e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(1); 462-466

Original Research Article

The Viral Contribution to Lymphoma: Pathogenesis, Diagnosis, and Therapeutic Opportunities

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Received: 01-10-2025 / Revised: 15-11-2025 / Accepted: 21-12-2025
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Conflict of interest: Nil

Abstract

Introduction: Several human viruses contribute directly or indirectly to lymphomagenesis by driving chronic antigenic stimulation, immune evasion, oncogenic signaling, and/or genomic instability. Epstein–Barr virus (EBV), Kaposi sarcoma herpesvirus (KSHV/HHV-8), human T-cell leukemia virus type 1 (HTLV-1), hepatitis C virus (HCV), and HIV (largely via immune dysregulation and cooperation with EBV/KSHV) represent the most clinically relevant viral associations in modern lymphoma classification.

Materials and Methods: A structured narrative review was performed using recent WHO/ICC classifications and post-2015 peer-reviewed literature addressing viral mechanisms, diagnostic approaches (histopathology, EBER-ISH, IHC, PCR/viral load, serology), and therapeutics including antivirals, immunotherapy, and adoptive cellular therapy.

Results: Viral-associated lymphomas show recognizable clinicopathologic patterns: EBV-associated B/T/NK lymphomas and PTLD; KSHV-driven primary effusion lymphoma and HHV8-associated large B-cell lymphomas; HTLV-1–driven adult T-cell leukemia/lymphoma; HCV-associated indolent B-cell lymphomas with potential regression after direct-acting antiviral therapy; and HIV-associated lymphomas influenced by immune suppression and high EBV/KSHV burden. Key therapeutic opportunities include etiologic viral suppression (HCV DAAs), immune reconstitution, targeted antibodies, checkpoint blockade in selected EBV-associated entities, and EBV-specific T-cell therapy (e.g., tabelecleucel) for EBV+ PTLD.

Conclusion: Integrating viral testing into lymphoma diagnostics improves classification, prognostication, and enables mechanism-based therapy—particularly antiviral cure for HCV-related lymphomas and cellular immunotherapy for EBV+ PTLD.

Keywords: Epstein–Barr virus; HHV-8/KSHV; HTLV-1; hepatitis C; HIV; lymphoma; EBER; PTLD; tabelecleucel; direct-acting antivirals.

DOI: 10.25258/ijcpr.18.1.75

Introduction

Lymphomas represent biologically diverse malignancies arising from B, T, or NK cells, and a substantial fraction are influenced by oncogenic viruses. Modern classifications explicitly recognize virus-driven or virus-enriched entities, reflecting the impact of viral latency programs, host immune status, and microenvironmental cues on disease phenotype. [1,2] Viral contributions to lymphomagenesis broadly fall into three categories: (i) direct transformation via viral oncogenes and latent gene expression (e.g., EBV, KSHV/HHV-8, HTLV-1), (ii) indirect oncogenesis through immune dysregulation and impaired tumor immune surveillance (notably HIV), and (iii) chronic antigenic stimulation leading to clonal B-cell expansion (classically HCV). [3–6] EBV is the most pervasive oncogenic virus linked to lymphoid malignancy. After primary infection, EBV establishes latency in B cells and can express distinct latency programs (I–III), each characterized by different sets of latent genes (e.g., EBNA, LMP1/LMP2) that promote cell survival, NF-κB signaling, and immune evasion. [7] EBV is implicated across a spectrum including Hodgkin lymphoma, Burkitt lymphoma, EBV+ diffuse large B-cell lymphoma (DLBCL), extranodal NK/T-cell lymphoma, and post-transplant lymphoproliferative disorders (PTLD), where iatrogenic immunosuppression permits expansion of EBV-infected clones. [1,7,8] KSHV/HHV-8 is essential for the diagnosis of primary effusion lymphoma (PEL) and is central to HHV8-associated

lymphoproliferative disorders that often emerge under immunodeficiency (HIV infection, transplantation), though cases also occur in immunocompetent hosts. [9,10] Viral proteins and cytokine dysregulation contribute to plasmablastic morphology, effusion-based presentation, and aggressive behavior in PEL. [9] HTLV-1, a retrovirus endemic in selected regions, drives adult T-cell leukemia/lymphoma (ATL) through long-term persistence, immune perturbation, and accumulation of host genetic/epigenetic alterations, producing a clinically aggressive malignancy with limited curative options beyond allogeneic transplantation in selected candidates. [11,12]

HCV-associated B-cell lymphomas highlight a clinically actionable viral–cancer relationship: eradication of HCV with direct-acting antivirals (DAAs) can induce hematologic responses, especially in indolent lymphomas, supporting causality and offering a low-toxicity therapeutic strategy in appropriate patients. [13,14] Finally, HIV increases lymphoma risk through CD4+ T-cell depletion, chronic B-cell activation, and diminished immune surveillance; EBV and KSHV frequently act as cooperating oncogenic drivers in HIV-associated lymphoma subtypes. [4,5]

Given these diverse mechanisms, virus-informed diagnosis is increasingly important—not only for accurate classification but also for enabling targeted interventions such as antiviral therapy, immune reconstitution, checkpoint blockade in select contexts, and EBV-specific adoptive cellular therapy in refractory EBV+ PTLD. [8,15]

Materials and Methods: Structured narrative review.

Data Sources: Key contemporary classification frameworks (WHO 5th edition; International Consensus Classification) and post-2015 peer-reviewed studies and reviews addressing viral pathogenesis, diagnostic standards, and therapeutics in virus-associated lymphomas.

Search Strategy (Conceptual): Search terms combined lymphoma subtypes with viral keywords (e.g., "EBV lymphoma EBER", "HHV-8 primary effusion lymphoma", "HTLV-1 adult T-cell leukemia/lymphoma", "HCV-associated indolent lymphoma direct acting antivirals", "HIV-associated lymphoma EBV KSHV") with emphasis on 2016 onward and inclusion of high-quality guidelines and trials.

Inclusion Criteria

1. Publications ≥2016 (2015 permitted only when essential background was unavoidable, but excluded from reference list per user requirement).
2. Human studies, consensus classifications, clinical trials, systematic reviews, and high-quality mechanistic reviews.
3. Clear linkage between a virus and lymphoma entity (causal or strongly enriched association), or clinically actionable diagnostic/therapeutic implications.
4. Articles detailing diagnostic methods (EBER in situ hybridization, viral IHC such as LANA-1 for HHV8, PCR/viral load assays) and/or therapeutic approaches (DAAs for HCV, anti-CD20 therapy/PTLD strategies, checkpoint inhibitors, adoptive EBV-specific T cells).

Exclusion Criteria

1. Case reports without broader clinical/diagnostic generalizability (unless addressing rare entities with otherwise limited literature).
2. Non-lymphoid malignancies without a lymphoma-relevant diagnostic or therapeutic translation.
3. Studies lacking clear virologic ascertainment (e.g., no EBER-ISH/IHC/PCR confirmation) for virus-associated claims.
4. Pre-2016 publications (to align with the "after 2015" reference requirement).

Data extraction and synthesis: Data were synthesized into: (i) virus–lymphoma mapping, (ii) dominant oncogenic mechanisms, (iii) diagnostic workflows and markers, and (iv) mechanism-based therapeutic opportunities, summarized in six publication-style tables.

Results

Table 1: Major virus-associated lymphomas and typical diagnostic virology

Virus	Key lymphoma/LPD entities (examples)	Hallmark virology in tissue
EBV	Classic Hodgkin lymphoma; EBV+ DLBCL; extranodal NK/T-cell lymphoma; PTLD; Burkitt lymphoma (subset)	**EBER-ISH+**; latency program varies; LMP1 often + in latency II/III
KSHV/HHV-8	Primary effusion lymphoma; HHV8+ DLBCL (NOS); germinotropic LPD; often linked with MCD spectrum	**LANA-1 IHC+** (defining); EBV co-positivity variable
HTLV-1	Adult T-cell leukemia/lymphoma	HTLV-1 proviral integration; serology/PCR supportive
HCV	Marginal zone lymphoma; lymphoplasmacytic lymphoma; DLBCL (subset)	HCV serology + RNA; lymphoma may respond to viral eradication
HIV (indirect)	DLBCL, Burkitt, primary CNS lymphoma, PEL, cHL in PWH	Often **EBV+** (many subtypes) and/or **KSHV+** in PEL

Contemporary classification highlights EBV and HHV-8 as direct oncogenic drivers in defined entities, while HCV provides a uniquely "treat-the-virus" paradigm in selected B-cell lymphomas.

Table 2: Core oncogenic mechanisms used by lymphoma-associated viruses

Virus	Dominant mechanisms relevant to lymphomagenesis
EBV	Latent proteins drive B-cell activation/survival (e.g., NF-κB signaling), immune evasion; latency program shapes phenotype
HHV-8	Viral latent proteins (e.g., LANA) maintain episomes; cytokine/IL-6 pathway effects; plasmablastic differentiation; synergy with immune deficiency
HTLV-1	Persistent provirus; Tax/HBZ-related immune dysregulation and oncogenic signaling; long latency with accumulation of host alterations
HCV	Chronic antigenic stimulation and inflammatory milieu; B-cell clonal selection; regression possible after viral cure
HIV	Reduced immune surveillance (CD4 depletion/dysfunction), chronic B-cell activation; facilitates EBV/KSHV-driven transformation

Mechanisms converge on sustained survival signaling and immune escape, explaining why immune status (HIV, transplant immunosuppression) strongly modulates incidence and behavior of virus-associated lymphomas.

Table 3: Practical diagnostic approach: tests and "what they answer"

Modality	What it detects	Best use-case
EBER in situ hybridization	EBV RNA in tumor cells	Gold standard for EBV association in tissue
LANA-1 immunohistochemistry	HHV-8 latent antigen	Defines HHV8-driven lymphoproliferations (e.g., PEL)
PCR / quantitative viral load	EBV DNAemia; HTLV-1 proviral load; HCV RNA	Risk stratification/monitoring (PTLD), supportive diagnosis
Serology	HCV exposure; HTLV-1 exposure	Screening and etiologic linkage
Flow cytometry / IHC panel	Lineage and phenotype	Integrates viral status with lymphoma subtype classification

Viral tests are not "add-ons"; they are classification-defining in HHV8 entities and often management-shaping in EBV PTLD and HCV-associated lymphomas.

Table 4: EBV latency patterns and typical lymphoma contexts (conceptual)

EBV latency	Key expressed genes (simplified)	Typical contexts
I	EBNA1 (restricted)	Burkitt lymphoma (subset)
II	LMP1/LMP2 + EBNA1	Hodgkin lymphoma; NK/T-cell lymphoma
III	Broad latent program (immunogenic)	PTLD; immunodeficiency-associated settings

Latency III is highly immunogenic, explaining why loss of immune control (post-transplant immunosuppression) strongly predisposes to EBV+ PTLD and why T-cell–based therapies are biologically rational.

Table 5: Therapeutic opportunities by virus and mechanism

Virus-driven setting	Core strategy	Examples
HCV-associated indolent B-cell lymphoma	**Eradicate virus**	DAAs as primary/adjunct therapy; hematologic responses reported
EBV+ PTLD	Reduce immunosuppression + anti-CD20 ± chemo; **EBV-specific cellular therapy** for refractory	Rituximab-based pathways; **tabelecleucel** (EU-approved)
EBV-associated lymphomas (selected)	Immunotherapy (context-dependent); investigational lytic induction + antivirals	Checkpoint blockade in selected EBV-enriched settings; trials ongoing
HHV8-associated lymphoproliferations	Treat underlying immunodeficiency; rituximab-based for HHV8 MCD spectrum; lymphoma-directed therapy for PEL	Rituximab improves outcomes in HHV8 MCD; PEL remains aggressive
HTLV-1 ATL	Multi-agent therapy + targeted agents; transplant in eligible; CCR4 targeting	Mogamulizumab (anti-CCR4) in ATL; allo-HSCT for cure in select

The most "actionable" viral links today are HCV (curative antivirals) and EBV PTLD (virus-specific cellular therapy), with HHV8 and HTLV-1 rapidly evolving toward immune/targeted strategies.

Table 6: Selected post-2015 clinical evidence highlighting virus-directed therapy

Virus/Entity	Intervention	Study type (year)	Key takeaway
EBV+ PTLD (R/R)	Tabelecleucel (EBV-specific T cells)	Phase 3 (2024)	Clinically meaningful responses in refractory disease
EBV+ PTLD	Risk stratification + multimodal management	Review/Update (2021–2023)	Emphasizes EBV DNAemia monitoring + stepwise therapy
HCV-associated lymphomas	DAAs (primary or combined with lymphoma therapy)	Prospective/observational (2018–2022)	Viral cure associated with lymphoma responses in selected patients
ATL (HTLV-1)	Mogamulizumab	Randomized/clinical evidence (2018+)	Demonstrates activity; immune context matters
HHV8 MCD spectrum	Rituximab-based	Reviews/guidance (2020–2021)	Rituximab + ART central in HIV-associated HHV8 MCD

Evidence is strongest where therapy targets the causal virus or restores virus-specific immunity (DAAs; EBV-specific T cells), supporting routine viral evaluation during diagnostic work-up.

Discussion

Our synthesis aligns with modern lymphoma frameworks that elevate viral status from an epidemiologic association to a diagnostic and therapeutic determinant. [1,2] EBV remains the most versatile viral driver, influencing B-cell, T-cell, and NK-cell neoplasms through latency-dependent gene expression that activates survival pathways and modulates immune recognition. [7,15]

Importantly, the immunogenicity of EBV latency programs provides a biological rationale for immune-based treatments. This is clearest in EBV+ PTLD, where loss of T-cell surveillance under immunosuppression permits outgrowth of EBV-infected clones; therefore, stepwise treatment prioritizes immune modulation (reduction of immunosuppression), anti-B-cell therapy (rituximab), and—when disease is refractory—restoration of EBV-specific immunity via adoptive T-cell therapy. [8,16] The conditional EU authorization of tabelecleucel (Ebvallo) and phase-3 efficacy data reinforce that "virus-specific cellular therapy" can be clinically scalable in ultra-rare, high-mortality settings. [17,18]

HHV-8-associated lymphoproliferative diseases exemplify viral oncogenesis in immunodeficiency, with entities such as PEL and HHV8+ DLBCL occupying a spectrum that overlaps clinically and pathologically. [9,10] Prior work emphasizes that HHV8 (LANA positivity) is classification-defining and that co-factors such as HIV, transplant status, and cytokine milieu shape presentations including effusion-based disease. [9,10] Similarly, HTLV-1–driven ATL illustrates long-latency retroviral oncogenesis in which persistent infection, immune dysregulation, and subsequent host genomic changes culminate in aggressive disease. [11,12] Contemporary studies highlight targeted approaches (e.g., CCR4-directed therapy) and the continued role of allogeneic transplant as the only potentially curative option for eligible patients. [19]

HCV-associated lymphoma is arguably the most therapeutically disruptive viral link in lymphoid oncology. Multiple post-2015 studies report that DAA-mediated HCV eradication is associated with hematologic responses in indolent B-cell lymphomas and may complement standard lymphoma therapy in aggressive subtypes, supporting a "treat the virus" strategy as part of lymphoma management in appropriate clinical contexts. [13,14,20] This contrasts with HIV-associated lymphomas, where modern antiretroviral therapy reduces—but does not eliminate—risk; EBV and HHV8 cooperation remains central, and outcomes are influenced by immune restoration and lymphoma-directed therapy. [4,5]

Overall, the field is moving from descriptive associations toward mechanism-based interventions: antiviral cure (HCV), virus-specific cellular therapy (EBV PTLD), and increasingly precise immune/targeted therapies in HTLV-1 and HHV-8 diseases. Future progress likely depends on standardized viral testing (tissue and blood), improved biomarkers of viral activity/latency, and combination regimens that simultaneously target tumor cell programs and the virus-shaped microenvironment. [1,15]

Conclusion

Virus-associated lymphomas represent a clinically meaningful subset where virologic evaluation improves classification, risk stratification, and enables targeted therapy. The strongest current examples of actionable viral oncology include

HCV eradication with DAAs for selected B-cell lymphomas and EBV-specific adoptive T-cell therapy for refractory EBV+ PTLD. Routine incorporation of viral tissue markers (EBER-ISH, LANA-1 IHC) and appropriate blood-based assays should be considered integral to lymphoma diagnostic pathways in modern practice.

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