Kaposi's Sarcoma-Associated Herpesvirus (KSHV)-Associated Disease in the AIDS Patient: An Update

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Abstract

In this book chapter, we review the current knowledge of the biology and pathogenesis of Kaposi's sarcomaassociated herpesvirus (KSHV). We describe the lifecycle of KSHV, the cancers associated with this virus, as well as current treatment modalities.

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3.1 Introduction

Approximately, 25 % of all human cancers are etiologically linked to an infectious agent including viruses and bacteria. These pathogens are usually controlled by the host immune system. In individuals that are immunodeficient, such as acquired immunodeficiency syndrome (**AIDS**) patients or patients receiving immunosuppressive therapies following organ transplantation, this checkpoint fails and there is a significantly higher risk for the development of cancers associated with infectious agents. It is important to remember, though, that temporal immune deficiency is a normal physiological process, e.g. during aging and infant development. Viruses contribute to cancer development either cell autonomously through the activities of viral oncogenes acting within a cell, or through paracrine mechanisms that modulate the transformed cell and the tumor microenvironment [27].

Kaposi's sarcoma (**KS**) was described in 1872 by Moritz Kaposi, the head of the Vienna dermatology clinic, as *"idiopathisches multiples Pigmentsarkom"* a rare angiosarcoma in elderly men of Mediterranean descent [49]. In the mid-1980s, the human immunodeficiency virus (**HIV**) epidemic lead to a significant increase in the incidence of KS in high-risk populations. Today, over 30 years later, the number of new HIV infections has declined due to combination Anti Retroviral Therapy (**cART**). Yet, because of cART the number of persons living with HIV is increasing and the mean age of the cohort of HIV-infected persons is also increasing. Many HIV-positive individuals are now entering the age bracket, in which Moritiz Kaposi initially described classic KS in the elderly. As a result, KS remains the single most common neoplasm seen in individuals living with HIV today [88].

Chang and Moore identified KSHV (also known as human herpesvirus 8) in KS lesions of AIDS patients in 1994 [13] using representational difference analysis. KSHV has since been found in HIV+ and HIV− negative KS patients as well as in a number of B-cell hyperplasias and frank lymphomas. Ninety-nine per cent of all KS lesions, regardless of clinical type or HIV status, contain KSHV viral DNA and express a least one viral protein, the latency-associated nuclear antigen (**LANA**), as well as all viral micro RNAs, thereby linking KS to KSHV infection [27].

3.2 KSHV and the Development of KS

KS is divided into four subtypes delineated by clinical manifestations: classic, endemic, AIDS-associated, and iatrogenic. Classic KS is a disease of elderly Mediterranean and Eastern European men, while endemic KS is found in parts of equatorial Africa such as Uganda, Zambia, Malawi, Kenya, and South Africa in the elderly as well as in children [59]. KS represents the most common cancer in countries with high, coincident HIV and KSHV prevalence [45]. In endemic regions, transmission of KSHV is thought to occur early in childhood [32]. Endemic KS tends to be more aggressive than classic KS of the elderly, and occurs at almost equal proportions in men and women, the elderly and children [27].

Widespread HIV infection has given rise to an epidemic of KS. KSHV antibodies prevalent in black South African HIV patients, and KS has become the most common neoplasm in regions of sub-Saharan Africa that are ravaged by HIV infection. In the U.S., KSHV antibody prevalence also exceeds 30% in cities with high HIV burden and in high-risk populations [54]. This is most likely, because among adults, HIV and KSHV are transmitted by similar routes, though the efficiency of KSHV transmission (or basic reproductive ratio, which is a function of viral load among other factors) is less that that of acute HIV-1 infection.

In 1981, KS was recognized as a defining pathology for HIV diagnosis but the introduction of cART has led to a substantial decline of AIDS-related KS in the United States. The Centers for Disease control (**CDC**) estimated in 2016 that the average American had a 1 in 99 chance of being diagnosed with HIV at some point in his or her life. Even in the cART era, standardized incidence rates for KS are higher than that of any other AIDS-defining or non-AIDS-defining cancers [61]. This suggests that KS will remain a permanent health problem for years to come. As HIV-positive men in the U.S. age, it is speculated that the incidence of AIDS-KS may rise again.

Iatrogenic KS occurs after solid organ transplantation in patients receiving immunosuppressive therapy [16]. KS comprises an estimated 3% of all tumors associated with transplantation [63]. Iatrogenic KS is observed in regions of high KSHV prevalence, such as Southern Italy, Saudi Arabia and Turkey. KSHV may already be present in the recipient prior to organ transplantation, and may be acquired during induced immunosuppression after transplantation, or may even be acquired through the graft itself [5]. The frequency of KS in AIDS patients is 20,000 times higher than in the general population [6] and the frequency of KS in transplant recipients is 500 times higher than in healthy individuals [91].

In the mid-1980s, incidence rates for KS displayed an exponential increase. Back then, KS was primarily observed in AIDS patients with a history of men who had sex with men, but not in individuals who became HIV-infected through blood transfusion [37]. In AIDS-associated KS, there was a correlation between incidence rates and the lifetime number of male sexual partners [59]. This established KSHV as a sexually transmitted agent responsible for the development of this cancer. Today, more women are becoming infected with HIV and consequently AIDS-KS is also seen in this group. Interestingly, African KS affects both genders; while classic (Mediterranean) KS affects predominantly elder men. The reason for the gender bias in classic KS is unknown. In the U.S., KS incidence rates follow a bimodal distribution that peaks at ages 30–36 and again at ages >70.

KS lesions are classified as plaque, patched, or nodular. As the KS tumor clinically advances, the KSHV-infected cells increase in number along with the endothelial cell population in the lesion. There is evidence for both polyclonality and monoclonality of the lesions [47, 76]. It is thought that KS likely initiates as a polyclonal hyperplasia and develops into a clonal neoplasia. Kaposi's sarcoma not only affects the skin but can also involve multiple organs such as the liver, lung, spleen, and gastrointestinal tract. In some forms of KS, only lymphoid and internal organs are affected. Oral KS in the setting of AIDS is associated with advanced

disease and visceral development. However, in the setting of cART-controlled HIV infection, it may occur in isolation and represent limited disease. Edema is common in KS patients. Aggressive types of KS can lead to foci formation in the visceral organs and ultimately result in hemorrhage and death.

KSHV viral load in PBMC rise up to 6 months prior to lesion formation [101]. A rise in viral load predicts the imminent appearance of KS [72]. However, systemic viral load in plasma varies widely across KS patients and does not correlate with the number of skin lesions [44]. Inhibitors of the viral polymerase reduce overall risk of future KS, but do not lead to regression of established KS lesions. KSHV is found in circulating B cells as well as monocytes, macrophages, endothelial cells, and epithelial cells [21, 77, 92]. The presence of the most common anti-KSHV antibodies, which are directed against the LANA protein, documents prior exposure but does not allow a prediction of KS development, since in HIV-positive individuals the median time from seroconversion to disease is seven years or greater [37, 59].

The KS lesion is highly angiogenic and is comprised of spindle-shaped cells, slit-like endothelium-lined vasculature and infiltrating blood cells. The spindle cells appear to arise from lymphatic endothelial cells and form the majority of the neoplasm [31]. In fact, experimental KSHV infection can reprogram the blood endothelial gene expression profile into that of the lymphatic endothelium and vice versa [42, 43, 98, 100], though the profile also shows the presence of mesenchymal markers including various Notch isoforms [15, 58] consistent with dedifferentiation into a progenitor stage.

The primary receptor for KSHV infection of endothelial cells is ephrin receptor tyrosine kinase A2 [41]. Ephrins and their corresponding kinases are differentially expressed across different cell lineages. Hence, the expression pattern of EphA2 may express the tropism of KSHV. It may also become a target of novel, directed KS therapy [14, 85]. KS tumor explants lose the virus after serial passage in tissue culture over time. KSHV-infected endothelial cell preparations in culture generally also lose the virus over time [40, 55].

3.3 KSHV and the Development of Lymphomas

KSHV is also found in B lymphoproliferative diseases; primary effusion lymphoma (**PEL**) and the plasmablastic variant of multicentric Castleman's disease (**MCD**). In fact, the first association of KS and a B-cell lymphoproliferative disorder, MCD, was reported in a patient who presented with both diseases [81]. Greater than 50% of KSHV-positive transplant recipients develop lymphoproliferative disease [35]. KSHV is most certainly the causal agent of both MCD and PEL [12, 90]. MCD is a B-cell lymphoproliferative disorder. Patients usually present with diffuse lymphadenopathys. In addition to B cell proliferation, MCD displays vascular proliferation of the germinal centers of the lymph node. There are two forms of MCD: (i) a plasmablastic variant form that is associated with lymphadenopathy and

immune dysregulation and (ii) a hyaline vascular form, which presents as a solid mass. Close to 100% of AIDS-associated MCD is associated with KSHV. AIDS-associated MCD is usually accompanied by the development of KS in the affected individual, often in the same lymph node.

MCD is a polyclonal tumor and is highly dependent on cytokines such as human interleukin 6 (IL-6) (reviewed in [103]). KSHV itself encodes a viral IL-6 that is also expressed in these lesions [71, 73, 94]. Expression of either human IL-6 or viral IL-6 in transgenic mice causes B-cell hyperplasia and lymphoma. Viral antigens can be detected in the immunoblastic B cells in the mantle zone of the lymph node. The plasmablasts in MCD express monotypic IgM light chains [29] and MCD patients frequently develop cytopenia, autoimmune disease and other malignancies such as KS and non-Hodgkin's lymphoma [1]. Anti-IL-6 or anti-IL-6R antibodies show efficacy in KSHV-negative Castleman's disease and there is every reason to believe that siltuximab or tocilizumab (also known as atlizumab) will also be active in KSHV-positive, HIV-associated MCD and perhaps even PEL.

PEL, sometimes referred to as body cavity-based lymphoma (BCBLs), represent a specific subset of non-Hodgkin's B-cell lymphoma (NHL) that involve body cavities (peritoneal, pleural or pericardial cavities) and form a distinct clinico-pathologic group from other NHL [67]. All PEL are KSHV-positive, and are often coinfected with EBV as well. These tumors are typically large-cell immunoblastic or anaplastic large-cell lymphomas that express CD45, but not CD19, carry clonal immunoglobulin gene rearrangements, and lack mutations in c-myc, bcl-2, ras, and p53 [1, 67].

PEL display the characteristics of a preterminal stage of B-cell differentiation. Since PEL have mutations in their immunoglobulin genes, they are thought to arise from post-germinal center B cells. However, PEL do not express immunoglobulins. Most PEL express CD138/syndecan-1 antigen, which is normally also expressed by a subset of plasma cells. Most PEL also express high levels of human IL-6 and IL10.

Although KSHV is linked to PEL and MCD in HIV patients, there are cases of KSHV-positive lymphomas that do not fit the classic PEL phenotypes. There appears to be a high incidence of KSHV infection in solid HIV-associated immunoblastic/plasmablastic non-Hodgkin's lymphomas that developed in patients lacking PEL and MCD [22] and yet others have found KSHV associated with solid lymphomas, which resemble PEL cell morphology but do not present as effusions [10]. KSHV has also been linked to cases of germinotropic lymphoproliferative disease (GLD) [28]. This disease also involves plasmablasts but unlike plasmablastic lymphomas, the GLD lymphomas contain polyclonal immunoglobulin receptors. This suggests a model in which KSHV infects an early germinal center B cell that can still differentiate into multiple lymphoma phenotypes dependent on secondary mutations to the cellular genome.

Finally, KSHV infection can also lead to KS-immune reconstitution syndrome (KS-IRIS) [8, 18] and KSHV-inflammatory cytokine syndrome (KICS) [74]. Patients with KICS have high KSHV viral loads and levels of viral IL-6, human IL-6, human IL-10 as well as C-reactive protein.

The evidence linking KSHV to KS, PEL, MCD and KICS, is overwhelming and has been confirmed by multiple laboratories and indepent methods such as the presence of viral DNA in the lesions, viral protein expression and anti-KSHV antibodies (directed against LANA/orf73, orf K8.1 and others). KSHV DNA has also been detected in multiple myeloma, primary pulmonary hypertension, angiosarcomas, as well as malignant skin tumors in posttransplant patients such as Bowen's disease, squamous cell carcinomas, actinic keratosis, and extramammary Paget's disease. However, these disease associations were never substantiated and have largely been discarded [1, 27].

3.4 Prevalence of Viral Infection

Several serology studies have suggested that KSHV infection is widespread in Africa with 30–60% of people being KSHV-positive, but is uncommon in the United States and Western Europe with seropositivity ranging from 3 to 10% in the general population [50]. KSHV seropositivity is considerably higher in high-risk populations reaching 38% in participants seen at AIDS clinical trials centers [54]. Regions such as Italy, Greece, Turkey, and Saudi Arabia show a higher prevalence of KSHV at about 4–35% [102], which correlates with correspondingly higher incidence rates for classical or transplant-associated KS. Transmission routes include sexual transmission, mother-to-child transmission, but probably all forms involve salivary transmission [9, 59, 96]. There is no evidence that transmission rates decline, as most KSHV transmission, similar to other herpesviruses, appears during episodes of asymptomatic shedding.

3.5 The KSHV Genome

A hallmark of herpesviruses including KSHV is their ability to establish a latent infection for the lifetime of their host. Pathogenesis caused by these viruses is usually seen in the context of host immunesuppression. All herpesviruses share a common evolutionary origin, which is evident from the homology seen among a substantial number of herpesviral genes (reviewed in [25]). Based on biological characteristics and genomic organization, herpesviruses are classified into three subfamilies: alpha, beta, and gamma. The gamma herpesviruses are lymphotropic and some are capable of undergoing lytic replication in epithelial, endothelial, or fibroblast cells. The gammaherpesvirinae are grouped into two classes: lymphocryptoviruses (gamma-1) and rhadinoviruses (gamma-2). Epstein–Barr virus (EBV) or human herpesvirus 4 (HHV4) is a lymphocryptovirus while KSHV or human herpesvirus 8 (HHV8) is a rhadinovirus.

During latent infection, viral gene expression is highly attenuated and the viral genome remains stably associated with the cell. In the lytic phase of infection, viral gene expression and DNA replication ensue, leading to the production of progeny virions and eventual lysis of the infected cell. The KSHV viral genome is comprised of a ~140 kb long unique region flanked by multiple terminal repeat sequences with the total genomic size being ~160–170 kb. KSHV encodes for more than 80 open reading frames (ORFs) that encode for proteins greater than 100 amino acids [83]. The viral genes encoded by KSHV can be divided into three classes—(i) genes common to all herpesviruses (ii) genes unique to KSHV (these are generally given a "K" designation followed by the number of the open reading frame (ORF), and (iii) KSHV encoded genes that are homologous to cellular genes (these may be unique to KSHV or shared with other herpesviruses), and are likely to have been usurped from the host genome during the course of evolution. It is likely that several viral genes contribute to the neoplastic process [19].

While there exist distinct clades of KSHV, most of the variation is concentrated in a few proteins, such as the extracellular regions of the K1 and K15 proteins, which are exposed to the host immune system, or in extended repeat regions, where the genome is inherently unstable, such as in the two origins of replication and the central protein coding region of LANA. Whole genome sequencing has shown that all other regions are conserved across strains with just a few single nucleotide variations inside protein coding regions [70]. At this point, none of the genomic variation seen within KSHV has been associated with overt clinical or cellular phenotypes, though specific point mutations in the viral micro RNA precursors lead to the absence of certain mature miRNAs in PEL or KS lesions.

3.6 Molecular Biology of KSHV-Associated Disease

KSHV gene expression in human KS, PEL and MCD disease has involved the use of microarrays to profile viral gene expression. Since the KSHV genome is orders of magnitude smaller than the human genome, it has been feasible to develop whole genome arrays based upon real-time quantitative RT-PCR for all individual viral genes and to analyze primary KS biopsy samples and KSHV-infected lymphomas [24, 33]. Conventional microarray-based viral gene expression in KSHV-infected lymphomas as well as RNAseq studies has also been performed. These techniques generate a viral signature for each disease state and offer a chance to classify KS beyond Moritz Kaposi's observational diagnosis. High-throughput genomic profiling offers the chance to accelerate our investigations into KSHV-associated cancers as much as it has benefited research into nonviral cancers. Microarray analyses of host cell transcription [34, 46, 51] proved that KSHV-positive PEL differ from other types of B-cell lymphomas. This is consistent with the idea that KSHV reprograms the tumor cell.

It has been shown that KSHV infection reprograms endothelial cells. Blood endothelial cells are reprogrammed toward lympathic endothelium and conversely, lymphatic endothelium is reprogrammed toward blood endothelium [42, 43, 98, 100]. Several studies have ascertained the host transcription profile in tissue culture models of KSHV infection [66, 68, 75, 79]. KS has a cellular transcription signature that is distinct from other cancers and tied to the unique pathology of this disease, as an angioproliferative, cytokine driven disease. For instance, c-Kit and other growth factor receptors in microarray studies of KSHV-infected endothelial cells led to a successful pilot study using the kinase inhibitor gleevec (Imatinib) [52]. Other studies found response rates of KS to a matrix metalloproteinase inhibitor [23] or anti-VEGF antibodies such as bevacicumab [95].

Every KS tumor transcribes high levels of the canonical KSHV latency transcripts encoding LANA, vFLIP, vCyclin, the viral micro RNAs, and Kaposin. These genes are under control of the same promoter and are expressed in every KS tumor cell [26, 30]. Kaposin is located immediately downstream of these three genes and in addition to the common promoter can be regulated by a promoter located between LANA and cyclin [56] and during lytic reactivation yet another, ORF-proximal promoter [84]. Like LANA, Kaposin too is expressed in every tumor cell [92] and has been shown to stabilize cellular cytokine mRNAs [62]. In addition to these latent proteins, many KS tumors as well as PEL engrafts [93, 97] express an extended set of proteins that were initially classified as lytic viral genes, but in the context of the tumor may be the result of abortive or incomplete viral reactivation. These include the KSHV interferon regulatory factor (vIRF-1) and G-coupled receptor (vGPCR) homologs [24] and the K1 constitutive signal protein [3, 97, 99, 104], as well as K15, a constitutive signaling protein located at opposite end of K1 [39]. This suggests that a subset of KS phenotypes may be attributable to these genes and the paracrine mechanisms that they invoke [4, 64, 65]. The vIRF-3, a duplicated KSHV IRF homolog, is constitutively transcribed in KSHV-infected PEL [80]. Thus, we speculate that KSHV has to interfere with the host cell's innate interferon response in every infected cell regardless of cell lineage or mode of infection and has thus placed multiple copies of the vIRFs, all of which interfere with normal interferon signaling, under different control elements, e.g., vIRF-3 is specific for B cells while vIRF-1 is specific for endothelial cells. Thus, both latent and select lytic genes can be considered tumor-specific therapy targets for KS.

3.7 Therapies to Treat KS, PEL, and MCD

Treatment modalities for KS include observation, local therapy, or systemic chemotherapy specifically paclitaxel and anthracyclines, such as doxorubicin/adriamycin [69], depending on the severity of the disease. Response rates approach 70% depending on comorbidities. KS is know to reapear and to require repeated treatment; a complete cure is seldom achieved as none of the anti-cancer treatments erradicate the latent virus. A key development was the demonstration that liposomal

formulation of the peggylated-anthracyclins were as efficactious as the initial drug, but had significant fewer side effects. No new theraphies against KS have been introduced since the liposomal anthracyclines such as liposomal Doxorubicin or liposomal Daunorubicin. Whether a protein-bound formulation of paclitaxel (Abraxane) has activity with reduced toxicity is unknown. Interferon alpha was initially approved to treat KS, but is no longer in use. KS is a highly angiogenic tumor but clinical trials targeting the angiogenic nature of KS have shown limited efficacy as single agent [95]. This is expected, since most of these agents, such as the humanized anti-VEGF antibody bevacicumab are tumorstatic and do not kill the tumor cell directly.

A clinical trial involving daily doses of Imatinib mesylate (Gleevec), which targets c-kit and platelet-derived growth factor receptor (PDGFR) signaling, resulted in clinical and histologic regression of cutaneous KS [52], as did a trial of a matrix metalloproteinase inhibitor [23]. As more receptor tyrosine kinase (RTK)-targeting molecules become available, targeting PDGFR, VEGFR, and related mediators of paracrine tumor promoters, offer promise for KS.

Organ transplants, who developed KS due to immunosuppressive therapy, benefited from treatment with rapamycin [91]. This observation has been repeated in multiple settings and switching from cyclosporine A or FK506, which suppress T cell activation, but not B cell or endothelial cell activation to rapamycin, which suppresses proliferation in all three cell types, has emerged as the informal standard of care of iatrogenic KS. Rapamycin/Sirolimus and its derivatives Temsirolimus and Everolimus are allosteric inhibitors of the mTOR pathway and display both immunosuppressive and antineoplastic properties. The clinical effect of rapamycin could be reproduced in animal models [82, 89]. Of note, rapamycin was active against doxorubicin-resistant PEL. Rapamycin acted via an antiangiogenic mechanism ultimately reducing the levels of VEGF and of VEGF receptor on endothelial cells. Again, as single agent rapamycin was tumorstatic, rather than tumortoxic. Newer, competitive inhibitors of the mTOR pathway are likely to produce superior results. Additional inhibitors targeting the active site of PI3K and mTOR have also proved effective in animal models [2, 7].

A series of clinical trials is exploring the efficacy of "imids", i.e., thalidomide, lenalidomide, and pomalidomide in KS that develops in HIV-suppressed indiviudals. These compounds have an as yet ill-defined mechanism of action that affects the immunesystem as well as potential KS tumor cells directly, through modulating gene expression [20]. In 2018 Pomalidomide received orphan drug designation for KS by the FDA of the US.

The risk for KS and virally associated lymphomas increases rapidly as the CD4+ cell counts of HIV-infected individuals diminish [17], and the risk of developing AIDS-associated cancers is lower for individuals who are less severely immune suppressed. Since the prevalence of KS in AIDS patients is very high, and HIV coinfection is thought to be an important factor in the development of KS, attempts to control KS by improving the immune system of HIV-infected individuals through cART are recommended. Indeed, the incidence of KS has declined considerably following the introduction of cART therapy and often cART alone will

lead to KS regression in AIDS patients. However, it is important to note that even in the face of cART therapy, the likelihood of an HIV-positive individual developing KS is still 20 times higher than uninfected individuals [17] and that by now one-fourth of KS develops in individuals who are HIV-suppressed [53].

Current treatments for MCD, PEL, and other AIDS lymphomas include standard chemotherapy such as CHOP, which contains four drugs; prednisone, vincristine, cyclophosphamide, and doxorubicin, or EPOCH, which in addition contains etoposide. These can be given coincidentally with cART [78, 86]. Case reports in the literature also suggest that Rituximab (rituxan) is effective against PEL. Rituximab is an anti-CD20 antibody, but because Rituximab targets normal B cells as well, it can be associated with an increased risk of infection when used in AIDS patients [48]. Scott et al. have reported on two MCD patients that went into sustained remission with just oral etoposide [86], but a more modern approach would be neutralizing human IL-6 using anti-IL-6 antibodies or anti-IL-6 receptor antibodies. Whether the concept of neutralizing paracrine factors can also be applied to viral IL-6 remains to be explored.

Another line of thinking has lead to exploratory studies using anti-herpesviral drugs that inhibit herpesviral replication such as ganciclovir or AZT [11, 38, 60, 94] in patients. There are two possible mechanisms of action. First, these inhibitors suppress viral dissemination and thus the pool of infected cells rather than acting directly on the tumor. Second, there is the observation that AZT as well as ganciclovir has direct cytotoxicity on the infected cell, and selectivity for infected cells, as only those cells express the viral kinases that convert these prodrugs into their active forms. The later can be enhanced by inducing viral reactivation using histone-deactylase inhibitors such as vorinostat, butyrate, or valproic acid. Cidofovir, another herpesvirus polymerase inhibitor, did not show a clinical benefit [57].

cART therapy has resulted in varying degrees of success with respect to decline in the incidence of non-Hodgkin lymphoma. It is estimated that cART therapy decreases the incidence of non-Hodgkin lymphoma anywhere in the range of 40–76%. Moreover, there is emerging evidence that protease inhibitors such as indinavir or nelfinavir, which also inhibit matrix metalloproteinase may have direct anti-KS activity [36] in addition to HAART-associated reconstitution of the immune system [87]. More information on current trials that are underway to treat KS, PEL and MCD can be gleaned by visiting the National Cancer Institute (NCI) website: http://www-dcs.nci.nih.gov/branches/aidstrials/adlist.html.

3.8 Conclusions

As a consequence of cART, the life expectancy of HIV-infected individuals now equals that of other persons with chronically managed diseases such as diabetis or heart disease. As these HIV-infected patients continue to age, there will be a corresponding increase in the incidence of AIDS-defining, since HIV+ are disproportionally exposed to KSHV, human papilloma virus, and Epstein–Barr Virus,

as well as cancers not associated with infectious causes. Most of the current therapies with the exception of anti-herpesviral drugs do not take advantage of the unique viral etiology of KSHV-associated cancers, and anti-herpesviral drugs themselves are not effective against latent virus. Thus, it will be important to show that "traditional" anticancer therapies are safe in the context of cART and HIV infection, and to develop future therapies that directly impact upon, and obliterate, the function of viral genes.

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