

REVIEW ARTICLE

Beyond Epstein–Barr virus: Unveiling the role of herpesviruses in lymphoma pathogenesis

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Abstract

Beyond the well-documented oncogenic role of Epstein–Barr virus (EBV), a growing body of evidence implicates other herpesviruses, notably Kaposi's sarcoma-associated herpesvirus and human herpesvirus (HHV) 6, in the pathogenesis of specific lymphoma subtypes. HHV-7 has also been detected in lymphoma tissues, though its contribution remains less defined. This review systematically examines the epidemiological associations and experimental insights linking these non-EBV herpesviruses to lymphoid malignancies. The discussion delves into the molecular mechanisms through which virally encoded molecules influence critical cellular programs, including the modulation of immune responses, epigenetic reprogramming, and the induction of chronic inflammation. We also review how these viruses hijack multilayered cellular networks, such as nuclear factor kappa B and Janus Kinase/signal transducer and activator of transcription signaling, and reprogram cellular metabolism to support malignant growth. A critical re-evaluation of the evidence for HHV-7 positions it as a putative cofactor in lymphomagenesis, contingent on host immunosuppression, rather than a primary oncogenic driver, highlighting the current absence of proven causality and robust *in vivo* models. Furthermore, this review provides a structured overview of the clinical implications of these viral associations. We also outline the established diagnostic tools, such as immunohistochemistry and quantitative protein-coupled receptor (PCR), and emerging technologies such as droplet digital PCR and liquid biopsy that hold considerable promise to refine disease monitoring. Meanwhile, we delineate standard-of-care treatments for virus-associated lymphomas from promising investigational approaches, including virus-targeted interventions and novel immunotherapies, offering a framework for both current clinical practice and future research.

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1. Introduction

Viral infections are a significant factor in global human oncology, contributing to approximately 12–15% of all cancer cases worldwide.¹ Within this landscape, the family *Herpesviridae* holds a prominent position.^{2,3} These large, double-stranded DNA viruses are ubiquitous in the human population and are characterized by their ability to establish lifelong latent infections, a biological hallmark that underpins their oncogenic potential.⁴ For decades, Epstein–Barr virus (EBV or HHV-4) has served as the archetypal oncogenic herpesvirus, with its etiological role firmly established in a range of lymphoid malignancies, including Burkitt lymphoma, Hodgkin lymphoma, and post-transplant lymphoproliferative disorders (PTLD).^{5–13}

However, the spectrum of herpesvirus-associated lymphomagenesis extends well beyond EBV. A substantial body of epidemiological, molecular, and clinical data generated over the past three decades has illuminated the roles of other family members, most prominently Kaposi's Sarcoma-associated herpesvirus (KSHV, or HHV-8) and human herpesvirus 6 (HHV-6A/B).^{14,15} The clinical relevance of these viruses has become increasingly apparent in an era marked by the widespread use of immunomodulating therapies and the rising prevalence of conditions associated with profound immune dysfunction, such as human immunodeficiency virus (HIV) infection and solid-organ or hematopoietic stem cell transplantation.^{16,17} In these settings of compromised immune surveillance, the oncogenic pathways of otherwise controlled herpesviruses are often unknown, leading to the development of aggressive lymphomas.^{14,18}

This review aims to synthesize the current understanding of the role of non-EBV herpesviruses—specifically HHV-6, HHV-7, and KSHV/HHV-8—in the pathogenesis of lymphoma. We systematically assess the epidemiological links between each virus and specific lymphoma entities, dissect the molecular circuitry engaged by viral gene products, and critically evaluate the experimental evidence supporting their oncogenic roles. A particular focus will be placed on providing a nuanced and rigorous re-evaluation of the evidence concerning HHV-7, distinguishing circumstantial association from proven causality. Finally, we present a structured overview of the evolving diagnostic and therapeutic landscape, providing a coherent framework to guide clinicians and researchers in the management and investigation of these complex malignancies.^{16,19}

2. The HHV family: A biological overview

Members of the order *Herpesvirales* are large, enveloped viruses containing a double-stranded DNA

genome housed within an icosahedral capsid.²⁰ Nine herpesviruses are endemic in the human population and are classified into three subfamilies—alpha-, beta-, and gammaherpesvirinae—based on their genomic structure, cellular tropism, and biological properties.^{20,21}

- Alphaherpesvirinae (e.g., herpes simplex virus-1, herpes simplex virus-2, and varicella zoster virus) are characterized by rapid replication in epithelial cells and the establishment of latency in sensory neurons. They are seldom linked to neoplastic disease.²⁰
- Betaherpesvirinae (e.g., human cytomegalovirus/HHV-5, HHV-6A/B, and HHV-7) exhibit slower replication kinetics and establish latency in a variety of cell types, including mononuclear cells and secretory glands.²²
- Gammaherpesvirinae (e.g., EBV and KSHV/HHV-8) are distinctly lymphotropic, targeting B-cells, T-cells, and myeloid compartments. This subfamily possesses the most potent and well-documented oncogenic potential.⁵

The quintessential biological feature shared across the entire herpesvirus family is the establishment of a biphasic life cycle consisting of a dormant latent phase and a productive lytic phase.²³ During latency, the viral genome persists as a circular, extrachromosomal episome within the nucleus of the host cell.^{20,24} To minimize immune detection, viral gene expression is highly restricted to a small set of latency-associated transcripts, which include non-coding RNAs, microRNAs (miRNAs), and proteins essential for episome maintenance and host cell modulation.²⁵ These latent proteins are masterful manipulators of the host cell environment, actively remodeling chromatin and hijacking cellular machinery to ensure viral genome persistence and promote cell survival.^{24,26} Periodically, in response to various stimuli such as immunosuppression or cellular stress, the virus can switch to the lytic cycle. This phase is characterized by the coordinated expression of the full repertoire of viral genes, leading to viral DNA replication, assembly of new virions, and ultimately, lysis of the host cell.²⁴ This intermittent reactivation is critical for viral dissemination to new hosts and, in the context of oncogenesis, can contribute to a pro-inflammatory tumor microenvironment through paracrine signaling.²⁷

3. General mechanisms of viral oncogenesis

Unlike retroviruses, which can cause cancer through insertional mutagenesis, DNA tumor viruses such as herpesviruses primarily rely on a sophisticated array of non-mutagenic strategies to transform host cells and promote malignancy. These mechanisms are not mutually exclusive and often work in concert to satisfy the classical “Hallmarks of Cancer.”^{14,28}

3.1. Expression of viral oncogenes and molecular mimicry

Gamma- and betaherpesviruses encode a formidable suite of viral oncogenes, many of which are functional homologs or mimics of key cellular regulatory proteins. For instance, KSHV encodes a viral Cyclin (vCyclin) that binds and activates CDK6, bypassing the G1/S cell cycle checkpoint by phosphorylating the tumor suppressor retinoblastoma (Rb).²⁵ It also expresses a viral FLICE-inhibitory protein (vFLIP) that provides a potent anti-apoptotic signal by constitutively activating the nuclear factor kappa B (NF- κ B) survival pathway.²⁷ Furthermore, viral cytokines, such as KSHV's viral interleukin-6 (vIL-6), mimic the function of human interleukin (IL)-6, driving proliferative and prosurvival signaling through the Janus Kinase/signal transducer and activator of transcription (JAK/STAT) pathway, particularly via STAT3 phosphorylation.²⁵ Latency-associated proteins, such as KSHV's latency-associated nuclear antigen (LANA), serve a dual function: They tether the viral episome to host chromosomes during mitosis to ensure its faithful segregation to daughter cells, while simultaneously inhibiting the function of tumor suppressors like p53 and Rb.²⁵

3.2. Epigenetic reprogramming of the host genome

Herpesviruses are masters of epigenetic manipulation, inducing genome-wide alterations in DNA methylation and histone modifications to create a cellular environment favorable for both viral persistence and malignant transformation. Viral proteins directly interact with the host's epigenetic machinery. KSHV's LANA, for example, recruits the polycomb repressive complex 2, leading to the deposition of repressive H3K27me3 marks at host gene promoters, effectively silencing tumor suppressor loci.²⁵ Similarly, the HHV-6B U94 protein interacts with DNA methyltransferase 1, contributing to aberrant DNA methylation patterns.²⁴ Beyond proteins, virally encoded miRNAs play a crucial role. KSHV miR-K12-11, a functional mimic of the cellular oncomiR miR-155, targets and suppresses negative regulators of key signaling pathways, thereby reinforcing prosurvival signals and blocking apoptosis.²⁷

3.3. Metabolic rewiring to fuel malignant growth

To meet the high energetic and biosynthetic demands of both viral replication and uncontrolled cellular proliferation, herpesviruses extensively reprogram host cell metabolism. This metabolic rewiring often mirrors the Warburg effect seen in many cancers, characterized by a shift toward aerobic glycolysis. KSHV's lytic oncoprotein, viral G protein-coupled receptor (vGPCR), upregulates HIF-1 α , a master regulator of glycolysis, driving this metabolic shift.²⁷ Proteomic studies have shown that other viral proteins

directly interact with metabolic enzymes; KSHV ORF45 binds to the mitochondrial trifunctional protein, diverting fatty-acid oxidation toward lipogenesis to provide building blocks for new membranes.²⁷ Similarly, HHV-6A infection has been shown to increase glutaminolysis by upregulating the enzyme GLS1 via MYC, generating α -ketoglutarate to fuel the tricarboxylic acid cycle and supply substrates for epigenetic-modifying enzymes.²⁴

3.4. Chronic inflammation and microenvironmental remodeling

Persistent viral infection and sporadic lytic reactivation create a state of chronic inflammation that is highly conducive to lymphomagenesis. The release of viral components acts as pathogen-associated molecular patterns, which are recognized by pattern recognition receptors like Toll-like receptors on bystander immune cells.¹⁴ This triggers the production of a pro-inflammatory cytokine and chemokine milieu, rich in factors such as IL-6, IL-10, and tumor necrosis factor alpha.²⁷ This inflammatory environment acts in a paracrine fashion to promote the survival and proliferation of lymphocytes, creating a fertile ground for the accumulation of genetic and epigenetic alterations that can lead to malignant transformation. In KSHV-associated multicentric Castleman disease (MCD), virally infected plasmablasts secrete both human and viral IL-6, creating a powerful autocrine and paracrine loop that drives systemic inflammation and B-cell proliferation.²⁵

3.5. Strategies of immune evasion and immunosuppression

A cornerstone of herpesvirus biology and oncogenesis is the evolution of a diverse arsenal of strategies to evade host immune surveillance.⁵ Viral proteins actively interfere with the antigen presentation pathway. KSHV proteins K3 and K5, for example, are E3 ubiquitin ligases that target major histocompatibility complex (MHC) Class I molecules for degradation, preventing the recognition of infected cells by cytotoxic T lymphocytes (CTLs).²⁵ HHV-6 U21 protein achieves a similar outcome by rerouting MHC-I molecules to lysosomes for destruction.²⁴ Viruses also encode homologs of chemokines and chemokine receptors that can subvert the immune response, for instance, by acting as decoy ligands that desensitize receptors on effector T-cells or by selectively attracting immunosuppressive cell types such as regulatory T-cells into the tumor microenvironment.^{14,29}

3.6. Synergy with host somatic genetics and viral co-infections

Virus-associated lymphomas are not solely the product of viral gene action; they arise from a complex interplay

between the virus, the host's genetic background, and co-infecting pathogens. Next-generation sequencing has revealed that virus-positive lymphomas harbor distinct mutational landscapes compared to their virus-negative counterparts. For example, KSHV-positive primary effusion lymphomas (PELs) frequently have inactivating mutations in *TP53* and *PRDM1* but rarely show *MYC* amplifications, suggesting that viral oncogenes can substitute for certain classic cellular driver mutations.^{5,30} In contrast, HHV-6-associated T-cell lymphomas are often enriched for mutations in epigenetic regulators such as *TET2* and *DNMT3A*, pointing to a “two-hit” model where viral factors synergize with pre-existing clonal hematopoiesis to drive transformation.²⁴ Furthermore, interactions between different viruses can amplify oncogenic effects. HHV-6A has been shown to transactivate the lytic promoter of KSHV, potentially enhancing its pathogenic effects in co-infected cells.²⁴

4. Non-EBV Herpesviruses and specific lymphoma subtypes

4.1. HHV-6A/B: A key player in T-cell lymphomagenesis

HHV-6 comprises two distinct but closely related species, HHV-6A and HHV-6B, which differ in their cellular tropism, receptor usage, and pathogenic associations.²⁴ While HHV-6B is the primary cause of exanthema subitum (roseola), which is a common childhood illness, HHV-6A is more frequently detected in the context of malignancy and in individuals with chromosomally integrated HHV-6, a condition where the viral genome is inherited through the germline.²⁴ Molecular surveys consistently show an enrichment of HHV-6A in lymphoma tissues compared to peripheral blood, suggesting a selective role in the tumor microenvironment.²⁴

The association between HHV-6 and lymphoma, particularly T-cell malignancies, is supported by compelling mechanistic data. A unique feature of HHV-6 is its ability to integrate its genome into the telomeres of host chromosomes, a process that can induce genomic instability, double-strand breaks, and complex chromosomal rearrangements—a potential substrate for malignant transformation.²⁴ Viral proteins, such as the immediate-early protein IE2, can act as transcriptional transactivators, upregulating cellular oncogenes such as *MYC* and the telomerase catalytic subunit *hTERT*.²⁴ Furthermore, HHV-6 can profoundly remodel the tumor microenvironment. Viral gene products mimic host cytokines and engage receptors such as OX40, polarizing T-cells toward a T-follicular helper phenotype and inducing a cytokine milieu rich in IL-6 and IL-10. This

creates an inflammatory niche highly reminiscent of that seen in angioimmunoblastic T-cell lymphoma (AITL).²⁴

Epidemiologically, the strongest link is with AITL, where HHV-6 DNA is detected in 25–40% of cases.³¹ Viral DNA is also found, albeit at lower frequencies, in other T-cell lymphomas such as peripheral T-cell lymphoma (PTCL), not otherwise specified, and in a subset of nodular sclerosis classical Hodgkin lymphoma.^{24,32} While definitive proof of causality remains elusive for many of these associations, the consistent detection of the virus, particularly HHV-6A, coupled with robust mechanistic plausibility, strongly supports a contributory role for HHV-6 in the pathogenesis of these lymphomas.^{24,32,33}

4.2. HHV-7: A critical re-evaluation of its role

HHV-7 is a ubiquitous β -herpesvirus, phylogenetically close to HHV-6, that infects over 95% of the adult population and establishes lifelong latency in CD4⁺ T-cells.³⁴ Its detection in various lymphoma tissues has led to speculation about a potential role in lymphomagenesis.²³ However, a rigorous and critical evaluation of the available evidence suggests that HHV-7 should be positioned as a putative cofactor or an opportunistic agent rather than a primary oncogenic driver. Unlike established oncoviruses, the evidence linking HHV-7 to lymphoma fails to satisfy key criteria required to establish causality.^{33–35}

4.2.1. Epidemiological findings: A lack of consistent statistical association

A fundamental requirement for implicating a virus in cancer is a strong and consistent epidemiological link.³³ While early studies using protein-coupled receptor (PCR) detected HHV-7 DNA in a minority (5–12%) of nodal and extranodal lymphomas, these findings have been inconsistent and have not demonstrated a clear enrichment in any specific lymphoma subtype.³³ More importantly, large-scale case-control studies employing modern, high-throughput methods like RNA-Seq-based virome analysis have failed to show a statistically significant association between HHV-7 and lymphoma development.³³ This stands in stark contrast to the powerful epidemiological evidence supporting the roles of EBV in Burkitt lymphoma or KSHV in primary effusion lymphoma.^{34,36} Pooled nested case-control studies have also yielded inconsistent results regarding HHV-7 and the risk of non-Hodgkin lymphoma.³⁷ Indeed, some studies have found that HHV-7 DNA is more prevalent in healthy control skin than in cutaneous T-cell lymphoma lesions, leading investigators to conclude against a pathogenic role and suggest instead that the skin may simply be a site of viral latency.³⁸ Earlier investigations using less sensitive techniques, such as Southern blot hybridization, found no significant HHV-7

load in lymphoma samples, concluding that a direct etiological role was unlikely.³⁴

4.2.2. The critical gap: Absence of *in vivo* models and proof of causality

Perhaps the most significant gap in the evidence is the complete absence of *in vivo* models demonstrating HHV-7-driven lymphomagenesis.³⁹ Animal models are a cornerstone of cancer research, providing the necessary platform to move from correlation to causation by showing that introduction of the virus can initiate or accelerate tumor development.⁴⁰ While *ex vivo* experiments have shown that HHV-7 can productively infect human lymphoid tissue explants, this demonstrates viral tropism, not oncogenic transformation.³⁹ Furthermore, unlike HHV-6, HHV-7 is not known to integrate into the host chromosome, removing a key mechanism of virus-induced genomic instability.²⁴ Robust *in vitro* transformation assays for HHV-7 are also lacking.³³ Without these critical pieces of experimental evidence, the case for HHV-7 as a primary oncovirus remains unsubstantiated.

4.2.3. Positioning HHV-7 as a putative cofactor in an immunocompromised milieu

The available data, while insufficient to prove causality, do not entirely exclude a role for HHV-7 in lymphomagenesis. The most plausible interpretation is that HHV-7 may act as a cofactor or an opportunistic pathogen within a pro-tumorigenic environment shaped by other factors, particularly host immunosuppression.³³ HHV-7 frequently co-infects with established oncoviruses such as EBV and HHV-6, and its reactivation is a common event in immunocompromised individuals—a population with a significantly elevated baseline risk for lymphoma.³³ Mechanistically, *in vitro* studies show that HHV-7 can encode proteins that modulate the immune system, such as downregulating MHC-I expression, which could theoretically create an immune-evasive niche that facilitates the growth of malignant cells driven by other factors.³³

This reframes the central question: Rather than asking if HHV-7 *causes* lymphoma, it may be more scientifically accurate to ask if HHV-7 reactivation is a *biomarker* of the underlying immune dysregulation that permits both lymphomagenesis and viral replication. In this model, the detection of active HHV-7 infection in a lymphoma patient may be an indicator of the degree of immune incompetence that predisposed the individual to cancer in the first place.³³ The virus could still contribute to the pathology by adding to the chronic inflammatory burden, but its primary significance might be diagnostic or prognostic rather than etiologic.

4.3. KSHV/HHV-8: A definitive human oncovirus

In stark contrast to the ambiguity surrounding HHV-7, KSHV/HHV-8 is a definitive human oncovirus, classified as a Group 1 carcinogen by the International Agency for Research on Cancer.²⁰ Discovered in 1994 in Kaposi's sarcoma lesions, this γ -herpesvirus is the etiological agent of PEL, a subset of MCD, and KSHV-associated germinotropic lymphoproliferative disorder (GLPD).⁴¹ KSHV pathogenesis is driven by a powerful repertoire of latent and lytic viral proteins that systematically hijack host cell pathways controlling proliferation, survival, angiogenesis, and inflammation.²⁵

Key latent proteins include LANA, which maintains the viral episome and inactivates p53 and Rb; vFLIP, which provides constitutive NF- κ B activation; and vCyclin, which drives cell cycle progression.²⁷ During lytic reactivation, proteins such as the vGPCR and vIL-6 are expressed, promoting angiogenesis and inflammation through paracrine signaling that remodels the tumor microenvironment.²⁷

The diseases for which a pathogenic association with KSHV/HHV-8 has been better defined are listed as follows:

- PEL: PEL is an aggressive B-cell neoplasm that typically arises in immunocompromised individuals, particularly those with HIV infection.⁴² It is characterized by lymphomatous effusions in body cavities (e.g., pleural, pericardial, and peritoneal) without a solid tumor mass.³¹ PEL cells are universally infected with KSHV, and co-infection with EBV is observed in over 80% of cases, suggesting synergistic pathogenesis.⁴²⁻⁴⁴
- KSHV-associated MCD: MCD is a systemic lymphoproliferative disorder characterized by polyclonal B-cell expansion and symptoms of severe inflammation, driven by the overproduction of cytokines, including KSHV's vIL-6.^{45,46} Unlike PEL, the B-cell proliferation in MCD is typically polyclonal, although it carries a high risk of progressing to KSHV-positive lymphoma.⁴¹
- KSHV-associated GLPD: GLPD is a rare and more indolent B-cell proliferation that, in contrast to PEL, typically occurs in immunocompetent individuals.⁴⁷ It is characterized by the infiltration of lymph node germinal centers by KSHV-positive plasmablasts, often co-infected with EBV.^{48,49}

5. Clinical implications: Diagnostics and therapeutics

The direct involvement of herpesviruses in the pathogenesis of certain lymphomas has profound

implications for their diagnosis, prognostication, and treatment. The clinical approach requires a multimodal strategy that integrates traditional pathology with advanced molecular techniques to detect and quantify the viral presence, followed by therapeutic regimens that may incorporate both standard chemotherapy and virus-targeted strategies.

5.1. Diagnostic armamentarium: From bench to bedside

Accurate diagnosis and classification of herpesvirus-associated lymphomas hinge on the direct demonstration of the virus within the neoplastic cell population. The diagnostic toolkit has evolved significantly, moving from standard histopathology to highly sensitive molecular assays that are reshaping disease monitoring.

5.1.1. Established methodologies for diagnosis and subtyping

A list of established methodologies for diagnosing and subtyping viral infections is given below:

- Immunohistochemistry (IHC): IHC remains a cornerstone of routine diagnostics. The detection of viral proteins within tumor cells provides definitive evidence of infection and is crucial for diagnosis. The most critical application is the use of a monoclonal antibody against the KSHV's LANA-1. IHC staining of LANA-1 reveals a characteristic punctate nuclear pattern in KSHV-infected cells and is considered essential for the diagnosis of Kaposi's sarcoma, PEL, and other KSHV-associated lymphoproliferations.⁵⁰
- *In situ* hybridization (ISH): ISH is a powerful technique that allows for the visualization of viral nucleic acids directly within the context of tissue architecture. Chromogenic ISH for EBV-encoded small RNAs is the gold standard for confirming EBV infection in tumor cells and is routinely used in the workup of lymphomas where EBV is implicated, including PEL, PTCLs, and PTLD.^{51,52} More advanced RNA-ISH techniques can also detect specific viral mRNAs, allowing for the differentiation of latent versus lytic infection states, which can have prognostic implications.⁵³
- Quantitative polymerase chain reaction (qPCR): qPCR is the standard method for quantifying viral DNA load in various sample types, including tumor tissue, whole blood, plasma, and body cavity fluids. It is widely used to monitor the activity of KSHV in MCD or PEL and can serve as a biomarker for treatment response.⁵⁴ However, its sensitivity can be limited for detecting very low viral loads, and its accuracy depends on the use of a reliable standard curve.^{30,55}

5.1.2. Emerging technologies shaping the future of diagnosis

Emerging technologies that may have future implications for the diagnosis of herpesviral infections are listed in the following:

- Droplet digital PCR (ddPCR): ddPCR represents a significant technological advancement over qPCR for nucleic acid quantification. By partitioning the sample into thousands of nanoliter-sized droplets, ddPCR allows for the absolute quantification of target molecules without the need for a standard curve. This approach provides superior sensitivity, precision, and greater tolerance to PCR inhibitors found in clinical samples.⁵⁶ These features make ddPCR an ideal tool for applications requiring high accuracy, such as the detection of minimal residual disease and the quantification of low-abundance viral targets, such as KSHV DNA in patients approaching remission.³⁰
- Liquid biopsy: Liquid biopsy is used for monitoring viral and tumor dynamics via cell-free DNA (cfDNA). The analysis of cfDNA circulating in the plasma is emerging as a transformative, minimally invasive tool in oncology.⁵⁷ In virus-associated lymphomas, liquid biopsy allows for the simultaneous detection of viral cfDNA and circulating tumor DNA, which carries tumor-specific genetic alterations.⁵⁸ This enables real-time, non-invasive monitoring of both viral load and tumor clonal evolution throughout the course of treatment. Dynamic changes in cfDNA levels have been shown to correlate strongly with treatment response and can predict relapse months before it becomes clinically evident, heralding a new era of personalized and dynamic disease management.⁵⁹

The convergence of ultra-sensitive quantification methods like ddPCR with the accessibility of liquid biopsy is fundamentally changing the definition of clinical remission. Historically, remission was determined by imaging and the absence of clinical symptoms. While qPCR introduced a molecular dimension, its sensitivity limits meant that a "negative" result could still harbor residual disease. The ability of ddPCR to detect vanishingly small quantities of viral or tumor cfDNA allows for the definition of a much deeper state of molecular remission. This has profound implications for clinical practice and trial design. Frequent, non-invasive monitoring can identify patients with molecular relapse long before clinical progression, creating a window of opportunity for pre-emptive therapeutic intervention and transforming post-treatment surveillance from a passive to an active process.⁶⁰

5.2. Therapeutic landscape: Current standards and future horizons

The treatment of herpesvirus-associated lymphomas is complex, often requiring a combination of cytotoxic chemotherapy to target the malignant cells and strategies to control the underlying viral driver and/or host immune status.

5.2.1. Standard-of-care treatments for herpesvirus-associated lymphomas

The optimal therapeutic approach is highly dependent on the specific lymphoma subtype, the associated virus, and the patient's immune status. Table 1 provides a comparative summary of management strategies for key herpesvirus-associated lymphomas.

For PEL, an aggressive subtype of KSHV-positive lymphoma, the standard of care involves intensive multi-agent chemotherapy regimens, such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, which have shown some efficacy in AIDS-related lymphomas.⁴² Prognosis remains poor, and high-dose chemotherapy with autologous stem cell transplantation (ASCT) may be considered in select relapsed/refractory cases, though the experience in this specific lymphoma subtype is still very limited.^{45,61} In contrast, KSHV-associated MCD management focuses on controlling the inflammatory cytokine storm and depleting the viral reservoir. Rituximab, an anti-CD20 antibody, is a key component of therapy, targeting the CD20-positive B-cells that are a source of IL-6, often combined with cytotoxic agents such as liposomal doxorubicin or etoposide in more severe cases.⁴⁶ KSHV-GLPD may be managed with

localized approaches such as surgery or radiotherapy for unifocal disease, with systemic chemotherapy reserved for more widespread cases.⁴⁷

The front-line treatment for HHV-6-associated angioimmunoblastic T-cell lymphoma (AITL) mirrors that of other nodal PTCLs, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens (e.g., CHOEP, including etoposide) being the standard backbone.^{62,63} Given the profound immune dysregulation characteristic of AITL, corticosteroids are often initially used to manage symptoms.^{62,63} For young, fit patients who achieve a response, consolidation with high-dose chemotherapy and ASCT is often recommended to improve long-term outcomes.⁶²⁻⁶⁴

5.2.2. Investigational and novel therapeutic strategies

Despite advances, outcomes for many herpesvirus-associated lymphomas remain suboptimal, driving the search for novel therapeutic strategies that target either the virus itself or the cellular pathways it exploits.^{66,67}

Regarding virus-targeted approaches, while standard antivirals such as ganciclovir have a role, their efficacy is largely limited to controlling lytic replication.⁶⁴ Novel strategies are being explored, including next-generation antivirals such as amenamevir, which targets the viral helicase-primase complex and may offer more effective suppression of reactivation.⁶⁵ Another approach involves targeting cellular “dependency factors,” such as the chaperone protein Hsp90, which are required for the stability of viral oncoproteins and thus represent a potential therapeutic vulnerability.^{25,66}

Table 1. Therapeutic nuances in selected herpesvirus-associated lymphomas

Lymphoma subtype	Associated virus (es)	Standard first-line therapy	Relapsed/Refractory options	Key investigational approaches
PEL	KSHV (HHV-8), often EBV ⁺	Dose-adjusted EPOCH or CHOP-like regimens. Adjunctive ART in HIV ⁺ patients. ⁴²	High-dose chemotherapy with ASCT (limited data). Palliative radiation for solid masses. ⁴⁵	Lenalidomide+EPOCH-R, ⁶⁵ daratumumab (anti-CD38), ⁶⁵ bortezomib, checkpoint inhibitors. ^{45,65,66}
AITL	HHV-6 (reactivation common)	CHOP or CHOEP. Corticosteroids for symptom control. Consolidation with ASCT in eligible patients. ^{62,63}	Allogeneic SCT. HDAC inhibitors (e.g., romidepsin), brentuximab vedotin (if CD30 ⁺). ⁶²	Hypomethylating agents, PI3K inhibitors. ^{62,63}
KSHV-GLPD/ KSHV-MCD	KSHV (HHV-8), often EBV ⁺	GLPD: Local radiotherapy or surgical excision for localized disease. Chemotherapy for systemic cases. ⁴⁷	MCD: Rituximab±chemotherapy (e.g., liposomal doxorubicin). Antivirals (ganciclovir). ⁴⁶	MCD: Etoposide, bortezomib. Siltuximab/tocilizumab (anti-IL-6/IL-6R) has been explored. ⁴⁶ Daratumumab. ⁶⁵

Abbreviations: AITL: Angioimmunoblastic T-cell lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; EBV: Epstein–Barr virus; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; GLPD: Germinotropic lymphoproliferative disorder; HDAC: Histone deacetylase; HHV: Human herpesvirus; IL: Interleukin; KSHV: Kaposi's sarcoma-associated herpesvirus; MCD: Multicentric Castleman disease; PI3K: Phosphoinositide 3-kinase; PEL: Primary effusion lymphoma; SCT: Stem cell transplantation.

Given the central role of immune evasion in viral oncogenesis, immunotherapy strategies hold tremendous promise. Checkpoint inhibitors, such as antibodies against programmed death-1 and programmed death-ligand 1, can reinvigorate exhausted antiviral T-cell responses and have shown promise in clinical trials, particularly in HIV-associated lymphomas.⁴⁵ More advanced cell-based therapies are also in development. These include chimeric antigen receptor T-cells and bi-specific T-cell engagers engineered to recognize and kill tumor cells expressing viral glycoproteins on their surface, offering the potential for highly specific and potent anti-tumor activity.^{65,68}

Regarding epigenetic and signaling pathway inhibitors, since herpesviruses extensively co-opt host signaling and epigenetic machinery, drugs targeting these pathways are of great interest. Proteasome inhibitors such as bortezomib can induce apoptosis in PEL and MCD cells, which are highly dependent on NF- κ B signaling.⁴⁵ Immunomodulatory drugs such as lenalidomide are being tested in combination with chemotherapy for PEL.^{65,69} For AITL, which is characterized by frequent mutations in epigenetic regulators, agents such as histone deacetylase inhibitors and hypomethylating agents have shown activity in the relapsed/refractory setting.^{64,70}

6. Conclusion and future directions

The study of non-EBV herpesviruses has significantly broadened our understanding of viral oncogenesis, revealing a complex spectrum of pathogenic involvement in lymphoid malignancies. KSHV/HHV-8 stands as a bona fide human oncovirus, the definitive etiological agent of PEL, MCD, and GLPD, driven by a potent array of viral oncogenes. HHV-6 has emerged as a significant contributor to the pathogenesis of T-cell lymphomas, particularly AITL, through mechanisms including genomic integration and microenvironmental remodeling. In contrast, the role of HHV-7 remains far more ambiguous. A critical appraisal of the current evidence, marked by inconsistent epidemiological data and a lack of causative experimental models, supports its classification as a putative cofactor that may exacerbate lymphomagenesis in the context of pre-existing immune dysregulation, rather than as a primary oncogenic driver.

Despite significant progress, several key questions remain unanswered, defining the future directions of research in this field. A deeper understanding of the viral latency reservoirs and the mechanisms that trigger reactivation is crucial for developing strategies to prevent lymphoma recurrence. The functional impact of the

vast repertoire of non-coding viral RNAs on the tumor microenvironment and host gene expression remains a largely unexplored frontier. The development of more sophisticated *in vivo* models that can faithfully recapitulate the complex interplay between viral infection, host genetics, and immune responses is essential to definitively establish causality and test novel therapeutic interventions. Finally, the application of multi-omics technologies to dissect the intricate crosstalk between viral oncoproteins and the host epigenetic machinery will undoubtedly uncover novel vulnerabilities that can be exploited for the development of targeted, more effective therapies for these challenging diseases.

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Conflict of interest

Pier Paolo Piccaluga is an Editorial Board Member of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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