

# Kaposi sarcoma

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**Abstract** | Kaposi sarcoma (KS) gained public attention as an AIDS-defining malignancy; its appearance on the skin was a highly stigmatizing sign of HIV infection during the height of the AIDS epidemic. The widespread introduction of effective antiretrovirals to control HIV by restoring immunocompetence reduced the prevalence of AIDS-related KS, although KS does occur in individuals with well-controlled HIV infection. KS also presents in individuals without HIV infection in older men (classic KS), in sub-Saharan Africa (endemic KS) and in transplant recipients (iatrogenic KS). The aetiologic agent of KS is KS herpesvirus (KSHV; also known as human herpesvirus-8), and viral proteins can induce KS-associated cellular changes that enable the virus to evade the host immune system and allow the infected cell to survive and proliferate despite viral infection. Currently, most cases of KS occur in sub-Saharan Africa, where KSHV infection is prevalent owing to transmission by saliva in childhood compounded by the ongoing AIDS epidemic. Treatment for early AIDS-related KS in previously untreated patients should start with the control of HIV with antiretrovirals, which frequently results in KS regression. In advanced-stage KS, chemotherapy with pegylated liposomal doxorubicin or paclitaxel is the most common treatment, although it is seldom curative. In sub-Saharan Africa, KS continues to have a poor prognosis. Newer treatments for KS based on the mechanisms of its pathogenesis are being explored.

Kaposi sarcoma (KS) was first reported in 1872 by Moritz Kaposi, a physician and dermatologist. He described several cases of a multifocal pigmented sarcoma of the skin in elderly European men, all of who died within 2 years<sup>1</sup>. Four main epidemiological forms of KS are now widely recognized (TABLE 1). The form of KS originally identified by Kaposi became known as classic KS or sporadic KS. Classic KS occurs mostly in elderly men of Mediterranean or Jewish ancestry and, unlike the cases originally described by Kaposi, typically shows an indolent, protracted clinical course and primarily affects skin on the legs. Starting in 1947, several reports documented cases of KS in Africa, including a lymphadenopathic form of KS in children<sup>2–4</sup>; this form of KS is now generally referred to as endemic KS. KS came to the forefront of public attention at the onset of the AIDS epidemic, and the first report of highly aggressive KS affecting young men who have sex with men (MSM)<sup>5</sup>, in 1981, occurred just before the realization that these men were severely immunodeficient and affected by opportunistic infections. This type of KS is now known as AIDS-related KS or epidemic KS. Note that, although KS is more commonly associated with HIV-1 infection than with HIV-2 infection<sup>6</sup>, we refer to HIV in general in this article as it cannot be ruled out that individuals infected with HIV-2 were included in the studies

discussed. KS also occurs in individuals with iatrogenic immunodeficiency, such as that seen in organ transplant recipients; this type of KS is known as iatrogenic KS<sup>7–9</sup>. Finally, of note, many cases of KS have been reported in MSM without HIV infection<sup>10</sup>, and KS in MSM without HIV infection is increasingly being recognized as a possible distinct fifth form of KS<sup>11–13</sup>.

The cause of KS was not known until 1994 when, on the basis of epidemiologic suggestions that this cancer had an infectious origin independent of HIV, a directed search led to the discovery of the KS herpesvirus (KSHV; also known as human herpesvirus-8 (HHV-8))<sup>14</sup>. It is now known that a combination of KSHV infection and impaired host immunity causes KS but, although AIDS-related KS and iatrogenic KS are associated with well-defined immunodeficiency, the impaired immune function in classic KS (thought to relate to ‘immunosenescence’; that is, an ageing immune system) and endemic KS (thought to relate to chronic infection and malnutrition) is not well characterized. In addition to KS, KSHV causes two lymphoproliferative disorders — primary effusion lymphoma (PEL)<sup>15</sup> and multicentric Castlemann disease (MCD)<sup>16</sup> — and an inflammatory syndrome called KSHV inflammatory cytokine syndrome<sup>17</sup> (BOX 1).

In this Primer, we describe the epidemiological and clinical features of the different epidemiological forms

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<https://doi.org/10.1038/s41572-019-0060-9>

Table 1 | Comparison of the epidemiological forms of KS

Form of KS	Clinical presentation	Risk factors	Progression
AIDS-related (also known as epidemic)	Multiple cutaneous lesions on the limbs, trunk and face. Mucosal lesions are common (identified in 20% of patients) and visceral involvement is seen in 15% of patients. Patients can also present with tumour-associated oedema	The risk of KS rises with declining CD4 cell counts and falls with the use of cART	May follow an indolent course but visceral involvement is not uncommon and may be aggressive. It may regress with effective cART
Iatrogenic	Often presents as cutaneous KS lesions but both mucosal and, rarely, visceral disease can occur	Occurs following solid-organ allograft; the risk of occurrence correlates with the level of immunosuppression. Hence, the risk of occurrence is higher in multi-organ transplants and with greater HLA mismatching	Usually localized but may involve organs. It may regress with the reduction in immunosuppression or with modification of the immunosuppressive regimen
Endemic	Children often present with multiple lymph nodes with lymphoedema and a very aggressive natural history of the disease, including visceral dissemination. Adults present with lower-limb lesions that resemble classic KS	Occurs most commonly in sub-Saharan Africa in individuals seronegative for HIV	In children, progression is often aggressive with widespread lymphadenopathy and visceral involvement. In adults, progression is indolent or locally invasive but occasionally has visceral involvement
Classic (also known as sporadic KS)	Typically confined to lower limbs with few lesions. Visceral and mucosal disease is rare and usually occurs in the gastrointestinal tract	Occurs in middle-aged and elderly individuals and is more common in men than in women. Ethnic groups from regions of high KS herpesvirus prevalence (Middle East, eastern Europe and the Mediterranean) are at increased risk	Usually indolent; rarely aggressive and disseminated
MSM without HIV infection	May occur at any skin sites, usually with few lesions. Visceral and mucosal disease is rare	MSM without HIV infection who are young or middle aged and are not immunocompromised	Usually indolent, although disseminated disease has been described

cART, combination antiretroviral therapy; HLA, human leukocyte antigen; KS, Kaposi sarcoma; MSM, men who have sex with men.

of KS and discuss our current understanding of the pathobiology of this disease. Treatment approaches for managing KS and improving quality of life (QOL) will also be considered.

### Epidemiology

KS was a rare disease before the AIDS epidemic in the early 1980s, when the reported incidence of classic KS ranged from 0.01 per 100,000 person-years for the UK<sup>18</sup> and 0.2 per 100,000 person-years for the USA to 1.6 per 100,000 person-years for Sardinia<sup>19</sup>; incidence was 2–3-fold higher in men than in women globally. Reported estimated incidence rates for endemic KS in Africa before the AIDS epidemic were higher for Zaire, Uganda, Tanzania and Cameroon (>6 per 1,000 person-years) than in southern and north Africa (0.5–1.5 per 1,000 person-years)<sup>20</sup>. To date, most studies of KS in Africa (comprising endemic and AIDS-related KS) reported KS as a percentage of all malignancies owing to a scarcity of population-based studies.

Incidence of KS is reported to currently be ~200-fold higher in recipients of solid-organ transplants (that is, in iatrogenic KS) than in the general population<sup>9</sup>. Furthermore, rates of iatrogenic KS in transplant recipients positively correlate with the prevalence of KSHV and rates of classic KS based on the area where the transplant recipient lives, and iatrogenic KS is also associated with the male sex and increased age<sup>21</sup>. Indeed, overall, the geographical variation in the incidence of KS is now known to reflect differences in the prevalence of KSHV<sup>22</sup> (FIG. 1).

Prevalence of KSHV is highest in sub-Saharan Africa, where in some populations the prevalence in adults is >90%. In the Mediterranean, prevalence is 20–30%, and in northern Europe, Asia and the USA, prevalence

is <10%. The reasons for the geographical variation in KSHV prevalence are not understood, but there is some evidence that environmental factors, such as co-infection with malaria and other parasitic infections, may increase shedding of KSHV in saliva, thereby increasing transmission rates<sup>23</sup>. Although these co-infections were reported to increase seropositivity for KSHV<sup>23</sup>, their effect on saliva shedding has not been convincingly demonstrated. It is also possible that saliva sharing is more common in highly endemic areas, where infection is acquired in childhood through practices such as the pre-mastication of food for infants, candy sharing among children and the sharing of toothbrushes<sup>24</sup>.

In the early 1980s, one of the first signs of the emerging AIDS epidemic was the frequent occurrence of KS in MSM<sup>5,25</sup>. In the USA, KS was reported to be 20,000 times more frequent in patients with AIDS than in the general population and to be 300 times more frequent in patients with AIDS than in other immune-suppressed patient groups<sup>26</sup>. Similar patterns of KS risk were reported in Europe and Australia<sup>27,28</sup>. Subsequent studies in the USA and Europe showed that the prevalence of KSHV in MSM is higher than the prevalence of KSHV in other HIV-infected risk groups<sup>29</sup>. In sub-Saharan Africa, the incidence of KS has increased around 20-fold since the onset of the AIDS epidemic in the early 1980s, making KS the most common cancer in men, and the second most common cancer in women, in countries such as Uganda, Malawi, Zimbabwe and Swaziland<sup>30,31</sup>.

The introduction of combination antiretroviral therapy (cART) in 1996 dramatically decreased the incidence of AIDS-related KS<sup>32</sup>. Indeed, an international study reporting cancer incidence data from 23 prospective studies from the USA, Europe and Australia revealed that

the overall incidence of KS in these countries decreased from 15.2 per 1,000 person-years in 1992 to 4.9 per 1,000 person-years between 1997 and 1999 (REF.<sup>33</sup>); this decrease was driven by a reduction in the number of cases of AIDS-related KS. The effect of cART on the incidence of AIDS-related KS in sub-Saharan Africa is difficult to quantify because fewer data are available<sup>34,35</sup>.

A 2017 study, based on over 200,000 patients, reported raw KS incidence per 100,000 person-years in 42 cohorts from 57 countries, including North America (237 per 100,000 person-years), Latin America (244 per 100,000 person-years), Europe (180 per 100,000 person-years), Asia-Pacific (52 per 100,000 person-years) and South Africa (280 per 100,000 person-years)<sup>36</sup>. KS risk was approximately two times higher in heterosexual men than in women and six times higher in MSM than in women<sup>36</sup>.

Despite a decrease in the incidence of AIDS-related KS globally since the introduction of cART, KS continues to occur in patients infected with HIV<sup>37,38</sup>.

### Box 1 | Diseases caused by KSHV

Kaposi sarcoma (KS) is an endothelial cell cancer with an inflammatory component and highly heterogenous histopathology and clinical behaviour. It is the most common disease caused by KS herpesvirus (KSHV).

Primary effusion lymphoma (PEL) is a B cell lymphoma that most commonly affects body cavities, including the peritoneal, pleural and pericardial cavities<sup>245</sup>. PEL can also present as solid lesions that form outside of body cavities<sup>246</sup>. In addition to being infected with KSHV, PEL tumour cells are frequently co-infected with Epstein-Barr virus (EBV). Despite being of B cell origin, the tumour cells frequently do not express immunoglobulin and other B cell antigens, but they express plasma cell antigens. The optimal clinical management of KSHV-associated PEL that occurs both within and outside of cavities remains uncertain. However, most clinicians would treat patients with HIV infection with combination antiretroviral therapy (cART) and combination anthracycline-based chemotherapy and patients without HIV infection with chemotherapy alone<sup>245</sup>. The most widely used chemotherapy regimen for PEL is probably EPOCH (that is, a combination of cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone); however, 1-year overall survival is only ~40%<sup>247</sup>, and some clinicians advocate combinations that include the proteasome inhibitor bortezomib<sup>248</sup>.

Multicentric Castlemann disease (MCD) is a lymphoproliferative disorder presenting with generalized lymphadenopathy (that is, lymph nodes that are abnormal in size, number or consistency) and systemic symptoms. These symptoms are thought to be caused by the excessive production of inflammatory cytokines, such as IL-6 (REF.<sup>249</sup>). Most cases of MCD occur in patients with KSHV and HIV infection; less than half of MCD cases are observed in individuals with KSHV infection who do not have HIV infection. There are specific pathologic features in the lymph nodes, and KSHV-infected cells can be identified that have plasmablastic morphology and express immunoglobulin- $\lambda$  light chains<sup>250,251</sup>. Patients with HIV infection diagnosed with KSHV-associated MCD should be treated with cART and immune-chemotherapy using a stratified approach that is based on disease severity. Treatment with rituximab, a monoclonal antibody, is the gold standard of care, but chemotherapy (using etoposide or liposomal anthracycline) should be added if life-threatening organ failure is present<sup>247</sup>.

KSHV-positive diffuse large B cell lymphoma, not otherwise specified, was previously called large B cell lymphoma arising in KSHV-associated MCD; it is a lymphoma subtype, composed of cells resembling plasmablasts, that is sometimes, but not always, seen in conjunction with clinical and histological features of MCD<sup>252</sup>. These lymphomas differ from PEL in that they lack EBV and are thought to arise from naive immunoglobulin M- $\lambda$ -positive B cells rather than terminally differentiated B cells.

KSHV inflammatory cytokine syndrome is a systemic disease, and patients with this disease show symptoms of systemic inflammation and cytokine release without any evidence of generalized lymphadenopathy or histological features of MCD in lymph node biopsies. These patients frequently have other KSHV-associated tumours, such as KS or PEL, and have a poor outcome, with a median survival of 13 months<sup>253</sup>. It is unclear how best to treat this disease.

Changes in the incidence and prevalence of KSHV in the HIV and cART era<sup>37,39</sup> may result in changes in the incidence patterns of all forms of KS, but thus far few studies have addressed this. There is some evidence that risk groups of individuals presenting with classic KS may be changing, as documented by a retrospective cohort study of classic KS in Paris between 2006 and 2015 that reported that <40% of patients were of Mediterranean origin and 28% were MSM<sup>13</sup>.

### Mechanisms/pathophysiology

KS is causally associated with KSHV infection, and progress has been made in our understanding of the role of this virus in KS pathogenesis. The virus was first identified in KS lesions using representational difference analysis, a method that combines subtractive hybridization with DNA amplification<sup>14</sup>.

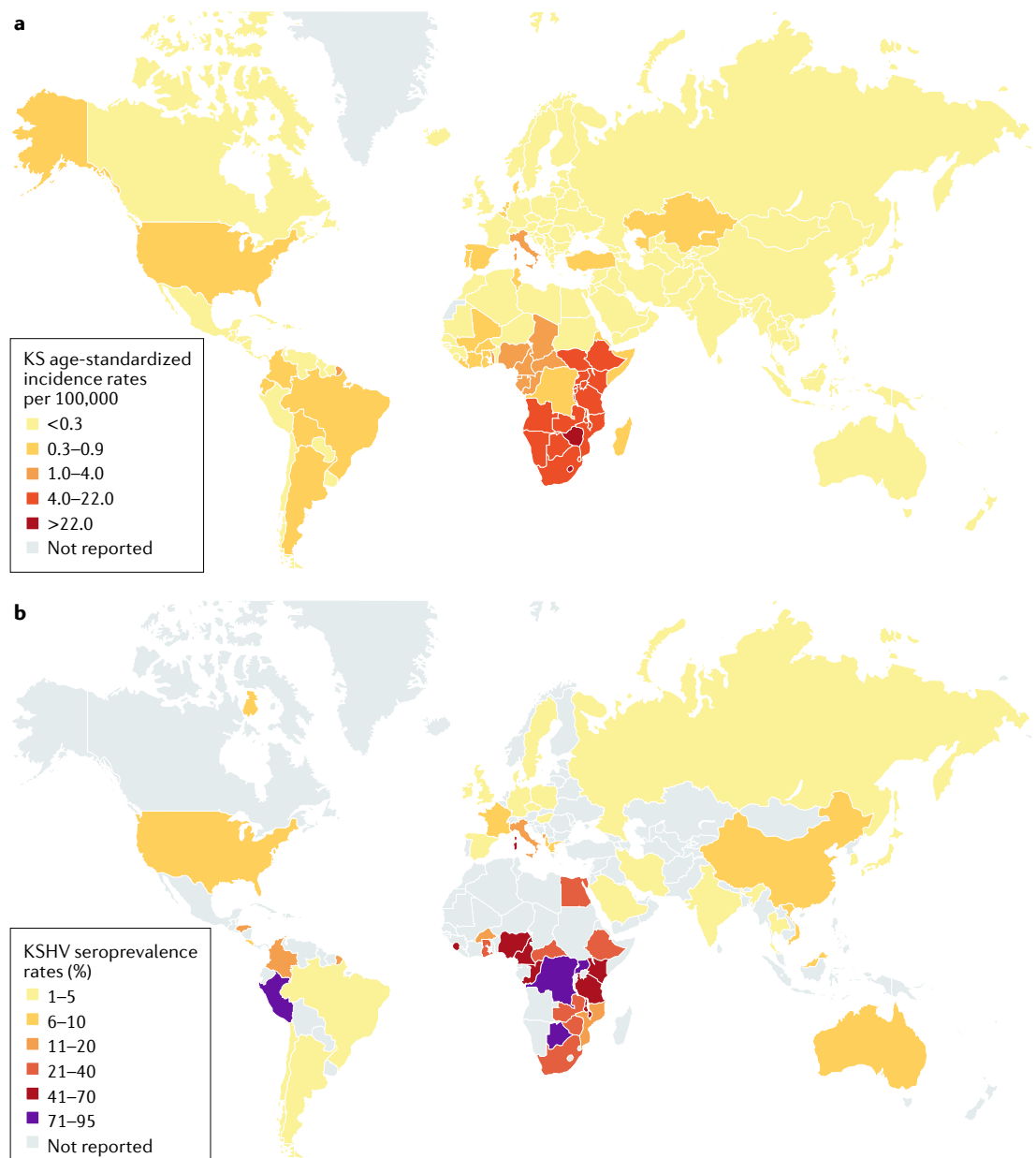
### The viral life cycle

KSHV can infect several different cell types, including endothelial cells, B cells, epithelial cells, dendritic cells, monocytes and fibroblasts<sup>40</sup>. To gain entry into endothelial cells, KSHV is thought to bind to several host cell surface receptors such as integrins (including  $\alpha 3 \beta 1$ ,  $\alpha V \beta 5$  and  $\alpha V \beta 3$ ), the cystine-glutamate transporter xCT, heparan sulfate and the tyrosine protein kinase receptor EPHA2. This binding induces a signal transduction cascade, which results in cellular changes that allow the virus to enter the cell and traffic within the cytoplasm<sup>41-43</sup>. As KS tumours express endothelial cell markers, endothelial cells are thought to be the KSHV-infected cell type in KS tumours. The KSHV-associated lymphoproliferative disorders PEL and MCD involve B cell infection by KSHV (BOX 1). KSHV is a linear double-stranded DNA virus with an icosahedral capsid, a tegument (the space between the envelope and nucleocapsid which contains proteins and RNAs) and an envelope<sup>42</sup> (FIG. 2). Glycoproteins in the viral envelope interact with cell-type-specific cellular entry receptors<sup>43</sup>. Viral entry results in the delivery of the virion capsid into the cytoplasm, followed by its uncoating and the delivery of the KSHV genome into the nucleus. In the nucleus, the genome circularizes, remaining as an episome. The virus then enters latency (its default pathway) or undergoes sporadic bouts of lytic reactivation during the lifecycle of the virus<sup>40</sup>.

**Latency.** Similar to other herpesviruses, infection with KSHV is lifelong because the virus can establish latency in human B cells and endothelial cells. During the latent state in cell culture studies, the virus expresses the latency locus, which includes *ORF71* (also called *ORFK13*; encoding viral FLICE inhibitory protein (vFLIP)), *ORF72* (encoding vCyclin), *ORF73* (encoding latency-associated nuclear protein (LANA)), *ORFK12* (encoding the kaposins, which are signalling proteins) and several microRNAs (miRNAs)<sup>44,45</sup>. Some additional genes, such as *K15* and *K1* (which encode transmembrane proteins), as well as viral IL-6 (*vIL6*), are also expressed at low levels<sup>46-48</sup>. The latent genes are expressed in most KSHV-infected tumour cells and are thought to promote tumorigenesis.

The latent KSHV genome forms an episome, which is tethered by the KSHV LANA to the host chromosome so that the viral genome is replicated with the host genome during normal cell division<sup>49</sup>. The protein products of other latent genes support the survival of the infected cell. For example, vFLIP activates I- $\kappa$ B kinase 1 (IKK1) to stimulate the nuclear factor- $\kappa$ B (NF- $\kappa$ B)

pathway to increase cell survival<sup>50–53</sup>. The viral miRNAs that are encoded during KSHV latency<sup>45,54,55</sup> help keep the infected cell alive, by inhibiting apoptosis, and the virus latent<sup>56</sup>; these viral miRNAs are expressed in KS, PEL and MCD<sup>57–59</sup>. Furthermore, similar to kaposin, KSHV mir-K12-10a possesses in vitro transforming abilities in NIH 3T3 cells and is contained within the



**Fig. 1 | Geographical prevalence of KS and seroprevalence of KSHV. a** | The age-standardized incidence rate of Kaposi sarcoma (KS) per 100,000 males is depicted, and rates (apart from for the USA) were obtained from the International Agency for Research on Cancer (IARC) *Cancer Incidence in Five Continents Volume X1* and ‘Cancer Today’ *Global Cancer Observatory* resources<sup>255,256</sup>. The rate provided for the USA is an average for 2000–2015 (0.7 affected individuals per 100,000 males) and rates are from *Surveillance, Epidemiology, and End Results (SEER)*. However, rates in some regions based on the population reported are higher than others, ranging from 1.7 affected individuals per 100,000 males (for Atlanta) to 0.1 affected individuals per 100,000 males (for Iowa and Utah). Overall rates in the USA show racial disparities: among non-Hispanic white individuals, white Hispanics and black individuals, the incidence rate is 0.4, 0.7 and 1 affected individual per 100,000 males, respectively. **b** | Seroprevalence rates were compiled from multiple studies<sup>6,39,180,257–294</sup>. The seroprevalence of KS herpesvirus (KSHV) infection in northern Europe, Asia and the USA is <10%, but in most of sub-Saharan Africa, overall seroprevalence is >40%. The Mediterranean region (that is, Italy, Sicily and Sardinia) has intermediate seroprevalence rates of 10–30%. Figure adapted from REF.<sup>22</sup>, Springer Nature Limited.



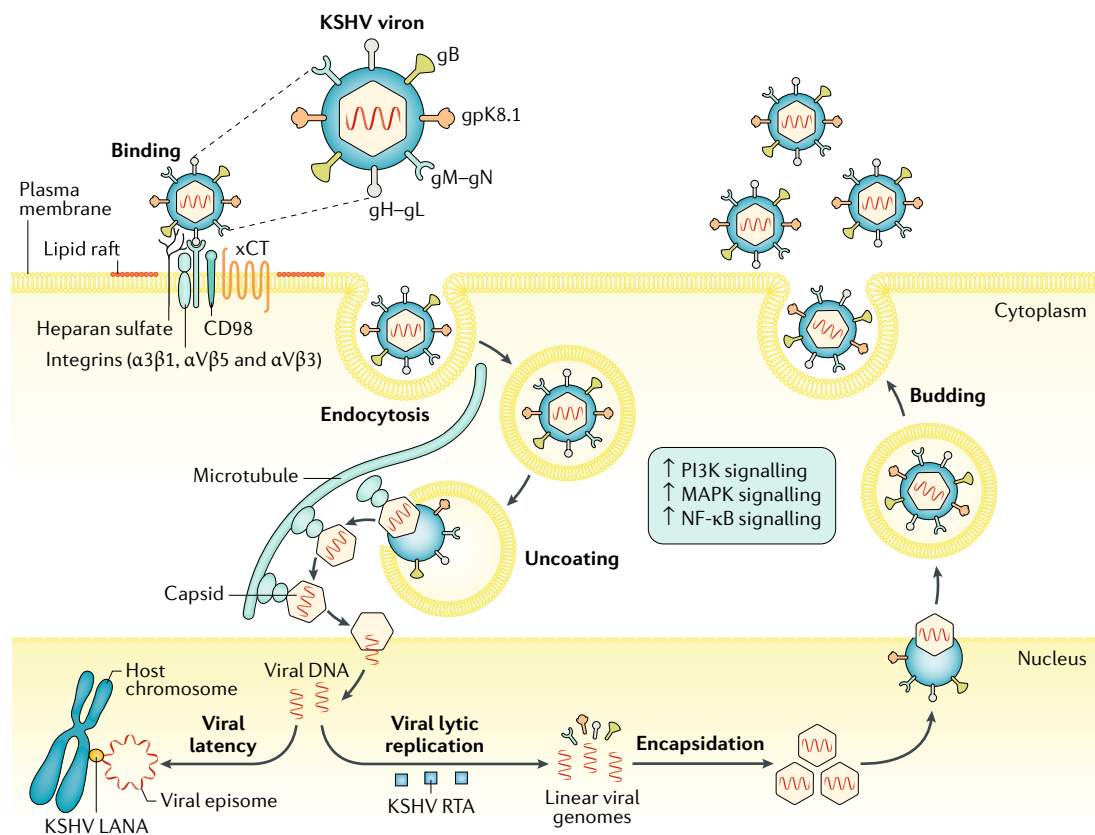


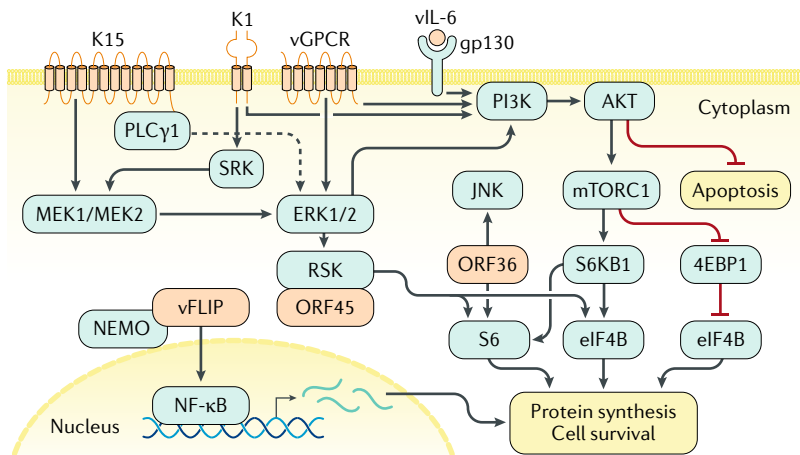
Fig. 2 | **The viral life cycle of KSHV.** The Kaposi sarcoma herpesvirus (KSHV) virion binds to receptors present on the cell surface (such as integrins, the cystine–glutamate transporter (xCT), CD98 and heparan sulfate) via glycoproteins (such as gpK8.1, gB, gM–gN and gH–gL) on its envelope; this binding, in most cases, results in the endocytosis of the virion into the cell<sup>42</sup>. The virion uncoats itself in the cell cytoplasm, and the capsid containing the viral genome traverses to the nucleus. The viral genome enters the nucleus, where it can remain latent as a circular episome tethered to host chromosomes via its latency-associated nuclear protein (LANA), or it can enter the lytic cycle where the viral genomes are replicated and new virions are produced through a complex mechanism of envelopment and ultimately released from the cell via budding. Note that KSHV proteins can increase host signalling through the phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and nuclear factor- $\kappa$ B (NF- $\kappa$ B) signalling pathways. RTA, replication and transcription activator.

open reading frame of kaposin<sup>60</sup>. Several KSHV miRNAs also promote endothelial cell reprogramming<sup>61</sup>, and KSHV miR-K12-3 induces the migration and invasion of endothelial cells by activating protein kinase B (AKT)<sup>62</sup>. Finally, KSHV miRK9\* targets the transcript of the major lytic switch protein (replication and transcription activator (RTA; also known as ORF50)) to prevent reactivation from latency<sup>63</sup>.

Of note, the expression of several of the KSHV latent genes and miRNAs in B cells predisposed mice to lymphomas and hyperplasia<sup>64–67</sup>, and the protein product of at least one of these latent genes, vFLIP, promotes vascular proliferation and an inflammatory phenotype when expressed in endothelial cells<sup>68</sup>. There have been attempts to target some of these latent viral proteins to inhibit their function, as exemplified by the inhibition of vFLIP with inhibitory peptides<sup>69,70</sup>, but these have been in experimental models in cell culture that have not reached clinical feasibility. Inhibitors of vFLIP have also been sought in cell-based drug screening assays using NF- $\kappa$ B reporter PEL cell lines. However, these assays identified a small molecule that selectively treats PEL

independently of vFLIP inhibition and does not target vFLIP in KS<sup>71</sup>. A number of studies have been aimed at targeting cellular genes that are activated by viral proteins to kill KSHV-infected cells, which is a practical approach as drugs that are already in clinical use for other diseases can be screened. An example is the use of rapamycin (also known as sirolimus), because the mechanistic target of rapamycin (mTOR) pathway is activated in latently infected tumour cells in both PEL and KS<sup>72–74</sup>. Another example is the use of HSP90 inhibitors, given that HSP90 chaperones vFLIP and LANA as well as members of the NF- $\kappa$ B, AKT and apoptosis pathways<sup>75,76</sup>.

**The lytic cycle.** The physiological stimuli that allow spontaneous reactivation of KSHV from latency are not well defined. However, it is clear that KSHV undergoes spontaneous lytic reactivation sporadically throughout the lifetime of the host. The lytic phase, during which viral genes are expressed in a temporal order, allows the replication of the viral genome and the production of infectious viral progeny. Immediate-early (IE) genes are



**Fig. 3 | Modulation of host signalling pathways by KSHV-encoded proteins.** A graphic representation illustrates how Kaposi sarcoma herpesvirus (KSHV) representative viral proteins (in orange) modulate host cellular signalling proteins (in blue) to promote cellular survival and the inhibition of apoptosis. Viral proteins including KSHV K15, K1, viral G protein-coupled receptor (vGPCR) and viral IL-6 (vIL-6) can activate the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mechanistic target of rapamycin (mTOR) pathway, thereby increasing cell survival and promoting protein synthesis. KSHV ORF36 acts further downstream and directly phosphorylates cellular ribosomal protein S6, which in turn leads to increased global protein synthesis. KSHV ORF36 also phosphorylates Jun N-terminal kinase (JNK). Some of the KSHV viral proteins, such as vGPCR, K1 and K15, also activate the extracellular-signal-regulated kinase 1 (ERK1)–ERK2 pathway to promote protein synthesis through the activation of ribosomal S6 kinase (RSK; which in turn phosphorylates S6), and KSHV ORF45 directly binds to RSK, leading to its activation. Note that there is a certain degree of crosstalk between both the PI3K–AKT–mTOR and ERK1–ERK2 pathways. Finally, KSHV viral FLICE inhibitory protein (vFLIP) potentially activates nuclear factor- $\kappa$ B (NF- $\kappa$ B) signalling by directly binding NF- $\kappa$ B essential modulator (NEMO). This signalling leads to degradation of the inhibitor of NF- $\kappa$ B, I $\kappa$ B $\alpha$ , and translocation of the NF- $\kappa$ B transcription factors into the nucleus. Dashed lines indicate indirect activation. 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; eIF4B, eukaryotic translation initiation factor 4B; gp130, membrane glycoprotein 130; MEK, MAPK/ERK kinase; mTORC1, mechanistic TOR complex 1; PLC $\gamma$ 1, phospholipase C,  $\gamma$ 1; SRK, Syk-related tyrosine kinase; S6KB1, ribosomal protein S6 kinase.

expressed first. The protein products of most IE genes control transcription and the key lytic protein — RTA — is encoded by an IE gene. RTA is a viral transcription factor that activates many viral and cellular promoters<sup>42</sup> and ensures the expression of viral genes required for viral replication. Delayed-early (DE) genes and late genes are expressed after IE genes<sup>42</sup>. Many of the DE genes encode proteins that control viral DNA replication, which takes place after the DE phase, occurs through a rolling circle mechanism and produces linear genomes that are packaged into capsids<sup>42</sup>. The late lytic phase results in the expression of all of the viral structural proteins and in the production of the infectious virus.

Similar to the protein products of latency genes, the protein products of lytic genes can contribute to tumorigenesis. However, in contrast to latent genes that are expressed in all tumour cells, lytic genes and the encoded viral proteins are produced only by a very low proportion of tumour cells<sup>42</sup>. Some lytic proteins may act in a paracrine fashion to stimulate tumour growth. For example, KSHV vIL-6 protein has been detected in the sera of patients with KS, PEL and MCD<sup>77</sup>, and the KSHV G protein-coupled receptor (vGPCR; a chemokine transmembrane receptor homologue) can constitutively

(that is, in the absence of a ligand) induce cellular signalling in cell culture and mouse models, leading to the expression of pro-inflammatory and angiogenic factors, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)<sup>78–80</sup>. Notably, vGPCR can induce vascular lesions in mice, even when expressed in small numbers of cells<sup>81–83</sup>, which is consistent with a model of paracrine oncogenesis<sup>84</sup>. However, expression of this protein has never been documented in human KS, although the K1 protein is thought to be expressed in a subset of KS tumours<sup>85</sup>.

The expression of KSHV lytic genes has been clinically targeted in both KS and MCD. In MCD, lytic viral replication can be prevented with zidovudine and valganciclovir. These inhibitors are prodrugs that are phosphorylated by the viral kinases ORF21 and ORF36 to produce their active forms<sup>86</sup>. Treatment with a combination of zidovudine and valganciclovir has yielded a clinical response of >80% in MCD, in which lytic viral replication appears to be consequential<sup>86</sup>. However, evidence that this approach is effective in patients with KS is limited. In patients with AIDS given ganciclovir to treat cytomegalovirus retinitis, the subsequent chance of developing KS was decreased by 75% compared with patients with cytomegalovirus retinitis not treated with ganciclovir<sup>87</sup>. However, another study showed that valganciclovir did not induce the regression of classic KS, highlighting that inhibiting the lytic replication of KS has not universally been useful in the treatment of KS<sup>88</sup>.

### Modulating host signalling pathways

As alluded to above, to survive and persist in its host, KSHV has evolved to modulate many host cell signalling pathways, including the phosphoinositide 3-kinase (PI3K)–AKT–mTOR pathway, the mitogen-activated protein kinase (MAPK) pathway and the NF- $\kappa$ B pathway<sup>42</sup>. These pathways are activated by multiple KSHV viral proteins (see below), which suggests that they are critically important for the virus. Furthermore, all of these pathways promote cell survival and cell proliferation and are upregulated in many different cancers. In short, the virus has chosen to target pathways that presumably allow for the survival of virus-infected cells.

The PI3K–AKT–mTOR pathway is activated in patients with KS or PEL<sup>72,73</sup> by viral proteins including KSHV vIL-6, vGPCR, K1, K15, ORF45 and ORF36 (REFS<sup>89–91</sup>) (FIG. 3). KSHV K1 and vGPCR can immortalize and transform endothelial cells and fibroblasts, respectively<sup>79,85,92</sup>. Furthermore, KSHV K1 can activate Syk-related tyrosine kinase (SRK) and PI3K–AKT signalling<sup>85,93,94</sup> to increase the survival of KSHV-infected cells<sup>95</sup>, and vGPCR can activate PI3K–AKT signalling<sup>96,97</sup> to induce KS-like lesions in a number of mouse models<sup>81–83</sup>. KSHV K15 activates the MAPK/ERK kinase 1 (MEK1)/MEK2–extracellular-signal-regulated kinase 1 (ERK1)/ERK2 pathway in a TNF receptor-associated factor 2 (TRAF2)-dependent manner<sup>98</sup>, and it can interact and activate phospholipase C,  $\gamma$ 1 (PLC $\gamma$ 1) to induce angiogenesis<sup>99</sup>. KSHV vGPCR can also activate MEK1/MEK2–ERK1/ERK2 signalling<sup>100</sup>.

KSHV vIL-6 is a viral homologue of human IL-6. Human IL-6 (hIL-6) must bind both membrane

glycoprotein 130 (gp130) (one subunit of the type I cytokine receptor) and IL-6 $\alpha$  chain to activate B cell signalling pathways whereas vIL-6 can activate these pathways by binding gp130 alone<sup>101</sup>. KSHV vIL-6 also activates the JAK–STAT, MAPK–ERK, and PI3K–AKT pathways upon binding to gp130 (REF.<sup>102</sup>). Interestingly, transgenic mice expressing vIL-6 develop an MCD-like disease<sup>103</sup>.

KSHV ORF36 encodes a serine/threonine viral protein kinase (vPK) that is expressed under conditions of hypoxia to activate Jun N-terminal kinase (JNK), a stress kinase that belongs to the MAPK family<sup>90,91,104</sup>. vPK appears to resemble cellular ribosomal protein S6 kinase (S6KB1; a kinase downstream of AKT–mTOR complex 1 (mTORC1) signalling) and to phosphorylate ribosomal protein S6 *in vitro* to increase protein synthesis and augment anchorage-independent growth, angiogenesis and cell proliferation<sup>91</sup>. In addition, KSHV vPK transgenic mice develop lymphomas<sup>105</sup>. Another protein, KSHV ORF45, binds to cellular ribosomal S6 kinase 1 (RSK1) and RSK2, stabilizing its interaction with ERK and preventing its dephosphorylation, which is important for lytic replication<sup>90</sup>.

As mentioned above, KSHV vFLIP is a potent activator of the pro-survival NF- $\kappa$ B pathway<sup>52,106,107</sup>; it activates NF- $\kappa$ B by interacting directly with NF- $\kappa$ B essential modulator (NEMO; also known as IKK $\gamma$ )<sup>51,53</sup>. Indeed, small interfering RNA (siRNA)-mediated depletion of vFLIP in PEL induces apoptosis, suggesting that vFLIP enhances cell survival<sup>52,108</sup>. Mice expressing vFLIP in the B cell compartment displayed MCD-like abnormalities<sup>67</sup>, whereas those expressing vFLIP in the endothelial compartment had a pro-inflammatory phenotype and some vascular abnormalities<sup>68</sup>.

Thus, KSHV encodes a multitude of proteins that modulate host cell signalling pathways to allow cell survival and cell proliferation and to augment viral replication. Although a number of these viral proteins are expressed, or highly induced, only during lytic replication, their expression leads to the production of secreted cytokines and growth factors that can influence neighbouring cells to induce angiogenesis and inflammation, thereby contributing to KS pathogenesis<sup>84</sup>.

#### **KSHV and the immune system**

Similar to other herpesviruses, KSHV establishes a delicate balance between activating and suppressing the immune response to establish a latent infection that lasts for the entire life of the infected host. Humoral and cellular immune responses to KSHV are evident, as reflected by the much higher incidence of KSHV infection in patients with immunodeficiencies than in individuals with an uncompromised immune system. Humoral responses were described soon after KSHV was discovered as the causative agent of KS and PEL. Specifically, PEL cell lines were positive for immunofluorescence when stained using patient sera; this nuclear staining was later shown to be LANA. Furthermore, when cells were induced to undergo lytic replication, patient sera strongly stained the cytoplasm of PEL cell lines consistent with it recognizing lytic antigens<sup>109</sup>. Subsequently, a large number of seroepidemiologic studies using

enzyme-linked immunosorbent assay (ELISA) relied on the presence of antibodies to a number of recombinant viral proteins<sup>29</sup>. Among the latent KSHV proteins, LANA seems to be most immunogenic, and among the lytic proteins, K8.1 has been used in most serologic assays. Systemic analysis of antibodies to all KSHV proteins showed that ORF38, ORF61, ORF59 and K5 elicited detectable responses in individuals with KSHV-associated diseases<sup>110</sup>. However, antibodies to KSHV are rarely neutralizing<sup>111</sup>.

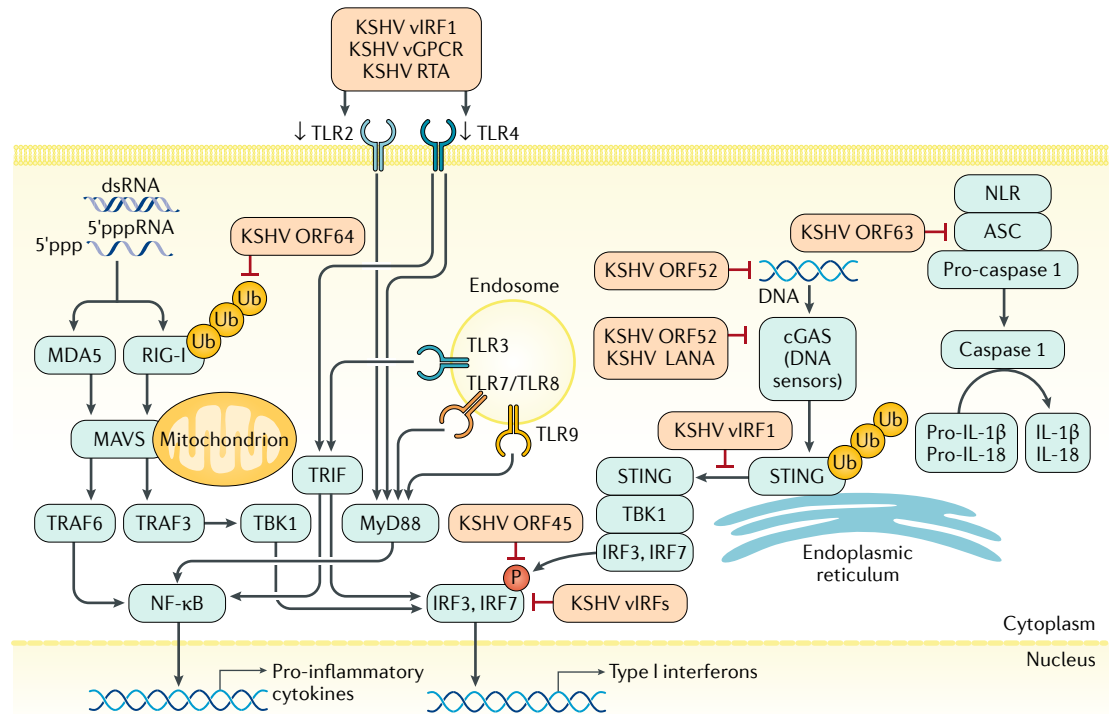
To assess cellular responses to KSHV, a systematic approach was recently used in which the whole KSHV proteome was examined by IFN $\gamma$  enzyme-linked immunospot (an immunoassay that measures the frequency of cytokine-secreting cells at the single-cell level)<sup>32</sup>. This study found variable responses of both CD4 and CD8 cells to a wide variety of viral antigens, indicating a lack of shared immunodominance among individuals.

In this subsection, we review the cell-intrinsic mechanisms used by KSHV to induce an immune response while, at least temporarily, simultaneously avoiding immune recognition to establish lifelong infection.

**Triggering an antiviral immune response.** Following viral entry or reactivation, the host mounts an immune response to KSHV via innate immune receptors such as Toll-like receptors (TLRs), retinoic acid-inducible gene I protein (RIG-I)-like receptors (RLRs), nucleotide-binding and leucine rich repeat or Nod-like receptors (NLRs), AIM2-like receptors (ALRs) and cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes protein (STING)<sup>112</sup>. TLRs are the first line of defence against many viruses; accordingly, KSHV activates TLR3 (REF.<sup>113</sup>), TLR4 (REF.<sup>114</sup>) and TLR9 (REF.<sup>115</sup>) in a cell-type-dependent manner, as well as the NLR proteins NOD-, LRR- and pyrin domain-containing 1 (NLRP1) and NLRP3, upon primary infection<sup>116</sup>. Moreover, the AIM2 family member IFI16 induces activation of the inflammasome upon KSHV infection<sup>117</sup>, and KSHV activates the cGAS–STING pathway during primary infection and reactivation<sup>118</sup>. Activation of TLRs and RLRs generally leads to the induction of type I interferon, which is considered antiviral. Furthermore, the activation of NLR-dependent inflammasomes leads to the production of pro-inflammatory cytokines such as IL-1 $\beta$  and IL-18. However, despite activating multiple innate immune receptors, KSHV persists for a lifetime in the infected host by encoding both lytic and latent proteins that inhibit host innate and adaptive immunity (FIG. 4).

**Evading the immune response.** KSHV K3 and K5 are lytic genes that encode modulator of immune recognition 1 (MIR1) and MIR2, respectively, both of which inhibit major histocompatibility complex (MHC) class I antigen presentation to prevent the immune system from detecting KSHV-infected cells<sup>119</sup>. MIR1 downregulates all four of the human leukocyte antigen (HLA) gene alleles or allotypes (*HLA-A*, *HLA-B*, *HLA-C* and *HLA-E*) and MIR2 downregulates *HLA-A* and *HLA-B*<sup>120</sup>.

KSHV homologues of interferon regulatory factors (IRFs), viral IRFs (vIRFs), are lytic proteins that inhibit type I interferons. The KSHV genome encodes four



**Fig. 4 | Modulation of innate host immunity by KSHV.** Kaposi sarcoma herpesvirus (KSHV) encodes an arsenal of viral proteins that modulate multiple innate immune pathways. KSHV viral interferon regulatory factor 1 (vIRF1), viral G protein-coupled receptor (vGPCR) and replication and transcription activator (RTA) can downregulate Toll-like receptor 2 (TLR2) and TLR4, and TRIF (also known as TIR domain-containing adaptor molecule 1 (TICAM1)), a TLR adaptor protein, is further inhibited by KSHV RTA. Inhibition of these TLR signalling pathways results in the downregulation of the type I interferon response. Ubiquitylation of the RNA sensor, retinoic acid-inducible protein (RIG-I), which is crucial for its activation, is inhibited by KSHV ORF64, resulting in the dampening of RIG-I activity and inhibition of the interferon response. KSHV vIRFs and ORF45 can inhibit activation of cellular IRFs such as IRF3 and IRF7. Cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes protein (STING) is a cytosolic DNA sensing pathway, and cGAS activation is inhibited by KSHV ORF52 and KSHV latency-associated nuclear protein (LANA), whereas KSHV vIRF1 prevents STING association with the serine/threonine-protein kinase TBK1, thereby inhibiting interferon production through the pathway mediated by IRF3 and IRF7. The NOD-, LRR- and pyrin domain-containing 1 (NLRP1) inflammasome, which comprises NLRP1, apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1, is inhibited by KSHV ORF63, resulting in inhibition of IL-1 $\beta$  and IL-18 activation. 5'ppp, 5'-triphosphate; dsRNA, double-stranded RNA; MAVS, mitochondrial antiviral-signalling protein; MDA5, melanoma differentiation-associated protein 5; MyD88, myeloid differentiation primary response protein MyD88; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NLR, Nod-like receptor; TRAF3, TNF receptor-associated factor 3; Ub, ubiquitin.

vIRFs: vIRF1, vIRF2, vIRF3 and vIRF4 (REF.<sup>121</sup>). At the transcriptional level, vIRF1 binds cellular IRF1 and IRF3 to prevent them from transactivating the promoters of interferon genes<sup>122</sup> and binds STING to inhibit cGAS–STING signalling and IFN $\beta$  induction<sup>123</sup>. KSHV ORF52 and LANA also inhibit the cGAS–STING pathway, but by targeting cGAS instead of STING<sup>124,125</sup>. vIRF2 impairs the induction of interferon gene expression by binding IRF1 and IRF3 to inhibit cellular IRF1-mediated and IRF3-mediated transcription<sup>126</sup>. Finally, vIRF3 binds IRF3 and IRF7 and prevents them from transactivating the promoters of IFN $\alpha$ 4 and IFN $\alpha$ 6 (REF.<sup>127</sup>). vIRF3 also dampens IFN $\gamma$ -mediated activation of the GAS promoter<sup>128</sup>. KSHV vIRF1 and vGPCR downregulate expression of TLR4 (REF.<sup>114</sup>), and RTA was reported to inhibit TLR2-dependent NF- $\kappa$ B activation<sup>129</sup>; RTA can also induce the ubiquitylation and degradation of IRF7 (REF.<sup>130</sup>). KSHV vIRF1 and vIRF2 expression reduced the level of IFN $\beta$ , both at the mRNA and protein level, following TLR3 activation<sup>121</sup>. KSHV ORF45 impairs IRF7

phosphorylation<sup>131</sup> and KSHV vIL-6 can be directly activated by IFN $\alpha$  to block interferon induction<sup>132</sup>.

In terms of RLRs and NLRs, KSHV ORF64 is a viral deubiquitinase that can deubiquitinate RIG-I to prevent RIG-I-mediated interferon induction<sup>133</sup>, and the KSHV tegument protein ORF63 inhibits the NLR inflammasomes, NLRP1 and NLRP3 (REF.<sup>116</sup>).

KSHV also encodes three CC-chemokine ligands (CCLs; formerly known as vMIPs): vCCL-1 (encoded by *ORFK6*), vCCL2 (encoded by *ORFK4*) and vCCL3 (encoded by *ORFK4.1*)<sup>134</sup>, which can negatively regulate inflammation. vCCL2 interacts with host CC-chemokine receptors (CCRs), including CCR1, CCR2, CCR5, CXC-chemokine receptor 1 (CXCR1), CXCR2 and CXCR4, to inhibit signalling from them. For example, vCCL2 prevents host CCL5 (also known as RANTES) and host CCL3 (also known as MIP1 $\alpha$ ) from binding to CCR5 (REFS<sup>135,136</sup>). vCCL2 also inhibits CD8 T cell migration and hinders cytotoxic T lymphocyte-mediated rejection of corneal and cardiac allografts



in an experimental model<sup>137</sup>. vCCL1 and vCCL2 also promote endothelial cell survival and virus replication<sup>138</sup>, which could play a role in KS pathogenesis.

Finally, the KSHV K14 gene encodes for a viral OX2 (vOX2), an immunoglobulin superfamily member with homology to the cellular OX2 membrane glycoprotein (OX2; also known as CD200) that binds to the receptor CD200R<sup>139</sup>. Both stimulatory and tolerogenic roles for cellular OX2 in presentation of the antigen have been proposed<sup>140,141</sup>. KSHV vOX2 fused to a crystallizable fragment (Fc) antibody domain suppressed neutrophil activation, decreased CCL2 (also known as MCP1) and IL-8 production and inhibited oxidative burst in neutrophils stimulated to undergo phagocytosis<sup>142</sup>. However, purified glycosylated vOX2 protein stimulated primary monocytes, macrophages and dendritic cells to express inflammatory cytokines including IL-1 $\beta$ , IL-6, monocyte chemoattractant protein 1 and TNF<sup>143</sup>. This induction of inflammatory cytokines may contribute to the inflammatory infiltrates seen in KS if vOX2 is expressed in cells in the lesions that are undergoing lytic replication.

## Diagnosis, screening and prevention

### Clinical manifestations

The clinical manifestations of the epidemiological forms of KS overlap, although certain characteristics are more commonly associated with one form of KS than with others. In all forms of KS, cutaneous lesions usually present as multiple, pigmented, raised or flat, painless lesions that do not blanch (that is, they do not lose colour with pressure) (FIG. 5). The earliest cutaneous lesions are often asymptomatic, innocuous-looking, pigmented macules or small papules that vary in colour from pale pink to vivid purple. Although KS is often diagnosed on the basis of the characteristic appearance of lesions

alone, the diagnosis should be confirmed histologically because even experienced clinicians can misdiagnose KS<sup>144</sup>. Larger plaques on the trunk often follow the skin creases as oblong lesions. Occasionally, lesions form exophytic, ulcerated and bleeding nodules that can be associated with painful oedema.

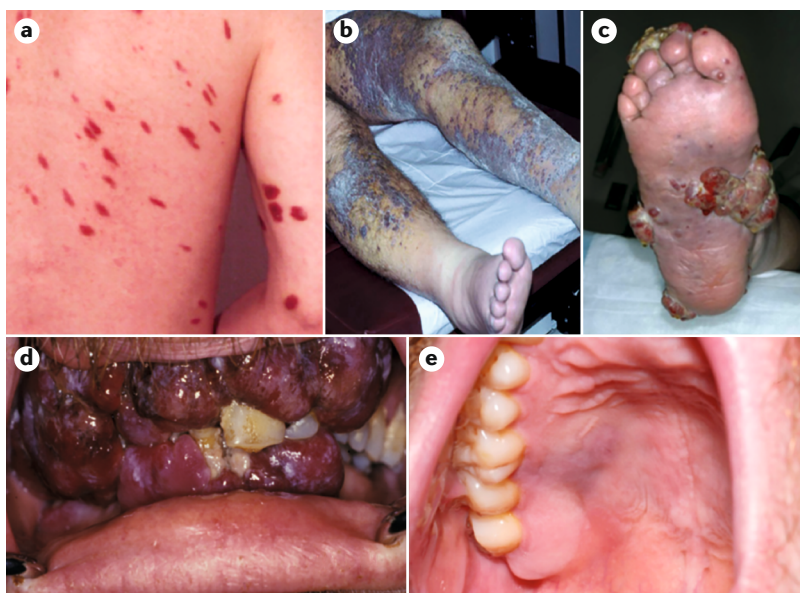
In AIDS-related KS, oral lesions (that is, in the palate and on gums) are common and may lead to dysphagia and secondary infection. Endemic KS is frequently associated with lymphoedema in African children and young adults, regardless of HIV status, and is difficult to control<sup>145</sup>. Finally, visceral lesions frequently can occur in the lungs and gastrointestinal tract and do so mostly in individuals with AIDS-related KS. Pulmonary lesions, which usually present with dyspnoea, dry cough and sometimes haemoptysis, with or without fever, are life-threatening. These lesions typically appear as a diffuse reticulo-nodular infiltrate and/or pleural effusion on chest radiography. Gastrointestinal lesions are usually asymptomatic, but may bleed or cause obstruction, and their presence is usually confirmed at endoscopy. Nevertheless, visceral lesions with KS are uncommon (in one study, only 15% of 469 patients had visceral lesions upon diagnosis with AIDS-related KS)<sup>146</sup>, and CT scans, bronchoscopy and endoscopy are not warranted in patients in the absence of symptoms indicative of visceral lesions.

To date, the staging of KS has not been unified or incorporated into the American Joint Committee on Cancer (AJCC) tumour, node and metastasis (TNM) staging system. Instead, the modified AIDS Clinical Trials Group (ACTG) staging classification, which is based on tumour, immune status and systemic illness (TIS), is used for AIDS-related KS<sup>147,148</sup> (TABLE 2), and the classification of classic KS focuses only on the tumour and originated from a case series of 300 patients<sup>149</sup> (TABLE 3). There are no specific staging systems for endemic or iatrogenic KS.

### Diagnosis

**Pathologic diagnosis.** When there is clinical suspicion of KS, a biopsy sample is taken to confirm the diagnosis histologically. Although this is straightforward in resource-rich settings, the process can be challenging in resource-limited settings, such as in Africa, where KS is most common, and macroscopic clinical visualization is often the only available means for diagnosing KS. Indeed, in one study from East Africa, visual diagnosis alone had only 80% positive predictive value for KS<sup>150</sup>; some patients were falsely diagnosed with KS, giving them an indication for needless chemotherapy and missing the correct, often easily treatable, diagnoses (for example, bacillary angiomatosis)<sup>151</sup>. To remedy this, several efforts have been aimed at increasing the histologic diagnosis of KS, including task shifting the performance of biopsies to non-physicians<sup>152</sup> as well as telermatology and telepathology<sup>153</sup>.

Pathologic diagnosis of KS can often be made using conventional haematoxylin and eosin (H&E) staining alone to assess for several basic features of KS that are present, to varying degrees, in all cases of the disease. These features include vascular proliferation in the



**Fig. 5 | Clinical manifestations of KS.** Different manifestations of Kaposi sarcoma (KS) include (part a) macular lesions on the back and nodules on the arm; (part b) extensive KS plaques on the legs with tumour-associated oedema; (part c) exophytic KS lesions on the foot; (part d) extensive gingival KS nodules; and (part e) flat, violaceous lesions on the hard palate. The image in part c is of a patient with classic KS; all other images are of patients with AIDS-related KS.

dermis (with the formation of slit-like spaces that are not lined by endothelium), an increased number of vessels without an endothelial cell lining, the presence of extravasated blood resulting in the formation of hyaline globules and haemosiderin accumulation and an inflammatory infiltrate (FIG. 6). Spindle cell proliferation is also a typical feature of KS. These spindle cells, which are characterized by elongated cytoplasm and nuclei and sometimes contain haemosiderin and hyaline inclusions, express endothelial markers and are considered to be the KS tumour cell. Although spindle cells are usually seen in sheets or fascicles (FIG. 6b), they may be difficult to distinguish in early lesions (FIG. 6c).

Pathologic classification has been described as including the following stages of tumour progression, which roughly correspond to the clinical appearance of the skin lesions (that is, morphotypes); however, frequent overlap between the stages exists, and it is unclear whether these stages occur in sequential order (note that pathologic stages are different from the clinical staging described in TABLE 2 for AIDS-related KS)<sup>154</sup>.

Macule or patch KS lesions may be the most difficult to distinguish histologically from other conditions as, although many of their features are evident on H&E staining alone, they can mimic other inflammatory skin disorders such as minor vascular anomalies and inflammatory conditions (FIG. 6c,d). Macule or patch KS lesions are characterized by a patchy, sparse perivascular infiltrate composed of lymphocytes and plasma cells; red blood cell (RBC) extravasation and siderophages (macrophages containing iron (that is, haemosiderin)); narrow cords of cells between collagen bundles; and, sometimes, fascicles of spindle cells.

Plaque KS lesions are characterized by a diffuse infiltrate of vessels throughout the dermis, with fascicles of spindle cells replacing the dermal collagen. Vascular spaces usually have jagged outlines and separate collagen bundles. There is commonly extravasation of RBCs with siderophages. Inflammatory infiltrate includes numerous macrophages, lymphocytes and, frequently, plasma cells.

Nodular KS lesions have the most distinct histology. They are characterized by well-defined nodules composed of sheets of spindle cells that replace the dermal collagen (FIG. 6e). A honeycomb-like pattern of vascular spaces filled with RBCs is frequently seen closely associated with interweaving spindle cells. Pseudovascular

spaces, where RBCs appear to directly contact spindle cells, are common. There is RBC extravasation, with siderophages and hyaline globules that are eosinophilic spheres 1–7 µm in diameter. Advanced cases of KS, such as the anaplastic variant, can display sheets of atypical spindle cells that mimic other sarcomas; in these cases, immunohistochemistry can aid diagnosis<sup>154</sup>.

#### *The role of immunohistochemistry in diagnosing KS.*

KS lesions have a heterogeneous cellular composition. Immunohistochemistry of the spindle cells using antibodies against vascular endothelial markers such as CD34 revealed that they have a vascular nature, and the subsequent detection of lymphatic endothelial markers in the spindle cells, such as podoplanin, LYVE1 and VEGF receptor 3, suggested that KS has a lymphatic endothelial cell origin<sup>155,156</sup>. However, KS lesions also express mesenchymal markers, such as vimentin<sup>157</sup>, and a mesenchymal origin of KS was recently proposed<sup>158</sup>. Most immunohistochemical evidence and gene expression and experimental data currently suggest that the spindle cells are lymphatic endothelial, vascular endothelial and/or mesenchymal cells that undergo reprogramming following KSHV infection to produce cells with an aberrant combined immunophenotype<sup>158,159</sup>. In addition to lymphocytes and plasma cells, histiocytes (that is, tissue macrophages) are abundant in KS lesions, and these can be identified with immunohistochemistry<sup>160,161</sup>. These immunohistochemical markers have aided our understanding of the cellular composition of KS and may still help in the differential diagnosis of KS in rare and complicated cases.

Immunohistochemical stains for antigens of KSHV (in addition to conventional H&E stains) are very useful in diagnosing KS. Specifically, antibodies that recognize KSHV LANA can be used in routine histopathology to confirm a KS diagnosis in difficult cases, and these are routinely used in many resource-rich pathology settings. Immunohistochemistry for LANA is particularly useful in diagnosing KS presenting with early macular or patch KS lesions or lesions that resemble other sarcomas. However, although LANA is thought to be expressed in every infected cell, the proportion of infected cells is variable, ranging from <10% to >90% of the total cell population in the lesional areas (FIG. 6d,f). Furthermore, LANA immunohistochemistry should be considered positive only when a distinct punctate nuclear pattern is seen, which prevents LANA staining from being confused with cytoplasmic haemosiderin or melanin when using a brown chromogen. Although LANA positivity confirms a diagnosis of KS, a negative stain may not rule out KS as sampling errors or false negatives can result from poor tissue preservation or other technical artefacts. Thus, whether a positive LANA stain is required to establish a diagnosis of KS is controversial and depends on specific circumstances.

**Molecular diagnosis.** When examined with sensitive nucleic acid amplification techniques, KS lesions almost always contain KSHV DNA. Indeed, a review in 2009 of >25 studies found that KSHV DNA is detected by PCR in >95% of all epidemiologic forms of KS<sup>29</sup>. Whether the

Table 2 | **The modified AIDS Clinical Trials Group staging of AIDS-related KS**

TIS staging of KS	Good risk (T0)	Poor risk (T1)
Tumour	Confined to skin and/or lymph nodes, or minimal oral disease	Tumour-associated oedema or ulceration, extensive oral KS, gastrointestinal KS or KS in other non-nodal viscera
Immune status <sup>a</sup>	CD4 cell count >150 per mm <sup>3</sup>	CD4 cell count <150 per mm <sup>3</sup>
Systemic illness	Karnofsky Performance Status >70 <sup>b</sup>	Karnofsky Performance Status <70 <sup>b</sup> or other HIV-related illness

KS, Kaposi sarcoma; TIS, tumour, immune status and systemic illness. <sup>a</sup>The original description of immune status used a cut-off of 200 CD4 cells per mm<sup>3</sup>; the post hoc analysis found a cut-off of 150 CD4 cells per mm<sup>3</sup> to be a better indicator of risk; however, in the era of highly active antiretroviral therapy, it is not clear that CD4 count is a prognostic factor<sup>147,148</sup>. <sup>b</sup>The Karnofsky Performance Status Scale, which ranges from 100 (best) to 0 (worst), assesses functional impairment<sup>295</sup>.

pathologic evaluation of the KS cases deemed negative for KSHV by PCR would result in 100% of KS cases being diagnosed is unknown. Regardless, the detection of KSHV DNA by PCR is highly, if not optimally, sensitive for KS, and the absence of KSHV DNA in a well-prepared sample essentially excludes the diagnosis. Except for in research laboratories, however, PCR for KSHV DNA is currently available only in a few highly specialized clinical molecular pathology laboratories. The specificity of detecting KSHV DNA is less clear, especially in KSHV-endemic geographic regions (for example, Africa), where up to 60% of persons in the general community are positive for KSHV antibodies. Data in this regard are very limited (14% of archival specimens from individuals without KS in Uganda were positive for KSHV DNA<sup>162</sup>), but they suggest that a quantitative threshold of KSHV DNA may distinguish KSHV-DNA-positive individuals with KS from KSHV-DNA-positive individuals without KS. If so, the automated objective molecular diagnosis of KS could conceivably be performed at the point of clinical care and, in large part, remove the expense and subjectivity of histopathologic diagnosis.

A similar approach has been implemented for tuberculosis with the GeneXpert platform (from Cepheid). A novel point-of-care device for KS diagnosis, which features multiple energy sources for use in areas where electricity is limited, is under development<sup>9,163–165</sup>. The latest stage of this device, which is called TINY (Tiny Isothermal Nucleic acid quantifications sYstem), relies on isothermal amplification and can be heated via electricity, sunlight or flame<sup>165</sup>. Pilot testing of this device in Uganda showed that KSHV DNA could be detected in KS biopsy samples in <3 hours after applying anaesthesia to the patient<sup>165</sup>. Broad implementation of this device could enable a definite diagnosis of the patient while still in the clinic rather than weeks later when relying on a pathologic diagnosis. A device such as TINY may lead to earlier diagnosis and prevent loss to follow-up.

### Screening

**The current status of KS screening.** Unlike for some cancers, there is no pre-neoplastic stage of KS for which screening can be performed. Furthermore, conventional screening by health-care practitioners for established KS before the development of clinical symptoms is of limited use because KS usually occurs first on visible skin and/or mucous membranes<sup>166</sup> and is thus initially observed by patients themselves. The exception is KS in the oral cavity, which could benefit from screening as it is often the first anatomic site of involvement in AIDS-related KS and might be missed by the patient. Other than screening for oral KS, the only other conceivable means of screening for preclinical KS would be to evaluate the lower respiratory tract or gastrointestinal tract for visceral lesions. Methods to perform such screening, however, are nonspecific (chest radiography or chest CT), expensive or associated with potential adverse events (bronchoscopy and endoscopy). Given that it is rare for KS to be present in visceral organs and not on visible mucous membranes or skin<sup>166</sup>, screening of the lower respiratory tract and gastrointestinal tract is not recommended.

Table 3 | Staging of classic KS

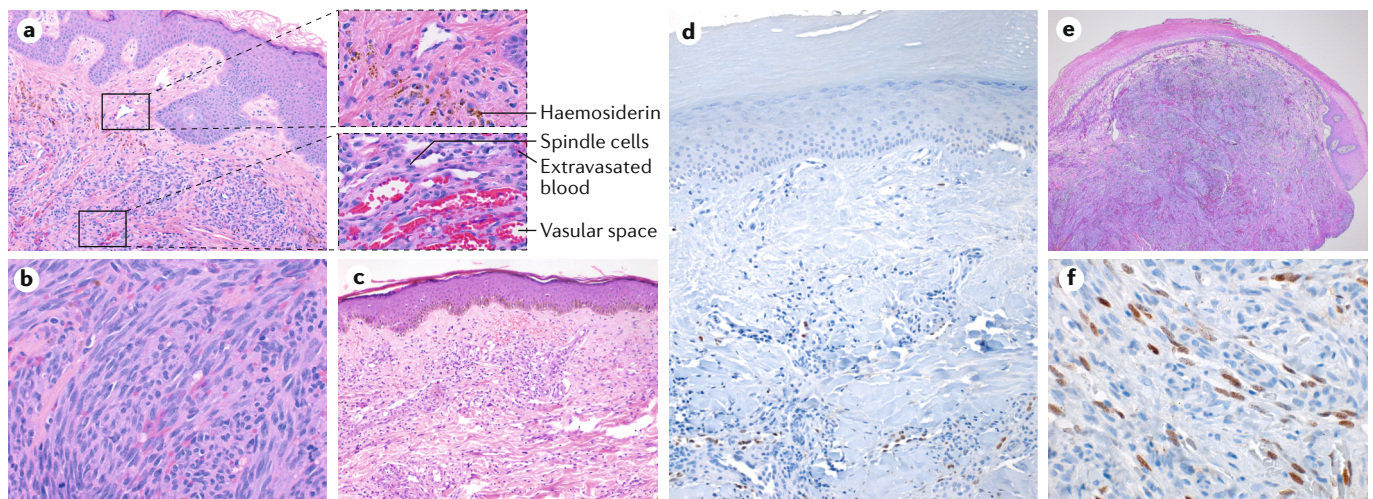
Stage	Description	Features
Stage 1 <sup>a</sup>	Maculonodular	Small macules and nodules primarily confined to the lower extremities
Stage 2 <sup>a</sup>	Infiltrative	Plaques mainly involving lower extremities, sometimes associated with a few nodules
Stage 3 <sup>a</sup>	Florid	Multiple angiomatous plaques and nodules involving the lower extremities that are often ulcerated
Stage 4	Disseminated	Multiple angiomatous nodules and plaques extending beyond the lower extremities

KS, Kaposi sarcoma. <sup>a</sup>Stages 1–3 are subdivided into slow (A) or rapid (B) KS progression. Rapid progression is defined as an increase in the number or total surface area of KS lesions over 3 months<sup>149</sup>.

**Benefit of early diagnosis.** Although a role for the formal screening for preclinical KS is limited (that is, it is useful only in the detection of lesions in the oral cavity), much could be gained by early detection of clinically apparent KS; preclinical screening and early detection of clinically apparent KS can be thought of as one intervention. Despite not being universally defined, early KS is generally agreed to be mild to moderate disease without symptomatic visceral symptoms, lymphatic obstruction or function-altering oedema, difficulty swallowing or chewing or any other functionally disabling manifestation<sup>167</sup>. An important rationale behind early detection is that early KS has a better clinical outcome than KS that is detected at a later stage. Indeed, even before cART, the stage at which KS was diagnosed was predictive of survival; patients with AIDS-related KS in the USA diagnosed with T0 tumours had a 1-year greater median survival than patients diagnosed with T1 tumours<sup>147</sup> (TABLE 2). The availability of cART has markedly improved the overall prognosis of KS, but the stage of KS at presentation remains similarly, if not more, important prognostically. In one of the largest studies of prognosis in the cART era, among 211 patients with AIDS-related KS in Italy, those with T1 disease at diagnosis had a 2.6-fold greater rate of death than those with T0 disease at diagnosis<sup>168</sup>. Among Swiss patients with AIDS-related KS, those with T1 disease at diagnosis had a 5.2 fold greater rate of death or need of chemotherapy than patients with T0 disease at diagnosis<sup>169</sup>. One study from South Africa found that individuals with T1 disease had a 2.4-fold higher mortality than individuals with T0 disease<sup>170</sup>.

Although the observational studies discussed suggest that the early detection of KS is clinically beneficial, and this is known to be the case for other cancers, these benefits have not been tested in randomized trials. This lack of randomized trials might explain why the evidence-based clinical guidelines of most national and international normative bodies for KS have not emphasized or mentioned early detection of the disease (although there





**Fig. 6 | Histopathology of KS.** **a** | Haematoxylin and eosin (H&E) staining of a skin biopsy sample showing characteristic features of Kaposi sarcoma (KS) is shown. Note the presence of spindle cells replacing dermal collagen, vascular spaces containing red blood cells, extravasated red blood cells and haemosiderin in macrophages (that is, siderophages). The original magnification is 20× (left panel) and 60× (right panels). **b** | H&E staining showing sheets of spindle cells in a biopsy sample of a nodular KS lesion. Original magnification 60×. **c** | A biopsy sample of a patch-stage KS lesion, stained with H&E, which has a sparse cellular infiltrate with many inflammatory cells (seen as dark, small cells). Original magnification is 20×. **d** | Immunohistochemistry for KS herpesvirus (KSHV) latency-associated nuclear protein (LANA) in a skin biopsy sample of patch-stage KS, in which cells with brown nuclei line vascular spaces. **e** | H&E staining of a nodular-stage KS lesion is shown at low power (4×), with a large nodule formed by swirling fascicles of spindle cells. Original magnification 20×. **f** | Immunohistochemistry for KSHV LANA in an area of a nodular KS lesion biopsy sample, showing immunoreactivity indicated by brown staining with a characteristic punctate pattern in the nuclei of spindle cells. Original magnification 60×.

are exceptions to this, such as in Uganda<sup>171</sup>). Formally proving the clinical benefits of early detection of KS experimentally would be time consuming and costly. In addition, the areas where the evidence would be most useful (that is, in sub-Saharan Africa) have the fewest resources to perform such studies. Therefore, individual practitioners and public health bodies must continue to make their own decisions on the utility of promoting early KS detection without gold-standard evidence. Inattention to KS has likely resulted in very few policy groups or individual practitioners ever considering the benefits of early detection of the disease. Also unproved is whether patients diagnosed with the fewest number and size of lesions (that is, with the smallest biological involvement) have the best prognosis, although observational research suggests that this is the case<sup>172</sup>.

In sum, detecting KS early will require the involvement of medical practitioners and patients. Medical providers can identify early-stage KS inexpensively by macroscopic examination of the oral cavity and complete examination of mucous membranes and skin. Although these examinations are neither time nor resource intensive, they are hindered by tight scheduling in resource-rich settings and by overwhelmed clinics, a lack of private space and cultural avoidance in many resource-limited settings. Even if medical providers always examined patients for KS, it would not mean that affected patients seek appropriate medical care earlier. In particular, patients in resource-limited settings are unlikely to recognize KS as a possibility when painless lesions appear on their skin. Indeed, a health-care-facility-based randomized trial of an intervention to improve early detection of KS failed to improve

outcomes in Zimbabwe<sup>173</sup>. The use of traditional healers by patients with KS in resource-limited settings may also delay early detection<sup>174</sup>. Thus, it is likely that the benefits of early KS detection will be realized only through community-based public education campaigns. Efforts in this regard have started in Uganda<sup>175</sup> but will require investment and scale-up to achieve impact.

### Prevention

No specific intervention is currently recommended in routine clinical practice to prevent KS. An anti-herpesvirus agent, ganciclovir, decreased the incidence of KS among individuals with HIV infection treated for cytomegalovirus retinitis in a trial mostly conducted before the cART era<sup>87</sup>. However, routine use of this drug in patients with HIV infection (or other populations with KSHV infection) is not indicated because of its toxicity. Therefore, interventions aimed at evading HIV infection (including pre-exposure prophylaxis)<sup>176</sup>, or suppressing HIV replication and maintaining the immune function of patients with HIV infection<sup>177</sup>, are currently the most practical ways to avoid developing KS. Avoidance of KSHV infection would also prevent KS, but there are no rigorously examined interventions for prevention of this infection, mainly because the specific routes of KSHV transmission are not understood. Saliva is the body fluid that most commonly harbours KSHV<sup>178</sup> and is thus likely the most important conduit for transmission. Therefore, in resource-rich settings, MSM (the group with the highest seroprevalence for KSHV infection)<sup>179,180</sup> should be counselled about the possible spread of KSHV through saliva<sup>181</sup>. Population-based studies of MSM in California, however, indicate very little awareness of



KSHV<sup>182</sup>. Furthermore, the use of saliva as a lubricant in anal sexual practices concentrated among MSM could play a role in KSHV transmission<sup>183</sup>. Considering the avoidance of this practice should at least be part of an educational message to at-risk populations. In Africa, non-sexual horizontal transmission in childhood is the principal route of spread in the highest prevalence areas<sup>184</sup>, but children are exposed to saliva in many ways<sup>24</sup> and a main form of exposure has not been identified. As such, there is currently no role for a broad recommendation to avoid saliva exposure in the general population.

### Management

In patients with forms of KS in which immunosuppression is potentially reversible, the first-line approach is to bolster the immune system; for example, the treatment of HIV with cART in patients with AIDS-related KS may cause regression of T0 tumours. Similarly, patients with iatrogenic KS may be treated by reducing the level of immunosuppression or by changing the immunosuppressive agents used, for example, by swapping calcineurin inhibitors for inhibitors of the PI3K–AKT–mTOR pathway, such as rapamycin. However, reducing immunosuppression in patients with iatrogenic KS may risk graft rejection. Treatments directed at the tumours are necessary in patients with AIDS-related KS and iatrogenic KS in whom agents targeting the immune system are insufficient, and in patients with endemic KS, classic KS or KS in MSM without HIV infection. High-quality evidence for the clinical management of KS is confined to the management of AIDS-related KS; the clinical approach for treating patients with other forms of KS is generally based on small retrospective case series and clinician experience rather than trial data.

For example, prospectively designed phase II trials in classic KS are scarce, usually include few patients, do not use standardized objective methods to document response and are rarely prospectively randomized. Despite these shortcomings, the current treatment options for classic KS include the observation of patients with a limited number of asymptomatic lesions that do not impair function; the management of symptoms from lower-extremity oedema with elastic compression stockings and various local and systemic tumour-directed therapies similar to those used for AIDS-related KS (see below). Of note, the choice of tumour-directed therapies for treating patients with classic KS depends on the number and anatomic distribution of the lesions, the pace at which the disease is progressing and the severity of other comorbidities; comorbidities are often present in elderly individuals presenting with classic KS (reviewed in REF.<sup>185</sup>).

### AIDS-related KS

**Cytotoxic therapy.** The clinical management of AIDS-related KS is largely determined by clinical staging. Patients with T0 early-stage disease should commence cART (if not already receiving this treatment for HIV), to which KS will often respond (that is, lesions will shrink by ≥50% in size and/or number) within 6–12 months. Indeed, up to 80% of patients with T0 stage KS that were not previously treated with cART will require no other treatment for KS than continued cART over 10 years<sup>146</sup>.

The management of T1 advanced-stage or progressive AIDS-related KS was established before effective cART was available and largely remains based on clinical trials from that time. Three sizeable randomized controlled trials conducted in the USA and the UK demonstrated the superiority of single-agent liposomal anthracyclines for treating patients with advanced-stage or progressive AIDS-related KS compared with conventional combination chemotherapy<sup>186–188</sup>. The safety and tolerability of liposomal anthracyclines in patients on cART has since been established<sup>189,190</sup>. Only one study has directly compared the efficacy of liposomal daunorubicin (DaunoXome) and pegylated liposomal doxorubicin (Caelyx or Doxil) in treating advanced-stage or disfiguring AIDS-related KS; as this study was underpowered, there is insufficient evidence to favour one agent over the other<sup>191</sup>. Nonetheless, on the basis of patient response rates and durations and on toxicity profiles, liposomal anthracyclines are considered the standard first-line chemotherapy for advanced AIDS-related KS, and most clinicians favour liposomal doxorubicin over liposomal daunorubicin as it is more widely available and has a less frequent administration schedule. Over 80% of patients with advanced AIDS-related KS have been reported to show tumour regression using the current approach of combining cART with liposomal doxorubicin<sup>189</sup>, although a minority of patients have anthracycline-refractory KS or relapse soon after completing chemotherapy and may be eligible for second-line therapy. A few patients with AIDS-related KS who are well established on cART and have an undetectable plasma HIV viral load and good CD4 cell counts still develop progressive or visceral KS<sup>192,193</sup>. These patients are generally treated with systemic chemotherapy using the same regimens.

Several phase II studies have demonstrated the efficacy of paclitaxel in treating patients with advanced-stage AIDS-related KS, including those with anthracycline-refractory disease<sup>194–196</sup>. Although the only head-to-head comparison of pegylated liposomal doxorubicin and paclitaxel in the treatment of advanced AIDS-related KS showed no significant differences in response rate ( $P = 0.49$ ), progression-free survival ( $P = 0.66$ ) or overall survival ( $P = 0.49$ ), there was significantly greater neurotoxicity ( $P = 0.045$ ) and alopecia ( $P < 0.001$ ) in the paclitaxel arm, making paclitaxel a less attractive first-line treatment option than pegylated liposomal doxorubicin<sup>197</sup>. Thus, in high-income settings, expensive liposomal anthracyclines are favoured for treating patients with AIDS-related KS, and paclitaxel, which is more affordable, is generally reserved for patients with recurrent or refractory AIDS-related KS. In low-income and middle-income settings, however, paclitaxel is becoming more widely available at a reasonable cost and may be preferred as a first-line regimen for treating patients with AIDS-related KS (BOX 2). Finally, a study conducted primarily in sub-Saharan Africa, where liposomal anthracyclines are generally unaffordable, showed that a routinely used combination of bleomycin and vincristine was inferior to paclitaxel for treating patients with advanced AIDS-related KS<sup>198</sup>.

## Box 2 | Treating AIDS-related KS in resource-limited settings

Although most research on the optimal management of AIDS-related Kaposi sarcoma (KS) has been conducted in high-income countries, the majority of individuals developing KS worldwide, particularly in its most advanced, aggressive forms, reside in low-income and lower-middle-income countries (primarily in sub-Saharan Africa). The rate at which AIDS-related KS responds to combination antiretroviral therapy (cART) alone is likely to be lower in low-resource settings, partly owing to constrained access to cancer care. In addition, the natural history of both AIDS-related KS and endemic KS, and the success of treating it, may be worsened by concurrent illnesses (for example, infections and malnutrition).

On a positive note, access to treatment in low-income and lower-middle-income countries is rapidly evolving, and the availability of affordable, essential chemotherapy drugs through generic manufacturers and donors is growing. The US National Comprehensive Cancer Network (NCCN), as part of a joint project with the African Cancer Coalition (ACC), the American Cancer Society (ACS) and the Clinton Health Access Initiative (CHAI), has recently adapted the NCCN guidelines to create guidelines for cancer in sub-Saharan Africa<sup>254</sup>. These guidelines represent both the optimal care that these countries aspire to provide and pragmatic approaches that provide effective treatment options for resource-constrained settings. These guidelines will likely be informed and modified in the future by ongoing research into the optimal treatment of AIDS-related KS by international clinical trials groups.

**Pathogenesis-directed therapy.** Two pathogenesis-directed therapies, IFN $\alpha$  and alitretinoin (a retinoid receptor pan-agonist), are approved for AIDS-related KS, but their use is largely historical. IFN $\alpha$  is a cytokine with direct antiproliferative and antiviral effects that can inhibit angiogenesis and modulate host cellular and humoral immune responses. The parenteral administration of recombinant IFN $\alpha$  was studied extensively in the 1980s and 1990s and induced regression of AIDS-related KS, particularly when combined with single inhibitors of HIV-1 nucleotide reverse transcriptase<sup>199</sup>. Although approved for AIDS-related KS treatment by various regulatory authorities in resource-rich countries, it is now rarely used owing to the availability of alternative agents that are more easily administered and have more favourable adverse event profiles. Topical alitretinoin gel<sup>200,201</sup> is thought to inhibit cell proliferation and promote cellular differentiation, and it induces the apoptosis of KS-infected cells in vitro.

Our growing understanding of KS pathogenesis has suggested multiple potential treatment targets for this disease, although none of the agents directed at these targets have yet been approved for treating patients. Nevertheless, the following treatments have shown promise in small clinical trials: imatinib, which inhibits tyrosine kinase-mediated transmembrane receptor signalling to prevent KS cell proliferation and angiogenesis<sup>202</sup>; bevacizumab, a monoclonal antibody against VEGF, an angiogenic growth factor that is highly expressed in KS lesions<sup>203</sup>; IL-12, a cytokine that enhances type 1 immune responses, mediates antiangiogenic effects and downregulates vGPCR activity<sup>204</sup>; immunomodulatory imide drugs, including thalidomide, lenalidomide and pomalidomide, all of which possess anti-inflammatory, antiangiogenic and immunomodulatory properties<sup>205,206</sup>; proteasome inhibitors, such as bortezomib<sup>207</sup>, which may promote the KSHV lytic cycle and/or inhibit NF- $\kappa$ B signalling; inhibitors of the constitutively activated PI3K-AKT-TOR pathway, such as rapamycin, which have activity against iatrogenic

and AIDS-related KS<sup>73,74</sup>; and agents such as timolol and propranolol that inhibit autocrine  $\beta$ -adrenergic-receptor-mediated signalling (through which KSHV usually drives the proliferation of transformed cells and represses the expression of viral lytic genes)<sup>208</sup>.

**KS immune reconstitution inflammatory syndrome.** KS immune reconstitution inflammatory syndrome (KS-IRIS) refers to the clinical worsening of existing KS or, less often, to the development or 'unmasking' of previously undiagnosed KS, following cART-mediated reconstitution of the immune system. Estimates of KS-IRIS frequency range from <10% to nearly 40% depending on the precise case definition applied, the case-detection approach and the clinical setting<sup>209-211</sup>. Moreover, there is no standard for distinguishing KS progression as an immune reconstitution-associated event from the natural history of KS. Most current definitions of KS-IRIS include evidence of progressive KS within 12 weeks of initiating cART in parallel with the suppression of HIV RNA levels by  $\geq 0.5-1 \log_{10}$  and/or an increase in CD4 T cell counts by at least 50 cells  $\mu\text{l}^{-1}$  compared with pre-cART levels; however, these definitions do not specify that 'inflammatory' characteristics of KS progression must be present. There is evidence that KS-IRIS occurs more frequently in sub-Saharan Africa than in the UK<sup>210</sup>; is more common among persons with T1 stage KS, high plasma HIV-1 RNA levels and detectable plasma KSHV DNA levels (than in patients with T0 stage KS, low plasma HIV-1 RNA levels and undetectable plasma KSHV DNA levels); and is less likely to be diagnosed among individuals receiving concomitant KS-specific chemotherapy and cART<sup>210,212</sup>.

There is no standard approach for managing KS-IRIS. In some cases, KS progression subsides and may reverse without additional treatment and without stopping cART. In other cases, immediate addition of chemotherapy to cART may be lifesaving and has been associated with improved patient survival<sup>210</sup>. Of note, KS-IRIS, unlike other manifestations of immune reconstitution, may be exacerbated by the addition of corticosteroids<sup>213</sup>, which should be avoided. Similar progression or unmasking of KS may occur following the treatment of KSHV-associated MCD with the monoclonal antibody rituximab<sup>214</sup>, even if the patients are on cART.

### Quality of life

Many physical and psychosocial problems associated with KS negatively influence QOL. For example, although gastrointestinal KS lesions are often asymptomatic, some may cause pain, bleeding, difficulty with feeding, diarrhoea, intestinal obstruction, malabsorption and weight loss. Pain, severe oedema and cellulitis can accompany ulcerated skin lesions, and oedema can also be present in the absence of skin lesions. Oedema of the lower extremities may impede or prevent ambulation, as can oedema of the external genitalia, which may also obstruct urination. Facial and periorbital oedema is disfiguring and, in extreme cases, may obstruct vision. Pulmonary lesions and effusions may be associated with dyspnoea, cough, haemoptysis and restricted activity. Skin lesions, particularly those on the face that

are hard to camouflage but also those on the torso and extremities, may lead to self-imposed social isolation, ostracism by others and psychological distress. Although many of these problems have most commonly been associated with AIDS-related KS, they may occur with all epidemiological forms of the disease.

Given that current treatments for KS are not curative, symptom palliation is often a major objective of KS therapy. In one study investigating preference techniques to value the potential health gains from different KS treatments<sup>215</sup>, 44% of respondents rated the presence of cutaneous lesions on the face and trunk (even in the absence of visceral involvement or oedema) as equivalent to death and indicated that fairly modest treatment effects greatly improved QOL. A number of studies have measured changes in QOL during the treatment of AIDS-related KS<sup>195,197,216–218</sup>. However, the methods used to assess QOL, including assessments of both general health and KS-specific signs and symptoms, have been inconsistent, as have the specific treatment interventions used, the prior KS treatment status of participants and the availability and use of antiretroviral therapy. Nonetheless, there is essentially unanimous agreement that chemotherapy for KS often improves QOL, despite the side effects of treatment. In particular, KS-associated pain and oedema were most likely to be positively influenced by chemotherapy<sup>195,197,216–218</sup>. Although improved QOL measures sometimes positively correlated with a measured objective response of KS to treatment (for example, shrinkage of the tumour by  $\geq 50\%$ )<sup>216,217</sup>, symptom palliation occurred in many individuals in the absence of the objective response<sup>197,216</sup>. These findings highlight the relevance of integrating measurements of QOL and patient benefit into the evaluation of the therapeutic efficacy of treatments for KS<sup>219</sup>. Cases of highly symptomatic AIDS-related KS have been reduced in high-resource settings but remain common in resource-constrained settings that account for the majority of new cases worldwide. Thus, using QOL as an integrated measure of therapeutic effectiveness in evaluating KS treatments in resource-constrained settings remains highly relevant.

## Outlook

### Basic science and pathophysiology

KSHV encodes viral proteins that are observed in KS lesions, where they can induce cellular changes by activating cellular pathways. Additionally, some KSHV proteins (for example vGPCR, vFLIP and LANA) may drive KS pathogenesis, thus representing potential therapeutic targets in KS; inhibitors of these proteins remain at the experimental stage and, even if they do become clinically available, this may take  $\geq 10$  years.

The cellular oncogenome of KS is poorly understood, and it is unclear whether KS is a polyclonal or monoclonal disease entity. In general terms, cancers originate from a single cell, therefore monoclonality is a feature of neoplastic diseases, whereas an inflammatory condition would arise from a number of different cells reacting to a stimulus and be polyclonal in origin. Indeed, most evidence suggests that KS can be both entities, sometimes being polyclonal<sup>220</sup> with other cases showing monoclonality<sup>221,222</sup>. These molecular findings may be

consistent with some cases behaving more aggressively than others, although a correlation of clonality with clinical behaviour has not been documented. This scenario is not unprecedented for a herpesvirus-driven disease, as Epstein–Barr-virus-associated post-transplant lymphoproliferative disorders range from reactive polyclonal proliferations to true lymphomas<sup>223</sup>. Cellular genetic alterations — namely, in the cancer-related genes *TP53* and *KRAS* — have been reported only in a few cases of KS<sup>224–226</sup>. Current genomic techniques and biocomputational methods in cohorts with annotated clinical information should provide a much broader understanding of the pathophysiology of KS, beyond KSHV infection, in the coming years.

### Clinical presentation

One of the difficulties in understanding KS is that its clinical presentation varies widely. Some patients with KS have indolent disease, which has led some researchers to conclude that KS may not result from a transformation event that leads to autonomously growing tumour cells; instead, it might represent a hyperplastic proliferative disease due to ongoing viral stimulation that drives angiogenesis and local and systemic inflammation<sup>227,228</sup>. By contrast, however, some patients with KS have aggressive, disseminated disease, with malignant behaviour. This heterogeneity is also seen at the histological level, where lesions that are largely composed of inflammatory infiltrates, including lymphocytes, plasma cells and macrophages or sheets of spindle cells, can be observed. The proportion of KSHV-infected cells also varies among lesions in patients with KS, ranging from a few to the majority of cells being positive for KSHV. The clinical or prognostic implication of these histological differences is not clear, and correlative analysis of the proportion of infected cells with the clinical features present is ongoing in AIDS Malignancy Consortium trials for KS.

### Prevention

The prevention of KS should be possible given that it is an infectious disease. An HIV vaccine would eliminate AIDS-related KS, and a KSHV vaccine would eliminate all cases of KS. Although progress is being made towards developing a KSHV vaccine (for example, by bettering our understanding of T cell responses to KSHV in humans<sup>32</sup> and testing, in mice, virus-like particles containing the gpK8.1, gB and gH–gL KSHV glycoproteins that are involved in virus entry into host cells<sup>229</sup>), a vaccine for use in humans is unlikely to be available in the near future. The development of a KSHV vaccine has been hampered by specific biological features of KSHV, such as latency and its ability to evade the host immune system<sup>230</sup>.

In addition, only a fraction of individuals infected with both HIV and KSHV develop KS<sup>38</sup>, suggesting that there are other causal factors in the aetiology of KS. The importance of an inflammatory milieu in the development of KS has received attention both at an anecdotal clinical macroscopic level<sup>231,232</sup> and in basic science investigation<sup>233</sup>. Moreover, emerging evidence suggests that biomarkers of inflammation are associated with the occurrence of KS in human studies. For example, a higher ratio of plasma kynurenine to tryptophan levels,

reflective of tryptophan metabolism, is associated with lower occurrence of KS<sup>234</sup>. Another study showed that CXCL10 (also known as IP10), IL-1 receptor type 2, soluble form (sIL-1RII), IL-2 receptor- $\alpha$  (IL-2RA) and CCL3 were markedly associated with KS after adjustment for age and smoking status<sup>235</sup>. Understanding which of these biomarkers are causal (and hence candidates for intervention), rather than markers of biological processes, is at the forefront of translational research.

Finally, as we increase our understanding of the risk factors for cART-resistant KS and for the development of KS-IRIS, particularly in low-resource environments, it may be possible to devise pre-emptive strategies, such as early initiation of KS-specific therapy, to prevent these adverse outcomes.

### Management

KS management in the near term is likely to capitalize on the growing understanding of KS pathogenesis, which has already provided a rationale for targeted treatments that have induced the regression of KS lesions and ameliorated disease symptoms. In addition to conducting larger efficacy trials of these drugs, especially orally bioavailable agents such as pomalidomide and bortezomib, there is a strong rationale to assess their efficacy as part of combination therapies that target multiple steps in KS development and progression and as adjuncts to established chemotherapy regimens. However, it has been difficult to mount large-scale efficacy trials of promising agents and drug combinations because of the declining incidence of AIDS-related KS in high-resource settings and the limited cancer research infrastructure in lower-resource settings where AIDS-related KS is still common.

Other novel therapeutic approaches being studied for treating other neoplasms — in particular, the blockade of inhibitory receptors (for example, programmed cell death protein 1 (PD1), programmed cell death 1 ligand 1 (PDL1) and cytotoxic T lymphocyte protein 4 (CTLA4)) that might otherwise prevent effective immune responses to virally induced neoplasms<sup>236</sup> — are being explored in KS. Indeed, PDL1 and PD1 are expressed in HIV-positive KS tissue samples<sup>237</sup>, including samples derived from patients on cART with well-controlled HIV and high CD4 cell counts<sup>238</sup>. Pilot studies of the use of immune checkpoint inhibitors in KS have been promising both in patients with HIV<sup>239</sup> and in patients who are HIV seronegative<sup>240</sup>.

Finally, of note, targeted approaches that utilize orally bioavailable drugs with acceptable safety profiles and that can be easily integrated into outpatient treatment regimens may be studied more intensively in high-incidence, low-resource settings than intravenous chemotherapy and radiation therapy.

### Integration

KS is a complex and heterogeneous disease, and, although the discovery of KSHV as its causal agent 24 years ago led to an improved understanding of its transmission and pathogenesis, much remains unclear. We do now have both epidemiologic and molecular evidence of causality, and it is clear that KSHV infection is necessary, although not sufficient, for KS to develop. However, a number of questions that have been speculated upon, but not fully experimentally validated, are outstanding. For example, it is unclear why KSHV is more highly seroprevalent in sub-Saharan Africa; one possible explanation for this is a greater propensity to share saliva in this area (see above), but genetic, nutritional and other factors may also contribute. Another interesting and outstanding question is why KS is more common in patients living near volcanoes than in patients living elsewhere<sup>241</sup>. It has been proposed that localized immunodeficiency in the skin favours the development of KS, and this may be induced in the extremities by exposure to volcanic soil leads<sup>242</sup> and by the use of topical steroids<sup>243</sup>. The much higher incidence of KS in men than in women remains poorly understood. A possible explanation is that there are gender disparities in the immune response to KSHV and that disease susceptibility is related to sex steroid hormones<sup>244</sup>.

Clinically there have been major strides in the management of KS, in particular with respect to AIDS-related KS in line with the improved control of HIV infection; AIDS-related KS incidence rates have declined with good HIV control, and effectively treating patients with KS with cART improves the outcome of early KS. However, the current treatment of AIDS-related KS that does not respond to HIV control is largely based on chemotherapy. More targeted biological treatments, such as those directly inhibiting vascular proliferation, or the targeting of latent viral proteins such as vFLIP, are only just being tested in experimental models or in clinical trials, and it is not clear whether any of these will be curative.

A preventive approach would be ideal to greatly reducing the global incidence of KS, and studies are underway to achieve this. In the meantime, as with other cancers in which a personalized, targeted approach has been used to tailor therapy, researchers will need to determine whether distinctive biomarkers or genetic features can inform clinicians on the best therapeutic interventions for KS. In contrast to most other cancers, the geographic location of the majority of KS patients in low-resource countries makes these studies challenging. Nevertheless, our increased understanding of the pathobiology of KS and our increased armamentarium of targeted agents and immunomodulators makes this an achievable goal.

Published online: 31 January 2019

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### Acknowledgements

The authors apologize to all the authors they could not cite owing to space constraints but whose contributions they greatly value. D.W. is supported by US federal funds from the National Cancer Institute, NIH, under contract HHSN261200800001E. E.C. and S.E.K. are partially supported by AIDS Malignancy Consortium (AMC) grant U01 CA121947. E.C. and J.M. are partially supported by the National Institutes of Health (NIH) grants UH2CA202723 and UH3CA202723. B.D. is supported by the NIH grants CA019014, CA096500, DE028211.

### Author contributions

Introduction (E.C. and S.E.K.); Epidemiology (E.C. and D.W.); Mechanisms/pathophysiology (E.C. and B.D.); Diagnosis, screening and prevention (E.C., J.M., S.E.K. and M.B.); Management (E.C., M.B. and S.E.K.); Quality of life (M.B. and S.E.K.); Outlook (E.C., M.B. and S.E.K.); Overview of the Primer (E.C.).

### Competing interests

The authors declare no competing interests.

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