HEMATOLOGY & INFECTIOUS DISEASE REFERENCE

AIDS-Related Lymphoma (ARL)

Pathophysiology, Histologic Subtypes, Clinical Presentation, and Contemporary Management

AIDS-Related Lymphoma (ARL) encompasses a heterogeneous group of aggressive lymphoid malignancies occurring in individuals infected with Human Immunodeficiency Virus (HIV). Non-Hodgkin lymphoma (NHL) is an AIDS-defining malignancy and remains a leading cause of cancer-related morbidity and mortality in people living with HIV (PLWH), even in the era of effective combination antiretroviral therapy (cART).

> **Clinical Paradigm Shift:** Prior to cART, severe immunosuppression precluded standard-dose chemotherapy, resulting in poor survival. Today, concurrent administration of cART alongside full-dose, curative-intent chemoimmunotherapy yields survival rates in PLWH that approach those of the HIV-negative population.

1. Pathogenesis & Oncogenic Mechanisms

Lymphomagenesis in HIV infection is driven by a multifactorial interplay between progressive loss of cell-mediated immunity, chronic antigenic stimulation, cytokine dysregulation, and co-infection with oncogenic herpesviruses. Notably, HIV does not directly infect malignant B-cells; rather, it creates a permissive microenvironment.

- **Loss of T-Cell Immunosurveillance:** Depletion and functional exhaustion of CD4+ helper T-cells impair cytotoxic CD8+ T-cell control over latently infected B-lymphocytes, allowing unchecked clonal proliferation.
- **Chronic B-Cell Hyperactivation:** HIV envelope proteins (such as gp120) and elevated pro-inflammatory cytokines (IL-6, IL-10) drive polyclonal B-cell activation. This increases somatic hypermutation and class-switch recombination errors, promoting chromosomal translocations (e.g., *MYC*, *BCL2*, *BCL6*).
- **Epstein-Barr Virus (EBV):** Present in 40% to 100% of ARLs depending on subtype. EBV expresses latent membrane proteins (LMP1, LMP2A) and nuclear antigens (EBNA) that mimic CD40 and B-cell receptor signaling, inhibiting apoptosis and driving transformation.
- **Kaposi Sarcoma-Associated Herpesvirus (KSHV / HHV-8):** Strongly linked to specific rare subtypes (Primary Effusion Lymphoma and Multicentric Castleman Disease-associated plasmablastic lymphoma) via viral homologs of cyclin D (v-cyclin) and IL-6 (vIL-6).

2. Major Histologic Subtypes

Over 95% of AIDS-related lymphomas are of B-cell origin, predominantly high-grade aggressive subtypes. Hodgkin lymphoma (cHL), while not formally an AIDS-defining condition, also occurs at a 5- to 15-fold higher incidence in PLWH.

Subtype	CD4+ Context	Viral Association	Key Pathologic & Clinical Features
Diffuse Large B-Cell Lymphoma (DLBCL)	Any CD4+ count (most common overall)	EBV+ in ~30–50% (higher in immunoblastic variant)	Most frequent ARL subtype (~45–50%). Frequently presents with advanced-stage disease (Ann Arbor III/IV) and prominent extranodal involvement (GI tract, liver, bone marrow).
Burkitt Lymphoma (BL)	Preserved CD4+ (>200 cells/μL)	EBV+ in ~30–40%	Accounts for ~20–30% of ARL. Characterized by t(8;14) *MYC* translocation, starry-sky histology, Ki-67 near 100%, rapid tumor doubling time, high risk of tumor lysis syndrome (TLS), and CNS spread.
Primary CNS Lymphoma (PCNSL)	Severe depletion (<50 cells/μL)	EBV+ in ~100%	Confined to brain parenchyma, leptomeninges, eyes, or spinal cord. Presents with focal neurological deficits, confusion, or seizures. Ring-enhancing lesions on MRI; must distinguish from cerebral toxoplasmosis.
Plasmablastic Lymphoma (PBL)	Low CD4+ (<200 cells/μL)	EBV+ in ~70–80%; occasional HHV-8	Aggressive neoplasm with immunoblastic morphology and plasma cell immunophenotype (CD20−, CD38+, CD138+, MUM1+). Classic predilection for the oral cavity and jaw, followed by GI tract.
Primary Effusion Lymphoma (PEL)	Severe depletion (<100 cells/μL)	HHV-8+ (100%); EBV+ (~70–80%)	Presents as malignant lymphomatous effusions in body cavities (pleural, pericardial, peritoneal) typically without a contiguous solid tumor mass. Often lacks pan-B-cell markers (CD19−, CD20−).

3. Clinical Presentation & Diagnostic Workup

Unlike sporadic lymphoma in HIV-negative hosts, ARL commonly manifests at an advanced stage with aggressive clinical kinetics and unusual anatomical distribution.

- **Constitutional ("B") Symptoms:** Unexplained fever (>38°C), drenching night sweats, and unintentional weight loss (>10% body weight over 6 months) occur in up to 70–80% of patients and must be carefully distinguished from opportunistic infections.
- **Extranodal & CNS Tropism:** Over 75% of patients present with extranodal disease at diagnosis. Common sites include the gastrointestinal tract (bleeding, obstruction, perforation), bone marrow (cytopenias), liver, and central nervous system (leptomeningeal or parenchymal involvement in 10–20%).
- **Tissue Diagnosis:** Excisional or incisional lymph node biopsy (or core needle biopsy of an extranodal mass) is mandatory for accurate histopathologic, immunohistochemical, and cytogenetic (FISH for *MYC*, *BCL2*, *BCL6*) classification. Fine-needle aspiration alone is insufficient.

- **Staging & Baseline Evaluation:** Whole-body ^{18}F-FDG PET/CT scan, bone marrow aspirate and trephine biopsy, diagnostic lumbar puncture (cytology and flow cytometry, mandatory for Burkitt lymphoma and high-risk DLBCL), baseline HIV viral load, CD4+ T-cell count, and serologies for Hepatitis B (HBV) and Hepatitis C (HCV).

4. Principles of Treatment & Supportive Care

Modern management integrates systemic chemoimmunotherapy with uninterrupted HIV suppression and rigorous infection prophylaxis.

Systemic Chemoimmunotherapy

- **DLBCL:** Infusional **EPOCH-R** (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, plus rituximab) or standard **R-CHOP**. Rituximab is routinely incorporated for CD20+ lymphomas, though careful monitoring for infectious complications is required when CD4+ counts are <50 cells/μL.
- **Burkitt Lymphoma:** Dose-adjusted **DA-EPOCH-R** (with intrathecal CNS prophylaxis) offers high cure rates with lower treatment-related toxicity compared to intensive regimens like CODOX-M/IVAC.
- **Plasmablastic & Primary Effusion Lymphoma:** Because tumor cells typically lack CD20, rituximab is omitted. Regimens include dose-adjusted EPOCH, often combined with proteasome inhibitors (e.g., bortezomib) or autologous stem cell transplantation (ASCT) in fit patients.
- **Primary CNS Lymphoma:** High-dose intravenous methotrexate-based regimens combined with cART to restore anti-EBV T-cell immunity; whole-brain radiotherapy is generally deferred due to late neurotoxicity.

Concurrent Antiretroviral Therapy (cART) & Prophylaxis

- **Uninterrupted cART:** Antiretroviral therapy should be initiated or continued throughout chemotherapy to promote immune reconstitution and improve overall survival.
- **Drug-Drug Interactions:** Strong CYP3A4 inhibitors—specifically ritonavir and cobicistat—must be avoided during chemotherapy, as they markedly increase exposure to vinca alkaloids (severe neurotoxicity) and cyclophosphamide/etoposide. Unboosted integrase strand transfer inhibitors (e.g., dolutegravir, bictegravir, raltegravir) are preferred.
- **Opportunistic Infection & TLS Prophylaxis:** Mandatory prophylaxis against *Pneumocystis jirovecii* pneumonia (TMP-SMX) regardless of CD4+ count during chemotherapy, granulocyte colony-stimulating factor (G-CSF) support for neutropenia, antiviral suppression for HBV carriers (entecavir/tenofovir) to prevent rituximab-induced reactivation, and aggressive hydration with allopurinol or rasburicase for tumor lysis syndrome prevention.