# Management of Recent Advances in Kaposi Sarcoma

**Essay**

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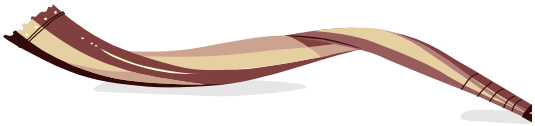

**Eman Sobhy Adarous**

# Introduction

Kaposi sarcoma (KS) is a low grade vascular tumor, first described in ١٨٧٢ by Moritz Kaposi. It manifests as nodular lesions on the skin, mucous membranes, or internal organs. Human herpes virus-٨ (HHV-٨) is implicated in the pathogenesis of KS ***(Egwuonwu et al.,*** ***).***

Classically, it consists of four clinical variants: Classic KS (CKS) - or Mediterranean KS-, iatrogenic KS, African KS, and Acquired immunodeficiency syndrome (AIDS) associated KS (AAKS). All four variants are associated with Human Herpesvirus-٨ (HHV-٨), and they show a similar histological pattern ***(Solivetti et al.,*** ***).***

KS therapy ranges from watchful waiting to aggressive chemotherapy and is largely dependent upon the lesion location, size, and extent. Localized, non-progressive disease is easily treated through cryotherapy, argon laser excision, local chemotherapeutic injection, or localized radiation. Response rates vary with each of these treatment regimens, but have been reported to reach up to ٩٠٪. For AIDS-associated and iatrogenic KS, immune reconstitution is sometimes sufficient to trigger tumor remission ***(Christin and Dittmer,*** ***).***

Incidence of KS among people with human immunodeficiency virus (HIV) or AIDS continued to decline

from the early- to the late- highly active antiretroviral therapy (HAART) period since the advent of HAART in ١٩٩٦. It also led to marked increases in their life expectancy ***(Franceschi et al.,*** ***).***

The use of Interferon- α (IFN-α-٢a and -٢b) in the treatment of KS in patients with AIDS due to HIV has been approved by the US FDA. The average response rate of KS to high-dose IFN-α therapy has been approximately ٣٠٪ ***(Berman et al., ٢٠٠٦).***

Radiotherapy is an effective and safe treatment modality for KS ***(Akmansu et al.,*** ***).***

Systemic chemotherapy treatment for KS is limited to widespread, symptomatic disease ***(Cattelan et al.,*** ***).***

The use of vascular endothelial growth factor (VEGF) inhibitors is an area of active investigation for patients with KS, and NCI-sponsored clinical trials are ongoing with Bevacizumab, Sunitinib, and Sorafenib ***(Sullivan et al.,*** ***).***

# Epidemiology

## Incidence:

KS has been categorized into four epidemiological types including the epidemic or AIDS associated KS (AAKS), an aggressive endemic (african) KS identified in sub-Saharan Africa in seronegative HIV in Africa and may carry indolent or aggressive courses, classical Kaposi sarcoma (CKS) form affecting older men of Mediterranean descent usually have benign course and iatrogenic KS resulting from immunosuppressant following organ transplantation. AAKS represents the vast majority of KS cases worldwide ***(Marshall et al.,  ).***

Even prior to the HIV epidemic, the incidence of Kaposi's sarcoma (KS) in equatorial Africa was among the highest in the world. In portions of Uganda, Tanzania, and what is now known as the Democratic Republic of Congo, the lifetime incidence of KS approached ١٦ per ١٠٠٠, thus earning the region the name "KS Belt" and non-HIV-related KS incidence was about ٣ to ١٠ times higher in this region as compared to countries further north and south ***(Sheila et al.,  ).*** KS was also endemic, although much rarer, in countries around the Mediterranean, particularly Italy, Greece, and the Middle East, but it was almost nonexistent elsewhere in the

world, except in immigrants from those endemic countries ***(Sitas and Newton, ٢٠٠٠)***. Endemic African Kaposi sarcoma has accounted for ١٠٪ of cancers and has been seen in a male-to-female ratio of ١٥:١ ***(Ruocco et al., ٢٠٠٢)***.

Before the discovery and widespread use of highly active antiretroviral therapy (HAART) KS was over ٢٠،٠٠٠ times more common in AIDS patients than the general population ***(Engels et al., ٢٠٠٦)***. However, several studies showed that HAART reduced the incidence of KS in high income countries ***(Pipkin et al., ٢٠٠٢)***. The cumulative incidence of KS declined from ١٤,٣٪ during (١٩٨٠ - ١٩٨٩) to ٦,٧٪ during (١٩٩٠-١٩٩٥) and to ١,٨٪ during ١٩٩٦ to ٢٠٠٦ ***(Simard et al, ٢٠٠٢)***.

In a Swiss HIV cohort study, the overall KS incidence was ٣٣,٣ per ١٠٠٠ HIV infected person year in ١٩٨٤–١٩٨٦ and did not change significantly in the subsequent periods until ١٩٩٦–١٩٩٨, when it fell to ٥,١ (٩٥٪ CI, ٣,٩–٦,٥) . The incidence further decreased to ١,٤ per ١٠٠٠ per year in ١٩٩٩–٢٠٠١ and remained constant thereafter ***(Franceschi et al., ٢٠٠٠)***. In another recent pan-European multi-centre study, there was a decrease in the incidence rate of KS from ٢٤,٧ cases (٩٥٪ CI ١٧,٢–٣٢,٢) per ١٠٠٠ per year in ١٩٩٤ to ٤,٧ (٩٥٪ CI ٢,٧–٦,٧) per ١٠٠٠ per year in ١٩٩٧ and ١,٧ (٩٥٪ CI ٠,٧–٣,٤) per ١٠٠٠ in recent years among HIV-infected individuals ***(Pipkin et al., ٢٠٠٢)***.

The incidence of Kaposi sarcoma (KS) has been estimated at ٠,٠٢-٠,٠٦٪ in USA. With CKS represents approximately ٠,٢٪ of cancer cases in the United States. Iatrogenic KS incidence among American renal transplant recipients is approximately ٠,٤٪.While incidence of KS among renal transplant recipients may be as high as ٣,٥٪ or higher in regions endemic for KS ***(Tornesello et al.,*** ).

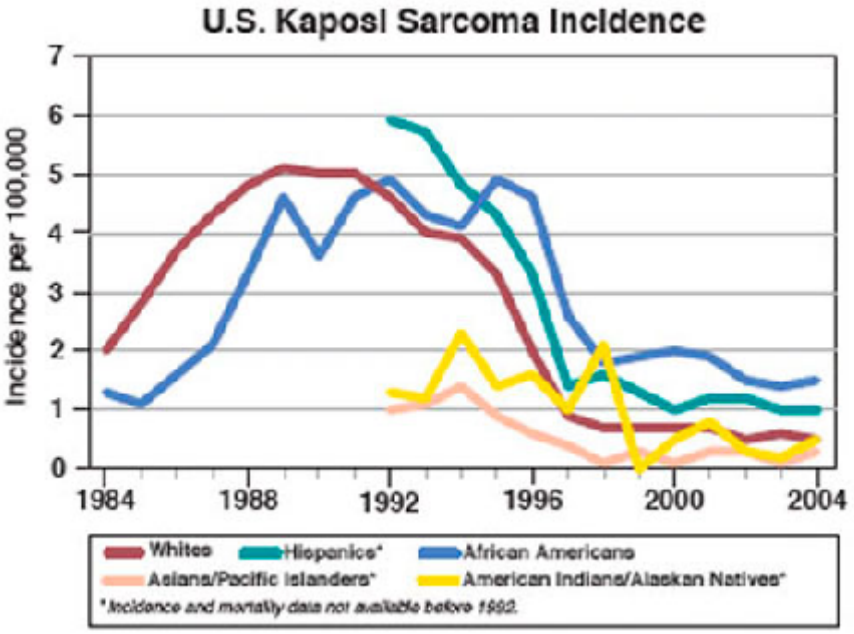


**Figure ١:** KS incidence in USA ***(Bleyer and Barr,*** ***).***

## Gender:

Despite the increasing burden of disease in women, little is known about KS in women. Because KS has historically been a male disease and cases in HIV-infected women in the

developed world are rare, studies of KS have been predominantly in men, the incidence of KS has increased exponentially in women since the beginning of the HIV pandemic. Prior to the onset of HIV, women accounted for ٥–١٠٪ of KS cases but now account for up to ٤٠٪ of incident KS in many African countries. In Uganda, the incidence of KS has become nearly equal in men and women, and it has surpassed cervical cancer as the most common female malignancy in the entire population ***(Phipps et al.,*** ***)***. The male-to-female-ratio is ٣:١ in non-AIDS KS ***(Jakob et al.,*** ***).*** While classic Kaposi sarcoma occurs more often in males, with a ratio of approximately ١٠ to ١٥ males to ١ female ***(NCI,*** ***)***.

## Age:

Although KS was rare in most parts of the world prior to the HIV/AIDS epidemic, an endemic form of KS was described in Uganda and other African countries over ٤٠ years ago . Endemic KS occurs more often in adults, but has been reported to be more aggressive in children. In Uganda, the incidence of pediatric KS has increased approximately ٢٠-fold during the HIV/AIDS epidemic and is now among the most common childhood cancers ***(Gantt et al.,*** ***)***.

Non-AIDS associated KS is mostly seen in elderly males from Mediterranean or Eastern European countries. With Mean age at onset of patients with CKS was ٦٩,٦ years ***(Jakob et al.,*** ***)***.

## Race:

In ٢٠٠٢, of ٦٦،٢٠٠ estimated KS cases worldwide, ٥٨،٨٠٠ were estimated to be in Africa ***(Parkin et al.,*** ***)***.

AAKS represents the vast majority of KS cases worldwide ***(Marshall et al.,*** ***)***. Sub-Saharan Africa remains the most affected region with HIV worldwide with heterosexual intercourse being the main mode of HIV transmission ***(Ruzagira et al.,*** ***)***.

CKS is a relatively indolent disease affecting elderly men from the Mediterranean region or of eastern European descent, besides Jews in whom it is the most common. It has been also reported in the Arab population living in Israel. Kaposi's sarcoma has been reported in Arabs after kidney transplantation; however, there are no reports of CKS occurring in non-Israeli Arabs ***(Kumar,*** ***)***.

## Etiology and Risk factors:

### *Viruses:*

#### *-Human Immunodeficiency Virus:*

Human immunodeficiency virus (HIV) is the causative agent of Acquired immunodeficiency syndrome (AIDS). HIV accounted for ٣٨,٦ million infections worldwide at the end of ٢٠٠٥. The four major routes of transmission are unprotected sexual intercourse, contaminated blood transfusion, breast milk, transmission from an infected mother to her baby at birth (vertical transmission) ***(Julie and Gideon,*** ***)***.

AAKS is an important, life-threatening opportunistic tumor among people living with HIV/AIDS in resource-limited settings ***(Chu et al.,*** ***)***.

Fewer than ٣٪ of all heterosexual intravenous drug users with HIV disease developed KS. The proportion of HIV disease patients with KS has steadily decreased since the epidemic was first identified in ١٩٨١ ***(Lodi et al.,*** ***)***. About ٤٨٪ of AIDS patients in ١٩٨١ had KS as their presenting AIDS diagnosis. By August ١٩٨٧, the cumulative proportion of AIDS patients with KS had diminished to fewer than ٢٠٪. The introduction of highly active antiretroviral therapy (HAART) has delayed or prevented the emergence of drug-resistant HIV strains, profoundly decreased viral load, led to increased survival, and

lessened the risk of opportunistic infections ***(Grabar et al., ٢٠٠٦)***.

In sub-Saharan Africa, women account for ٦٠٪ of HIV infected adults ***(Mugo et al., )***. The prevalence in women climbs steeply in the late teens, which is five years before this occurs in men ***(Jewkes and Morrell, )***.

Men who have sex with men (MSM) in the Middle East and North Africa (MENA) are a largely hidden population because of a prevailing stigma. Data from available studies indicate that the practice of anal sex contributes by considerable proportions to HIV transmission of up to ٢٦٪ in a number of MENA countries such as in Egypt, Lebanon, and Yemen. Also, reports reveal that homosexual/bisexual sex contributed cumulatively about ١٣٪ of HIV infections in Egypt, Lebanon, and Oman since the first HIV/AIDS diagnoses in these countries ***(Mumtaz et al., )***.

In Egypt less than ١ percent of the population estimated to be HIV-positive so Egypt is a low-HIV-prevalence country. Unsafe behaviors among most-at-risk populations and limited condom use among the general population place Egypt at risk of a broader epidemic. According to the National AIDS Program (NAP), there were ١،١٥٥ people living with

HIV/AIDS in Egypt by the end of ٢٠٠٧. United Nations program on AIDS estimates for ٢٠٠٥ were higher, putting the number of HIV-positive Egyptians at ٥،٣٠٠ ***(United States Agency for International Development,*** ***)***.

Egypt reported its first case of HIV/AIDS in ١٩٨٦. Among officially reported cases, heterosexual intercourse was the primary mode of transmission (٤٩,١٪), followed by homosexual intercourse (٢٢,٩٪), renal dialysis (١٢٪), and blood transfusion (٦,٢٪). Injecting drug use accounted for ٢,٩٪ of HIV infections and mother-to-child transmission for ١.٦٪; ٥,٢٪ are from "unknown" causes. Males are four times more likely to have HIV than females, but this may be due to more men being tested than women. Other people likely to be exposed to HIV in Egypt include street children, prisoners, and refugees ***(National AIDS program,*** ***).***

***-Human Herpes Virus-. (HHV-: ):***

In the last ١٥ years since its discovery, Kaposi's Sarcoma-associated Herpes virus (KSHV), also known as human herpes virus ٨ (HHV-٨) is the most recently identified human tumor virus, and is associated with the pathogenesis of Kaposi's sarcoma ***(Cai et al.,*** ***)***.

KSHV is a member of the lymphotropic (or γ) herpesvirus subfamily; KSHV's primary target cell is the B cell ***(Ganem,*** ***)***.

HHV-٨ replication is necessary for KS tumor growth and maintenance, and the detection of replicating HHV-٨ in the peripheral blood predicts the development of all types of KS ***(Phipps et al.,*** ***)***.

Several cytokines and growth factors have been shown to support the growth of cultured KS spindle cells; these include interleukin IL-١b, IL-٦, the soluble IL-٦ receptor a, oncostatin M, and tumor necrosis factor TNF-α. The evidence suggests that cytokines can increase the frequency and aggressiveness of KS by enhancing the effect of angiogenic factors or by reactivating KSHV reinfection, which is etiologically closely associated with KS ***(Su et al.,*** ***)***.

In many parts of Africa where KS is endemic, the HHV٨ seroprevalence in the general population is often above ٢٠٪ while lower rates ranging from ٠–٢٠٪ have been reported from countries in Europe and North America where KS occurs rarely ***(Ogoina et al.,*** ***)***.

The modes of transmission of HHV٨ are yet to be fully elucidated. In the United States, sex between men may be an

important route of transmission because this is the main behavioral risk factor for KS. There is weak evidence of sexual transmission of HHV٨ in the South African population, although the increase in risk with increasing number of sexual partners was not great. Furthermore, no difference was seen in the seroprevalence of HHV٨ in those individuals with or without HIV infection. However, throughout sub-Saharan Africa, where KS was seen in children even before the advent of AIDS, other routes of transmission must also be occurring ***(Sitas and Newton, ٢٠٠٠)***. The definite route of transmission of HHV-٨ is still debated. The possible routes of transmission including horizontal, sexual, vertical, blood borne, and through organ transplantation ***(Sunil et al., ٢٠٠٧)***.

Infection with this virus is thought to be lifelong, but a healthy immune system will keep the virus in check. Many people infected with KSHV will never show any symptoms. KS occurs when someone who has been infected with KSHV becomes immunocompromised due to AIDS, medical treatment or very rarely aging ***(Bu et al., ٢٠٠٠)***.

KS is an angioproliferative disease occurring in several clinical-epidemio-logic forms but all associated with infection by HHV-٨. At early stages, KS is a reactive disease associated