

# HATiP

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## Kaposi's sarcoma: a clinical review

In 1981, doctors in California and New York City began to report seeing clusters of cases of a rare disease that in the US had previously been observed only among elderly men of Jewish, Arabic or Mediterranean origin: Kaposi's sarcoma (KS) (CDC 1981, Friedman-Kien 1981).

KS is an abnormal growth of vascular or lymphatic endothelial cells (the flat cells that line the blood and lymphatic vessels) that eventually develops into a true sarcoma (a cancer of the connective tissue).

In 1871, a Hungarian physician, Dr. Moritz Kaposi, had first identified the disease in the elderly men. This form of the disease is now referred to as "classic" KS and was characterised by the presentation of disseminated blood- or bruise-coloured skin lesions (flat plaques or nodules) in the skin, usually on the lower extremities though sometimes on the hands and arms. The lesions were slow to grow and rarely ever life-threatening (Kaposi).

But the KS cases in 1981 were unusual because they were in much younger men — all men having sex with men (MSM) — and because the disease was far more aggressive than the indolent classic KS, spreading beyond the skin into the bone, lymph, mouth, gastrointestinal tract and lungs. In addition, these cases were often paired with other rare infections that did not normally affect people with healthy immune systems, such as *Pneumocystis jirovecii* pneumonia (formerly called PCP), and ultimately resulted in premature death.

The newly identified syndrome was at first called "Kaposi's Sarcoma and Opportunistic Infections (KS/OI)," but once it was recognised that KS wasn't always required for these other illnesses to develop, but was rather just one of the first, most noticeable signs of a progressively weakening immune system — the name was changed to Acquired Immune Deficiency Syndrome (AIDS) (CDC 1982). But KS was quite literally and historically, the very first recognised "AIDS-defining" illness.

A few years later, HIV was discovered to be the cause of AIDS and about ten years after that, another virus, human herpesvirus 8 (HHV8 or sometimes KSHV) was linked to the form of KS which had become so aggressive in the context of AIDS. And since that time, with the advent of antiretroviral therapy (ART), KS has once again become rather rare in the US and Western Europe. When it does occur, it is much more manageable due to ART and advances in cancer chemotherapy.

But in sub-Saharan Africa — which was already home to its own endemic form of KS, as is so often the case, the management of KS is more complicated due to the high burden of HIV, poor or delayed access to completely suppressive ART, and limited capacity to properly diagnose or treat cancer of any kind.

### The different classes of KS

As noted above, KS has been divided into several classes essentially by epidemiology (though the course of disease differs as well) (Sissolak and Mayaud have written one of the best recent comprehensive review on KS, see references — and go into more detail than we can in this article).

- Classic KS: Almost exclusively seen in elderly men (possibly due to hormonal factors) of Mediterranean, Middle Eastern or

Eastern European origin, this KS commonly only involves the skin and rarely spreads to other parts of the body. Of note, classic KS has also been observed in older HIV-negative MSM (Friedman-Kien 1990).

- Iatrogenic KS: In the 1960s, rare cases of KS began to be reported in people being treated with immunosuppressive drugs, especially those who had received organ transplants (Siegel, Penn). This form of KS is rarely aggressive and usually goes away once the immunosuppressive treatment is stopped.
- Endemic or African KS: In the 1950s and 1960s, a number of reports from east and central Africa described KS as a relatively common, though sometimes much more aggressive form of classic KS that could also affect children and young adults (Oettle, Lothe and Murray, Davies). In 1971, Taylor et al defined four basic clinical variations of African KS: 1) a benign disease similar to classic KS but in much younger people; 2) an aggressive and destructive form affecting skin and bone but localised to the extremities; 3) a potentially fatal form with lymph node involvement in young children — still much more common in boys than in girls; and 4) a widely disseminated aggressive form that could involve the internal organs and was fatal within 3 years in nearly all cases. Although HHV8 and HIV were still unknown, given the reports of iatrogenic KS, researchers investigating African KS were already beginning to guess that immune suppression played a part in the development of aggressive disease, years before the first reports of AIDS (Master).
- Epidemic or AIDS-related KS: follows a variable course, though without ART, it is eventually always progressive. In the developed world, AIDS-related KS was mostly seen in MSM, who had a 50% greater risk of developing it than other HIV-infected populations (Katz), although it has also been seen in the IDU population (Atkinson).

But in Africa, AIDS-related KS occurs in a context where there already was a common and severe form of endemic KS. Although KS was common in Uganda before the HIV epidemic, a recent survey of over 12,600 participants of The AIDS Support Organization (TASO) in Uganda has found that the risk of developing KS in the first 4-27 months after signing up with the non-governmental organisation was increased significantly compared to the general population, with a standardised incidence ratio of 6.4 (95% confidence intervals, 4.8–8.4) (Mbulaiteye 2006).

"We estimate that 20% to 40% of patients suffering from HIV disease will develop cancer at one stage," Dr Alexander von Paleske, a consultant haematologist and oncologist for the Princess Marina Hospital in Gaborone said during a presentation at the Botswana International HIV Conference in September, 2006. He noted that there had been a surge in the number of KS cases in Botswana: "KS now accounts for roughly more than 80% in patients with HIV disease suffering from cancer."

This increase has included women. One classical feature of KS was that it rarely ever affected women, but HIV has changed that in Africa. Although still more common in men, in many parts of Africa, KS is now the leading cause of malignancy in women with HIV (Mbulaiteye 2006, Chokunonga, von Paleske).

HIV has also greatly increased the risk in children (Wabinga, Mbulaiteye 2006).

In addition, even though it is still an AIDS-defining event, AIDS-related KS in Africa is not so closely linked with advanced immune suppression (Mbulaiteye 2006).

"KS can develop at any stage of HIV disease — even when the CD4 count is 500," said Dr von Paleske, although he added that "mostly the CD4 count is below 300."

## HHV8 and the mysteries surrounding its transmission

In 1994, Chang *et al.* reported the discovery that KSHV or HHV8 was associated with KS, and subsequent studies found the virus was consistently present in KS lesions from each type of KS (Kedes). Like other viruses associated with cancers (such as the closely related EBV), HHV8 is associated with more than one malignancy (in particular, HHV8 has also been linked to primary effusion lymphoma and multicentric Castleman's disease) and only some people with the virus go on to develop KS or these other even rarer conditions (more below).

The case for a causative role of HHV8 in KS was confirmed when longitudinal studies demonstrated that becoming infected with HHV8 predicted the subsequent risk of developing KS in people with HIV (Moore, Renwick, Martin 1998, Gao 1996).

But how exactly HHV8 is spread from one individual to another remains something of a mystery — sexual transmission is presumed to account for some cases but that explains only a part of the overall global HHV8 prevalence. Nevertheless, how it is more commonly transmitted may have implications for who is likely to develop KS, and who is not. (Much of the following is described in more detail in a review on the topic by Dr Chong Gee Teo of the Centers for Disease Control (see references)).

Because of the greater risk of KS in MSM among people with HIV in the in the US and Western Europe, it has long been believed that whatever caused KS was sexually transmitted in that population. Subsequently, this appeared to be supported by serological evidence that found a HHV8 prevalence of ~30% among MSM with HIV without KS (Dukers, Gao 1996; Kedes 1996), while the prevalence was considerably lower among MSM without HIV, and even less frequent among men in the general population (Martin 1998).

However, behavioral and epidemiological studies have yielded conflicting findings about the specific routes of sexual transmission. Perhaps the most important take-home message from one cohort study, the San Francisco Men's Health Study, was that the risk of HHV8 infection was increased with the amount of sexual activity and number of partners (Martin 1998).

There is also evidence of transmission among adult heterosexual men and women, again with a correlation in the number of partners in sub-Saharan Africa (Sitas, Whitby 1999). And in regions with classic and endemic KS, women are also infected with HHV8 even though, in the absence of HIV-infection, they are much less likely to develop KS.

Overall, as suggested by the regional burden of classic KS and endemic KS, the rates of HHV8 are extremely low among the general population in US and Northern Europe, around 10-20% in Italy and Greece and ranging between 20 and 60% in Africa.

But in the Mediterranean, Middle East and Africa, much of the HHV8 transmission actually seems to occur during childhood, via a non-sexual route.

Gessain *et al.* reported on a key study of HHV8 seroprevalence in 258 children and adolescents, 32 mother-and-child pairs, and 189 pregnant women from Yaounde, Cameroon. Initially, seroprevalence was high in newborns but dropped dramatically as infants lost their maternal antibodies by 2 years of age (so transmission was not vertical). "Then, beginning around 4 years of age, a regular

increase of HHV8 antibodies took place, reaching 39% in the 12- to 14-year age group and 48% above 15 years, a rate similar (54.5%) to that observed in pregnant women," the authors wrote.

Similar patterns, of a third to one half of infections occurring sometime during childhood, have been reported by studies in Italy, Zambia, Uganda, South Africa (Whitby 2000, Olsen, Mbulaiteye 2003, Sitas). In Egypt, studies suggest that up to 45% of children are infected by the age of 10 years, but with little increase prevalence at older ages (suggesting little transmission between adults among the population) (Andreoni).

## Why some people get KS when others do not — and can ART or behaviour change prevent it?

Given Kaposi's identification of KS in the 1800s, HHV8 must have been endemic in Africa and the Mediterranean long before HIV began spreading, and to some degree, the regional differences in the distribution of HHV8 explains the difference in prevalence of KS (for instance, why endemic KS is more common than classic) (Plancoulaine and Gessain).

But it doesn't explain everything. There are other factors as well, perhaps most notably since KS is still more common among men than women (although in AIDS-related KS in Africa, it is still common enough). Genetic predisposition (HLA type) may also play a role (Alkharsah), as could genetic differences in the HHV8 itself (Zong, White).

Over the years, epidemiological studies have produced findings with dubious clinical utility, such as reports that smoking tobacco may have protective effects (Goedert). Other reports suggest a higher risk of KS among people with certain environmental exposures such as chronic exposure to volcanic soils or prolonged working or walking in river or lake water (Ziegler 1997). These exposures, which can lead to skin disease or changed immune function in the skin, could be compatible with other findings from Uganda that decreased delayed hypersensitivity responses in the skin, and findings from Italy that increased corticosteroid usage on the skin, are both associated with higher rates of KS (Ziegler 1993, Goedert).

HIV also plays an obvious role both by reducing the ability of the immune system to control HHV8, and by more direct interactions of HIV proteins such as tat, which has been shown to re-activate other latent viruses, and to induce angiogenesis (the development of blood vessels which can feed KS tumours) (Ensoli 1993). If so, it is possible that some HIV-1 subtypes may be more prone to reactivate HHV8 than others since tat varies from subtype to subtype. However, HIV can also cause generalised immune activation and the secretion of inflammatory cytokines such as TNF-alpha, IL-6, or growth factors that may also make KS more aggressive (Ensoli 1992, Miles, Dourado).

The incidence of KS in the US and Western Europe dropped dramatically by the time that fully suppressive ART began being used — at least partly because of ART, though there also may have been a decrease in HHV8 transmission among MSM (Jacobson 1999 and 2000, Buchbinder). For instance, Ledergerber *et al.* analysed data from over 6,000 people in the Swiss HIV Cohort Study, comparing new AIDS-defining illnesses between 1992-1994 and 1997-1998 and found that AIDS-defining illnesses, including KS, declined by about 80%. "Our data indicate that patients cease to be at risk of Kaposi's sarcoma once immune function has been improved by combination therapy," they wrote.

The rollout of ART should reduce the incidence of KS, or at least aggressive KS, in Africa as well. But in most African settings, despite

WHO guidance to start ART at 350 cells, programmes only begin treatment much later. And according to the TASO survey in Uganda, many people develop KS at higher CD4 cell counts before they qualify for ART (Mbulaiteye 2006). Furthermore, ART coverage is still low, and many people do not present for care and treatment until they are already quite ill. So ART should not be expected to have a dramatic impact on the incidence of ART in most settings quite yet. Furthermore, little is known about the risk of KS developing in people who may have incompletely suppressed HIV on ART, which will be the case in many programmes without access to routine viral load monitoring.

Another important observation noted in the Ugandan survey and other studies, is that despite a dramatic increase in the incidence of KS in Africa since HIV, it is still less common in Africa than it is in the HIV/HHV8-coinfected population in the US or Western Europe. "KS incidence in our cohort was much lower (240 vs. 5,700 per 100,000 person-years (Atkinson)) than in HIV-infected MSM with AIDS in the U.S.," wrote Mbulaiteye *et al.* And before ART, in the San Francisco Men's Health study, the 10-year probability that coinfected men would develop KS was 49.6% (Martin 1998).

Rates as high as in the US would spell disaster in Africa, given the high prevalence of HHV8 and the high burden of HIV in most settings.

It is quite possible the incidence of KS is actually higher than has been reported and that it just isn't diagnosed as often (see below) – but the difference is just too great for that to explain it away fully. It may also be that patients die with other infections before they develop KS.

Another potential explanation for the difference is that HIV-infected people who are subsequently or simultaneously infected with HHV8 (as would have happened to many of the coinfected MSM in the US and Europe) are less able to develop a competent immune response to the virus (Jacobsen, Renwick) while infection during childhood in Africa prior to HIV infection, "might be associated with more effective immunologic control and lower subsequent risk of KS," wrote Mbulaiteye *et al.*

This should strengthen the case for positive prevention among people with HIV. Although the epidemiological studies have yet to agree upon the precise mode of sexual transmission, cutting down on the number of sexual partners (or being faithful to just one) could possibly reduce the risk of sexual transmission of the virus that causes KS in adults, and the subsequent risk of developing KS.

However, until more is known about how HHV8 infection is acquired during childhood, it will still be difficult to prevent horizontal transmission to and amongst children with HIV or to children without HIV who are still at risk of endemic KS in Africa. Since transmission, particularly from saliva, is unlikely to be "curtailed by behavioral change" in this population, Dr Teo's review concludes that what is really needed to stop the spread of HHV8 is a vaccine.

## Characteristics and symptoms associated with KS

Healthcare workers should maintain a high index of suspicion for KS, given how common it is in people with HIV. The earlier the condition is recognised and treated, the better the chances of a good outcome. But unfortunately, many patients only present with very advanced cases.

Again, KS can occur while CD4 cell counts are high, and before there any other symptomatic disease, but is more aggressive at lower CD4 cell counts, and may occur alongside other serious

illness (that will need concurrent diagnosis and treatment for the best outcomes).

Early KS lesions may be very subtle, suggestive of a bruise or a pigmented callous (Wilson) usually starting in the head or neck area, upper torso or lower extremities (Sissolak and Mayaud). As they grow, they form flat patches, or firm, raised, round or oval nodules. If pressed, these lesions do not become pale (as a bruise would).

The lesions may occur anywhere in the body, notably the face, hands, anorectal or genital regions, mucous membranes (around the eye, inside the mouth), lymph nodes, lungs and gastrointestinal tract, but they are especially common on the limbs and feet. Often, there is swelling (oedema) appearing at the edges of lesions, at which point the lesions may start to become painful.

When many nodules are present, they may follow skin-fold lines. In some cases, the nodules can ulcerate, bleed and become infected with secondary infections. They can also coalesce and cover large areas (Sissolak and Mayaud).

Blocked fluid drainage in associated lymph nodes can cause serious swelling, especially in the feet, lower legs or genitals. Swelling may also occur around the eyes and face (von Paleske).

Lesions and swelling can be disfiguring and people with KS end up being stigmatised and socially excluded.

When KS occurs on the thighs and soles of the feet, the lesions may become large plaques that are often swollen and extremely painful, making walking difficult, limiting mobility and causing functional disability. With invasive deep tumours, there may even be bone involvement (Master). Secondary infections can form seeping, malodorous wounds, which also cause the patient much distress.

KS can also involve the membranes in and around the eye. KS of the conjunctiva appears as flat or nodular reddish lesions, surrounded by tortuous vessels, and may also involve the eyelids and other ocular structures (Kagu, Shuler, Kurumety).

KS in the oral cavity is particularly common, and the initial site of involvement at presentation in about 20% of the cases (Flaitz). KS usually affects the palate (roof of the mouth) the gingiva (gums) or base of the tongue. Initially lesions may go unnoticed, but as they progress, secondary infections with thrush, pain and bleeding are common. Oral KS can cause difficulties talking or eating, and could ultimately lead to malnutrition and wasting. It is also commonly associated with other visceral involvement in the lungs, gastrointestinal tract or other internal organs (Kagu, Ficarra).

Many people with KS have gastrointestinal involvement or lesions in the spleen, liver and other internal organs, but these rarely appear to cause symptoms and go undetected. However, sometimes KS causes a blockage in the intestines, resulting in nausea, vomiting, abdominal pain, weight loss and occasionally bleeding that may be mistaken for ulcerative colitis.

Patients with KS who present with difficulty breathing, progressive shortness of breath and cough may also have KS in the lungs (pulmonary KS). This is the most serious form of KS, and can rapidly lead to sometimes bloody pleural effusions (fluid in the thoracic cavity), pulmonary failure and death within months if untreated (Aboulafia, Gill).

## Multicentric Castleman's Disease:

KS, however, is sometimes closely associated with a condition called multicentric Castleman's Disease (MDC), which is a pseudo-lymphoma or a non-cancerous proliferation of B cells in the lymph nodes that is either caused or exacerbated by HHV8 (Soulier, Hengge). It causes lymphadenopathy, hypoalbuminuria and often proteinuria as well as "B symptoms" including high fevers, anaemia,



weight loss, fatigue, weight loss, loss of appetite, and low white blood cell counts. It is consistently associated with a poor prognosis for the person with KS.

## Real World Case Study, #1 from Dr. Kevin Bezanson

### The boy in Zomba, pt 1

**"We had a boy, 14 years old, who I was asked to see shortly after arriving in Zomba in 2004. I saw him initially on the surgical ward at Zomba Central Hospital. He was admitted to surgery because he had a draining wound in his groin, but the surgeon who saw him recognized it as KS. His entire left leg was swollen and hard with KS nodules, and he was draining from infected lymph nodes in his groin. He was incredibly thin and cachectic." (More on the boy's subsequent management below).**

## Diagnosis of KS

When there are just a few lesions on the skin, it may be difficult to distinguish between KS and some other growths, such as benign haemangiomas or the opportunistic condition, bacillary angiomatosis. Bacillary angiomatosis (caused by various *Bartonella* spp) requires medical treatment (with antibiotics such as erythromycin or doxycycline), but it is much less common than KS. It can form blood or purple-coloured eruptions, sometimes with crusting, but rarely forms plaques. Nevertheless, the medical literature is peppered with reports where it has been mistaken as KS (Kiss). Dr Graeme Meintjes of GF Jooste Hospital in Cape Town recommends performing a biopsy (punch or excision) on nodular lesions that enlarge rapidly, in order to exclude this condition.

But while "definitive" diagnosis of a KS lesion requires a biopsy, the capacity to do pathology in most settings in Africa is extremely limited. Factors such as the severity of the case at presentation, the suffering the patient is experiencing, how far the patient must travel (and the related time and expense to them) must be factored how clinician's proceed with the diagnosis. Many experienced clinicians make a presumptive diagnosis, particularly in advanced cases — although most would recommend biopsy for atypical lesions.

"More than 90% of patients with KS don't need a biopsy," said Dr von Paleske. "I get quite a few patients with obvious KS and it takes a long time for biopsies, especially when they come from the district hospitals to get the biopsy results back. You must be 100% sure that the patient has KS, and if you only have 1 or 2 lesions of the skin, that is not enough to be certain. But when you are sure, don't do a biopsy."

Dr. Margaret Borok, director of the KS clinic at the Parirenyatwa Hospital in Harare, has chosen the middle path.

"In our practice, we do a biopsy if it is possible in order to confirm the diagnosis and for accurate records. But if I am sure of the clinical diagnosis, I do not wait for the biopsy result to commence treatment," she said.

As for KS-like lesions in other parts of the body, the diagnostic approach may vary upon the immune status of the individual the condition is occurring in, and whether the lesions are occurring together with KS skin lesions or in isolation. For instance, if a lone lesion is observed in the conjunctiva, the patient should be referred

to an ophthalmologist. Lymph node-only KS requires biopsy, according to Dr von Paleske.

Even in well-resourced settings, diagnosis of KS in the GI tract is only considered necessary if patients with KS have serious GI symptoms (see above), because it typically requires an upper and lower GI endoscopy. The diagnosis is normally made visually because the diagnostic yield from biopsy is low (the lesions are typically below the mucosa). Likewise, where available, a bronchoscopy can detect bright red discrete lesions in the lungs — which are not biopsied however, because of the risk of rupturing and bleeding.

Though chest x-ray results are less specific (and are sometimes confused with TB, for instance), they are less invasive and more readily accessible in Africa. On chest x-ray, typically, KS will show up with diffuse infiltration in both lungs, mostly in the lower lung fields, in a symmetrical pattern with irregular nodules of varying size. There may also be hilar and mediastinal lymphadenopathy and occasional pericardial or pleural effusions. "If the pleural effusions are bloody, think first of KS," said Dr von Paleske, "not of TB."

Because of the severity of pulmonary KS, Dr von Paleske also recommends x-rays for every KS patient:

"Each and every patient who comes to your clinic has to get a chest x-ray when you suspect KS. The reason for that is you simply cannot correlate the extent of KS with the lung involvement. You might have one or two skin lesions, a little bit of palatal involvement and a massive infiltration into the lung."

KS in the palate of the mouth, in particular, is consistently associated with pulmonary KS.

"I have seen so many patients put on TB treatment without positive sputum and no x-rays, just a chronic cough and haemoptysis [shortness of breath], but with obvious KS lesions in the mouth, said Dr Carla Simmons of the Kitovu Mobile Clinic in Uganda. "They often respond well to chemo and I just stop the TB treatment."

## Staging

Unfortunately, it is necessary to distinguish between people with a good or poor risk of survival, since resources for treatment are often limited, and the need for appropriate palliative care so great. But since KS is a multicentric disease, conventional cancer staging is useless.

The most commonly used staging system for KS is based on a system developed by the AIDS Clinical Trials Group Oncology Committee (which divides patients into good or poor-risk groups for survival according to the extent of tumours, immune status (CD4 cell count) and severity of systemic HIV-associated illness [TIS] (Krown 1989). What follows is Dr von Paleske's adaptation:

Good Prognosis ( All criteria must be fulfilled)	Poor Prognosis ( One criterion is enough)
Skin infiltrates (lesions) and/or	Oedema or tumour ulceration
Lymph node infiltration and/or	Extensive oral infiltrates
Flat palatal infiltrates	GI-tract infiltration
	Infiltration of visceral organs (most commonly the lung)
CD4 cell >150	CD4 cells < 150
No oral candidiasis	Pat. Has/had oral candidiasis
No B-Symptoms	B-Symptoms present

B-symptoms: weight loss >10% during last six months, night sweats, unexplained fever.

“From our experience at Princess Marina Hospital more than 80% are falling in the poor prognostic [category] unfortunately,” said Dr von Paleske.

“In my practice patients usually present late and with a heavy tumour burden,” agreed Dr Borok in Harare, who added that in Zimbabwe they sometimes use a clinical staging system that does not need a CD4 count (staging patients from 1 to 4 based on the extent of the lesions and A or B according to absence or presence of B symptoms).

## Therapy for KS

In resource-limited settings, there is no such thing as an optimal standardised regimen for AIDS-related KS. It is important to keep in mind that most of the reports in the literature come from well-resourced countries, where more optimal treatment is generally started much sooner, and in people with much less advanced disease than typically occurs in sub-Saharan Africa, for instance. Many chemotherapeutic drugs are not available in many settings – furthermore, while ART is freely provided in most settings, other treatment for KS isn't always.

For instance, patients must pay for chemo in Zimbabwe – and it is expensive.

“There is very poor support for those who cannot pay. I can sometimes arrange free treatment through a social welfare-type fund which operates in the hospital but this is not easy and does not apply as a routine measure for indigent patients,” said Dr. Borok.

“Chemo is available at our site,” said Dr. Halima Dawood of Grey's Hospital in KwaZulu Natal, South Africa, “but there are waiting lists.”

“We use vincristine and ART –however, vincristine is often out of stock,” said Dr. Anthony Harries of the MoH in Malawi. “During our last supervision, 74% of all ART facilities in the public sector had no vincristine in their pharmacies.”

So healthcare workers generally have to do the best they can with whatever treatment approaches they have at hand. In this context, it becomes all the more important to engage the person with KS and their family in the treatment decision-making process – taking into consideration the stage of disease, whether the course of KS is indolent or rapidly progressive, whether it is causing functional disabilities or leading to their stigmatisation, and individual circumstances (whether they must travel long distances for treatment, or the financial implications for care and treatment)."

The Southern African HIV Handbook of Medicine suggests keeping the following principles in mind:

“Because palliation of KS-related symptoms is the primary goal of treatment, assessment of the therapeutic benefit of an agent should include:

- Assessment of the agent's toxicity
- Achievement of objective tumour regression
- Relief of tumour-related symptoms
- Prevention of new disease"

## Management of suffering and pain from KS

KS usually only causes physical pain once it has become extensive, affecting the lymph nodes and causing oedema. However, by the point many people with KS come in for care, they may be deeply distressed – and the most pressing need may be to assess their

situation and take the necessary steps to relieve the patient's discomfort, taking into consideration their needs holistically.

Symptom control is a key aspect of palliative care, and HIV clinicians should institute effective pain assessment and management, according to WHO guidelines for pain control, as early as possible. Even when someone with KS is on ART and chemotherapy that might achieve a complete response, healthcare workers should keep in mind how to make the subject more comfortable until their KS improves.

“Just because you're on ARV's doesn't mean you don't need palliative care. These patients are in extreme pain and they still need morphine,” said Dr Simmons of Kitovu Mobile AIDS Home Care and Orphans Program, Uganda.

## Real World Case Study #2, Dr Julia Downing

**We had a patient a few years ago who had severe KS in his legs – unfortunately he did not come for care until it was very severe in the right leg – he was in a lot of pain and his leg was very swollen with open lesions on it. We tried to give him some chemotherapy – which was not available near his home so he had to come into Kampala – he had three doses of vincristine which was all we had available and the swelling reduced a bit – however her was not well enough to travel to Kampala and so we treated him at home.**

**The main issues for him were:**

- **Stigma from the KS which could not be hidden**
- **Pain – it was very painful and we had to put him on 10mg oral morphine 4 hourly which was increased eventually to 25mg 4 hourly**
- **Immobility – due to the pain and swelling he was not mobile – he needed help to do everything and spent most of the time lying down on a mat on the floor.**
- **Due to the advanced state of his disease he was cachexic and so had related problems of the skin, sores etc.**

## Practical advice on reducing suffering in people with KS

A pain assessment should be performed on every patient with aggressive KS. An excellent resource containing some basic pain assessment tools and effective pain management protocols is *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in sub-Saharan Africa*. The following bits of practical advice on how to reduce suffering among people with KS are adapted from the guide (The link for the guide is below in the resources section).

Dexamethasone or betamethasone 2mg daily is useful as a co-analgesic where there is significant oedema and inflammation and amitriptyline 10-25mg nocte as a co-analgesic for the management of neuropathic pain. Patients who experience lymphoedema may receive some benefit from gentle lymphoedema massage.

## Assessment of fungating tumours:

Skin tumours that cannot be excised may give rise to very unpleasant odours, which may be distressing to the patient. Such

tumours include advanced Kaposi's sarcoma ...[that presents]... as ulcerated enlarging growths and are often complicated by pain, bleeding, unpleasant odour, and secondary infection.

### Management:

It is important to apply general principles of wound care to managing KS lesions. This may be challenging in resource-poor settings where there is no access to water for regular cleansing of the wound.

### Non-pharmacological wound care:

Cleanse regularly with salt water; use ripe paw paw for sloughing (crush and apply twice daily for 5 days (Hospice Africa Uganda, 2002)), or apply charcoal, live yoghurt, or honey to the wound. Commenting on this practice, Dr. Borok added that in Zimbabwe, "we use icing sugar, as it's cheaper than honey."

### Pharmacological wound care:

Treat topically with metronidazole, which reduces the offensive odour, dries up the discharge, assists with haemostasis and treats infection caused by anaerobic organisms. If topical metronidazole is not available, crushed metronidazole tablets can be used for topical application on the fungating area. If the wound presents with a sinus metronidazole tablets or pessaries can be inserted into the sinus or orifice leading to smelly growth. The number of tablets depends on the size of the wound. Leave wound uncovered if possible (Hospice Africa Uganda, 2002).

Metronidazole can also be administered orally for systemic effect - 200–400 mg PO 3 times/day.

Another resource on managing fungating wounds can be found online [here](#):

A patient with KS needs significant emotional support not only in dealing with the HIV diagnosis and physical distress but also with the disfigurement, change in body image and social isolation that can occur as a result of this distressing manifestation of HIV.

Any HIV care team looking for further assistance in providing symptom relief and supportive care is advised to look up the palliative care organizations listed in the resources section below – with one caveat.

"Too many practitioners still see palliative care as a withdrawal of treatment whereas we include active, sometimes aggressive, treatment," said Dr. Liz Gwyther, who is chairperson of the Hospice Palliative Care Association of South Africa. "For instance, a key role of the palliative care team is to facilitate the patient's access to ART as this provides the most effective control of the condition. KS of skin and soft tissue also respond to radiotherapy that may be offered as a palliative intervention where radiotherapy services are available. *Palliative* chemotherapy may also be effective."

"I use morphine where needed and often," said Dr. Borok. "But I find that once patients are stable on ART and have received chemo, they may be able to stop morphine and other analgesics and their quality of life and level of functioning improves greatly."

## HIV management

Treating HIV disease with ART and managing concurrent infections, both to restore immune function and reduce the potential for HIV and opportunistic infections to stimulate KS lesions, should be the foundation of any treatment strategy in a person with HIV and KS. "KS is AIDS defining and requires HAART irrespective of CD4 count," said Dr. Dawood.

ART has been shown to decrease the incidence of KS (as described earlier) and improves survival in people with KS. For instance, an analysis of survival data the Multicenter AIDS Cohort Study (MACS) involving 287 men with KS during the period 1990–1999 found that among the 15% of those who received ART there was improved survival ( $p=0.0001$ ) and with an 81% reduced risk of death (Tam).

ART has been shown to lead to complete or partial remission of KS, particularly in many people with less extensive disease. There has been some speculation that HIV protease inhibitors can also have a direct effect on KS (Sgadari), although a recent study by Martinez *et al.* concluded that responses were the same whether subjects were on a protease or non-nucleoside analogue reverse-transcriptase-inhibitor (NNRTI)-based regimen.

One of the first case studies of ART in KS patients reported that ART resolved KS completely in seven of nine people (Monticelli). A subsequent study found in 78 people with KS found that treatment with ART led to a more durable response than chemotherapy on its own (Bower 1999). A study of 53 people diagnosed with KS at a mean CD4 count of 174 showed that the magnitude of CD4 count increase after commencing ART predicted the likelihood that KS would regress once ART began. In total, 72% of those who started ART after a KS diagnosis had a complete or partial remission of their KS within 48 weeks (Renato). However, a more recent French study in 138 patients with KS reported that achieving an undetectable HIV viral load was strongly associated with KS remission ( $P \leq 0.004$  at all time points), while CD4 cell count was not (Martinez).

ART may improve outcomes in resource-limited settings as well. In the Home Based AIDS Care (HBAC) Project in Tororo, Uganda, taking a nevirapine-based regimen appeared to have a similar impact on KS as in reports in North America and Europe (Asiimwe). Among 1125 study subjects followed over two-and-a-half years in the study, there were 16 KS cases diagnosed at baseline and 17 occurred over the course of the study.

23 subjects (69.7%) experienced regression of their KS lesions and 10 (30.3%) subjects died with persistent KS, and this mortality was associated with visceral KS (Adjusted Hazard Ratio (AHR) =32; 95% CI; (4–268.6) - see

<http://www.aidsmap.com/en/news/25269956-68DC-4B24-84CA-A81245827555.asp>

This high rate of mortality reflects the fact that many KS cases remain difficult to manage; so it is important not to have unrealistic expectations of what can be achieved by ART – particularly when KS is more established.

"In our experience, advanced KS, especially of the limbs when the lymph nodes are involved, does not respond to ART or to chemotherapy," said Dr. Simmons. Speaking at the African Palliative Care Association Conference in Nairobi last September, she also described one typical case of "a man with KS on his tongue about the size of a lemon. He can't eat, therefore he's malnourished, he's on the ARVs but they're not doing him any good." That patient died after one month.

"However, the greatest response we have seen is with patients who have KS involving the mucous membranes, lungs or gut. We have seen some truly remarkable changes with these patients especially when they are on a regimen with a PI (*Kaletra* is used in Uganda)."

Yet the fact that her team has seen some good results in people with visceral KS underscores that ART is worth trying even in patients who might be expected to have a poor prognosis.



## More ART caveats

### KS Immune Reconstitution Inflammatory Syndrome (KS IRIS) :

There have been a couple of reports that ART may sometimes trigger a “KS IRIS”, a paradoxical inflammatory response that could actually reactivate KS or HHV8 and lead to progressive disease in a small number of people. According to Bower *et al.*, out of over 5,832 total people put on ART in the Chelsea and Westminster HIV cohort, 150 people had a new presentation of KS on ART. Ten of these cases proved to be reactivated progressive KS in people with increasing CD4 cell counts.

In a comparison of the individuals with KS IRIS and those whose KS did not progress, the researchers found that KS IRIS was diagnosed in patients with higher CD4 counts (median, 335 vs. 121 in the “non-IRIS” KS patients ( $p = 0.03$ )), with KS-associated oedema ( $p = 0.01$ ), and the use of both protease inhibitors and non-nucleosides together ( $p = 0.03$ ).

“We had a case of IRIS with KS in a health worker that was heartbreaking,” said Dr Bezanson, who complained of the difficulties in managing his colleague’s pain at an under-resourced site in Malawi. “He had pulmonary KS, and all we had was [corticosteroids and oral morphine. It was awful — maybe more awful for knowing what good palliative care could be, and just not being able to operationalise it.”

“We’ve seen a couple of KS IRIS’s. It can be catastrophic in the lung, or in the palate, as it can obstruct the airway, said Dr Francois Venter of the Reproductive Health and HIV Research Unit at the University of the Witwatersrand, Johannesburg.

“We had a pregnant woman almost demise from obstruction — she needed ventilation till the swelling went down.”

### KS on incompletely suppressive ART:

Another issue that remains to be addressed is what will happen in settings without laboratory monitoring of patients on ART (by CD4 or viral load). Data from well-resourced settings suggest that if ART starts to fail and HIV viral load increases, KS is likely to progress again (Lyter).

### Indolent KS in older people on suppressive ART:

Another sign that ART by itself may not totally remove the risk of KS comes from recent reports of older MSM who have developed what appears to be “classic” KS despite being on suppressive ART. Older is a relative term: the median age was 51 years (range, 41 to 74). They had been living with diagnosed HIV infection for a median of 18 years (range, four to 24 years) with a median duration of antiretroviral therapy was seven years (range, under one year to 19 years). Thus far, however, the course of KS has been relatively indolent in these men — see

<http://www.aidsmap.com/en/news/455F8259-3882-4AC3-8F9F-D51EC735B26D.asp>

## Treatment options for less advanced, less aggressive disease or individual lesions

People with less aggressive KS may benefit from treatment of lesions that cause cosmetic problems (particularly since lesions can sometimes be a very visible sign of HIV/AIDS and lead to stigmatisation) or for lesions that cause other discomfort. KS may not be severe enough to justify the expense and risk the side effects of whole body chemotherapy.

### Interferon Alpha:

One approach in better-resourced settings has sometimes been to use interferon alpha in people with higher CD4 cell counts who have early, more indolent KS limited to the skin. In this group, it has been shown to improve KS in about 30-40% of people taking it, although achieving the best response normally takes months on treatment (Krown 2001). Early studies used very high doses (30 million units, 3 times a week or 36 million units/m<sup>2</sup> per day, subcutaneously), but subsequent studies in combination with antiretrovirals reported similar results using 1 to 10 million international units per day, with less toxicity at lower doses.

Interferon causes flu-like side-effects, neutropenia — a shortage of white blood cells called neutrophils which fight infections that can leave the individual vulnerable to bacterial infections — and hepatotoxicity. People taking it must be monitored closely, particularly if they are also on ART. Although it has been used in some parts of Africa, this treatment approach isn’t affordable or available in many settings.

### Local therapy:

Individual skin lesions can be injected with chemotherapy drugs such as diluted vinblastine or vincristine, which causes the lesion to swell up painfully but then shrink or disappear (Boudreaux). However, if done for cosmetic purposes, the patient should know that it generally leaves a scar.

Other approaches to treating skin lesions including removing them surgically or freezing them with liquid nitrogen (cryotherapy) (Tappero). Cryotherapy is usually reserved for thin areas of skin such as the face and the genitals, and is most successful if the KS lesion is flat, not nodular, and relatively small.

Studies have reported good responses for both methods for individual treated lesions, however, people with KS should be advised that local therapy does not achieve lasting results — and that it will not prevent progression of KS elsewhere on the body.

### Radiotherapy:

Localised radiation therapy (radiotherapy) can be used to treat KS lesions in the mouth or throat, painful skin lesions or lesions that are causing blockages in the lymph nodes of the face, arms and legs. It is also effective for lesions on the eyelids or the white of the eye. The idea is to kill the over-active tumour cells with a series of low doses of radiation, leaving the rest of the body untouched. Again, it will not put a halt to systemic progression, so the strategy in Botswana, according to Dr von Paleske, is to use radiotherapy to achieve further tumour remission once treatment with systemic chemotherapy has stabilised the patient.

Side-effects can include short-term reddening of the skin and hair loss and, in the mouth, inflammation of the mucous membranes (mucositis), which can sometimes be severe or even life-threatening. The lesions usually leave a scar, like a mole, where pigmentation remains in the skin. This is particularly common when long-standing lesions are treated.

Dosing regimens vary by setting but radiotherapy is not widely available in every country. According to WHO figures, radiotherapy is available for about only 20% of cancer patients in Africa (Boyle). For example, it is not available in Malawi, according to Dr Harries. Furthermore, access tends to be centralised so people must often travel far from their home to access it.



## Treatment options for more advanced aggressive disease

Chemotherapy: Again, factors such as the patient's prognosis and whether treatment will improve the quality of life need to be taken into consideration when deciding whether to use chemotherapy, because the drugs used in cancer chemotherapy cause significant side effects such as anaemia and neutropenia, hair loss (alopecia) and diarrhoea.

In better-resourced countries, the current standard of care for KS is liposomal doxorubicin, which is marketed as Caelyx. The liposomes are fatty envelopes that preferentially target the drug to tumour cells rather than healthy cells. It is administered as a slow 30- to 60-minute infusion 20 mg/m<sup>2</sup> every 2 or 3 weeks.

Studies suggested objective response rates that are dramatically better (46-59% without ART) and faster than combination chemotherapy with ABV (Adriamycin (doxorubicin), or BV (bleomycin, vincristine) — with markedly less toxicity (it does not lead to alopecia, nausea or vomiting but may cause neutropenia, and occasionally acute transient reactions to the infusion) (Northfelt, Stewart). One study of Caelyx combined with ART in 54 people with KS reported complete or partial responses in 81.5% of patients within 8 weeks (Lichterfeld).

But this is an expensive drug, and is primarily only be available for patients in private care with good medical aid schemes. A similar drug, *DaunoXome*, and the new drug, paclitaxel (*Taxol*) have also contributed to improved management of KS in Europe and the US but are not widely available in Africa.

Most programmes in Africa remain dependent upon the old chemotherapy drugs: many of which have been reported to have some activity against KS either as single agents or in combinations, including but not limited to etoposide, vinblastine, vincristine, bleomycin, doxorubicin, and actinomycin D. It is difficult to compare the activity of these drugs across studies — many were conducted years ago, were uncontrolled, and did not apply strict standardised response criteria.

What may better set them apart are their respective toxicities, which should be taken into consideration when treating someone. For example, if the patient already has anaemia, it would be better to use a drug like vincristine, which is less prone to cause this condition than some other chemotherapeutic drugs. However, in settings without close monitoring of liver function tests, vincristine may not be as good a choice to use in someone on an ART regimen containing d4T, since both drugs may cause peripheral neuropathy.

Clinicians should also be aware that there may also be some drug-drug interactions between vincristine/vinblastine and ARVs metabolized in the liver.

"Our main problem with vincristine is constipation (thus it requires good diet advice), said Dr. Harries, "and peripheral neuropathy which can be dealt with to some extent by limiting total number of doses."

Dr von Paleske says that some of the neurotoxicity on vincristine is avoidable by closer monitoring of liver function tests (he recommends only using vincristine when alkaline phosphatase levels are below 300 IU/l).

## Chemotherapy drugs, dosages, and their respective toxicities:

- **Etoposide**
  - Intravenously 150 mg/m<sup>2</sup> per day for 3 days, every four weeks,
  - Oral dosing
    - a single weekly dose 150-400 mg/week
    - 25 mg/m<sup>2</sup> twice a day for seven days, every other week
    - 50 mg per day for 3 weeks
    - 50 per day for seven days, every other week, increased up to 100 mg in non-responders
  - Toxicity: Alopecia, mucositis, neutropenia
- **Doxorubicin**
  - 15/mg/m<sup>2</sup> per week or 20 mg/m<sup>2</sup> every 2 weeks
  - Toxicity: Alopecia, mucositis, neutropenia, cardiac toxicity at high doses
- **Vinblastine**
  - 4 mg weekly, increase 2 mg each week if tolerated (the average tolerated dose is 6 mg per week)
  - Toxicity: Neutropenia
- **Vincristine**
  - 2 mg per week for 2-5 weeks, then given weekly every other week
  - Toxicity: Peripheral neuropathy, constipation
- **Bleomycin**
  - Intramuscularly 5 mg/day for 3 days every 3 weeks
  - As a continuous infusion 6 mg/m<sup>2</sup> per day for four days every 4 weeks, or 20 mg/m<sup>2</sup> per day for 3 days every 3 weeks
  - Toxicity: Fever, skin and pulmonary toxicity

## Reports from the field on chemotherapy

At Princess Marina Hospital in Botswana, Dr von Paleske said that they have had some good responses with the ABV combination given every three weeks. In the medical literature, the most commonly used doses are doxorubicin 20 mg/m<sup>2</sup>, bleomycin 10 U/m<sup>2</sup>, and vincristine 1-2mg, but doses tend to be individualised based upon tolerability.

Dr Haruna Jabril, a paediatrician at the same hospital, has reported similar success with the same regimen in children (although the doses are adjusted). "We had 15 cases over a six year period, five of which had disseminated disease requiring chemotherapy in addition to HAART — with an initial excellent response. Two had died following relapse and three are still alive. The oldest survivor is now 14 years old; she was diagnosed in 2002 with disseminated KS affecting her lungs, and needed urgent radiation therapy followed by HAART and chemotherapy."

Other experts we contacted reported mixed success to HATIP with different chemotherapeutic regimens.

For instance, Dr. Julius Onyango of the Kisumu Hospice in Kenya reports some success treating patients with doxorubicin (60 to 100mg depending on the lesions), vincristine 2mg and *Endoxan* (cyclophosphamide) given every three weeks.

Meanwhile, Dr Borok in Harare prefers to use two drugs (vincristine 1.4mg/m<sup>2</sup>, max 2mg and bleomycin 15 mg/m<sup>2</sup> or doxorubicin 40mg/m<sup>2</sup>, max 50mg at four-week intervals.

"It is difficult, expensive and impractical for patients to come back more often than every four (perhaps every three) weeks," said Dr. Borok.

Others report responses using just one chemotherapeutic drug on its own.

"I have seen many patients do quite well on vincristine given weekly and the response is enhanced if they are on ART," said Dr Zipporah Ali, who is the national coordinator for the Kenya Hospices and Palliative Care Association. Likewise, in Tanzania, Dr. Karilyn Collins has also reported "very good results with vincristine, a course of 6 I/V infusions, weekly, especially when combined with ART."

"We use doxorubicin 50 mg every three to four weeks for 6 doses. We have problems with anaemia but usually get over those if we get them off AZT and give high doses of haematinics," said Dr Simmons of Kitovu Mobile AIDS Home Care and Orphans Program in Uganda.

And a study in Zimbabwe reported better results using better quality of life outcomes with oral etoposide than radiotherapy or the combination of actinomycin D, and BV (Olweny).

And yet, it is important to stress that many people won't respond on the old standard chemotherapeutic drugs – perhaps because they present too late with disease. Even in the more recent clinical trials against the liposomal anthracyclines in well-resourced countries where people present with earlier disease, combination chemotherapy (ABV or BV) only achieved complete or partial tumour regression in about a quarter of the subjects.

In addition, "patients who have a poor performance status and/or very low CD4 tend to tolerate chemotherapy less well," said Dr Graeme Meintjes in Cape Town. "If their poor performance status is due to a factor that is remediable in the short term such as an opportunistic infection then chemotherapy should be delayed until after this has been addressed. However, if it is related to disseminated KS then obviously chemotherapy cannot be delayed. In patients with poor performance status and/or CD4<100 it may be appropriate to adopt a low intensity chemotherapy regimen for initial therapy. And in certain patients who are too ill to tolerate any chemotherapy palliative therapy alone may be more appropriate."

"The major issue is taking the decision to treat them as they usually present very ill," said Dr Jabril. "I have always tended to treat as the option is to wait for response to HAART and allow them to build up their CD4 count and be fit enough for therapy. Invariably they do not last that long and therefore I treat them while HAART continues. Fortunately again when they suffered episodes of neutropenia, filgrastim (granulocyte colony stimulating factor [G-CSF]) was available to boost up the ANC."

But he has seen relapses in at least a couple of the children with KS, and doesn't yet know how to treat them. Other clinicians reported having a similar dilemmas in some of their patients.

"We had pretty good initial responses to ABV for disseminated KS in adults," said Dr Francois Venter "but they usually die from disseminated KS after a few months."

"Doctors must realise that chemo is not always effective and when to stop it," said Dr. Simmons. "We had a patient last year, a young man in his thirties who came to us for pain management. He had been in Kampala for six months on chemo. He had contractures at both hips and knees. He had spent over half a million shillings on chemo and finally came home when his money ran out. We started him on morphine for pain management and he died two weeks later. He could have had months of comfort at home if the doctors treating him had faced reality."

### The boy in Zomba (Real World Case Study #1), from Dr. Kevin Bezanson - Pt 2

#### Difficulty providing adequate curative or palliative management

**"[Because of the draining wound] we attempted to treat him with antibiotics, but due to stock-outs had very limited options. I think he ended up getting chloramphenicol. We did have vincristine as well, strangely in huge amounts, so we gave him a dose as well –in retrospect more for ourselves than for him. We had no narcotic analgesics, apart from some Tramadol [an opiate only about 10% as potent as morphine] that the surgeon had access to from a shipment of drugs from his sponsoring hospital. So we gave him some, which seemed to improve his pain somewhat. At the time our ARV program was just starting. We discussed starting ARV's with his grandfather who was his guardian and caregiver, but due to the very advanced condition, active infection which we could not treat effectively, and limited ARV supplies, we decided to treat him palliatively. But in this context that meant sending him home with 2 weeks supply of Tramadol and dressings.**

**He died at home. I have no idea how comfortably or not."**

#### Surgery

Dr von Paleske said that the only recourse for some patients is surgery – and by that he meant amputation.

"Some of the patients don't respond. They come in with these huge (ulcerating) lesions and they need amputation of the leg because the chemotherapy doesn't really improve it much. That is the sad story about it. So surgery really is a disfiguring and disabling intervention here," he said.

The only situation where amputation would seem justifiable would be if the KS were under control everywhere else in the body.

"The biggest palliative challenge is the patients with oedematous limbs – it's horrible: They have a very compromised QOL, the treatments don't really work, and they are at high risk for DVT. I've had many people on ART, and they still seem to do poorly – largely as their mobility is so impaired, or their legs get infected; it's a palliative challenge. We have, on occasion, recommended amputation, but many patients refuse. They need active management at home, usually, with lots of counseling – and lots of morphine, if needed (which is often!)"

"I have found that surgeons are very reluctant to amputate because the skin above the diseased area is often unhealthy or involved with infiltrative KS and/or lymphoedema. In addition, patients may not withstand surgery well because of their advanced HIV disease," said Dr Borok.

### Bereavement support

Care providers need to keep in mind that KS is one of those conditions from which some people with HIV do not fully recover.

When the disease remains progressive — despite pain management and palliative therapies including ART and chemotherapy—healthcare teams should forge working partnerships with local hospices and palliative care organizations to provide further supportive care and bereavement counseling to people (and their families) who are permanently disfigured, disabled or dying because of KS.

Providing complete holistic care through the entire continuum of illness may also improve health-seeking behaviour in families who are much more likely to be HIV- affected.

For instance, although resources constrained what the Malawian team was able to do to help the boy from Zomba, "I did see his grandfather again who thanked me when he brought another grandson, 8 years old, to the clinic a few months later," said Dr. Bezanson. "He thankfully did not have KS, but was quite ill as well. But he responded beautifully to ARVs and was back at school and thriving a few months later."

### And yet, sometimes combining treatment approaches can work

#### Real World Kaposi's Sarcoma Case Study #3, from Dr Karilyn Collins, Tanzania

**"John was 23 when he was admitted to hospital as an emergency one night in 2004, bleeding profusely from a lesion on his right eyelid. He needed 5 units of blood overnight and the bleeding continued the next day. He was tested and found to be HIV-positive and we diagnosed the lesion as KS from its appearance. We decided to try vincristine as he was likely to bleed to death and we had no other answer. After the first IV infusion of 2mg, the bleed stopped and the lesion started to shrink. His CD4 count was measured and found to be 10 and he was started on ART. The vincristine was continued for 6 weeks and the lesion on the eyelid practically disappeared. However new very florid lesions appeared on his lower limbs — possibly KS-IRIS? He had radiotherapy for these and again made a very good recovery with little residual scarring. About a year later, he developed an isolated painful lesion on his little toe, the toe was amputated and the pathology showed nodular KS. He developed another toe lesion about 6 months later that he asked to be surgically removed. Since then he has had no further problems with KS and has a very satisfactory CD4 count."**

### Resources

- The AIDSMap Palliative Care Portal: <http://www.aidsmap.com/cms1038390.asp>
- The African Palliative Care Association: <http://www.apca.co.ug/>
- The Hospice Palliative Care Association South Africa: <http://www.hospicepalliativecaresa.co.za/>
- The International Association for Hospice and Palliative Care: <http://www.hospicecare.com>
- The International Children's Palliative Care Network: <http://www.icpcn.org.uk/> (in particular, see their international directory)
- The Association for the Physically Disabled (APD) helps South Africans with physical disabilities: <http://www.apd.org.za/>
- Foundation for Hospices in Sub-Saharan Africa (FHSSA): [www.fhssa.org](http://www.fhssa.org)
- The WHO pain ladder: <http://www.who.int/cancer/palliative/painladder/en/>
- *A Clinical Guide to Supportive and Palliative Care for HIV/AIDS in Sub-Saharan Africa* addresses the many aspects of palliative care that are key in caring for the person living with HIV/AIDS from an African perspective: to read online: <http://www.fhssa.org/i4a/pages/Index.cfm?pageID=3361>

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## References in order of first appearance

- Centers for Disease Control (CDC). *Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California*. MMWR Morb Mortal Wkly Rep;30(25):305-8, 1981.
- Friedman-Kien AE. *Disseminated Kaposi's sarcoma syndrome in young homosexual men*. J Am Acad Dermatol; 5:468-71, 1981.
- Kaposi M. *Idiopathisches multiples Pigmentsarkom der Haut*. Arch Dermatol Syph;4:265–73, 1872.
- CDC. *Current Trends Update on Acquired Immune Deficiency Syndrome (AIDS) –United States*. 31(37);507-508,513-514, 1982.
- Sissolak G, Mayaud P. *AIDS-related Kaposi's sarcoma: epidemiological, diagnostic, treatment and control aspects in sub-Saharan Africa*. Trop Med Int Health;10(10):981-92, 2005.
- Friedman-Kien AE. *Kaposi's Sarcoma in HIV-negative homosexual men*. Lancet 335(8682), 168, 1990.
- Siegel JH et al. *Disseminated visceral Kaposi's sarcoma. Appearance after human renal homograft operation*. JAMA;207(8):1493-6, 1969.
- Penn I. *Kaposi's sarcoma in organ transplant recipients: report of 20 cases*. Transplantation 27, 8–11, 1979.
- Oettle AG. *Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes*. Acta Union Int Cancer 18:330–63, 1962.
- Lothe F, Murray JF. *Kaposi's sarcoma: autopsy findings in the African*. Acta Unio Int Contra Cancrum. 18:429–452, 1962.
- Davies JN et al. *Cancer in an African community, 1897–1956. An analysis of the records of Mengo hospital, Kampala, Uganda*. British Medical Journal 1(5378):259-64, 1964.
- Taylor JF et al. *Kaposi's sarcoma in Uganda: a clinicopathological study*. International Journal of Cancer 8, 122–135, 1971.
- Master SP, Taylor JF, Kyalwazi SK, Ziegler JL. *Immunological studies in Kaposi's sarcoma in Uganda*. Br Med J 1(5696):600-2, 1970.
- Atkinson JO et al. *The incidence of Kaposi sarcoma among injection drug users with AIDS in the United States*. J Acquir Immune Defic Syndr 37: 1282-1287, 2004.
- Mbulaiteye SM et al. *Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study*. Int J Cancer;118(4):985-90, 2006.
- Von Paleske A. *HIV and Cancer*. Botswana International HIV Conference, Gaborone, 2006.
- Wabinga HR et al. *Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997*. Br J Cancer 82:1585–92, 2000.
- Chokunonga E, Levy I M, Bassett MT, Borok MZ, Manuchaza BG, Chirenje MZ, Parkin DM. *AIDS and cancer in Africa: The evolving epidemic in Zimbabwe*. AIDS;13:2583-8, 1999.
- Chang Y et al. *Identification of new human herpes virus-like DNA sequences in AIDS-associated Kaposi's sarcoma*. Science 266: 1865-1869, 1994.
- Teo CG. *Conceptual emergence of Human Herpesvirus 8 (Kaposi's Sarcoma-associated Herpesvirus) as an oral herpesvirus*. Adv Dent Res 19:85-90, 2006. This can be downloaded here: <http://adr.iadrjournals.org/cgi/reprint/19/1/85.pdf>
- Kedes DH et al. *The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission*. Nature Medicine 2, 918–924, 1996.
- Moore PS et al. *Kaposi's sarcoma-associated herpesvirus infection prior to onset of Kaposi's sarcoma*. AIDS 10:175–80, 1996.
- Renwick N et al. *Seroconversion for human herpesvirus 8 during HIV infection is highly predictive of Kaposi's sarcoma*. AIDS 12:2481–8, 1998.
- Martin JN et al. *Sexual transmission and the natural history of human herpesvirus 8 infection*. New England Journal of Medicine 338(14): 948-954, 1998.
- Gao S-J et al. *Seroconversion to antibodies against Kaposi's sarcoma associated herpesvirus-like latent nuclear antigens before the development of Kaposi's sarcoma*. New England Journal of Medicine 335: 233-241, 1996.
- Dukers NH et al. *Risk factors for human herpesvirus 8 seropositivity and seroconversion in a cohort of homosexual men*. Am J Epidemiol 151:213-224, 2000.
- Sitas F et al. *Antibodies against human herpesvirus 8 in black South African patients with cancer*. N Engl J Med 340:1863-1871, 1999.
- Whitby D et al. *Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women*. J Infect Dis 179:234-236, 1999.
- Gessain A et al. *Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa*. Int J Cancer 81(2):189-92, 1999.
- Whitby D et al. *Detection of antibodies to human herpesvirus 8 in Italian children: evidence for horizontal transmission*. Br J Cancer 82:702-704, 2000.
- Olsen SJ et al. *Increasing Kaposi's sarcoma-associated herpesvirus seroprevalence with age*
- in a highly Kaposi's sarcoma endemic region, Zambia in 1985. AIDS 12:1921-1925, 1998.
- Mbulaiteye SM et al. *Human herpesvirus 8 infection and transfusion history in children with sickle-cell disease in Uganda*. J Natl Cancer Inst 95:1330–5, 2003.
- Andreoni M et al. *Primary human herpesvirus 8 infection in immunocompetent children*. J Am Med Assoc 287:1295-1300, 2002.
- Plancoulaine S et al. *Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population*. Lancet 356:1062-1065, 2000.
- Malope BI et al. *Transmission of Kaposi sarcoma-associated herpesvirus between mothers and children in a South African population*. J Acquir Immune Defic Syndr ;44(3):351-5, 2007.
- Angeloni A et al. *High prevalence of antibodies to human herpesvirus 8 in relatives of patients with classic Kaposi's sarcoma from Sardinia*. J Infect Dis 177:1715-1718, 1998.
- Goedert JJ et al. *Risk factors for classical Kaposi's sarcoma*. J Natl Cancer Inst. 94(22):1712-8, 2002.
- Mbulaiteye SM et al. *Immune deficiency and risk for malignancy among persons with AIDS*. J Acquir Immune Defic Syndr 32:527–33, 2003.
- Whitby D et al. *Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma*. Lancet 346:799-802, 1995



- Gao SJ et al. *KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma*. *Nat Med* 1996;2:925-8.
- Alkharsah KR et al. *Influence of HLA alleles on shedding of Kaposi sarcoma-associated herpesvirus in saliva in an African population*. *J Infect Dis* 195:809-16, 2007.
- Zong J-C et al. *Evaluation of global clustering patterns and strain variation over an extended ORF26 gene locus from Kaposi's sarcoma herpesvirus*. *J Clin Virol*. 40(1): 19-25, 2007.
- White, T et al. *Genetic diversity of the KSHV K1 protein in AIDS-KS in Zimbabwe*. *J of Clinical Virology*, in press.
- Ziegler JL et al. *Risk factors for Kaposi's sarcoma in HIV-positive subjects in Uganda*. *AIDS* 11(13):1619-26, 1997.
- Ziegler JL. *Endemic Kaposi's sarcoma in Africa and local volcanic soils*. *Lancet* 342:1348-51, 1993.
- Ensoli B et al. *Release, uptake, and effects of extracellular human immunodeficiency virus type 1 Tat protein on cell growth and viral transactivation*. *J Virol*. 67(1): 277-287, 1993.
- Ensoli B, Barillari G, Gallo RC. *Cytokines and growth factors in the pathogenesis of AIDS-associated Kaposi's sarcoma*. *Immunol Rev*. 127:147-155, 1992.
- Miles SA. *Pathogenesis of HIV-related Kaposi's sarcoma*. *Curr Opin Oncol*. 1994 Sep;6(5):497-502.
- Dourado I et al. *Interleukin 6 and AIDS Kaposi's sarcoma*. *Int Conf AIDS*. 1994 Aug 7-12; 10: 321 (abstract no. PC0213).
- Jacobson LP et al. *Interaction of human immunodeficiency virus type 1 and human herpesvirus type 8 infections on the incidence of Kaposi's sarcoma*. *J Infect Dis* 2000;181:1940-9.
- Jacobson LP et al. *Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals*. *Multicenter AIDS Cohort Study*. *J Acq Immun Defic Synd* 21(suppl 1): S34-41, 1999.
- Buchbinder SP et al. *Combination antiretroviral therapy and incidence of AIDS-related malignancies*. *J Acq Immun Defic Synd* 21(suppl 1): S23-26, 1999.
- Ledergerber B et al. *Risk of HIV related Kaposi's sarcoma and non-Hodgkin's lymphoma with potent antiretroviral therapy: prospective cohort study*. *British Medical Journal* 319(7201): 23-24, 1999.
- Wilson D et al (ed). *South African Handbook of HIV Medicine*. Cape Town, Oxford University Press Southern Africa, Chapter 19, 2002.
- Kagu MB et al. *AIDS-associated Kaposi's sarcoma in Northeastern Nigeria*. *Singapore Med J*. 47(12):1069-74, 2006.
- Shuler JD et al. *Kaposi sarcoma of the conjunctiva and eyelids associated with the acquired immunodeficiency syndrome*. *Arch Ophthalmol* 107:858-62, 1989.
- Kurumety UR, Lustbader JM. *Kaposi's sarcoma of the bulbar conjunctiva as an initial clinical manifestation of acquired immunodeficiency syndrome*. *Arch Ophthalmol* 113:978, 1995.
- Flaitz CM et al: *Kaposi's sarcoma associated herpesvirus-like DNA sequences (KSHV/HHV-8) in oral AIDS-Kaposi's sarcoma: a PCR and clinicopathologic study*. *Oral Surg Oral Med Oral Pathol Oral Radiol and Endod* 83:259-264, 1997.
- Ficarra G et al. *Kaposi's sarcoma of the oral cavity: a study of 134 patients with a review of the pathogenesis, epidemiology, clinical aspects, and treatment*. *Oral Surg Oral Med Oral Pathol* 66:543-50, 1988.
- Aboulafia DM: *The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma*. *Chest* 117:1128-1145, 2000.
- Gill PS et al. *Pulmonary Kaposi's sarcoma: clinical findings and results of therapy*. *American Journal of Medicine* 87, 57-61, 1989.
- Soulier J, Grollet L, Oksenhendler E, et al. *Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castlemann's disease*. *Blood* 86:1276-80, 1995.
- Hengge UR et al. *Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy*. *Lancet Infect. Dis*. 2:281-292, 2002.
- Kiss A et al. *Misdiagnosed bacillary angiomatosis*. *S Afr Med J*. 97(11):1050, 2007.
- Krown SE et al. *Kaposi's sarcoma in the acquired immune deficiency syndrome: a proposal for uniform evaluation, response, and staging criteria*. *AIDS Clinical Trials Group Oncology Committee*. *Journal of Clinical Oncology* 7, 1201-1207, 1989.
- Tam HK et al. *Effect of highly active antiretroviral therapy on survival among HIV-infected men with Kaposi sarcoma or non-Hodgkin lymphoma*. *Int J Cancer*. 98(6):916-22, 2002.
- Sgadari C et al. *HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma*. *Nature Medicine* 8(3): 225-232, 2002.
- Martinez V et al. *Remission from Kaposi's sarcoma on HAART is associated with suppression of HIV replication and is independent of protease inhibitor therapy*. *Br J Cancer*. 94(7):1000-6, 2006.
- Monticelli A et al. *Regression of AIDS-related Kaposi's sarcoma following combined antiretroviral treatment*. *Revista Argentina de Microbiologia* 32(4): 206-208, 2000.
- Bower M et al. *Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma*. *AIDS*. 1999 Oct 22;13(15):2105-11.
- Renato M et al. *Effects of HAART regimens as exclusive treatment of slow proliferating Kaposi's sarcoma*. *Thirteenth International AIDS Conference, Durban, abstract TuOrB302*, 2000.
- Asiimwe F et al. *Clinical outcomes of HIV-infected patients with Kaposi's sarcoma receiving antiretroviral therapy in rural Uganda*. *Fourteenth Conference on Retroviruses and Opportunistic Infections, abstract 880*, 2007.
- Bower M et al. *Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma*. *J Clin Oncol*.1;23(22):5224-8, 2005.
- Lyter DW et al. *Temporal relationship of changes in plasma HIV RNA levels and clinical progression or regression of Kaposi's sarcoma*. *Fifth Conference on Retroviruses and Opportunistic Infections, Chicago, abstract 433*, 1998.
- Krown SE. *Management of Kaposi sarcoma: the role of interferon and thalidomide*. *Current Opinions in Oncology* 13, 374-381, 2001.
- Boudreaux AA et al. *Intralesional vinblastine for cutaneous Kaposi's sarcoma associated with acquired immunodeficiency syndrome. A clinical trial to evaluate efficacy and discomfort associated with infection*. *Journal of the American Academy of Dermatology* 28, 61-65.
- Tappero JW et al. *Cryotherapy for cutaneous Kaposi's sarcoma associated with AIDS: a phase II trial*. *JAIDS* 4, 839-846, 1991.
- Northfelt DW et al. *Pegylated liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial*. *Journal of Clinical Oncology* 16, 2445-2451, 1998.

- Stewart S et al. *Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma*. *Journal of Clinical Oncology* 16(2): 683-691, 1998.
- Lichterfeld M et al. *Treatment of HIV-1-associated Kaposi's sarcoma with pegylated liposomal doxorubicin and HAART simultaneously induces effective tumor remission and CD4+ T cell recovery*. *Infection* 33; 140-7, 2005.
- Olweny C, Borok M et al Olweny, C.L., M. Borok, I. Gudza, J. Clinch, M. Cheang, C. Kiire, L. Levy, D. Otim-Oyet, J. Nyamaswa, and H. Schipper. *Treatment of AIDS-associated Kaposi's sarcoma in Zimbabwe: Results of a randomized quality of life focused clinical trial*. *Int. J. Cancer*. 113:632-639, 2005.

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