*CORRESPONDENCE
Hossein Bannazadeh Baghi
✉ hbannazadeh@tbzmed.ac.ir;
✉ hb.zadeh@gmail.com

†These authors have contributed equally to
this work

Coinfection of EBV with other pathogens: a narrative review

Fatemeh Ebrahimi[1,2†], Reyhaneh Rasizadeh[2,3,4†],
Shabnam Sharaflou[1], Parisa Shiri Aghbash[2,4], Ali Shamekh[2,4],
Abolfazl Jafari-Sales[3,5] and Hossein Bannazadeh Baghi[2,3,4*]

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran, [2]Department of
Virology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran, [3]Infectious and
Tropical Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [4]Immunology
Research Center, Tabriz University of Medical Sciences, Tabriz, Iran, [5]Department of Microbiology
School of Basic Sciences, Kazerun Branch, Islamic Azad University, Kazerun, Iran

The Epstein-Barr viwrus (EBV) is a common herpesvirus that affects more than
90% of people worldwide. Even while EBV infections are frequently
asymptomatic, they can cause autoimmune diseases and a number of cancers,
especially in those with impaired immune systems. The intricate relationships
between EBV and other coinfecting pathogens, including as human
immunodeficiency virus (HIV), human papilloma virus (HPV), cytomegalovirus
(CMV), and Plasmodium species, are examined in this study. We investigated the
fundamental processes of these coinfections, their effects on the course of the
disease, and their practical ramifications. The study reviewed how co-infections
with EBV might modify immune responses, promote oncogenesis, and make
treatment plans more challenging. In this review, we also discussed current
therapeutic strategies, such as targeted molecular interventions, EBV vaccines,
and adoptive T-cell therapy. The review underscores the need for more research
to provide more focused and effective therapies that address the mutually
reinforcing effects of numerous infections in disorders linked with EBV.

KEYWORDS

EBV, coinfection, HPV, SARS-CoV-2, HHV-6, *Helicobacter*

1 Introduction

The Epstein-Barr virus (EBV) is a widespread virus with a global seroprevalence rate of
almost 90% (1). This enveloped virus contains a linear, double-stranded DNA genome of
approximately 170 kilo base pairs, encoding over 80 proteins and 46 functional small
untranslated RNAs (2). Despite its prevalence, EBV has evolved mechanisms for long-term
survival and persistence in human hosts (3). While many infected individuals remain
asymptomatic throughout their lives, EBV infection in immunocompromised individuals
can lead to serious health conditions, including malignancies and organ failure (3).

EBV was initially identified through the electron microscopy examination of Burkitt's
lymphoma tumor cells in 1964 (4). Subsequently, four years later, the virus was conclusively

linked to infectious mononucleosis (IM); while its etiological significance in the disease was firmly established by 1973 (4). Furthermore, the initial virus directly linked to a human cancer was the widely prevalent B-lymphotropic herpesvirus, commonly referred to as EBV (5). Since its initial identification and correlation with Burkitt lymphoma (BL) fifty years ago, EBV has been associated with various lymphomas and epithelial malignancies (5).

The EBV presents a complex interplay of prevalence, clinical manifestations, and geographical considerations (6). Most of the malignancies caused by EBV are seen in immunocompromised patients; while they can also occur sporadically in individuals without apparent immunodeficiency (6). There are geographically unique zones where certain malignancies linked to EBV are mostly recorded. In regions of sub-Saharan Africa and New Guinea where holoendemic falciparum malaria is rife, endemic Burkitt lymphoma is observed (7). Native Americans and people from Southeast Asia are more likely to develop nasopharyngeal carcinoma due to environmental and dietary exposure to substances that may promote tumor growth (7). East Asia also presents a higher incidence of EBV-related T-cell/Natural killer (NK)-cell malignancies, suggesting multifactorial risks involving genetic and environmental influences (8).

Many B-cell-derived lymphoid neoplasms, such as Burkitt's lymphoma, lymphomas developing in immunocompromised patients (including human immunodeficiency virus (HIV)-associated and post-transplant lymphomas), and Hodgkin's lymphoma are linked to EBV (9, 10). Furthermore, EBV has been associated to nasopharyngeal cancers, a subgroup of gastric malignancies, and several T-cell lymphomas, including

angioimmunoblastic T-cell lymphoma, extranodal nasal-type NK/T-cell lymphoma, and other uncommon histotypes (11). It infects squamous epithelium of the oropharynx and nasopharynx, glandular epithelium of the thyroid, stomach, and salivary glands, B and T lymphocytes, follicular dendritic cells, smooth muscle cells, and many other cells and tissues (12, 13). The majority of EBV-associated cancers originate from B cells, which constitute the main cellular reservoir for EBV persistence. EBV encodes a wide range of products that facilitate EBV infection, immortalization, and transformation by imitating or activating cytokines, signal transducers, and antiapoptotic molecules (12, 13).

In clinical settings, EBV is commonly associated with IM, characterized by systemic symptoms such as fever, sore throat, exhaustion, malaise, and lymphadenopathy (14). Over 90% of IM cases are caused by EBV (15). IM exhibits a widespread global prevalence, predominantly affecting adolescents and young adults from affluent socioeconomic backgrounds in industrialized nations, whereas primary infection typically manifests later in life, usually between the ages of 10 and 30 (16). Conversely, its occurrence is less frequent in tropical and underdeveloped regions, as well as among individuals with lower socioeconomic status. In these populations, EBV infection typically occurs asymptomatically during early childhood (4).

Moreover, EBV coinfection with other pathogens can lead to severe complications from both pathogens, which can reactivate under immunosuppression (Figure 1). This dual infection not only complicates the clinical presentation but also depresses the host immune response, increasing the risk of recurrent infections and highlighting the need for greater attention to the clinical features
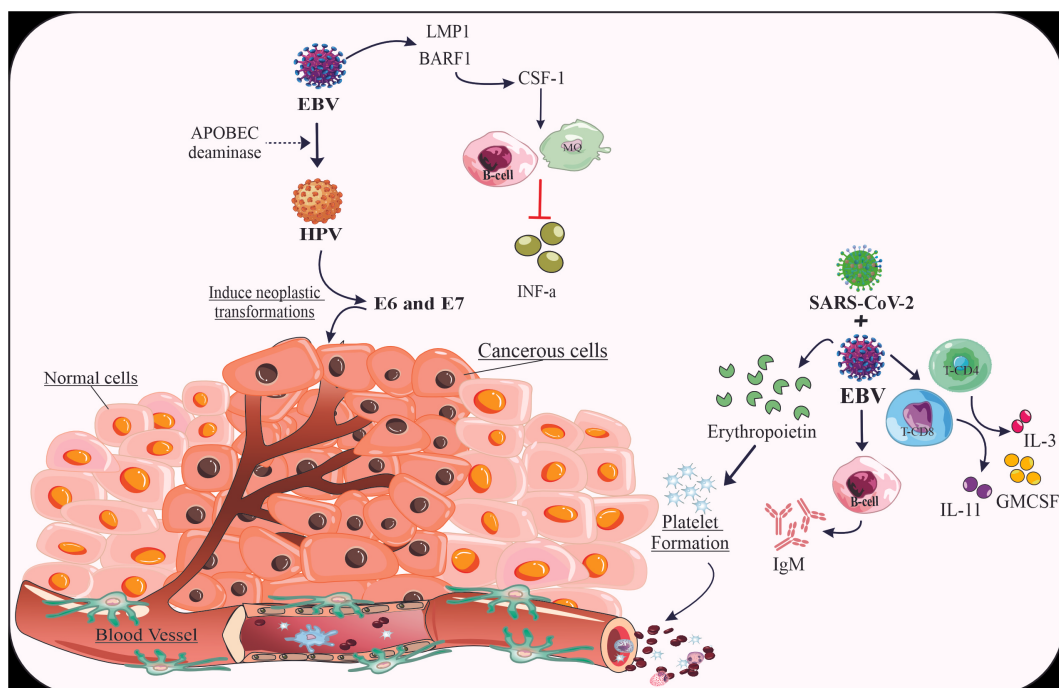

FIGURE 1
The mechanisms related to the co-infection of EBV virus with HPV and SARS-CoV-2. The coinfection of HPV and SARS-CoV-2 with EBV can promote the severity of malignancy by inducing the expression of genes and cytokines related to specific pathways.

and management of such coinfections (17). Furthermore, EBV coinfection may exacerbate thrombocytopenia by triggering complex immune responses that lead to platelet depletion, highlighting the intricate relationship between viral infections and hematological abnormalities (18).

The complex interactions between EBV and various coinfecting pathogens have emerged as a critical area of research in recent years. These coinfections, involving viruses such as HIV, human papilloma virus (HPV), and cytomegalovirus (CMV), as well as parasites like Plasmodium species, can significantly alter disease progression, immune responses, and clinical outcomes. The synergistic effects of EBV coinfections may contribute to the development and exacerbation of various malignancies and other associated conditions. Understanding these intricate relationships is crucial for developing more effective diagnostic, preventive, and therapeutic strategies for EBV-related diseases. The aim of this study is to provide a comprehensive review of EBV coinfections with various pathogens, focusing on their mechanisms of interaction, impact on disease progression, and clinical implications. Additionally, this study seeks to explore current and potential future treatment approaches for EBV-associated diseases in the context of coinfections, highlighting the need for targeted therapeutic strategies that address the complex interplay between multiple pathogens.

2 EBV infection

2.1 Primary infection

A primary EBV infection can result in a range of clinical symptoms, and trigger a number of cancers (19). Typically, affected individuals have peripheral blood lymphocytosis, containing abnormal lymphocytes (20). Usually symmetrical, the lymphadenopathy affects the posterior cervical chain more predominantly compared to the anterior chain (20). Moreover, along with less common signs including palate petechiae, periorbital or palpebral edema, and maculopapular or morbilliform rashes, severe weariness may be evident (21). Up to 50% of the patients develop splenomegaly; while hepatomegaly and jaundice are less common (22). Nonetheless, the disease presents in a number of various forms. Some patients with IM exhibit the so-called "glandular" form of the infection, in which the size of the lymph nodes is disproportionate to the pharyngeal symptoms; others experience a systemic form of the infection, characterized by a predominant fever and fatigue, with either mild or nonexistent lymphadenopathy and pharyngitis (23). Moreover, in several cases, hepatitis coexists with other characteristic signs of immune modulation (24). According to a study, prior viral infections, such as the influenza virus, may have an impact on the severity and commencement of host's immune modulation, increasing the proportion of T cells that mount an immune response against the EBV infection (25). The majority of people who have a primary EBV infection recover without any adverse events and show a good level of long-lasting immunity (26). While weariness frequently lasts for weeks or months, acute symptoms usually subside within one to two weeks (26).

2.2 EBV latency

EBV establishes latency following primary infection, which is a critical aspect of its lifecycle (27). During this phase, the virus remains dormant in B lymphocytes and other cell types, allowing it to evade the host immune response (27). The establishment of latency involves several mechanisms, including the infection of naïve B cells, immune evasion strategies, and the expression of specific latency-associated genes (27).

The establishment of latency during EBV infection is a complex process that involves several key steps and mechanisms (28). Initially, EBV infects differentiated epithelial cells, particularly in the stratified squamous epithelium of the oral cavity or pharynx, which serves as the primary site for infection and viral multiplication (28). However, EBV predominantly establishes latency in B lymphocytes, which are the main reservoir for the virus (28). This preference for B cells is a distinctive feature of EBV compared to other herpesviruses, such as herpes simplex virus (HSV), which typically enter a lytic cycle upon infection of many cell types (28).

Upon infection of primary B cells, EBV triggers the expression of both latent and lytic genes during what is termed the pre-latent phase (28). This phase can last for several weeks, during which the virus expresses lytic genes without producing infectious viral particles. This initial expression of lytic genes may help the virus evade cell death and promote B cell immortalization (28). Key latent genes, including the EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs), are expressed shortly after infection (28). Notably, EBNA-2 plays a crucial role in reprogramming the resting B cell transcriptome, facilitating the transition to latency (28).

Depending on the specific viral genes expressed, there are three main types of EBV latency:

Type I Latency: In this type, only the EBNA-1 nuclear antigen and two small non-coding RNAs called EBER-1 and EBER-2 are expressed (29).

Type II Latency: In addition to EBNA-1, EBER-1, and EBER-2, the virus also expresses three membrane proteins: LMP-1, LMP-2A, and LMP-2B (29).

Type III Latency: This is the most immunogenic type, with the expression of all six nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and -LP), all three latent membrane proteins (LMP-1, -2A, -2B), and the EBER RNAs (29).

Type I latency expresses only the EBNA-1 antigen and EBERs, primarily associated with endemic Burkitt's lymphoma and allowing immune evasion, but can reactivate under immunosuppression (30). Type II latency includes additional proteins (LMP-1 and LMP-2), linked to Hodgkin's lymphoma and nasopharyngeal carcinoma, enhancing oncogenic potential through altered immune responses (30). Type III latency expresses all nuclear and membrane proteins, found in immunoblastic lymphomas, leading to aggressive disease due to its high immunogenicity and severe consequences in immunocompromised patients. Understanding these latency types is crucial for managing EBV-related diseases effectively (31). During latency, the viral genome is replicated only once per cell cycle,

ensuring its maintenance in the host cells without causing active disease (30).

2.3 Congenital and perinatal infections

Less than 5% of pregnant women are susceptible to EBV, making intrauterine infections with the virus uncommon (32). Furthermore, there has been no evidence of congenital malformations in the offsprings of women who did develop primary EBV infection during pregnancy, according to prospective investigations of susceptible (i.e., seronegative) women (33). There have been rare reports of infants with congenital malformations (biliary atresia, congenital heart disease, hypotonia, micrognathia, cataracts, and thrombocytopenia) and their possible association with EBV infection; nevertheless, the general evidence does not support EBV as a major cause of congenital infection (34). In particular, there has been no signs of EBV infection found in cord blood samples or in extensive investigations involving children with congenital abnormalities (34).

2.4 Additional symptoms

EBV can impact almost every organ system and has been linked to a wide range of illness presentations, including pancreatitis, myocarditis, pneumonia, mesenteric adenitis, myositis, glomerulonephritis, and genital ulcers (35). Other unusual symptoms that have also been linked to primary EBV infection include: Guillain-Barré syndrome, meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, and optic neuritis (36). Hemolytic anemia, thrombocytopenia, aplastic anemia, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, and disseminated intravascular coagulation are examples of its associated hematologic disorders (37). Furthermore, EBV infection can lead to a variety of acute side effects as well as more chronic ones in some hosts (38). The complications of EBV (39) are summarized in Table 1. The proposed pathogenesis of EBV co-infection with other pathogens is outlined in Table 2.

3 EBV coinfection with HPV

Numerous groups of DNA and RNA viruses that are required, but are usually insufficient, for the development of cancers are classified as oncogenic viruses (40). Around 12% of malignancies globally are caused by viral infections, the great majority (>85%) of which occur in impoverished nations and regions (41, 42).

Two DNA viruses, HPV and EBV, were reported to be connected to 38% of all malignancies brought on by viruses (43). Coinfections, like HPV/EBV, can heighten the risk of cancer by impacting immune function, playing a role in cancer development, and affecting how cancer responds to treatment (44). Specifically, the presence of both HPV and EBV might influence the onset of prostate cancer by altering cellular behavior (44).

TABLE 1 The complications of EBV.

EBV complications	
Acute	Rash
	Airway obstruction
	Splenic (e.g. splenomegaly)
	Lemierre's disease
Delayed	Chronic active EBV infection
	Multiple sclerosis (MS)
	Oral hairy leukoplakia
	Lymphoproliferative disorders
	Hemophagocytic lymphohistiocytosis
	Lymphomatoid granulomatosis
	X-linked lymphoproliferative disease
	Post-transplant lymphoproliferative disease
Malignancy	Burkitt's lymphoma
	Hodgkin's lymphoma
	Nasopharyngeal carcinoma
	Gastric carcinoma
	T cell lymphoma

The viruses connected to the majority of cancer cases are caused by HPVs, which include cervical carcinoma as well as a number of other epithelial cancers (45, 46). There is a growing likelihood that a single patient will have infections from two or more different virus types (47, 48). It is not necessary for all the viral infections to coexist within the carcinoma cells for implementing their carcinogenic effects (48). Over the past 20 years, significant emphasis has been made on the observation that individuals with HIV infection are at a higher risk of contracting some malignancies, such cervical carcinoma as well as certain non-Hodgkin lymphomas (48). Notably, malignancies that arise in the presence of HIV-induced immunosuppression are often associated with other infections by cancer-causing viruses such as HPV and EBV (49). Nevertheless, little is known about the specific mechanism of the cooperation, and more research is required to determine whether this cooperation is essential for the growth of tumors (50–53). It is commonly known that HPV affects the prognosis and carcinogenesis of cervical cancer; while numerous researchers have discovered that HPV infection is also an etiologic factor for NPC (50–53). Furthermore, according to Whitaker et al. (54), both HPV and EBV gene sequences have been detected across normal, benign, and malignant specimens in prostate tissues. Recent experimental findings propose a collaborative role between HPV and EBV in promoting cell proliferation in cervical cells (54). However, the implications of their presence in prostate tissues remain uncertain

TABLE 2 Proposed pathogenesis of EBV coinfection with other pathogens.

Coinfecting Pathogen	Proposed Mechanisms
HPV	Cooperation between HPV E6/E7 and EBV LMP1/BARF1 oncoproteins in inducing neoplastic transformation APOBEC3 deaminases promote HPV and EBV coinfection Lytic EBV cycle plays a role in virus-mediated oncogenesis EBV BARF1 inhibits macrophage activation and IFN-α secretion
Plasmodium falciparum (Malaria)	*P. falciparum* CIDR1α protein directly triggers EBV reactivation EBV infection impairs antimalarial immunity and worsens malaria morbidity *P. falciparum* disrupts CD8+ T-cell immunity against EBV
Plasmodium vivax (Malaria)	EBV infection may worsen *P. vivax* malaria infection by altering hematological parameters and impairing antibody responses
CMV	Immunological disruptions imposed by underlying conditions (e.g., hematological diseases, transplantation) increases EBV and CMV reactivation rates Mechanisms in primary EBV/CMV infections in children are unclear
Human Herpesvirus 6 (HHV-6)	HHV-6 infection is associated with increased expression of EBV LMP-1 in nasopharyngeal carcinoma (NPC)
Kaposi's Sarcoma-Associated Herpesvirus (KSHV/HHV-8)	EBV gene expression supports KSHV persistence in B cells EBV co-infection is required for long-term KSHV infection and the transformation of B cells Co-infection increases the risk of primary effusion lymphoma (PEL) development
HIV	HIV-induced CD4+ T cell destruction EBV co-infection enhancement by HIV EBV-mediated B cell susceptibility to HIV CXCR4 and CD4 receptor involvement in HIV infection Integration of CXCR4-tropic HIV-1 into B cell genome CD8+ T-cell response control of EBV/HIV dual-infected B cells HIV-induced exhaustion of virus-specific T cells PD-1 expression as a marker of T cell exhaustion in HIV infection Contribution of other immune checkpoint inhibitors to CD8 T-cell exhaustion Weakening of immune response against EBV by HIV co-infection Complexity of HIV's impact on EBV-linked lymphomas Persistence of EBV-associated lymphomas despite antiretroviral therapy Role of HIV-related inflammation and antigens in boosting EBV-linked lymphoma growth Potential increase in mutation rates in co-infected cells by HIV Contribution of HIV-induced enzymes to mutation and cancer development

(54). While it's possible they are harmless, HPV type 18, known for its high oncogenic potential, may be associated with certain prostate cancers (54). Furthermore, the identification of HPV-associated koilocytes in prostate cancer specimens suggests prior HPV infection and hints at its potential oncogenic effects in the development of prostate cancer (54). Additionally, there are reports indicating the simultaneous presence of EBV and HPV in various epithelial malignancies, including some cases of breast cancer (55).

The beginning of a neoplastic transformation and carcinogenesis is significantly influenced by the co-infection of HPV and EBV (56). It's interesting to note that there is a relationship between EBV and HPV (whole viruses) as well as a relationship between HPV and EBV oncoproteins (for example, latent membrane protein-1 (LMP1) decreases apoptosis *in vitro*) (57). EBV, like high-risk HPVs, can infect and immortalize human primary epithelial cells *in vitro* (58). Among the EBV genes consistently expressed in the infected cells are EBERs, EBNA1, LMP1, LMP2A, BARF0, and BARF1 (58). Notably, only LMP1 and BARF1 have been found to be capable of inducing malignant transformation in rodent fibroblasts, classifying them as viral oncogenes (58). BARF1 is consistently expressed at high levels in nasopharyngeal cancer, EBV-associated gastric carcinomas, and EBV-immortalized epithelial cells *in vitro* (58). Furthermore, BARF1's interaction with colony-stimulating factor-1 inhibits macrophage

activation and interferon-alpha secretion in EBV-infected B-cells. It's hypothesized that EBV oncoproteins, along with HPV's E6/E7 oncoproteins, cooperate to induce neoplastic transformations (58). Double transgenic cells and animal models are considered the best approaches to test this hypothesis effectively (58). Moreover, APOBEC3 deaminases may facilitate the co-infection of EBV and HPV (59).

According to research on the functions of chromatin, dynamic interactions between the chromatins of the virus and the host are crucial in regulating viral infections (60–62). Infections in addition to the way that proteins are encoded by viruses, interact to modify the chromatin (60–62). These interactions are particularly important for a number of epigenetic processes, including higher-order chromosomal structures that regulate the production and maintenance of viral episomes following viral infections, chromatin assembly, and histone and DNA modifications (60–62). EBV and HPV seem to cooperate in promoting cervical carcinogenesis through both direct and indirect mechanisms (63). Directly, EBV may infect epithelial cells alongside HPV, potentially synergizing with HPV oncoproteins (63). The combined effects of viral proteins like EBV's LMP1 and HPV's E6/E7 can lead to increased cell proliferation, resistance to apoptosis, and enhanced invasiveness (63). These proteins work together to disrupt cell cycle controls, impair DNA damage responses, and promote EMT (63). Indirectly,

EBV infection of tumor-infiltrating lymphocytes may generate local immunosuppression, helping HPV-infected cells evade immune surveillance (63). Additionally, EBV proteins like BARF1 may further contribute to immune evasion and oncogenic changes (63). The coinfection appears to favor the establishment of EBV latency in cervical epithelial cells, possibly facilitated by HPV-induced DNA damage, leading to long-term viral persistence and continued oncogenic effects (63). Cancers caused by oncogenic viruses are a major worldwide concern (64). In the global battle against cancer, notable advancements are still being achieved by preventing the production and distribution of secure and efficient vaccinations against these viruses, as well as by figuring out the oncogenic pathways these viruses employ, making it possible to create novel therapeutic approaches for various human cancers linked to viruses (64). Despite the fact that HPV vaccines exist (64), there are no effective ones available for EBV (almost 50 years after EBV's discovery).

The study conducted by Lu et al. (65) explores DZ1, a DNAzyme targeting the LMP1 gene, as a therapy for EBV-associated carcinomas. DZ1 effectively reduces LMP1 expression in B95-8 cells, inhibits cell growth, and induces apoptosis by downregulating the Bcl-2 gene (65). There is hope for DZ1 therapeutic techniques for the treatment of EBV-related malignancies as the DZ1 treatment is deemed safe and effective in several models (65). HPV and EBV coinfections increase cancer risk by altering immune responses and promoting tumor growth. HPV is linked to cervical and nasopharyngeal cancers, while both viruses may influence prostate and breast cancers. Emerging treatments, like DNAzyme, show promise in targeting EBV-related cancers, but more research is needed to understand their combined oncogenic effects.

4 EBV coinfection with SARS-CoV-2

Due to the great importance of the diseases caused by the two mentioned viruses in children, we examine this co-infection only in children and refrain from examining it in adults (66). Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (67). Most COVID-19 cases in children were mild and the treatment consisted of supportive care; only a small number needed hospitalization and mortality rate was lower than 0.1% of diagnosed children (68–71). As we are discovering more about SARS-CoV-2 infection each day, differences between adults and pediatric disease are probably due to changes within both the immune function and the angiotensin-converting enzyme (ACE) 2 receptor, used by the virus to enter type II pneumocytes in the lung (72, 73). The immune system of children is highly prepared to novel pathogens, due to high levels of innate IgM antibodies with broad reactivity, in addition to the production of the anti-inflammatory interleukin (IL)-10 by the neonatal B cells (72). Other probable explanations are alternations in T cell populations in adults due to continuous antigen stimulation and thymic involution, varied levels of ACE-2 expression in children, and the simultaneous presence of other viruses in the respiratory

mucosa of children, competing with SARS-CoV-2 (74). Besides, children have fewer comorbidities and a stronger pulmonary regenerative potential than adults (75). A 5-year-old boy with prolonged fever was admitted to hospital. Initially treated for tonsillitis, his symptoms worsened. Tests revealed COVID-19 IgM antibodies and acute EBV infection (75). The child had respiratory and gastrointestinal symptoms, lymphadenitis, and thrombocytosis. Though not fully meeting criteria for multisystem inflammatory syndrome in children (MIS-C), the dual infection caused severe inflammation. With symptomatic treatment, the child's condition improved (75).

Pediatricians find it challenging to distinguish between COVID-19 infection and other possible childhood viruses as the SARS-CoV-2 pandemic continues to spread around the world (76). Nearly all medical resources are focused on treating COVID-19 infections, while diagnosing or anticipating the illness's consequences in children remains difficult (76). It is already well known that children have received fewer COVID-19 diagnoses than adults (76). According to the World Health Organization, most of the pediatric cases in China have been moderate; nevertheless, 2.5% of pediatric cases have been reported to have serious illness (76). For youngsters, fever, pharyngeal erythema, and cough are the most commonly reported signs and symptoms. Other less typical indications and symptoms consist of diarrhea, weariness, rhinorrhea, nausea, and congestion in the nose (71). A tiny percentage exhibit dyspnea, a high temperature that doesn't subside, lethargy, elevated enzyme levels, and serious illness (71). A high incidence rate of MIS-C has been recorded since May 2020 in a number of highly endemic countries (77–80). Fever, increased inflammatory markers, and organ dysfunction not linked to another infectious etiology, are all included (81). 25 days is the median time between the beginning of COVID-19 symptoms and MIS (81). When compared to nasopharyngeal reverse transcription-polymerase chain reaction (RT-PCR), the greater percentage of positive serologic testing is an indication of a disease-related late consequence (66, 77, 81–83). Apart from fever, the most typical MIS manifestations are cardiovascular, mucocutaneous (rash, mucous membrane alterations, conjunctival injection), respiratory (including sore throat), headache, limb and periorbital edema, and gastrointestinal (diarrhea, vomiting, abdominal discomfort) (80–82). Laboratory results that are related to these conditions include hypertriglyceridemia, elevated D-dimer and fibrinogen, thrombocytopenia, lymphopenia, elevated troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP), and elevated inflammation markers (neutrophilia, C-reactive protein, ferritin, and erythrocyte sedimentation rate) (83). There are certain patients who fit in the category of macrophage activation syndrome (MAS) (75). The presenting child had a prolonged fever lasting more than ten days, cough, diarrhea, exhaustion, cervical lymphadenopathy, and pharyngeal erythema in addition to a negative reverse transcriptase protein chain reaction (RT-PCR) and a positive serology for COVID-19 (increased IgM levels, which are higher during weeks two and three of the illness) (75). It was first suspected that certain inflammatory markers, such as C-reactive protein (CRP) and d-Dimer, were elevated in which we in favor of MIS-C (75). Nevertheless, several confounding factors, such as lymphocytosis and thrombocytosis, were detected in

laboratory data that were inconsistent with MIS-C. Children with confirmed COVID-19 do not exhibit a consistent pattern of laboratory abnormalities; however, hospitalized patients frequently have lymphopenia (caused by the destruction of infected T lymphocyte cells) and thrombocytopenia along with other abnormalities related to coagulation parameters (75). Conversely, EBV, a common pathogen that causes illness in youngsters, has similar symptoms with COVID-19. The majority of people on the planet are infected with EBV, which is common in the natural environment (75). The primary infection in young children typically manifests as asymptomatic or causes an acute illness that is frequently misdiagnosed as EBV-related (75). It can also manifest as the full-blown IM clinic, which includes fever, pharyngitis, lymphadenopathy, hepato-splenomegaly, and fatigue (75). Recovery from IM is sluggish, and the typical length is 16 days, far longer than other acute viral diseases (84). During a primary EBV infection, a strong innate and adaptive immune response takes place. The initial line of defense is the innate immune system, causing fever, exhaustion, and headache (84). Both CD4 and CD8 T cells respond well to EBV antigens; however, it is believed that CD8 T cells specific to EBV lytic antigens are primarily responsible for the extensive lymphocytosis in the blood which is a characteristic sign of IM (85). SARS-CoV-2 and EBV are two viruses that alter the immune system. When SARS-CoV-2 or EBV infections occur, thrombocytosis is not usually the case; instead, mild thrombocytopenia is seen (18, 86). Children's thrombocytosis is typically reactive, more common during the healing stage of an infection or inflammation, and is usually transitory, going away as soon as the main stimulus stops (86). Mainly, the increased release of several cytokines in response to infections is the mechanism underlying the reactive thrombocytosis (86). Numerous cytokines, including IL-3, IL-11, granulocyte-macrophage colony-stimulating factor, and erythropoietin, can stimulate platelet formation; however, thrombopoietin and IL-6, which are first raised in response to infections, play the most important roles (86). Thrombocytosis in this instance is an amplification of the body's reaction to the two illnesses together (86). Even with the remarkably elevated platelet count —which can occasionally surpass 1,000,000 cells/mm3—thrombotic and/or hemorrhagic consequences are very remarkable (86). In summary, distinguishing COVID-19 from EBV in children is challenging due to overlapping symptoms. Co-infection can cause immune system alterations, including reactive thrombocytosis. Careful diagnosis and further research are essential for managing these cases effectively.

5 EBV coinfection with HIV

Acquired immune deficiency syndrome (AIDS) is caused by HIV infection, which destroys CD4+ T cells, leading to immunodeficiency and susceptibility to infections (87). Moreover, the majority of individuals who contract HIV are already infected with EBV, as EBV infection typically occurs during childhood and adolescence (88). HIV co-infection boosts EBV replication and the development of EBV-related cancers (89). EBV transforms B cells, making them vulnerable to HIV-1 infection, particularly through

CXCR4 and CD4 receptors. In laboratory experiments, CXCR4-tropic HIV-1 integrates into these B cells' genome, similar to how it does in CD4+ T cells (90). A humanized mouse model has been developed to study EBV and HIV-1 interaction *in vivo* (90). These mice mimic the aspects of EBV and HIV infection observed in humans (90). In the mouse model, EBV/HIV dual-infected B cells were identified but were controlled by CD8+ T-cell immune response (90).

In HIV-1 infection, PD-1 expression on virus-specific T cells indicates immune exhaustion and disease progression, correlating with reduced CD8 T-cell function, higher viral load, and lower CD4 counts (91). Cytomegalovirus-specific CD8 T cells in the same individuals do not show increased PD-1 levels, suggesting HIV-specific defects due to antigen exposure (91). Long-term studies show that PD-1 levels decrease with ART, and long-term non-progressors (LTNPs) have lower PD-1 levels and better T-cell function (91). Other immune checkpoints like LAG3, TIM-3, and TIGIT also contribute to T-cell exhaustion. Co-expression of PD-1 with TIGIT is linked to disease progression, and multiple checkpoints correlate with HIV load and T-cell function (91).

The findings indicate that HIV co-infection weakens the immune response against EBV, particularly for high-immunogenic lymphomas (where all latent EBV proteins are expressed, known as latency III). However, for lymphomas linked to EBV latency I and II, like Burkitt's lymphoma, Hodgkin's lymphoma, and primary effusion lymphoma, the impact of HIV co-infection is more complex (92). These lymphomas also occur more frequently in individuals co-infected with HIV (92). Interestingly, their incidence has, however, not decreased, and for Burkitt's and EBV-associated Hodgkin's lymphoma, they have even increased after the introduction of antiretroviral therapy (93). Therefore, they now compose around half of the EBV-associated lymphomas in people living with HIV. Hodgkin's and Burkitt's lymphomas are believed to originate from germinal centers (93), a location where HIV can continue to proliferate even when receiving antiretroviral therapy (94). The inflammation caused by HIV, along with HIV-related antigens, might boost the growth of EBV-linked lymphoma cells, which are already prone to mutations (95, 96). This could lead to genetic changes like c-myc translocation, possibly triggered by the EBV (95, 96). In people with both viruses, HIV may increase mutation rates in certain cells, particularly those affected by specific HIV strains. Moreover, HIV infection produces enzymes that induce mutations, contributing to cancer development (95, 96). HIV boosts EBV replication and increases the risk of EBV-related cancers like Burkitt's and Hodgkin's lymphomas. HIV weakens the immune system, leading to higher incidence of these cancers, even with antiretroviral therapy.

6 EBV coinfection with *Helicobacter*

In recent years, bacterial and viral infections have been associated with the onset of gastric disorders such as gastric cancer (GC), mucosa-assisted lymphoid tissue (MALT) lymphoma, and chronic gastritis (97–101). Notably, the roles of

Helicobacter pylori and EBV in stomach cancer development have been elucidated (10). The International Agency for Research on Cancer classified *H. pylori* as a group 1 carcinogen in 1994; while EBV keeps its genome within the host cells, eluding the immune system and preventing cell death, facilitating the process of neoplasia (102, 103). Currently, there is a discussion and developing evidence on the involvement of EBV infection in inflammatory gastrointestinal diseases (104–106). The development of gastric disorders is mostly attributed to the virulence factors of H. pylori, which include the genes cagA, vacA, and oipA. The most researched *H. pylori* virulence factor is called CagA, which is a polymorphic gene (107). The 3′ region of the gene has a variable number of repeat sequences. The CagA protein has Glu-Pro-IleTyr-Ala (EPIYA) motifs in all of its repeated regions. VacA ranks second most regarded as a virulence factor for *H. pylori* (107). The vacA gene structure is known to contain three distinct regions: the intermediate (i) region (i1 and i2), the middle (m) region (m1 and m2), and the signal (s) region (s1 and s2) (107). Ultimately, it was shown that OipA is a protein which induces a proinflammatory response and conditions the gastric epithelial cells' ability to produce IL-8 (108). It is evident that eliminating the bacteria seems to reduce the incidence of stomach cancer in individuals who are at higher risks (109). The efficacy of eradication regimens may be impacted by resistance to antibiotics, especially Clarithromycin, a crucial medication in this process (110). Common clarithromycin resistance is explained by point mutations in the 23S rRNA gene (111).

After infecting cells in the oropharynx, EBV spreads to the lymphoid tissues and infects the present B lymphocytes (112). Research on the relationship between EBV and autoimmune diseases as well as its role as a triggering mechanism in MS have been conducted both *in vitro* and *in vivo* (113, 114). Patients with mononucleosis syndrome have also recently been reported to have secondary hemophagocytic lymphohistiocytosis (HLH) (115), which is characterized by hemophagocytosis and histiocyte proliferation as reported by Cascio et al. in cases of severe infection (115–118). Recent research demonstrating the potential of pathogenicity of co-infection with both *H. pylori* and EBV raises questions about the importance of the involved inflammatory responses to the tissue or the increased interaction between the EBV's CagA protein and H. pylori, which promotes the activation of B lymphocytes passing through the stomach mucosa (119).

The study conducted in Sicily examined the prevalence of *H. pylori* and EBV co-infections, along with the presence of specific genetic markers and antibiotic resistance in stomach biopsies from adult patients with and without gastric illness (120). Among 24 patients with chronic gastritis (CGA) and 24 individuals without gastric disease (NGD), a significant co-infection rate was observed, with 42% of individuals harboring both pathogens, and a higher dual prevalence of 54% in CGA patients (120). The research identified key genetic markers, such as the cagA, vacA, and oipA genes, and resistance patterns in H. pylori, suggesting that childhood is a crucial period for acquiring these infections (120). This co-infection has the potential to jointly alter the gastric mucosa, thereby influencing the clinical outcomes in affected individuals (120).

Furthermore, the cagA gene is exclusively linked to s1i1m1 or s1i1m2 vacA gene mosaicism (109, 110). The study found that 80% of GCA patients and 90% of NGD patients had the "OFF" status of the oipA gene (120). High rates of *H. pylori* resistance to clarithromycin suggest that empirical therapy should be reconsidered in Sicily. Co-infection with *H. pylori* and EBV was prevalent, with 75% of NGD and 54% of GCA patients harboring both pathogens. Further research is needed to understand their role in gastric disease (120).

Moreover, using radiological and morphological investigations, the authors conclude by urging researchers to apply both new and existing knowledge within a multidisciplinary team investigation for a more clinical amplification of the microbiological features of the gastrointestinal tract (121, 122). The aim of virologist researchers is to provide an efficient vaccination-based prevention. Currently, the authors support uniform vaccination schedules as a means of promoting health (123, 124). *H. pylori* and EBV are linked to gastric disorders. H. pylori's virulence factors (CagA, VacA, OipA) and EBV's immune evasion both contribute to cancer risk. High co-infection rates and antibiotic resistance complicate treatment. More research and improved prevention strategies are needed.

7 EBV coinfection with malaria

Each year, over 200 million people worldwide contract Plasmodium infections, resulting in approximately 1 million deaths, primarily among children under the age of 5 and pregnant women (125). In sub-Saharan Africa, *Plasmodium falciparum* is the culprit behind over 90% of these infections. The spectrum of disease severity varies, from mild febrile illness to critical conditions like cerebral malaria and severe malarial anaemia (125).

One of the crucial aspects of *P. falciparum*'s biology is its capacity to make infected red blood cells (RBCs) stick to the walls of small blood vessels (126, 127). This adherence of parasitized cells leads to significant blockages in tissue blood flow (126, 127). Moreover, in severe malaria cases, there could be notable decreases in the flexibility of healthy, uninfected RBCs (126, 127).

Given their wide geographic distribution, EBV and Plasmodium coinfection is frequent in Africa (128). EBV and Plasmodium have long been associated with the emergence of endemic Burkitt's lymphoma (eBL), the predominant pediatric cancer affecting children aged 5 to 9 in equatorial Africa (129, 130). This malignancy is a significant health concern in the region, with both pathogens playing pivotal roles in its development. While EBV is recognized as a contributing factor to eBL, particularly in its endemic form, Plasmodium's involvement underscores the complexity of this malignancy's etiology (129, 130). The coexistence of these two pathogens in equatorial Africa highlights the intricate interplay between infectious agents and the oncogenic processes leading to eBL, necessitating further investigation into their synergistic effects and potential therapeutic interventions (129, 130). In this region, children typically acquire EBV infection around the age of six months, coinciding with a decline in maternal antibodies that offer passive protection (131). This transition

marks a period of heightened susceptibility to primary Plasmodium infection, suggesting a potential interplay between the acquisition of EBV and the vulnerability to malaria (131).

Moreover, acute *P. falciparum* infection has been demonstrated to affect EBV persistence. This impact includes increased EBV levels in circulation and elevated antibody titers against the Z Epstein-Barr replication activator (ZEBRA) protein and viral capsid antigen (VCA) in peripheral blood (128, 132–134). Donati et al. demonstrated that in children living in malaria-endemic regions, EBV loads can decrease to undetectable levels after the initiation of antimalarial treatment (133).

Though the precise mechanisms through which acute malaria triggers lytic EBV infection remain unclear, prolonged and severe exposure to *P. falciparum* malaria compromises T-cell immunity, particularly CD8+ T cells, leading to a loss of viral control (130, 135, 136). Additionally, studies have shown that the polyclonal B cell activator Cysteine-rich inter-domain region 1α (CIDR1α) of the *P. falciparum* membrane protein 1 directly triggers EBV reactivation during malaria infection, heightening the likelihood of BL development in children living in malaria-endemic regions (128). Recently, instances of concurrent infection involving various Plasmodium species and EBV have been reported. In the Southeast Anatolia and Cukurova regions of Turkey, where *Plasmodium vivax* predominates as the primary cause of malaria, a notable case occurred in 2013 involving a 5-year-old child (137). This case marked the initial documented occurrence of *Plasmodium vivax* malaria coupled with EBV coinfection in the region (137). In a study conducted by Wedderburn et al., co-infection with *Plasmodium brasilianum* and EBV in marmoset mice led to more severe glomerulonephritis and longer periods of parasitemia compared to the mice infected with *P. brasilianum* alone (138). Furthermore, acute EBV infection has immunosuppressive effects on the development of humoral antimalarial immunity (125). Also, EBV infection may impact the morbidity of *P. vivax* malaria by altering hematological parameters and impairing long-term acquired antibody responses to specific *P. vivax* proteins (139). These findings indicate that acute EBV infection disrupts the immune responses to malaria. Reactivated EBV, triggered by certain risk factors, may further modify malaria immunity and worsen the disease (140, 141). Extensive research has shown that unchecked EBV reactivation can exacerbate various illnesses and increase the risk of developing tumors and malignancies like nasopharyngeal carcinoma and post-transplant lymphoproliferative disorders (140, 141).

The early production of pro-inflammatory cytokines by the innate immune cells, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-6, and others, enables quicker inhibition and clearance of the parasite, along with enhanced phagocytosis (142, 143). Dendritic Cells (DCs) infected with the gamma herpesvirus MHV68 display antigens less effectively compared to the uninfected DCs (144). Moreover, EBV can impact the functional abilities of the infected cells, hence diminishing their phagocytic ability response to other pathogens like bacteria and preventing the release of important cytokines (e.g. TNF-α) (145, 146). EBV prevents the growth of dendritic cells by inducing apoptosis in their monocytic precursors when IL-4 and granulocyte macrophage-colony-stimulating factor (GM-CSF) are present (147). Together, EBV and malaria co-infection is common in Africa and contributes to Burkitt's lymphoma in children. Malaria can boost EBV levels and weaken immune responses, worsening both infections.

8 EBV coinfection with CMV (HHV-5)

Common among the general population, CMV infection poses a significant risk in transplantation, leading to higher chances of allograft rejection, morbidity, and mortality (148). CMV directly damages different organ systems, resulting in conditions like pneumonia, gastrointestinal tract disease, and hepatitis (149, 150). CMV infection can also induce indirect immunosuppressive effects, such as disruptions in T-cell production, alterations in major histocompatibility antigen expression, and changes in cytokine and chemokine activity (150, 151). These effects further elevate the risk of opportunistic infections (150, 151). Even with advanced treatment and prevention methods, patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) face amplified mortality risks due to double-stranded DNA (dsDNA) viruses. Reactivation of various herpes viruses, notably CMV, frequently occurs post-HSCT (152). Additionally, the reactivation of EBV is common and can lead to severe complications like post-transplant lymphoproliferative disorder (PTLD) (152).

Some studies have examined the correlation between CMV reactivation and EBV in recipients of HSCT. According to the research conducted by Fan et al., pre-infection with either CMV or EBV did not notably influence the incidence of coinfection with EBV or CMV, respectively (153). Two studies (154, 155) have explored the connection between donor/recipient serostatus and the likelihood of CMV-EBV coinfection in renal transplant recipients. In the first study, all five instances of CMV-EBV coinfection were observed in cases where both the donor and recipient tested positive for CMV. In the second study, donor CMV seropositivity emerged as the sole clinical factor significantly linked to the combined CMV-EBV reactivation. Additionally, CMV-EBV coinfection was notably associated with elevated CMV and EBV viral loads exceeding detectable levels, as well as with increased CMV and EBV DNAemia (154, 155). Another study conducted by Li et al. (152) suggests that CMV reactivation negatively impacts HSCT outcomes regardless of EBV reactivation.

Numerous studies indicate that EBV and CMV often co-infect patients alongside other pathogens, but little is known about this phenomenon in children with primary EBV/CMV infection (17). In a retrospective analysis, children with suspected IM were studied (17). Results showed a significantly higher occurrence of multiple infections in children with primary EBV, CMV, or EBV/CMV infection compared to other groups (17). Moreover, patients with multi-pathogen infection and EBV/CMV primary infection experienced more severe symptoms and longer hospital stays. These findings underscore the need for further research in this area (17).

Furthermore, the frequency of CMV and EBV infections is notably higher in patients with hematological diseases, suggesting a possible association between the two conditions (156). While

Burkitt's lymphoma stands out as the primary hematological disorder linked to EBV infection, studies also indicate a connection between EBV infection and the development of various hematological diseases, particularly AML and ALL (156). Conversely, CMV infection is often associated with the onset or worsened prognosis of ALL (156). The risk of CMV infection appears to be influenced by blood transfusions, although it remains uncertain whether such transfusions elevate the risk of EBV infection. Epidemiological surveillance of both infections in patients with hematological diseases is crucial for enhancing their clinical management (156). Moreover, the reactivation rates for both viruses tend to increase among patients with hematological diseases, potentially due to the immunological status imposed by the underlying hematological condition (156).

In summary, EBV and CMV coinfection is a significant concern, particularly in immunocompromised populations like transplant recipients and those with hematological diseases. This coinfection can lead to more severe outcomes, longer hospital stays, and increased complications. The interplay between these viruses, as well as their individual and combined effects on the immune system and disease progression, underscores the need for vigilant monitoring and tailored management strategies in at-risk populations.

9 EBV coinfection with HHV-6

The herpesvirus family includes HHV-6 viruses, of which HHV-6A and HHV-6B are the prominent subtypes that are classified based on genetic, antigenic, and possible variations in each of their pathogenicity (157, 158). Most children are infected with this virus during their early years of life, and like most other herpes viruses, it remains dormant in the body after the primary infection (159).

In EBV-related NPC, there's a notable trend of HHV-6/EBV coinfection. In a study of 34 NPC tumor samples, 14.7% tested positive for HHV-6 DNA and 94.1% for EBV DNA (160). Conversely, none of the nasopharyngeal tissue samples from five controls showed positivity for either viruses (160). Furthermore, the presence of HHV-6 infection in NPC specimens has been associated with increased expression of EBV LMP-1 (161).

While evidence indicates that HHV-6 is present in specific cancer types, solely detecting the virus within the tumor cells does not suffice to definitively attribute a direct role to HHV-6 in tumorigenesis (162). Credible signs of a virus playing a causal role in cancer include its prevalence across a significant portion of cases, its pervasiveness within most tumor cells, and its capacity to induce cell transformation in laboratory conditions (162). Although HHV-6 may not directly induce cancer, it can act as a contributing factor, indirectly fostering tumor cell growth, potentially through collaboration with other viruses (162). Alternatively, HHV-6 might be an opportunistic virus thriving in the immunodeficient tumor microenvironment (162). Despite numerous studies, conclusively, linking HHV-6 to various human cancers remains unclear (162). Some evidence suggests that HHV-6 could collaborate with other viruses like EBV, HPV, and HHV-8 in cancer development,

implicating it in conditions such as nodular sclerosis Hodgkin lymphoma, gastrointestinal cancer, glial tumors, and oral cancers. However, further research is necessary to elucidate HHV-6's precise role in tumorigenesis (162).

Taken together, the relationship between EBV and HHV-6 is complex, particularly in the context of nasopharyngeal carcinoma (NPC) and other cancers. While HHV-6 is frequently detected alongside EBV in certain tumors, its exact role in carcinogenesis remains unclear. HHV-6 may act as a cofactor in cancer development, potentially collaborating with EBV and other viruses, but further research is needed to fully elucidate its role in tumorigenesis and its interactions with EBV.

10 EBV coinfection with KSHV (HHV-8)

Although human herpes virus 8 (HHV-8) is known to be associated with Kaposi sarcomas, it can also cause primary effusion lymphoma (PEL) and Castleman's disease (MCD) (163). EBV and Kaposi sarcoma-associated herpesvirus (KSHV), the two human γ-herpesviruses, are classified as WHO class I carcinogens (164). Numerous neoplasms can result from HHV8 and EBV infections, either synchronously or alone (165). Most research has been done on the two human tumor viruses, KSHV and EBV, separately (166). According to recent research, KSHV persistence may require co-infection with EBV, as seen in PEL, one of their related cancers (167). The two viruses attack B cells in submucosal secondary lymphoid tissues, including the tonsils, and are assumed to be mainly spread via salivary fluids (168, 169). Since 1995, KSHV infection has been linked to PELs, and since then, detecting KSHV has been crucial in the diagnosis of PELs (170). In well-established PEL cell lines, co-infection is commonly observed, resulting in the two viral genomes being preserved, independently replicating, and being divided into the daughter cells (166, 171). In vitro studies have revealed that KSHV may infect peripheral B cells on its own, but it cannot convert them and thus cannot persist (172). Research conducted on mice have also shown that co-infection with EBV raises the likelihood of KSHV persistence (173). Co-infection with EBV stimulates B cells, promotes long-term KSHV infection, and allows for cell proliferation via transformation (172). KSHV genomes appear to be maintained by EBV co-infection; this is shown by the higher number of KSHV genomes per cell seen in the co-infected cells, although the precise mechanism is unclear (172). PEL cells require latent KSHV gene expression primarily LANA, vFLIP, and vIRF3—in addition to EBV genes in order to survive, since these genes engage with tumor suppressors and impede apoptotic mechanisms (174, 175). Through its association with KSHV terminal repeat sequences, LANA mediates the KSHV episome's persistence (176). Additional viral genes are not necessary for this persistence, and LANA knockdown results in the loss of episomes (177). NF-κB is essentially active in PEL and can be activated by vFLIP (178). Due to its increased apoptosis and decreased proliferation upon knockdown, vIRF3 is necessary for the survival of both EBV+ and EBV⁻ PEL cells (179). Epidemiology

evidence suggests that KSHV infection is almost always associated with EBV co-infection and that one of the strongest environmental risk factors for KSHV seropositivity is EBV seropositivity (180, 181). As a result, EBV gene expression supports B cell transformation, proliferation, and survival while also aiding in KSHV persistence in the B cells. This permits EBV co-infection-induced KSHV persistence (167). Research indicates that KSHV and EBV both have a role in the development of primary effusion lymphomas, and that co-infection can raise the risk of developing tumors by influencing the tumor microenvironment and promoting its development and longevity (182). The interplay between EBV and KSHV is significant in several malignancies, particularly PEL. EBV appears to play a crucial role in supporting KSHV persistence and transformation in B cells. Their co-infection can enhance viral genome maintenance, cell survival, and tumor development. This synergistic relationship highlights the importance of considering viral co-infections in the pathogenesis and management of certain lymphoproliferative disorders.

11 Treatment approaches

Recent advancements in understanding the pathobiology of EBV oncogenesis have paved the way for novel therapeutic strategies (11). These approaches capitalize on insights into the virus' immunogenic and transforming properties, as well as its role in immunological dysregulation (11). Among these techniques, adoptive T-cell therapies, EBV vaccines, inhibition of EBV-induced carcinogenic signaling pathways, and the induction of lytic viral infection alongside antiviral drugs are the most investigated ones (11). Although there have been significant advancements in the treatment of EBV-associated cancers, there are still a number of obstacles to overcome (183).

Research on drug discovery of viral target inhibitors and EBV-activated cellular targets, disruption of latent infection, and development of immunotherapeutic agents, such as vaccines and adoptive cellular therapies, are all included in the scope of current and future studies (184).

Target-based therapy development offers a promising approach for treating cancers associated with EBV. Specifically, T cell-based immunotherapy targets viral proteins produced by tumor cells, which serve as immunogenic tumor-specific targets (185, 186). Since oncogenic viral proteins manipulate cell signaling pathways involved in cell survival and proliferation, potential targets for therapy can be readily identified. Initial attempts to modify immune responses to the virus for treating EBV-associated malignancies were focused on PTLD (185, 186). These efforts involved infusing unmodified donor mononuclear cells into post-transplant patients, yielding high response rates, however, unselected cell populations carry a risk of graft-versus-host disease (GVHD) (185, 186). Subsequent research found that using cytotoxic T lymphocytes (CTLs) specific for EBV-encoded antigens may provide more potent anti-tumor effects without increasing the risk of GVHD (187, 188).

Currently, preemptive CTL therapy is preferred because it seems to work better than direct PTLD therapy, however, treating advanced PTLD with CTLs can cause significant side effects due to strong inflammatory responses. Despite this, this method can still lead to complete remission (187).

In the last decade, our understanding of how EBV triggers cell transformation and evades host immune defenses has greatly improved (187). The use of polyclonal EBV-specific CTLs has shown success in preventing and treating PTLD patients (187). This experience highlights the need for further research to validate the effectiveness of CTL-based therapies in treating diseases associated with EBV, such as NPC (189). While initial results are promising, enhancing T-cell responses to less immunogenic targets like LMP-1 and LMP-2 is crucial to improve treatment outcomes (189). CTL treatment shows promise in the prevention of PTLD, although specific intervention criteria remain unclear. Monitoring EBV DNA load can be helpful, but its predictive accuracy is limited, necessitating additional parameters to evaluate EBV-specific T cell responses (189). Various other virus-targeted treatment approaches are also under investigation, including triggering the EBV tumor cells' lytic cycle; although challenges exist due to the highly controlled promoters of key lytic genes (189). Clinical trials focusing on understanding the viral and cellular mechanisms regulating the transcription of these genes can help confirm the practical applicability of this method. Additionally, treatment strategies aiming to eliminate EBV episomes from tumor cells, such as hydroxyurea administration, hold clinical significance (189).

As more clinics adopt immunotherapy to treat EBV-related cancers, new advanced strategies are poised to move swiftly from research to bedside (190). One such approach is RNA interference (RNAi), a recently discovered process that targets specific genes by degrading mRNAs within cells (190). This natural defense mechanism is found in animals and plants, offering potential effectiveness against viral infections (190). RNAi involves cleaving double-stranded RNA, typical of viruses, into small segments (siRNA), about 21–23 nucleotides long. These siRNAs are processed by Dicer and incorporated into the RNA Induced Silencing Complex (RISC), which degrades single-stranded RNA molecules in the cytoplasm, like mRNAs. RNAi holds promise for treating genetic diseases and gene-related disorders, including cancer (191–193). Specifically, recent studies have shown the effectiveness of RNA interference (RNAi) in inhibiting cancer growth in virus-associated cancers (191–193). In these cases, the silencing of a crucial viral protein necessary for cell transformation has been found to hinder the growth of cancerous cells, while leaving healthy cellular networks intact (191–193). Moreover, recent studies focusing on EBV-related cancers have revealed that silencing LMP-1 in NPC cells notably diminishes tumor cell metastasis, offering promising therapeutic strategies for treating not only nasopharyngeal carcinoma but also other EBV-related cancers (193). The full use of RNAi's therapeutic potential will be possible if issues with siRNA delivery efficiency are resolved (194).

Treatment strategies for EBV-associated cancers have diversified, including T-cell therapies, vaccines, and targeting of viral pathways. While cytotoxic T lymphocyte therapy shows promise, especially for PTLD, emerging techniques like RNA interference offer new possibilities. Despite progress, challenges in efficacy and delivery persist, driving ongoing research to refine these approaches.

12 Conclusion

In conclusion, the prevalent EBV is known to coexist and coinfect with various other pathogens, leading to intricate interactions that can contribute to the development and progression of several cancers and other diseases. The coinfection of EBV with HPV is proposed to involve cooperation between viral oncoproteins, chromatin interactions, and the potential involvement of the EBV lytic cycle in oncogenesis. EBV's coinfection with Plasmodium species, particularly *P. falciparum* and *P. vivax*, has been implicated in the pathogenesis of endemic Burkitt's lymphoma and the exacerbation of malaria morbidity through mechanisms such as the disruption of antimalarial immunity and CD8+ T-cell responses. Coinfections with CMV and other herpesviruses, including HHV-6 and KSHV/HHV-8, have been associated with increased viral loads, altered disease progression, and the facilitation of viral persistence and transformation of infected cells. These intricate coinfection scenarios highlight the need for further research to elucidate the underlying mechanisms and develop targeted therapeutic strategies that address the synergistic effects of multiple pathogens. Understanding the complex interplay between EBV and other microbial agents will be crucial in combating the oncogenic potential of these coinfections and thus improving the clinical outcomes for affected patients.

Author contributions

FE: Investigation, Writing – original draft, Writing – review & editing. RR: Investigation, Writing – original draft, Writing – review & editing. SS: Investigation, Writing – original draft, Writing – review & editing. PSA: Writing – review & editing. AS: Writing – review & editing. AJS: Writing – review & editing. HBB: Conceptualization, Supervision, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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