

HIV/AIDS Associated Lymphoma: Review

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Abstract: Lymphoma is one of the hematologic malignancies that occur at a higher rate in human immunodeficiency virus-infected individuals. It is one of the most frequent neoplastic causes of death in those individuals. Non-Hodgkin's lymphoma and Hodgkin's lymphomas are acquired immunodeficiency syndrome defining lymphoma and non-acquired immunodeficiency syndrome defining lymphoma, respectively. Non-Hodgkin's lymphoma is the most common type of lymphoma in human immunodeficiency virus-positive people. The lymphoma that develops in patients infected with the human immunodeficiency virus/acquired immunodeficiency syndrome is heterogeneous in terms of morphology, pathogenesis pathways, and cellular derivation. A narrative review was conducted on the basis of relevant literature on the current topic to summarize the current epidemiology, pathogenesis, laboratory diagnosis, and treatment of lymphoma in human immunodeficiency virus-infected patients. The finding showed that although the incidence of non-Hodgkin's lymphoma has decreased after the advent of highly active antiretroviral therapy, it has remained higher in human immunodeficiency virus-infected people than in the general population. On the other hand, the incidence of Hodgkin's lymphoma has increased after the introduction of highly active antiretroviral therapy. Therefore, it is recommended that people living with human immunodeficiency virus/ acquired immunodeficiency syndrome be screened for the development of lymphoma to increase their survival time and quality of life, and further research is required regarding the pathogenesis, treatment, and laboratory diagnosis of human immunodeficiency virus/ acquired immunodeficiency syndrome-associated lymphoma.

Keywords: AIDS-associated lymphoma, HIV, HIV-related lymphoma, HL, lymphoma, NHL

Introduction

Background Information

Globally, the Human Immunodeficiency Virus (HIV) it remains a critical health problem; as of 2020, 37.7 million and 1.5 million people were living with HIV (PLWHIV) and newly infected with HIV worldwide, respectively. In addition, nearly 680,000 people died from diseases associated with Acquired Immunodeficiency Syndrome (AIDS).¹ HIV-infected people are more likely to develop the various disease, including cancer. Severe immunosuppression occurred at advanced HIV infection is a risk factor for the occurrence of a variety of malignancies.²

Malignancies have become the leading cause of morbidity and mortality in HIV-positive people as their life expectancy has improved in the highly active antiretroviral therapy (HAART) era.³ As a result, malignancies develop in 25% to 40% of people living with HIV/AIDS.⁴ More than 28% of HIV-related deaths are attributed to malignant tumors, and more than 40% of HIV-infected people are eventually diagnosed with AIDS-associated lymphomas.⁵

HIV/AIDS-associated lymphomas are hematological neoplasms that develop from T and B lymphocytes, immune system cells, at various stages of differentiation.⁶ Nearly 90% of lymphoma originates from B cells, and some distinct subtypes of lymphomas are more common than the other types. Some of these can occur among both HIV-infected and non-infected people, whereas others appear to be more common in HIV-infected people.³ HIV/AIDS-associated lymphomas are malignancies that have fast-spreading and invasive characteristics. If left untreated, it can lead to death within weeks or months after being diagnosed.⁴ In the early times, HIV/AIDS-associated lymphomas had been described by morphology and primary location of lymphomas, such as systemic, primary central nervous system, and

body cavity. However, the world health organization (WHO) now classifies as distinct disease entities based on morphology, immuno-phenotype, and molecular alterations.³

The association between lymphomas and acquired immunodeficiency became recognized in the early 1980s, at the start of the AIDS epidemic,⁵ and now, in HIV infection, lymphoma becomes a major complication as well as a severe cause of morbidity and mortality when it occurs in high frequency.^{6,7} Based on the immune status of HIV-positive individuals, cancer in HIV-infected people is categorized as either AIDS-defining or non-AIDS-defining cancer. In HIV-positive individuals, lymphoma accounts for more than 50% of all AIDS-defining cancers.⁸

This review summarizes the most up-to-date information on the pathophysiology, subtypes, epidemiology, laboratory diagnosis, and treatment of HIV/AIDS-related lymphoma. Early detection of lymphoma in HIV/AIDS infected people is vital to increasing their survival life span and recovery. In addition to this, early identification of the etiology of lymphoma is essential for the clinician to facilitate the early prevention of lymphoma complications. It also guides early therapeutic decision-making for physicians about lymphoma. The above-listed problems encourage us to review the pathogenesis, sub-type, epidemiology, laboratory diagnosis, and treatment of HIV/AIDS-associated lymphoma.

Subtypes of HIV/AIDS-Related Lymphoma

Lymphoma in HIV-infected people is heterogeneous and subdivided into different histologic types.⁹ Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) are the main types of lymphoma developed in HIV-infected people.¹⁰ NHL and HL account for approximately 3% and 0.5% of all cancers diagnosed worldwide, respectively. NHL and HL account for approximately 3% and 0.5% of all cancers diagnosed worldwide, respectively. The relative risk of developing NHL in patients with AIDS at an early stage of the HIV epidemic was > 100 times higher than the general population.^{10–12}

In developed countries, NHLs are the most common and leading cause of HIV infection-associated death, accounting for 23% to 30% of all AIDS-related causes of death.¹³ It is the most aggressive type and occurs in patients at an advanced stage of HIV infection,¹⁴ with a low cluster of differentiation (CD) 4+ count (less than 100 cells/ μ L) and a high HIV viral load.⁴ The clinical course of AIDS-associated-NHL is much more aggressive than patients without HIV infection. In general, AIDS-associated NHL is characterized by higher grade (40–60%), extranodal disease (80%), advanced clinical stage (60–70%), often presenting with B symptoms (fever, night sweats, and weight loss), and shortened survival compared with lymphoma in HIV-non-infected.¹⁵ The most common subtypes of AIDS-associated-NHL are Burkitt's lymphoma (BL), diffuse large cell lymphoma (DLBCL), primary central nervous system lymphoma (PCNSL), plasmablastic lymphoma (PBL), and primary effusion lymphoma (PEL).^{13,16} The relative frequencies of DLBCL, BL, and all other subtypes of lymphomas are 50%, 40%, and 10%, respectively.¹⁷ These subtypes of HIV/AIDS-associated NHL differ from each other in terms of site of development, Epstein - Barr virus (EBV) or human herpesvirus (HHV) 8 type infection of neoplastic cells, and the frequency of various molecular lesions, including chromosomal translocations and mutations involving immunoglobulin genes and/or oncogenes.¹³

HL is the other main type of lymphoma that frequently occurs in HIV-infected patients.¹⁸ Its incidence in HIV-positive patients is 5–10 times higher than in the general population and has been increasing since the introduction of HAART.¹⁹

Diffuse Large B Cell Lymphomas (DLBCL)

Diffuse large B cell lymphoma is an aggressive B-cell lymphoma. It is identified by diffuse proliferation of large neoplastic B lymphoid cells with nuclei equal to or larger than normal histiocytic nuclei.²⁰ The disease is presents at an advanced stage of disease and with B symptoms. It occurs at nodal or extranodal sites, the gastrointestinal tract being the most common site, mainly in severely immunosuppressed patients.^{5,21} It is the most common AIDS associated lymphoma subtype, comprising about 45–50% of all lymphomas seen in this group.^{4,21,22} DLBCL occurs at all ages and causes a rapidly enlarging lymph nodal mass, commonly in the neck or abdomen. Approximately 30% of patients present with B symptoms, and up to 40% of patients experience extranodal extramedullary disease.²³

DLBCL can be developed in both HIV-infected and non-infected people, but there are some variations between these two groups. Based on cell morphology and gene expression profiling, DLBCL in HIV infection has been sub-classified

into centroblasts (germinal center B-cell type) and immunoblastic (activated B cell type) groups. The immunoblastic type most frequently occurs at the AIDS stage and is mostly associated with EBV infection, with reported rates approaching 90%.^{3,9} Centroblastic DLBCL is defined as lymphomas with a predominance of centroblasts, whereas immunoblastic DLBCL is defined as lymphomas with more than 90% immunoblasts or plasmablasts. In HIV-positive patients, these subtypes occur at roughly equal frequency, with the relative increasing frequency of the centroblastic subtype and decreasing frequency of the immunoblastic subtype in the HAART era.²⁴ Systemic DLBCL often has high-risk characteristics such as advanced lymphoma stage, extra nodal involvement, and poor performance status. In addition, the tumor cells are often infected with EBV.²⁵

Burkitt's Lymphoma (BL)

Burkitt's lymphoma is the second most common subtype of NHL that occurs in HIV-positive patients with a relatively high CD4 cell count. Patients usually have poor-performance status and elevated lactate dehydrogenase levels. Extranodal involvement is frequent, with central nervous system involvement occurring in 8 to 28% of instances.⁵ It frequently occurs at a younger age, and CD4 cell counts above 200 cells/ μ L.²⁶ It arises from B-cells and is a fast-growing type of tumor. Moreover, it is lethal if left untreated.²⁷

BL accounts for 10–35% of AIDS-defining lymphoma and is associated with a high rate of oral cavity involvement. Oral cavity BL is characterized by massive, ulcerated intra-oral masses that encompass the gingiva with one or more teeth, as well as the jaw or maxilla. These tumoral lumps grow fast, and physical examinations frequently reveal a submandibular lymph node.²⁸

BL is sub-classified into three clinical variants: endemic, sporadic, and immunodeficiency-related.^{27,29} The immunodeficiency-related BL subtype is most common in HIV/AIDS patients and accounts for 30 to 40% of AIDS-related NHL.²⁷ In terms of geographical distribution and EBV connection, these subtypes differ from one another. The endemic variant is strongly associated with EBV infections; around 98% of endemic BL cells contain the EBV genome. Conversely, only 5–10% of tumor cells from sporadic BL are EBV-positive. Furthermore, EBV infections occur in 30–40% of the immunodeficiency-related BL subtypes associated with HIV, showing an intermediate association with EBV infections, ie, 30–40%.³⁰

Primary Central Nervous System Lymphoma (PCNSL)

A subtype of NHL that affects the central nervous system, including the brain, spine, cerebrospinal fluid, and eyes, is known as primary central nervous system lymphoma.³¹ It develops in patients with severe immune suppression, in which its incidence has decreased since the introduction of HAART. HIV-associated PCNSL is typically EBV-positive. Moreover, most of the time, patients present with changes in mental status or focal neurologic symptoms, and, unlike HIV-negative PCNSL, they tend to present with multiple brain lesions.^{6,22} The most common symptoms of PCNSL are changes in mental state and intracranial pressure symptoms like headache, nausea, vomiting, papilledema, and local compression symptoms such as epilepsy, memory loss, unstable gait, visual impairment, blurred speech.³²

In HIV-positive patients, the immuno-phenotype of PCNSL varies from that of immunocompetent patients, in which in HIV-related lymphoma cells and cerebrospinal fluid, EBV is almost always detectable, while in the HIV-negative population, it is rarely present in PCNSL.⁵ About 4% of all primary brain tumors and 1% of all cases of NHL are accounted for by PCNSL. Moreover, 1.6–9.0% of HIV/AIDS patients are diagnosed with PCNSL, and it is the second most common intracranial mass injury in these patients.³³ Unlike other brain cancers, it frequently responds well to chemotherapy and radiation therapy, but survival is usually poor compared to lymphomas outside the CNS.³¹

Primary Effusion Lymphoma (PEL)

Primary effusion lymphoma is a unique subtype of aggressive B-cell NHL. It is caused by HHV8, also known as Kaposi sarcoma-associated herpesvirus (KSHV).^{34,35} It is rare, accounting for 4% of HIV-related NHL and 0.3% of NHL in the general population. Even though its pathogenesis is unknown, EBV co-infection is present in 60–90% of PEL cases. Malignant lymphomatous effusion is found in the pleural space, peritoneal cavity, and pericardium.³⁶

PEL is present in two forms: classical (serous cavities with recurrent malignant effusion but no tumor mass) and extra-nodal (masses in other organs, particularly lymph nodes, gastrointestinal tract, central nervous system, and skin with or without effusion).³⁷

The cells are of B-cell origin, but they rarely express CD20. Most cells express Latency-Associated Nuclear Antigen (LANA)-1, v-cyclin, v-FLIP (a viral analog of the FLICE inhibitory protein), and Kaposi. Viral-IL6 is expressed in 2% to 5% of PEL cells. Vascular endothelial growth factor expression is high in PEL-derived cell lines and can be detected in the effusions of patients with PEL, suggesting that vascular endothelial growth factor may play a role in the origin of the effusions.³⁸ Although the cells are originated from B cells, they typically express neither a B- nor a T-cell immune-phenotype and fail to express surface or cytoplasmic immunoglobulin. The tumor cells are typically positive for CD45, CD30, CD38, and CD138, suggesting plasmablastic differentiation.³⁸

PEL has a poor prognosis since it occurs in an immunocompromised condition, despite attempts to restore the host immune response with HAART and develop molecular-targeted therapeutics against activated tumor growth and survival signaling.³⁹ Although most studies show that PEL has occurred in patients with low CD4 cell counts, sometimes it develops in patients with high CD4 cell counts.⁴⁰

Plasmablastic Lymphoma (PBL)

PBL arises from the post-germinal center, terminally differentiated, activated B-cells which are in transition from immunoblasts to plasma cells. The frequency of PBL associated with HIV is around 2% of all AIDS-associated lymphoma.⁴¹ It is a rare type of lymphoma, and HIV infection is closely linked to it and occurs mainly in the oral cavity.⁴² It is extremely aggressive, with an extensive proliferation of giant neoplastic cells that seem like B-cell immunoblasts but have a plasma cell immunophenotype.⁴³

PBL arises from plasma blast, which is an activated B lymphocyte that has undergone somatic hyper mutation and class-switching recombination.⁴⁴ Although PBL has frequently occurred in the oral cavity, nearly 45% of PBL occurs in the extra-oral cavity. Most patients present with rapid growth, disease in the advanced clinical stage has increased lactate dehydrogenase, and B symptoms.⁴⁵

Hodgkin Lymphoma (HL)

HL is one of the most dominant non-AIDS-defining malignancies, and its incidence has risen since the introduction of HAART. The median age of HL in HIV-infected people is in their 30s.⁴⁶ It arises from the germinal center and manifests Hodgkin Reed–Sternberg (HRS) cells. Its incidence is higher in immunocompromised people, particularly in PLWHIV.⁴⁷ The occurrence of HL in an extreme immunodeficiency state is lower relative to mild immune compromise. This could be a lack of necessary immunological interaction between HRS cells and non-neoplastic inflammatory cells.²⁴ HRS cells interact with their microenvironment through cell-cell interaction and production of growth factors and cytokines, which results in a surrounding cellular environment that protects it from host immune attack. In addition, cell-cell signaling and cytokine production by the surrounding environmental cells also support the HRS cell proliferation by providing the required signals that enable the HRS cell itself to proliferate and live.¹⁹

Compared to HL in the general population, HIV-associated HL reveals many distinct characteristics. It exhibits an unusually aggressive clinical behavior and is associated with a poor prognosis, high frequency of systemic symptoms, including B symptom.^{48,49}

HL is sub-divided into classical Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant HL (NLPH).^{50,51} CHL accounts for greater than 90% of cases of HL, which behaves in an aggressive neoplasm, whereas in most cases, NLPHL has an indolent nature. CHL is a neoplastic disease with heterogeneous epidemiological, clinical, pathological, and virological features. It accounts for 10% of all lymphomas and is the most prevalent malignancy in patients under 20 years.^{11,52}

As with Kaposi's sarcoma (KS) and NHL, HIV infection significantly elevates the risk of CHL. Unlike those tumors, HIV-CHL does not have an AIDS diagnosis. HIV-related CHL has extranodal involvement that can lead to organ failure that is a life-threatening condition. In the United States, CHL is the fifth most common HIV tumor next to NHL, KS, lung cancer, and anal cancer.⁵³

CHL is further sub-classified into four histological subtypes based on the location of affected lymph nodes and how those nodes look under a microscope. These are lymphocyte-rich CHL, nodular sclerosis CHL (NSCHL), mixed cellularity CHL (MCCHL), and lymphocyte depleted CHL.⁵⁰ HIV-associated HL has a different incidence of histological subtypes and clinical presentation outcomes. The frequency of the increased risks of HL in people with AIDS varies among subtypes, with an 18-fold increase in the risk of MCCHL, a 35-fold increase in lymphocyte depleted CHL, and a 5-fold increase in NSCHL. Unlike the predominance of NSCHL in the general population, MCCHL is the most common HL subtype among HIV-infected individuals.¹⁹

Epidemiology and Pathogenesis of HIV/AIDS Associated Lymphomas

Pathogenesis of HIV/AIDS-Associated Lymphomas

Factors contributing to the higher prevalence of malignancies in HIV-infected patients are multifaceted. These include chronic antigenic stimulation, inflammation, and cytokine dysregulation. Furthermore, patients with HIV/AIDS have a higher risk of contracting oncogenic viruses.⁵⁴ Thus, the pathogenesis of HIV/AIDS-associated lymphoma is a combination of factors, including an impaired immune system, genetic alterations, viral infection, and chronic B cell activation. Most of these lymphomas are of the B-cell lineage and harbor clonal rearrangement of immunoglobulin genes.^{6,51} As a result of the decreased immune system and increased opportunities for virus-driven oncogenesis, immunodeficiency states typically increase vulnerability to malignancies. The two oncogenic viruses, namely EBV and KSHV, are pathogenically associated with particular forms of HIV/AIDS-associated lymphoma.⁵¹ BL, DLBCL with plasmacytoid differentiation, and most HIV-associated PBL are linked to EBV infection, while PEL and its solid variants are consistently linked to KSHV.¹⁷

Beyond inadequate immune surveillance, the high incidence of NHL in the HAART era suggests additional pathways are involved in HIV lymphomagenesis. Chronic B-cell activation facilitated by HIV-mediated immunological failure, which is responsible for hypergammaglobulinemia, impaired humoral immunity, and florid germinal center hyperplasia (all of which characterize early HIV infection), has been linked to lymphoma formation.⁵⁵

Some of the HIV gene products, particularly Tat, are possibly oncogenic in their role as trans-activators of cellular genes, such as interleukin (IL) 6 and IL10, leading to deregulation of the pRb2/p130 oncosuppressor protein. However, the contribution of HIV in lymphoma pathogenesis is mostly an indirect mechanism.⁵⁶ The typical reason for the increase of human immune deficiency associated with non-Hodgkin's lymphoma (HIV-NHL) is as a result of HIV-driven immune dysfunction.⁵⁷

Chronic activation of antigens triggered by HIV infection may contribute to the production of polyclonal B-cells, and therefore, this encourages the occurrence of monoclonal B cells. Circulating immunoglobulin-free light chains are found to be elevated in patients at increased risk of HIV/AIDS-associated lymphomas, and this may represent markers of polyclonal activation of B-cells.⁶ An overproduction of B-cell stimulatory cytokines often precedes the onset of HIV-NHL, which further supports B-cell activation and possibly drives the generation of activation-induced deoxyribonucleic acid (DNA) modification errors and oncogenic translocations, giving B cells the transformed phenotype.⁵⁷ The following are the key processes by which HIV causes PBL to develop: prolonged B-cell proliferation/exhaustion due to chronic antigenic stimulation; the length and severity of immunodeficiency or immunosuppression.⁴²

Epstein-Barr Virus (EBV)

Viral infections are responsible for approximately 15% to 20% of all human cancers. Many viral infections are associated with an increased risk of lymphoma. EBV is identified in neoplastic cells in most cases of HL, as well as in some of the NHL developed in HIV-infected individuals.⁵⁸

The EBV is the human gamma-1 herpesvirus, predominant in all populations, and is present as a latent asymptomatic infection. It has a high growth-transforming potential for lymphocytes and is etiologically associated with various lymphoproliferative lesions and malignant lymphomas.⁵⁹ Lymphoproliferative diseases, including AIDS-defining lymphomas such as BL and other NHL, as well as HIV-related HL, may be directly caused by EBV. The occurrence of EBV in HL and NHL is higher in HIV-infected individuals than in the general population.⁶⁰ BL is another type of AIDS-related NHL that is associated with EBV, and EBV is found in many cases of BL.⁸ EBV is present in almost all cases of endemic BL, about 30% of sporadic BL, and 40% of BL-associated immunodeficiency.²⁹

PBL is strongly associated with EBV infection, and EBV infection promotes lymphomagenesis of B cells by preventing B-cell apoptosis through several EBV antigen-related mechanisms. EBV is found in HIV-associated PBL in 74% of PBL tumor cell cases.⁴²

HIV-related HL is frequently associated with EBV, and the role of EBV in the pathogenesis of NHL in HIV infection is different, with most cases of PCNSL expressing EBV proteins.⁶¹ In HL, 80–100% of tissues from HIV-infected individuals have revealed a high degree of EBV interaction, and the EBV-transforming protein, EBV-encoded latent membrane protein (LMP)-1, is expressed in nearly all cases of human immune deficiency associated Hodgkin's lymphoma (HIV-HL). Because of this, HL tends to be an EBV-driven lymphoma in HIV-infected individuals.^{47,56} Moreover, in comparison to HIV-negative people who are 20–50% positive for EBV, almost all cases of CHL in people with HIV infection are associated with EBV infection. Clinical findings have shown that moderate immune activation or reconstitution after HAART may increase the stimulation of B cells as well as the burden of lymphocytes infected with EBV and the consequent risk of developing CHL.⁶²

Constitutive nuclear factor kappa-B (NF- κ B) activation is vital for HRS cell survival, and its activation results from various mechanisms. CD30, CD40, receptor activator of NF- κ B, and receptor activator of NF- κ B ligand, which activates the classic NF- κ B pathway, is expressed by HRS cells. Ligands for these receptors are commonly expressed on activated CD4⁺ T cells and other bystander cells surrounding HRS cells, such as eosinophils, neutrophils, and B-cell subsets. In EBV-positive CHL cases, the LMP-1 gene likewise contributes to NF- κ B activation because it mimics activated CD40 receptors. In HIV/AIDS patients with severe immunosuppression, the acquisition of an antiapoptotic phenotype by HRS cells is not a result of CD40–CD40L interactions; rather, it is induced by EBV-encoded LMP-1, which is functionally homologous to activated CD40. Accordingly, EBV is thought to play a crucial role in the pathogenesis of lymphomas in patients with immunosuppression.⁶³

EBV can be identified in approximately one-third and in all cases of non-HIV-associated HL and HIV-associated HL, respectively. HRS cells in HIV-HL express the EBV-transforming protein, LMP-1, and the EBV genomes from multiple disease sites in the same HIV-HL patient are episomal and clonal, implying that EBV is directly involved in lymphomagenesis.¹⁹ EBV is linked to lymphoproliferation and can contribute to the development of lymphoproliferative diseases such as B-cell NHL and HL. HIV-positive people are more prone to getting EBV lymphoproliferative disease. The EBV causes half of all HIV/AIDS-associated lymphoma and nearly all cases of HIV-associated HL.⁶⁰ EBV is present in 30–50% of BL. EBV-positive HIV-associated lymphomas often express EBV encoding the transforming antigen LMP-1, which activates cell proliferation by activating the NF-B pathway and can induce overexpression of B-cell lymphoma (BCL) 2, which promotes survival of B-cells and lymphomagenesis.⁶

Kaposi Sarcoma-Associated Herpesvirus (KSHV)

In 1995, HHV8 was identified as the causative agent of PEL when its DNA was found in all of the analyzed body-cavity-based lymphoma fluids associated with AIDS in serous cavities.³⁷ KSHV is a gamma-herpesvirus and has the ability to express viral homologs of human regulatory proteins such as cyclin D, IL-6, BCL-2, and others.³⁸

KSHV is the second major opportunistic virus that is able to directly promote the development of HIV-associated lymphomas, particularly PEL. The expression of a distinct set of KSHV-encoded proteins is currently believed to contribute to PEL pathogenesis. In particular, KSHV encodes a viral homolog of FLICE inhibitory protein (vFLIP), a potent activator of the NF- κ B pathway essential for the survival of PEL cells.¹⁷

There are five latent gene products that play a significant role in the development of PEL and are involved in lymphomagenesis: LANA-1; LANA-2/viral interferon regulatory factor (vIRF)-3; viral homolog of cyclin D (v-Cyclin); viral homolog of v-FLIP, and Kaposi (K12). In terms of oncogenesis associated with LANA-1, the C terminus of LANA-1 binds to tumor protein (TP) 53, resulting in the inhibition of TP53-dependent apoptosis, and it also binds to retinoblastoma (RB), inducing cell proliferation through the RB-E2F pathway. In addition, v-Cyclin binds to cyclin-dependent kinase 6 (CDK6), leading to the inactivation of RB protein, while v-FLIP inhibits apoptosis by blockade of caspase activation mediated by FAS and tumor necrosis factor, and it activates the NF- κ B pathway through activation of I κ B kinase γ (IKK γ). Kaposi, encoded by K12, has at least 3 isoforms, termed Kaposi A, B, and C, which differ in the start site of each translation on messenger ribonucleic acid (mRNA). Kaposi A is involved in oncogenesis through

cytokine-1. Kaposi B stabilizes cytokine expressions such as IL6 and granulocyte-macrophage-colony-stimulating factor by stabilization of cytokine mRNA containing adenylate-uridylylate-rich elements important for latent infection of HHV8. LANA-2/vIRF-3 is involved in drug resistance by binding to polymerized microtubules, decreasing their stability.^{38,39}

Epidemiology of HIV/AIDS Associated Lymphoma Before and After HAART Introduction

The risk of developing lymphomas in individuals infected with HIV is higher than in the general population. This is due to the consequence of continuing virus-mediated immune destruction and stimulation on cancer risk despite the beneficial effects of HAART. Before the advent of HAART, in HIV-infected individuals, the incidence of HL was 5–10 times, and the relative risk of NHL was estimated as 60–200 fold greater than the general population, respectively.^{16,19,50}

The advent of HAART has enhanced immune function and decreased the risk of developing AIDS in HIV-positive people. Moreover, the risk of developing AIDS-defining cancers, such as KS and most NHL, has decreased dramatically in line with the enhanced viral control achieved by HAART, while BL has remained stable.^{62,63} However, after the advent of HAART, the incidence of HL in HIV-infected individuals has remained constant or increased.^{46,62,63}

In San Diego County, the incidence of NHL decreased from 29.6 per 1000 person-years in the pre-HAART era to 6.5 per 1000 person-years in the post-HAART era. The proportion of patients who had NHL of central nervous system origin decreased from 28% in the pre-HAART era to 17% in the post-HAART era.⁶⁴ Across Europe, the incidence of NHL has decreased from 1.99 to 0.3% over 26,764 person-years of prospective follow-up from May 1994 to December 2009.⁶⁵ In France, AIDS-associated lymphoma has decreased from 86.0 per 10,000 to 42.9 per 10,000 person-years. The incidence of PCNS has also decreased from 27.8 per 10,000 to 9.7 per 10,000 person-years.⁶⁶

The incidence of HL in 1980 to 1989 and 1990 to 1995 was 30.9 and 30.4, respectively. However its incidence was increased to 49.3. 105 person per year in 1996 to 2000.⁶⁷ The incidence of HL is nearly 14 times higher than that of the general population, with variation based on the era of diagnosis; standardized incidence is 4.5 times higher than the general population in the pre-HAART era compared to 32 times higher in the HAART era. The Swiss HIV cohort study showed that HL standardized incidence was 9 times increased in the pre-HAART era, compared with 21 times increased in the early HAART era and 28 times increased in the late HAART era.¹⁹

Some types of lymphomas have decreased while other types have remained stable or increased after the introduction of HAART. For example, the frequency of highly aggressive B-cell lymphomas such as immunoblastic DLBCL in the pre-HAART period has decreased from 38% of HIV-associated NHL cases to 19% in the post-HAART era. The prevalence of PCNSL also decreased from 28% to 17%. By contrast, the proportion of centroblasts DLBCL increased from 21% to 44%, and BL increased from 4% to 9%.⁶⁴ Although the risk of acquiring AIDS-defining cancers such as NHL has decreased significantly after the advent of HAART, the death rate of patients on HAART has increased. For example, the death rate before and after HAART was 10% and 28%, respectively.⁶⁸

Clifford showed that the risk of developing HL was 17 times among HIV-infected individuals than in the general population. The standardized incidence ratio of HL before and after HAART was 17.3 (95% CI=10.2 to 27.4) and 36.2 (95% CI = 16.4 to 68.9), respectively.⁶⁹ Moreover, the standardized incidence ratio of NHL before HAART was 76.4 (95% CI = 66.5 to 87.4) and after HAART it was 24.2 (95% CI = 15.0 to 37.1).⁶⁹ Herida also showed that the standardized incidence ratio of HL increased after the advent of HAART, 22.75 (95% CI=17.27–29.40) and 31.66 (95% CI, 25.79–38.47) before and after HAART introduction, respectively.⁷⁰ Furthermore, Franceschi showed the standardized incidence ratio HL before and after HAART introduction was 9.2 (95% CI=3.6–19) and 28.1 (14.9–48.2), respectively. While the standardized incidence ratio NHL before was 103 (95% CI=88.8–119), and after HAART introduction, it was 16.2 (11.1–22.9).⁷¹

Laboratory Diagnosis of HIV/AIDS Associated Lymphoma

Although HAART is effective in decreasing the risk of the occurrence of cancer and the risk of mortality due to cancer, death due to cancer is increased in the HAART era. As a result, it is essential to screen for cancer among patients with HIV/AIDS even after HAART starts.⁷² Severe immune deficiency and AIDS, including the AIDS-defining malignancies, are caused when HIV affects CD4 cells. Therefore, cancer screening can and should be part of routine clinical care for PLWH.⁷³

An excisional biopsy is required to ensure adequate tissue for morphologic and molecular analysis. First, a morphologic analysis of tissue samples is carried out to get crucial information on the lymph node architecture and growth pattern. Additional biomarkers and genetic testing are commonly utilized to further categorize lymphoma types, determine clonality, prognosis, and treatment targets.⁷⁴ Lymphomas are morphologically and immunophenotypically heterogeneous, and the different subtypes of lymphomas cannot be differentiated by only standard pathologic review. Therefore, various markers of the cell surface have been used to distinguish specific lymphoma subtypes.¹⁶ Morphological review Molecular diagnostics, immunohistochemistry, and flow cytometry laboratory tests are used for the diagnosis of lymphoma.⁷⁴

Laboratory Diagnosis of DLBCL

The best form of diagnosis is based on a surgical excision biopsy. This enables the evaluation of nodal architecture as well as sufficient material for phenotypic and molecular analysis. An unfixed biopsy is required for flow cytometric assays and the extraction of high-quality DNA and RNA. Needle-core and endoscopic biopsies should only be used in patients for whom surgery is not an option or would be too risky. The recommended immunohistochemical panels are CD20, CD79a, BCL6, CD10, MYC, BCL2, Ki67, IRF4, CyclinD1, CD5, and CD23.⁷⁵

The Centroblastic type of DLBCL is identified by diffuse sheets of large lymphoid cells with round or oval nuclei and prominent nucleoli. They often express CD10 and BCL6 (germinal center-associated markers) and are typically CD20 positive.⁶ The immunoblastic type of DLBC has features of plasmacytoid differentiation, and these tumors are CD10-negative but positive for MUM1/IRF4 and CD138 (markers associated with plasma cell derivation).⁶

Laboratory Diagnosis of HL

HIV-associated HL is characterized by the high incidence of unfavorable histological subtypes, ie, MC and LD.⁴⁹ Mixed cellularity is the most common HL subtype in HIV-infected individuals, while nodular sclerosis is less prevalent than in HIV-uninfected individuals. The incidence of each type of HL decreased with decreasing CD4 counts, but the nodular sclerosis subtype decreased more rapidly than the MC subtype, which increases the proportion of MC subtype in people with HIV/AIDS.⁶⁷ Mixed cellularity classic HL is morphologically identified by HRS cells surrounded by eosinophils, neutrophils, histiocytes, and plasma cells.⁷⁶

Laboratory Diagnosis of BL

BL has the typical histologic features of HIV-infected patients, which are characterized by cohesive sheets of small to medium-sized malignant cells containing moderately abundant basophilic cytoplasm and round, regular nuclei with two to five distinct nucleoli. The appearance of abundant mitotic figures and numerous, evenly distributed tangible body macrophages with abundant clear cytoplasm that lead to a starry-sky pattern are classical pathologic features of BL.³ A medium-sized CD10 positive B-cell population with a high proliferative rate and the presentation of a translocation involving the MYC gene are used for the diagnosis of BL.²⁴

The cells are often more pleomorphic in size and shape, with fewer nucleoli and a plasmacytoid appearance. Nearly 80% of BL have translocations t(8; 14), which involve the juxtaposition of the MYC gene on chromosome 8q24 and the heavy chain locus on chromosome 14q32. In the remaining 20%, the translocations with the MYC gene involve the kappa or lambda light chain loci on chromosomes 2 and 8, respectively. BL in HIV infection displays plasmacytoid features, which are rarely seen in HIV negative individuals who develop BL.⁸ All three variants exhibit very high mitotic rates with CD19, CD20, CD79a, and CD10 expression and are BCL2 negative. The prevalence of EBV positive varies from 30% in classic BL to 50% to 70% in BL associated with plasmacytoid differentiation.⁶

Laboratory Diagnosis of PEL

Malignant cells in PEL are large and pleomorphic, often with plasmacytoid features resembling immunoblasts. In PEL, the appearance of the cells is large, with moderately to abundant deeply basophilic cytoplasm, a large round to irregular nuclei, and prominent nucleoli. Although cells in PEL express CD45, which confirms their origin is lymphoid, they are a “null” lymphocyte phenotype because they do not show typical B-cell immune-phenotype characteristics such as classic B-cell markers (CD19, CD20, CD79a) and T-cell markers (CD3, CD4, CD8) and are indeterminate by

immunohistochemistry. CD30, a marker found in 70% of CLH and HRS cells, is commonly observed in PEL. However, CD15 is typically not expressed. Markers of plasma cell differentiation, including CD38 and CD138, are present in PEL cells, which indicates plasmablastic differentiation.^{6,35,36}

Laboratory Diagnosis of PBL

PBL is a high-grade neoplasm that has both the features of B-cell and plasma-cell neoplasms. The morphological characteristics of PBL differ slightly according to the location of the disease. Diffuse sheets of large immunoblastic cells with abundant cytoplasm, vesicular chromatin, and prominent, frequently centrally located nucleoli are seen in most cases of PBL occurring in the oral cavity/jaw in the area of HIV infection.⁷⁷

PBL can be differentiated from the immunoblast type of DLBCL, BL from BL of the plasmacytoid subtype and PEL using the following characteristics: DLBCL frequently expresses CD20 and CD45, whereas PBL expresses plasma cell markers. Cells of BL are medium in size, relatively uniform in morphology, and have a starry sky pattern. BL tumor cells express the B cell markers CD45 and CD20 and also express the germinal center B cell markers CD10 and Bcl-6. They are negative for plasma cell markers. The immunophenotype of PBL is the same as that of PEL. While PEL often clinically manifests as effusion without solid tumors and usually occurs in body cavities.⁷⁸

PBL is a high-grade cytomorphic neoplasm like large immunoblasts or large plasma cells that express markers of plasma cells but lack markers of B cells. The diagnosis of PBL may be complex because the tumor cells are not differentiated from plasmablastic myeloma or plasmablastic morphology lymphomas. It is positive for CD79a, IRF-4/MUM-1, CD38, and CD138, similar to neoplastic plasma cells. However, it is negative for the B-cell markers CD19, CD20, and PAX-5.⁴¹ On histological examination, PBL tumor cells have diffuse proliferation and a scattered dispersion of macrophages. They are typically large, round to oval in form, with basophilic cytoplasm, deviated nuclei, and large, centered nucleoli.⁷⁸

Treatment of HIV/AIDS Associated Lymphoma

Over the last 30 years, the treatment of HIV-associated lymphoma has evolved in tandem with improved control of HIV replication and immune function preservation. The need to balance the administration of effective cytotoxic treatment with its effect on immune function and infectious complications drove therapeutic questions during this period.⁶ The first step in the treatment of HIV-related lymphomas consists of establishing the precise histological subtype of the lymphoproliferative disease, the extent of the disease, performance status, and the burden of the coexisting comorbidities. The best first-line treatment for HIV-related lymphomas has yet to be determined. According to consensus, the appropriate therapy should consider the stage, international prognostic index, performance status, comorbidities, and lymphoma subtype.⁷⁹ The advent of HAART has had a significant impact on the outcome of HIV-associated lymphomas, with median survival rates rising dramatically. Although the reasons are abundant, they can all be traced back to HAART's beneficial effects on immune function. Individuals with good immune function have a lower risk of infection, which allows for better chemotherapy administration.⁶ Nowadays, it is advised that all HIV-positive patients with malignancies continue to take HAART while undergoing chemotherapy.⁵ The most common therapeutic strategy for HIV/AIDS-associated lymphoma is chemotherapy. In a pooled analysis of 1546 patients with AIDS-related lymphomas who were enrolled in prospective clinical trials, chemotherapy with more dose-intensive regimens resulted in higher complete response rates.⁸⁰ Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), R-DA-EPOCH, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine with rituximab (R-CODOX-M/IVAC), R-hyper-CVAD, and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), which are recommended for lymphomas in HIV-negative patients, are also used in HIV/AIDS patients.⁸¹

In the previous study, factors such as patient-specific (age and performance status), HIV-specific (history of AIDS and low CD4+ count), and lymphoma-specific factors (stage, lactate dehydrogenase levels, extranodal disease, and a high international prognostic index) factors were all associated to a poor prognosis in early HIV/AIDS-related lymphoma studies.⁴

Infection prophylaxis: There are no comparative studies, and only guideline for opportunistic infections prophylaxis in HIV-associated malignancies has been published. During immunosuppressive treatment, Cotrimoxazole prophylaxis against *Pneumocystis jirovecii* pneumonia and toxoplasmosis should be given regardless of CD4 cell count. At least in certain situations such as low CD4 count, prolonged and profound neutropenia, prolonged use of steroids etc., prophylaxis against other infections is generally recommended.⁵

DLBCL

Over the last three decades, HIV-DLBCL treatment has progressed, with significant improvements in survival rates. Patients with ARLs had a poor prognosis before the advent of HAART, with a median overall survival (OS) of only six months because of infections and chemotherapy failure. However, the survival rate of HIV-lymphoma patients improved dramatically after the advent of HAART.⁸²

Before HAART, HIV-DLBCL patients experienced significant toxicity and shorter remissions on chemotherapy-related to their advanced HIV infection. Thus, reduced-intensity chemotherapy became the standard of care, but this approach is now obsolete with the current HAART.¹⁸ At this time, except when treating rare stage I, low-risk patients who often receive R-CHOP combination chemotherapy and radiation, the backbone of ongoing clinical trials at the AIDS Malignancy Consortium (AMC) is a combination chemotherapy regimen of rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin–cyclophosphamide dose-adjusted to CD4 count (R-EPOCH).⁸³

In a Spanish study of patients treated with the standard-of-care regimen R-CHOP, HIV-positive patients had similar disease-free survival but a significantly lower OS rate than HIV-negative patients. Conversely, a French study found that HIV-positive DLBCL patients had survival rates comparable to their HIV-negative counterparts.⁸⁴ Little et al found that dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) achieved a 74% complete response in patients with aggressive HIV lymphomas, with a 53-month OS rate of 79%. The result was superior compared to the previous outcomes of CHOP, which demonstrated 33% complete response with a 36-month OS of 25%. According to the National Comprehensive Cancer Network's guidelines, R-EPOCH is the preferred treatment for HIV-DLBCL.⁸² According to a prospective observational cohort study, the 2-year progression-free survival and OS rates among patients treated with R-CHOP did not differ from those of their HIV-negative counterparts.²⁵

Although the overall rate of CNS relapse in all DLBCL subsets is only about 5%, clinical risk factors, such as the involvement of specific anatomic sites, are linked to a significantly higher rate of CNS spread.⁸⁵ Regardless of the fact that CNS spread is a feared and frequently fatal complication of DLBCL, there is no widespread agreement on which patients should receive CNS prophylaxis or the most effective delivery method.^{85,86}

CNS prophylaxis is a candidate treatment for patients with an estimated CNS relapse rate of >10%. However, the risk of toxicity should be taken into consideration for every individual patient while taking prophylaxis.⁸⁶ Patients with any of the following factors should be offered CNS prophylaxis: CNS-international prognostic index levels are high, involvement of three or more extranodal sites (testicular, renal/adrenal, and intravascular) regardless of CNS-international prognostic index or anatomical sites.⁸⁶

BL

Before HAART, patients with HIV-associated NHL had a lower success rate with combination chemotherapy than HIV-negative patients with similar NHL histopathology. Opportunistic infections were a common cause of early death. However, in the HAART era, the improved immune function has led to a re-evaluation of full-dose chemotherapy. Furthermore, HIV-positive patients with BL and good immune function may benefit from more aggressive, low-side-effect chemotherapeutic treatments.⁸⁷

Intensive therapies used in the general population were avoided in HIV-related cases of BL prior to the HAART era, just as they were in DLBCL. 2-year event-free survival of 80% was found in a retrospective study of cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC) given with HAART. Another prospective study of 13 patients treated with hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) plus methotrexate and high-dose cytarabine with HAART showed a 92% complete response rate but a 2-year OS rate of only 38%.¹⁸

A standard combination chemotherapy regimen containing R-CODOX-M/IVAC was evaluated prospectively in a multicenter BL trial, demonstrating that it could be safely and effectively administered to HIV-positive patients on HAART.⁸⁷ In a study of 13 patients with BL and immunodeficiency (of whom 11 patients had HIV infection) who received short-course low-intensity R-EPOCH, the overall survival rate was found to be 90% after a median follow-up of 73 months.⁸⁸

According to the findings of two prospective parallel observational cohort studies, intensive chemotherapy with rituximab was highly effective in patients with HIV-related BL, despite significant toxicity, which resulted in cycle modifications and delays in a significant number of patients (nearly 50%). The main prognostic factors for OS were the severity of the immune defect as measured by CD4 cell count and the presence of bone marrow involvement. One large randomized trial in adult patients with BL showed that the addition of rituximab to the LMB regimen significantly improves event-free survival and OS without increasing toxic effects.⁸⁹

PEL

In a study of 248 cases of PBL, 50% of which had received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), or CHOP-like regimens, while 23% had been treated with more intensive regimens, such as EPOCH, hyper-CVAD, and CODOX-M/IVAC showed an OS rate to chemotherapy of 77%, with 46% of patients achieving a complete response and 31% a partial response.⁹⁰

Because of its resistance to cytotoxic therapies, PEL treatment has been linked to a poor prognosis. Several factors have been looked into as potential prognostic indicators. In a retrospective study of 28 HIV-positive patients with PEL, poor performance status and absence of HAART before PEL diagnosis were common. In another study of 104 patients with PEL, the number and location of affected cavities appeared to play a role in prognosis. Specifically, the involvement of more than one body cavity was associated with an OS of 4 months, in comparison to 18 months in patients with only one cavity involved.³⁶

The median progression-free and OS of PBL patients range between 6 and 7 months and 11–13 months, respectively, with no differences between CHOP/CHOP-like and more intensive regimens. Autologous stem cell transplantation may play a role in improving the outcomes of complete response patients.⁴³ The achievement of a complete response with chemotherapy remains the strongest prognostic factor for these patients, with a median OS of 48 months compared to 3 months for those who do not achieve a complete response.⁹⁰

Although dose-adjusted CHOP-like regimens are frequently prescribed, there is no definitive guideline for the treatment of PEL. Given the disease's rarity, the therapeutic focus is being redirected to personalized and targeted approaches in the experimental realm. Current clinical trials include combining lenalidomide and rituximab in the EPOCH regimen and using tacecleucel to treat people with relapsed/refractory EBV-associated disease.⁹¹

PBL

PBL has a poor prognosis, with median OS rates ranging from 4 to 18 months in the past. Poor performance status, advanced stage, and MYC aberrations have all been linked to a poor prognosis.⁹²

Patients with PBL have received a wide range of treatments, ranging from local control with radiotherapy in patients with the localized disease to various chemotherapy combinations. Chemotherapy treatments have included CHOP or CHOP-like regimens, Hyper-CVAD-MA (hyperfractionated cyclophosphamide, vincristine, doxorubicin dexamethasone, and high-dose methotrexate and cytarabine), CODOX-M/IVAC, cyclophosphamide, Oncovin, methyl-CCNU, and bleomycin (COMB), and infusional EPOCH. Following the initiation of HAART, patients with HIV have experienced spontaneous regressions.⁴⁴

PCNSL

OS of patients with HIV-PCNSL before the advent of HAART was 2 months, and although OS has improved with HAART-associated immune reconstitution, median OS is generally reported to be 1 year.⁹³

Prior to the development of effective HAART, the most common treatment for HIV-PCNSL was palliative whole brain radiation, which caused long-term neurotoxicity. Patients with HIV-PCNSL can now be treated with curative intent due to modern HAART; however, radiation-sparing approaches have yet to be studied prospectively. Several cytotoxic chemotherapy approaches have been shown to prolong survival in HIV-PCNSL patients in the past. High-dose methotrexate with leucovorin rescue and rituximab are relatively non-myelotoxic and have been used successfully in other HIV-associated lymphomas.⁹³

HL

Prior to the introduction of HAART, the prognosis of HL was worse than that of the general population due to poor chemotherapy tolerance, high rates of opportunistic infections, and toxic deaths. In patients who responded to HAART, chemotherapy and OS rates improved significantly; indeed, a low CD4 count remains an independent adverse prognostic factor.⁵ The most widely utilized initial systemic therapy for HL is a combination of ABVD. In the pre-HAART era, when ABVD was given to HIV-HL patients, the objective response rate was 62%, with a median OS of only 1.5 years. However, when ABVD was reexamined in conjunction with HAART in a cohort of 62 high-risk HIV-HL patients, 87% of whom achieved a complete response, with a 5-year OS and event-free survival of 76% and 71%, respectively.¹⁹ ABVD and HAART have been linked to higher cure rates. Three large retrospective studies showed that the complete response rate was 74–87% and the five-year OS rate was 76–81%.⁵

Conclusion

Lymphoma can develop in all individuals who are at risk of HIV/AIDS, and its pathogenesis, morphology, and clinical presentation are heterogeneous. Although the advent of HAART makes the most types of NHL have significantly decreased, it remains the most common cause of morbidity and mortality in these patients compared to the general population. On the other hand, the incidence of HL has increased after the advent of HAART. After HAART's introduction, the management of lymphoma became similar to that of the general population as a result of the immune reconstitution of the patients. Additionally, the patients had a good response to chemotherapy, except with some drug-drug interactions. However, the best treatment for lymphoma still needs to be investigated. In general, this review revealed that while the incidence of HIV/AIDS-associated NHL has decreased since the introduction of HAART, it remains a major cause of morbidity and mortality in HIV/AIDS-infected individuals compared to the general population. In addition, after the advent of HAART, the incidence of HL has increased. Therefore, it is recommended that further research on lymphoma that occurs in HIV/AIDS patients regarding its pathogenesis and treatment is needed. In addition, routine screening of lymphoma in these patients is needed to decrease its role as a cause of morbidity and mortality.

Declaration

We declare that this review paper is our original work.

Abbreviations

AIDS, acquired immunodeficiency syndrome; BCL, B-cell lymphoma; BL, Burkitt's lymphoma; CD, cluster of differentiation; CHL, classical Hodgkin lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CODOXM/IVAC, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine with rituximab; CODOX-M/IVAC, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, and cytarabine; DLBCL, diffuse large cell lymphoma; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; EBV, Epstein - Barr virus; HAART, highly active antiretroviral therapy; HHV, human herpesvirus; HIV, human immunodeficiency virus; HIV-HL, human immune deficiency virus associated Hodgkin lymphoma; HIV-NHL, human immune deficiency virus associated non-Hodgkin lymphoma; HL, Hodgkin lymphoma; HRS, Hodgkin Reed-Sternberg; hyper-CVAD, hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IL, Interleukin; KS, Kaposi's sarcoma; KSHV, Kaposi sarcoma-associated herpesvirus; LANA, latency-associated nuclear antigen; LMP, latent membrane protein; MCCHL, mixed cellularity classical Hodgkin lymphoma; mRNA, messenger ribonucleic acid; NF- κ B, nuclear factor kappa-B; NHL, non-Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NSCHL, nodular sclerosis classical Hodgkin lymphoma; OS, overall survival; PBL, plasmablastic lymphoma; PCNSL, primary central nervous system lymphoma; PEL, primary effusion lymphoma; PLWHIV, people living with human immunodeficiency virus; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin-cyclophosphamide; TP, tumor protein.

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