

Clinical Features of AIDS

HIV infection: patterns of advanced immune deficiency

Opportunistic infections · HIV-associated neoplasms · Neurologic disease ·
Clinicopathologic effects of therapy

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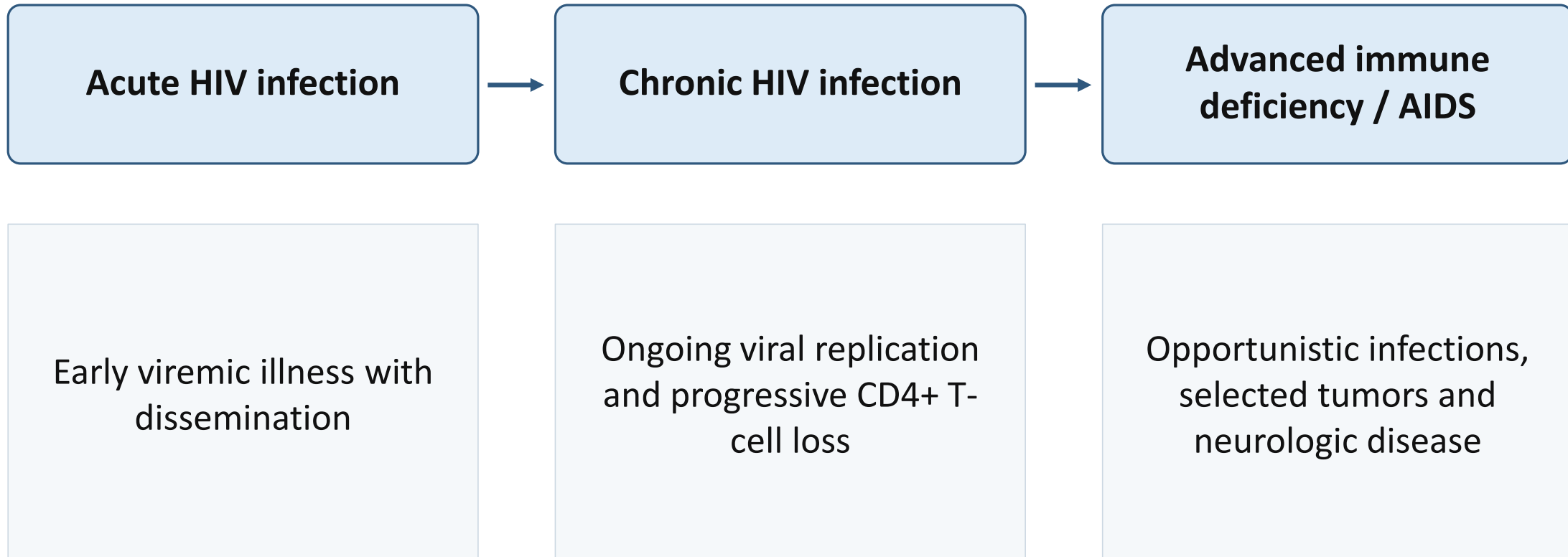
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Learning objectives

- Recognize major AIDS presentations and the patterns of opportunistic infection.
- Connect severe immune deficiency to characteristic infectious and neoplastic complications.
- Explain the histopathologic evolution of lymphoid tissues in HIV infection.
- Assess how antiretroviral therapy changes morbidity and clinical presentation.

AIDS represents the terminal clinical phase of untreated HIV infection



Clinical presentation is multisystemic

- Constitutional: Prolonged fever, weight loss and generalized lymphadenopathy.
- Gastrointestinal: Persistent diarrhea, opportunistic esophagitis and colitis.
- Infectious: Multiple pathogens can affect several organs simultaneously.
- Neurologic and neoplastic complications may dominate the presentation.

Untreated AIDS and the ART era

Untreated or poorly controlled infection

- Progressive CD4+ T-cell depletion
- High frequency of severe opportunistic infections
- Marked risk of selected oncogenic-virus tumors

Effective antiretroviral therapy

- Reduced viremia and progressive immune restoration
- Major decline in many classic AIDS events
- Greater prominence of chronic non-AIDS morbidity

Clinical spectra vary geographically

- The distribution of opportunistic agents is shaped by regional pathogen exposure.
- Tuberculosis is a particularly important contributor to AIDS mortality globally.
- Availability and effectiveness of ART strongly modify observed case mixes.
- Historical pre-ART percentages should not be generalized to treated populations.

Why opportunistic infections emerge

**Latent or low-virulence
organism**



**Loss of cell-mediated
immune containment**



**Reactivation or
disseminated infection**

Organisms may persist
despite previous immune
control

Advanced CD4+ T-cell
dysfunction reduces
pathogen surveillance

Organ-specific symptoms
or multi-organ disease
become clinically apparent

Sources of infection in AIDS

Reactivation of latent infection

- Pneumocystis jirovecii (source describes reactivation)
- Cytomegalovirus or herpesviruses
- Tuberculosis and toxoplasmosis

Opportunistic exposure / acquisition

- Environmental fungi and other microorganisms
- Enteric protozoa and bacteria
- Primary infection can occur despite previous immune history

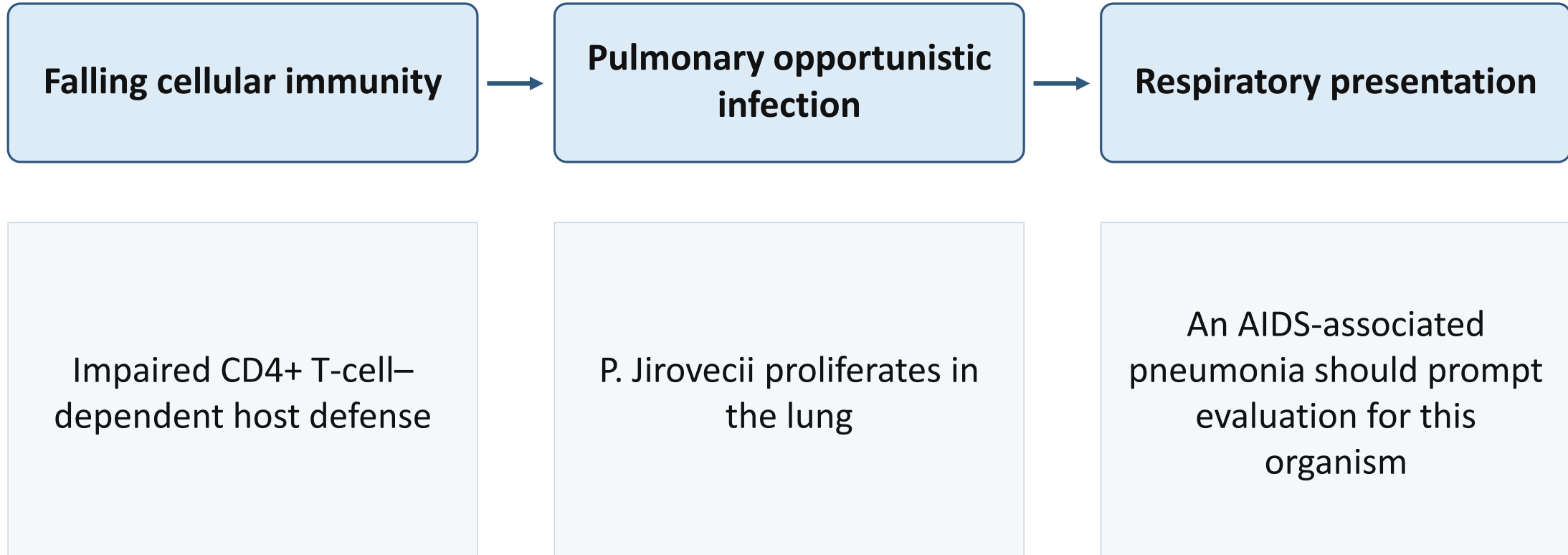
Recognize infections by target organ

Predominant syndrome	Key source-listed pathogens	Clinical pointer
Lung	Pneumocystis; Mycobacterium tuberculosis	Pneumonia; Tuberculosis may disseminate
CNS	Cryptococcus; Toxoplasma; JC virus	Meningitis; Encephalitis/mass; PML
Eye / gut	Cytomegalovirus	Retinitis; Esophagitis; Colitis
Oral / esophageal	Candida; HSV	Candidiasis; Mucocutaneous ulcers
Intestine	Cryptosporidium; Cystoisospora; Microsporidia	Persistent watery diarrhea

Pneumocystis pneumonia remains a classic AIDS complication

- Pneumocystis jirovecii causes pneumonia in advanced cellular immune deficiency.
- A 15–30% cumulative occurrence in untreated HIV infection.
- Before effective ART, the infection was an initial manifestation in about 20% of cases.
- ART responders now experience substantially less Pneumocystis pneumonia.

Pneumocystis: Clinicopathologic reasoning



Candida: Oral disease as a warning sign

- Candidiasis is the most common fungal infection described in AIDS by Robbins.
- Common sites are the oral cavity, vagina and esophagus.
- In previously asymptomatic HIV infection, oral candidiasis suggests immune deterioration.
- Esophageal candidiasis is an AIDS-indicator condition in the source surveillance table.

Mucosal and invasive candidiasis

Mucosal involvement

- Oral, vaginal and esophageal disease predominate.
- Reflects deficient mucosal host defense.
- Oral involvement may signal progression.

Invasive disease

- Relatively infrequent in AIDS alone.
- More likely with drug-related neutropenia.
- Indwelling catheters add risk.

Cytomegalovirus: Severe immunosuppression

- CMV can cause disseminated disease or organ-restricted eye and gastrointestinal infection.
- CMV retinitis occurs almost exclusively with CD4+ T-cell counts below 50 cells/ μ L.
- Retinitis in roughly one quarter of cases historically, with major ART-era decline.
- A visual complaint in advanced AIDS raises concern for CMV retinitis.

CMV disease: Retina and gastrointestinal tract

Retinal disease

- Chorioretinitis / retinitis
- Predominantly severe CD4+ T-cell depletion
- Once frequent; Now much reduced with ART

Gastrointestinal disease

- Esophagitis or colitis
- Colitis may produce multiple mucosal ulcers
- Reported in 5–10% of cases in source-era cohorts

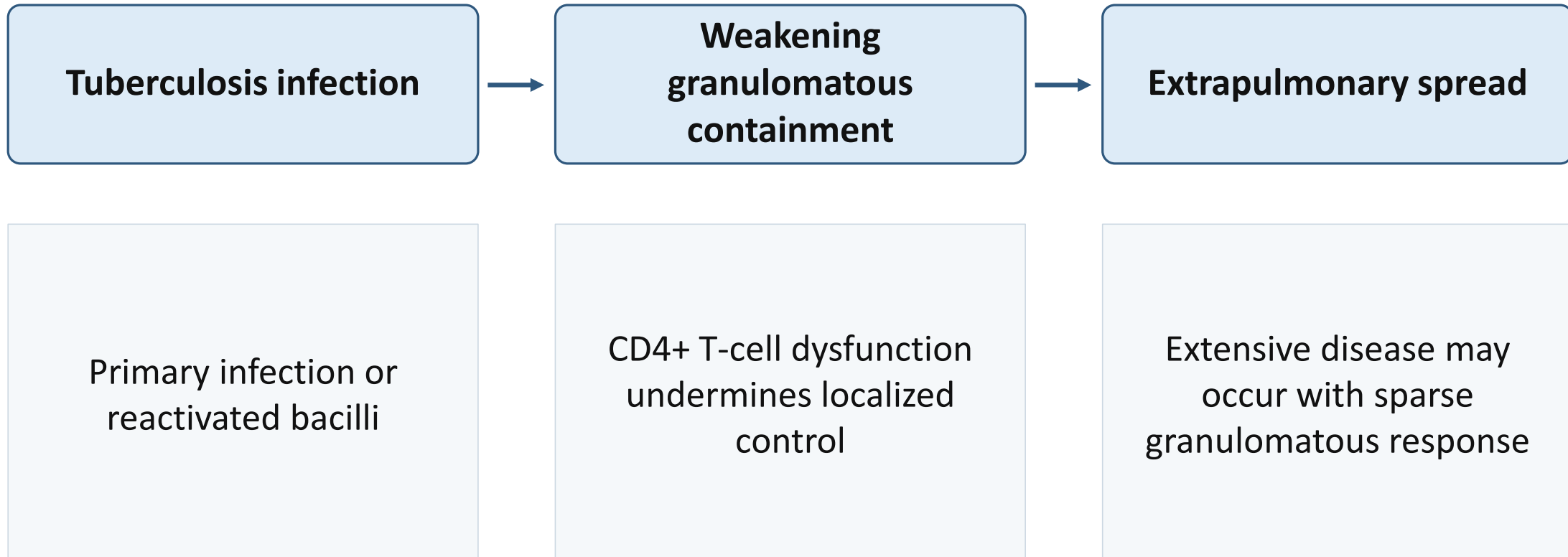
Mycobacterial disease: Tuberculosis versus MAC

Feature	M. Tuberculosis	M. Avium-intracellulare complex
Timing	Can appear earlier in AIDS	Usually late, marked immune deficiency
Origin	Primary infection or reactivation	Disseminated opportunistic infection
Distribution	Pulmonary or multiple organs	Systemic dissemination emphasized
Important distinction	Drug resistance is a concern	Severity reflects profound immunosuppression

Tuberculosis in patients with AIDS

- HIV increases susceptibility to both new tuberculosis and reactivation of latent infection.
- The lung may be the only site, or infection may involve multiple organs.
- Dissemination becomes more likely as CD4+ T-cell depletion worsens.
- Tuberculosis as a major contributor to global AIDS deaths.

TB dissemination tracks impaired cellular immunity



MAC: A late disseminated opportunistic infection

- Atypical mycobacterial infection is most closely associated with advanced AIDS.
- M. Avium-intracellulare complex as the principal example.
- Dissemination distinguishes the usual AIDS presentation from a localized process.
- A late systemic presentation should prompt consideration of severe immunodeficiency.

Cryptococcus: Meningitis is the dominant syndrome

- *Cryptococcus neoformans* is a major opportunistic fungal pathogen.
- The characteristic AIDS presentation is cryptococcal meningitis.
- Cryptococcosis in about 10% of historical AIDS cases.
- Clinical involvement reflects failure to contain infection within the CNS.

Toxoplasma: A major cause of AIDS brain masses

- Toxoplasma gondii causes encephalitis in advanced HIV infection.
- The source attributes approximately half of CNS mass lesions in AIDS to toxoplasmosis.
- A focal CNS lesion must be distinguished from other infection and neoplasia.
- The clinical problem combines immune status, neuroanatomic findings and tissue diagnosis when needed.

JC virus: Progressive multifocal leukoencephalopathy

- JC virus is classified as a human papovavirus in the source text.
- In HIV infection it causes progressive multifocal leukoencephalopathy (PML).
- PML is an important CNS opportunistic infection rather than a tumor.
- Robbins locates further CNS pathology details in the nervous system chapter.

CNS opportunistic infections: Syndrome recognition

Agent	Syndrome emphasized by Robbins	Distinguishing clue
Cryptococcus neoformans	Meningitis	Meningeal presentation
Toxoplasma gondii	Encephalitis / mass lesion	Focal mass-effect presentation
JC virus	PML	Progressive demyelinating syndrome
CMV	Possible CNS infection	Profound immunosuppression context

Herpes simplex virus: Extensive mucosal ulcers

- HSV may produce ulceration of oral and esophageal mucosa.
- Genital and perianal mucocutaneous sites are also commonly involved.
- Distribution can involve multiple sites in a severely immunosuppressed patient.
- Persistent or atypical ulcers should be investigated for an infectious cause.

Chronic watery diarrhea: Protozoal infections

- *Cryptosporidium* and *Cystoisospora belli* are prominent protozoal causes.
- Microsporidia are additional opportunistic intestinal pathogens.
- Untreated advanced AIDS may produce profuse, persistent watery diarrhea.
- Fluid loss can be substantial and makes the illness clinically consequential.

Diarrhea: Protozoal versus bacterial possibilities

Protozoal / microsporidial

- Cryptosporidium
- Cystoisospora belli
- Microsporidia

Bacterial / mycobacterial

- Salmonella
- Shigella
- M. Avium-intracellulare

Additional source-listed AIDS infections

Microbial group	Examples	AIDS-indicator manifestation
Fungal	Histoplasma; Coccidioides	Disseminated infection
Bacterial	Nocardia	Pneumonia, meningitis or disseminated disease
Bacterial	Salmonella	Disseminated infection
Viral	Varicella-zoster virus	Localized or disseminated infection

AIDS surveillance infections: Category map

Group	Organisms Table 6.16	Illustrative site
Protozoa / related	Cryptosporidium; Cystoisospora; Toxoplasma; Pneumocystis	Enteritis; Brain; Lung
Fungi	Candida; Cryptococcus; Histoplasma; Coccidioides	Esophagus; CNS; Systemic
Bacteria	Mycobacteria; Nocardia; Salmonella	Systemic or focal infection
Viruses	CMV; HSV; VZV; JC virus	Retina, gut, mucosa, CNS

AIDS indicators are context-specific

- The source reproduces a historic CDC clinical-category framework (A, B and C).
- Category C encompasses AIDS indicator infections, neoplasms and neurologic conditions.
- The older source table also stratifies CD4+ T-cell categories.
- This historical classification should not be presented as a verified current surveillance rule.

AIDS-associated tumor biology: Three linked processes

Chronic viral infection

Loss of effective immune control

Clonal neoplastic proliferation

HHV8, EBV and oncogenic HPV can persist in hosts

Defective cell-mediated surveillance permits infected-cell expansion

Additional growth and genetic events contribute to malignancy

Major AIDS-associated tumors and viral associations

Tumor / lesion	Virus emphasized	Clinicopathologic consequence
Kaposi sarcoma	HHV8 / KSHV	Vascular spindle-cell lesions
Aggressive B-cell lymphoma	EBV in a subset; HHV8 in selected types	Often extranodal
Cervical squamous carcinoma	Oncogenic HPV	Precursor squamous lesions
Anal squamous carcinoma	Oncogenic HPV	HPV-driven epithelial neoplasia

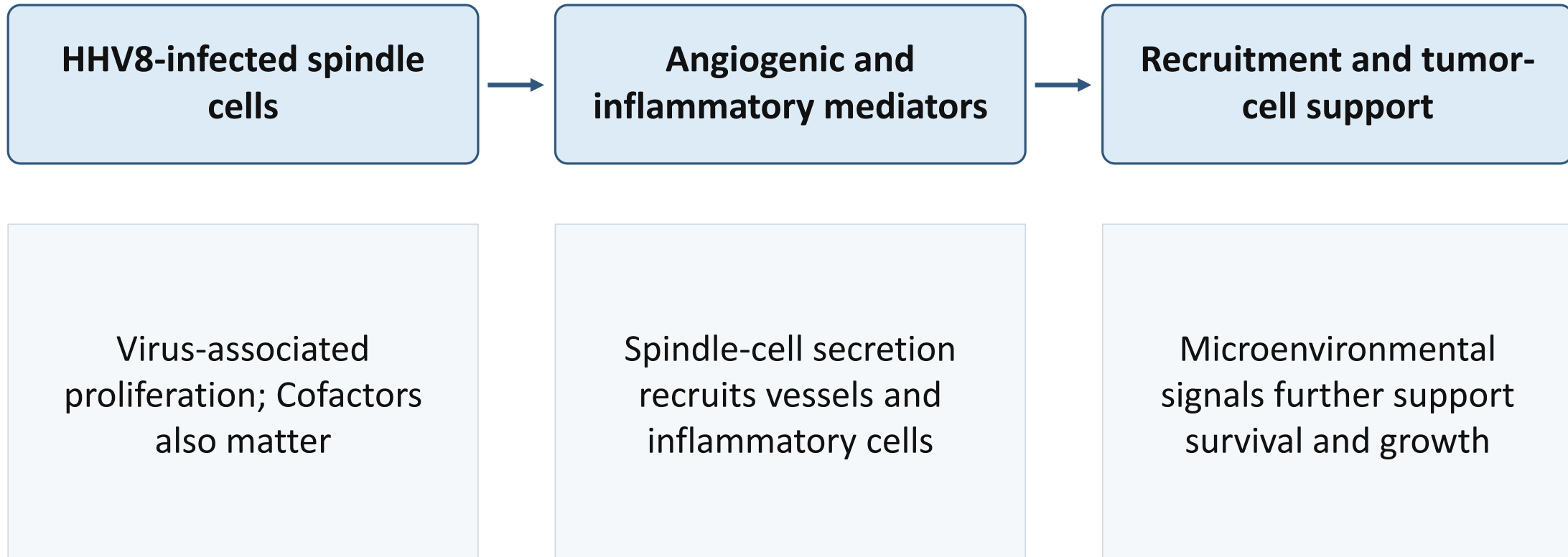
Kaposi sarcoma: Characteristic epidemiology

- KS is strongly associated with infection by human herpesvirus 8.
- AIDS-associated disease can involve skin, mucosal surfaces and visceral organs.
- The source describes a dramatic incidence decline in regions with effective ART.
- KS remains prominent where HIV disease is frequent and inadequately treated.

Kaposi sarcoma morphology: An interpretive checklist

Component	Source-described finding	Interpretation
Tumor cells	Proliferating spindle-shaped cells	Vascular/mesenchymal phenotype
Vascular spaces	Numerous slit-like channels	Angiogenic architecture
Inflammation	Lymphocytes and macrophages	Reactive microenvironment
Clonality	Polyclonal/oligoclonal in many lesions	Growth biology may be heterogeneous

Kaposi sarcoma: A self-reinforcing microenvironment



HHV8 is necessary but not sufficient for KS

- HHV8 infection causally established in Kaposi sarcoma.
- Latent viral proteins may stimulate proliferation and reduce apoptosis.
- Additional cofactors are required; AIDS-associated immunosuppression is important.
- The precise sequence of all HHV8-dependent transforming events remains incompletely understood.

Disseminated Kaposi sarcoma: Anatomic extent

Site	Expected clinical context	Teaching implication
Skin / mucosa	Visible vascular lesions	May be multisite
Gastrointestinal tract	Visceral involvement	External disease does not establish full extent
Lymph nodes	Nodal involvement	Evaluate multisystem spread
Lungs	Pulmonary involvement	Visceral presentation may dominate

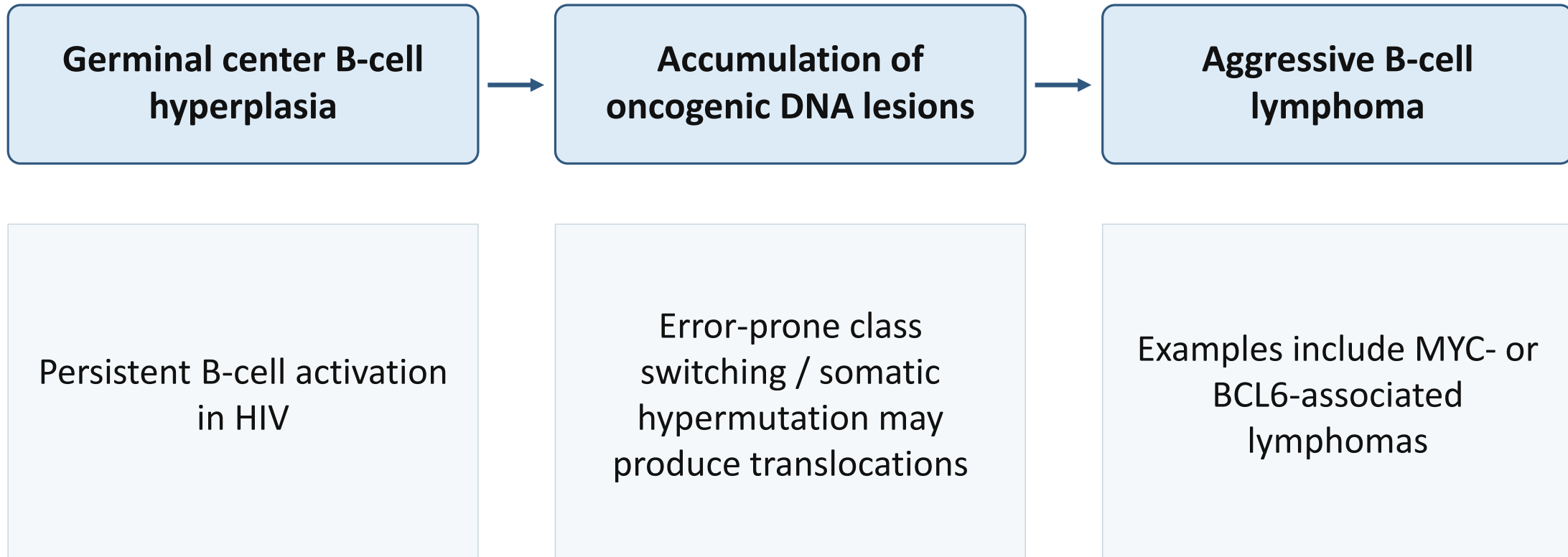
HHV8 also participates in B-cell disease

- HHV8 can be present in the B-cell compartment, not only endothelial-lineage lesions.
- Primary effusion lymphoma is an HHV8-associated neoplasm.
- Multicentric Castleman disease is an HHV8-linked B-cell lymphoproliferative disorder.
- The association is distinct from the vascular phenotype of KS.

Lymphoma is an important AIDS-associated malignancy

- Lymphomas are predominantly derived from transformed B cells.
- Roughly 5% of AIDS patients present with lymphoma and another 5% develop it later.
- The source estimates a markedly increased risk of aggressive B-cell lymphoma and Hodgkin lymphoma.
- ART reduced incidence in some populations, but residual risk persists.

Two complementary paths to HIV-associated B-cell lymphoma



Virus-driven lymphoma: Loss of immune surveillance

Latent EBV / HHV8 in B cells



CD8+ T-cell control becomes inadequate



Expansion of virus-infected B-cell clones

Oncogenic viruses can persist without clinical lymphoma

Cell-mediated immunity ordinarily restrains proliferation

Additional mutations enable malignant outgrowth

Germinal-center activation creates genetic risk

- Early HIV infection may produce marked germinal-center B-cell hyperplasia.
- Class-switch recombination and somatic hypermutation involve DNA damage.
- Activation-induced cytidine deaminase participates in these error-prone reactions.
- Aberrant oncogene/Ig-locus rearrangement can contribute to Burkitt or large B-cell lymphoma.

EBV-related aggressive lymphoma in AIDS

- Failure of T-cell surveillance allows EBV-infected B cells to expand.
- Immune activation and cytokines, including IL-6, may support proliferation.
- Successive mutations can convert proliferating clones into malignant lymphoma.
- Frequent extranodal sites include CNS, gut, orbit and lung.

HIV-associated lymphoma: Viral and nonviral pathways

Virus-associated tumors

- EBV-positive aggressive B-cell lymphomas
- HHV8-associated primary effusion lymphoma
- EBV-associated Hodgkin lymphoma

Not necessarily virus-associated

- Burkitt lymphoma with MYC rearrangement
- Large B-cell lymphoma with BCL6 rearrangement
- May arise despite preserved CD4+ T-cell counts

Primary effusion lymphoma: Distinctive presentation

- Primary effusion lymphoma usually presents as a malignant body-cavity effusion.
- HHV8 infection is a defining viral association in the source.
- Tumor cells often harbor both HHV8 and EBV.
- This illustrates oncogenic cooperation between two persistent viruses.

HIV-associated Hodgkin lymphoma

- Hodgkin lymphoma incidence is elevated in HIV infection.
- The source reports EBV within Reed–Sternberg cells in virtually all HIV-associated cases.
- Low CD4+ T-cell counts are present in many, but not all, patients.
- Its reactive inflammatory background contrasts with the neoplastic B-cell component.

Oral hairy leukoplakia is EBV-associated

- EBV can drive squamous epithelial proliferation in the oral mucosa.
- The resulting white projections commonly involve the tongue.
- It is distinct from Candida infection despite both appearing as oral white lesions.
- Oral lesions can provide important clues to the underlying immune defect.

White oral lesions: Two infectious mechanisms

Candidiasis

- Fungal mucosal infection
- Can signal immunologic deterioration
- Oral and esophageal involvement are common

Hairy leukoplakia

- EBV-driven squamous proliferation
- Projections on the tongue
- A virus-associated epithelial lesion

HPV-associated carcinomas in HIV infection

- Invasive cervical cancer and anal cancer are AIDS-associated epithelial neoplasms.
- Oncogenic HPV is central to the pathogenesis of these tumors.
- Immune deficiency weakens control of HPV-infected epithelial cells.
- Clinical consequences include precursor lesions and invasive carcinoma.

HIV–HPV interaction: Epithelial neoplasia risk

Persistent oncogenic HPV



**Deficient immune
surveillance**



**Squamous precursor
lesion → carcinoma**

Persistent virus-infected
squamous epithelium

Lower CD4+ T-cell counts
correlate with elevated
lesion frequency

Progression risk can be
accelerated in HIV
infection

Cervical squamous intraepithelial lesions

- Increased frequency of cervical squamous intraepithelial lesions in HIV-infected females.
- Precursor lesions are especially prevalent in women with lower CD4+ T-cell counts.
- The source describes accelerated progression from precursor lesion to carcinoma.
- Gynecologic examination is therefore emphasized in routine care.

AIDS-associated tumors: Practical distinction

Disease	Primary tissue phenotype	Pathogenetic association
Kaposi sarcoma	Spindle-cell / vascular proliferation	HHV8, plus host cofactors
B-cell lymphoma	Lymphoid neoplasm	B-cell hyperplasia ± EBV/HHV8
Cervical cancer	Squamous epithelial malignancy	Oncogenic HPV
Anal cancer	Squamous epithelial malignancy	Oncogenic HPV

Neurologic involvement may be the earliest clinical clue

- Neurologic disease is common in advanced HIV infection.
- Neurologic manifestations can precede recognition of the underlying infection.
- The source reports substantial clinical and autopsy involvement in historical AIDS cohorts.
- The differential includes direct HIV-related injury, infections and neoplasms.

CNS disease: Major mechanistic categories

Category	Examples	Clinical implication
Direct / immune-mediated	HIV-associated neurocognitive disorder	Progressive cognitive dysfunction
Opportunistic infection	Cryptococcus; Toxoplasma; JC virus	Meningitis; Mass lesion; PML
Neoplasm	Primary CNS lymphoma	Space-occupying disease
Other HIV-associated	Aseptic meningitis; Myelopathy; Neuropathy	Diverse neurologic syndromes

HIV-associated neurocognitive disorder

**HIV-infected microglial
compartment**



**Local immune response in
CNS**



**Progressive
encephalopathy**

Brain-resident myeloid
lineage is implicated

Neuroinflammation can
amplify damage

Cognitive impairment may
be a major clinical
manifestation

Additional HIV-related neurologic manifestations

- A self-limited meningoencephalitis may accompany early seroconversion.
- Aseptic meningitis is another recognized HIV-related manifestation.
- Vacuolar myelopathy and peripheral neuropathies broaden the neurologic spectrum.
- Opportunistic CNS infections and neoplasms remain distinct diagnostic categories.

AIDS morphology is not individually pathognomonic

- Opportunistic infections, Kaposi sarcoma and B-cell lymphoma dominate pathologic findings.
- None of these lesions by itself is uniquely restricted to HIV infection.
- The immune status and pattern of concurrent lesions are clinically informative.
- Robbins refers detailed organ-specific pathology to other chapters.

Lymph node evolution: Early versus advanced HIV

Early lymph node

- Marked B-cell follicular hyperplasia
- Large, irregular or serpiginous germinal centers
- Thinned mantle zones and expanded follicles

Late lymph node

- Severe lymphoid depletion and involution
- Disrupted follicular dendritic-cell network
- Hyalinized germinal centers / atrophic nodes

Early lymphadenopathy reflects polyclonal B-cell activation

Chronic antigenic stimulation



Germinal-center hyperplasia



Enlarged lymph nodes

HIV-associated immune dysregulation stimulates B cells

Prominent follicles can impinge on T-cell regions

Morphology mirrors clinical generalized lymphadenopathy

Late lymphoid involution: Loss of immune architecture

- Progression may replace follicular hyperplasia with marked tissue atrophy.
- FDC networks become disorganized, and germinal centers may be hyalinized.
- Lymph nodes may contain opportunistic organisms within macrophages.
- Spleen and thymus may also become severely lymphocyte-depleted.

In advanced AIDS, inflammation can be deceptively sparse

- Profound CD4+ T-cell deficiency alters the expected tissue response to infection.
- Mycobacteria may fail to produce well-formed granulomas.
- Lymph nodes and involved organs may appear unexpectedly hypocellular.
- Special stains can be necessary to demonstrate microorganisms.

Mycobacterial infection: Differing tissue reactions

Immune-competent setting

- Activated cell-mediated response
- Granulomatous inflammation can contain bacilli
- Organized host reaction is often recognizable

Advanced AIDS

- Deficient CD4+ T-cell response
- Granulomas may be poorly formed or absent
- High organism burden may be subtle on routine stains

How ART reverses the AIDS trajectory

Suppress viral replication



Halt progressive CD4+ T-cell loss



Gradual immune recovery

Multidrug regimens
interrupt different HIV
lifecycle steps

Sustained viral control
limits further immunologic
injury

Peripheral CD4+ T-cell
counts may rise over years

ART reduces classic AIDS morbidity

- Effective regimens combine active drugs to limit emergence of resistance.
- The source describes durable viral suppression while effective treatment continues.
- Pneumocystis disease and Kaposi sarcoma became much less frequent in effectively treated populations.
- Prevention of HIV transmission is an additional public-health benefit.

Viral suppression is not eradication

- HIV DNA persists within lymphoid tissues despite successful treatment.
- A sustained undetectable plasma viral load does not establish virologic cure.
- The source notes viral rebound after treatment discontinuation.
- Persistent reservoirs are a fundamental reason long-term management remains necessary.

Immune reconstitution inflammatory syndrome (IRIS)

**Severe immune depletion
before ART**



**ART-induced immune
restoration**



**Inflammatory clinical
deterioration**

High residual burden of
microbial antigens can
persist

CD4+ counts rise as viral
load declines

Dysregulated immune
responses can reveal or
exacerbate inflammatory
illness

IRIS: Identify the paradox

- Clinical worsening can occur after ART is started in patients with advanced immunosuppression.
- This may coincide with rising CD4+ T cells and falling HIV viral load.
- Excessive response to persistent microbial antigens.
- Deterioration alone should not automatically be interpreted as ART virologic failure.

Long-term ART: Adverse effects in the source

Domain	Examples listed by Robbins	Clinical consequence
Adipose distribution	Lipoatrophy; Central fat accumulation	Altered body fat phenotype
Metabolic	Dyslipidemia; Insulin resistance	Metabolic risk
Neurologic	Peripheral neuropathy	Nervous system morbidity
Organ toxicity	Cardiac, renal and hepatic effects	Long-term monitoring concerns

Non-AIDS morbidity becomes prominent with longer survival

- Effective ART extends survival and frequently restores peripheral CD4+ T-cell counts.
- Cancer and cardiovascular, kidney and liver disease become important morbidity drivers.
- The mechanisms are incompletely understood in the source.
- Persistent inflammation and residual immune dysfunction are proposed contributors.

Clinical reasoning: Progression versus immune recovery

Uncontrolled HIV / AIDS progression

- Falling CD4+ T-cell counts
- Opportunistic infection or neoplasm
- Uncontrolled or increasing HIV replication

Immune restoration with IRIS

- ART-associated falling viral load
- Rising CD4+ T-cell counts
- Inflammatory exacerbation despite virologic improvement

Case: Fever, weight loss and chronic diarrhea

A patient with advanced, untreated HIV has weight loss, persistent fever, and profuse watery diarrhea.

Organism groups to consider

- Cryptosporidium or Cystoisospora
- Microsporidia; Enteric bacteria
- Disseminated mycobacterial infection

Case: Focal brain lesion in advanced AIDS

A patient with advanced HIV infection develops a focal neurologic syndrome and a brain mass lesion.

Source-based major considerations

- Toxoplasma encephalitis
- Primary CNS lymphoma
- Other causes require independent assessment

Case: Oral white lesion

A person with HIV develops a white lesion on the tongue; The source provides two biologically distinct causes.

Differential to articulate

- Candida-associated mucosal infection
- EBV-driven oral hairy leukoplakia
- Site, morphology and tests help distinguish them

Case: Lymph node biopsy

An enlarged node in an earlier HIV phase shows exuberant large follicles; In a later phase another biopsy is hypocellular.

Expected interpretation

- Early: Polyclonal B-cell stimulation
- Late: Lymphoid involution and FDC damage
- Late opportunists may need special stains

Syndrome-to-pathogen review

Presentation	Important association	Underlying theme
Pneumonia	Pneumocystis jirovecii	Compromised cellular immunity
Retinitis	Cytomegalovirus	Very low CD4+ counts
Meningitis	Cryptococcus neoformans	CNS opportunistic fungus
Focal CNS mass	Toxoplasma; Lymphoma differential	Opportunism or neoplasia
Visceral vascular lesions	Kaposi sarcoma / HHV8	Impaired tumor-virus surveillance

Integrated clinical conclusions

- AIDS manifests as progressive immune failure with infections, selected neoplasms and neurologic syndromes.
- Site and tempo help prioritize infectious differential diagnoses.
- HHV8, EBV and HPV link deficient viral immune surveillance to malignancy.
- ART alters the disease spectrum but does not eliminate viral reservoirs or chronic morbidity.

Reference and interpretive limits

- Primary source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed., Chapter 6, pp. 226–230.
- Context: preceding “Natural History of HIV Infection” section, pp. 224–226.
- The clinical frequency estimates reflect the cohorts and treatment context cited in that edition.
- This pathology lecture is not a current HIV treatment or surveillance manual.