

STRATEGIES TO IMPROVE KAPOSI SARCOMA OUTCOMES (SIKO): AN EDUCATIONAL INTERVENTION IN ZIMBABWE



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The SIKO study comprises an educational intervention at both urban and rural primary care centres to increase early recognition and diagnosis of AIDS-KS, and to integrate palliative care principles into its management. The study has developed a management algorithm to include digital communication with the referral centre in Harare. It is hoped that the SIKO interventions will result in earlier diagnosis, improved quality of life, survival and retention in care of patients with AIDS-KS.

In recent years, the prevalence of HIV-1 infection has decreased in many African countries, including Zimbabwe.¹ In addition, deaths from acquired immune deficiency syndrome (AIDS) have reached a plateau: the decline is attributable partly to improved access to treatment for human immunodeficiency virus type 1 (HIV-1) infection following support by PEPFAR and other global health programmes. However, even with the rollout of antiretroviral therapy (ART), malignancies associated with HIV-1 infection, in particular AIDS-associated Kaposi sarcoma (AIDS-KS), remain a major cause of morbidity and mortality. AIDS-KS is the third leading cause of death among people initiating antiretroviral therapy in southern Africa. Reduction in the burden of AIDS-KS in Africa will require improved strategies to address the prevention and treatment of this malignancy, and its associated symptoms, particularly in primary care settings. In order to realize the greatest possible benefits from ART in Africa, it is important that AIDS-KS treatment strategies be developed that are feasible and sustainable in resource constrained areas.

Burden of AIDS-KS in the era of ART rollout in Africa

AIDS-KS results from co-infection with HIV-1 and Kaposi sarcoma-associated herpes virus (KSHV or human herpes virus-8, HHV-8). The high prevalence of HIV-1/KSHV co-infection in sub-Saharan Africa places 30–50% of HIV-1

infected Africans at risk for the development of AIDS-KS.²⁻⁷ The availability of ART was associated with a dramatic decrease in AIDS-KS incidence in the developed countries.⁸ For various reasons initiation of ART as part of AIDS-KS treatment in Africa presents unique challenges: frequent co-morbid conditions, late presentation, persisting limitations in access to ART, the need for concomitant chemotherapy and a high mortality rate. Indeed, AIDS-KS continues to be a significant cause of morbidity and mortality in sub-Saharan Africa despite increased access to ART in recent years. KS is the third leading cause of death in ART programmes in southern Africa, causing 14% of deaths after initiation of ART⁹⁻¹⁰ compared to 21% and 20% of deaths from *M. tuberculosis* and *Cryptococcus neoformans* infections, respectively.

Kaposi sarcoma burden in Zimbabwe

Zimbabwe was one of the countries around the world that was hardest hit by the AIDS epidemic with approximately 1.5 million people living with HIV-1 infection.¹² Since 30% of HIV-1 infected Zimbabweans are co-infected with KSHV¹², there are large numbers of Zimbabweans who are at risk of developing of AIDS-KS. Between 1987 and 1995 the incidence of KS increased over 40-fold in Zimbabwean men and over 200-fold in Zimbabwean women.¹⁴ The peak incidence of KS is in 20–40 year-old men and 20–30 year old women. Among adults, KS is the most common cancer in men

and the second most common in women. For those under 15 years of age, KS remains in the top five cancers for both girls (9.5% of all female paediatric cancers in 2010) and boys (12% of all male paediatric cancers in 2010).

Treatment outcomes of AIDS-KS in Zimbabwe

In the pre-ART era, five year survival from KS in Zimbabwe was 4% compared to 15% five year survival in the United States.¹⁵ The disparity between AIDS-KS treatment outcomes has persisted despite the wider availability of ART in Africa. In recent studies conducted in Europe and North America the rate of partial or complete response to ART with chemotherapy has ranged from 30% to 80%.¹⁶⁻²¹ After 96 weeks of ART, despite suppression of plasma HIV-1 RNA below the limits of detection and significant increases in CD4+ lymphocytes, only 19% of Zimbabweans had complete or partial resolution of AIDS-KS clinical disease and 16% had died.²² The most common cause of death was infection (bacterial sepsis, pneumonia and cryptococcal meningitis), and all deaths during the first 24 weeks after the initiation of ART were attributed to infectious complications. Infections also caused significant morbidity during ART and 66% required treatment for one or more new or recurrent infections. The use of adjunctive chemotherapy was associated with a 4.8-fold increase in the odds of survival compared to ART alone.

Importantly, 34% of participants had no improvement in the KS quality of life module score after 24 weeks of treatment, indicating that more effective treatment of symptoms related to AIDS-KS and associated co-morbidities is needed for a large portion of AIDS-KS patients after beginning ART.²³ Compared to African AIDS patients without KS, African AIDS-KS patients have worse clinical outcomes²⁴⁻²⁵, so the discrepancies between AIDS-KS outcomes in Africa and developed countries are not solely attributable to difficulties in the use of ART in African settings. Rather, it is likely that treatment of AIDS-KS in African settings poses unique challenges and alternative, innovative approaches are needed to improve AIDS-KS treatment outcomes in Africa.

Current approach to delivery of care to people with AIDS-KS in Zimbabwe

The Parirenyatwa Hospital KS Clinic located in Harare, the capital city of Zimbabwe, serves as a KS referral centre for the northern two-thirds of Zimbabwe and provides care for approximately 1,100 to 1,200 AIDS-KS patients annually. However, Zimbabwe is predominantly a rural country and over 80% of the population lives in small towns, villages and rural areas. Medical care in these areas is provided through a system of health centres and district hospitals which are staffed by generalist medical officers and nurses. Although

Figure 1: The SIKO Kaposi sarcoma standardized examination checklist



SIKO KS Standardized Examination (KS-SE) Checklist
 Complete for all patients at initial (intake) visit and every year thereafter
****If patient has KS, place completed form in patient folder****
****If patient does not have KS, place completed form in SIKO filing cabinet****

Clinic Name: _____ Date: _____
 Patient Name: _____ OI Clinic No.: _____

A. EXAMINATION: KS ORAL DISEASE **O No KS SEEN**

ASK: Do you have any lesions in your mouth? Yes No
 Do you have pain or difficulty in swallowing? Yes No

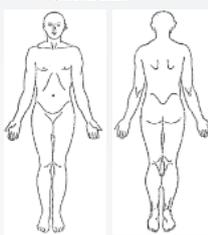
LOOK:	Normal	Flat KS Lesions	Raised KS Lesions
Lips			
Inner lip			
Inside cheek			
Hard and Soft Palate			
Tongue			
Floor of Mouth			
Gums			

B. EXAMINATION: KS SKIN DISEASE **O No KS SEEN**

ASK: Have you noticed any disease on your skin? Yes No

LOOK:	Patch / Macule	Plaque / Elevated	Nodule
No Skin Disease			
Scanty (<5)			
Mild (5 - <20)			
Moderate (20-50)			
Severe (50+)			

	None	Some Pitting	Severe or Non Pitting
Leg edema			
Other sites (e.g. face, arms, genitals): Specify: _____			



C. EXAMINATION: LYMPHNODES (GLANDS) **O No GLANDS FELT**

SK: Have you noticed any lumps/glands on your body? Yes No

FEEL:	None	Yes, few (1 or 2)	Yes, many (3 or more)
Sub-mental (chin) / Sub-mandibular (jaw)			
Cervical (neck)			
Supraclavicular			
Axillary (armpit)			
Epitrochlear (elbow)			
Groin/Femoral			

D. EXAMINATION: CHEST **O NORMAL**

ASK ABOUT

	None	Duration Less than a month	Duration more than a month
Cough			
Difficult breathing			
Chest pain			

EXAMINE

	None	Location (e.g. right / left & anterior / posterior)	Generalized
Dullness			
Crackles			
Wheezes			

E. EXAMINATION: ABDOMEN **O NORMAL**

ASK

	None	Duration (< month or > month)	Severity (mild or severe)
Nausea			
Vomiting			
Abdomen pain			
Rectal bleeding			

FEEL

	No	Yes	If yes, size (cm):
Hepatomegaly (RUQ)			
Splenomegaly (LUQ)			
Ascites			

CXR:
 None Normal Hilus LN Pulmonary Infiltrate Pleural/Pericardial

Comments: _____

Table 1: Summary of recommendations for AIDS-KS management in recent international guidelines

Source	Kaposi sarcoma-related recommendations			
	Screening	Diagnosis	Staging	Treatment
Integrated management of adolescent and adult illness, chronic HIV care module (WHO 2006) http://www.who.int/3by5/publications/documents/imai/en	None	None	None	None
Primary care guidelines for the management of persons infected with HIV (IDSA 2009) Aberg et al., <i>Clin Infect Dis</i> 2009; 49:651–81	Examine skin and mouth for KS lesions	None	None	None
Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents (NIH/CDC/IDSA, 2013) http://aidsinfo.nih.gov/guidelines	None	None	None	ART for all KS; ART with chemotherapy for visceral and disseminated disease
Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (US DHHS 2013) http://aidsinfo.nih.gov/guidelines	None	None	None	None
Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (WHO, 2013) http://www.who.int/hiv/pub/guidelines/arv2013/download/en/	None	Criteria for clinical and definitive diagnoses	None	None
Integrated management of childhood illness, <i>Manual on Paediatric HIV Care and Treatment for District Hospitals</i> (WHO 2011)	None	None	None	None
Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children (US DHHS, 2009) http://aidsinfo.nih.gov/guidelines	None	None	None	None

access to ART through these facilities is increasing through the efforts of the Ministry of Health to decentralize ART in Zimbabwe, AIDS-KS treatment is centralized at tertiary referral centres such as the Parirenyatwa Hospital in Harare where laboratory facilities and chemotherapy drugs are available; patients with AIDS-KS are often diagnosed late in the course of their illness, resulting in a high tumour burden on presentation. In a study conducted in Harare, after 96 weeks of ART, despite suppression of plasma HIV-1 RNA below the limits of detection only 19% of Zimbabweans had complete or partial resolution of AIDS-KS disease and 16% died; in addition, 34% of participants had no improvement in their quality of life after 24 weeks of treatment, indicating that more effective treatment of symptoms related to AIDS-KS and associated co-morbidities is needed for a large portion of AIDS-KS patients after beginning ART.³⁰

Palliative care for AIDS-KS in Zimbabwe

Patients with AIDS-KS experience a high burden of pain and other chronic symptoms, over a long period of time, and have

a disease course marked by cumulative exacerbations and remissions, making palliative care highly relevant to this population.²⁷ The World Health Organization (WHO) has recognized that development of palliative care for HIV/AIDS has been relatively neglected in Africa and made enhancement of palliative care for HIV/AIDS in Africa a priority in 2002.²⁸ Although much progress has been made in enhancing access to palliative care in Zimbabwe, little is known about the role of palliative care to improve outcomes specifically in the treatment of patients with AIDS-KS in resource-poor areas. (For this study, we are using the WHO definition of palliative care: “An approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.) Essential elements of palliative care relevant to AIDS-KS are the focus of palliative care on providing relief from pain and other distressing symptoms and enhancing quality of life, and

Figure 2: The SIKO standardized palliative care checklist

SIKO Standardized Palliative Care Checklist
(TO BE COMPLETED FOR EVERY PATIENT WITH KS
COMPLETE A NEW FORM FOR EACH VISIT DATE)

Clinic Name: _____ Visit Date: _____
Patient Name: _____ OI Clinic No.: _____
 Baseline Follow-up visit number #: _____

1. MODIFIED APCA PALLIATIVE OUTCOMES SCALE (POS) QUESTIONS	RESPONSE OPTIONS	SELECT ONE
Q1. Please rate your pain from 0=no pain to 5=worst pain during the last 3 days	0 =No pain at all 1 =Slight pain 2 =Moderate pain 3 =Severe pain (interferes with activities of daily life) 4 =Very severe pain 5 =Overwhelming (the worst pain you can imagine)	
Q1.1. How long have you had the pain?	0 =Days 1 =Weeks 2 =Months 3 =Years 4 = Not applicable, no pain	
Q1.2. What is the nature of pain?	1 =Neuropathic (burning, shooting, numb, radiating, lancinating, electrical, pins and needles) 2 =Not Neuropathic 3 =Not applicable, no pain	
Q1.3. What aggravates the pain?	0 = Nothing 1 = Sleep or resting in certain positions 2 = Movement 3 = Not applicable, no pain	
Q1.4. What relieves the pain?	0 = Nothing 1 = Sleep or resting in certain positions 2 = Movement 3 = Not applicable, no pain	
Q2. Have any other symptoms (e.g. nausea, coughing or constipation) been affecting you in the last 3 days?	0 = No symptoms at all 1 = Slight symptoms 2 = Moderate symptoms 3 = Severe symptoms (interferes with activities of daily life) 4 = Very severe symptoms 5 = Overwhelming. The worst symptoms you can imagine	
Q3. Have you been feeling worried about your illness in the past 3 days?	0 = Not at all worried 1 = Worried very occasionally 2 = Worried some of the time 3 = Worried a lot of the time 4 = Worried most of the time 5 = Worried all of the time	
Q4. Over the past 3 days have you been able to share how you are feeling with your family or friends?	0 = Not at all 1 = Only once 2 = Occasionally 3 = Fairly frequently 4 = Often 5 = Yes, I've talked freely	
Q5. Over the past 3 days have you felt that life was worthwhile?	0 = Not at all 1 = Not very often 2 = Occasionally 3 = Some of the time 4 = Most of the time 5 = Yes, all the time	
Q6. Over the past 3 days have you felt at peace?	0 = Not at all 1 = Not very often 2 = Occasionally 3 = Some of the time 4 = Most of the time 5 = Yes, all the time	
Q7. Have you had enough help and advice for your family to plan for the future?	0 = None 1 = Very little 2 = For a few things 3 = For several things 4 = For most things 5 = As much as wanted	
Q8. How much information have you and your family been given about your disease?	0 = None 1 = Very little 2 = Some 3 = Quite a lot 4 = A great deal 5 = As much as wanted	

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SIKO Standardized Palliative Care Checklist
(TO BE COMPLETED FOR EVERY PATIENT WITH KS
COMPLETE A NEW FORM FOR EACH VISIT DATE)

2.0 LOCATION: Mark location(s) of pain on the body diagrams.

2.1 SHORTNESS OF BREATH ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No breathlessness at all	0
<input type="checkbox"/>	Mild shortness of breath	1
<input type="checkbox"/>	Moderate shortness of breath or breathing difficulty	2
<input type="checkbox"/>	Severe shortness of breath or very hard breathing	3
<input type="checkbox"/>	Extremely severe (unable to sleep or do anything)	4

2.2 COUGH ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No cough	0
<input type="checkbox"/>	Mild cough	1
<input type="checkbox"/>	Moderate cough	2
<input type="checkbox"/>	Severe cough	3

2.3 LYMPHEDEMA ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No lymphedema	0
<input type="checkbox"/>	Mild lymphedema	1
<input type="checkbox"/>	Moderate lymphedema	2
<input type="checkbox"/>	Severe lymphedema	3

2.4 CONSTIPATION ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No Constipation	0
<input type="checkbox"/>	Mild Constipation	1
<input type="checkbox"/>	Moderate Constipation	2
<input type="checkbox"/>	Severe Constipation	3

2.5 DIARRHEA ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No Diarrhea	0
<input type="checkbox"/>	Mild Diarrhea	1
<input type="checkbox"/>	Moderate Diarrhea	2
<input type="checkbox"/>	Severe Diarrhea	3

2.6 NAUSEA/VOMITING ASSESSMENT

Select One	Description	Score
<input type="checkbox"/>	No nausea	0
<input type="checkbox"/>	Mild nausea	1
<input type="checkbox"/>	Moderate nausea	2
<input type="checkbox"/>	Severe nausea	3
<input type="checkbox"/>	Vomiting	4

2.7 SORE MOUTH Yes No

2.8 OTHER SYMPTOMS (describe): _____

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the applicability of palliative care early in the course of illness, in conjunction with other therapies that are intended to prolong life.²⁶

Need for evidenced-based strategies for AIDS-KS management in Zimbabwe

As summarized, available data provide evidence that:

- ▶ KS is the most commonly reported cancer in Zimbabwe, despite increased availability of ART for the treatment of HIV-1 infection;
- ▶ since advanced AIDS-KS is often refractory to ART alone and optimal treatment usually requires combination ART and chemotherapy, earlier diagnosis of KS by primary care providers could improve treatment outcomes and provide cost savings;
- ▶ infectious complications are a common cause of morbidity and mortality during treatment of AIDS-KS in Zimbabwe and better strategies are needed to prevent, diagnose and treat infections in people with AIDS-KS;
- ▶ data on how best to incorporate palliative care approaches at the time of AIDS-KS diagnosis to improve overall treatment of AIDS-KS are lacking;
- ▶ access to effective AIDS-KS treatment in community settings is limited.

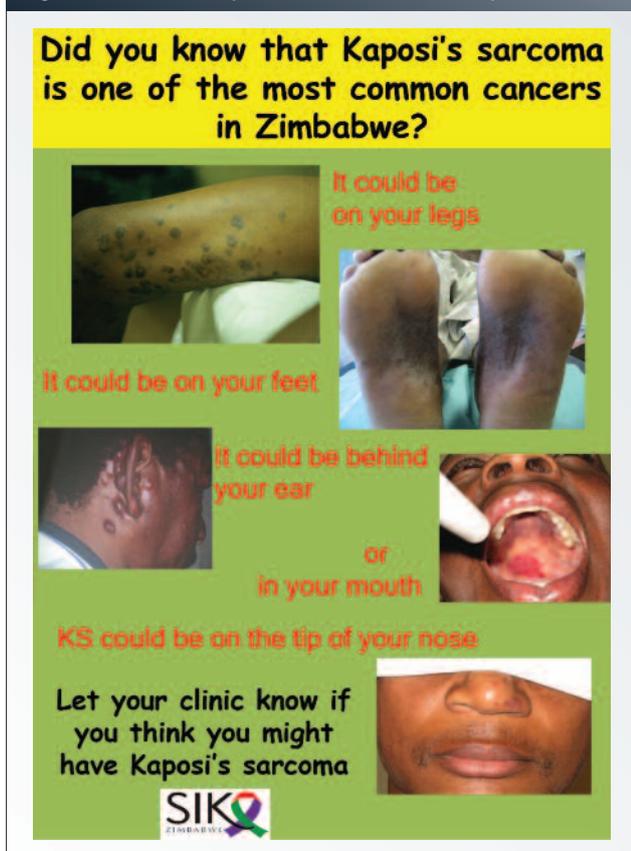
Therefore, in order to provide effective medical care to people with AIDS-KS, alternative strategies for the sustainable delivery of AIDS-KS care in Zimbabwe and other African settings must be developed. Effective and efficient management of AIDS-KS in resource-constrained settings will require the integration of KS screening, diagnosis, tumour staging and treatment into primary care settings. Efforts must be made to diagnose KS in community care settings at early stages when it is most likely to respond to ART alone and thereby reduce the need for expensive and potentially toxic chemotherapy. Current international guidelines for the management of HIV infection contain few recommendations for the management of AIDS-KS (Table 1). If AIDS-KS is to be effectively managed in primary care settings, evidence-based recommendations for screening, diagnosis, staging and treatment must be developed. It was with this background in mind that the SIKO study was designed.

SIKO interventions

SIKO was designed to address the issues described above in primary care delivery in Zimbabwe. The study comprises three interventions:

- ▶ **KS Standardized Evaluation (KS-SE).** Since early KS diagnosis is highly dependent on detection of suspected

Figure 3: An information poster to raise awareness of Kaposi sarcoma



lesions by clinical examination, the KS-SE (Figure 1) was designed as a simple examination tool that focuses on improving bedside diagnostic skills to assess the common clinical presentation of KS disease by thorough physical examination of the skin, mouth, internal organs and lymphatics. Information collected as part of the KS-SE will be recorded on a KS-SE flow sheet, which will serve as a written record for future reference in the clinical management of the patient by primary care providers and consultants.

- **Palliative care education and integration of palliative care into primary care of people with AIDS-KS.** SIKO will implement a training programme for all levels of primary care providers (doctors, nurses and allied health professionals) involved in the clinical assessment and management of AIDS-KS at the study sites. This will take place in conjunction with the KS training programme already being conducted. A palliative care checklist was designed in order to help site staff assess the specific palliative care needs of any patient diagnosed with KS (Figure 2). Staff will also be trained in the use of a standard quality of life questionnaire which has been used extensively in other studies of KS in Zimbabwe (Functional Living Index in Cancer FLIC).

- **KS management strategy.** An algorithm-based KS management strategy will be developed together with other materials to increase awareness and to educate the community and health providers (Figure 3). Advanced KS disease (T1 stage) will be managed in consultation with KS specialists at UZCHS. Patients who live in or near Harare will be referred to the Parirenyatwa KS Clinic for further evaluation. Currently, general care for HIV-infected patients is free in government institutions (this includes out-patient clinic consultations, cotrimoxazole prophylaxis and antiretroviral therapy); this does not include chemotherapy for which patients are charged separately as are all patients with AIDS-related and non-AIDS-related cancers. Patients in rural areas will be managed through long-distance mobile telephone consultations between primary care providers and specialists at UZCHS. The mobile KS consultations (with digital photographs as necessary) will allow KS consultants to assess patients directly in collaboration with the primary care provider and institute early chemotherapy if needed, to improve KS outcomes. Moreover, mobile specialist consultations will strengthen lines of communication between consultants and primary care providers and will provide the opportunity for further dissemination of knowledge related to AIDS-KS care to primary care providers. The mobile telephone system in Zimbabwe is well developed, and its use is feasible and affordable; there is no record of prior experience in using this strategy for distance consultation for management of AIDS-KS in a rural setting in Africa.

The SIKO strategy will be algorithm-based so that it will be easily integrated into current Ministry of Health, PEPFAR and WHO training guidelines and the national Zimbabwe guidelines. Since the WHO Integrated Management of Adolescent and Adult Illness (IMAI) for first level facility health workers is being used in many countries in sub-Saharan Africa, if the SIKO strategy is successful it will be easily adapted into IMAI guidelines assuring rapid dissemination and impact on AIDS-KS care.

The effectiveness of the SIKO interventions will be evaluated in a community-based clinical trial with randomized step-wedge design.²⁹ Each of the eight urban and rural sites will be randomized to begin their interventions at different time points. The total length of the study will be 156 weeks and the total evaluation period (monitoring and intervention period) will be 102 weeks (2 years). More details on the clinical trial design are available on Clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT01764360).

SIKO implementation phase

The study preparation period began in mid-2012 with eight primary care sites, four sites in rural/small towns and four sites in the Harare urban area. Training materials were developed using principles of adult education and were then piloted at the Parirenyatwa Family Care Clinic. Feedback from the faculty, house officers and nursing staff was used to refine the design and individual elements of the training materials as needed, and then training of the two SIKO teams took place. This “training of trainers” served to train the SIKO monitoring team (who were trained in site monitoring) and the SIKO implementation team (who were trained in the delivery of the SIKO interventions). During the preparation phase, SIKO personnel travelled to the sites to meet with all care providers and other site staff to inform them of the purpose and general plan of the study to engage them in the study, asking for their assistance in the documentation of all KS diagnoses, and for their participation in the SIKO interventions. The latter were not described in explicit terms.

During the monitoring period, starting in January 2013, the monitoring team visited all the sites training them to keep a daily log of the total number of HIV-positive patient visits, the number of new KS diagnoses (incident cases) made that day and the number of patients already diagnosed with KS seen that day (prevalent cases). All KS patients seen at the sites were asked to participate in the study and the quality of life questionnaire was distributed. All sites continued to deliver their usual standard of care to patients. At the writing of this article the monitoring period was ongoing for all eight sites.

During the intervention period, begun in May 2013, the sites were randomly assigned to start the SIKO interventions. One additional site will begin the SIKO interventions every seven weeks. The single intervention team consists of a physician experienced in KS care, a palliative care doctor and a specialist nurse, and a KS specialist nurse. The intervention team will visit the site for a half day at the assigned start of the intervention, two weeks later and then every four weeks throughout the study. Care will be taken to ensure that the intervention team and the monitoring teams and their site visits remain mutually exclusive in order to ensure that data collection is not biased by the implementation of the intervention. During the intervention period, the three interventions will be implemented at the sites and follow-up provided as needed. At the writing of this article the intervention period had commenced at four sites.

Outcomes of the SIKO training interventions

We expect that implementation of the KS-SE as part of the SIKO intervention will lead to more active surveillance for KS disease by primary care providers. This in turn will lead to a greater number of overall KS diagnoses and, more importantly, a greater number of early stage diagnoses in primary care settings. This should lead to a broad improvement in the treatment of KS. It is expected that the SIKO intervention will enhance access to palliative care via knowledgeable primary care providers in rural and urban Zimbabwe, resulting in decreased physical and emotional symptoms of distress and, therefore, improved quality of life for patients with AIDS-KS. The outcome measure for this analysis will be the change in the FLI-C score before and after the SIKO training interventions.

We expect that the overall impact of all the interventions included in the SIKO package will be improved AIDS-KS survival and increased retention in care.

Conclusion

We have proposed interventions to improve AIDS-KS diagnosis and treatment in primary care settings in Zimbabwe. These interventions are currently being evaluated in a community-based clinical trial. If the evaluation of the SIKO interventions does indeed provide evidence for improved KS outcomes in Zimbabwe we will immediately begin a programme to disseminate this knowledge to a broad spectrum of primary care providers across the country in a stepped approach.

In coordination with the Zimbabwean Ministry of Health, we would conduct training in the use of the KS-SE through a series of training courses targeted at primary care providers in each of Zimbabwe's provinces and begin work with the Ministry of Health to develop sustainable plans for expanding the distance and mobile KS and palliative care consultative services. It may be that this model would serve as a template for earlier diagnosis of other AIDS-related cancers which could possibly be prevented, and certainly better treated, if diagnosed at an early stage. ●

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Dr Margaret Borok, FRCP is an experienced clinician and teacher at the UZCHS. Since 1998 she has worked with Dr Tom Campbell of the University of Colorado Denver, in collaborative operational

and clinical research in the epidemiology and treatment of AIDS-KS. She and Dr Campbell are currently collaborating in two randomized clinical trials, funded by NIAID and NCI through the AIDS Clinical Trials Group and the AIDS Malignancy Consortium.

Dr Thomas Campbell has significant experience in clinical and translational investigation of HIV/AIDS and AIDS-KS in African settings that are highly relevant to the aims of this project.

Dr James Hakim, FRCP is an internist and clinical epidemiologist with broad exposure to a wide spectrum of communicable and

non-communicable diseases seen in sub-Saharan Africa.

Dr Jean Kutner is an experienced clinician/geriatrician. She is an innovative researcher in the field of palliative care.

Dr Samantha MaWhinney, ScD is Professor of statistics and currently Programme Director of the Department of Biostatistics and Informatics in the Colorado School of Public Health.

Dr Eric Simoes has a broad background in infectious diseases with specific training and expertise in epidemiology, and development and assessment of WHO guidelines.

References

- UNAIDS 2012. Global AIDS Response Progress Report. 2012. Zimbabwe Country Report. Available at: http://www.unaids.org/en/dataanalysis/knownyourresponse/countryprogressreports/2012countries/ce_ZW_Narrative_Report.pdf.
- Baeten JM, Chohan BH, Lavreys L et al. Correlates of human herpesvirus 8 seropositivity among heterosexual men in Kenya. *AIDS* 2002; 16:2073-8. PMID: 12370507
- Eltom MA, Mbulaitye SM, Dada AJ, Whitby D, and Biggar RJ. Transmission of human herpesvirus 8 by sexual activity among adults in Lagos, Nigeria. *AIDS* 2002; 16:2473-8. PMID: 12461423
- Lavreys L, Chohan B, Ashley R et al. Human herpesvirus 8: Seroprevalence and correlates in prostitutes in Mombasa, Kenya. *J Infect Dis* 2003; 187:359-63. PMID: 12552419
- Klaskala W, Brayfield BP, Kankasa C et al. Epidemiological characteristics of human herpesvirus-8 infection in a large population of antenatal women in Zambia. *J Med Virol* 2007; 75:93-100. PMID: 15543582
- Olsen SJ, Chang Y, Moore PS, Biggar RJ, and Melbye M. Increasing Kaposi's sarcoma-associated herpesvirus seroprevalence with age in a highly Kaposi's sarcoma endemic region, Zambia in 1985. *AIDS* 1998; 12:1921-5. PMID: 9792393
- Newton R, Ziegler J, Bourbouli D et al. The seroepidemiology of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in adults with cancer in Uganda. *Int J Cancer* 2003; 103:226-32.
- Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980 – 2002. *AIDS* 2006;20:1645-54. PMID 16868446
- Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008; 22:1897–908. PMID: 18784453
- Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. *AIDS* 2006; 20:2355–2360. PMID: 17117022
- Castelnuovo B, Manabe YC, Kiragga A, Kanya M, Easterbrook P, Kambugu A. Cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome in the first 3 years after antiretroviral therapy initiation in an urban African cohort. *Clin Infect Dis*. 2009; 49:965–72. PMID: 19673615
- http://www.unaids.org/globalreport/global_report.htm
- Campbell TB, Borok M, Ndemera B, Fiorillo S, White IE, Zhang XQ, Machekano R, Katzenstein D, Gwanzura L. Lack of Evidence for Frequent Heterosexual Transmission of Human Herpesvirus 8 (HHV-8) in Zimbabwe. *Clin Infect Dis* 2009;48:1601-8. PMID: PMC2720069
- Chokunonga E, Levy LM, Bassett MT, Borok MZ, Mauchaza BG, Chirenje ZM, Parkin DM, AIDS and cancer in Africa: The evolving epidemic in Zimbabwe. *AIDS* 1999; 13:2583-2588. PMID 10630528
- Gondos A, Chokunonga E, Brenner H, Parkin DM, Sankila R, Borok M, Chirenje ZM, Nyakabau AM, Bassett MT. Cancer Survival in a Southern African Urban Population. *Int J Cancer* 2004;112:860-864. PMID 15386382
- Boffi EI Amari, Toutous-Trellu L, Gayet-Ageron A, Baumann M, Cathomas G, Steffen I, Erb P, Mueller NJ, Furrer H, Cavassini M, Vernazza P, Hirsch HH, Bernasconi E, Hirschel B, the Swiss HIV Cohort Study. Predicting the evolution of Kaposi sarcoma, in the highly active antiretroviral era. *AIDS* 2008; 22:1019-28. PMID: 18520345
- Martin-Carbonero L, Barrios A, Saballs P, Sirena G, Santos J, Palacios R, Eulalio Valencia M, Alegre M, Podzamczar, D., Gonzalez-Lahoz J, and the Caelyx/KS Spanish Study Group. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. *AIDS* 2004; 18:1737-40. PMID: 15280789
- Lichterfeld M, Qurishi N, Hoffmann C, Hochdorfer B, Brockmeyer NH, Arasteh K, Mauss S, Rockstroh JK, German Clinical AIDS Working Group. 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* 2004; 33:140-147. PMID: 15940415
- Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. *Oncologist* 2007; 12:114-23. PMID: 17227906
- Nguyen HQ, Magare AS, Kitahat MM, Van Rompaey SE, Wald A, Casper C. Persistent Kaposi sarcoma in the era of highly active antiretroviral therapy: characterizing the predictors of clinical response. *AIDS* 2008; 22:937-45. PMID: PMC2730951
- Martin-Carbonero L, Palacios R, Valencia E, Saballs P, Sirena G, Santos I, Baldobi F, Alegre M, Goyenechea A, Pedreira J, Gonzalez del Castillo J, Martinez- Lacasa J, Ocampo A, Alsina M, Santos J, Podzamczar D, Gonzalez-Lahoz J, Caelyx/Kaposi's Sarcoma Spanish Group. Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. *Clin Infect Dis* 2008; 47:410-417. PMID: 18582203
- Borok M, Fiorillo S, Gudza I, Putnam B, Ndemera B, White IE, Watson H, Gwanzura L, Schooley RT, Campbell TB. Evaluation of plasma human Herpesvirus 8 DNA as a marker of clinical outcomes during antiretroviral therapy of AIDS-related Kaposi sarcoma in Zimbabwe. *Clin Infect Dis*. 2010; 51:342–349. PMID: 20572760
- M. Borok, unpublished data
- Makombe SD, Harries AD, Yu JK-L, Hochgesang M, Mhango E, Weigel R, Pasulani O, Fitzgerald M, Schouten EJ, Libamba E. Outcomes of patients with Kaposi sarcoma who start antiretroviral therapy under routine programme conditions in Malawi. *Tropical Doctor*. 2008; 385–7. PMID: 18302849
- Nelson BC, Borok MB, Makadzange T, Mhlanga T, Campbell TB. AIDS-related Kaposi sarcoma: Outcomes after initiation of highly active antiretroviral therapy under routine conditions in Zimbabwe. International Conference on AIDS Malignancies and Opportunistic Infections. Bethesda, 2010.
- <http://www.who.int/cancer/palliative/definition/en/>
- Peter A. Selwyn, Mimi Rivard. Palliative Care for AIDS: Challenges and Opportunities in the Era of Highly Active Anti-Retroviral Therapy. *Journal of Palliative Medicine*. June 2003, 6(3): 475-487. PMID: 14509497
- Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative Care: The World Health Organization's Global Perspective. Vol. 24 No. 2 August 2002 *J Pain and Symptom Manage*. PMID: 12231124
- Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. *BMC Medical Research Methodology* 2006; 6:54 doi:10.1186/1471-2288-6-54. PMID: 17092344
- Borok M, Fiorillo S, Gudza I, Putnam B, Ndemera B, White IE, Watson H, Gwanzura L, Schooley RT, Campbell TB. Evaluation of plasma human Herpesvirus 8 DNA as a marker of clinical outcomes during antiretroviral therapy of AIDS-related Kaposi sarcoma in Zimbabwe. *Clin Infect Dis* 2010; 51:342–349. PMID: 20572760