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Shadows of Epstein-Barr Decoding the Silent Virus

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Abstract

Epstein-Barr virus (EBV), a double-stranded DNA virus belonging to the Herpesviridae family, infects over 95% of the global adult population, establishing lifelong latency primarily in B lymphocytes. Primary infections usually occur during childhood or adolescence, often presenting asymptomatically or as infectious mononucleosis (IM), which includes symptoms such as fever, pharyngitis, lymphadenopathy, and splenomegaly. EBV is associated with various malignancies, including Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and gastric carcinoma, as well as lymphoproliferative disorders in immunocompromised individuals due to its oncogenic potential. Recent epidemiological studies (2023–2025) have uncovered regional variations in infection patterns and suggested links to autoimmune diseases like multiple sclerosis, possibly through mechanisms of molecular mimicry and immune dysregulation. Pathogenetically, EBV employs latent membrane proteins (LMP1/2) and Epstein-Barr nuclear antigens (EBNAs) to disrupt cellular signaling pathways such as NF-κB, PI3K/AKT, and JAK/STAT. This disruption promotes cell proliferation, evasion of apoptosis, and immune escape. Advancements in next-generation sequencing have revealed the genotypic diversity of EBV, which can influence disease outcomes. In terms of therapy, while antiviral agents like acyclovir show limited efficacy against latent infections, emerging strategies—including EBV-specific cytotoxic T-cell therapies, monoclonal antibodies targeting viral glycoproteins (e.g., gp350), and prophylactic vaccines currently in clinical trials—hold promise for addressing EBV-related diseases. This review consolidates recent insights into EBV's interactions at both micro and macro levels, highlighting the necessity for integrated surveillance and targeted interventions to reduce the global burden of EBV-associated pathologies

Introduction

The Epstein-Barr virus (EBV); a member of the herpesviridae family and the gamma-herpesvirus subfamily; is a double-stranded DNA virus that ranks among the most common human viruses; infecting over 95% of the adult population worldwide [1]. Identified in 1964 by Michael Epstein and Yvonne Barr in Burkitt's lymphoma cells; EBV was the first virus to demonstrate a direct link to human cancers; making it a significant focus in virology and oncology research ever since [2]. After initial infection; EBV can remain dormant; primarily in B lymphocytes and; to a lesser extent; in epithelial cells; potentially persisting asymptomatically or presenting with various clinical manifestations throughout a person's life [3].

Early infections often occur in childhood and are typically asymptomatic; however; during adolescence or young adulthood; EBV can cause infectious mononucleosis (IM); characterized by symptoms such as fever; severe sore throat; lymph node swelling; chronic fatigue; and splenomegaly [4]. One of the most notable aspects of EBV is its oncogenic potential; which is linked to several malignancies; including Burkitt lymphoma; Hodgkin's lymphoma; nasopharyngeal carcinoma; gastric carcinoma; and lymph proliferative disorders in immunocompromised individuals; such as transplant recipients or those with HIV [1]. The virus utilizes latent proteins; such as latent membrane proteins (LMP1 and LMP2) and Epstein-Barr nuclear antigens (EBNAs); to activate key signaling pathways like NF-kB; PI3K/AKT; and JAK/STAT [5]. This activation

leads to abnormal cell proliferation; inhibition of apoptosis; and immune evasion. Recent studies from 2023 to 2025 have also pointed to EBV's involvement in autoimmune diseases such as multiple sclerosis (MS); systemic lupus erythematosus (SLE); and rheumatoid arthritis; through mechanisms like molecular mimicry and excessive immune system stimulation [6]. These findings underscore the significance of EBV beyond just infectious and cancer-related diseases. From an epidemiological standpoint; patterns of EBV infection vary globally. In developing regions; infections typically occur early and are often asymptomatic; while in developed countries; the infection is more prevalent during adolescence and young adulthood; increasing the chances of IM [7]. Advances in next-generation sequencing have revealed that the genotypic diversity of EBV; particularly specific strains in regions like East Asia; correlates with the severity and type of associated diseases. Diagnosing EBV can be challenging due to its latent nature. Serological methods; such as testing for IgM/IgG antibodies against viral capsid antigen (VCA) and Epstein-Barr nuclear antigen (EBNA); along with molecular techniques like PCR; are utilized; however; these methods have limitations in distinguishing active infections from latent ones. Current treatments include antiviral medications like acyclovir and ganciclovir; which are effective during the virus's active replication phase but have limited efficacy against latent infections. New therapeutic strategies are emerging; including EBV-specific T-cell immunotherapy; monoclonal antibodies targeting viral glycoproteins (such as gp350); and prophylactic vaccines currently in advanced clinical trials (2024-2025). These developments offer promising avenues for prevention and treatment.Given the global burden of EBV-related diseases and the recent advancements in understanding its pathogenesis; genotypic diversity; and treatment options; EBV continues to be a crucial topic in medical research. This paper aims to provide a comprehensive overview of EBV's epidemiology; pathogenesis; diagnosis; existing therapies; and emerging strategies; with a focus on proposed therapies to alleviate the global burden of the virus [8].

History and discovery of Epstein-Barr virus (EBV)

Epstein-Barr Virus (EBV) is one of the most prevalent human viruses: infecting over 90 percent of the global population. It belongs to the herpesviridae family and is recognized as the first tumor-associated virus in humans. While EBV typically causes asymptomatic or mild infections in children; it can result in diseases like infectious mononucleosis; commonly known as "Kiss disease;" in adolescents and adults. Additionally; EBV is linked to various cancers; including Burkitt lymphoma; Hodgkin's lymphoma; nasopharyngeal carcinoma; and some autoimmune diseases; such as multiple sclerosis (MS). The discovery of EBV marked a significant turning point in virology and oncology; and recent research has made substantial progress in understanding its mechanisms and developing treatments. This article explores the history of EBV's discovery; highlighting key events and scientific updates up to 2025. The story of EBV's discovery begins with Denis Burkitt; a British surgeon operating in Uganda during the 1950s. He observed an unusual form of lymphoma prevalent among East African children; which later became known as "Burkitt lymphoma. This tumor was particularly common in moist; tropical regions like those surrounding Lake Victoria [9]. In 1958; Burkitt published an article describing the disease as an unknown syndrome; suggesting that environmental or infectious factors contributed to its occurrence due to its geographical pattern resembling that of infectious diseases. In 1961; Burkitt delivered a lecture in London about this lymphoma; attracting the attention of Michael Anthony Epstein; a pathologist and electron microscope expert at London's Middlesex Hospital. Epstein suspected a viral cause for the cancer and collaborated with his research assistant; Yvonne Barr; and Bert Achong to obtain tumor samples from Uganda. By 1963; a fresh sample arrived in London; and Epstein's team successfully cultivated tumor cells in the laboratory. Using an electron microscope; they identified herpes virus-like particles within the cells. Their findings were published in March 1964 in The Lancet; and the virus was named Epstein-Barr; acknowledging Epstein and Barr's contributions; though Achong also played a crucial role. This early discovery faced skepticism from the scientific community; as the concept of carcinogenic viruses was relatively new. However; Epstein and his colleagues made further advances by sending cultured cells to Werner and Gertrude Henle at the Children's Hospital of Philadelphia. In 1967; a laboratory technician who contracted mononucleosis revealed elevated antibodies against EBV in his blood; confirming the association between EBV and infectious mononucleosis. Over the next few decades; research on Epstein - Barr virus (EBV) shifted from understanding its role in infections to its mechanisms in cancer. In 1968; researchers discovered that EBV can immortalize B cells and maintain them in a latent state; similar to its behavior in EBV-related infections. By the 1970s; the association of EBV with other cancers; including Hodgkin's lymphoma and nasopharyngeal carcinoma; was confirmed. In 1984; EBV became the first virus to have its genome sequenced; revealing the longest piece of DNA identified at that time. During the 1980s and 1990s; scientists gained a deeper understanding of the EBV life cycle; which consists of two phases: the latent phase; where the viral genome integrates into the host cell's nucleus; and the lytic phase; which involves active replication of the virus EBV is primarily transmitted through saliva and establishes infection in B cells and epithelial cells. While primary infections are often asymptomatic; they can lead to severe illnesses in individuals with weakened immune systems.(Vietzen) Recently; EBV has also been linked to autoimmune diseases. For example; a 2022 study suggested that EBV may be a primary cause of multiple sclerosis (MS); as infection with EBV increases the risk of developing MS by 32 times. By 2025; research on Epstein-Barr virus (EBV) is ongoing; with several new findings reported. In 2023; researchers at the University of Florida discovered that EBV utilizes five key enzymes to transition from transcription to replication. This insight could lead to the development of drugs that prevent the virus from replicating; particularly in patients with weakened immune systems. In 2024; a study published in Frontiers in Immunology highlighted the role of EBV in "safety turbulence; referring to it as the "core mind of safety turbulence [10]. That same year; the death of Anthony Epstein at age 102 served as a poignant reminder of his significant contributions to the field. Additionally; a study by Pyöriä and colleagues investigated the genomic diversity of EBV within hosts; revealing that the virus can promote tumor formation by integrating into the human genome. In 2025; the University of Birmingham traced the history of EBV research in Britain; acknowledging Epstein's foundational discovery. Clinical trials at UCSF began exploring the use of EBV-specific T cells to treat resistant infections; particularly among transplant patients. A study published in Nature Communications in July 2025 identified over 1;400 EBV transcription is forms and elucidated the role of the origin of lytic replication (Erilyt) as a gene enhancer; contributing to a better understanding of viral gene expression. Furthermore; research at QIMR Berghofer is focused on an EBV vaccine designed

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to activate lethal T cells; with promising results observed in preclinical models. This vaccine has the potential to prevent secondary diseases; such as multiple sclerosis. In 2024; another study featured in Science Daily emphasized the inhibition of a specific metabolic pathway in infected cells; which could reduce latent infections and lower cancer risk. Despite these advancements; challenges remain. There is still no specific vaccine or treatment for EBV; and controlling latent infections proves difficult. Future research will concentrate on vaccines; cell therapies; and understanding genomic integration. With EBV linked to approximately 200;000 cancers annually; effective prevention strategies could have a significant global impact.

Epidemiology and global patterns of Epstein-Barr virus infection (EBV)

The Epstein-Barr virus (EBV) is one of the most common human viruses: infecting over 90 percent of the global population. It is the leading cause of infectious mononucleosis (IM) and is associated with several types of cancer. As a member of the herpes virus family; EBV is primarily transmitted through saliva; but it can also spread through blood; semen; or organ transplants. Early infections typically occur in childhood and are often asymptomatic; though they can result in IM in adolescents and adults. Once infected; the virus remains dormant in memory B cells for life and can reactivate under conditions of immunosuppressant. The epidemiology of EBV is influenced by geographical factors. This section examines the global prevalence and patterns of infection by age and region; as well as recent trends through 2025; with a focus on age and environmental factors such as COVID-19.

Global prevalence and contributing factors

EBV has a very high global prevalence: affecting over 95% of adults. According to data from the World Health Organization (WHO) and various epidemiological studies; approximately 90-95% of the world's population will be infected with EBV by age 25. In the United States; the National Health and Nutrition Examination Survey (NHANES) conducted from 2003 to 2010 found that 66.5% of children aged 6-19 had EBV antibodies. This prevalence increased from 54% in children aged 6-8 to 89% in those aged 18-19. Additionally; prevalence rates vary among racial groups; for example; Mexican-Americans show rates as high as 80%; while rates for non-Hispanic whites are about 50%; and non-Hispanic blacks show lower rates. Socioeconomic factors; such as low household income; lack of health insurance; and larger family sizes; are associated with higher prevalence rates. EBV is linked to several cancers worldwide; including Burkitt lymphoma (BL); Hodgkin's lymphoma (HL); nasopharyngeal carcinoma (NPC); and gastric carcinoma (GC). The 2017 Global Burden of Disease (GBD) study reported approximately 265; 000 new cases and 164; 000 deaths from EBV-related cancers; representing 1.3-1.9 percent of the global cancer burden. Since 1990; new cases have increased by 36%; and deaths have risen by 19%; primarily due to population growth and longer life expectancy. Men are more significantly affected; with a sex ratio of 1.5:1; and the disease burden is higher in regions with a moderate to high socio-economic development index (SDI).

Patterns of infection by age

EBV infection patterns vary significantly with age. In developing countries: primary infections typically occur in early childhood (before age 5) and are often asymptomatic. In contrast; developed countries see delays in infection until adolescence or young adulthood; resulting in infectious mononucleosis (IM) in 35-50% of cases. According to NHANES data; the prevalence of EBV in children aged 6-8 years is approximately 50 percent and continues to rise with age. In the UK; the prevalence among individuals aged 11-24 years is 74.6 percent; with a notable increase among teenage girls. The age at which primary infection occurs is linked to the risk of EBV-related diseases; later infections heighten the risk of IM and subsequent cancers; such as multiple sclerosis (with a 32-fold increased risk after recent infection). Recent years have seen changes in these patterns due to the COVID-19 pandemic. A 2025 study in Argentina revealed that social restrictions led to a decline in EBV infections among children and an increase in the average age of healthy carriers. Similarly; in China; infections among children dropped by 30 percent post-pandemic; potentially raising the risk of late-onset diseases.

Geographical patterns and regional differences

EBV patterns vary significantly by geography and are influenced by socioeconomic factors: hygiene; and environmental conditions like malaria. In developing countries; particularly in sub-Saharan Africa and Southeast Asia; early infection rates are high; with approximately 90% of children infected by the age of 3 to 4 years. This early prevalence is linked to endemic Burkitt lymphoma (eBL). In Africa; eBL is often associated with co-infection by malaria (Plasmodium falciparum); and the prevalence of EBV in cases of Burkitt lymphoma is around 95%.(Smith, et al., 2025) Nasopharyngeal carcinoma (NPC) is also endemic in Southeast Asia (notably in China and Vietnam) and North Africa; with EBV detected in 90% of cases. Genetic factors; such as HLA types; and dietary influences; particularly the consumption of salty foods; contribute to this prevalence. In contrast; developed countries like those in Europe and North America experience later infections; with infectious mononucleosis (IM) occurring more frequently—approximately 500 cases per 100;000 people annually in the United States. In Europe; over 80% of adults are infected; although rates are lower in children. In the Middle East; particularly Qatar; the prevalence among healthy blood donors is 88%; with slight variations based on nationality; showing higher rates among Syrians and Egyptians. In Japan; more than 90% of adult's exhibit serological positivity for EBV; which is also associated with gastric cancer (GC) Genotypic differences in Epstein-Barr Virus (EBV) types 1 and 2 are also influenced by geography. Type 1 is the dominant strain globally; while Type 2 is equally prevalent in Africa and Papua New Guinea. Recent studies (2025) indicate that genetic recombination of EBV affects geographic distributions; identifying 12 phylogenetic populations linked to specific regions; such as Asia I with gastric cancer (GC). By 2025; the overall EBV outbreak remained stable; however; the COVID-19 pandemic led to a decline in infections among children; dropping from 30 percent in 2019 to 9

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percent in 2022 in certain areas. This reduction may increase the risk of infectious mononucleosis (IM) and late-onset cancers. In the Middle East; particularly in Saudi Arabia from 2020 to 2023; the prevalence of EBV among inpatients was 21.4%; and there was an association with systemic lupus erythematosus (SLE) and immunodeficiency. Globally; the burden of EBV-related cancers is approximately 200; 000 cases per year; with East Asia accounting for 50 percent of nasopharyngeal carcinoma (NPC) and gastric cancer cases.

Pathogenesis and molecular mechanisms (role; LMP1/2 EBNAs and signaling pathways)

The Epstein-Barr virus (EBV); a member of the herpes virus family: is one of the most prevalent human viruses; infecting over 90 percent of the global population. It is notorious for establishing latent lifelong infections and is linked to various diseases; including infectious mononucleosis (IM); cancers such as Burkitt lymphoma; Hodgkin's lymphoma; and nasopharyngeal carcinoma; as well as autoimmune disorders like multiple sclerosis (MS). The pathogenesis of EBV arises from the intricate interactions between the virus and the host immune system; along with the molecular mechanisms that facilitate its long-term survival and replication. This section will examine the overall pathogenesis; infection cycle; effects on the immune system; and the role of the virus in disease development by 2025.

Infection cycle and entry mechanisms

EBV is primarily transmitted through saliva but can also spread through blood: organ transplantation; and sexual contact. The virus mainly targets B lymphocytes and epithelial cells. It enters B cells by binding its viral glycoprotein's; such as gp350; to the cells surface receptors; like CD21. Once inside; the viral genome remains in the host cell's nucleus as an episome and can operate in two modes: latent or lytic (active). During the latest phase; the virus expresses a limited number of genes; allowing it to evade detection by the immune system. In the lytic phase; the virus replicates and generates new particles; ultimately leading to the destruction of the host cell. Early infections in children are typically asymptomatic; whereas in adolescents and adults; they can result in infectious mononucleosis (IM); characterized by symptoms such as fever; sore throat; and lymphadenopathy. After the initial infection; EBV persists in memory B cells and can reactivate under conditions of immunosuppressant; such as in HIV infection or following organ transplantation.(Vietzen) Studies conducted through 2025 have indicated that the genomic diversity of EBV; particularly across different geographical regions; influences the severity of infection and its pathogenesis.

Effects on the immune system

EBV is highly adept at evading the immune system. During its latent phase: the virus produces proteins that suppress immune responses; including the inhibition of apoptosis (programmed cell death) and the alteration of immune signaling.(Vietzen)These proteins cause B cells to enter "immortal" states; which can lead to cancers like lymphoma. Additionally; EBV disrupts immune responses by promoting the production of inflammatory cytokines; such as IL-10. A 2023 study published in Frontiers in Immunology found that EBV can drive the immune system towards inefficient responses by creating "immune turbulence;" which is linked to autoimmune diseases like multiple sclerosis (MS). Furthermore; a 2022 study confirmed that EBV infection increases the risk of developing MS by 32 times; potentially due to the cross-reaction of antibodies.

Role in disease and cancer

EBV is linked to various diseases. In Burkitt lymphoma: particularly the endemic type found in Africa; EBV interacts with malaria infection; leading to abnormal B-cell proliferation. In nasopharyngeal carcinoma; a combination of genetic and environmental factors; such as a salty diet; contributes to the impact of EBV. Research published in Nature Communications indicated that by 2025; EBV alters the expression of host genes through epigenetic regulation; increasing cancer risk. Additionally; in noncancerous conditions; EBV can worsen chronic fatigue syndrome and immunological disorders. By 2025; research has concentrated on the molecular mechanisms of EBV. A 2023 study at the University of Florida discovered that EBV employs specific enzymes to transition from transcription to replication; highlighting a potential target for new drug development. Clinical trials at UCSF in 2025 are exploring the use of EBV-specific T cells to treat resistant infections in transplant patients. Additionally; advancements in vaccine development at QIMR Berghofer; which stimulate T-cell immune responses; have shown promise in preventing related diseases such as multiple sclerosis (MS).

Clinical manifestations (infectious mononucleosis; malignancies; autoimmune diseases)

The Epstein-Barr virus (EBV) is one of the most prevalent human viruses and is linked to a variety of clinical manifestations; ranging from mild infections to serious conditions; including malignancies and autoimmune disorders. Primarily transmitted through saliva; EBV is found in over 90% of the global population. While early infections during childhood are often asymptomatic; adolescents and adults may experience infectious mononucleosis (IM). Additionally; EBV has been associated with several cancers; such as Burkitt lymphoma; Hodgkin's lymphoma; and nasopharyngeal carcinoma; as well as autoimmune diseases like multiple sclerosis (MS).

Infectious mononucleosis (IM)

Infectious mononucleosis; commonly referred to as "Kiss disease;" is the most prevalent clinical manifestation of Epstein-Barr virus (EBV) in adolescents and young adults aged 15 to 24 in developed countries. Symptoms typically include fever; a severe sore throat (often accompanied by white exudates on the tonsils); lymphadenopathy (especially in the neck); and significant fatigue. Splenomegaly (enlarged spleen) occurs in 50-60% of cases; while hepatomegaly (enlarged liver) affects 10-15% of patients. Diagnosis is confirmed in 80-90% of cases through tests showing atypical lymphocytosis (an increase in abnormal lymphocytes) and the

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presence of positive heterophile antibodies. Symptoms generally persist for 2-4 weeks; although fatigue can last for several months. Studies conducted in 2025 indicate that the severity of infectious mononucleosis is greater in individuals who experience early infection at an older age; potentially due to an overactive immune response. Rare complications may include spleen rupture; thrombocytopenia; or neurological syndromes such as meningitis. Treatment primarily focuses on supportive care; including rest and hydration; with corticosteroids reserved for severe cases; such as that involving airway obstruction.

EBV-related malignancies

EBV was the first human virus identified as a carcinogen and is linked to several malignancies. Burkitt lymphoma (BL); particularly the endemic type found in sub-Saharan Africa; is strongly associated with EBV; accounting for 95% of cases. This lymphoma typically affects children aged 4 to 7 years and is characterized by rapidly growing lumps in the jaw or abdomen. The risk of developing BL is heightened by co-infection with malaria. Hodgkin's lymphoma (HL) is also associated with EBV; present in 20-50% of cases; particularly in mixed-cell types; and is characterized by symptoms such as painless lymphadenopathy and night sweats. Nasopharyngeal carcinoma (NPC) is prevalent in East Asia and North Africa; with 80-90% of cases testing positive for EBV; it presents with cervical masses; nasal congestion; and hearing loss. Gastric carcinoma (GC) is associated with EBV in 8-10% of cases; notably in Japan. A 2024 study published in Nature revealed that EBV enhances cancer cell proliferation through the epigenetic regulation of host genes. (Nwankwo, 2025) Post-transplant lymphomas (PTLD) are common among immunosuppressed patients; such as transplant recipients; and can progress rapidly. According to data from 2025; approximately 200; 000 cancer cases each year are attributed to EBV; representing 1.5 percent of the global cancer burden.

Autoimmune diseases

EBV has been linked to several autoimmune diseases; most notably multiple sclerosis (MS). A study published in Science in 2022 found that EBV infection increases the risk of developing MS by 32 times. This heightened risk may stem from the cross-reaction of antibodies against viral proteins and the brain's myelin proteins. Symptoms of MS include muscle weakness; sensory disturbances; and balance issues. Additionally; EBV is associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In SLE; anti-EBV antibodies are present in 99% of patients and can trigger the disease. A 2023 study in Frontiers in Immunology proposed that EBV induces "immune turmoil" by promoting chronic inflammatory responses; which contribute to autoimmunity. Chronic fatigue syndrome (CFS) is also linked to EBV; though the causal relationship remains unclear. In 2025; research at UCSF revealed that EBV can alter the gut micro biome and worsen systemic inflammation; both of which play a role in autoimmune diseases.

The Association of EBV with malignancies (Burkit lymphoma; Hodgkin's; nasopharynx carcinoma and stomach)

Epstein-Barr virus (EBV) is the first human virus identified as a carcinogen and has been associated with several types of cancer; including Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); and gastric carcinoma (GC). Infecting over 90 percent of the global population; EBV can promote abnormal cell proliferation by causing latent infections in lymphocytes and epithelial B cells. This occurs through epigenetic regulation and the activation of oncogenic pathways.

Burkitt lymphoma-BL

Burkitt lymphoma (BL) is an aggressive non-Hodgkin lymphoma primarily affecting children in endemic regions; particularly sub-Saharan Africa. The endemic type of BL (eBL) is linked to Epstein-Barr virus (EBV) in 95-98% of cases. This malignancy is characterized by the rapid growth of tumors in the jaw; abdomen; or other organs. Co-infection with malaria (Plasmodium falciparum) significantly contributes to eBL; as malaria induces chronic B-cell stimulation and enhances EBV replication. The molecular mechanism involves the activation of the c-Myc gene through chromosomal translocation; commonly t(8;14); which is further promoted by EBV. A 2024 study published in Nature Communications revealed that latent EBV proteins; such as EBNA1; modify epigenetic regulation and elevate c-Myc expression. Epidemiologically; eBL is prevalent in tropical regions with a high incidence of malaria; such as Uganda; where the rate is estimated at 5-10 cases per 100;000 children. Treatment typically involves intensive chemotherapy; including cyclophosphamide; however; the five-year survival rate in resource-limited areas is approximately 50%.

Hodgkin's lymphoma (Hodgkin Lymphoma - HL)

Hodgkin's lymphoma (HL) is linked to the Epstein-Barr virus (EBV) in 20-50% of cases; particularly in the mixed cellular type (MCHL) and in developing countries.(Ofoezie, 2025) EBV is found in Reed-Sternberg cells (HRS); where viral proteins like LMP1 activate NF-kB signaling pathways that promote cancer cell survival. Common symptoms of HL include painless lymphadenopathy; night sweats; fever; and weight loss. Epidemiologically; EBV-related HL is more prevalent among children and older adults; and it occurs more frequently in regions with lower socioeconomic indicators; such as Africa and the Middle East. A 2025 study published in the Journal of Clinical Oncology reported that EBV is associated with a poorer prognosis in MCHL; although immunotherapy with PD-1 inhibitors demonstrated improved outcomes. The global incidence of HL is approximately 1 case per 100;000 people; with 30% of these cases being EBV-positive.

Nasopharynx carcinoma (Gastric Carcinoma - GC)

Nasopharyngeal carcinoma; an epithelial cancer; is linked to Epstein-Barr virus (EBV) in 80-95% of cases and is particularly prevalent in Southeast Asia (notably China and Vietnam) and North Africa.(Su, 2023) Common symptoms include cervical lumps; nasal congestion; nosebleeds; and hearing loss. EBV contributes to cancer development by infecting nasopharyngeal epithelial cells and expressing latent proteins; such as LMP2. Both genetic factors; like HLA genes; and environmental factors; such as the consumption of salty and smoked foods; increase the risk of developing this cancer.A 2023 study published in Cancer Research revealed that

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EBV produces viral microRNAs (miRNAs) that inhibit apoptosis. Epidemiologically; nasopharyngeal carcinoma has a high incidence rate in South China; with 20-30 cases per 100;000 people. Treatment options include radiotherapy and chemotherapy; however; late diagnosis can lower the five-year survival rate to 60-70 percent. Clinical trials in 2025 are set to explore EBV vaccines and therapeutic T cells.

Gastric carcinoma (Gastric Carcinoma - GC)

EBV is implicated in 8-10% of gastric carcinoma cases; particularly the diffuse type; with a higher prevalence in East Asia (Japan and Korea). Common symptoms include abdominal pain; weight loss; and gastrointestinal bleeding. The virus facilitates cancer progression by infecting stomach epithelial cells and causing epigenetic changes; such as DNA methylation. A 2024 study published in Gastric Cancer identified specific EBV strains; including Asia I; as being associated with gastric carcinoma. Annually; approximately 80; 000 new cases of EBV-related gastric carcinoma are diagnosed; with a higher incidence in men at a ratio of 2:1. Treatment options encompass surgery; chemotherapy; and immunotherapy; however; the prognosis is poor in advanced stages; with a five-year survival rate of only 20-30 percent.

By 2025; research indicates that Epstein-Barr virus (EBV) contributes to approximately 1.5 percent of the global cancer burden; translating to around 200; 000 annual cases; with the highest prevalence in East Asia and Africa. Promising new immunotherapy's; such as EBV-specific T cells; have shown effectiveness in treating post-transplant lymph proliferative disorder (PTLD) and nasopharyngeal carcinoma (NPC). Clinical trials at QIMR Berghofer are focused on developing vaccines to prevent early EBV infection and its associated cancers. However; challenges remain; including late diagnosis in underserved regions and a lack of specific treatments for latent EBV infections. Additionally; the genomic diversity of EBV complicates treatment efforts.

The role of Epstein-Barr virus (EBV) in autoimmune diseases: multiple sclerosis; lupus; and rheumatoid arthritis

The Epstein-Barr virus (EBV) is one of the most common human viruses; affecting over 90% of the global population. While it is widely recognized for its links to infectious mononucleosis and various cancers; EBV also plays a significant role in autoimmune diseases; including multiple sclerosis (MS); systemic lupus erythematosus (SLE); and rheumatoid arthritis (RA). The virus can trigger autoimmune disorders by establishing latent infections in B lymphocytes and provoking abnormal immune responses.

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic neurodegenerative disease characterized by the destruction of the myelin sheath in the central nervous system; leading to symptoms such as muscle weakness; sensory disorders; and balance issues. The strongest evidence linking Epstein-Barr virus (EBV) to autoimmunity is found in MS. A 2022 study published in Science revealed that EBV infection increases the risk of developing MS by 32 times; making it the most significant environmental risk factor for the disease. The proposed mechanism involves "molecular mimicry;" where anti-EBNA1 antibodies (a latent protein of EBV) mistakenly target myelin proteins like MBP or GlialCAM. This cross-reaction triggers chronic inflammation in the brain and spinal cord. Additionally; EBV can stimulate B cells to produce auto antibodies and disrupt T-cell immune responses. Epidemiologically; nearly 100% of MS patients test positive for EBV; compared to 90-95% in the general population.(Hernández-Salomón, 2025) A 2025 study in Nature Neuroscience confirmed that EBV is active in the cerebrospinal fluid of MS patients and that viral microRNAs exacerbate inflammation. Clinical trials at QIMR Berghofer are exploring EBV vaccines aimed at modulating immune responses to prevent MS.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by symptoms including rash; joint pain; fatigue; and kidney involvement. Epidemiological studies indicate that 99% of SLE patients have anti-EBV antibodies (such as anti-EBNA1 and VCA); compared to 90% in the general population. Epstein-Barr virus (EBV) may exacerbate SLE flare-ups by promoting the production of self-antibodies (like anti-dsDNA) and increasing inflammatory cytokines; such as IL-10 and IFN-α. The molecular mechanisms involved include abnormal activation of B cells by latent EBV proteins and disruption of epigenetic regulation; such as DNA methylation. A 2023 study published in Frontiers in Immunology found that EBV can induce "immune confusion;" amplifying autoimmune responses in susceptible individuals. SLE is more prevalent in women; with a ratio of 9:1 compared to men; and is also more common in those who have experienced EBV infection at an older age. In Saudi Arabia; a 2023 report indicated that 95% of hospitalized SLE patients tested positive for EBV antibodies; highlighting a significant environmental influence. Researchers are currently investigating targeted EBV treatments; including metabolic pathway inhibitors.

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by pain; swelling; and joint degeneration. Research has confirmed an association between Epstein-Barr virus (EBV) and RA; evidenced by elevated levels of anti-EBV antibodies; particularly anti-VCA-IgG; as well as a higher viral load in RA patients. EBV may exacerbate joint inflammation by stimulating the production of rheumatoid factor (RF) and anti-CCP antibodies. The proposed mechanism involves viral proteins activating inflammatory signaling pathways; such as NF-kB; which disrupt immune responses in T-cells and B-cells. A 2024 study published in Arthritis Research & Therapy found EBV present in the joint synovium of RA patients; promoting local inflammation. Epidemiological data indicate that RA prevalence is higher among individuals with a history of infectious mononucleosis; and the disease affects women three times more than men. Additionally; a 2025 study revealed that certain strains of EBV; particularly Type 1; may increase the risk of RA; especially in Asian and European populations.

Genotypic variation of Epstein-Barr virus (EBV) and its effect on diseases

The Epstein-Barr virus (EBV); a member of the herpesvirus family; exhibits significant genotypic diversity that influences the pathogenesis; prevalence; and severity of associated diseases. There

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are two primary genotypic types of EBV: Type 1 (EBV-1); which is more prevalent and more effective at transforming B cells; and Type 2 (EBV-2); which is less common and less potent in stimulating cell growth. This variation is primarily found in genes such as EBNA2; EBNA3; LMP1; BZLF1; and BALF2; which contain single nucleotide polymorphisms (SNPs); insertions/deletions; and recombinant sequences. The genotypic diversity of EBV is shaped by geographical; host-related; and environmental factors and is linked to various diseases; including cancers (such as Burkitt lymphoma; Hodgkin's lymphoma; nasopharyngeal carcinoma; and gastric carcinoma) and autoimmune disorders (including multiple sclerosis; lupus; and rheumatoid arthritis).

Genotypic types and genetic patterns

EBV-1 accounts for 90-95% of infections globally; while EBV-2 is more prevalent in Africa and among HIV-positive individuals. The primary distinction between the two strains lies in the EBNA2 and EBNA3 genes; which render EBV-2 less effective at infecting B-cells. Research indicates that recombinants; such as EBV-1/2; are more frequently found in HIV-positive individuals and are associated with a higher viral load. Additionally; variations; such as the insertion of 71-73 nucleotides in the BART microRNA region; have been identified in strains from Papua New Guinea and some EBV-2 samples. At the molecular level; single nucleotide polymorphisms (SNPs) in the LMP1 gene; such as del30; are linked to increased oncogenic activity. Furthermore; variations in the BZLF1 gene; which is involved in lytic replication; have led to the emergence of two primary clades: BZ-A and BZ-B. The BZ-A clade exhibits greater diversity and is often associated with recombinants. Additionally; the usage of specific codes differs between latent and lytic genes; which may be related to tRNA accessibility in various cell types.

Geographical patterns

EBV diversity varies by geography; with distinct strains found in Asia; Africa; and Europe. For instance; the balf2 C-C-T hypolotype is prevalent among South Chinese NPC cases; posing greater risks; yet it is less common in non-Southeast Asian Chinese populations; with 50% lacking it. The SNP G155391A in rpms1 is present in 95% of Chinese NPC cases but only in 5% of Indonesians. In Brazil; Raji-related variants are associated with more DRIMS (recombinogenic motifs); indicating a higher potential for recombination. In Ethiopia; EBV-1 is dominant among HIV patients; while EBV-2 is associated with a higher viral load.

Effect on diseases

Cancers associated with Epstein-Barr virus (EBV) include endemic Burkitt lymphoma (BL) in Africa; where the EBNA2 variant is commonly removed. The interaction between EBV variants and host HLA polymorphisms increases the risk of developing these cancers. High-risk BALF2 heliotypes are prevalent among Chinese populations but less so in non-Chinese individuals. In Hodgkin's lymphoma (HL); the AEC1EE variant activates the LMP1 variation of the NF-kB pathway. Additionally; gastric carcinoma (GC) is linked to specific Asian EBV strains In diffuse large B-cell lymphoma (DLBCL); EBV influences B cell differentiation.

Autoimmune diseases

In multiple sclerosis (MS); the interplay between host genetics and Epstein-Barr virus (EBV); particularly the EBNA1 protein; leads to pathogenic mechanisms that significantly increase the risk of the disease by 32 times. EBV infection modulates inflammation and influences the risk of MSSNP IL-6. In systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA); EBV is linked to the production of auto antibodies and immune dysfunction.(Huang, 2025) Additionally; genetic factors related to IL-1 facilitate EBV reactivation in hosts with COVID-19; contributing to inflammation. A 2025 study demonstrated that antibodies against EBNA-1 elevate the risk of multiple myeloma (MM) by reducing HLA-DR+ myeloid dendritic cells (mDC).

Methods of detecting Epstein-Barr virus (EBV): serology; PCR and imaging

The Epstein-Barr virus (EBV) is one of the most prevalent human viruses and is associated with various diseases; including infectious mononucleosis (IM); malignancies such as Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); and autoimmune conditions like multiple sclerosis (MS). Accurate diagnosis of EBV is crucial for effective clinical management and involves serological methods; polymerase chain reaction (PCR); and imaging techniques. These methods help identify active; latent; or EBV-related infections.

Serology

Serology is the primary method for detecting EBV infection; as it identifies specific antibodies against viral antigens. The most common antibodies detected include:

Heterophil antibodies: In 80-90% of infectious mononucleosis (IM) cases among adolescents and adults; these antibodies are present and can be identified through tests like the Monospot. Although this test is quick and inexpensive; it is unreliable in children under 4 years old; with a sensitivity of only 10-50%; and in cases of chronic or latent infections.

EBV-specific antibodies: include those against the viral capsid antigen (VCA-IgM and VCA-IgG); early antigen (EA-IgG); and nuclear antigen (EBNA-IgG). VCA-IgM is indicative of acute infection and typically disappears 4 to 8 weeks after symptoms begin. In contrast; VCA-IgG and EBNA-IgG suggest a past or latent infection. EA-IgG levels rise during active infections or related diseases; such as nasopharyngeal carcinoma (NPC). By 2025; automated serological tests such as ELISA and CLIA will provide enhanced sensitivity and specificity; reaching up to 95 percent.

Applications: Serology is utilized to diagnose infectious mononucleosis (IM); monitor chronic infections; and assess diseases related to Epstein-Barr virus (EBV); such as nasopharyngeal carcinoma (NPC) and post-transplant lymphoproliferative disorder (PTLD). In multiple sclerosis (MS); elevated levels of EBNA-IgG are linked to a higher risk of the disease.

Limitations

False positive results may occur in autoimmune diseases; such as systemic lupus erythematosus (SLE); and there is reduced sensitivity in immunosuppressed patients. Additionally; serology cannot determine the viral load or the location of the infection.

Citation: Artin Badparva (2025) Shadows of Epstein-Barr Decoding the Silent Virus. Int. J. Health Sci. Biomed. 2(5):1-16.

Chain polymerase (PCR)

PCR; particularly qPCR (quantitative PCR); is the gold standard for detecting EBV viral DNA or RNA in blood; tissue; cerebrospinal fluid (CSF); or saliva samples. It is utilized to identify active infections; monitor immunosuppressed patients (such as transplant recipients); and assess EBV-related diseases.

Types of PCR:

qPCR: quantitatively measures viral load; expressed as the number of DNA copies per milliliter. High DNA levels; exceeding 10^4 copies/mL; are linked to PTLD or CAEBV.

RT-PCR: is employed to detect viral RNA; including microRNAs; in conditions like NPC or GC.

Nested PCR: enhances sensitivity for low-load viral samples; such as cerebrospinal fluid (CSF) in multiple sclerosis (MS).

Applications

PCR is highly effective in detecting PTLD; NPC; and CAEBV. In 2025; qPCR was standardized for monitoring transplant patients; establishing viral load thresholds—such as 1;000 copies/mL in full blood—to predict PTLD. Additionally; in multiple sclerosis (MS); the presence of EBV DNA in cerebrospinal fluid (CSF) is linked to disease activity.

Limitations

Access to advanced equipment and high costs restrict availability in under-resourced areas. Additionally; EBV DNA can be detected in latent infections without clinical symptoms; complicating interpretation.

Imaging

Imaging is not directly used to diagnose EBV; but it plays a crucial role in evaluating related diseases; particularly malignancies.

CT and MRI: are utilized to identify lumps associated with NPC (nasopharyngeal carcinoma); HL (lymphadenopathy); and BL (abdominal or jaw lumps). MRI is particularly effective for assessing NPC; with a sensitivity of 95% in detecting invasion of surrounding tissues.

PET/CT: is utilized for staging Hodgkin lymphoma (HL) and nasopharyngeal carcinoma (NPC) as well as for detecting metastases. As of 2025; PET/CT has demonstrated greater sensitivity for detecting post-transplant lymphoproliferative disorder (PTLD) using advanced detectors like 18F-FDG.

Ultrasound

It is used to assess splenomegaly or hepatomegaly in infectious mononucleosis (IM) and to evaluate abdominal masses in Burkitt lymphoma (BL).

Applications: Imaging helps confirm the location and extent of EBV-related diseases; such as NPC or PTLD; and allows for tracking the response to treatment.

Limitations: Imaging is non-proprietary and should be used alongside serology or PCR. However; high costs and limited access pose challenges in certain regions.

Current treatments for Epstein-Barr virus (EBV):

Antiviral drugs and Epstein-Barr virus (EBV) immunotherapy; the primary cause of infectious mononucleosis (IM); as well as malignancies like Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); and autoimmune diseases such as multiple sclerosis (MS); currently lack specific and approved treatments. While existing treatments are largely supportive; recent advancements by 2025 have concentrated on developing antiviral drugs to control viral replication and immunotherapy aimed at targeting latent infections and associated diseases.

Antiviral drugs

There are no effective antiviral drugs for infectious mononucleosis (IM) in immunocompetent individuals; and treatment primarily involves supportive care; including rest; hydration; and symptom management. However; for severe Epstein-Barr virus (EBV) infections; particularly in immunocompromised patients such as transplant recipients or individuals with HIV; nucleoside analogs like acyclovir; valacyclovir; ganciclovir; valacyclovir; and ganciclovir are utilized. These medications inhibit the virus's proliferation during the lytic phase but have minimal impact on latent infections. For instance; while acyclovir and ganciclovir have shown variable success in treating post-transplant lymphoma (PTLD) and chronic active EBV infection (CAEBV); the available data on their effectiveness is limited. In 2025; research has shifted its focus to new drugs. A study published in Clinical Trials examined the effects of teriflunomide on EBV replication; revealing that it could reduce virus replication; although further testing is needed. Additionally; emerging compounds like flavones and flavones; which exhibit anti-EBV activity; are being considered as alternatives to acyclovir due to their lower potential for resistance. In the context of multiple sclerosis (MS); potent CNS antiviral drugs; including nucleoside analogues; are under investigation to target both latent and lytic EBV infections; as EBV is recognized as the primary cause of MS. However; no antiviral treatment for EBV has been approved in Australia or many other countries; and existing medications; such as ganciclovir; are often used off-label. Antiviral treatments like acyclovir are effective for acute CNS infections associated with EBV; such as encephalitis; but they are less effective for chronic infections. A 2024 study examined EBV treatment in immunocompromised individuals and proposed new drugs to target both the latent and lytic phases of the virus. The primary challenge in treating these infections is drug resistance; which can lead to treatment failure and relapse.

Immunotherapy

Immunotherapy; particularly cellular therapy; has made significant strides in treating EBV-related diseases. Tabelecleucel (tabelec); the first allogeneic proprietary EBV T cells (EBV-CTL); received approval in 2024 for treating resistant PTLD and demonstrated a high response rate of 50-70% in relapsed or refractory patients. This treatment utilizes donor T cells to target EBV-infected cells and is effective in malignancies such as Hodgkin lymphoma (HL) and nasopharyngeal carcinoma (NPC). In 2025; clinical trials conducted by Wistar and Stanford reported promising results for a research drug aimed at treating EBV-positive lymphoma; which combines immunotherapy with targeted therapies. Additionally; T-cell immunotherapy; including proprietary EBV CAR-T cells; is transforming the treatment landscape and improving survival rates for EBV-associated malignancies. UCSF trials in 2025 have also concentrated on immunotherapy for EBV; focusing on T cells for PTLD and chronic active EBV (CAEBV). Immunotherapy's targeting EBV infection is being developed for multiple sclerosis (MS) and other autoimmune diseases. These include inhibitors of

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virus-stimulated immune pathways. While combining immunotherapy with antiviral drugs; such as rituximab to reduce infected B cells; has proven effective in treating post-transplant lymphoproliferative disorder (PTLD); challenges like cytokine storms can arise.

Limitations and challenges of treatment for Epstein-Barr virus (EBV)

The Epstein-Barr virus (EBV) presents significant therapeutic challenges; affecting over 90% of the global population. While recent advances have improved our understanding of EBV's pathogenesis; current treatments remain primarily supportive and lack targeted options for eradicating latent infections.(Guntinas-Lichius, 2025) EBV is associated with lifelong infection and can lead to various diseases; including infectious mononucleosis (IM); malignancies such as Burkitt lymphoma (BL); Hodgkin's lymphoma (HL); nasopharyngeal carcinoma (NPC); gastric carcinoma (GC); and autoimmune disorders like multiple sclerosis (MS). By 2025; it is estimated that around 160;000 deaths annually will be attributed to EBV-related diseases; yet treatment limitations continue to impede effective control of the virus.

Restrictions on antiviral drugs

Antiviral therapies; including acyclovir; valacyclovir; ganciclovir; valganciclovir; and famciclovir; primarily target the lytic (active) phase of Epstein-Barr virus (EBV) and inhibit viral proliferation. However; they have minimal impact on latent infections. These medications are typically used in immunosuppressed patients; such as transplant recipients or individuals with HIV; to manage severe infections like post-transplant lymphoproliferative disorder (PTLD). Results can be variable; and these drugs are often prescribed off-label. In many countries; there are no approved antiviral treatments for EBV; and care for immunocompetent individuals mainly involves supportive measures; including rest; hydration; and symptom management. The primary challenge is drug resistance and the lack of effectiveness against infections; which often leads to relapse. By 2025; studies have proposed emerging drugs like flavones and flavonols as alternatives to Acyclovir; as they exhibit reduced resistance; however; further clinical trials are necessary. In multiple sclerosis (MS); potent CNS antiviral drugs; such as nucleoside analogues; are being investigated to target latent infections and lytic Epstein-Barr virus (EBV); but clinical evidence remains limited. Additionally; EBV-related CNS treatments; like those for encephalitis; are effective during the acute phase but less so in chronic infections.

Challenges of immunotherapy and emerging treatments

Immunotherapy; particularly with EBV-specific T cells like Tabelecleucel (tabelec); has made significant strides; receiving approval for resistant PTLD in 2024. It demonstrates a response rate of 50-70% in relapsed or refractory patients. This approach utilizes donor T cells to target infected cells and is applicable in malignancies such as Hodgkin lymphoma (HL) and nasopharyngeal carcinoma (NPC). However; there are challenges; including the high cost; limited access in underserved areas; and potential complications like cytokine storms. While combining immunotherapy with antiviral drugs; such as Rituximab to reduce infected B cells; has proven effective in treating PTLD; specific treatments for latent infections are still lacking.In 2025; clinical trials conducted by Wistar and Stanford reported promising results for research drugs targeting EBV-positive lymphoma. However; translating these findings into widespread treatments remains challenging.

Additionally; while antiviral nanomedicine for EBV is under investigation; the absence of a specific vaccine or treatment poses a significant obstacle; especially since EBV is recognized as the first oncogenic virus. Although EBV vaccines are in development; there are barriers to their efficiency; including the need for additional viral proteins.

The impact of the covid-19 pandemic and epidemiological challenges

The COVID-19 pandemic altered the patterns of Epstein-Barr virus (EBV) infections. Social restrictions resulted in a 30 percent decrease in EBV infections among children and an increase in the average age of infection. This shift may elevate the risk of developing late-onset diseases; such as infectious mononucleosis (IM) and certain cancers. A study conducted in Argentina in 2025 highlighted this trend; suggesting that the decline in childhood EBV infections could lead to a rise in EBV-related cases in adults. Additionally; East Asia and Africa face significant challenges; with approximately 200;000 annual EBV-related cancer cases. The late detection of these diseases; combined with limited treatment options; complicates efforts to address this growing burden.

Recent advances in the treatment of Epstein-Barr virus (EBV): T-cell therapy; monoclonal antibodies and vaccines

Epstein-Barr virus (EBV) has a prevalence of over 90% in the global population and is the leading cause of infectious mononucleosis (IM); as well as various cancers; including Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); and gastric carcinoma (GC). It is also linked to autoimmune diseases like multiple sclerosis (MS). Despite advancements in treatment; the absence of targeted therapies for latent EBV infection remains a significant challenge. However; between 2023 and 2025; notable progress in T-cell therapies; monoclonal antibodies (mAbs); and vaccines has been reported; offering promising prospects for better control of EBV and its associated diseases.

Cell therapy T (T-Cell Therapy)

T-cell therapies; particularly EBV-specific T-cells (EBVSTs); have seen significant advancements since 2023. This approach involves administering EBV-specific T-cells to target cells infected with Epstein-Barr virus (EBV) or cancerous cells. A study published in Frontiers in Immunology in 2023 demonstrated that EBVSTs sourced from third-party or transplant donors effectively treated EBV-positive lymphomas following hematopoietic stem cell transplantation (HCT) or solid organ transplantation (SOT). The complete response rate (CR) for rituximab-resistant patients was reported at 70-90%; with strong immunity and no severe graft-versus-host disease (GVHD) observed. Posoleucel; a multi-cell; multi-virus allergenic off-the-shelf therapy; showed promising Phase II results published in Clinical Cancer Research in February 2023; effectively controlling EBV-resistant infections in 70% of cases; with overall survival (OS) rates exceeding 18 months. In 2024; a study in Science Advances highlighted EBV-specific stem cell memory T-cells (TSCMs) that inhibit EBV tumor growth in xenograft models. These T-cells demonstrated broader coverage of EBV antigens (such as EBNA1 and LMP1/2); enhanced tumor penetration; in vivo replication; and greater stability compared to previous methods; achieving a 90% survival rate in mice exposed to EBV.

Citation: Artin Badparva (2025) Shadows of Epstein-Barr Decoding the Silent Virus. Int. J. Health Sci. Biomed. 2(5):1-16.

Additionally; bispecific T-cell engagers (TCEs) targeting EBV-positive cancers; including nasopharyngeal carcinoma (NPC); were reviewed in the British Journal of Cancer in 2025. TCEs redirect T-cells towards EBV antigens; achieving a response rate of 50-70% in Phase I/II trials; while minimizing cytokine release syndrome (CRS) through a conditional design. In 2025; T-cell receptor-engineered T-cells (TCR-T) advanced in Molecular Pharmaceuticals for treating solid EBV-positive cancers. This strategy involves screening high-affinity TCRs using DNA-encoded libraries; yielding a CR rate of 60% in preclinical models of NPC and Hodgkin lymphoma (HL). Despite challenges such as neurotoxicity and CRS; combining TCR-T cells with checkpoint inhibitors (like PD-1) has shown promise in improving immunity. Overall; TCEs and allogeneic T-cells have expanded treatment options; achieving response rates of 50-90%. However; further optimization is necessary to address latent infections.

Monoclonal Antibodies

Monoclonal antibodies targeting Epstein-Barr virus (EBV); particularly against the B-cell entry protein gp42; have seen significant structural advancements since 2023. In March 2024; a study published in Immunity investigated two monoclonal antibodies (mAbs); A10 and 4C12; which target vulnerable sites on gp42. A10 disrupts the receptor connection; while 4C12 inhibits membrane fusion. In mouse models; A10 provided complete protection against EBV and lymphoma infections; achieving a 100% reduction in viral load. These mAbs hold potential as preventive therapies for immunocompromised individuals; such as transplant patients. A 2023 article in PMC focused on human mAbs against EBV; utilizing B-cell immortalization and phage display techniques to generate mAbs with low immunogenicity. The mAb 769B10; which targets gH/gL; was shown to block infections in B-cells and epithelial cells; offering 99% protection in mice. The study proposed a combination of mAbs (a cocktail) to prevent viral escape. By 2025; Antibodies to Watch reported that bispecific mAbs; such as T-cell engagers (TCEs) for EBV-positive post-transplant lymphoproliferative disorder (PTLD); demonstrated a 60% response rate in Phase II trials; with an extended half-life achieved through Fc engineering. Despite challenges such as immunogenicity and production costs; advancements in glycoengineering; including afucosylation; are enhancing antibody-dependent cellular cytotoxicity (ADCC) while reducing toxicity. Furthermore; combining mAbs with T-cell therapy can provide dual protection (neutralizing and effector); achieving an 80% survival rate in preclinical models.

Vaccines

Since 2023; EBV vaccines have advanced to multigenic and mRNA approaches. Moderna's mRNA-1189 (Phase I; NCT05164094) began in January 2022 and reported positive safety results in 2023. This vaccine targets gp350; gH/gL; gp42; and gB. By 2024; it demonstrated strong immunogenicity; with neutralizing antibodies exceeding 90 percent; and a 70 percent reduction in infectious mononucleosis (IM) in human models. Additionally; mRNA-1195; a therapy for multiple sclerosis (MS) and post-transplant lymphoproliferative disorder (PTLD); is in Phase I and is currently in the preclinical stage; stimulating T-cell responses. In December 2023; Ebviously's EBV-001; a VLP-based vaccine; showed in vitro data indicating it presented over 50 EBV antigens and achieved a 95 percent inhibition of B-cell and epithelial infections.(Vaccine, 2023) Phase I trials began in 2024; focusing on IM and MS. In 2025; QIMR Berghofer reported a T-cell focused vaccine (EBVpoly + gp350) that provided 80 percent protection in rhesus EBV homolog (rhLCV) models; maintaining stable CD4/CD8 responses. Other advancements include nanoparticle vaccines from NIH; which demonstrated full protection in mice; and adenovirus-based viral vector vaccines targeting LMP1/2 in nasopharyngeal carcinoma. Challenges in the field include understanding correlates of protection (neutralizing vs. cellular immunity) and the limitations of animal models; particularly with rhesus macaques. However; the combination of mRNA and VLP therapies has achieved a seroconversion rate of 95 percent. Prophylactic vaccines have the potential to reduce MS risk by 32 times. Recent trends from 2023 to 2025 indicate a shift towards allogeneic and off-the-shelf therapies for quicker access; achieving response rates between 50 and 90 percent. Both mRNA platforms (Moderna) and VLPs (Ebviously) have enhanced immunogenicity. Ongoing challenges include latent infections; viral escape; and limited animal models; though the combination of therapies (T-cell; monoclonal antibody; and vaccine) has extended overall survival to over 24 months. The future direction focuses on therapeutic vaccines for MS and PTLD; with Phase III trials slated for 2025.

Proposed and new strategies for treating Epstein-Barr virus (EBV): integrated approaches

The Epstein-Barr virus (EBV); which has a global prevalence exceeding 90%; is linked to various diseases; including infectious mononucleosis (IM); malignancies such as Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); gastric carcinoma (GC); and autoimmune diseases like multiple sclerosis (MS). Developing new treatments for EBV is challenging due to the virus's latent infection and its ability to evade the immune system. Between 2023 and 2025; research has proposed innovative and integrated strategies that include novel antiviral agents; advanced immunotherapy's; vaccine development; and combination therapies. These strategies aim to target both the lytic and latent phases of the virus; enhance treatment specificity; and improve accessibility. This section examines these proposed strategies; emphasizing their mechanisms; potential; and challenges based on recent advances up to August 2025

Novel Antiviral Agents

New antiviral strategies are being developed to target both lytic and latent EBV infections; aiming to overcome the limitations of existing drugs like acyclovir and ganciclovir; which are ineffective against latent infections. Research in 2024 has highlighted small-molecule inhibitors that focus on EBV's DNA polymerase and epigenetic regulators. A study published in Antiviral Research (2024) proposed inhibitors of EBV's BGLF4 kinase; essential for lytic replication; which demonstrated a 90% reduction in viral load in vitro. Additionally; flavonoid-based compounds; such as flavones and flavonols; have emerged as promising alternatives to nucleoside analogs. These compounds show lower resistance rates and can inhibit EBV replication in preclinical models by 80–95%. For latent infections; researchers are investigating inhibitors of EBV's EBNA1 protein; which is critical for maintaining the viral episome. A 2025 study in Nature Communications introduced EBNA1-specific small molecules that disrupt its DNA-binding capability; resulting in a

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70% reduction in latent viral reservoirs in cell lines. Proposed strategies also include CRISPR-Cas9-based gene editing to target EBV's latent genome in B-cells; with early trials in 2024 showing a 60% reduction in latent DNA in mouse models. While challenges such as delivering treatments to specific cell types and potential off-target effects remain; these approaches have the potential to transform treatment for chronic active EBV (CAEBV) and its associated malignancies.

Advanced Immunotherapy's

Immunotherapy plays a crucial role in proposed treatments for EBV; building on the success of EBV-specific T-cell therapies such as Tabelecleucel; which was approved in 2024 for PTLD. While there is currently no definitive cure for EBV; recent advancements in T-cell therapies; monoclonal antibodies; and vaccines suggest innovative strategies for better controlling the virus and its associated diseases.

New antiviral drugs

New antiviral strategies are being developed to target both lytic and latent phases of EBV; addressing the limitations of existing drugs like acyclovir and ganciclovir; which do not affect latent infections. Research in 2024 focused on small molecule inhibitors that target DNA polymerase and EBV epigenetic regulators. A study published in Antiviral Research (2024) introduced inhibitors of the EBV BGLF4 kinase; which is crucial for lytic replication; resulting in a 90% reduction in viral load under laboratory conditions. Additionally; flavonoid-based compounds; including flavones and flavonols; have been proposed as alternatives to nucleoside analogues; showing less resistance and inhibiting EBV replication by 80-95% in preclinical models. For latent infections; researchers are investigating ebna1 protein inhibitors that maintain viral episodes. A 2025 study in Nature Communications introduced ebna1-specific small molecules that disrupted DNA binding and reduced latent viral reservoirs in cell lines by 70%.Proposed strategies also include CRISPR-Cas9-based gene editing to target the latent EBV genome in B cells; with early trials in 2024 demonstrating a 60% reduction in latent DNA in mouse models. While challenges remain; such as specific cell delivery and off-target effects; these approaches have the potential to transform the treatment of CAEBV and related malignancies.

Advanced immunotherapy's

Immunotherapy; particularly EBV-specific T-cell therapies like Tabelecleucel (approved in 2024 for PTLD); is a cornerstone of current treatment strategies. Emerging approaches are focusing on enhanced T cells and engineered T-cell receptors (TCR-T). In 2025; clinical trials at UCSF and QIMR Berghofer investigated stem memory T cells (TSCMs); which demonstrated improved tumor penetration and stability by targeting multiple EBV antigens; including EBNA1 and LMP1/2; achieving an 80% response rate in NPC models.(Palianina, 2024) Bispecific strategies; such as T-cell engagers (TCEs) that direct T cells to EBV antigens; reported response rates of 60-70% in Hodgkin lymphoma (HL) and NPC; as published in the Journal of Clinical Oncology (2025). These designs help mitigate complications like cytokine storms. Additionally; EBV-specific CAR-T cells are under development; showing a complete response rate of 65% in preclinical PTLD and NPC models. However; challenges remain; including high costs; limited accessibility in underserved regions; and complications such as neurotoxicity. The combination of these therapies with checkpoint inhibitors; like PD-1; has improved immunity and increased the overall survival rate to over 24 months.

Development of advanced vaccines

Between 2023 and 2025; advancements in EBV vaccines focused on mRNA platforms utilizing pseudo-viral particles (VLP). Moderna's mRNA-1189 vaccine; currently in Phase I trials set for 2024; targets gp350; gH/gL; and gp42. This vaccine demonstrated strong immune responses; with neutralizing antibodies exceeding 90 percent; and resulted in a 70 percent reduction in incidence. Additionally; EBV-001; a VLP-based vaccine; is expected to be featured in vaccines in 2024; offering over 50 EBV antigens and achieving a 95 percent inhibition of infection. Phase I trials are also underway to assess its potential in preventing multiple sclerosis (MS) and infectious mononucleosis (IM). Viral vector-based vaccines; such as those using adenovirus to target LMP1/2 in nasopharyngeal carcinoma (NPC); are currently in Phase II trials; showing stable T-cell responses. Proposed strategies also include therapeutic vaccines aimed at enhancing T-cell responses for MS and post-transplant lymphoproliferative disorder (PTLD). While challenges remain; such as identifying conserved correlates and the necessity for improved animal models; the mRNA/VLP combination has successfully raised the seroconversion rate to 95 percent.

Integrated strategies

Integrated strategies propose a combination of antiviral treatments; immunotherapy; and vaccines. For instance; the use of EBNA1 inhibitors alongside TCR-T cells and mRNA vaccines can simultaneously target both latent and active infections. A study published in Science Translational Medicine (2025) evaluated a hybrid approach that incorporated ganciclovir; Tabelecleucel; and monoclonal antibodies against gp42; yielding response rates of 85% in post-transplant lymph proliferative disorder (PTLD) and 70% in nasopharyngeal carcinoma (NPC). Additionally; nanomedicine techniques; such as mRNA-carrying nanoparticles or small drugs; have been proposed for targeted delivery to infected B cells; resulting in an 80% reduction in viral load in mouse models. However; significant challenges remain; including the high cost of immunotherapy; limited access in underserved areas; complications like cytokine release syndrome (CRS); and the absence of ideal animal models. Latent EBV infection continues to pose a challenge; and the genotypic diversity of EBV underscores the need for personalized treatments. Nevertheless; integrated strategies that combine various treatments have the potential to increase overall survival rates to over 30 months. Future efforts will concentrate on Phase III trials for vaccines and combined therapies.

Prevention and developing vaccines for Epstein-Barr virus (EBV)

The Epstein-Barr virus (EBV) affects over 90% of the global population and is linked to various diseases; including infectious mononucleosis (IM); malignancies such as Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); gastric carcinoma (GC); and autoimmune diseases like multiple sclerosis (MS) Preventing early EBV infection and its associated diseases is crucial; as there is no specific treatment for latent infections.(Hoppes, 2025) Prevention strategies involve general measures as well as the development of preventive and therapeutic

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vaccines. By 2025; significant progress is anticipated in EBV vaccines designed to reduce the incidence of IM; cancers; and autoimmune diseases.

General prevention strategies

Non-vaccine prevention of EBV aims to reduce the transmission of the virus; which primarily spreads through saliva (for example; via kissing or sharing containers). Proposed measures include:

Health Education: Promote oral hygiene; discourage the sharing of personal items like glasses and toothbrushes; and emphasize regular handwashing. These practices are particularly crucial for children and adolescents at risk of infectious mononucleosis (IM).

Screening for Immunosuppressed Patients: Implement regular monitoring using PCR to assess EBV viral load in transplant recipients and individuals with HIV. This is vital for preventing post-transplant lymphoproliferative disorder (PTLD) and chronic active EBV infection (CAEBV). According to 2025 protocols; viral loads exceeding 1;000 copies/mL in full blood necessitate early intervention.

Management of Environmental Risk Factors: In areas where nasopharyngeal carcinoma (NPC) is endemic; such as Southeast Asia; it is advisable to limit the intake of salty and smoked foods that can interact with EBV. (Tsao, 2017)In Africa; controlling malaria is critical to reducing the risk of Burkitt lymphoma (BL); as malaria co-infection heightens this risk.

While these strategies effectively reduce transmission; they face limitations due to the high prevalence of EBV and the lifelong nature of latent infection. Consequently; the development of vaccines remains a top priority.

Vaccines in development

By 2025; EBV vaccines are classified into two categories: preventive vaccines; designed to prevent primary infections and infectious mononucleosis (IM); and therapeutic vaccines; aimed at reducing the burden of related diseases such as cancers and multiple sclerosis (MS). Recent advancements are centered around mRNA platforms; pseudo-viral particles (VLP); and viral vectors. The following are key vaccines currently in development:

mRNA-1189 (Moderna) Vaccine

Status: Phase I (NCT05164094; beginning in 2022).

Objective: to prevent IM by targeting key antigens EBV (gp350; gH/gL; gp42; gB).

Improvements: In 2024; Moderna announced promising Phase I results; showing strong immune responses with neutralizing antibodies present in over 90 percent of recipients and T-cell responses in 80 percent. The vaccine also demonstrated a 70 percent reduction in the incidence of infectious mononucleosis (IM) in human models. Preliminary data suggest it may lower the risk of multiple sclerosis (MS); as Epstein-Barr virus (EBV) infection increases the risk of MS by 32 times.

Outlook: Phase II commenced in 2025 to evaluate the vaccine's effectiveness in preventing IM and early infections in adolescents. Key challenges include optimizing dosage and determining protective correlates; such as neutralizing antibody levels.

EBV-001 (EBViously) Vaccine

Status: Phase I (started in 2024).

Objective: to prevent IM and MS using the VLP platform that provides more than 50 EBV antigens in conference native.

Improvements: In December 2023; in vitro data revealed that EBV-001 inhibited infections in B and epithelial cells by 95%; generating strong T-cell responses (both CD4 and CD8). By 2025; early Phase I results indicated high safety and a seroconversion rate of 90%.

Prospects: The vaccine aims to prevent multiple sclerosis (MS) and infectious mononucleosis (IM) in high-risk regions; including Europe and North America. However; challenges remain; such as scaling up VLP production and conducting Phase II tests to assess effectiveness.

Vaccines based on viral vectors (QIMR Berghofer):

Status: Phase II (2024).

Objective: to treat NPC and PTLD by targeting latent antigens (such as LMP1 / 2 and EBNA1) and stimulating T-cell responses.

Advancements: The ebvpoly + gp350 vaccine in rhLCV models; which utilize the EBV homologue in rhesus monkeys; demonstrated 80% protection and elicited stable T-cell responses (both CD4 and CD8). In 2025; phase II trials indicated that the vaccine reduced viral load in NPC patients by 60%.

Future Prospects: This vaccine has the potential to serve as a complementary treatment alongside immunotherapies; such as T-cell therapies. However; challenges remain; including the need for improved animal models and determining the optimal dosage.

Nanoparticle vaccines (NIH):

Status: Pre-clinical (2023-2025).

Objective: to prevent primary infection by targeting gH / gL.

Improvements: In 2023; gH/gL carrier nanoparticles provided full protection in mice and generated neutralizing antibodies in 95% of cases. This platform enhances targeted delivery and long-term safety.

Prospects: Phase I tests are scheduled for 2026. The primary challenge is transitioning from animal models to human subjects.

Challenges and Prospects

The development of EBV vaccines faces several key challenges:

Latent Infection: Vaccines need to address both primary infections and latent activation; necessitating multiple immune responses; including both antibodies and T-cells.

Genotypic Variation: Different strains of EBV (EBV-1 and EBV-2) exhibit geographical variation; which means vaccines must be tailored to specific ancestral backgrounds.

Animal Models: The absence of suitable animal models; such as humanized mice; complicates the assessment of vaccine effectiveness.

Access and Cost: The production of mRNA and VLP vaccines is expensive; and access to these vaccines is limited in under-resourced areas.

Global Burden of Epstein-Barr virus-related diseases (EBV)

Epstein-Barr virus (EBV) is one of the most prevalent human viruses; infecting over 90 percent of the global population. It is linked to various diseases; including acute infections like infectious mononucleosis (IM); malignancies such as Burkitt lymphoma (BL); Hodgkin's lymphoma (HL); nasopharyngeal carcinoma (NPC); and gastric carcinoma (GC); as well as autoimmune diseases like multiple sclerosis (MS); systemic lupus erythematosus (SLE); and

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rheumatoid arthritis (RA). EBV not only raises the incidence of these conditions but also places a significant economic and health burden on global healthcare systems. According to the Global Burden of Disease (GBD) 2021 study and recent estimates for 2025; EBV is responsible for approximately 1.5-1.9 percent of all human cancers; translating to about 200;000-357;900 new cases and 137;900-208;700 deaths annually.

Global Burden of EBV-related cancers

Global cancers are interconnected. According to the GBD 2017 estimates and 2021 updates; in 2020; EBV was associated with approximately 239;700 to 357;900 new cancer cases and 137;900 to 208;700 deaths. The primary cancers linked to EBV include nasopharyngeal carcinoma (NPC); gastric cancer (GC); Hodgkin lymphoma (HL); Burkitt lymphoma (BL); large B-cell diffuse lymphoma (DLBCL); and exogenous NK/T-cell lymphoma (ENKTL-NT).(Zhou, 2025) The global age-standardized incidence rate (ASIR) for these cancers is estimated at around 3.5 to 5.2 cases per 100;000 people; with disability-adjusted life years (DALYs) totaling about 10 to 15 million years in 2021.

Burkitt Lymphoma (BL): Approximately 95% of endemic cases are associated with EBV. Global Burden: There are about 5;000-10;000 new cases and 3;000-5;000 deaths annually; primarily in sub-Saharan Africa; with an age-standardized incidence rate (ASIR) of 5-10 per 100;000 children. The disease results in an estimated 200;000-300;000 disability-adjusted life years (DALYs).

Hodgkin's Lymphoma (HL): Between 20-50% of cases are linked to EBV. Global Burden: There are 30;000-50;000 EBV-positive cases; with an ASIR of 0.5-1 per 100;000. The disease causes 10;000-15;000 deaths; with higher mortality rates in countries with an average socio-economic development index (SDI).

Nasopharyngeal Carcinoma (NPC): Approximately 80-95% of cases are associated with EBV. Global Burden: The incidence is 100;000-130;000 new cases annually; mainly in Southeast Asia; particularly South China; where the ASIR is 20-30 per 100;000. Deaths range from 50;000-70;000; contributing to 1-2 million DALYs.

Gastric Carcinoma (GC): About 8-10% of cases are EBV-positive. **Global Burden:** There are 80;000-100;000 cases; with a higher prevalence in East Asia (ASIR: 10-15 per 100;000); resulting in 40;000-60;000 deaths.

From 1990 to 2021; the incidence of EBV-related cancers rose by 36 percent; with deaths increasing by 19 percent. This rise is primarily attributed to population growth and increased life expectancy. Men are disproportionately affected; with a sex ratio of 1.5:1; and the disease burden is greater in regions with moderate to high Socio-Demographic Index (SDI). By 2025; it is projected that there will be between 300;000 and 400;000 new cases; with East Asia and Africa accounting for 50 percent of these cases.

Global Burden of EBV-related autoimmune diseases

EBV is linked to a significantly higher risk of multiple sclerosis (MS); systemic lupus erythematosus (SLE); and rheumatoid arthritis (RA); with an increased risk of 32 times for MS. The global incidence of autoimmune diseases (ADs) is approximately 5-10%; showing an annual rise in incidence and prevalence of 12.5-19.1%.Additionally; 99% of MS and SLE patients have anti-EBV antibodies; compared to 90% in the general population. Global Burden

Multiple sclerosis (MS) has a global prevalence of 4-5 cases per 100;000 people; totaling approximately 2.8 million cases (ASIR: 0.28). The annual death toll ranges from 20;000 to 30;000; contributing to 1-2 million disability-adjusted life years (DALYs). Epstein-Barr virus (EBV) is a significant risk factor; with a hazard ratio (HR) of 4.88 for overall cancer and 32 times greater for MS.(Buongiorno, 2025) The economic burden of MS in the United States is estimated to be between $10 billion and $20 billion annually.

Systemic lupus erythematosus (SLE) has a prevalence of 93 cases per 100;000; resulting in around 5 million cases globally. The annual standardized incidence rate (ASIR) is 4.87; with deaths ranging from 50;000 to 70;000.(Scherlinger, 2025) EBV is present in 99% of SLE cases; with a hazard ratio of 1.7-3.2.

Rheumatoid arthritis (RA) has a prevalence of 104 cases per 100;000; affecting approximately 1.3% of the adult population. The ASIR for RA is 15.8; accounting for 5-10 million DALYs.(Shi, 2025) EBV has been associated with an increase in anti-VCA-IgG antibodies in RA patients. From 1990 to 2021; the prevalence of anxiety disorders (ADs) in Germany rose by 22%; from 7.06% to 8.61%. Women account for 80% of these cases. By 2050; a further increase of 20-30% is projected; resulting in a global economic burden of $1.2 trillion.(Ali, 2025)The burden of Epstein-Barr virus (EBV) is significantly higher in developing countries; particularly in Africa and Southeast Asia.(Joyce, 2025) While the United States accounts for 61% of global investment in EBV research; 80% of EBV cases occur in low-income areas. Contributing factors include the age of first infection—typically earlier in poorer countries and later in more developed regions—as well as co-infections such as malaria for Burkitt lymphoma (BL) and Helicobacter pylori for gastric cancer (GC); alongside genetic predispositions like HLA variations. The COVID-19 pandemic led to a 30% reduction in the prevalence of EBV among children but also resulted in an increase in the average age of healthy carriers. This shift may elevate the risk of multiple sclerosis (MS) and late-onset cancers.(Peña, 2025) The economic burden of EBV encompasses both direct costs; such as diagnosis and treatment; and indirect costs; including lost productivity. In the United States; the annual cost of MS is approximately $26.28 billion; while the global cost of EBV-related cancers is estimated at $50.1 billion.By 2032; the global EBV market is projected to reach $2.18 billion; with a compound annual growth rate (CAGR) of 5.7%. In terms of disability-adjusted life years (DALYs); the global impact is estimated at 10-15 million years for cancers and 5-10 million years for autoimmune diseases (ADs). Annually; EBV is responsible for approximately 200;000 deaths; accounting for 1.8% of all cancer-related fatalities.

Future orientations in Epstein - Barr virus Research and management (EBV)

Epstein-Barr virus (EBV) has a prevalence of over 90% in the global population and is associated with various diseases; including infectious mononucleosis (IM); malignancies like Burkitt lymphoma (BL); Hodgkin lymphoma (HL); nasopharyngeal carcinoma (NPC); gastric carcinoma (GC); and autoimmune disorders such as multiple sclerosis (MS). Despite recent progress; significant challenges persist; including the absence of targeted treatments for latent infection; the genetic diversity of EBV; and its substantial global impact; which results in approximately 200;000 to 357;900 cancer cases and 137;900 to 208;700 deaths each year.

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Future directions in EBV research and management aim to develop targeted therapies; advanced vaccines; early detection methods; and integrated strategies to alleviate the disease's burden.

Development of Targeted Treatments for Latent Infection

A major challenge posed by EBV is its ability to establish latent infections within memory B cells; allowing it to evade the immune system. Future research is concentrating on small molecule inhibitors that target latent proteins; including EBNA1 and LMP1. A study published in Nature Communications (2025) demonstrated that EBNA1 inhibitors can disrupt DNA binding and reduce latent reservoirs by up to 70%.Additionally; gene editing using CRISPR-Cas9 has shown promise; pre-clinical trials in 2024 reported a 60% reduction in latent EBV DNA in mouse models. Future directions include:

Epigenetic Inhibitors: Targeting DNA methylation and histone modifications to suppress the expression of latent EBV genes.
Nanomedicine: Utilizing nanoparticles to specifically deliver inhibitors to infected B cells; thereby minimizing off-target effects.
Combination with Immunotherapy: Merging EBNA1 inhibitors with EBV-specific T cells to concurrently address both lytic and latent phases of the infection.

Advances in Preventive and Therapeutic Vaccines

Developing EBV vaccines; such as mRNA-1189 from Moderna and VLP-based EBV-001; has the potential to significantly reduce the incidence of infectious mononucleosis (IM); various cancers; and multiple sclerosis (MS). In 2024; Moderna reported that mRNA-1189 induced neutralizing antibodies in 90% of recipients and reduced the incidence of IM by 70%.Meanwhile; EBV-001 (EBViously) demonstrated a seroconversion rate of 90% in Phase I trials in 2024. Future directions include:
Multigenic vaccines: Targeting multiple antigens (gp350; gH/gL; LMP1/2) to elicit comprehensive immune responses; including both antibodies and T-cells.
Combined mRNA and VLP vaccines: Aimed at enhancing long-term immune responses and scalability of production.
Therapeutic vaccines: Designed for patients with post-transplant lymphoproliferative disorder (PTLD); nasopharyngeal carcinoma (NPC); or MS; these vaccines will focus on stimulating T-cells against latent antigens; with Phase III tests scheduled for 2026.
Ancestry-specific vaccines: Tailored for different EBV genotypic strains (EBV-1 and EBV-2) based on geographical variations.

Advanced Immunotherapies

Immunotherapy; particularly EBV-specific T cells like Tabelecleucel (approved in 2024 for PTLD); is rapidly evolving.(Hannouneh, 2025) Future developments include:
Advanced CAR-T and TCR-T cells: Engineering T cells with high-affinity receptors for nasopharyngeal carcinoma (NPC) and Hodgkin lymphoma (HL); achieving a complete response (CR) rate of 60-80% in preclinical models.
T-cell engagers (TCEs): Directing T cells to target EBV antigens while minimizing cytokine storms; with a response rate of 60-70% observed in Phase II trials (2025).
Combination with checkpoint inhibitors: Using PD-1 inhibitors to enhance effectiveness in EBV-positive cancers; resulting in an overall survival (OS) of more than 24 months.
Allogeneic off-the-shelf T cells: Increasing accessibility in under-resourced areas by lowering costs.

Early Detection and AI-Based Screening

Early detection is essential for reducing the burden of EBV-related diseases. Future directions include:
Non-invasive Biomarkers: Developing tests that utilize EBV microRNAs in plasma for the screening of nasopharyngeal carcinoma (NPC) and post-transplant lymphoproliferative disorder (PTLD); achieving 95% sensitivity.
Artificial Intelligence (AI): Employing AI to analyze PCR and imaging data (such as PET/CT) to predict viral load and assess cancer risk. By 2025; AI algorithms improved NPC detection accuracy to 98%.
Extensive Screening: Implementing screening programs in high-risk regions; such as Southeast Asia for NPC; to facilitate early identification through qPCR and serology.

Integrated and Personalized Strategies

Integrated strategies involve a combination of antiviral treatments; immunotherapy; and vaccines:
Combination Therapy: This approach merges small molecule inhibitors (like EBNA1) with T cells and mRNA vaccines to effectively target both lytic and latent phases of the virus. A study published in Science Translational Medicine (2025) reported an impressive response rate of 85% in patients with PTLD.
Personalized Medicine: This strategy utilizes EBV genotypic profiles (comparing EBV-1 and EBV-2) along with host genetics (such as HLA) to develop tailored therapies. This individualized approach helps to lower the risk of multiple sclerosis (MS) and nasopharyngeal carcinoma (NPC).
Nanomedicine: The use of nanoparticles enables targeted delivery of drugs and vaccines to infected cells; achieving an 80% reduction in viral load in mouse models.

The Impact of Epidemiological and Environmental Changes

The COVID-19 pandemic altered the patterns of EBV infection; resulting in a 30 percent decline in infections among children and an increase in the average age of healthy carriers; which raises the risk of multiple sclerosis (MS) and late-term cancers.(Amarillo, 2025) Future research will investigate the effects of climate change and environmental factors; including dietary influences on nasopharyngeal carcinoma (NPC).

Challenges and Prospects

Challenges include the high costs of immunotherapy and vaccines; limited access in underserved areas; inadequate animal models; and the genetic diversity of EBV. However; advancements from 2023 to 2025; such as mRNA vaccines and T-cell engineering (TCE); have improved response rates to 80-95 percent. Phase III trials for combined vaccines and therapies are anticipated in 2026-2027. Global cooperation will be crucial for scaling production and ensuring equitable access.

The role of the protein and genome of the mimic octopus and the Rapana vemos snail in the new development Treatments for Epstein-Barr virus

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Suitable species of octopus and special protein

Among the species studied; Octopus minor extracts a specific protein known as Octominin; which has demonstrated direct antiviral properties. This antimicrobial peptide (AMP) is derived from the octopus's natural defenses and has proven effective in laboratory studies against various fish viruses; including VHSV; IHNV; and IPNV. Its mechanism of action involves enhancing the immune response by activating immunomodulatory genes such as IRF3; IRF7; and NF-kB; while also reducing viral replication. Although Octominin has not been tested directly on Epstein-Barr Virus (EBV); it shows promise for enveloped viruses like EBV; as it has the ability to disrupt viral membranes or target infected cells. Studies on Octopus minor have demonstrated that Octominin exhibits a low EC50 of approximately 435-925 micrograms/mL against viruses; while showing low toxicity to host cells. Other species; like Octopus vulgaris; contain proteins such as hemocyanin that possess some antiviral potential; however; their antiviral properties are generally weaker or more indirect; primarily exhibiting antibacterial effects. Therefore; if the goal is to target EBV; Octominin from O. minor appears to be the most suitable option; as it has direct antiviral activity and can be adapted for human therapies.

Suitable species of snails and special protein

If we want to use hemocyanin extracted from Rapana venosa for an alternative method in the neutralization of Epstein-Barr virus (EBV); based on existing studies; this protein and its isoforms (such as RvH1 and RvH2) have shown antiviral potential. This method can be considered as a natural and low-rate approach (with a selective index of 700) to reduce the proliferation of the virus.

Proposed neutralization mechanism (second way)

Interaction with Virus Glycoproteins: RVH homocyanin from Rapana venosa; particularly its glycosylated units RvH1-a and RvH2-e; likely interacts with glycoproteins coated by EBV; such as gp350 or gp42; via its carbohydrate chains. This interaction may inhibit or disrupt the virus's entry into host cells; such as B lymphocytes; through van der Waals forces or specific binding. This mechanism resembles the antiviral effects observed against other viruses; including HSV-1 and RSV.

Reduced virus replication: In in vitro tests; RvH1 decreases EBV replication by up to 57%; while RvH2-e can inhibit it by as much as 100% at low concentrations (1-10 micrograms/mL). The effective dose for 50% inhibition (ID50) of RvH is approximately 1 microgram/mL; suggesting a strong potential for neutralization with low toxicity (CC50 is around 700 micrograms/mL).

Advantages over the first way (such as Octominin): This method emphasizes glycosylation; which may be more effective for latent EBV viruses since carbohydrate chains can target the virus during its entry or activation stages. In contrast; peptides such as Octominin primarily focus on disrupting the viral membrane.

How to apply practically (proposed approach)

To neutralize EBV using this method; the following steps can be considered. Please note that these are based on laboratory results rather than clinical studies; as human research is still limited:

Extraction and Preparation: Hemocyanin is extracted from the hemolymph of Rapana venosa. The isoforms RvH1 and RvH2 are then separated through chromatography to isolate active units; such as cRvH2-E. These glycosylated units are crucial because the native molecule is significantly less effective without the presence of arbohydrate chains.

Combining auxiliary factors: can enhance the efficiency of neutralization. For instance; pairing epigenetic inhibitors like vorinostat with this approach can activate the latent virus; allowing for the subsequent neutralization of its homocyanin. In cellular models; such as Raji or B95-8 lines; the compound has demonstrated the ability to inhibit proliferation by up to 100%.

Evaluation of the effect: By using PCR to measure EBV viral DNA; we can investigate the decline in genomic equivalents. Studies have shown that this method can reduce proliferation in lymphoblastoid cells by up to 100%.

Therapeutic potential: This method; characterized by low detoxification; shows promise for treating EBV-related diseases; such as infectious mononucleosis or lymphoma. However; further research is needed to develop appropriate pharmacological formulations; including injections or oral treatments.

Limitations: These effects have only been observed in in vitro experiments and have not yet received approval for human use. (Dolashka, 2011) While toxicity is low; there is a possibility of immune reactions occurring in the body.

Suggestion: If the goal is to completely eliminate the virus; combining this approach with immunotherapy; such as EBV-specific T cells; can enhance its effectiveness.

Conclusion

The Epstein-Barr virus (EBV); a common human virus; is responsible for diseases such as mononucleosis; lymphoma; and related cancers; and it increases the risk of autoimmune diseases like multiple sclerosis (MS). Research through September 2025 has highlighted advancements; including Phase 1 vaccines from companies like ModeX Therapeutics and PARP1 inhibitors that target EBV. Insights into the molecular mimicry of the virus; inspired by natural examples like the mimic octopus; have identified vulnerable sites for targeted treatments. Additionally; homocyanin compounds derived from the Rapana venosa snail exhibit strong antiviral activity against EBV; presenting a natural source for novel drugs. By combining these biomimicry and natural approaches with early screening; we can potentially alleviate the burden of EBV-related diseases. However; further studies are necessary to confirm the efficacy and safety of these treatments. Ultimately; EBV represents a manageable challenge thanks to ongoing medical innovations.

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