Review

The Impact of Co-Infections for Human Gammaherpesvirus Infection and Associated Pathologies

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Abstract: The two oncogenic human gammaherpesviruses Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV) cause significant disease burden, particularly in immuno-suppressed individuals. Both viruses display latent and lytic phases of their life cycle with different outcomes for their associated pathologies. The high prevalence of infectious diseases in Sub-Saharan Africa (SSA), particularly HIV/AIDS, tuberculosis, malaria, and more recently, COVID-19, as well as their associated inflammatory responses, could potentially impact either virus' infectious course. However, acute or lytically active EBV and/or KSHV infections often present with symptoms mimicking these predominant diseases leading to misdiagnosis or underdiagnosis of oncogenic herpesvirus-associated pathologies. EBV and/or KSHV infections are generally acquired early in life and remain latent until lytic reactivation is triggered by various stimuli. This review summarizes known associations between infectious agents prevalent in SSA and underlying EBV and/or KSHV infection. While presenting an overview of both viruses' biphasic life cycles, this review aims to highlight the importance of co-infections in the correct identification of risk factors for and diagnoses of EBV- and/or KSHV-associated pathologies, particularly in SSA, where both oncogenic herpesviruses as well as other infectious agents are highly pervasive and can lead to substantial morbidity and mortality.

Keywords: Epstein-Barr virus (EBV or HHV-4); Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8); human immunodeficiency virus (HIV); *Mycobacterium tuberculosis* (Mtb); *Plasmodium falciparum*; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); malaria; COVID-19; Sub-Saharan Africa (SSA)

1. Introduction

Human herpesviruses are large, enveloped, linear, double-stranded (ds) DNA viruses with genomes that range between 125 and 240 kb in length. With few exceptions, they occur at a high prevalence in the human population and are associated with a wide spectrum of clinical manifestations, ranging from asymptomatic infection to severe disease. Herpesviruses are characterized by their ability to establish life-long latent infections, maintaining their genome in a persistent circular form. While the initial lytic cycle of primary infection leads to the generation of large numbers of virions, latency is characterized by the absence of virus production, where only a limited set of viral genes is expressed. Latency can be interrupted by periods of intermittent lytic reactivation where infectious progeny is produced and shed [1,2].

There are currently eight known human herpesviruses with distinct host cell specificities and clinical characteristics, which are classified into three subfamilies: alpha-, beta-, and gammaherpesvirinae. The alphaherpesvirus group comprises herpes simplex virus type 1 (HSV-1 or HHV-1), herpes simplex virus type 2 (HSV-2 or HHV-2), and Varicella-Zoster virus (VZV or HHV-3), while human cytomegalovirus (HCMV or HHV-5), human herpesvirus-6 (HHV-6), and human herpesvirus-7 (HHV-7) belong to the betaherpesvirus group. The two oncogenic herpesviruses Epstein-Barr virus (EBV or HHV-4) and Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8) are members of the gammaherpesvirus group. Importantly, the alpha- and betaherpesvirus subfamilies mainly attribute their pathogenic potential to viral replication and lytic reactivation, while life-long latent infection typically has minimal impact upon the host. However, both latent and lytic gene products contribute to malignant transformation and associated pathologies caused by the gammaherpesvirus subfamily [3].

Various environmental factors can upset the delicate balance between herpesvirus latency and lytic reactivation, which can lead to disease onset. Most of these factors have been identified by in vitro experiments and include chemical stressors that impact specific intracellular signaling cascades and/or epigenetic regulation. Clinically, triggers of lytic reactivation also include hypoxia, inflammation (including oxidative and nitrative stress), DNA damage due to UV exposure, or high levels of autonomic nervous system (ANS) activity [4–6]. Importantly, various co-infections have been reported to lead to herpesvirus reactivation, which has been, for example, observed on herpesvirus-infected B cells when the infected B cell responds to unrelated infections [7].

Pathologies associated with the two oncogenic gammaherpesviruses EBV and KSHV are particularly prevalent in human immunodeficiency virus (HIV)-infected individuals, with Kaposi's sarcoma (KS) being the most common acquired immunodeficiency syndrome (AIDS)-related malignancy worldwide. Due to the high prevalence of HIV/AIDS and other infectious diseases in Sub-Saharan Africa (SSA), such as tuberculosis, malaria, and more recently, COVID-19, special focus must be placed on co-infections implicated in herpesvirus-associated pathologies, particularly those with oncogenic potential. Although both EBV and KSHV are highly prevalent in SSA, the influence of co-infections on their associated diseases is not well understood. This review will therefore focus on known and emerging co-infections in SSA and their impact on the lytic reactivation of the two human oncogenic herpesviruses EBV and KSHV.

2. Epidemiology of the Oncogenic Gammaherpesviruses EBV and KSHV

2.1. EBV

EBV infects almost 90% of the global population, but primary EBV infection rates differ according to geographic region, age, and socioeconomic status, with higher rates of infection in developing countries [8–10]. EBV consists of two different genotypes, type 1 and 2, or A and B, respectively, based on the differences in the EBV-associated genes, EBNA-2 and EBNA-3 [11,12]. Type 1 EBV has been shown to have a worldwide distribution, whereas type 2 EBV is particularly prevalent in SSA. These strains differ in their ability to induce growth transformation, with type 1 transforming B cells into lymphoblastoid cell lines more efficiently than type 2 [11,13,14].

EBV is mainly transmitted through infected saliva, primarily in childhood; however, it can also spread via blood transfusions and organ transplants [15–18]. It has been suggested that almost all children in underdeveloped countries are EBV-seropositive by the age of 6 years old compared to developed countries where seropositivity peaks at 2–4 and 14–18 years of age and thereafter increases with age [19–21].

While primary EBV infection is asymptomatic in most cases, it can lead to infectious mononucleosis (IM) (a self-limiting disease characterized by lymph node inflammation in the neck region [15]). Studies have established that most primary EBV infections in children under 2 years of age are asymptomatic; however, some children between 10 and 48 months old can display symptoms such as fever, tonsillar pharyngitis, prominent

cervical lymphadenopathy, and respiratory symptoms during IM [22–24] with a large difference in heterophile antibody responses between infants less than 2 years of age (27.3%), children between 25 and 48 months old (76.2%), and young adults (96%) [23].

Long-term EBV infection is further associated with several malignancies such as Burkitt's lymphoma (BL), Hodgkin's lymphoma (HL), T-cell lymphomas, nasopharyngeal carcinoma, gastric cancer, and post-transplant lymphoproliferative disease, particularly in immunosuppressed and immunocompromised individuals, especially patients with HIV/AIDS, transplant recipients, or those undergoing chemotherapy [15,25–32]. In these patients, EBV-infected cells are able to evade the host's immune system, enable metabolic reprogramming, modulate apoptosis, and encourage cancer metastasis and tumor proliferation [25].

In SSA, EBV co-infections with HIV, *Mycobacterium tuberculosis* (Mtb), *Plasmodium* sp., and other viruses, such as KSHV, HCMV, and HSV, are particularly relevant to address. Symptoms of EBV-associated pathologies are often disguised by these prevalent diseases and left undiagnosed, potentially exacerbating EBV viral infection in the host [33–38].

EBV-associated cancers account for approximately 1.5% of all human cancers globally [39] and are responsible for 137,900–208,700 cancer-related deaths annually [40]. The fact that EBV was initially discovered in African BL cell cultures is evidence of the disease's high impact in this region, especially with the lack of efficient healthcare infrastructure and virus control strategies [40,41]. Endemic BL has been shown to have a particularly high impact in SSA affecting 80% of all pediatric patients presenting with hematologic malignancies and is further exacerbated by the high incidences of *Plasmodium* sp. and HIV infection in SSA countries [42].

2.2. KSHV

Unlike EBV, KSHV infection is not ubiquitous, and its prevalence varies geographically with seropositivity rates of less than 10% in the U.S. and Europe, moderate rates of 20–30% in Mediterranean countries, and high rates of 30–50% in SSA [43–46]. Based on sequence variations of the hypervariable Open Reading Frame (ORF)-K1 gene, KSHV can be subtyped into the overarching groups A, B, C, D, E, and F [47], with subtype A commonly observed in Northern Europe and America and subtype B being more predominant on the African continent and being considered the oldest existing strain [48]. There are several routes of KSHV transmission, such as through blood transfusions [49] or sexual contact [50]; however, similar to EBV, transmission via saliva during early childhood is considered the main route of transmission in endemic areas such as SSA [43,51–53].

KSHV is the causative agent of KS, primary effusion lymphoma (PEL), multicentric Castleman disease (MCD), and KSHV-associated cytokine syndrome (KICS), which primarily develop in HIV-infected individuals [54–56]. PEL, MCD, and KICS are rare but likely underreported KSHV-associated pathologies [57], whereas KS is considered the most common AIDS-related malignancy worldwide. Although KS is a relatively rare cancer on a global level, it is epidemic in SSA where both HIV and KSHV prevalence are exceptionally high. GLOBOCAN reported KS incidence rates of 8.5 (males) and 4.7 (females) per 100,000 in Southern Africa compared to incidences below 0.5 per 100,000 for Western European countries or Asia, in 2020 [58]. Although advances in KS management of HIV-infected individuals were made by the introduction of antiretroviral therapy (ART), over 34,000 new cases and over 15,000 deaths were still reported in 2020 with KS being the leading cause of death in Mozambique and Uganda [58].

While HIV-related immune suppression, as defined by low CD4 counts, is considered the most critical mechanism promoting pathogenesis [59], other KSHV-associated malignancies such as MCD display preserved counts [60], highlighting the heterogeneity of KSHV-dependent pathologies. In addition to HIV, co-infection such as with Mtb, *Plasmodium* sp., HCMV, and HSV is highly common in SSA. The high burden of tuberculosis (TB), for instance, often leads to overdiagnoses of TB, and due to similar clinical presentation of

lytic KSHV infection (such as fever, night sweats, inflammation and respiratory symptoms), underdiagnosis of KSHV-associated diseases [46].

Important to note, and different from EBV-associated malignancies, is that both lytic and latent gene products are involved in KSHV-associated tumorigenesis and are distinct between different KSHV-associated malignancies. While KS and PEL are generally characterized by latent gene products [61,62], lytic gene products leading to inflammatory symptoms are predominant in MCD and KICS, with fatal outcomes when untreated [55,63].

3. The Life Cycle of Oncogenic Gammaherpesviruses

3.1. The EBV Life Cycle and the Contribution of Key Latent and Lytic Gene Products

Both phases of the EBV life cycle play important roles in viral pathogenesis and the development of EBV-associated diseases [64]. However, latently infected B cells are predominantly associated with EBV-associated malignancies due to the disruption of cell growth, signal transduction mechanisms, and transcription control by a restricted set of latent genes produced [65]. EBV causes primary infection by replicating in the mucosal epithelium, thereby initially infecting oropharyngeal mucosa cells prior to infection of resting B lymphocytes in the underlying secondary lymphoid tissues [66]. The EBV virions generated and released from the epithelial cells favor B cells due to the presence of particular envelope glycoproteins and vice versa, thereby also allowing the virions to particularly infect naïve B lymphocytes [67,68].

The transformation of naïve B lymphocytes into EBV-infected memory B lymphocytes to establish latency is categorized into different latency stages/programs (0–III) depending on the expression of specific EBV-produced proteins [69]. EBV-infected B cells initially proliferate into activated lymphoblast cells and migrate to the germinal center (GC) of the lymph node follicle establishing the latency III program [69], resulting in the production of EBV nuclear antigens (EBNA)-1, -2, -3A, -3B, -3C, and leader protein (-LP) and latency membrane proteins (LMP)-1, -2A, and -2B, which regulate the growth of EBV [69–71]. EBNA-1, one of the most important latency proteins, shares structural homologies with the KSHV key latency protein latency-associated nuclear antigen (LANA, see Section 3.2) and is expressed during all latency program stages and during lytic replication [72]. In the GC, the latency I program is established with the production of EBNA-1 only [73–75] and the latency II program with EBNA-1, EBV-encoded small RNAs (EBERs), viral microRNAs (v-miRs), BamHI fragment A rightward transcripts (BARTs, i.e., transcripts of the viral genome), LMP-1, and LMP-2A [76,77]. These viral proteins and RNAs contribute to viral immune evasion, immunomodulation, prevention of apoptosis, limitation of viral replication, and survival by limiting interferon (IFN) signaling [78–81].

EBV-infected memory B lymphocytes in latency program 0 establish latency by persisting in a quiescent state with limited replication of only parts of the viral genome and limited expression of viral proteins [82,83]. The viral genome exists in the nucleus as a chromatinized, covalently closed, circular genome and is able to replicate once per cell cycle driven by the host's DNA polymerase [84], remaining undetected in the host for years until reactivated. EBNA-1 is a sequence-specific multifunctional DNA-binding protein responsible for EBV episomal stability, persistence, and maintenance during latency 0 due to its anti-apoptotic properties and its ability to act as a transcriptional transactivator such as for LMP-1 [85–87]. EBNA-1 tethers the viral episome to the host genome and leads to subsequent B-cell immortalization [86].

The ability to maintain latency further relies on epigenetic mechanisms such as DNA methylation, which facilitates transcriptional silencing of the immediate early genes, BZLF1 (ZEBRA/Zta) and BRLF1 (Rta) [88,89]. The suppressive histone modification H3K27me3, as well as the presence of type II histone deacetylating complexes (HDACs) at the promoter region, further contributes to silencing BZLF1 (Zta) transcription [90,91].

Interestingly, reactive oxygen species (ROS) production by EBV was found to be required to immortalize B cells with a role in signal transduction and activation of transcrip-

tion 3 (STAT3) phosphorylation; also, LMP-1 was shown to depend on ROS production, aiding its crucial role in the survival of latently infected cells [92,93].

During any of the latency stages, the memory B lymphocytes can differentiate into plasma cells and cause reactivation of the EBV infection with the production of new viral particles, which can be shed into the saliva [64]. Lytic reactivation of EBV can be triggered by many different factors, including psychological stress, immunosuppression, immunodeficiency, and the presence of foreign antigens due to new infections, which can lead to uncontrolled replication of EBV, potentially resulting in lymphoproliferative diseases [94,95]. During lytic reactivation of EBV, viral gene expression occurs in a sequential and regulated manner and is governed by the production and upregulation of the immediate early genes BZLF1 (ZEBRA/Zta) and BRLF1 (Rta), which activate a cascade of gene expression and signaling pathways [96]. The immediate early genes induce the expression of early genes responsible for viral DNA replication, such as BALF5, BALF2, BMRF1, and BSLF1, as well as late genes BCRF1 (vIL-10), BcLF1, and BNRF1, responsible for protecting the virus from the host immune system and for viral particle formation, respectively [97].

Activation of transcription factors via phosphorylation, as well as activation of cellular kinases such as JNK, MAPK/p38, ERK, PKC, PKD, and/or PI3K signaling/AKT, is important for reactivation and oncogenesis [95,98]. LMP-1 plays a critical role in cell proliferation, anti-apoptosis, transformation, metastasis, and invasion through NF-κB, PI3K, JAK/STAT-mediated, and MAPK-associated signaling activity [99]. EBNA-1 and LMP-2A are also associated with the inhibition of TGFβ1-induced apoptosis [99]. Conversely to its role in latency, ROS generation in EBV-transformed cell lines, induced via the interaction of the JNK and p38-MAPK signaling pathways, results in cellular apoptosis [100].

During lytic reactivation, cytokines such as interleukin (IL)-6, IL-8, IL-10, IL-13, and VEGF are upregulated by BZLF1 (Zta), increasing inflammation and potentially cellular proliferation [101]. The loss of control of any suppressive mechanism of the immediate early genes, BZLF1 (Zta) and BRLF1 (Rta), are fundamental for reactivation and transcriptional regulation of EBV [95,98].

3.2. The KSHV Life Cycle and the Contribution of Key Latent and Lytic Gene Products

Displaying broad cellular tropism, KSHV can infect various cell types in vivo, including peripheral B cells, monocytes, keratinocytes, endothelial cells, epithelial cells, and macrophages [102,103]. As infection mainly occurs upon oral exposure to infected saliva, cells that are associated with the mucosa (e.g., mucosa-associated lymphocytes, macrophages, and/or epithelial cells) are targeted first during primary infection. It is assumed that KSHV migrates within dendritic cells to lymphoid organs, from where it further infects B and T cells [104,105].

Latent and lytic infection phases have distinct viral gene expression patterns [106–108], which unfold differently among various cell types and are characteristic for each KSHV-associated disease; however, gene products of both phases are involved in tumorigenesis [61,62,109]. Importantly and unique among herpesviruses, the pool of latent cells is maintained by lytically active cells, emphasizing how both viral cycles play their role in pathogenesis [6]. B cells and monocytes are considered the major reservoir of latent KSHV, and in KS as well as PEL, gene expression is predominantly latent. Whereas 99% of tumor cells (primarily of endothelial origin) in KS lesions are latently KSHV-infected, high rates of proliferation occur in spindle cells, accounting for only 1% of tumor cells, and have been reported to contribute to higher motility, proliferation, and sustaining angiogenesis [103,110–112]. In MCD, both lytic and latent genes are expressed in B cells surrounding the GCs of lymph nodes [55].

Latency is a controlled but reversible state where the KSHV genome persists as a highly ordered chromatin structure within the host, and lytic gene expression is suppressed [102,103]. The major latency locus of KSHV consists of ORF K12 (Kaposins A–C), ORF71 (v-FLIP), ORF72 (v-CYC), and ORF73 (LANA), as well as 12 pre-miRNA sequences [113–116]. Structurally homologous to the EBV key latency protein EBNA-1 (see

Section 3.1), LANA is the major regulator of latency and is considered a multifunctional oncoprotein. Through its interaction with chromatin-associated proteins, LANA is essential for cellular persistence of the KSHV episome within the host as it regulates chromatin dynamics and the replication of the KSHV genome with a stable copy number ensuring proper segregation of the episome to daughter cells [102,104,105].

Similar to EBV, the latent KSHV genome is characterized by a specific landscape of epigenetic modifications where viral gene expression is silenced through viral DNA methylation and histone modifications [117]. DNA-hypermethylation was shown to correlate with the suppression of gene expression in PEL cells [118], while inhibition of DNA methyltransferases induces lytic reactivation, highlighting the role of DNA methylation during latency [119]. High levels of repressive histone modifications such as H3K9me3 and H3K27me3 are especially found in late gene regions during latency, as reviewed in Toth et al. [120]. Interestingly, several loci of the KSHV latent genome, such as the immediate early gene replication and transcriptional activator (Rta), still show activating histone modifications such as H3K9/K14ac and H3K4me3, whereas constitutive heterochromatin markers such as H3K9me3 were largely absent. Specific epigenetic patterns identified in the study by Günther and Grundhoff are thought to enable rapid chromatin remodeling for the lytic switch [117].

LANA's key role in the repression of lytic gene expression is emphasized by its interactions with chromatin-associated and epigenetic regulatory factors, as well as the DNA methylation machinery [121,122]. Moreover, LANA can directly repress lytic reactivation by interacting with DNA-binding proteins such as RBP-jK. This interaction inhibits Rta activation [121,123]. LANA also plays a key role in the oncogenic transformation of KSHV-infected cells; for example, it impairs TGFβ signaling, leading to the inhibition of TGFβ-mediated antiproliferative effects [124]. It was also shown to be involved in JAK3/STAT3 signaling to promote angiogenic factors [125]. Importantly, LANA can directly inhibit tumor suppressor protein p53 and p73 functions, thereby maintaining the viral episome within the infected cell and contributing to oncogenesis [126,127].

In contrast to latency, the repertoire of viral lytic genes is much bigger and can be activated by host and viral factors as well as environmental stimuli in a strictly regulated manner from immediate early genes required for gene transcription such as ORF50 (Rta), ORF45, K8α, K4.2, K4.1, K4, ORF48, ORF29b, K3, and ORF70, to early genes involved in DNA replication (K8, K5, K2, K12, ORF6, ORF57, ORF74, K9, ORF59, K3, ORF37, K1, K8.1, ORF21, vIL-6, PAN RNA, vIRF1, K1, and ORF65), to late genes like glycoproteins gB and K8.1 involved in viral assembly [125,128–130]. Of these, Rta, encoding for an E3 ubiquitin ligase involved in dynamic chromatin remodeling, is a critical lytic gene. Once active, it leads to the degradation of viral lytic replication repressors and the activation of lytic promoters, resulting in lytic gene expression and the production of new infectious virions. Rta can initiate DNA binding of RBP-jK, thereby activating the Notch signaling pathway, which was shown to be sufficient to activate lytic replication [131–133]. Epigenetic modifications caused by overexpression of histone demethylases or inhibition of transcriptional repressors such as PcG proteins were also found to be critical for the switch between latency and lytic replication [134]. Since KSHV proteins interact with the host cell chromatin, it is plausible that epigenetic reprogramming plays an important role in the pathogenesis of KSHV-associated malignancies [135].

The KSHV lytic phase can be reactivated by inflammatory cytokines such as hepatocyte growth factor (HGF), oncostatin M (OSM), or IFNγ that are also stimulated by other infectious agents [108]. Various co-infections besides HIV, such as HSV-1 and -2, HHV-6, and HCMV are potent cofactors that activate KSHV lytic reactivation and thereby affect KSHV pathogenesis, highlighting the complexity of mechanisms and the influence of co-infections for disease development and outcome [136–138], see Section 4.

Once activated, several lytic genes such as viral protein kinase (vPK/ORF36), viral G-protein-coupled receptor (vGPCR/ORF74), viral interferon regulatory factor 1 (vIRF1/K9), and viral IL-6 (vIL-6/K2), as well as membrane proteins K1 and K15, were found to have

oncogenic functions, stimulating cellular proliferation, transformation, angiogenesis, and cytokine production [139–143].

4. Co-Infection and/or Inflammation Triggers Lytic Reactivation of Oncogenic Gammaherpesviruses

While latency represents a long-term underlying infection with EBV or KSHV of its respective host cells and leads to viral persistence with minimal viral gene transcription, lytic reactivation, potentially triggered by various environmental stimuli, can lead to acute disease onset. The following sections will focus on co-infections relevant in SSA, implicated in EBV- and/or KSHV-associated pathologies.

4.1. Lytic Reactivation of EBV

In the context of co-infections, associated inflammation typically leads to the production of cytokines and chemokines and the disruption of signaling pathways, which can promote lytic reactivation. EBV-produced viral cytokine homologs, such as BCRF1 (vIL-10), act as antagonists, which negatively regulate IL-12 resulting in IFNγ production and leading to cellular apoptosis [144]. Upregulation of cytokines such as TNFα, TNFβ, and G-CSF are also suggested to contribute to reactivation [145]. Induction of inflammation by exosomes carrying viral proteins has also been suggested [146]. Different pathways, such as NF-κB, JAK/STAT, MAPK/ERK, and PI3K/AKT pathways, are activated by inflammatory signals and associated with lytic reactivation and subsequent oncogenesis [99].

Co-infections such as with HIV, Mtb, and *Plasmodium* sp. have previously been shown to exacerbate EBV infection, especially in immunocompromised or immunosuppressed individuals, allowing latent EBV infection to opportunistically reactivate [95]. More recently, co-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been suggested to be associated with lytic EBV reactivation [147].

Serological assays that are able to differentiate between acute or past infections are based on the detection of viral capsid antigen (VCA) IgM and early antigen-diffuse (EA-D) IgG (acute infection) and EBNA-1 IgG (past infection), respectively. However, during lytic reactivation, all EBV antigens are present, i.e., VCA IgM, EA-D IgG, and EBNA-1 IgG [147].

4.1.1. HIV

HIV is an RNA virus from the retrovirus family of lentiviruses [148], being responsible for approximately 84.2 million infections and 40.1 million mortalities worldwide [149]. South Africa has one of the largest HIV-seropositive populations globally [150,151], with approximately 7.5 million people living with HIV, leading to approximately 51,000 HIV-related deaths in 2021 [152]. Although global HIV infection is still rising, the introduction of ART has led to a substantial decrease in AIDS, the most advanced stage of HIV infection, and a higher survival rate for HIV-positive individuals [153,154]. This, on the other hand, has led to a higher prevalence of HIV-related malignancies as the HIV-positive population ages [155–157].

HIV-associated lymphoproliferative disorders such as diffuse large B-cell lymphoma (DLBCL), BL, HL, and EBV-associated smooth muscle tumors can be a result of uncontrolled EBV infection due to the immunocompromised state of the host [151,158,159]. A very early study by Rahman et al. (1991) showed EBV lytic reactivation in 49 male HIV seroconverters within 6 months of HIV infection. It was further demonstrated that IgG antibody titers against EBV EA (associated with primary/acute EBV infection) were increased, and EBV infection remained activated even up until 18 months after HIV seroconversion, suggesting a role for this herpesvirus in HIV pathogenesis [160]. Whitehurst et al. (2022) demonstrated a direct effect of HIV co-infection on the pathogenesis and progression of EBV-related diseases. Co-infection with HIV increased systemic EBV replication and immune activation as well as EBV-induced tumorigenesis in a humanized mouse model of EBV infection [161]. EBV/HIV-infected mice produced a greater number of tumors at a distinct anatomical site, with the expression of LMP1 and EBNA-2 indicating latency program III gene expression in

all EBV-infected tumors with or without HIV infection [161]. Conversely, a study conducted using HIV-positive samples from a cohort of children demonstrated that EBV co-infection affected HIV viral load: the highest mean HIV viral load was observed in EBV co-infected samples compared to other viral co-infected samples, with an increase in the production of IFNγ, IL-2, and TGFβ in the HIV/EBV co-infected group [162–165]. Importantly, the increased EBV shedding in patients with HIV-1 infection was found to be decreased by the use of ART [166–168].

It is suggested that the CD4$^+$ T-cell depletion and associated CD8$^+$ T-cell deterioration and NK cell differentiation to the less protective CD56$^-$CD16$^+$ phenotype due to HIV infection increases EBV-associated malignancies [169]. However, it has also been shown that B cells are more susceptible to HIV infection during EBV B-cell transformation in a CXCR4- and CD4-dependent manner in vitro [170], suggesting a bidirectional effect of HIV/EBV co-infection.

4.1.2. Mycobacterium Tuberculosis

The acid-fast bacterium Mtb is the causative agent of TB, affecting approximately 10.6 million individuals worldwide, with South Africa contributing approximately 87% of all globally estimated incident TB cases in 2018 [171]. Approximately 53% of HIV-positive individuals in South Africa were reported to be co-infected with Mtb in 2021, representing the most common cause of death among HIV-infected people, accounting for one-third of AIDS-related deaths [152,172].

The direct effect and mechanistic relationship between EBV infection and TB pathogenesis still needs to be evaluated; however, a link due to the high Mtb/HIV co-infection rate in South Africa and the ubiquitous nature of EBV has been suggested, which may be dependent on the stage of EBV infection and timing of Mtb infection [173].

In a very early case report from 1986, EBV was detected in an active TB-positive patient, confirmed by the detection of anti-VCA IgM and IgG antibodies [174]. In a recent case study, it was shown that EBV infection is sometimes overlooked during differential diagnosis, despite the presence of evidence indicating past EBV infection of the patient. This oversight is attributed to the prominence given to the patient's history of HIV/Mtb infection, which is considered more clinically significant [175].

EBV has been detected in lung TB, which is associated with multidrug resistance (MDR-TB). In a study including 233 patients, EBV was observed in 27% of HIV-negative lung TB patients and in 21.9% of HIV-positive lung TB patients. Although there was no correlation between EBV and the presence or absence of HIV, EBV and the detection of other HHVs were associated with MDR-TB in HIV patients [176].

Interestingly, a murine model of mice latently infected with the murine gamma-herpesvirus 68 (MHV68), which is genetically related to EBV and KSHV, demonstrated moderate protection from virulent Mtb infection by limiting Mtb growth and dissemination due to the increased response of IFNγ and the possible elicitation of a polyclonal T-cell response. This suggests that human gammaherpesvirus infection could have a significant influence on TB pathogenesis, although it may often be unrecognized, particularly in countries with a high burden of TB, such as South Africa [177].

4.1.3. *Plasmodium* sp.

Malaria is an infectious disease caused by apicomplexan parasites of the *Plasmodium* genus, which are transmitted by the *Anopheles* mosquito [178]. Malaria accounts for approximately 241 million estimated cases globally, resulting in over half a million deaths in 2020 [178,179]. In SSA, malaria is endemic and accounts for approximately 100 million cases and an estimated 275,000 deaths [178].

Endemic BL, a common pediatric cancer in Africa, is classified by the presence of EBV and *Plasmodium* sp. infection; however, the exact extent of their respective contributions is not yet fully elucidated. It has been reported that the cysteine-rich inter-domain region 1α (CIDR1α) of the *Plasmodium falciparum* membrane protein 1 can directly induce EBV

reactivation, thus increasing the risk of BL. CIDR1α activates the memory component of B cells in which EBV is known to persist in a latent form. It was observed that CIDR1α binds to EBV-positive B cells and increases the number of cells that switch to the viral lytic cycle, thereby increasing the immediate early gene BZLF1 (Zta) expression [180].

Co-infection with EBV has been proposed to contribute to a greater risk of malaria-associated morbidity and mortality in children from SSA [181]. The timing of EBV/*Plasmodium* sp. co-infection plays a crucial role in the development of severe malaria, as acute EBV infection during *Plasmodium* infection is essential for the heightened lethality of the co-infection. Since children in SSA often acquire both EBV and *Plasmodium* sp. within their first year of life, it is likely that EBV infection is in the acute phase during their initial malaria episode. This implies that complications leading to childhood malaria deaths may be partially attributed to EBV infection. In experiments conducted on mice, those infected with MHV68 and subsequently infected with *Plasmodium* sp. within 7–15 days experienced severe anemia and succumbed to the infection. However, mice infected with *Plasmodium* at a much later stage did not exhibit the same complications and survived [181].

Evidence of previous *P. falciparum* infection on EBV kinetics was reported by a study on children presenting with acute uncomplicated *P. falciparum* malaria (referred to as acute Kisumu; A-KSM) who showed higher EBV viral loads and stronger anti-VCA IgG antibody responses. This study also looked at KSHV and *Plasmodium* sp. infection suggesting that malaria drives both EBV and KSHV lytic reactivation [182] (see Section 4.2.3).

Other studies have suggested expansion of EBV-infected B cells during malaria, especially in children [37,183]. It has also been shown that binding of *P. falciparum* erythrocyte membrane protein 1 (*Pf*EMP1) to latently EBV-infected B cells caused lytic reactivation with the aid of CIDRα1 indicated by a higher EBV DNA level in the plasma of children and pregnant women with malaria than those without malaria. However, the interplay between host factors in recurrent malaria episodes and co-infection with EBV, leading to the development of endemic BL, still needs to be elucidated [184].

4.1.4. SARS-CoV-2

SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), which was declared a global health pandemic in 2020. SARS-CoV-2, a single-stranded RNA virus, is part of the Coronaviridae family and is responsible for approximately 765 million global infections to date [185–189]. The virus infects the upper respiratory tract, with disease progression leading to inflammation of the alveoli in the lungs resulting in limited gaseous exchange, uncontrolled immune responses (also termed the "cytokine storm"), and potentially fatal respiratory distress [190,191].

In South Africa, the SARS-CoV-2 pandemic occurred against the backdrop of high HIV, Mtb, herpesvirus, and respiratory infections, as well as non-communicable disease burdens. The pandemic contributed to approximately 4 million confirmed infections and approximately 100,000 confirmed deaths ranking South Africa as one of the most severely affected countries on the African continent [188,189,192].

Recent studies have shown increasing evidence to suggest a link between SARS-CoV-2 infection and EBV reactivation resulting in heightened fever and inflammatory responses in COVID-19 patients [193]. However, the question of whether SARS-CoV-2 triggers EBV reactivation or if EBV directly exacerbates SARS-CoV-2 infection remains uncertain and requires further investigation.

In a clinical study conducted by Chen et al. (2021) in Wuhan, China, 55.2% of hospitalized COVID-19 patients with confirmed past EBV infection displayed positive EBV VCA IgM, indicative of EBV reactivation within two weeks of testing positive for SARS-CoV-2. This suggested a correlation between EBV reactivation and the acute phase of COVID-19 [193]. Moreover, a study conducted by Paolucci et al. (2020) demonstrated that the overall median EBV DNA level was significantly increased in intensive care unit (ICU) patients compared to sub-intensive care unit (SICU) in Italy, with EBV reactivation observed in 95.2% of ICU patients and 83.6% of SICU patients [194]. The presence of

EBV DNA correlated with a significant loss of NK and CD8^{+} T cells in these COVID-19 patients [194]. These data correlate with a study conducted in France demonstrating that EBV reactivation led to longer median ICU stays, with 82% of COVID-19 ICU patients displaying EBV reactivation [194,195]. A retrospective study from Wuhan, China, found that 13.3% of patients in the ICU developed EBV reactivation with higher 28-day and 14-day mortality rates than the remainder of patients without EBV reactivation and who also received more immune-supportive treatment than non-EBV patients [196].

A study by Verma et al. (2021) indicated that the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) was upregulated during lytic EBV infection due to the EBV lytic activator, BZLF1 (Zta), targeting methylated promoters, thus increasing SARS-CoV-2 susceptibility in the human oral epithelium [197].

A more recent study suggested that SARS-CoV-2 infection does indeed increase EBV reactivation as demonstrated by the detection of EBV DNA in plasma samples. EBNA-1 IgG indicates previous EBV infection; therefore, primary EBV infections were defined in the study by the absence of EBNA-1 IgG in samples and were excluded from analysis, thus revealing 27.1% of EBV reactivation in the COVID-19-positive sample group, compared to only 12.5% of reactivations in the COVID-19-negative group [147].

To investigate the effect of "long COVID" on EBV reactivation, Gold et al. (2021) reported increased EBV EA IgG or EBV VCA IgM in 66.7% of "long COVID" subjects and in 10% of control subjects with a similar trend observed in patients 21–90 days following acute SARS-CoV-2 infection [198]. This suggests that EBV reactivation may occur soon after or concurrently with acute COVID-19 and as a result of COVID-19-associated inflammation (i.e., the "cytokine storm") rather than SARS-CoV-2 infection [198]. It has been suggested that EBV reactivation could be the cause of "long COVID" symptoms due to impaired mitochondrial functions during the host immune response to COVID-19 and long-term symptoms [199]. Moreover, the proinflammatory cytokine IL-6 has been associated with increased EBV reactivation in COVID-19 patients, as significant levels of EBV viremia were found in 78% of critically ill COVID-19 patients compared to only 44.4% in non-COVID-19 patients [195]. However, the specific mechanisms underlying this relationship were not clearly defined.

4.1.5. Other Co-Infections

HCMV and EBV co-infection are commonly detected in immune-competent children [200] and is suggested to facilitate multi-pathogen infection such as with respiratory syncytial virus (RSV), Chlamydia pneumonia (CP), HHV-6, -7, and/or measles virus, among others [200]. It is speculated that EBV/HCMV co-infection can influence B-cell responses and NK cell cytokine production and the frequency of NKG2C^{+} and CD57^{+}NKG2C^{+} NK cell differentiation; however, the mechanisms governing this are unknown [200–202]. Recently, a role for EBV/HCMV-associated reactivation in hematopoietic stem cell transplantation (HSCT) patients has been reported, increasing the incidence of hemorrhagic cystitis and thereby reducing the overall survival rate of HSCT patients [203].

Co-infection of EBV with HSV has been observed in a rare clinical case of Erythema multiforme in a young child. Elevated levels of antibodies to both IgM HSV and EBV were detected with no other viral infections [204]. Another study demonstrated an association of EBV-seropositivity with the presence of HCMV and HSV-1 viral antibodies [205].

It has also been observed that EBV and HPV co-infection leads to a dysregulation of miRNA expression. Both viruses can synergistically dysregulate miR-21 and miR-200c, the expression of which has been shown to have a role in cervical carcinogenesis [206]. EBV was suggested to impair T-cell immunity in advanced stages of cervical cancer, contributing to the immune evasion of HPV-infected epithelial cells. The interaction between EBV LMP1 and HPV viral proteins altered NF-κB and MAPK signaling, among others, in a murine model [207], while another study highlighted the necessity of HPV viral oncoproteins E6 and E7 in EBV lytic replication in oral keratinocytes [208]. A helper role of EBV in cervical

cancer development has been suggested by several studies due to the presence of both HPV and EBV DNA sequences in malignant tissues [209–216].

Recently, EBV has been detected in a newly emerging hemorrhagic fever known as thrombocytopenia syndrome (SFTS) caused by a bunyavirus transmitted through tick bites with a fatality rate of up to 30%. EBV reactivation was seen in 4 out of 22 (18.2%) SFTS patients from Qingdao City, China. Previous EBV infection was observed in more than 90% of the SFTS patients in this study as defined by EBV IgG levels suggesting that EBV was reactivated rather than being a primary infection [217].

4.2. Lytic Reactivation of KSHV

Factors that are known to induce lytic KSHV reactivation are oxidative stress, hypoxia, inflammation, and immune suppression [108,218], as well as various co-infections such as with HIV, Mtb, *Plasmodium* sp., HSV-1, HSV-2, HHV-6, and HCMV, and more recently SARS-CoV-2 [136–138,219,220].

ROS and cytokine production in the context of inflammation and co-infection can induce cellular pathways that involve NF-κB inhibition as well as p38, JNK, and ERK1/2 signaling, ultimately leading to KSHV reactivation [221,222]. Under hypoxic conditions, which usually promote cell cycle arrest and hinder DNA replication in order to decrease the energy consumption of the cell, KSHV LANA has been shown to maintain genome replication of both the host and the virus [223]. Moreover, in vitro studies showed that lytic reactivation occurs upon acute and chronic exposure of PEL B-cell lines to hypoxia, leading to an increase in KSHV lytic proteins as well as secreted vIL-6 [224].

Compared to EBV diagnostics (see Section 4.1), there are no clinically utilized, standardized high-sensitivity serological tests for KSHV infection, and serological differentiation of KSHV acute and past infection, as well as reactivation, is not well established [225]. However, in-house ELISA platforms to quantify lytic K8.1 and latent LANA are well recognized to assess general KSHV seropositivity [226].

4.2.1. HIV

Although the introduction of ART has had a major effect of reducing KS incidence and improving prognosis when included as therapy for HIV-infected individuals, HIV-related immune suppression, e.g., defined by low CD4 counts (<200 cells/μL), still remains the most important mechanism promoting KSHV-driven pathogenesis [59]. While there has been a decline in the incidence of KS in HIV-infected individuals due to ART, a rising number of KS patients with CD4 counts over 300 cells/μL have been reported [227]. This could be explained by HIV-unrelated KS because the life expectancy of HIV-infected patients on ART has increased or to HIV-related effects that do not depend on T-cell immunosuppression. In other KSHV-related diseases, such as MCD, patients show preserved CD4 counts [60], highlighting that KSHV-dependent malignancies are highly heterogeneous, and research in these populations remains a priority in AIDS research.

Lytic reactivation of KSHV in the context of underlying HIV infection was shown to be directly influenced by HIV proteins such as transactivator of transcription (Tat), which can activate the immediate early gene Rta as shown in an in vitro study using a PEL cell line [228]. Moreover, HIV Tat mimics growth factors and signaling molecules and can function as an angiogenic factor, thereby activating the tyrosine kinase receptor VEGF-A through direct binding, resulting in growth of KS lesions [229]. HIV has also been shown to potently induce lytic replication of KSHV via activation of the KSHV Rta in a Tat-independent manner [228].

Late stages of HIV infections and/or AIDS are characterized by chronic inflammation. HIV-1 Tat can induce cytokines, which, in turn, were shown to induce KSHV lytic reactivation [59]. The induction of inflammatory cytokine secretion is due to Tat modulation of signaling pathways controlling the inflammatory response in the cell, such as activation of JAK/STAT [230], contributing to lytic KSHV replication [230]. Lytic replication of KSHV was also found to be induced by soluble factors produced by or in response to

HIV-1-infected T cells co-cultured with a KSHV-infected cell line (BCBL-1), as an increase in KSHV mRNA transcripts, proteins, and infectious virions has been shown [231].

Due to HIV-related immune suppression, lytically activated cells are not eliminated by the host immune system, further fueling HIV/KS pathogenesis [232].

4.2.2. Mycobacterium Tuberculosis

The context of the high prevalence of Mtb in SSA has led to overdiagnosis and overtreatment of TB, leaving KSHV-related pathologies that may symptomatically mimic TB misdiagnosed and, therefore, untreated [46]. KSHV-MCD, for instance, is rare but likely underdiagnosed and is characterized by nonspecific inflammation symptomatically similar to HIV/TB, complicating accurate diagnosis. Indeed, when investigating a large patient cohort ($n = 682$) from South Africa presenting with typical TB symptoms, a subset of patients fitted the KICS working case definition [56], with one patient retrospectively being diagnosed with MCD [46].

The impact of Mtb/KSHV co-infection was also addressed in a study comparing KSHV viral loads and KSHV antibodies in patients with underlying Mtb infection, which revealed significantly higher titers in Mtb/KSHV patients than in controls [233]. Virulence factors secreted by Mtb were shown to influence KSHV-infected cells and induce KSHV lytic reactivation in vitro, such as the early secreted antigenic target 6kDa (ESAT-6), which was confirmed by lytic gene expression of Rta, vGPCR, and K8.1 in HUVEC endothelial cells and PEL cells [234]. As ESAT-6 can be secreted into the extracellular space, co-infection between Mtb and KSHV does not have to occur in the same cell, although this is very likely due to similar tropism including macrophages, dendritic cells, epithelial, and endothelial cells [234].

4.2.3. *Plasmodium* sp.

As KSHV seroprevalence is particularly high in SSA, where malaria is endemic, an association between these two diseases has been suggested in the literature [235–237]. A study investigating KSHV seroconversion in Kenyan children further showed that infection with *P. falciparum* increases the risk of KSHV seropositivity at an early age [238]. Several factors, such as impaired immune functions, favor the development of KS and other KSHV-associated pathologies. Furthermore, malaria triggers a T helper type 2 (Th2) immune response, which is also very common in helminth infections, and characterized by the production of the cytokines IL-4, IL-5, and IL-13. IL-4 was shown to reactivate gammaherpesviruses in a mouse model and specifically reactivate KSHV in vitro with increased expression of immediate early and late lytic transcripts [239]. A recent study by Olouch et al. (2023) examined KSHV serological patterns of children with acute malaria and demonstrated that KSHV latency was disrupted by acute malaria episodes. Not only was acute *P. falciparum* infection characterized by distinct serological profiles, but KSHV lytic antigens were also increased in patients with acute malaria [182].

Ruocco et al. (2011) proposed an "oncodrug" hypothesis, claiming that cancer development is favored by immunosuppressive properties of anti-malaria drugs such as quinine. Indeed, iatrogenic immunosuppression can last for years, which makes KSHV-infected individuals more susceptible to lytic reactivation [240]. Several species of *Plasmodium* can cause severe anemia [241], which, in turn, triggers hypoxia, a known risk factor for lytic reactivation of KSHV, as stated above [224].

4.2.4. SARS-CoV-2

While several co-morbidities are known to increase the risk of a fatal COVID-19 outcome, co-infection with oncogenic viruses is of particular significance for long-term cancer risk and KSHV-associated pathogenesis [242]. Observational studies conducted in South Africa identified an association between KSHV viral load and COVID-19 outcomes [243]. Although the study design could not determine whether disease synergy was at play, several SARS-CoV-2 proteins have indeed been shown to induce lytic reactivation of KSHV

in vitro, such as SARS-CoV-2 Spike (S) and nucleocapsid (N) proteins when ectopically expressed [220]. Not only the virus itself, but drugs that are used in the treatment of COVID-19, such as azithromycin and nafamostat mesylate, but not remdesivir, induced KSHV lytic reactivation in iSKL.219 cells [220]. Further, a potential interplay between SARS-CoV-2 and KSHV was suggested by data showing upregulated ACE2 expression in AIDS-KS tissue, although the underlying mechanisms of KSHV-mediated regulation of ACE2 expression remain unknown [220]. An association between KSHV and SARS-CoV-2 was also indicated in a clinical case of a woman with confirmed KS without visual skin lesions who was hospitalized for COVID-19 and showed subsequent recurrence of KS. Both KSHV and SARS-CoV-2 were detected by transmission electron microscopy (TEM) of the patient's biopsies, and the recurrence of KS was speculated to be promoted by inflammation caused by SARS-CoV-2 infection [244]. Clinical manifestation of lytic reactivation of other herpesviruses (EBV, HCMV, HSV) was substantially higher in patients co-infected with SARS-CoV-2, especially those with severe symptoms as well as those who were vaccinated against SARS-CoV-2 [245]. Lytic reactivation of KSHV in the post-pandemic era should therefore remain a research focus, especially in populations with a high prevalence of HIV and other infectious diseases.

4.2.5. Other Co-Infections

HCMV, a betaherpesvirus, occurs ubiquitously, can be vertically transmitted, and represents an important opportunistic infection in HIV-infected individuals [59,246,247]. Immunosuppression is critical for the reactivation of both KSHV and HCMV, and interactions between the two viruses are very likely, not least due to similar cellular tropisms. Lytic replication of KSHV was reported to be induced by the direct activation of Rta by gene products of the HCMV UL112-114 locus, encoding four phosphoproteins synthesized via alternative splicing [248]. Latently KSHV-infected human fibroblasts were induced to lytic replication by infection with HCMV, giving rise to new virion progeny. It was further shown that HCMV infection led to higher KSHV replication in endothelial cells and activated lytic replication in keratinocytes [136]. KSHV reactivation by HCMV might be cell type dependent and have different underlying mechanisms, which was suggested by studies in which a laboratory HCMV strain was unable to induce KSHV lytic reactivation in a BCBL-1 cell line [249].

Other herpesviruses, such as HSV-1 and HSV-2, have been described as cofactors with the potential to reactivate KSHV [137,219]. HSV-1 infection was shown to activate Rta through cellular miRNAs. Upon infection with HSV-1, miR-498, and miR-320d (both of which directly target Rta at its 3′ UTR and inhibit its expression) were downregulated. This was corroborated in experiments overexpressing miR-498 and miR-320d, which resulted in the inhibition of lytic reactivation, whereas miR-498 and miR-320d repression enhanced lytic replication of KSHV [219]. In addition, the PI3K/AKT and ERK/MAPK pathways were found to be stimulated by HSV-1 infection-promoting lytic reactivation [250]. Likewise, HSV-2 infection was shown to lead to Rta activation, resulting in lytic KSHV gene transcription, expression of viral proteins, and production of infectious viral particles in BCBL-1 [137]. Furthermore, HHV-6 was found to be a potent factor inducing lytic replication of KSHV. Co-culture experiments of BCBL-1 cells with HHV-6-infected cells showed an increase in KSHV lytic transcripts after 8 h, which further induced other proteins of the lytic cycle [138]. HHV-6 could also influence the KSHV lytic cycle by regulating cytokines such as TNFα, IL-β, and IFNs [251].

4.3. The Interplay between EBV and KSHV

Co-infection with the two gammaherpesviruses, EBV and KSHV, has been described in immunocompromised hosts with AIDS-associated PEL. Both viruses negatively affect the others' gene expression level following physical interaction on a molecular level. EBV lytic replication is inhibited by KSHV Rta, while KSHV lytic gene expression is inhibited by EBV BZLF1 (Zta) [252].

KSHV lytic replication can also be suppressed by EBV LMP-1. However, LMP-1 can be induced by KSHV Rta in latently EBV-infected cells, which can result in the suppression of lytic replication of both EBV and KSHV. Although EBV and KSHV can suppress each other's lytic replicative cycles during co-infection, they can be mutually beneficial during long-term latency, whereby they enable each other to escape the host's immune response [59].

Interestingly, KSHV Rta has also been suggested to increase EBV infectivity by upregulating the expression of the EBV entry receptor CD21 [59]. Another study demonstrated that during dual infection of EBV and KSHV, EBV's ability to transform B cells in vivo was adequate to facilitate KSHV infection [36], which suggests that EBV may also enhance KSHV genome maintenance [33].

In vitro studies further demonstrated that both viruses could be maintained in a BC-1 cell line, derived from a body cavity-based B-cell lymphoma, and could be differentially induced from their latent state into their lytic state using sodium butyrate and 12-O-tetradecanoylphorbol-13-acetate (TPA), respectively. However, only EBV displayed the release of infectious virions from BC-1 cells, whereas there was little evidence that KSHV intranuclear nucleocapsids were released [253]. This shows that the mechanistic pathways for lytic reactivation of these two viruses could slightly differ, allowing for differential induction.

5. Conclusions

The high prevalence of infectious diseases in SSA, primarily HIV/AIDS, TB, and malaria represent an unknown risk for pathologies associated with the oncogenic gamma-herpesviruses, EBV and KSHV. Lytic reactivation of these viruses is often associated with nonspecific inflammatory symptoms and is, therefore, likely to be misdiagnosed as a pathology caused by one of the more predominant infectious agents in the SSA context. More recently, SARS-CoV-2 infection might impact EBV/KSHV-associated diseases, which could, in turn, exacerbate COVID-19 progression and outcome and/or lead to "long COVID" and/or malignant transformation.

There are neither prophylactic nor therapeutic vaccines against EBV and/or KSHV infection available; therefore, clinical awareness of EBV- and KSHV-associated pathologies and early diagnosis of diseases linked to these two human oncogenic herpesviruses will facilitate successful intervention strategies, particularly in vulnerable populations with high HIV prevalence and high exposure to other circulating infectious diseases. Identification of these populations and implementation of diagnostic platforms for EBV and KSHV in relevant clinical settings is highly recommended. Moreover, anti-oxidant and anti-inflammatory drugs for the symptomatic treatment of co-infections could be promising preventative and therapeutic means for effectively targeting oncogenic herpesvirus reactivation (Figure 1).
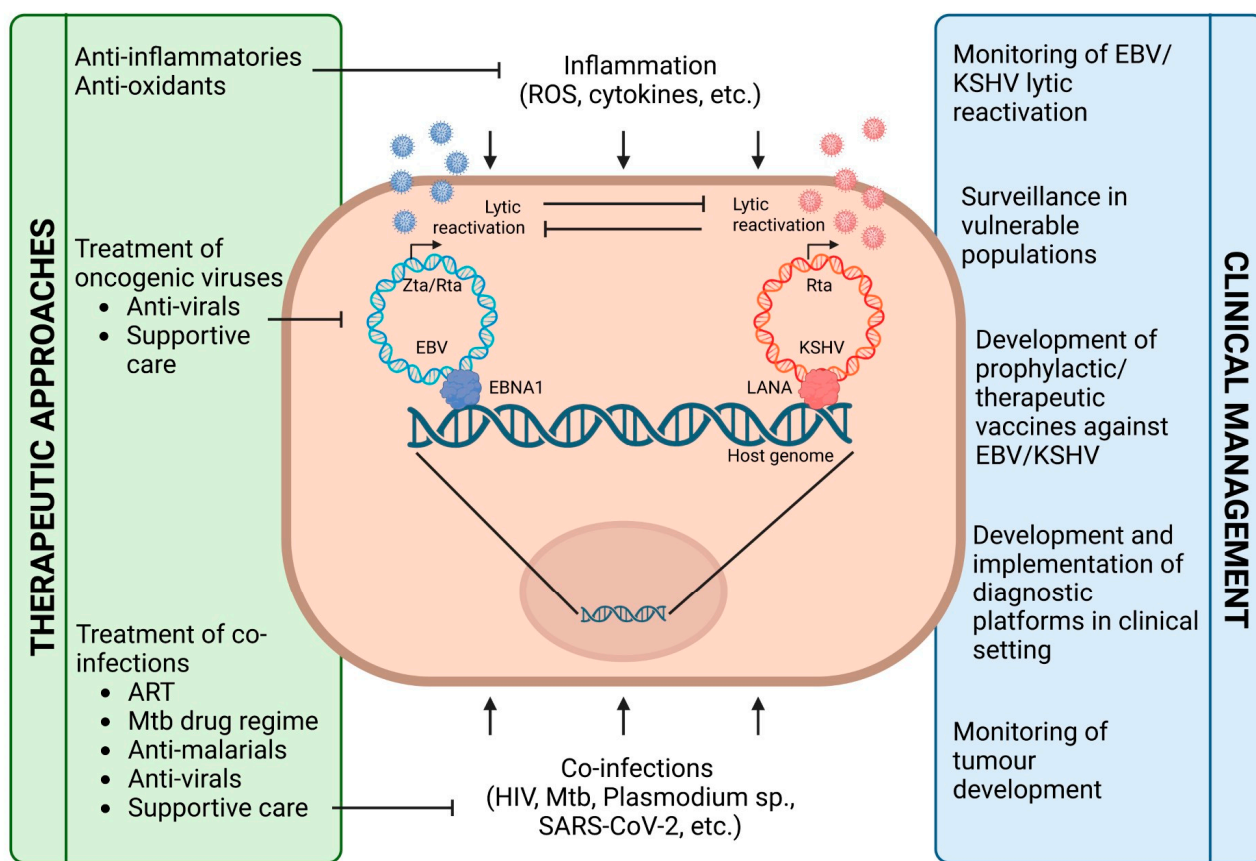
Figure 1. Co-infections and inflammation impact EBV and KSHV lytic reactivation. Preventative and/or therapeutic approaches using anti-inflammatory and anti-oxidative drugs, as well as specific treatment of co-infections, may improve EBV/KSHV-associated disease outcomes, which should be monitored in high-risk populations. (Figure created with Biorender.com (accessed on 14 July 2023)).

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References

1. Boehmer, P.E.; Nimonkar, A.V. Herpes virus replication. *IUBMB Life* **2003**, *55*, 13–22. [CrossRef] [PubMed]
2. Grinde, B. Herpesviruses: Latency and reactivation–viral strategies and host response. *J. Oral Microbiol.* **2013**, *5*, 22766. [CrossRef] [PubMed]
3. Adler, B.; Sattler, C.; Adler, H. Herpesviruses and Their Host Cells: A Successful Liaison. *Trends Microbiol.* **2017**, *25*, 229–241. [CrossRef] [PubMed]
4. Wilson, A.C.; Mohr, I. A cultured affair: HSV latency and reactivation in neurons. *Trends Microbiol.* **2012**, *20*, 604–611. [CrossRef]

5. Kobayashi, M.; Wilson, A.C.; Chao, M.V.; Mohr, I. Control of viral latency in neurons by axonal mTOR signaling and the 4E-BP translation repressor. *Genes Dev.* **2012**, *26*, 1527–1532. [CrossRef]

6. Aneja, K.K.; Yuan, Y. Reactivation and Lytic Replication of Kaposi's Sarcoma-Associated Herpesvirus: An Update. *Front. Microbiol.* **2017**, *8*, 613. [CrossRef]

7. Odumade, O.A.; Hogquist, K.A.; Balfour, H.H., Jr. Progress and problems in understanding and managing primary Epstein-Barr virus infections. *Clin. Microbiol. Rev.* **2011**, *24*, 193–209. [CrossRef]

8. Kerr, J.R. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. *J. Clin. Pathol.* **2019**, *72*, 651–658. [CrossRef]

9. Wang, M.; Gu, B.; Chen, X.; Wang, Y.; Li, P.; Wang, K. The function and therapeutic potential of Epstein-Barr virus-encoded microRNAs in cancer. *Mol. Ther.-Nucleic Acids* **2019**, *17*, 657–668. [CrossRef]

10. Smatti, M.K.; Al-Sadeq, D.W.; Ali, N.H.; Pintus, G.; Abou-Saleh, H.; Nasrallah, G.K. Epstein–Barr Virus Epidemiology, Serology, and Genetic Variability of LMP-1 Oncogene Among Healthy Population: An Update. *Front. Oncol.* **2018**, *8*, 211. [CrossRef]

11. Palser, A.L.; Grayson, N.E.; White, R.E.; Corton, C.; Correia, S.; Ba Abdullah, M.M.; Watson, S.J.; Cotten, M.; Arrand, J.R.; Murray, P.G.; et al. Genome diversity of Epstein-Barr virus from multiple tumor types and normal infection. *J. Virol.* **2015**, *89*, 5222–5237. [CrossRef] [PubMed]

12. Correia, S.; Bridges, R.; Wegner, F.; Venturini, C.; Palser, A.; Middeldorp, J.M.; Cohen, J.I.; Lorenzetti, M.A.; Bassano, I.; White, R.E.; et al. Sequence Variation of Epstein-Barr Virus: Viral Types, Geography, Codon Usage, and Diseases. *J. Virol.* **2018**, *92*, e01132-01118. [CrossRef] [PubMed]

13. Rickinson, A.B.; Young, L.S.; Rowe, M. Influence of the Epstein-Barr virus nuclear antigen EBNA 2 on the growth phenotype of virus-transformed B cells. *J. Virol.* **1987**, *61*, 1310–1317. [CrossRef]

14. Tzellos, S.; Correia, P.B.; Karstegl, C.E.; Cancian, L.; Cano-Flanagan, J.; McClellan, M.J.; West, M.J.; Farrell, P.J. A single amino acid in EBNA-2 determines superior B lymphoblastoid cell line growth maintenance by Epstein-Barr virus type 1 EBNA-2. *J. Virol.* **2014**, *88*, 8743–8753. [CrossRef]

15. Kuri, A.; Jacobs, B.M.; Vickaryous, N.; Pakpoor, J.; Middeldorp, J.; Giovannoni, G.; Dobson, R. Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. *BMC Public Health* **2020**, *20*, 912. [CrossRef]

16. Chen, J.; Longnecker, R. Epithelial cell infection by Epstein-Barr virus. *FEMS Microbiol. Rev.* **2019**, *43*, 674–683. [CrossRef] [PubMed]

17. Faulkner, G.C.; Krajewski, A.S.; Crawford, D.H. The ins and outs of EBV infection. *Trends Microbiol.* **2000**, *8*, 185–189. [CrossRef]

18. Alfieri, C.; Tanner, J.; Carpentier, L.; Perpete, C.; Savoie, A.; Paradis, K.; Delage, G.; Joncas, J. Epstein-Barr virus transmission from a blood donor to an organ transplant recipient with recovery of the same virus strain from the recipient's blood and oropharynx. *Blood* **1996**, *87*, 812–817. [CrossRef]

19. Niederman, J.; Evans, A.; Subrahmanyan, L.; McCollum, R. Prevalence, incidence and persistence of EB virus antibody in young adults. *N. Engl. J. Med.* **1970**, *282*, 361–365. [CrossRef]

20. Papesch, M.; Watkins, R. Epstein-Barr virus infectious mononucleosis. *Clin. Otolaryngol. Allied Sci.* **2001**, *26*, 3–8. [CrossRef]

21. Trottier, H.; Buteau, C.; Robitaille, N.; Duval, M.; Tucci, M.; Lacroix, J.; Alfieri, C. Transfusion-related Epstein-Barr virus infection among stem cell transplant recipients: A retrospective cohort study in children. *Transfusion* **2012**, *52*, 2653–2663. [CrossRef] [PubMed]

22. Fleisher, G.; Henle, W.; Henle, G.; Lennette, E.T.; Biggar, R.J. Primary infection with Epstein-Barr virus in infants in the United States: Clinical and serologic observations. *J. Infect. Dis.* **1979**, *139*, 553–558. [CrossRef]

23. Horwitz, C.A.; Henle, W.; Henle, G.; Goldfarb, M.; Kubic, P.; Gehrz, R.C.; Balfour, H.H.; Fleisher, G.R.; Krivit, W. Clinical and Laboratory Evaluation of Infants and Children With Epstein-Barr Virus-Induced Infectious Mononucleosis: Report of 32 Patients (Aged 10–48 Months). *Blood* **1981**, *57*, 933–938. [CrossRef]

24. Biggar, R.J.; Henle, G.; Böcker, J.; Lennette, E.T.; Fleisher, G.; Henle, W. Primary Epstein-Barr virus infections in African infants. II. Clinical and serological observations during seroconversion. *Int. J. Cancer* **1978**, *22*, 244–250. [CrossRef] [PubMed]

25. Richardo, T.; Prattapong, P.; Ngernsombat, C.; Wisetyaningsih, N.; Iizasa, H.; Yoshiyama, H.; Janvilisri, T. Epstein-Barr Virus Mediated Signaling in Nasopharyngeal Carcinoma Carcinogenesis. *Cancers* **2020**, *12*, 2441. [CrossRef]

26. Kaymaz, Y.; Oduor, C.I.; Aydemir, O.; Luftig, M.A.; Otieno, J.A.; Ong'echa, J.M.; Bailey, J.A.; Moormann, A.M. Epstein-Barr Virus Genomes Reveal Population Structure and Type 1 Association with Endemic Burkitt Lymphoma. *J. Virol.* **2020**, *94*, e02007-19. [CrossRef]

27. Mpunga, T.; Clifford, G.M.; Morgan, E.A.; Milner, D.A., Jr.; de Martel, C.; Munyanshongore, C.; Muvugabigwi, G.; Combes, J.D. Epstein-Barr virus prevalence among subtypes of malignant lymphoma in Rwanda, 2012 to 2018. *Int. J. Cancer* **2022**, *150*, 753–760. [CrossRef] [PubMed]

28. Means, R.E.; Lang, S.M.; Jung, J.U. Human gammaherpesvirus immune evasion strategies. In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*; Cambridge University Press: Cambridge, UK, 2007.

29. Gulley, M.L.; Tang, W. Laboratory assays for Epstein-Barr virus-related disease. *J. Mol. Diagn.* **2008**, *10*, 279–292. [CrossRef] [PubMed]

30. Chetaille, B.; Bertucci, F.; Finetti, P.; Esterni, B.; Stamatoullas, A.; Picquenot, J.M.; Copin, M.C.; Morschhauser, F.; Casasnovas, O.; Petrella, T. Molecular profiling of classical Hodgkin lymphoma tissues uncovers variations in the tumor microenvironment and correlations with EBV infection and outcome. *Blood J. Am. Soc. Hematol.* **2009**, *113*, 2765–3775. [CrossRef]

31. Neri, A.; Barriga, F.; Inghirami, G.; Knowles, D.M.; Neequaye, J.; Magrath, I.T.; Dalla-Favera, R. Epstein-Barr Virus Infection Precedes Clonal Expansion in Burkitt's and Acquired Immunodeficiency Syndrome-Associated Lymphoma. *Blood* **1991**, *77*, 1092–1095. [CrossRef]

32. Rasul, A.E.; Nagy, N.; Sohlberg, E.; Ádori, M.; Claesson, H.-E.; Klein, G.; Klein, E. Simultaneous detection of the two main proliferation driving EBV encoded proteins, EBNA-2 and LMP-1 in single B cells. *J. Immunol. Methods* **2012**, *385*, 60–70. [CrossRef]

33. Bigi, R.; Landis, J.T.; An, H.; Caro-Vegas, C.; Raab-Traub, N.; Dittmer, D.P. Epstein–Barr virus enhances genome maintenance of Kaposi sarcoma-associated herpesvirus. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E11379–E11387. [CrossRef] [PubMed]

34. Hernández, D.M.; Valderrama, S.; Gualtero, S.; Hernández, C.; López, M.; Herrera, M.V.; Solano, J.; Fiorentino, S.; Quijano, S. Loss of T-cell multifunctionality and TCR-Vβ repertoire against Epstein-Barr virus is associated with worse prognosis and clinical parameters in HIV+ patients. *Front. Immunol.* **2018**, *9*, 2291. [CrossRef] [PubMed]

35. Lam, J.K.P.; Azzi, T.; Hui, K.F.; Wong, A.M.G.; McHugh, D.; Caduff, N.; Chan, K.H.; Münz, C.; Chiang, A.K.S. Co-infection of Cytomegalovirus and Epstein-Barr Virus Diminishes the Frequency of CD56(dim)NKG2A(+)KIR(-) NK Cells and Contributes to Suboptimal Control of EBV in Immunosuppressed Children With Post-transplant Lymphoproliferative Disorder. *Front. Immunol.* **2020**, *11*, 1231. [CrossRef] [PubMed]

36. McHugh, D.; Caduff, N.; Barros, M.H.M.; Rämer, P.C.; Raykova, A.; Murer, A.; Landtwing, V.; Quast, I.; Styles, C.T.; Spohn, M.; et al. Persistent KSHV Infection Increases EBV-Associated Tumor Formation In Vivo via Enhanced EBV Lytic Gene Expression. *Cell Host Microbe* **2017**, *22*, 61–73.e67. [CrossRef]

37. Moormann, A.M.; Chelimo, K.; Sumba, O.P.; Lutzke, M.L.; Ploutz-Snyder, R.; Newton, D.; Kazura, J.; Rochford, R. Exposure to holoendemic malaria results in elevated Epstein-Barr virus loads in children. *J. Infect. Dis.* **2005**, *191*, 1233–1238. [CrossRef] [PubMed]

38. Wu, H.; Li, T.; Zeng, M.; Peng, T. Herpes simplex virus type 1 infection activates the Epstein-Barr virus replicative cycle via a CREB-dependent mechanism. *Cell Microbiol.* **2012**, *14*, 546–559. [CrossRef] [PubMed]

39. Farrell, P.J. Epstein-Barr Virus and Cancer. *Annu. Rev. Pathol.* **2019**, *14*, 29–53. [CrossRef] [PubMed]

40. Wong, Y.; Meehan, M.T.; Burrows, S.R.; Doolan, D.L.; Miles, J.J. Estimating the global burden of Epstein–Barr virus-related cancers. *J. Cancer Res. Clin. Oncol.* **2022**, *148*, 31–46. [CrossRef] [PubMed]

41. Diakite, M.; Shaw-Saliba, K.; Lau, C.-Y. Malignancy and viral infections in Sub-Saharan Africa: A review. *Front. Virol.* **2023**, *3*. [CrossRef]

42. Sinfield, R.; Molyneux, E.; Banda, K.; Borgstein, E.; Broadhead, R.; Hesseling, P.; Newton, R.; Casabonne, D.; Mkandawire, N.; Nkume, H. Spectrum and presentation of pediatric malignancies in the HIV era: Experience from Blantyre, Malawi, 1998–2003. *Pediatr. Blood Cancer* **2007**, *48*, 515–520. [CrossRef] [PubMed]

43. Uldrick, T.S.; Whitby, D. Update on KSHV epidemiology, Kaposi Sarcoma pathogenesis, and treatment of Kaposi Sarcoma. *Cancer Lett.* **2011**, *305*, 150–162. [CrossRef] [PubMed]

44. Dedicoat, M.; Newton, R. Review of the distribution of Kaposi's sarcoma-associated herpesvirus (KSHV) in Africa in relation to the incidence of Kaposi's sarcoma. *Br. J. Cancer* **2003**, *88*, 1–3. [CrossRef] [PubMed]

45. Newton, R.; Ziegler, J.; Bourboulia, D.; Casabonne, D.; Beral, V.; Mbidde, E.; Carpenter, L.; Reeves, G.; Parkin, D.M.; Wabinga, H. The sero-epidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in adults with cancer in Uganda. *Int. J. Cancer* **2003**, *103*, 226–232. [CrossRef] [PubMed]

46. Blumenthal, M.J.; Schutz, C.; Barr, D.; Locketz, M.; Marshall, V.; Whitby, D.; Katz, A.A.; Uldrick, T.; Meintjes, G.; Schäfer, G. The Contribution of Kaposi's Sarcoma–Associated Herpesvirus to Mortality in Hospitalized Human Immunodeficiency Virus–Infected Patients Being Investigated for Tuberculosis in South Africa. *J. Infect. Dis.* **2019**, *220*, 841–851. [CrossRef]

47. Zhang, Z.; Chen, W.; Sanders, M.K.; Brulois, K.F.; Dittmer, D.P.; Damania, B. The K1 Protein of Kaposi's Sarcoma-Associated Herpesvirus Augments Viral Lytic Replication. *J. Virol.* **2016**, *90*, 7657–7666. [CrossRef]

48. Tornesello, M.L.; Biryahwaho, B.; Downing, R.; Hatzakis, A.; Alessi, E.; Cusini, M.; Ruocco, V.; Katongole-Mbidde, E.; Loquercio, G.; Buonaguro, L.; et al. Human herpesvirus type 8 variants circulating in Europe, Africa and North America in classic, endemic and epidemic Kaposi's sarcoma lesions during pre-AIDS and AIDS era. *Virology* **2010**, *398*, 280–289. [CrossRef]

49. Hladik, W.; Dollard, S.C.; Mermin, J.; Fowlkes, A.L.; Downing, R.; Amin, M.M.; Banage, F.; Nzaro, E.; Kataaha, P.; Dondero, T.J. Transmission of human herpesvirus 8 by blood transfusion. *N. Engl. J. Med.* **2006**, *355*, 1331–1338. [CrossRef]

50. de Sanjose, S.; Mbisa, G.; Perez-Alvarez, S.; Benavente, Y.; Sukvirach, S.; Hieu, N.T.; Shin, H.-R.; Anh, P.T.H.; Thomas, J.; Lazcano, E. Geographic variation in the prevalence of Kaposi sarcoma–associated herpesvirus and risk factors for transmission. *J. Infect. Dis.* **2009**, *199*, 1449–1456. [CrossRef]

51. de França, T.R.T.; de Araújo, R.A.; Ribeiro, C.M.B.; Leao, J.C. Salivary shedding of HHV-8 in people infected or not by human immunodeficiency virus 1. *J. Oral Pathol. Med.* **2011**, *40*, 97–102. [CrossRef]

52. Giffin, L.; Damania, B. KSHV: Pathways to tumorigenesis and persistent infection. *Adv. Virus Res.* **2014**, *88*, 111–159.

53. Minhas, V.; Wood, C. Epidemiology and transmission of Kaposi's sarcoma-associated herpesvirus. *Viruses* **2014**, *6*, 4178–4194. [CrossRef]

54. Chang, Y.; Cesarman, E.; Pessin, M.S.; Lee, F.; Culpepper, J.; Knowles, D.M.; Moore, P.S. Identification of herpesvirus-like DNA sequences in AIDS-sssociated kaposi's sarcoma. *Science* **1994**, *266*, 1865–1869. [CrossRef] [PubMed]

55. Polizzotto, M.N.; Uldrick, T.S.; Hu, D.; Yarchoan, R. Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: Multicentric Castleman disease (KSHV–MCD) and the KSHV inflammatory cytokine syndrome. *Front. Microbiol.* **2012**, *3*, 73. [CrossRef]

56. Polizzotto, M.N.; Uldrick, T.S.; Wyvill, K.M.; Aleman, K.; Marshall, V.; Wang, V.; Whitby, D.; Pittaluga, S.; Jaffe, E.S.; Millo, C. Clinical features and outcomes of patients with symptomatic Kaposi sarcoma herpesvirus (KSHV)-associated inflammation: Prospective characterization of KSHV inflammatory cytokine syndrome (KICS). *Clin. Infect. Dis.* **2016**, *62*, 730–738. [CrossRef] [PubMed]

57. Gonçalves, P.H.; Uldrick, T.S.; Yarchoan, R. HIV-associated Kaposi sarcoma and related diseases. *AIDS* **2017**, *31*, 1903. [CrossRef] [PubMed]

58. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]

59. Thakker, S.; Verma, S.C. Co-infections and pathogenesis of KSHV-associated malignancies. *Front. Microbiol.* **2016**, *7*, 151. [CrossRef]

60. Powles, T.; Stebbing, J.; Bazeos, A.; Hatzimichael, E.; Mandalia, S.; Nelson, M.; Gazzard, B.; Bower, M. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. *Ann. Oncol.* **2009**, *20*, 775–779. [CrossRef]

61. Staskus, K.A.; Sun, R.; Miller, G.; Racz, P.; Jaslowski, A.; Metroka, C.; Brett-Smith, H.; Haase, A.T. Cellular tropism and viral interleukin-6 expression distinguish human herpesvirus 8 involvement in Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. *J. Virol.* **1999**, *73*, 4181–4187. [CrossRef]

62. Parravicini, C.; Chandran, B.; Corbellino, M.; Berti, E.; Paulli, M.; Moore, P.S.; Chang, Y. Differential viral protein expression in Kaposi's sarcoma-associated herpesvirus-infected diseases: Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. *Am. J. Pathol.* **2000**, *156*, 743–749. [CrossRef] [PubMed]

63. Uldrick, T.S.; Wang, V.; O'Mahony, D.; Aleman, K.; Wyvill, K.M.; Marshall, V.; Steinberg, S.M.; Pittaluga, S.; Maric, I.; Whitby, D. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. *Clin. Infect. Dis.* **2010**, *51*, 350–358. [CrossRef]

64. Thorley-Lawson, D.A. EBV persistence—Introducing the virus. Epstein Barr Virus Volume 1: One Herpes Virus: Many Diseases. *Curr. Top. Microbiol. Immunol.* **2015**, *390 Pt 1*, 151–209. [PubMed]

65. Yap, L.F.; Wong, A.K.C.; Paterson, I.C.; Young, L.S. Functional Implications of Epstein-Barr Virus Lytic Genes in Carcinogenesis. *Cancers* **2022**, *14*, 5780. [CrossRef] [PubMed]

66. Tugizov, S.M. Molecular Pathogenesis of Human Immunodeficiency Virus-Associated Disease of Oropharyngeal Mucosal Epithelium. *Biomedicines* **2023**, *11*, 1444. [CrossRef]

67. Wang, X.; Kenyon, W.J.; Li, Q.; Müllberg, J.; Hutt-Fletcher, L.M. Epstein-Barr Virus Uses Different Complexes of Glycoproteins gH and gL To Infect B Lymphocytes and Epithelial Cells. *J. Virol.* **1998**, *72*, 5552–5558. [CrossRef]

68. Borza, C.M.; Hutt-Fletcher, L.M. Alternate replication in B cells and epithelial cells switches tropism of Epstein–Barr virus. *Nat. Med.* **2002**, *8*, 594–599. [CrossRef]

69. Burton, E.M.; Voyer, J.; Gewurz, B.E. Epstein–Barr virus latency programs dynamically sensitize B cells to ferroptosis. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2118300119. [CrossRef]

70. Bouvard, V.; Baan, R.; Straif, K.; Grosse, Y.; Secretan, B.; El Ghissassi, F.; Benbrahim-Tallaa, L.; Guha, N.; Freeman, C.; Galichet, L. A review of human carcinogens—Part B: Biological agents. *Lancet Oncol.* **2009**, *10*, 321–322. [CrossRef]

71. Yin, H.; Qu, J.; Peng, Q.; Gan, R. Molecular mechanisms of EBV-driven cell cycle progression and oncogenesis. *Med. Microbiol. Immunol.* **2019**, *208*, 573–583. [CrossRef]

72. Deakyne, J.S.; Malecka, K.A.; Messick, T.E.; Lieberman, P.M. Structural and Functional Basis for an EBNA1 Hexameric Ring in Epstein-Barr Virus Episome Maintenance. *J. Virol.* **2017**, *91*, e01046-17. [CrossRef] [PubMed]

73. Rowe, M.; Rowe, D.T.; Gregory, C.D.; Young, L.S.; Farrell, P.J.; Rupani, H.; Rickinson, A.B. Differences in B cell growth phenotype reflect novel patterns of Epstein-Barr virus latent gene expression in Burkitt's lymphoma cells. *EMBO J.* **1987**, *6*, 2743–2751. [CrossRef]

74. Hatzubai, A.; Anafi, M.; Masucci, M.G.; Dillner, J.; Lerner, R.A.; Klein, G.; Sulitzeanu, D. Down-regulation of the EBV-encoded membrane protein (LMP) in Burkitt lymphomas. *Int. J. Cancer* **1987**, *40*, 358–364. [CrossRef]

75. Gregory, C.D.; Rowe, M.; Rickinson, A.B. Different Epstein-Barr virus-B cell interactions in phenotypically distinct clones of a Burkitt's lymphoma cell line. *J. Gen. Virol.* **1990**, *71*, 1481–1495. [CrossRef] [PubMed]

76. Babcock, G.J.; Thorley-Lawson, D.A. Tonsillar memory B cells, latently infected with Epstein-Barr virus, express the restricted pattern of latent genes previously found only in Epstein-Barr virus-associated tumors. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 12250–12255. [CrossRef] [PubMed]

77. Luo, B.; Wang, Y.; Wang, X.-F.; Liang, H.; Yan, L.-P.; Huang, B.-H.; Zhao, P. Expression of Epstein-Barr virus genes in EBV-associated gastric carcinomas. *World J. Gastroenterol. WJG* **2005**, *11*, 629. [CrossRef]

78. Hochberg, D.; Middeldorp, J.M.; Catalina, M.; Sullivan, J.L.; Luzuriaga, K.; Thorley-Lawson, D.A. Demonstration of the Burkitt's lymphoma Epstein-Barr virus phenotype in dividing latently infected memory cells in vivo. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 239–244. [CrossRef]

79. Desbien, A.L.; Kappler, J.W.; Marrack, P. The Epstein–Barr virus Bcl-2 homolog, BHRF1, blocks apoptosis by binding to a limited amount of Bim. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5663–5668. [CrossRef]

80. Bentz, G.; Liu, R.; Hahn, A.; Shackelford, J.; Pagano, J. Epstein-Barr virus immediate-early protein RTA negatively regulates interferon regulatory factors. *Virology* **2010**, *402*, 121. [CrossRef]

81. Geiger, T.R.; Martin, J.M. The Epstein-Barr virus-encoded LMP-1 oncoprotein negatively affects Tyk2 phosphorylation and interferon signaling in human B cells. *J. Virol.* **2006**, *80*, 11638–11650. [CrossRef]

82. Amon, W.; Farrell, P.J. Reactivation of Epstein-Barr virus from latency. *Rev. Med. Virol.* **2005**, *15*, 149–156. [CrossRef] [PubMed]

83. Morgan, S.M.; Tanizawa, H.; Caruso, L.B.; Hulse, M.; Kossenkov, A.; Madzo, J.; Keith, K.; Tan, Y.; Boyle, S.; Lieberman, P.M.; et al. The three-dimensional structure of Epstein-Barr virus genome varies by latency type and is regulated by PARP1 enzymatic activity. *Nat. Commun.* **2022**, *13*, 187. [CrossRef]

84. Kim, K.-D.; Tanizawa, H.; De Leo, A.; Vladimirova, O.; Kossenkov, A.; Lu, F.; Showe, L.C.; Noma, K.-I.; Lieberman, P.M. Epigenetic specifications of host chromosome docking sites for latent Epstein-Barr virus. *Nat. Commun.* **2020**, *11*, 877. [CrossRef] [PubMed]

85. Ning, S. Innate immune modulation in EBV infection. *Herpesviridae* **2011**, *2*, 1. [CrossRef] [PubMed]

86. Lu, F.; Wikramasinghe, P.; Norseen, J.; Tsai, K.; Wang, P.; Showe, L.; Davuluri, R.V.; Lieberman, P.M. Genome-wide analysis of host-chromosome binding sites for Epstein-Barr Virus Nuclear Antigen 1 (EBNA1). *Virol. J.* **2010**, *7*, 262. [CrossRef]

87. Verhoeven, R.J.A.; Tong, S.; Zong, J.; Chen, Y.; Tsao, S.W.; Pan, J.; Chen, H. NF-κB Signaling Regulates Epstein-Barr Virus BamHI-Q-Driven EBNA1 Expression. *Cancers* **2018**, *10*, 119. [CrossRef]

88. Countryman, J.; Jenson, H.; Seibl, R.; Wolf, H.; Miller, G. Polymorphic proteins encoded within BZLF1 of defective and standard Epstein-Barr viruses disrupt latency. *J. Virol.* **1987**, *61*, 3672–3679. [CrossRef]

89. Ragoczy, T.; Heston, L.; Miller, G. The Epstein-Barr virus Rta protein activates lytic cycle genes and can disrupt latency in B lymphocytes. *J. Virol.* **1998**, *72*, 7978–7984. [CrossRef]

90. Leong, M.M.L.; Cheung, A.K.L.; Dai, W.; Tsao, S.W.; Tsang, C.M.; Dawson, C.W.; Mun Yee Ko, J.; Lung, M.L. EBV infection is associated with histone bivalent switch modifications in squamous epithelial cells. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 14144–14153. [CrossRef]

91. Gruffat, H.; Manet, E.; Sergeant, A. MEF2-mediated recruitment of class II HDAC at the EBV immediate early gene BZLF1 links latency and chromatin remodeling. *EMBO Rep.* **2002**, *3*, 141–146. [CrossRef]

92. Gruhne, B.; Sompallae, R.; Marescotti, D.; Kamranvar, S.A.; Gastaldello, S.; Masucci, M.G. The Epstein–Barr virus nuclear antigen-1 promotes genomic instability via induction of reactive oxygen species. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 2313–2318. [CrossRef] [PubMed]

93. Chen, X.; Kamranvar, S.A.; Masucci, M. Oxidative stress enables Epstein–Barr virus-induced B-cell transformation by posttranscriptional regulation of viral and cellular growth-promoting factors. *Oncogene* **2016**, *35*, 3807–3816. [CrossRef] [PubMed]

94. Ichikawa, A.; Arakawa, F.; Kiyasu, J.; Sato, K.; Miyoshi, H.; Niino, D.; Kimura, Y.; Takeuchi, M.; Yoshida, M.; Ishibashi, Y. Methotrexate/iatrogenic lymphoproliferative disorders in rheumatoid arthritis: Histology, E pstein–B arr virus, and clonality are important predictors of disease progression and regression. *Eur. J. Haematol.* **2013**, *91*, 20–28. [CrossRef]

95. Sausen, D.G.; Bhutta, M.S.; Gallo, E.S.; Dahari, H.; Borenstein, R. Stress-Induced Epstein-Barr Virus Reactivation. *Biomolecules* **2021**, *11*, 1380. [CrossRef]

96. Jiang, L.; Lan, R.; Huang, T.; Chan, C.-F.; Li, H.; Lear, S.; Zong, J.; Wong, W.-Y.; Muk-Lan Lee, M.; Dow Chan, B.; et al. EBNA1-targeted probe for the imaging and growth inhibition of tumours associated with the Epstein–Barr virus. *Nat. Biomed. Eng.* **2017**, *1*, 0042. [CrossRef]

97. Hjalgrim, H.F.J.; Melbye, M. The epidemiology of EBV and its association with malignant disease. In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*; Arvin, A., Campadelli-Fiume, G., Mocarski, E., Moore, P.S., Roizman, B., Whitley, R., Yamanishi, K., Eds.; Cambridge University Press: Cambridge, UK, 2007.

98. Kenney, S.C.; Mertz, J.E. Regulation of the latent-lytic switch in Epstein–Barr virus. *Semin. Cancer Biol.* **2014**, *26*, 60–68. [CrossRef]

99. Luo, Y.; Liu, Y.; Wang, C.; Gan, R. Signaling pathways of EBV-induced oncogenesis. *Cancer Cell Int.* **2021**, *21*, 93. [CrossRef] [PubMed]

100. Park, G.B.; Kim, Y.S.; Lee, H.-K.; Song, H.; Cho, D.-H.; Lee, W.J.; Hur, D.Y. Endoplasmic reticulum stress-mediated apoptosis of EBV-transformed B cells by cross-linking of CD70 is dependent upon generation of reactive oxygen species and activation of p38 MAPK and JNK pathway. *J. Immunol.* **2010**, *185*, 7274–7284. [CrossRef]

101. Murata, T.; Sugimoto, A.; Inagaki, T.; Yanagi, Y.; Watanabe, T.; Sato, Y.; Kimura, H. Molecular Basis of Epstein-Barr Virus Latency Establishment and Lytic Reactivation. *Viruses* **2021**, *13*, 2344. [CrossRef]

102. Yan, L.; Majerciak, V.; Zheng, Z.-M.; Lan, K. Towards better understanding of KSHV life cycle: From transcription and posttranscriptional regulations to pathogenesis. *Virol. Sin.* **2019**, *34*, 135–161. [CrossRef]

103. Ganem, D. KSHV-induced oncogenesis. In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*; Cambridge University Press: Cambridge, UK, 2007.

104. Lagos, D.; Boshoff, C. Immunobiology and host response to KSHV infection. In *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*; Cambridge University Press: Cambridge, UK, 2007.

105. Dollery, S.J. Towards understanding KSHV fusion and entry. *Viruses* **2019**, *11*, 1073. [CrossRef]

106. Della Bella, S.; Taddeo, A.; Calabro, M.L.; Brambilla, L.; Bellinvia, M.; Bergamo, E.; Clerici, M.; Villa, M.L. Peripheral blood endothelial progenitors as potential reservoirs of Kaposi's sarcoma-associated herpesvirus. *PLoS ONE* **2008**, *3*, e1520. [CrossRef] [PubMed]

107. Monini, P.; Colombini, S.; Sturzl, M.; Goletti, D.; Cafaro, A.; Sgadari, C.; Butto, S.; Franco, M.; Leone, P.; Fais, S. Reactivation and persistence of human herpesvirus-8 infection in B cells and monocytes by Th-1 cytokines increased in Kaposi's sarcoma. *Blood J. Am. Soc. Hematol.* **1999**, *93*, 4044–4058.

108. Ye, F.; Lei, X.; Gao, S.-J. Mechanisms of Kaposi's sarcoma-associated herpesvirus latency and reactivation. *Adv. Virol.* **2011**, *2011*, 3468–3478. [CrossRef]

109. Burbelo, P.D.; Issa, A.T.; Ching, K.H.; Wyvill, K.M.; Little, R.F.; Iadarola, M.J.; Kovacs, J.A.; Yarchoan, R. Distinct profiles of antibodies to Kaposi sarcoma-associated herpesvirus antigens in patients with Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. *J. Infect. Dis.* **2010**, *201*, 1919–1922. [CrossRef]

110. Gaglia, M.M. Kaposi's sarcoma-associated herpesvirus at 27. *Tumour Virus Res.* **2021**, *12*, 200223. [CrossRef]

111. Boshoff, C.; Schulz, T.F.; Kennedy, M.M.; Graham, A.K.; Fisher, C.; Thomas, A.; McGee, J.O.D.; Weiss, R.A.; O'Leary, J.J. Kaposi's sarcoma-associated herpesvirus infects endothelial and spindle cells. *Nat. Med.* **1995**, *1*, 1274–1278. [CrossRef]

112. Chandran, B. Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. *J. Virol.* **2010**, *84*, 2188–2199. [CrossRef]

113. Kedes, D.H.; Lagunoff, M.; Renne, R.; Ganem, D. Identification of the gene encoding the major latency-associated nuclear antigen of the Kaposi's sarcoma-associated herpesvirus. *J. Clin. Investig.* **1997**, *100*, 2606–2610. [CrossRef] [PubMed]

114. Rainbow, L.; Platt, G.M.; Simpson, G.R.; Sarid, R.; Gao, S.-J.; Stoiber, H.; Herrington, C.S.; Moore, P.S.; Schulz, T.F. The 222-to 234-kilodalton latent nuclear protein (LNA) of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) is encoded by orf73 and is a component of the latency-associated nuclear antigen. *J. Virol.* **1997**, *71*, 5915–5921. [CrossRef]

115. Sadler, R.; Wu, L.; Forghani, B.; Renne, R.; Zhong, W.; Herndier, B.; Ganem, D. A complex translational program generates multiple novel proteins from the latently expressed kaposin (K12) locus of Kaposi's sarcoma-associated herpesvirus. *J. Virol.* **1999**, *73*, 5722–5730. [CrossRef] [PubMed]

116. Uppal, T.; Banerjee, S.; Sun, Z.; Verma, S.C.; Robertson, E.S. KSHV LANA—The master regulator of KSHV latency. *Viruses* **2014**, *6*, 4961–4998. [CrossRef] [PubMed]

117. Günther, T.; Grundhoff, A. The epigenetic landscape of latent Kaposi sarcoma-associated herpesvirus genomes. *PLoS Pathog.* **2010**, *6*, e1000935. [CrossRef] [PubMed]

118. Journo, G.; Tushinsky, C.; Shterngas, A.; Avital, N.; Eran, Y.; Karpuj, M.V.; Frenkel-Morgenstern, M.; Shamay, M. Modulation of cellular CpG DNA methylation by Kaposi's sarcoma-associated herpesvirus. *J. Virol.* **2018**, *92*, e00008-18. [CrossRef]

119. Campbell, M.; Yang, W.-S.; Yeh, W.W.; Kao, C.-H.; Chang, P.-C. Epigenetic regulation of Kaposi's sarcoma-associated herpesvirus latency. *Front. Microbiol.* **2020**, *11*, 850. [CrossRef] [PubMed]

120. Toth, Z.; Brulois, K.; Jung, J.U. The chromatin landscape of Kaposi's sarcoma-associated herpesvirus. *Viruses* **2013**, *5*, 1346–1373. [CrossRef]

121. Chen, H.-S.; Lu, F.; Lieberman, P.M. Epigenetic regulation of EBV and KSHV latency. *Curr. Opin. Virol.* **2013**, *3*, 251–259. [CrossRef]

122. Shamay, M.; Krithivas, A.; Zhang, J.; Hayward, S.D. Recruitment of the de novo DNA methyltransferase Dnmt3a by Kaposi's sarcoma-associated herpesvirus LANA. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 14554–14559. [CrossRef]

123. West, J.T.; Wood, C. The role of Kaposi's sarcoma-associated herpesvirus/human herpesvirus-8 regulator of transcription activation (RTA) in control of gene expression. *Oncogene* **2003**, *22*, 5150–5163. [CrossRef]

124. Di Bartolo, D.L.; Cannon, M.; Liu, Y.-F.; Renne, R.; Chadburn, A.; Boshoff, C.; Cesarman, E. KSHV LANA inhibits TGF-β signaling through epigenetic silencing of the TGF-β type II receptor. *Blood J. Am. Soc. Hematol.* **2008**, *111*, 4731–4740. [CrossRef]

125. Purushothaman, P.; Uppal, T.; Verma, S.C. Molecular biology of KSHV lytic reactivation. *Viruses* **2015**, *7*, 116–153. [CrossRef]

126. Friborg, J., Jr.; Kong, W.-P.; Hottiger, M.O.; Nabel, G.J. p53 inhibition by the LANA protein of KSHV protects against cell death. *Nature* **1999**, *402*, 889–894. [CrossRef] [PubMed]

127. Santag, S.; Jäger, W.; Karsten, C.; Kati, S.; Pietrek, M.; Steinemann, D.; Sarek, G.; Ojala, P.; Schulz, T. Recruitment of the tumour suppressor protein p73 by Kaposi's Sarcoma Herpesvirus latent nuclear antigen contributes to the survival of primary effusion lymphoma cells. *Oncogene* **2013**, *32*, 3676–3685. [CrossRef] [PubMed]

128. Zhu, F.X.; Cusano, T.; Yuan, Y. Identification of the immediate-early transcripts of Kaposi's sarcoma-associated herpesvirus. *J. Virol.* **1999**, *73*, 5556–5567. [CrossRef]

129. Saveliev, A.K.; Zhu, F.X.; Yuan, Y. Transcription mapping and expression patterns of genes in the major immediate-early region of Kaposi's sarcoma-associated herpesvirus. *Virology* **2002**, *299*, 301–314. [CrossRef] [PubMed]

130. Lacoste, V.; de La Fuente, C.; Kashanchi, F.; Pumfery, A. Kaposi's sarcoma-associated herpesvirus immediate early gene activity. *Front. Biosci.-Landmark* **2004**, *9*, 2245–2272. [CrossRef]

131. Lan, K.; Murakami, M.; Choudhuri, T.; Kuppers, D.A.; Robertson, E.S. Intracellular-activated Notch1 can reactivate Kaposi's sarcoma-associated herpesvirus from latency. *Virology* **2006**, *351*, 393–403. [CrossRef]

132. Chang, H.; Dittmer, D.P.; Chul, S.-Y.; Hong, Y.; Jung, J.U. Role of Notch signal transduction in Kaposi's sarcoma-associated herpesvirus gene expression. *J. Virol.* **2005**, *79*, 14371–14382. [CrossRef]

133. Carroll, K.D.; Bu, W.; Palmeri, D.; Spadavecchia, S.; Lynch, S.J.; Marras, S.A.; Tyagi, S.; Lukac, D.M. Kaposi's Sarcoma-associated herpesvirus lytic switch protein stimulates DNA binding of RBP-Jk/CSL to activate the Notch pathway. *J. Virol.* **2006**, *80*, 9697–9709. [CrossRef]

134. Toth, Z.; Maglinte, D.T.; Lee, S.H.; Lee, H.-R.; Wong, L.-Y.; Brulois, K.F.; Lee, S.; Buckley, J.D.; Laird, P.W.; Marquez, V.E. Epigenetic analysis of KSHV latent and lytic genomes. *PLoS Pathog.* **2010**, *6*, e1001013. [CrossRef]

135. Fröhlich, J.; Grundhoff, A. Epigenetic control in Kaposi sarcoma-associated herpesvirus infection and associated disease. *Proc. Semin. Immunopathol.* **2020**, *42*, 143–157. [CrossRef]

136. Vieira, J.; O'Hearn, P.; Kimball, L.; Chandran, B.; Corey, L. Activation of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) lytic replication by human cytomegalovirus. *J. Virol.* **2001**, *75*, 1378–1386. [CrossRef]

137. Tang, Q.; Qin, D.; Lv, Z.; Zhu, X.; Ma, X.; Yan, Q.; Zeng, Y.; Guo, Y.; Feng, N.; Lu, C. Herpes simplex virus type 2 triggers reactivation of Kaposi's sarcoma-associated herpesvirus from latency and collaborates with HIV-1 Tat. *PLoS ONE* **2012**, *7*, e31652. [CrossRef] [PubMed]

138. Lu, C.; Zeng, Y.; Huang, Z.; Huang, L.; Qian, C.; Tang, G.; Qin, D. Human herpesvirus 6 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus. *Am. J. Pathol.* **2005**, *166*, 173–183. [CrossRef] [PubMed]

139. Anders, P.M.; Montgomery, N.D.; Montgomery, S.A.; Bhatt, A.P.; Dittmer, D.P.; Damania, B. Human herpesvirus–encoded kinase induces B cell lymphomas in vivo. *J. Clin. Investig.* **2018**, *128*, 2519–2534. [CrossRef] [PubMed]

140. Bhatt, A.P.; Wong, J.P.; Weinberg, M.S.; Host, K.M.; Giffin, L.C.; Buijnink, J.; Van Dijk, E.; Izumiya, Y.; Kung, H.-J.; Temple, B.R. A viral kinase mimics S6 kinase to enhance cell proliferation. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 7876–7881. [CrossRef]

141. Montaner, S.; Sodhi, A.; Molinolo, A.; Bugge, T.H.; Sawai, E.T.; He, Y.; Li, Y.; Ray, P.E.; Gutkind, J.S. Endothelial infection with KSHV genes in vivo reveals that vGPCR initiates Kaposi's sarcomagenesis and can promote the tumorigenic potential of viral latent genes. *Cancer Cell* **2003**, *3*, 23–36. [CrossRef]

142. Ma, Z.; Jacobs, S.R.; West, J.A.; Stopford, C.; Zhang, Z.; Davis, Z.; Barber, G.N.; Glaunsinger, B.A.; Dittmer, D.P.; Damania, B. Modulation of the cGAS-STING DNA sensing pathway by gammaherpesviruses. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E4306–E4315. [CrossRef]

143. Abere, B.; Schulz, T.F. KSHV non-structural membrane proteins involved in the activation of intracellular signaling pathways and the pathogenesis of Kaposi's sarcoma. *Curr. Opin. Virol.* **2016**, *20*, 11–19. [CrossRef]

144. Arvin, A.; Campadelli-Fiume, G.; Mocarski, E.; Moore, P.S.; Roizman, B.; Whitley, R.; Yamanishi, K. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*; Cambridge University Press: Cambridge, UK, 2007.

145. Spender, L.C.; Cornish, G.H.; Rowland, B.; Kempkes, B.; Farrell, P.J. Direct and indirect regulation of cytokine and cell cycle proteins by EBNA-2 during Epstein-Barr virus infection. *J. Virol.* **2001**, *75*, 3537–3546. [CrossRef]

146. Mrad, M.F.; Saba, E.S.; Nakib, L.; Khoury, S.J. Exosomes from subjects with multiple sclerosis express EBV-derived proteins and activate monocyte-derived macrophages. *Neurol.-Neuroimmunol. Neuroinflamm.* **2021**, *8*, e1004. [CrossRef]

147. Bernal, K.D.E.; Whitehurst, C.B. Incidence of Epstein-Barr virus reactivation is elevated in COVID-19 patients. *Virus Res.* **2023**, *334*, 199157. [CrossRef]

148. Chinen, J.; Shearer, W.T. Molecular virology and immunology of HIV infection. *J. Allergy Clin. Immunol.* **2002**, *110*, 189–198. [CrossRef] [PubMed]

149. UNAIDS Global HIV & AIDS statistics—Fact sheet 2022. Available online: https://www.unaids.org/en/resources/fact-sheet (accessed on 6 July 2023).

150. Satoh, S.; Boyer, E. HIV in South Africa. *Lancet* **2019**, *394*, 467. [CrossRef]

151. Cassim, S.; Antel, K.; Chetty, D.R.; Oosthuizen, J.; Opie, J.; Mohamed, Z.; Verburgh, E. Diffuse large B-cell lymphoma in a South African cohort with a high HIV prevalence: An analysis by cell-of-origin, Epstein–Barr virus infection and survival. *Pathology* **2020**, *52*, 453–459. [CrossRef] [PubMed]

152. WHO HIV Data and Statistics. Available online: https://www.who.int/data/gho/data/indicators (accessed on 15 May 2023).

153. Heath, K.; Levi, J.; Hill, A. The Joint United Nations Programme on HIV/AIDS 95–95–95 targets: Worldwide clinical and cost benefits of generic manufacture. *AIDS* **2021**, *35*, S197–S203. [CrossRef] [PubMed]

154. Palmisano, L.; Vella, S. A brief history of antiretroviral therapy of HIV infection: Success and challenges. *Ann. Dell'istituto Super. Di Sanità* **2011**, *47*, 44–48.

155. Grulich, A.E.; Van Leeuwen, M.T.; Falster, M.O.; Vajdic, C.M. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: A meta-analysis. *Lancet* **2007**, *370*, 59–67. [CrossRef] [PubMed]

156. Frisch, M.; Biggar, R.J.; Engels, E.A.; Goedert, J.J.; AIDS-Cancer Match Registry Study Group. Association of cancer with AIDS-related immunosuppression in adults. *Jama* **2001**, *285*, 1736–1745. [CrossRef] [PubMed]

157. Coghill, A.E.; Newcomb, P.A.; Madeleine, M.M.; Richardson, B.A.; Mutyaba, I.; Okuku, F.; Phipps, W.; Wabinga, H.; Orem, J.; Casper, C. Contribution of HIV infection to mortality among cancer patients in Uganda. *AIDS* **2013**, *27*, 2933. [CrossRef]

158. Carbone, A.; Cesarman, E.; Spina, M.; Gloghini, A.; Schulz, T.F. HIV-associated lymphomas and gamma-herpesviruses. *Blood* **2009**, *113*, 1213–1224. [CrossRef] [PubMed]

159. Pather, S.; Wainwright, R.D.; Sahid, F.; Mashele, T.; van den Berg, E.J.; Mohanlal, R.D. Human immunodeficiency virus-related Epstein-Barr virus-associated smooth muscle tumours: South African experience from Chris Hani Baragwanath Academic Hospital. *South. Afr. J. Infect. Dis.* **2017**, *32*, 115–118.

160. Rahman, M.A.; Kingsley, L.A.; Atchison, R.W.; Belle, S.; Breinig, M.C.; Ho, M.; Rinaldo, C.R. Reactivation of Epstein-Barr virus during early infection with human immunodeficiency virus. *J. Clin. Microbiol.* **1991**, *29*, 1215–1220. [CrossRef] [PubMed]

161. Whitehurst, C.B.; Rizk, M.; Teklezghi, A.; Spagnuolo, R.A.; Pagano, J.S.; Wahl, A. HIV Co-infection Augments EBV-Induced Tumorigenesis in vivo. *Front. Virol.* **2022**, *2*, 861628. [CrossRef]

162. Nazim, F.; Kayani, H.A.; Ali Nathwani, A.; Mir, F.; Abidi, S.H. CMV and EBV Co-Infection in HIV-Infected Children: Infection Rates and Analysis of Differential Expression of Cytokines in HIV Mono- and HIV-CMV-EBV Co-Infected Groups. *Viruses* **2022**, *14*, 1823. [CrossRef]

163. Mujtaba, S.; Varma, S.; Sehgal, S. Coinfection with epstein barr virus in north Indian patients with HIV/AIDS. *Indian J. Pathol. Microbiol.* **2005**, *48*, 349–353.

164. Stevens, S.J.; Blank, B.S.; Smits, P.H.; Meenhorst, P.L.; Middeldorp, J.M. High Epstein–Barr virus (EBV) DNA loads in HIV-infected patients: Correlation with antiretroviral therapy and quantitative EBV serology. *AIDS* **2002**, *16*, 993–1001. [CrossRef]

165. Slyker, J.A.; Casper, C.; Tapia, K.; Richardson, B.; Bunts, L.; Huang, M.-L.; Maleche-Obimbo, E.; Nduati, R.; John-Stewart, G. Clinical and virologic manifestations of primary Epstein-Barr virus (EBV) infection in Kenyan infants born to HIV-infected women. *J. Infect. Dis.* **2013**, *207*, 1798–1806. [CrossRef]

166. Ferbas, J.; Rahman, M.A.; Kingsley, L.A.; Armstrong, J.A.; Ho, M.; Zhou, S.Y.J.; Rinaldo, C.R., Jr. Frequent oropharyngeal shedding of Epstein-Barr virus in homosexual men during early HIV infection. *AIDS* **1992**, *6*, 1273–1278. [CrossRef] [PubMed]

167. Diaz-Mitoma, F.; Ruiz, A.; Flowerdew, G.; Houston, S.; Romanowski, B.; Kovithavongs, T.; Preiksaitis, J.; Tyrrell, D.L. High levels of Epstein-Barr virus in the oropharynx: A predictor of disease progression in human immunodeficiency virus infection. *J. Med. Virol.* **1990**, *31*, 69–75. [CrossRef] [PubMed]

168. Yan, Y.; Ren, Y.; Chen, R.; Hu, J.; Ji, Y.; Yang, J.; Shen, J.; Hu, L.; Pei, H.; Wang, J.; et al. Evaluation of Epstein-Barr Virus Salivary Shedding in HIV/AIDS Patients and HAART Use: A Retrospective Cohort Study. *Virol. Sin.* **2018**, *33*, 227–233. [CrossRef] [PubMed]

169. Münz, C. Modification of EBV-Associated Pathologies and Immune Control by Coinfections. *Front. Oncol.* **2021**, *11*, 756480. [CrossRef] [PubMed]

170. McHugh, D.; Myburgh, R.; Caduff, N.; Spohn, M.; Kok, Y.L.; Keller, C.W.; Murer, A.; Chatterjee, B.; Rühl, J.; Engelmann, C.; et al. EBV renders B cells susceptible to HIV-1 in humanized mice. *Life Sci. Alliance* **2020**, *3*, e202000640. [CrossRef] [PubMed]

171. Koch, A.; Mizrahi, V. Mycobacterium tuberculosis. *Trends Microbiol.* **2018**, *26*, 555–556. [CrossRef] [PubMed]

172. van de Water, B.J.; Fulcher, I.; Cilliers, S.; Meyer, N.; Wilson, M.; Young, C.; Gaunt, B.; le Roux, K. Association of HIV infection and antiretroviral therapy with the occurrence of an unfavorable TB treatment outcome in a rural district hospital in Eastern Cape, South Africa: A retrospective cohort study. *PLoS ONE* **2022**, *17*, e0266082. [CrossRef] [PubMed]

173. Whittaker, E.; López-Varela, E.; Broderick, C.; Seddon, J.A. Examining the Complex Relationship Between Tuberculosis and Other Infectious Diseases in Children. *Front. Pediatr.* **2019**, *7*, 233. [CrossRef]

174. Gledhill, R.; Greyling, M. Epstein-Barr virus infection in a patient with active pulmonary tuberculosis-a case report. *South Afr. Med. J.* **1986**, *70*, 761–762.

175. Kakoullis, L.; Hentschel, C.; Colgrove, R. Headache, Fever, and Myalgias in an HIV-Positive Male with a History of Tuberculosis: Epstein–Barr Virus Aseptic Meningitis. *Trop. Med. Infect. Dis.* **2023**, *8*, 191.

176. Shibanov, A.; Vasilèva, I.; Karazhas, N.; Abramchenko, A.; Pul'nova, N.Y.; Ribalkina, T.y.; Bosh'yan, R. Lung tuberculosis characteristics in association with herpesvirus infection. *ERJ Open Res.* **2022**, *8*, 168. [CrossRef]

177. Miller, H.E.; Johnson, K.E.; Tarakanova, V.L.; Robinson, R.T. γ-herpesvirus latency attenuates Mycobacterium tuberculosis infection in mice. *Tuberculosis* **2019**, *116*, 56–60. [CrossRef]

178. World Health Organization. *World Malaria Report 2022*; World Health Organization: Geneva, Switzerland, 2022.

179. Schofield, L.; Grau, G.E. Immunological processes in malaria pathogenesis. *Nat. Rev. Immunol.* **2005**, *5*, 722–735. [CrossRef]

180. Chêne, A.; Donati, D.; Guerreiro-Cacais, A.O.; Levitsky, V.; Chen, Q.; Falk, K.I.; Orem, J.; Kironde, F.; Wahlgren, M.; Bejarano, M.T. A Molecular Link between Malaria and Epstein–Barr Virus Reactivation. *PLOS Pathog.* **2007**, *3*, e80. [CrossRef]

181. Matar, C.G.; Anthony, N.R.; O'Flaherty, B.M.; Jacobs, N.T.; Priyamvada, L.; Engwerda, C.R.; Speck, S.H.; Lamb, T.J. Gammaherpesvirus Co-infection with Malaria Suppresses Anti-parasitic Humoral Immunity. *PLOS Pathog.* **2015**, *11*, e1004858. [CrossRef]

182. Oluoch, P.O.; Forconi, C.S.; Oduor, C.I.; Ritacco, D.A.; Akala, H.M.; Bailey, J.A.; Juliano, J.J.; Ong'echa, J.M.; Münz, C.; Moormann, A.M. Distinctive Kaposi Sarcoma-Associated Herpesvirus Serological Profile during Acute Plasmodium falciparum Malaria Episodes. *Int. J. Mol. Sci.* **2023**, *24*, 6711. [CrossRef]

183. Simone, O.; Bejarano, M.T.; Pierce, S.K.; Antonaci, S.; Wahlgren, M.; Troye-Blomberg, M.; Donati, D. TLRs innate immunereceptors and Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) CIDR1α-driven human polyclonal B-cell activation. *Acta Trop.* **2011**, *119*, 144–150. [CrossRef] [PubMed]

184. Moormann, A.M.; Snider, C.J.; Chelimo, K. The company malaria keeps: How co-infection with Epstein-Barr virus leads to endemic Burkitt lymphoma. *Curr. Opin. Infect. Dis.* **2011**, *24*, 435–441. [CrossRef]

185. Harrison, A.G.; Lin, T.; Wang, P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. *Trends Immunol.* **2020**, *41*, 1100–1115. [CrossRef] [PubMed]

186. Jackson, C.B.; Farzan, M.; Chen, B.; Choe, H. Mechanisms of SARS-CoV-2 entry into cells. *Nat. Rev. Mol. Cell Biol.* **2022**, *23*, 3–20. [CrossRef] [PubMed]

187. Happi, A.N.; Ugwu, C.A.; Happi, C.T. Tracking the emergence of new SARS-CoV-2 variants in South Africa. *Nat. Med.* **2021**, *27*, 372–373. [CrossRef]

188. WHO COVID-19 Dashboard. World Health Organization (WHO): Geneva, Switzerland. Available online: https://covid19.who. int/ (accessed on 4 May 2023).

189. Mathieu, E.; Ritchie, H.; Rodés-Guirao, L.; Appel, C.; Giattino, C.; Hasell, J.; Macdonald, B.; Dattani, S.; Beltekian, D.; Ortiz-Ospina, E.; et al. Coronavirus Pandemic (COVID-19). Available online: https://ourworldindata.org/coronavirus (accessed on 15 May 2023).

190. Lamers, M.M.; Haagmans, B.L. SARS-CoV-2 pathogenesis. *Nat. Rev. Microbiol.* **2022**, *20*, 270–284. [CrossRef]

191. Hafezi, B.; Chan, L.; Knapp, J.P.; Karimi, N.; Alizadeh, K.; Mehrani, Y.; Bridle, B.W.; Karimi, K. Cytokine Storm Syndrome in SARS-CoV-2 Infections: A Functional Role of Mast Cells. *Cells* **2021**, *10*, 1761. [CrossRef]

192. Tegally, H.; Wilkinson, E.; Giovanetti, M.; Iranzadeh, A.; Fonseca, V.; Giandhari, J.; Doolabh, D.; Pillay, S.; San, E.J.; Msomi, N.; et al. Detection of a SARS-CoV-2 variant of concern in South Africa. *Nature* **2021**, *592*, 438–443. [CrossRef]

193. Chen, T.; Song, J.; Liu, H.; Zheng, H.; Chen, C. Positive Epstein–Barr virus detection in coronavirus disease 2019 (COVID-19) patients. *Sci. Rep.* **2021**, *11*, 10902. [CrossRef]

194. Paolucci, S.; Cassaniti, I.; Novazzi, F.; Fiorina, L.; Piralla, A.; Comolli, G.; Bruno, R.; Maserati, R.; Gulminetti, R.; Novati, S.; et al. EBV DNA increase in COVID-19 patients with impaired lymphocyte subpopulation count. *Int. J. Infect. Dis.* **2021**, *104*, 315–319. [CrossRef] [PubMed]

195. Simonnet, A.; Engelmann, I.; Moreau, A.-S.; Garcia, B.; Six, S.; El Kalioubie, A.; Robriquet, L.; Hober, D.; Jourdain, M. High incidence of Epstein–Barr virus, cytomegalovirus, and human-herpes virus-6 reactivations in critically ill patients with COVID-19. *Infect. Dis. Now* **2021**, *51*, 296–299. [CrossRef] [PubMed]

196. Xie, Y.; Cao, S.; Dong, H.; Lv, H.; Teng, X.; Zhang, J.; Wang, T.; Zhang, X.; Qin, Y.; Chai, Y.; et al. Clinical characteristics and outcomes of critically ill patients with acute COVID-19 with Epstein-Barr virus reactivation. *BMC Infect. Dis.* **2021**, *21*, 955. [CrossRef] [PubMed]

197. Verma, D.; Church, T.; Swaminathan, S. Epstein-Barr Virus Lytic Replication Induces ACE2 Expression and Enhances SARS-CoV-2 Pseudotyped Virus Entry in Epithelial Cells. *J. Virol.* **2021**, *95*, e0019221. [CrossRef] [PubMed]

198. Gold, J.E.; Okyay, R.A.; Licht, W.E.; Hurley, D.J. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens* **2021**, *10*, 763. [CrossRef]

199. Nunn, A.V.; Guy, G.W.; Botchway, S.W.; Bell, J.D. SARS-CoV-2 and EBV; the cost of a second mitochondrial "whammy"? *Immun. Ageing* **2021**, *18*, 1–4. [CrossRef]

200. Wang, X.; Yang, K.; Wei, C.; Huang, Y.; Zhao, D. Coinfection with EBV/CMV and other respiratory agents in children with suspected infectious mononucleosis. *Virol. J.* **2010**, *7*, 247. [CrossRef]

201. Ito, Y.; Shibata-Watanabe, Y.; Kawada, J.; Maruyama, K.; Yagasaki, H.; Kojima, S.; Kimura, H. Cytomegalovirus and Epstein-Barr virus coinfection in three toddlers with prolonged illnesses. *J. Med. Virol.* **2009**, *81*, 1399–1402. [CrossRef] [PubMed]

202. Mehraein, Y.; Lennerz, C.; Ehlhardt, S.; Zang, K.D.; Madry, H. Replicative multivirus infection with cytomegalovirus, herpes simplex virus 1, and parvovirus B19, and latent Epstein-Barr virus infection in the synovial tissue of a psoriatic arthritis patient. *J. Clin. Virol.* **2004**, *31*, 25–31. [CrossRef] [PubMed]

203. Li, S.-S.; Zhang, N.; Jia, M.; Su, M. Association Between Cytomegalovirus and Epstein-Barr Virus Co-Reactivation and Hematopoietic Stem Cell Transplantation. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 818167. [CrossRef] [PubMed]

204. Mosca de Cerqueira, A.M.; de Cerqueira, F.M.; Campos Moreira, L.F.; Oliveira, S.D.S. Coinfection by herpes simplex virus and Epstein-Barr virus causing erythema multiforme. *Proc. J. Am. Acad. Dermatol.* **2010**, *62*, AB36.

205. Delaney, A.S.; Thomas, W.; Balfour, H.H., Jr. Coprevalence of Epstein-Barr Virus, Cytomegalovirus, and Herpes Simplex Virus Type-1 Antibodies Among United States Children and Factors Associated With Their Acquisition. *J. Pediatr. Infect. Dis. Soc.* **2014**, *4*, 323–329. [CrossRef]

206. Okoye, J.O.; Ngokere, A.A.; Onyenekwe, C.C.; Omotuyi, O.; Dada, D.I. Epstein-Barr virus, human papillomavirus and herpes simplex virus 2 co-presence severely dysregulates miRNA expression. *Afr. J. Lab. Med.* **2021**, *10*, 975. [CrossRef]

207. Blanco, R.; Carrillo-Beltrán, D.; Osorio, J.C.; Calaf, G.M.; Aguayo, F. Role of Epstein-Barr Virus and Human Papillomavirus Coinfection in Cervical Cancer: Epidemiology, Mechanisms and Perspectives. *Pathogens* **2020**, *9*, 685. [CrossRef]

208. Makielski, K.R.; Lee, D.; Lorenz, L.D.; Nawandar, D.M.; Chiu, Y.-F.; Kenney, S.C.; Lambert, P.F. Human papillomavirus promotes Epstein-Barr virus maintenance and lytic reactivation in immortalized oral keratinocytes. *Virology* **2016**, *495*, 52–62. [CrossRef]

209. Szkaradkiewicz, A.; Wal, M.; Kuch, A.; Pieta, P. Human papillomavirus (HPV) and Epstein-Barr virus (EBV) cervical infections in women with normal and abnormal cytology. *Pol. J. Microbiol.* **2004**, *53*, 95–99.

210. Khenchouche, A.; Sadouki, N.; Boudriche, A.; Houali, K.; Graba, A.; Ooka, T.; Bouguermouh, A. Human papillomavirus and Epstein-Barr virus co-infection in cervical carcinoma in Algerian women. *Virol. J.* **2013**, *10*, 340. [CrossRef]

211. Santos, N.B.M.; Villanova, F.E.; Andrade, P.M.; Ribalta, J.; Focchi, J.; Otsuka, A.Y.; Dale Silva, I. Epstein-Barr virus detection in invasive and pre-invasive lesions of the uterine cervix. *Oncol. Rep.* **2009**, *21*, 403–405. [PubMed]

212. Sosse, S.A.; Tadlaoui, K.A.; Benhassou, M.; Elkarroumi, M.; Elmzibri, M.; Ennaji, M.M. Viral co-infection of oncogenic Human papillomavirus with Epstein–Barr Virus, Human herpesvirus 8 and Herpes Simplex Virus type 2 in malignant cervical cancer. *Res. Sq.* **2022**. [CrossRef]

213. Sfanos, K.S.; Sauvageot, J.; Fedor, H.L.; Dick, J.D.; De Marzo, A.M.; Isaacs, W.B. A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. *Prostate* **2008**, *68*, 306–320. [CrossRef]

214. Grinstein, S.; Preciado, M.V.; Gattuso, P.; Chabay, P.A.; Warren, W.H.; De Matteo, E.; Gould, V.E. Demonstration of Epstein-Barr virus in carcinomas of various sites. *Cancer Res.* **2002**, *62*, 4876–4878.

215. Nahand, J.S.; Khanaliha, K.; Mirzaei, H.; Moghoofei, M.; Baghi, H.B.; Esghaei, M.; Khatami, A.R.; Fatemipour, M.; Bokharaei-Salim, F. Possible role of HPV/EBV coinfection in anoikis resistance and development in prostate cancer. *BMC Cancer* **2021**, *21*, 926. [CrossRef] [PubMed]

216. Glenn, W.K.; Heng, B.; Delprado, W.; Iacopetta, B.; Whitaker, N.J.; Lawson, J.S. Epstein-Barr virus, human papillomavirus and mouse mammary tumour virus as multiple viruses in breast cancer. *PLoS ONE* **2012**, *7*, e48788. [CrossRef]

217. Fang, L.-Z.; Dong, Y.-H.; Yan, Z.-J.; Zhou, C.-M.; Yu, X.-J.; Qin, X.-R. Reactivation of Epstein-Barr virus in SFTSV infected patients. *Infect. Med.* **2023**. [CrossRef]

218. Chen, J.; Ueda, K.; Sakakibara, S.; Okuno, T.; Parravicini, C.; Corbellino, M.; Yamanishi, K. Activation of latent Kaposi's sarcoma-associated herpesvirus by demethylation of the promoter of the lytic transactivator. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 4119–4124. [CrossRef]

219. Yan, Q.; Li, W.; Tang, Q.; Yao, S.; Lv, Z.; Feng, N.; Ma, X.; Bai, Z.; Zeng, Y.; Qin, D. Cellular microRNAs 498 and 320d regulate herpes simplex virus 1 induction of Kaposi's sarcoma-associated herpesvirus lytic replication by targeting RTA. *PLoS ONE* **2013**, *8*, e55832. [CrossRef]

220. Chen, J.; Dai, L.; Barrett, L.; James, J.; Plaisance-Bonstaff, K.; Post, S.R.; Qin, Z. SARS-CoV-2 proteins and anti-COVID-19 drugs induce lytic reactivation of an oncogenic virus. *Commun. Biol.* **2021**, *4*, 682. [CrossRef]

221. Li, X.; Feng, J.; Sun, R. Oxidative stress induces reactivation of Kaposi's sarcoma-associated herpesvirus and death of primary effusion lymphoma cells. *J. Virol.* **2011**, *85*, 715–724. [CrossRef] [PubMed]

222. Ye, F.; Zhou, F.; Bedolla, R.G.; Jones, T.; Lei, X.; Kang, T.; Guadalupe, M.; Gao, S.J. Reactive oxygen species hydrogen peroxide mediates Kaposi's sarcoma-associated herpesvirus reactivation from latency. *PLoS Pathog.* **2011**, *7*, e1002054. [CrossRef] [PubMed]

223. Singh, R.K.; Lamplugh, Z.L.; Lang, F.; Yuan, Y.; Lieberman, P.; You, J.; Robertson, E.S. KSHV-encoded LANA protects the cellular replication machinery from hypoxia induced degradation. *PLoS Pathog.* **2019**, *15*, e1008025. [CrossRef] [PubMed]

224. Davis, D.A.; Rinderknecht, A.S.; Zoeteweij, J.P.; Aoki, Y.; Read-Connole, E.L.; Tosato, G.; Blauvelt, A.; Yarchoan, R. Hypoxia induces lytic replication of Kaposi sarcoma–associated herpesvirus. *Blood J. Am. Soc. Hematol.* **2001**, *97*, 3244–3250. [CrossRef]

225. Iftode, N.; Rădulescu, M.A.; Aramă, Ș.S.; Aramă, V. Update on Kaposi sarcoma-associated herpesvirus (KSHV or HHV8)–review. *Rom. J. Intern. Med.* **2020**, *58*, 199–208. [CrossRef]

226. Mbisa, G.L.; Miley, W.; Gamache, C.J.; Gillette, W.K.; Esposito, D.; Hopkins, R.; Busch, M.P.; Schreiber, G.B.; Little, R.F.; Yarchoan, R.; et al. Detection of antibodies to Kaposi's sarcoma-associated herpesvirus: A new approach using K8.1 ELISA and a newly developed recombinant LANA ELISA. *J. Immunol. Methods* **2010**, *356*, 39–46. [CrossRef]

227. Labo, N.; Miley, W.; Benson, C.A.; Campbell, T.B.; Whitby, D. Epidemiology of Kaposi's sarcoma-associated herpesvirus in HIV-1-infected US persons in the era of combination antiretroviral therapy. *Aids* **2015**, *29*, 1217–1225. [CrossRef]

228. Varthakavi, V.; Smith, R.M.; Deng, H.; Sun, R.; Spearman, P. Human immunodeficiency virus type-1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus through induction of KSHV Rta. *Virology* **2002**, *297*, 270–280. [CrossRef]

229. Albini, A.; Soldi, R.; Giunciuclio, D.; Giraudo, E.; Benelli, R.; Primo, L.; Noonan, D.; Salio, M.; Camussi, G.; Rock, W. The angiogenesis induced by HIV–1 Tat protein is mediated by the Flk–1/KDR receptor on vascular endothelial cells. *Nat. Med.* **1996**, *2*, 1371–1375. [CrossRef]

230. Zeng, Y.; Zhang, X.; Huang, Z.; Cheng, L.; Yao, S.; Qin, D.; Chen, X.; Tang, Q.; Lv, Z.; Zhang, L. Intracellular Tat of human immunodeficiency virus type 1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus: Role of JAK/STAT signaling. *J. Virol.* **2007**, *81*, 2401–2417. [CrossRef]

231. Mercader, M.; Taddeo, B.; Panella, J.R.; Chandran, B.; Nickoloff, B.J.; Foreman, K.E. Induction of HHV-8 lytic cycle replication by inflammatory cytokines produced by HIV-1-infected T cells. *Am. J. Pathol.* **2000**, *156*, 1961–1971. [CrossRef] [PubMed]

232. Cavallin, L.E.; Goldschmidt-Clermont, P.; Mesri, E.A. Molecular and cellular mechanisms of KSHV oncogenesis of Kaposi's sarcoma associated with HIV/AIDS. *PLoS Pathog.* **2014**, *10*, e1004154. [CrossRef] [PubMed]

233. Su, C.-C.; Lai, C.-L.; Tsao, S.-M.; Lin, M.-N.; Hsieh, T.-C.; Lu, J.-J.; Chu, T.-Y. High prevalence of human herpesvirus type 8 infection in patients with pulmonary tuberculosis in Taiwan. *Clin. Microbiol. Infect.* **2015**, *21*, 266.e5–266.e7. [CrossRef] [PubMed]

234. Dai, L.; Jung, B.G.; Chen, J.; Samten, B.; Forrest, J.C.; Post, S.R.; Qin, Z. The potential impacts of early secreted antigenic target of 6 kDa of Mycobacterium tuberculosis on KSHV-infected cells. *J. Med. Virol.* **2021**, *93*, 4028–4032. [CrossRef] [PubMed]

235. Wakeham, K.; Webb, E.L.; Sebina, I.; Muhangi, L.; Miley, W.; Johnson, W.T.; Ndibazza, J.; Elliott, A.M.; Whitby, D.; Newton, R. Parasite infection is associated with Kaposi's sarcoma associated herpesvirus (KSHV) in Ugandan women. *Infect. Agents Cancer* **2011**, *6*, 1–7. [CrossRef]

236. Crispo, A.; Tamburini, M.; De Marco, M.; Ascierto, P.; Silvestro, P.; Ronga, D.; Tridente, V.; Desicato, S.; Carbone, S.; Fabbrocini, G. HHV-8 prevalence, immunosuppression and Kaposi's sarcoma in South Italy. *Int. J. Mol. Med.* **2001**, *7*, 535–538. [CrossRef]

237. Coluzzi, M.; Calabro, M.; Manno, D.; Chieco-Bianchi, L.; Schulz, T.; Ascoli, V. Reduced seroprevalence of Kaposi's sarcoma-associated herpesvirus (KSHV), human herpesvirus 8 (HHV8), related to suppression of Anopheles density in Italy. *Med. Vet. Entomol.* **2003**, *17*, 461–464. [CrossRef]

238. Sabourin, K.R.; Daud, I.; Ogolla, S.; Labo, N.; Miley, W.; Lamb, M.; Newton, R.; Whitby, D.; Rochford, R. Malaria Is Associated With Kaposi Sarcoma-Associated Herpesvirus Seroconversion in a Cohort of Western Kenyan Children. *J. Infect. Dis.* **2021**, *224*, 303–311. [CrossRef]

239. Reese, T.; Wakeman, B.; Choi, H.; Hufford, M.; Huang, S.; Zhang, X.; Buck, M.; Jezewski, A.; Kambal, A.; Liu, C. Helminth infection reactivates latent γ-herpesvirus via cytokine competition at a viral promoter. *Science* **2014**, *345*, 573–577. [CrossRef]

240. Ruocco, V.; Ruocco, E.; Schwartz, R.A.; Janniger, C.K. Kaposi sarcoma and quinine: A potentially overlooked triggering factor in millions of Africans. *J. Am. Acad. Dermatol.* **2011**, *64*, 434–436. [CrossRef]

241. Haldar, K.; Mohandas, N. Malaria, erythrocytic infection, and anemia. *Hematology. ASH Educ.* **2009**, 87–93. [CrossRef] [PubMed]

242. Jyotsana, N.; King, M.R. The impact of COVID-19 on cancer risk and treatment. *Cell. Mol. Bioeng.* **2020**, *13*, 285–291. [CrossRef] [PubMed]

243. Blumenthal, M.J.; Lambarey, H.; Chetram, A.; Riou, C.; Wilkinson, R.J.; Schäfer, G. Kaposi's Sarcoma-Associated Herpesvirus, but Not Epstein-Barr Virus, Co-infection Associates With Coronavirus Disease 2019 Severity and Outcome in South African Patients. *Front. Microbiol.* **2022**, *12*, 795555. [CrossRef]

244. Leoni, E.; Cerati, M.; Finzi, G.; Lombardo, M.; Sessa, F. COVID-19 and HHV8 first spotted together: An affair under electron microscopy. *J. Eur. Acad. Dermatol. Venereol.* **2021**, *35*, e311. [CrossRef] [PubMed]

245. Saade, A.; Moratelli, G.; Azoulay, E.; Darmon, M. Herpesvirus reactivation during severe COVID-19 and high rate of immune defect. *Infect. Dis. Now* **2021**, *51*, 676–679. [CrossRef] [PubMed]

246. Adland, E.; Klenerman, P.; Goulder, P.; Matthews, P.C. Ongoing burden of disease and mortality from HIV/CMV coinfection in Africa in the antiretroviral therapy era. *Front. Microbiol.* **2015**, *6*, 1016. [CrossRef] [PubMed]

247. Bates, M.; Brantsaeter, A.B. Human cytomegalovirus (CMV) in Africa: A neglected but important pathogen. *J. Virus Erad.* **2016**, *2*, 136–142. [CrossRef] [PubMed]

248. Park, M.-Y.; Kim, Y.-E.; Seo, M.-R.; Lee, J.-R.; Lee, C.H.; Ahn, J.-H. Interactions among four proteins encoded by the human cytomegalovirus UL112-113 region regulate their intranuclear targeting and the recruitment of UL44 to prereplication foci. *J. Virol.* **2006**, *80*, 2718–2727. [CrossRef]

249. Cheng, B.; Martínez, F.P.; Katano, H.; Tang, Q. Evidence of inability of human cytomegalovirus to reactivate Kaposi's sarcoma-associated herpesvirus from latency in body cavity-based lymphocytes. *J. Clin. Virol.* **2009**, *46*, 244–248. [CrossRef]

250. Qin, D.; Feng, N.; Fan, W.; Ma, X.; Yan, Q.; Lv, Z.; Zeng, Y.; Zhu, J.; Lu, C. Activation of PI3K/AKT and ERK MAPK signal pathways is required for the induction of lytic cycle replication of Kaposi's sarcoma-associated herpesvirus by herpes simplex virus type 1. *BMC Microbiol.* **2011**, *11*, 240. [CrossRef]

251. Meeuwsen, S.; Persoon-Deen, C.; Bsibsi, M.; Bajramovic, J.J.; Ravid, R.; De Bolle, L.; van Noort, J.M. Modulation of the cytokine network in human adult astrocytes by human herpesvirus-6A. *J. Neuroimmunol.* **2005**, *164*, 37–47. [CrossRef] [PubMed]

252. Jiang, Y.; Xu, D.; Zhao, Y.; Zhang, L. Mutual inhibition between Kaposi's sarcoma-associated herpesvirus and Epstein-Barr virus lytic replication initiators in dually-infected primary effusion lymphoma. *PLoS ONE* **2008**, *3*, e1569. [CrossRef] [PubMed]

253. Miller, G.; Heston, L.; Grogan, E.; Gradoville, L.; Rigsby, M.; Sun, R.; Shedd, D.; Kushnaryov, V.M.; Grossberg, S.; Chang, Y. Selective switch between latency and lytic replication of Kaposi's sarcoma herpesvirus and Epstein-Barr virus in dually infected body cavity lymphoma cells. *J. Virol.* **1997**, *71*, 314–324. [CrossRef] [PubMed]