

Natural History of HIV Infection

Acute infection • clinical latency • progression to AIDS

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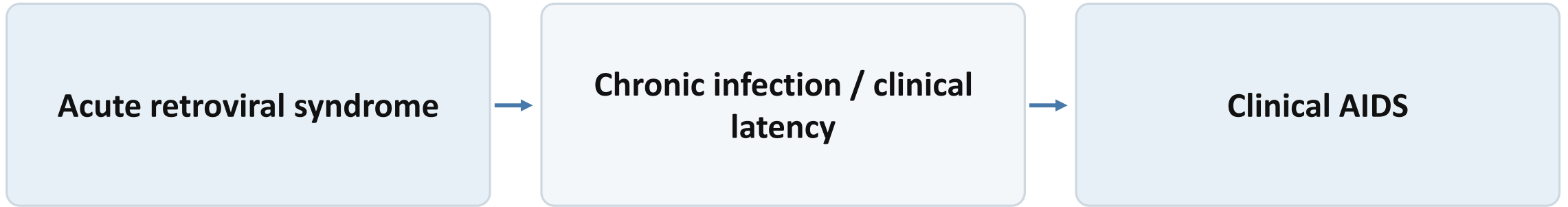
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Learning objectives: Explain the course of untreated HIV infection

- Trace infection from the mucosal portal to systemic viremia.
- Explain how antiviral immunity produces partial control without eradication.
- Interpret viral set point and CD4+ T-cell depletion across stages.
- Recognize typical and atypical patterns of progression to AIDS.

Three phases organize the natural history



- The phases describe manifestations of infection, not abrupt biological switches.
- The sequence reflects the untreated course.

Clinical appearance is not equivalent to virologic activity

Clinical expression

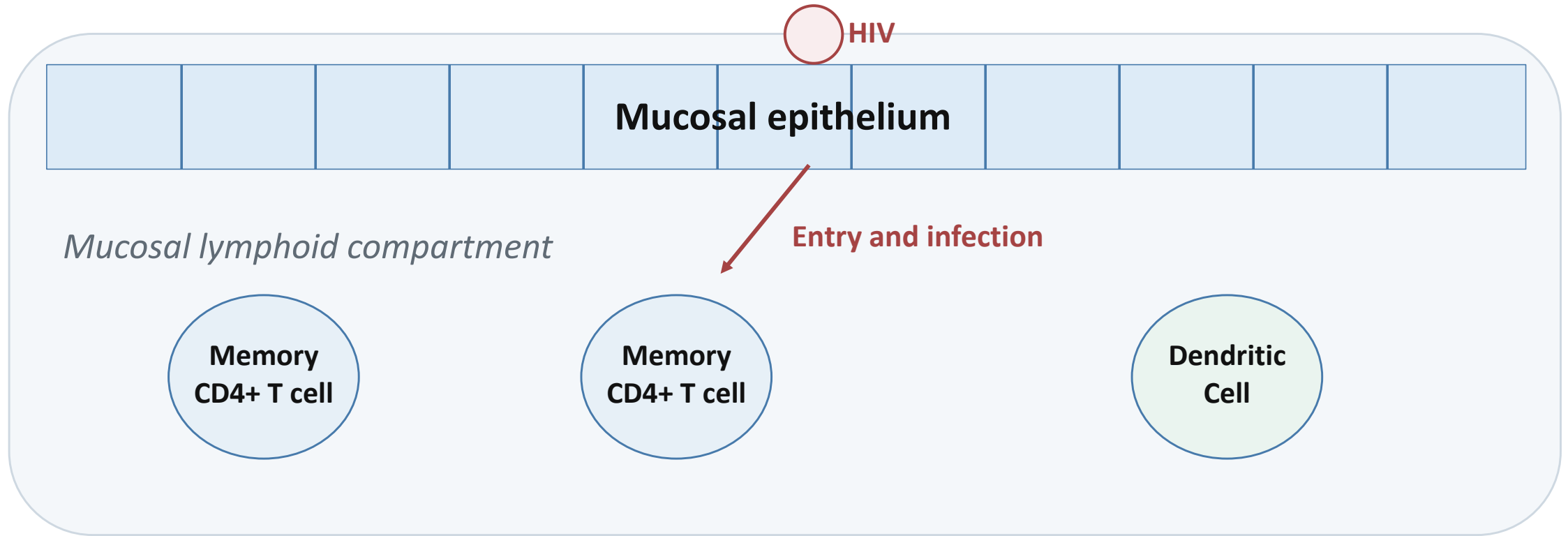
- Acute: Short, systemic illness
- Middle phase: Few or no symptoms
- Advanced disease: Severe syndromes

Virologic and immunologic state

- Early peak of dissemination and viremia
- Persistent lymphoid replication and CD4+ loss
- Rising viral burden and failed host defense

A clinically silent interval is not a virologically silent interval.

Initial infection begins at a mucosal portal



- Mucosal memory CD4+ T cells are early targets of infection and death.
- A local event initiates broader infection of lymphoid tissue.

Mucosal barrier integrity modifies susceptibility

- Damage to the epithelium favors establishment of mucosal infection.
- Defects in mucosal barrier function are additional predisposing factors.
- Local entry conditions influence the efficiency of initial infection.

Memory CD4+ T cells are abundant at the mucosal portal

Why they are vulnerable

- Memory T cells constitute a large mucosal compartment.
- These cells are susceptible to HIV infection.
- Local infection directly injures the target-cell pool.

Immediate consequences

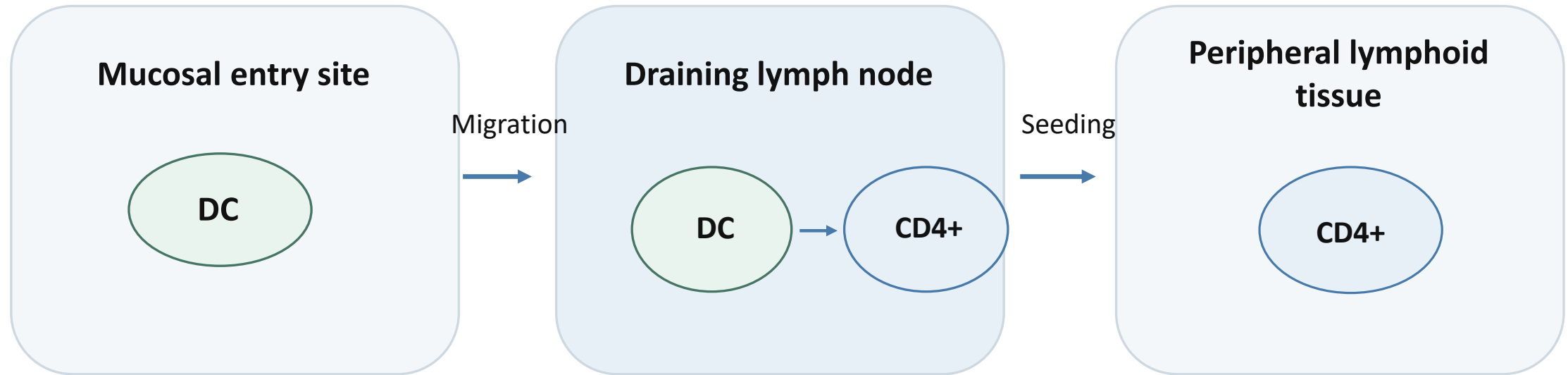
- Numerous infected cells die during early infection.
- Mucosal lymphocyte depletion can be substantial.
- Blood counts do not reveal the full tissue injury.

Early mucosal depletion precedes the full systemic picture



- A major immunologic injury can occur before overt AIDS.
- Early damage is concentrated in tissue, not necessarily peripheral blood.

Dendritic cells connect entry sites to lymph nodes



- DCs can capture HIV at the site of entry and move to regional lymph nodes.
- Direct DC-to-T-cell transfer promotes establishment of lymphoid infection.

Lymph nodes become early amplification sites

- HIV replication can be detected in lymph nodes within days of exposure.
- The lymphoid compartment supports sustained viral multiplication.
- Replication at these sites precedes broad hematogenous dissemination.

Viremia follows lymphoid amplification



- Viremia denotes HIV in circulating blood.
- It marks systemic spread rather than the initial local infection.

Systemic dissemination seeds multiple immune compartments

Dissemination process

- The bloodstream distributes virus beyond entry sites.
- Peripheral lymphoid tissues become infected.
- Infection becomes widely established.

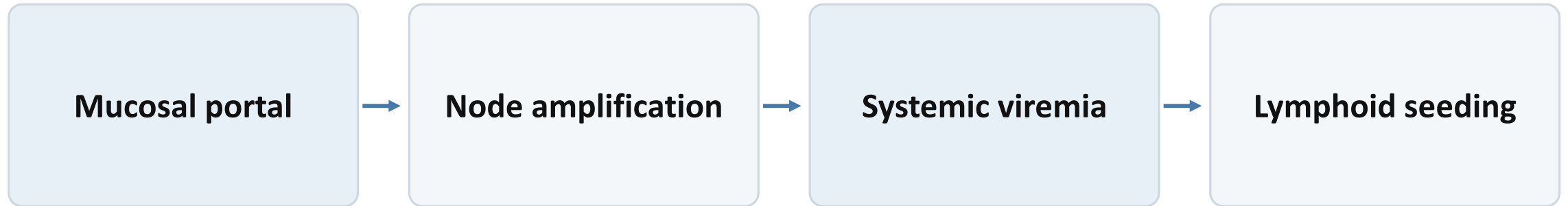
Host-cell targets

- CD4+ helper T lymphocytes are infected.
- Macrophages also become infected.
- Immune-system sites carry a substantial viral burden.

Early blood sampling underrepresents tissue infection

- Relatively few infected cells may initially be detected in blood.
- Mucosal and lymphoid tissue infection can already be extensive.
- Tissue-level immunopathology should not be inferred from blood-cell frequencies alone.

Establishment of primary infection: The full causal sequence



- The order explains why local infection has systemic consequences.
- Host immune activation occurs in response to this disseminated infection.

Viral cytopathic injury and host response coexist

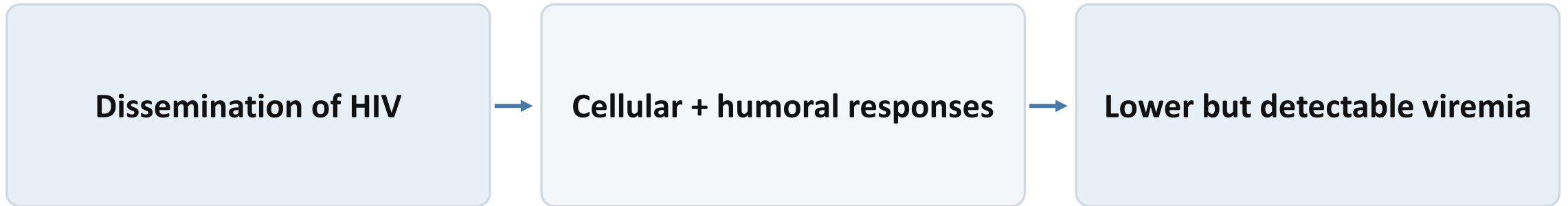
Direct infection-related events

- Susceptible mucosal CD4+ cells become infected.
- Infected cells die; Viral replication expands.
- Lymphoid tissue contains replicating virus.

Host-response events

- HIV-specific cytotoxic T cells develop.
- Antiviral antibodies appear.
- Immune containment lowers circulating virus.

Adaptive immunity restrains early viremia



- The antiviral response is effective enough to lower circulating RNA.
- A decline in viremia is not equivalent to clearance of infection.

HIV-specific cytotoxic T cells emerge early

- CD8+ cytotoxic T lymphocytes (CTLs) target HIV peptide-bearing infected cells.
- A virus-specific CTL response is detectable approximately 2–3 weeks after infection.
- The CTL response peaks around 9–12 weeks in the course depicted by Robbins.

Antiviral humoral responses develop during primary infection

- Antibodies to HIV emerge with seroconversion.
- Seroconversion usually within 3–7 weeks of presumed exposure.
- The humoral immune response peaks at about 12 weeks figure.

Cellular and humoral responses have related but distinct roles

Cellular response

- Virus-specific CD8+ CTLs arise within weeks.
- CD8+ T-cell clones expand substantially.
- CTLs contribute to early viral containment.

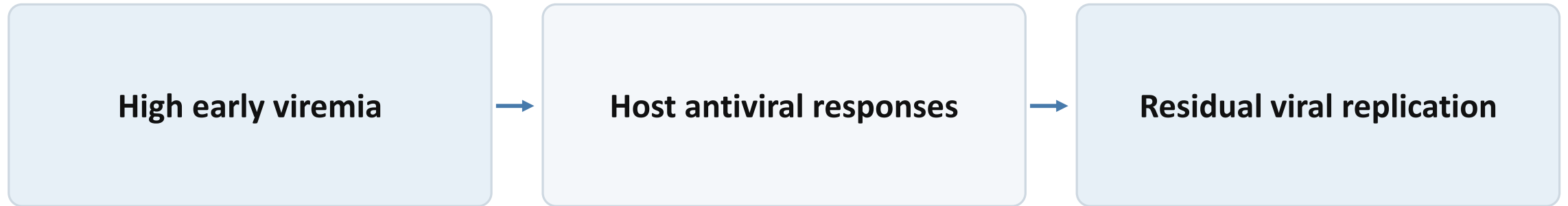
Humoral response

- Seroconversion marks development of antibodies.
- Anti-HIV antibody responses increase during the acute phase.
- Antibodies accompany partial reduction of viremia.

Acute viremia falls as immune containment develops

- Circulating HIV rises during early dissemination.
- Cellular and antibody responses reduce circulating viral production.
- By approximately 12 weeks, viremia often falls to lower but detectable levels.

Immune control is substantial but incomplete



- HIV remains established in lymphoid tissue.
- The chronic phase begins despite partial immunologic control.

Acute retroviral syndrome reflects dissemination and response

- The illness accompanies the initial widespread spread of HIV.
- Symptoms arise during the early period of host immune activation.
- The clinical syndrome is nonspecific and self-limited in typical cases.

The timing of acute illness is characteristically delayed

Textbook-described untreated natural history; Individual courses vary.

- Typical onset 3–6 weeks after infection.
- The syndrome usually resolves spontaneously over 2–4 weeks.
- A mild or absent acute illness does not preclude established infection.

Acute retroviral syndrome: Constitutional manifestations

Systemic findings	Interpretation
Fever and fatigue	Nonspecific expression of acute systemic illness
Sore throat and myalgia	Flu-like clinical presentation
Weight loss	Constitutional effect during acute infection

Acute retroviral syndrome: Accompanying manifestations

Additional feature	Clinical context
Rash	May accompany systemic illness
Cervical adenopathy	Reflects lymphoid/systemic involvement
Diarrhea or vomiting	Possible gastrointestinal symptoms

Clinical exercise: A flu-like illness after exposure

CLINICAL VIGNETTE

Several weeks after a suspected exposure, a patient develops fever, sore throat, myalgia, cervical lymphadenopathy and rash.

Which phase of infection is compatible with this presentation?

The symptom cluster and timing fit the acute retroviral syndrome; Clinical features alone are not diagnostic.

A resolving illness does not mean the virus has disappeared

What often improves

- Fever and constitutional symptoms subside.
- Acute viral syndrome is typically self-limited.
- Clinical appearance may return to normal.

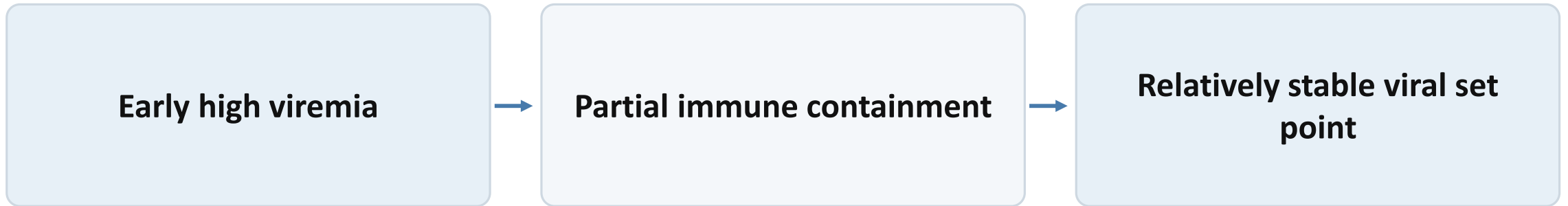
What persists

- HIV remains in lymphoid compartments.
- Some viral replication continues.
- The individual enters clinical latency, not cure.

Plasma HIV RNA is a marker of active systemic infection

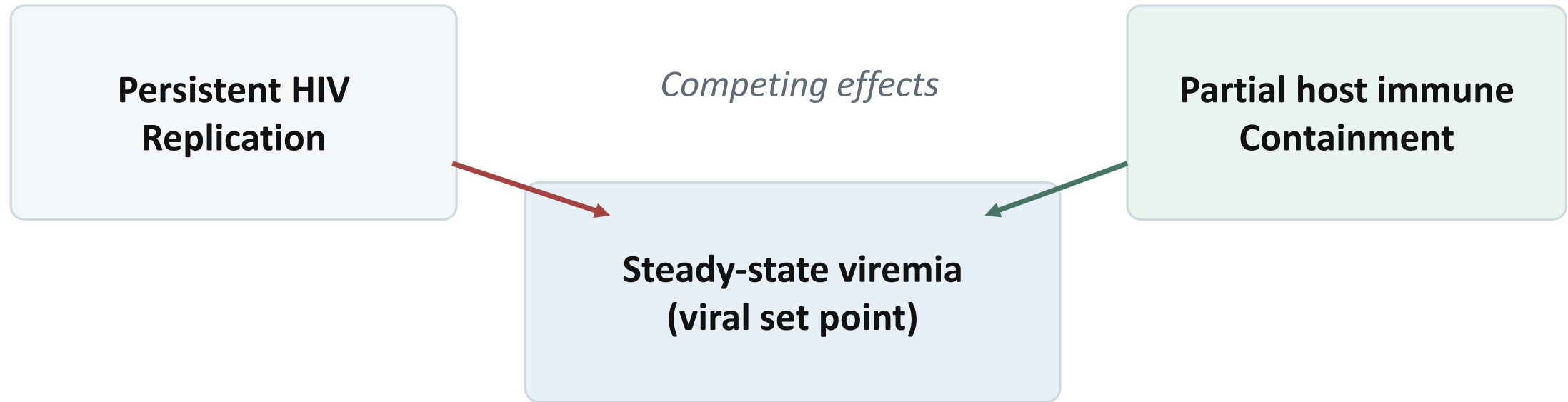
- The measurable amount of HIV-1 RNA in blood is the viral load.
- Its level changes rapidly during primary infection.
- It has value for interpreting disease evolution and virologic activity.

The viral set point follows the acute decline



- The set point describes a steady-state balance, not absence of virus.
- It may remain approximately stable in an untreated patient for several years.

The set point reflects competing biological processes



- The set point is a dynamic equilibrium, not virologic eradication.
- A higher sustained viral burden predicts more rapid subsequent CD4+ loss.

The viral set point predicts subsequent immunologic decline

- The steady-state viral load is a prognostic correlate of HIV progression.
- Higher sustained viral burdens are associated with faster CD4+ depletion.
- The host–virus balance helps explain variable untreated trajectories.

Viral load and CD4+ count answer different questions

Plasma HIV RNA

- Reflects circulating viral burden.
- Tracks viral replication and its containment.
- Set point has prognostic relevance.

CD4+ T-cell count

- Reflects immune-system depletion.
- Declines across progressive untreated infection.
- Helps identify advanced immunodeficiency.

These measurements are complementary, not interchangeable.

Robbins reproduces historical CDC CD4+ categories

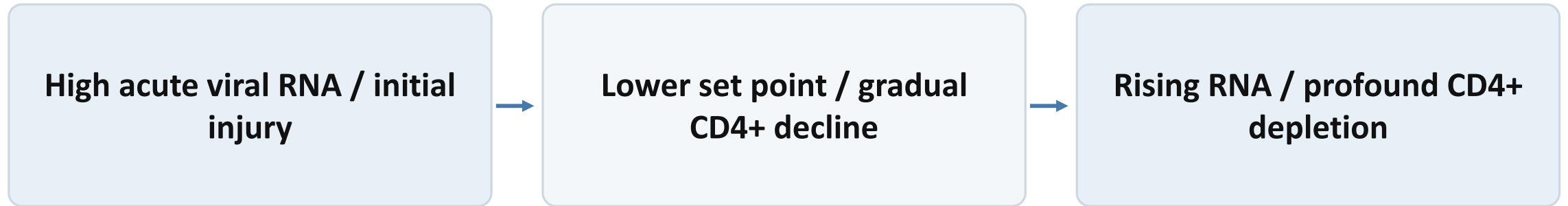
Category	CD4+ T cells/ μ L	Historical interpretation
1	≥ 500	Higher count category
2	200–499	Intermediate count category
3	< 200	Severely depleted category

CDC 1993 classification reproduced by the textbook; Not a current ART initiation rule.

Loss of CD4+ cells reflects waning immune containment

- Persistent HIV infection reduces the size of the helper T-cell pool.
- CD4+ loss impairs the host ability to coordinate effective immune responses.
- A declining CD4+ count signals increasing immunologic vulnerability.

Untreated natural history: Two changing measures



- This is a qualitative sequence, not measured trajectories or rates.
- Viremia and immune-cell loss need not change in parallel at every moment.

Clinical latency is defined by symptoms—not absent replication

- Patients frequently have few or no overt manifestations of HIV infection.
- Lymph nodes and spleen remain sites of HIV replication and cell destruction.
- Peripheral blood CD4+ T-cell counts continue to decrease over time.

Lymphoid organs are central to the chronic phase

Lymph nodes

- Major sites of persistent viral multiplication.
- Contain susceptible and infected T cells.
- Ongoing cell turnover can be extensive.

Spleen

- Another secondary lymphoid site of replication.
- Infection and immune-cell destruction persist.
- Systemic lymphoid damage may accumulate.

Peripheral blood is only a small part of the T-cell system

- That most T cells reside in secondary lymphoid organs.
- The burden of infected cells may therefore be greater in lymphoid tissue than blood.
- Blood tests provide an important but incomplete view of tissue events.

Tissue infection can far exceed circulating-cell infection

Lymphoid tissue

- Large population of CD4+ T cells.
- Ongoing viral production and target-cell loss.
- Central site of chronic immunopathology.

Peripheral blood

- Many circulating T cells are not infected.
- Fewer infected cells may be sampled.
- Absolute CD4+ counts still track immune decline.

Chronic infection involves continuing cell replacement and loss

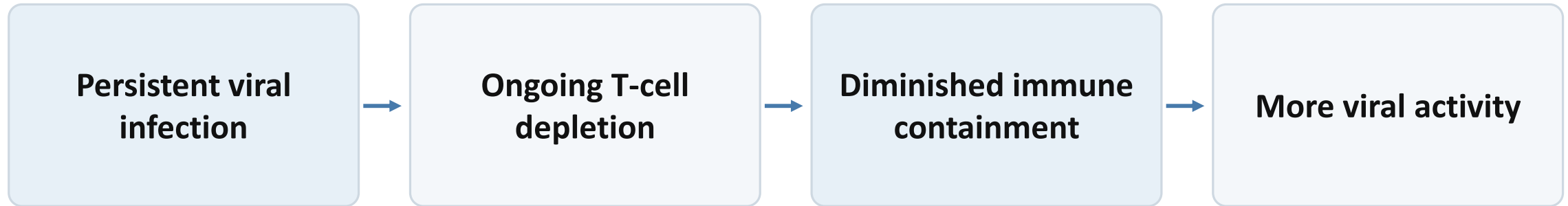


- Early in chronic disease, new T cells can replace much of the loss.
- Persistent turnover does not imply stable long-term immune function.

Early compensation can conceal cumulative immune damage

- Continuous cell destruction may initially be matched by replenishment.
- Peripheral CD4+ cell counts can decline slowly rather than abruptly.
- Clinical wellness may coexist with substantial tissue turnover.

Progressive decline reflects a self-amplifying cycle



- Years of cumulative imbalance erode both lymphoid and circulating CD4+ pools.
- Ultimately, replacement no longer offsets sustained losses.

Rising viral burden accompanies failing immune control

- The proportion of surviving CD4+ cells infected with HIV may increase.
- Viral burden per infected CD4+ cell may also rise.
- Plasma HIV RNA increases when control of viral replication deteriorates.

Why HIV may escape immune containment

Loss of host capacity

- CD4+ cells needed for effective adaptive immunity are depleted.
- The ability to sustain effective antiviral responses weakens.
- Opportunistic organisms exploit this failure.

Viral evasive properties

- Antigenic variation reduces immune recognition.
- MHC class I down-modulation may impair CTL recognition.
- Coreceptor usage may change in some patients.

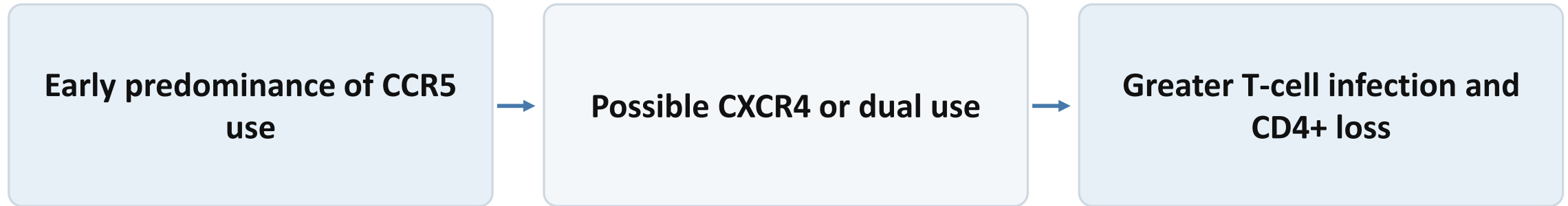
Antigenic variation challenges sustained antiviral recognition

- Viral variation can alter immune targets over time.
- Previously generated adaptive responses may become less effective.
- This contributes to continued replication despite host immunity.

MHC class I down-modulation can weaken CTL recognition

- HIV may down-modulate MHC class I molecules on infected cells.
- This may reduce presentation of viral antigens to CD8+ CTLs.
- Incomplete CTL recognition facilitates persistence of infected cells.

Coreceptor evolution may accompany faster immune decline



- The proposed switch does not occur identically in every patient.
- The source links coreceptor switching with more rapid CD4+ decline.

The chronic phase has more than one clinical phenotype

Asymptomatic infection

- Few or no apparent manifestations.
- Continuing lymphoid replication.
- Progressive loss of CD4+ cells may be silent.

Minor associated illness

- Oral or vaginal candidiasis can appear.
- Herpes zoster may occur.
- Tuberculosis and immune thrombocytopenia are also noted.

Minor conditions may signal waning host defenses

Finding during chronic infection	Clinical significance in Robbins
Oral candidiasis (thrush)	Opportunistic infection during waning cellular immunity
Herpes zoster	Possible infection in the chronic phase
Tuberculosis	Can occur relatively early; region-dependent burden
Autoimmune thrombocytopenia	Immune dysregulation may accompany infection

Transition to AIDS represents failure of immune defense

- CD4+ depletion eventually reaches a clinically consequential level.
- Viral load increases dramatically as host control breaks down.
- Serious AIDS-associated diseases become likely.

The shift from latency to AIDS is mechanistically coherent



- There is no requirement for a new infection with HIV to cause this transition.
- The process reflects cumulative loss of containment of the established infection.

Advanced infection produces persistent constitutional illness

- Prolonged fever, fatigue, and weight loss may develop.
- Diarrhea and generalized lymph-node enlargement may accompany disease.
- The pattern reflects severe systemic illness and impaired immunity.

Clinical AIDS is recognized through severe indicator conditions

Major category	Illustrative consequences
Serious opportunistic infections	Disease in the setting of advanced immune dysfunction
Secondary neoplasms	Tumors associated with profound immune impairment
Clinical neurologic disease	Central nervous system manifestations of HIV-related illness

Persistent HIV creates both infectious and noninfectious damage

Infectious burden

- Susceptibility to opportunistic pathogens increases.
- Organ-specific infections may become life threatening.
- Protection against latent pathogens weakens.

Other consequences

- Secondary neoplasms can emerge.
- Neurologic disease can become clinically manifest.
- Severe constitutional symptoms accompany immunodeficiency.

Typical progression is variable, even without therapy

- Progression to AIDS after about 7–10 untreated years in most patients.
- This is a historical untreated-course description, not an individual prediction.
- Both unusually rapid and unusually slow courses are recognized.

Patterns of untreated progression

Pattern	Natural-history feature	Interpretation
Typical progressor	Chronic interval often 7–10 years	Gradual erosion of host defense
Rapid progressor	Middle phase may shorten to 2–3 years	Accelerated immune decline
Long-term nonprogressor	Sustained clinical stability for ≥ 10 years	Unusually effective control
Elite controller	Exceptionally low untreated viremia	Rare degree of viral containment

These are qualitative, textbook-described untreated phenotypes; Definitions vary by study.

Rapid progressors compress the chronic interval

- A minority develops advanced disease more quickly than the typical course.
- A chronic phase of only 2–3 years after primary infection.
- A short interval still follows the same broad mechanism of immune deterioration.

Long-term nonprogression is uncommon

- Approximately 1% who remain asymptomatic for a decade or longer without ART.
- CD4+ T-cell counts can remain stable despite established infection.
- Low viral loads distinguish these individuals from typical progression.

Long-term nonprogressors and elite controllers are related labels

Long-term nonprogressors

- Long untreated clinical stability.
- Typically low measurable HIV RNA.
- Stable CD4+ cells are a central feature.

Elite controllers

- Very low untreated plasma HIV RNA.
- Exceptional ability to contain replication.
- Immune correlates remain incompletely defined.

Effective immune control is not explained by a single mechanism

- Slow progressors are heterogeneous in host and viral characteristics.
- Many isolates do not have major qualitative viral defects.
- The textbook does not identify one universal correlate of protection.

Potent T-cell responses may accompany slow progression

CD4+ immune responses

- Higher HIV-specific helper T-cell responses in some individuals.
- Responses may be maintained over years.
- Helper functions support broader immunity.

CD8+ immune responses

- Strong antiviral cytotoxic responses may persist.
- Responses may be maintained during long untreated infection.
- They contribute to sustained containment.

HLA genetic variation is associated with progression heterogeneity

- Certain inherited HLA alleles correlate with slower progression.
- The proposed explanation is more potent antiviral T-cell recognition.
- Association does not establish a universal predictive genotype.

Clinical exercise: Apparent health with falling CD4+ cells

CLINICAL VIGNETTE

An untreated patient reports no symptoms. Over serial visits, the peripheral CD4+ T-cell count declines while HIV RNA remains detectable.

Does the absence of symptoms indicate viral latency?

No. “Clinical latency” permits ongoing lymphoid replication and progressive immune injury.

Clinical exercise: Progression with rising HIV RNA

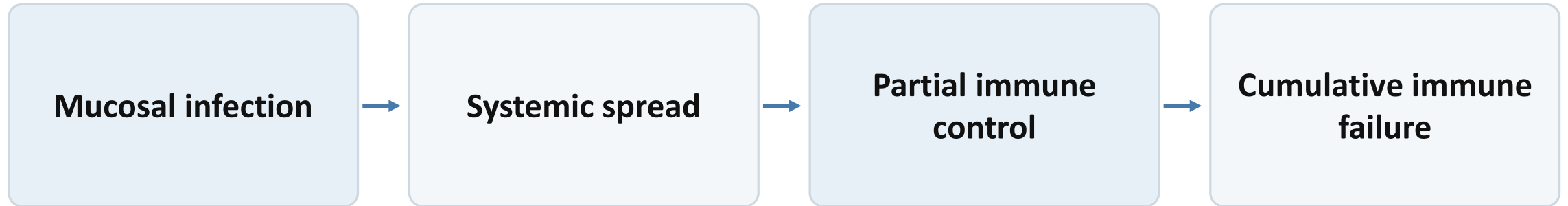
CLINICAL VIGNETTE

After years of untreated infection, a patient develops weight loss, persistent fever and an opportunistic infection; HIV RNA has increased.

What integrated mechanism accounts for the change?

Progressive CD4+ loss weakens containment, permitting increased viral burden and advanced disease.

Integrating natural history into one explanatory chain



- Acute syndrome corresponds to early spread and antiviral response.
- Clinical latency conceals ongoing CD4+ attrition until severe disease appears.

Comparison: Acute infection, latency and AIDS

Feature	Acute infection	Clinical latency	AIDS
Virologic pattern	Dissemination; high viremia	Persistent replication	Marked viral increase
CD4+ cells	Early mucosal loss	Continuing depletion	Profound loss
Clinical pattern	Flu-like syndrome possible	Few/no symptoms	Severe associated disease
Host control	Developing responses	Partial containment	Control fails

Qualitative comparison; Clinical phenotype and rate of progression vary.

Principal mechanistic insights

- The mucosal and secondary lymphoid compartments determine early and chronic pathobiology.
- Immune responses suppress viremia but do not eliminate established infection.
- Cumulative CD4+ depletion converts clinical latency into advanced immunodeficiency.
- Host and viral heterogeneity explain unusual progression phenotypes.

Final clinical interpretation

- A self-limited acute syndrome can still be followed by persistent HIV infection.
- Clinical wellness must not be confused with the absence of ongoing immune injury.
- Viral set point and CD4+ T-cell trajectory provide complementary biological information.
- The classic untreated course is fundamentally altered by effective ART.

Primary reading and historical framework

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026)

Diseases of the Immune System

Natural History of HIV Infection

The timelines and immune-cell categories discussed here represent the textbook's historical natural-history framework; they are not a contemporary treatment guideline.