Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

Pharmacy Review

Ebola

I have recently returned from Sierra Leone after helping with an Ebola clinical trial with a team from Oxford University, funded by the Wellcome Trust. The clinical trial results are not yet available, and I am not going to pre-empt the results.

The journal *PharmaTimes* has published a series of articles on Ebola in their March edition.[1] The articles estimate the cost of the epidemic as more than £30 billion (US$40 billion), which includes loss of earnings and costs to the economy of West Africa, not just Sierra Leone, Guinea, and Liberia.

The simplest way to reduce mortality is with early rehydration and electrolyte replacement. The article lists some of the vaccines and drug treatments either currently being studied, or in the pipeline, 3 vaccines, 3 drug treatments, and antibodies from survivors.

An article in the online journal *mBio*, published by *the American Society of Microbiology*[2] looks at known and supposed methods of transmission of Ebola. Surfaces in Ebola treatment centres, including the outside of workers' masks, have been shown to contain virus material, but there is no evidence of infection from visibly clean surfaces. There have been very few cases from contact with asymptomatic patients in the early stage of the disease.

The vast majority of cases concern contact symptomatic Ebola patients. As patients become more ill with Ebola, the number of virus particles shed increases. After death there is a high risk of infection. In one incident, 300 positive cases were the result of 1 unsafe burial.

Ebola is highly infectious and exposure to as few as 10 virus particles can cause infection. It is possible that infection occurs through the inhalation of virus particles from body fluids. Infection in animals has been proven to occur through inhalation, but this has not been established in humans.

Full personal protective equipment (PPE) prevents infection, provided that doffing (undressing and removal) is done in a controlled manner preventing contact with the outside of the PPE.

There have been two health workers infected in the USA who came into contact with an Ebola patient, but the mode of transmission is unknown, as they were wearing PPE.

As I write the latest news is that after a drop in cases, the numbers have once again gone up, but nowhere near the levels seen earlier in the epidemic.

A World Health Organization (WHO) press release (widely reported in the media) said that vaccine trials will not produce any useful data as the number of cases is falling. The WHO also reported that 'two drugs Zmapp made by Zmapp Pharmaceuticals and sIRNA by Tekmira Pharmaceuticals are also being tested and it is hoped that they will produce some limited results on efficacy'.

We all hope that the current epidemic will resolve, and that international resources will be more rapidly made available in future outbreaks. To prevent the high numbers of deaths seen in the current outbreak. The Ebola Virus in the current West Africa outbreak is a different strain from previous outbreaks, which may explain the much higher number of cases. Poor living conditions and poverty are also factors.

I was told in Sierra Leone that the rapid diagnosis kits used were useless as they gave a significant number of false-positive and false-negative results, so it was never sure from the results if a patient had Ebola or not. The tests were abandoned in favour of the more lengthy viral Polymerase Chain Reaction (PCR) tests.

Too much medicine

The *British Medical Journal* has published a series of articles, 'Too Much Medicine' about the dangers of over treatment. This is nothing new as the WHO Model Formulary (which has not been revised since 2008) has in its introduction some guidelines about treating patients:
General advice to prescribers:
Rational approach to therapeutics:
Drugs should only be prescribed when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risks involved. Bad prescribing habits lead to ineffective and unsafe treatment, exacerbation or prolongation of illness, distress and harm to the patient, and higher cost.

1. Define the patient's problem;
2. Specify the therapeutic objective;
3. Select the therapeutic strategies:
   a. Non-pharmacological treatment;
   b. Pharmacological treatment;
3. Selecting the correct group of drugs;
4. Selecting the drug from the chosen group (to suit an individual patient);
5. Giving information, instructions, and warnings;
6. Monitoring treatment.

If a decision has not been made about the treatment outcome, it needs to be considered whether or not the patient needs the treatment. Monitoring treatment is important because it may indicate that the treatment isn't working, or if the patient suffers from adverse effects and stops long-term treatment.

The edition published on 4th March 2015 has 'Too Much Medicine'[3] as its theme and the phrase can be used to describe a variety of problems including: overdiagnosis; overtreatment; and turning an ordinary event into a medical diagnosis ('medicalisation'), for example old age.

An article in the same edition[4] looked at overprescribing of antimalarials in Ghana. Rapid diagnostic tests were used in drug stores (called chemical shops in Ghana). After proper training, especially to prevent the spread of Hepatitis B, the tests were used. The outcome

was that fewer antimalarials were used, but that the patients proven to have malaria were still receiving adequate treatment.

In the study, three quarters of the patients presenting with fever tested negative for malaria and required only simple analgesia. Correct rapid diagnosis is appropriate for many conditions.

New medicines, better medicines, better use of medicines

In May 2014, the Royal Pharmaceutical Society of Great Britain published a report 'new medicines, better medicines, better use of medicines'.[5]

The first part of the report covers the history of medicine development, antibiotic development, neglected diseases (some are tropical diseases, others rare genetic disorders), new uses for old drugs, selecting appropriate medicines for individual patients.

The second part of the report looks at the better use of medicines. Using medicines only when appropriate, improving patients' awareness of their medical condition to improve compliance with treatment.

The wide-ranging report deals also with medication errors including better prescribing, ensuring the correct medicines are dispensed, and getting an accurate drug history of the patient. Accurate drug histories are important to make sure vital medicines are not omitted, and to prevent drug interactions.

The correct use of antibiotics is mentioned, using them only when necessary. The development of new antibiotics presents a problem. There have been no new classes of antibiotics since 1987, and it would be difficult for the pharmaceutical industry to make a profit on development costs if new antibiotics are kept in reserve and very rarely used as a last resort.

One specific problem of prescribing antibiotics is mentioned that, in developed countries, children are significantly heavier at a given age, and the recommended doses for a given age group may not be sufficient to treat them. To reduce the risks of the infection and of antibiotic resistance the weight of children should be taken into account. In addition for obese patients, the doses required need to be adjusted as many drugs are not distributed into fat, and if a dose is based only on weight, patients will be over-dosed.

The 120-page report is worth looking at; the important points are in highlighted boxes, making reading it easier.

New guide to medicines and drugs

A few years ago I reviewed the British Medical Association publication, 'A New Guide to Medicines and Drugs', a new edition has been published at the beginning of this year,[6] it has been updated and includes new classes of medicines, for example monoclonal antibodies (the 'mab's'). It is still one of the best reference books available on the UK market, and relatively inexpensive at £18.99.

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Public Health Review

Impact of Ebola on public health programmes

Normally our public health reviews scan recent literature to highlight a current public health issue. Since the Ebola outbreak of 2013-2015 in West Africa is such a recent event itself, much of the available information on its impact must also be gleaned from the press and agency reports. Hopefully a more permanent documentation of the lessons from Ebola can occur as time gives a longer perspective on our public health systems.

First we will briefly set the stage and show how Ebola Virus Diseases (EVD) disrupted the public health system by damaging the already weak human, material and infrastructural resources of the health system. Then we briefly examine effects on specific public health programmes including immunisation, antenatal care, malaria prevention and food/nutrition.

Overview of the Ebola effect on health systems

As of mid-April 2015, the World Health Organization (WHO) reported that 861 health workers had contracted EVD and 499 had died.[1] Using data on WHO country profile websites[2] and Ebola statistical updates[3] as of April 2015, doctors, nurses and midwives were only 0.02% of the population of the three countries, but accounted for 3% of Ebola cases and 5% of Ebola deaths.

Not only did the loss of health workers make it difficult or impossible to run a health clinic, the fact that those entrusted with community health were dying created fear. 'Lack of trust in government-supported services after the death of a healthcare worker with symptoms of Ebola resulted in ongoing Ebola transmission in two Liberia counties. Ebola transmission was facilitated by attempts to avoid cremation of the deceased patient, and delays in identifying and monitoring contacts.'[4]

The reason health workers were dying in such relatively large numbers could be traced to the inadequacies in basic equipment, supplies and adherence to procedures to prevent infection in the workplace.[5] Infection prevention and control (IPC) has received much attention in terms of preventing the spread of EVD, but if such measures had been in place prior to the Ebola outbreak to enable safe handling of blood and other samples, and safe disposal of human and hospital wastes, EVD would not have gotten a foothold within the health services.

WHO did update its infection prevention guidelines with special reference to hemorrhagic fevers in December 2014.[6] Efforts to promote IPC in all healthcare procedures has long predated the current EVD outbreak.

For example, for more than a decade, Jhpiego has been an international leader in advocating for and implementing evidence-based standards for infection prevention (IP) practices that protect both client and healthcare worker.[7]

Immunisation programmes

When clinics close or are understaffed, child health programmes like immunisation halt. The fact that needles are involved increases the risks that such efforts could spread EVD if not done with care.

Saki Takahashi and colleagues undertook a projection in late 2014 of what the disruption in health services would mean for the spread of measles. They estimated that after 6-18 months of health service disruption, the pool of unvaccinated and susceptible children could increase to over 200 000 resulting in 2000 to 16 000 additional deaths.[8]

Unfortunately, the response needed to be guarded. WHO recommends that countries for the moment avoid mass gatherings. Vaccination campaigns are advised to be postponed until the country has been declared Ebola free after 42 days without detection of any new cases.[9]

The reality was not as dire, but disturbing none-the-less. 'This January a measles outbreak erupted. So far this year, there have been 562 cases; seven were fatal.' In addition, more than 500 children came down with whooping cough. This led Liberia to launch a nationwide measles vaccination campaign in May, wherein health officials hoped to reach almost 700 000 children in a country of 4 million people.[10]

Antenatal care

Several Non-Government Organisations in Sierra Leone reported on the views of children on the effects of the EVD epidemic in their communities. A common perspective was that, 'all health resources were focused on Ebola, neglecting other conditions'. Because of this, the report also explained, 'Pregnant women and new mothers lost out on access to the pre- and post-natal care that is required to reduce maternal mortality rates'.[11]

In Liberia, Lyengar and colleagues studied maternal and child health service utilisation in two counties during the EVD outbreak. They found that Bong and Margibi Counties in Liberia experienced a large drop in utilisation of maternal healthcare services during what now appears to be the peak of the Ebola outbreak. 'In Bong County, totals were less than 14% of the peak numbers during the outbreak for number of antenatal visits and pregnant women receiving intermittent preventive treatment for malaria in pregnancy (IPTp).'[12]

Bednets for malaria

Models have shown that an additional 3.5 million malaria cases may have resulted from the inability of the health services during the Ebola outbreak to provide prevention and treatment services.[13] Regular net distribution is crucial 'because nets degrade over time as a result of wear and tear and waning insecticide concentration'.

Although malaria mortality has been reducing generally in Africa, in part through distribution of free insecticide-treated bed nets (ITNs), 'the Ebola outbreak has brought those efforts to a standstill in the three affected countries'.[14] Liberia had planned a national campaign to distribute ITNs in 2014, but that was postponed.

It had been hoped that in preventing malaria, people would be less likely to have fevers that were not Ebola and therefore less likely to come in contact with real Ebola patients in Ebola treatment units. World Malaria Day 2015 (25th April) was used to launch of the distribution of 2.8 million mosquito nets in Liberia.[15] This began with two-day training sessions for general community health volunteers who would help distribute the nets and reinforce their use.[16]

Nutrition and food security

'The world's worst Ebola epidemic has endangered harvests and sent food prices soaring in West Africa', according to the United Nations Food and Agriculture Organisation (FAO).[17] The situation was made worse by restrictions on people's movements and the establishment of quarantine zones. Not only were farmers affected by EVD, but many workplaces closed either due to fear or loss of staff, such that food was no longer affordable or accessible.

Using Liberia as an example, the World Food Programme reported that restricted movement and border closures constrained food transporters/traders from moving food within Liberia. Areas with high incidences of EVD are among the most productive agriculture regions (Central and Northwest).[18]

The overall effect of these market challenges is that people began reducing the number of meals they ate each day. Even when food is available, prices increase, especially for imported supplies that were to replace lost production on the local farms. Overall the situation was 'compounded by the fact that household incomes and savings are decreasing, as people are either unable or too afraid to work. And as more and more people contract the virus or die from it, families are also losing key sources of revenue'.[19]

In conclusion, Ebola caused major disruptions of already weak health systems such that basic preventive and public health services were severely curtailed or halted. This led to what could be termed collateral deaths by people who caught malaria since they did not have an ITN, who could not protect their pregnancies through regular antenatal care, who could not get enough to eat and stave off nutrition-related illnesses, and who could not receive life-saving vaccinations. The next disaster might be a disease like Middle East Respiratory Syndrome, or an earthquake or typhoon. It could even be man-made civil wars. The key lesson from Ebola is that contingency planning needs to be in place to ensure that basic public health services can continue.

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Dermatology Review

Kaposi's sarcoma is a significant problem even in the era of highly active antiretroviral therapy

Kaposi's sarcoma (KS) was the first tumor to be described in association with HIV infection and is an AIDS-defining condition. It remains a significant problem in sub-Saharan Africa even in the era of highly active antiretroviral therapy (HAART), and recent published studies on HIV-related KS come mainly from observations of KS in African populations. This article gives an overview of the current status of HIV-KS in Africa.

KS is a malignancy of the lymphatic endothelium resulting in angioproliferative lesions, which most commonly involve the skin. There are 4 clinical variants of KS: 'classical KS' which was first described in 1872 in Europe; 'endemic KS' which was described in the 1950s in young predominantly male individuals mainly in sub-Saharan Africa; 'iatrogenic KS' as a consequence of long-term immunosuppressant medication; and 'epidemic KS' which is associated with AIDs and was first described in 1981. All epidemiological types of KS are associated with Human Herpes Virus type 8 (HHV-8), which is also know as KS-associated herpes virus (KSHV). Histologically and clinically these variants are similar but their clinical course and prognosis vary. African endemic KS is generally an indolent disease in the majority of cases. In contrast HIV-KS can be an aggressive disease with advancing HIV immunosuppression and is associated with significant morbidity and mortality.[1] Prior to 1981, African endemic KS comprised less than 10% of all malignancies in sub-Saharan Africa (in 1971 it comprised 9% of all cancers seen in Uganda). Now KS, largely as a consequence of the HIV pandemic, is one of the most common malignancies in sub-Saharan Africa and the most common malignancy in HIV-infected individuals with a recorded prevalence of more than 50% of all cancers in some regions of Africa.[2] The pathogenesis of HIV-KS is multifactorial and involves an interaction of HIV immunosuppression, HHV-8 co-infection, HIV-1 replication induced pro-angiogenic transactivating (*tat*) protein, and inflammatory cytokines. Histologically, KS lesions are characterised by proliferating spindle cells, angiogenesis, erythrocyte-replete vascular slits, oedema, and a variable inflammatory cell infiltrate. Prior to the availability of HAART in sub-Saharan Africa, HIV-KS mortality was high with a 12 month overall survival of only 30-40%. Since the introduction of HAART there has been a general decline in the incidence of HIV immunosuppression-related KS and a significant improvement in survival of patients with established HIV-KS. However, immune reconstitution inflammatory syndrome (IRIS)-associated KS is now a well-recognised potential complication following ART initiation.[2-5]

Clinical features of HIV-KS

In HIV seropositive individuals cutaneous KS is the most common clinical presentation in adults, whereas children more commonly present with enlarged lymph nodes. Skin lesions often begin as violaceous macules before progressing to papules, plaques, nodules and even tumorous lesions. Cutaneous lesions have also been described as 'fungating', 'vegetative' and 'verrucous'. Skin lesions can occur at all sites on the body

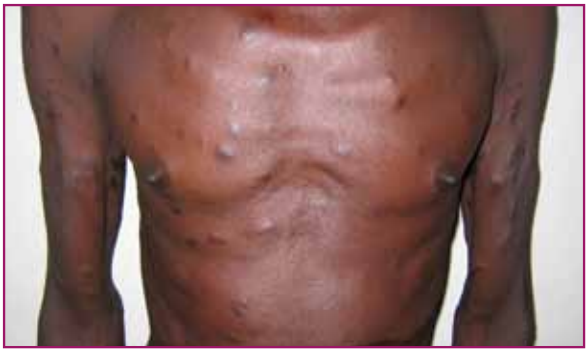

Figure 1: Widespread cutaneous HIV-KS

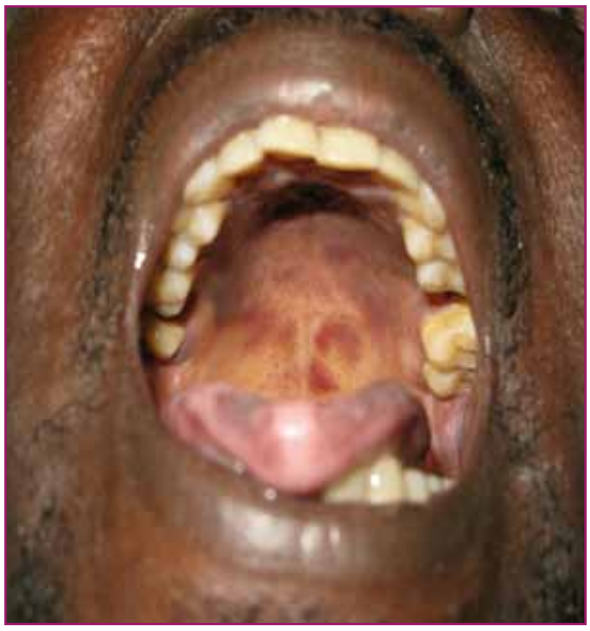

Figure 2: Patient in figure 1 with oral mucosal KS

and are usually symmetrical (Figure 1). Cutaneous disease is usually asymptomatic but can be disfiguring and stigmatising. Ulceration, bleeding, and secondary bacterial infection can complicate large cutaneous KS lesions. KS is commonly associated with non-pitting oedema, which signifies lymphoedema and this most commonly involves the face, genitals and limbs. KS lymphoedema can become painful and cause functional impairment. Cutaneous KS is not life-threatening but visceral KS can lead to severe complications associated with bleeding and obstruction. The lymph nodes are the most commonly involved extra-cutaneous site followed by the gastrointestinal tract. Oral mucosal involvement, particularly of the hard palate, gingivae and tongue, is seen in approximately 20% of HIV-KS cases (Figure 2). Oral KS is often a useful indicator of visceral involvement and is believed to be associated with a worse prognosis. Pulmonary KS, although less common, is associated with the worst prognosis and requires urgent management. It is associated with symptoms of cough, dyspnea, and haemoptysis. Systemic gastrointestinal and pulmonary KS may occur in the absence of skin lesions.

Figure 3: IRIS-KS manifesting with rapid expansion of existing lesions and development of new lesions associated with significant oedema

IRIS-associated KS

Improved access to ART has dramatically reduced HIV-associated mortality and commencement of antiretroviral therapy (ART) earlier in the course of advancing HIV immunosuppression significantly improves outcomes. However, ART-associated immune reconstitution has been associated with a paradoxical worsening of some diseases or development of new disease, a phenomenon known as IRIS. The risk of IRIS is highest amongst individuals who have been diagnosed with HIV late in the course of HIV immunosuppression and therefore have been commenced on ART with a low baseline CD4 count. This clinical scenario is not uncommon in sub-Saharan Africa and therefore IRIS-related diseases, in particular opportunistic infections, have been a significant problem. This includes IRIS-associated cryptococcosis and tuberculosis, which are associated with considerable morbidity. In sub-Saharan Africa IRIS-associated KS is now also a well-recognised complication. Unmasking IRIS-KS (the development of KS *de novo* with successful immune reconstitution following ART initiation) and paradoxical IRIS-KS (a paradoxical worsening of existing KS despite successful immune reconstitution following ART initiation) has a prevalence of 7%-31%.[4] This wide variation in prevalence is probably a consequence of differences in initial severity of KS, the stage at HIV immunosuppression when ART is commenced, and differences in ART regimens and protocols in different settings. IRIS-KS can develop quickly and be severe. Onset is between 1-22 weeks, but usually occurs within the first 3 months after ART initiation[4,5] as is the case with most IRIS-associated diseases. It is associated with a rapidly declining HIV viral load and improving CD4 counts. IRIS-KS often presents with inflammation and enlargement of existing cutaneous KS lesions and/or worsening of KS-associated oedema (Figure 3). Existing lesions may also extend and new lesions may appear at different anatomical sites. The increasing size or extension of cutaneous KS lesions can be dramatic and alarming. The significant oedema associated with IRIS-KS can cause discomfort. Severe facial and periorbital odema associated with KS has been reported to be so severe as to prevent patients from opening their eyes. IRIS-KS is associated with a high-risk of gastrointestinal and pulmonary involvement, and serious and life-threatening complications of IRIS-KS include gastrointestinal bleeding and acute airway obstruction. A worsening of pulmonary KS as a consequence of IRIS in particular requires vigilant and close monitoring.[5] Patients should be counseled and supported to continue with ART despite any sudden deterioration of visible cutaneous KS following ART initiation. It is also important to differentiate IRIS-KS from worsening KS as a consequence of ART failure.

Diagnosis

KS in HIV-infected individuals is an AIDs-defining diagnosis irrespective of the CD4 count. Although the risk of KS is higher with advancing HIV immunosuppression, it can occur also at relatively high CD4 counts before ART initiation. The cutaneous lesions of KS are often easily recognisable and pathognomonic. However, there is a wide differential diagnosis of cutaneous angiomatous lesions and diseases such as bacillary angiomatosis, lymphoma, haemangiomas, sarcoidosis, vasculitis and others have been misdiagnosed as KS. Therefore, if possible, a biopsy is recommended to confirm the diagnosis of KS. In resource-limited settings stools are usually evaluated for occult blood to screen for GI involvement. Endoscopy establishes the diagnosis. Similarly a chest X-ray may identify pulmonary involvement but a definitive diagnosis requires a bronchoscopy.

The most widely accepted staging system for HIV-KS in adults is the AIDS Clinical Trials Group (ACTG) criteria which classifies disease according to three criteria: tumour extent, immune status, and associated systemic illness, each of which is subdivided into good and poor prognostic indicators.[6]

Treatment

Despite the potential risk of IRIS-KS, ART had been shown to decrease the incidence of new KS among HIV-infected individuals and is also associated with the resolution of KS lesions. ART-associated regression of KS is believed to be related to a number of factors: a reduction in HIV viral load and therefore tat-induced angioproliferation, improved immune responses to HHV-8, and the direct anti-angiogenic effect of some protease inhibitors. Therefore, HIV-KS is managed by ART initiation if patients are ART naïve with the aim of reversing HIV immunosuppression. ART alone is usually adequate for KS localised to the skin and mucous membranes. Systemic cytotoxic chemotherapy is necessary for advanced disease at risk of complications. This includes symptomatic visceral disease, IRIS-KS, and extensive lymphedema. Radiotherapy may be required in cases of airways obstruction and is also very effective for large, troublesome cutaneous lesions and localised painful lymphoedema. Radiotherapy is also given to palliate patients with very low CD4 counts who require systemic chemotherapy, but will not tolerate the side effects. In some centres chemotherapy is deferred in patients with low CD4 counts until their CD4 count improves with ART.[3]

A recent Cochrane Review assessed the effectiveness of current therapeutic regimens for severe or progressive HIV-KS. They identified six randomised controlled trials and three observational studies that assessed the efficacy of HAART monotherapy and combinations of HAART and chemotherapy. Seven of the nine studies included patients with mild to moderate (T0) KS as well as severe (T1) KS, and therefore data could only be extracted from 792 adults with severe HIV-KS. The review's findings concluded that HAART in combination with chemotherapy demonstrates greater efficacy in reducing disease progression compared to HAART alone in patients with severe or progressive KS. They observed no difference between the efficacy of liposomal doxorubicin, liposomal daunorubicin and paclitaxel in patients on HAART.[7] However, these chemotherapy regimens are not widely available in resource-limited regions and there are limited studies evaluating HAART chemotherapy regimens for HIV-KS in Africa where first-line therapy often still consists of combinations of vincristine, doxorubicin, and bleomycin (ABV). Oral etoposide is also used when intravenous drug therapy is not available or possible because of limitations of resource. The first randomised controlled trial of HAART versus HAART and chemotherapy for HIV-KS in Africa was only recently published in 2012 and demonstrated higher overall KS response over 12 months for HAART/chemotherapy combination therapy.[3]

Corticosteroids have no role in the management of KS. Corticosteroids have been associated with the development of new KS or progression of existing KS, possibly as a consequence of its effect on HHV-8 viral replication. Corticosteroids use in HIV-infected patients with KS should be avoided except in circumstances when it is absolutely necessary for the treatment of other diseases. In such instances patients require careful monitoring for any worsening of any visceral KS.

In the case of IRIS-KS, ART should be continued. Chemotherapy is indicated and is effective in suppressing IRIS-associated flare. It is possible that chemotherapy for extensive KS prior to ART initiation may help to prevent IRIS-KS, but this has not been systematically investigated. Close clinical monitoring is recommended in seropositive patients with existing KS when initiating, changing or resuming ART because of the risk of paradoxical IRIS.

In conclusion, sub-Saharan Africa still has the highest burden of HIV-KS globally. This has been attributed to a number of factors: the high seroprevalence of HHV-8, advanced HIV immunosuppression before ART initiation, and the risk of IRIS-KS. The clinical course of HIV-KS is unpredictable: it can produce mild and limited disease or severe and progressive disease. Furthermore, ART can lead to regression of KS or a paradoxical worsening. Following the diagnosis of cutaneous HIV-KS, patients should be carefully assessed for possible visceral involvement and monitored for disease progression after ART initiation.

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