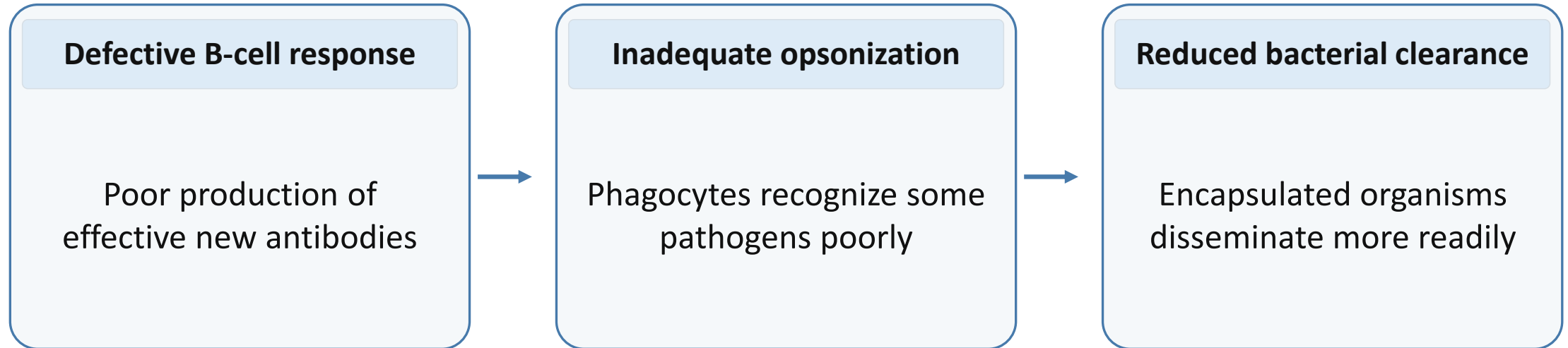
- Germinal-center hyperplasia.
- Increased plasma cells.
- Hypergammaglobulinemia and possible immune complexes.

Specific antibody failure

- Poor de novo responses to new antigens.
- Weak T-dependent and some T-independent responses.
- Inadequate opsonizing antibody defense.

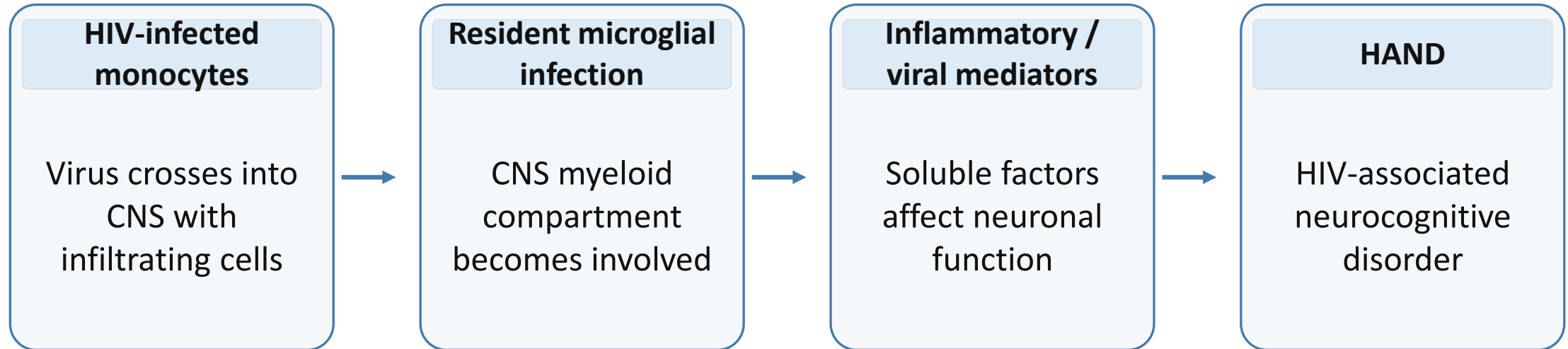
Quantity of serum immunoglobulin is not synonymous with protective specificity.

Humoral failure impairs encapsulated bacterial clearance



This vulnerability with *Streptococcus pneumoniae* and *Haemophilus influenzae*.

CNS involvement centers on infected myeloid cells



The source treats neurological injury as predominantly indirect rather than widespread neuronal infection.

Neuronal injury can exceed apparent tissue destruction

Where HIV is found

- Infiltrating macrophages and resident microglia.
- Neurons and astrocytes are not major sites of productive infection account.

How symptoms arise

- Viral proteins may impair neural function.
- Inflammatory mediators from infected microglia may contribute.
- Clinical dysfunction can outweigh observed structural lesions.

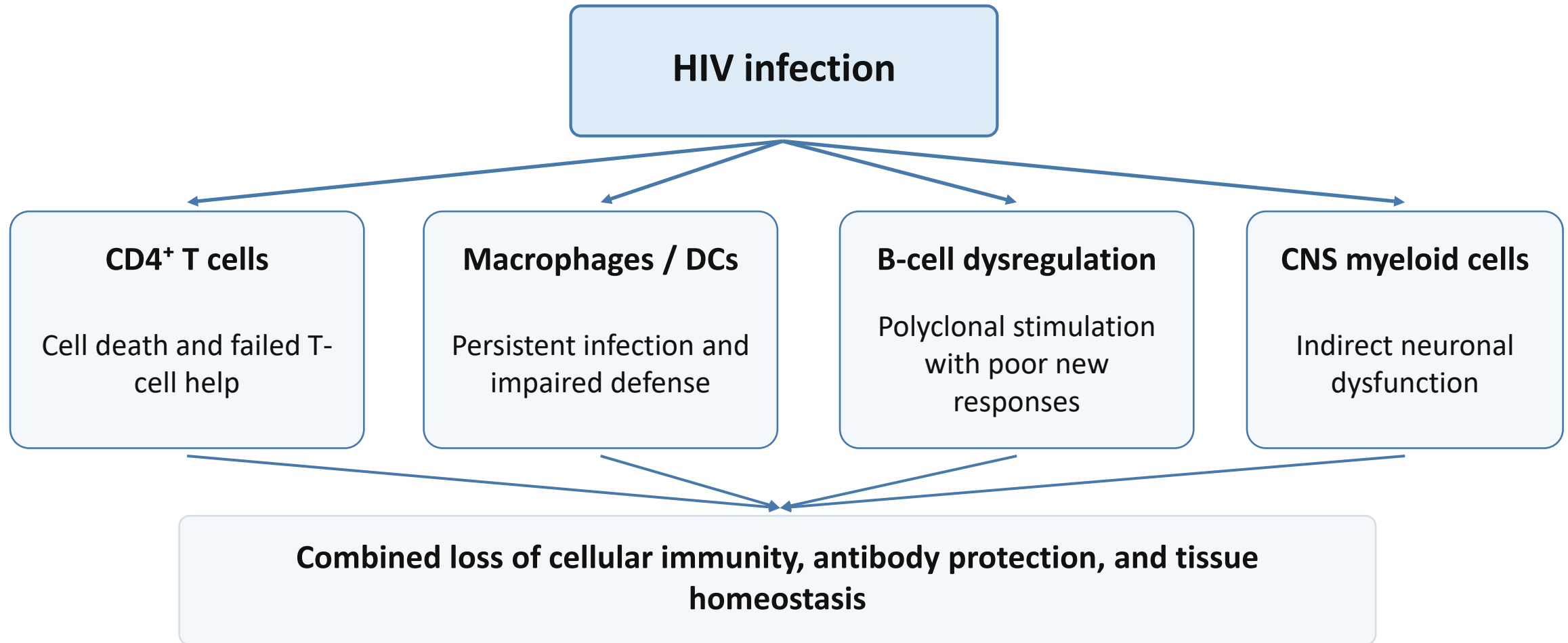
This mismatch supports a soluble-mediator model of neurologic dysfunction.

Proposed mediators of HIV-related CNS dysfunction

Proposed mediator	Source indicated	Pathogenetic interpretation
IL-1, TNF, IL-6	Infected / activated microglia	Neuroinflammatory signaling
gp41	HIV envelope protein	Nitric-oxide induction has been implicated
gp120	Soluble viral envelope glycoprotein	Direct neuronal toxicity has been postulated

Robbins explicitly characterizes the precise mechanisms of CNS injury as incompletely understood.

An integrated view explains multisystem HIV injury



Mechanism predicts the immune defect

Dominant lesion	Functional consequence	Clinical correlation
CD4 ⁺ death / poor Th1 signaling	Weak cell-mediated immunity	Opportunistic intracellular infections
Loss of immune coordination	Reduced effective antibody responses	Susceptibility to encapsulated bacteria
Macrophage / DC abnormalities	Poor ingestion, presentation, and pathogen control	Additional vulnerability to infection
CNS myeloid infection	Indirect neuronal impairment	Neurocognitive symptoms

Application: Why does coreceptor identity matter?

An HIV isolate infects CD4⁺ lymphocytes but requires CXCR4 rather than CCR5 for entry. A second isolate uses CCR5 predominantly.

Explain the mechanism:

- Classify the two isolates using the source terminology.
- Which isolate is associated with stronger T-cell tropism?
- Why is CD4 binding alone insufficient?

Application: Why can antibody levels be high but ineffective?

A patient with advanced HIV infection has marked polyclonal hypergammaglobulinemia yet develops recurrent infection by an encapsulated bacterium.

Explain the mechanism:

- Which B-cell phenotype explains the increased immunoglobulins?
- Why may newly generated protective antibodies still be deficient?
- How does this lead to impaired bacterial clearance?

Application: Why can HIV injure the CNS indirectly?

An HIV-infected patient develops cognitive dysfunction. Tissue analysis localizes most detectable HIV to macrophages and microglia rather than neurons.

Explain the mechanism:

- What cellular route may carry virus into the CNS?
- Name two classes of mediators proposed to cause neural dysfunction.
- Why might symptoms be severe despite relatively modest structural lesions?

Five causal links explain HIV-associated immunodeficiency

- CD4 + coreceptor engagement initiates entry; Gp41 completes fusion.
- Reverse transcription and integration enable lifelong genomic persistence.
- Cell activation can convert latent infection into destructive replication.
- Direct death, bystander injury, tissue damage, and poor renewal deplete T cells.
- Myeloid, B-cell, and CNS effects expand disease beyond CD4⁺ lymphopenia.

Primary reference

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th edition (2026).
- Chapter 6, “Diseases of the Immune System,” pp. 220–224.
- Section: “Pathogenesis of HIV Infection and AIDS.”
- Source-associated material: Figs. 6.38–6.40 and Table 6.14 (not reproduced).