

# ESMO SUMMIT AFRICA

## HIV-RELATED MALIGNANCIES IN SUB-SAHARAN AFRICA: UNIQUE CHALLENGES

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# DISCLOSURE

I have no conflict of interest.

# What is this New Yorker doing at a European-African meeting?

## Krown family "Ancestral Village"

Vishnevets was located at the headwaters of two major river systems, the Sluch and the Goryn in the southern part of Volhynia adjacent to the border of Galicia and directly in the path of the Nazi invasion of the Soviet Union. It was destroyed in 1943.

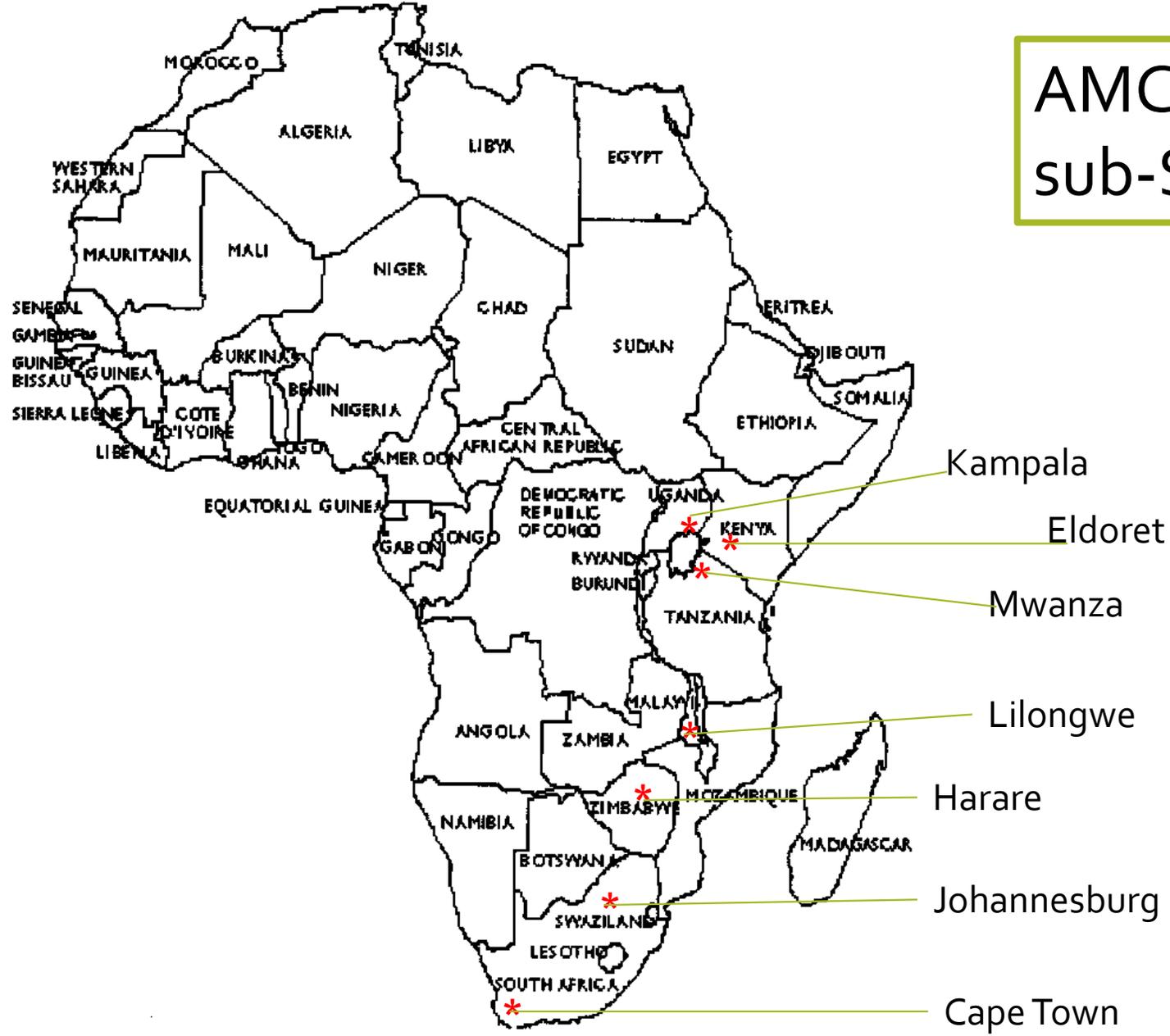


# AIDS Malignancy Consortium (AMC): An NCI-Funded Clinical Trials Group est'd 1995 Mission Statement

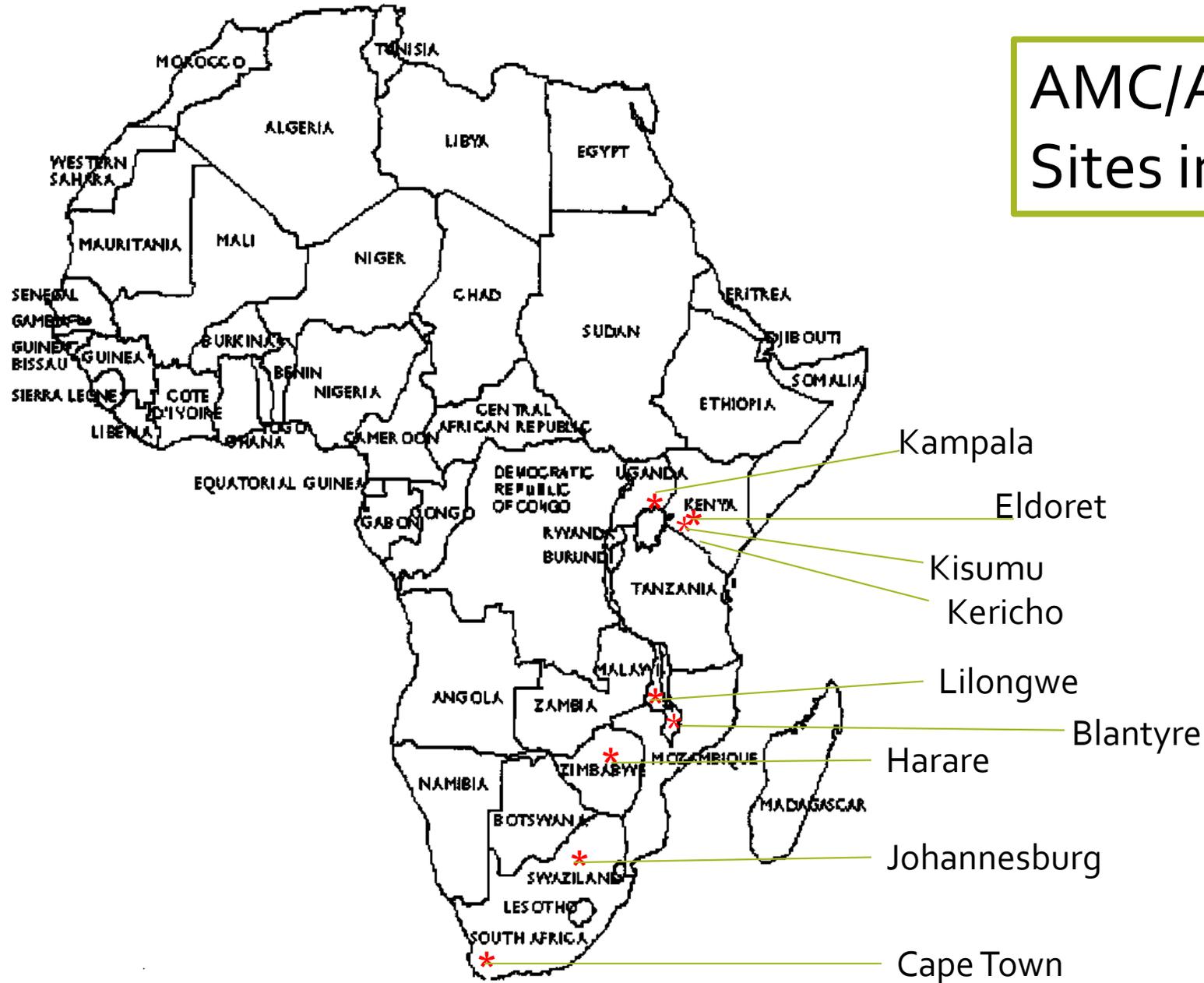
“The mission of the AMC is to investigate new treatment and prevention interventions for malignancies in people living with HIV **both in the USA and internationally** and to study the pathobiology of these tumors in the context of clinical trials”



# AMC Trials Sites in sub-Saharan Africa

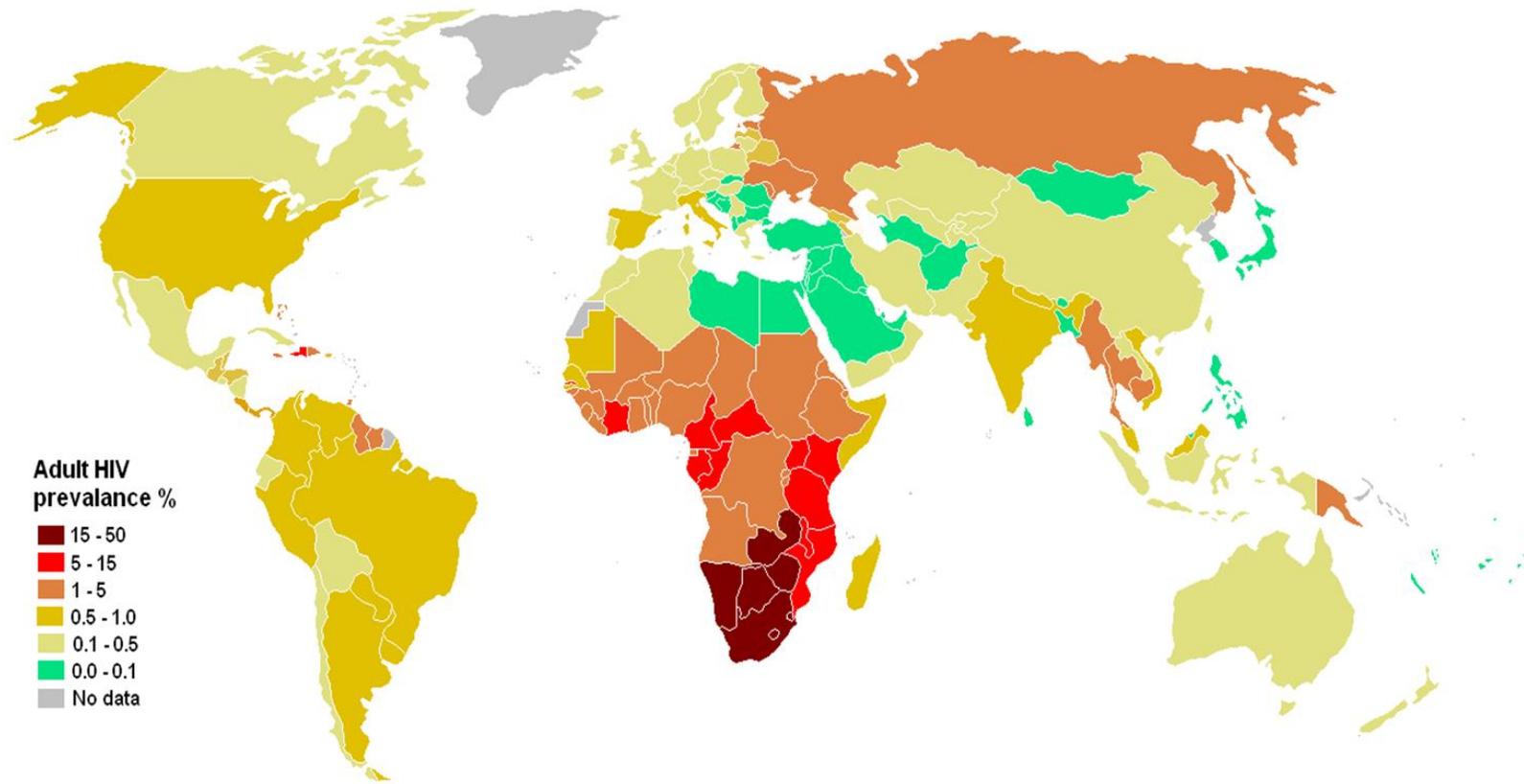


# AMC/ACTG KS Trials Sites in SSA



# HIV Burden is Highest in Sub-Saharan Africa

~70% of Global HIV Burden



# Cancer as an Opportunistic Complication of HIV Infection

- Cancer was one of the first heralds of the AIDS epidemic and cancers were among the first “AIDS-defining” conditions:
  - Kaposi sarcoma
  - Non-Hodgkin lymphoma
  - Invasive Cervical Cancer
- Other “non-AIDS-defining” cancers noted to occur in excess in HIV+ people – many, but not all, are infection-related and/or associated with immunosuppression, but HIV itself may be associated independently with increased risk.
- Risk and spectrum of HIV cancers may vary by geography – e.g., in Africa:
  - High rates of KSHV infection
  - High rates of HPV infection and weak cervical cancer screening infrastructure
  - High rates of chronic hepatitis B and C
  - High rates of OSSN (ocular surface squamous neoplasia) - ? Etiology (HPV; UV)
  - ? Role of infectious, genetic and/or environmental co-factors

# Standard Categories of HIV-Associated Malignancies

## “AIDS-Defining” Malignancies (ADCs)

- Kaposi Sarcoma
- Non-Hodgkin Lymphomas
- Invasive Cervical Cancer

## “Non-AIDS-Defining” Malignancies (NADCs)

- Hodgkin Disease
- Anal Cancer
- Ocular Surface Squamous Neoplasia
- Hepatocellular Carcinoma
- Lung Cancer, Breast Cancer, Prostate Cancer, etc, etc, etc

# Is There a Better Way to Categorize HIV-Associated Malignancies?

## Infection-Related

- Kaposi Sarcoma and other KSHV/HHV-8-associated neoplasms (PEL, MCD)
- EBV-related Cancers (NHLs, HD)
- Cervical and Anal Cancers (HPV)
- Hepatocellular Cancer (Hep B/Hep C)
- OSSN (? HPV)

## Infection-Unrelated

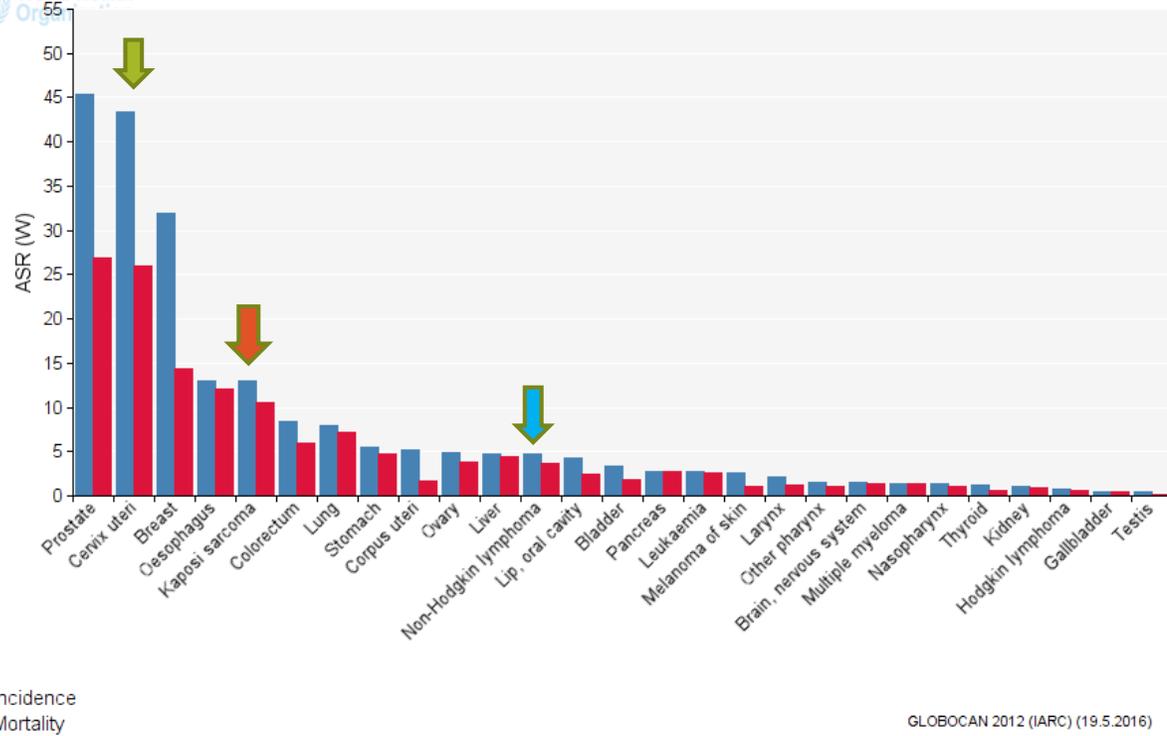
- Most cancers whose risk increases with increasing age and/or with exposure to non-infectious carcinogens

See: Borges AH et al.: Clin Infect Dis. 2016 Dec 15;63(12):1668-1676. Epub 2016 Sep 8

## NA Accord Cohort Analysis of HIV Mortality (Clin Infect Dis 2010; 50:1387-96)

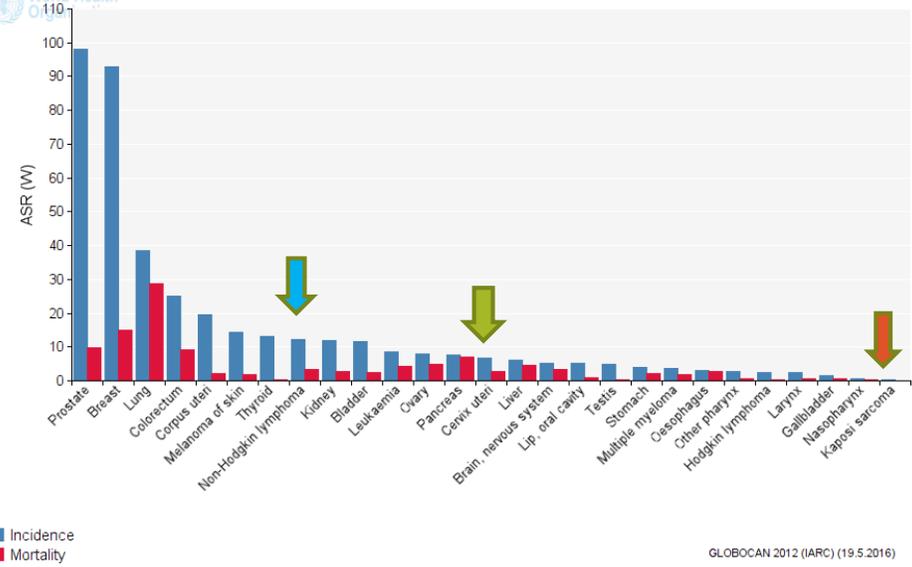
- 39,372 patients enrolled in 13 HIV+ cohorts in Europe and N. America initiating ART from 1996 -2006
- 1597 of 1876 deaths with definitive cause of death
- 556 deaths (34%) were AIDS-related, excluding cancer
- 425 deaths (26%) were linked to AIDS-related and non-AIDS-related malignancy
  - 236 (14% of overall total) were AIDS-related malignancies
  - 189 (11.8% of overall total) were non-AIDS malignancies
- 126 deaths (7.9%) from cardiovascular disease & stroke

International Agency for Research on Cancer Kenya, Zimbabwe, Uganda, Tanzania, Malawi, South African Republic: Both sexes, all ages



GLOBOCAN 2012 (IARC) (19.5.2016)

International Agency for Research on Cancer United States of America: Both sexes, all ages



GLOBOCAN 2012 (IARC) (19.5.2016)

## Global Burden of Cervical Cancer in HIV-Positive Women on Antiretroviral Therapy. (Rohner et al, CROI 2016; abstract 617).

- 65,726 women from 55 countries in large cohort studies
- Adjusted HR\* (95% CI) for invasive cervical cancer 5 years after starting ART:

Europe	1.0
North America	0.7 (0.3 – 1.4)
Latin America	2.2 (1.2 – 4.2)
Southern Africa	12.4 (7.8 – 20)

\*Adjusted for age, year of ART start and current CD<sub>4</sub> cell counts.

Regional differences not explained by differences in CD<sub>4</sub> counts, age or year of ART initiation.

Rates did not decline with time on ART in Southern Africa.

Increased HR in Latin America and Southern Africa may be linked to both higher prevalence and incidence of HPV infection and limited access to effective cervical cancer screening.

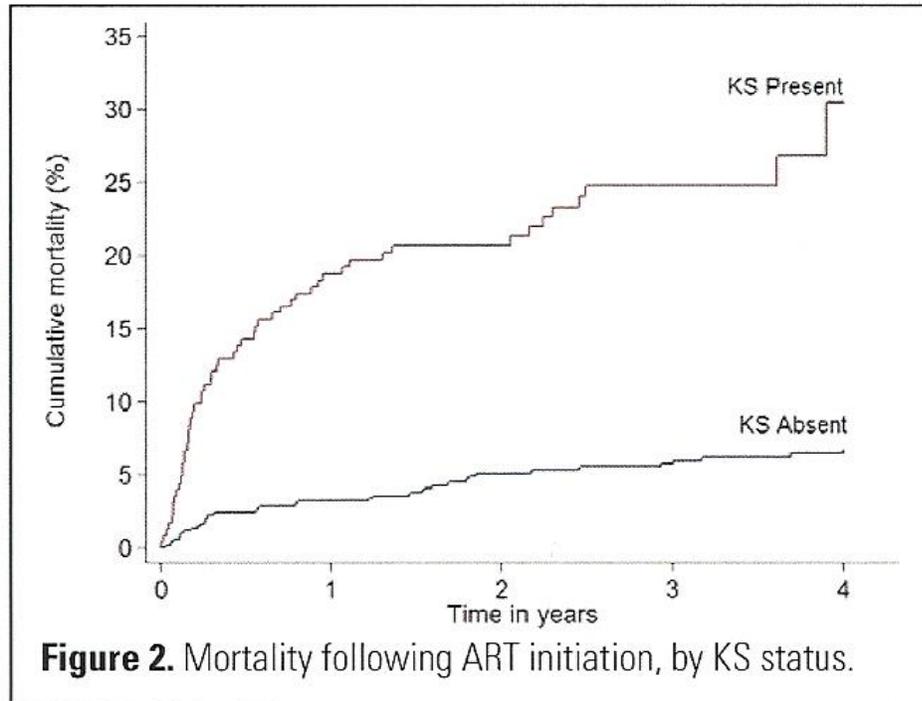
## Estimated Number of Cases and Age-Standardized Incidence Rates for Kaposi Sarcoma in Regions of Sub-Saharan Africa (GLOBOCAN 2012)

	MALES		FEMALES	
	# of Cases	Incidence/100,000	# of Cases	Incidence/100,000
Eastern Africa	19,800	15.1	11,100	7.6
Southern Africa	2,200	7.6	1,400	4.7
Middle Africa	500	1.2	200	0.4
Western Africa	1,100	0.9	900	0.6
<b>Sub-Saharan Africa</b>	<b>23,600</b>	<b>7.2</b>	<b>13,600</b>	<b>3.7</b>

84% of KS cases worldwide in SSA in 2012; 80% of SSA total in Eastern Africa

- ~6% of all incident cancers in SSA in 2012
- ~11% of all incident cancers in Eastern Africa in 2012

# KS Impact on Survival in Uganda



S. Asiimwe et al., presented at ICMAOI, November 2013.

Among HIV-infected adults newly initiating ART in Uganda, those with KS had higher mortality than those without KS.

Adjusted HR of 4.7 (2.5-8.9) for death at 1 year,  $p < 0.001$

Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability Adjusted Life-years for 32 Cancer Groups, 1990 to 2015. A Systematic Analysis for the Global Burden of Disease Study.

Global Burden of Disease Cancer Collaboration

JAMA Oncology, doi:10.1001/jamaoncol.2016.5688; Published on line December 3, 2016.

“Deaths due to Kaposi sarcoma are not separately included because these were attributed to human immunodeficiency virus/AIDS in the GBD study.”

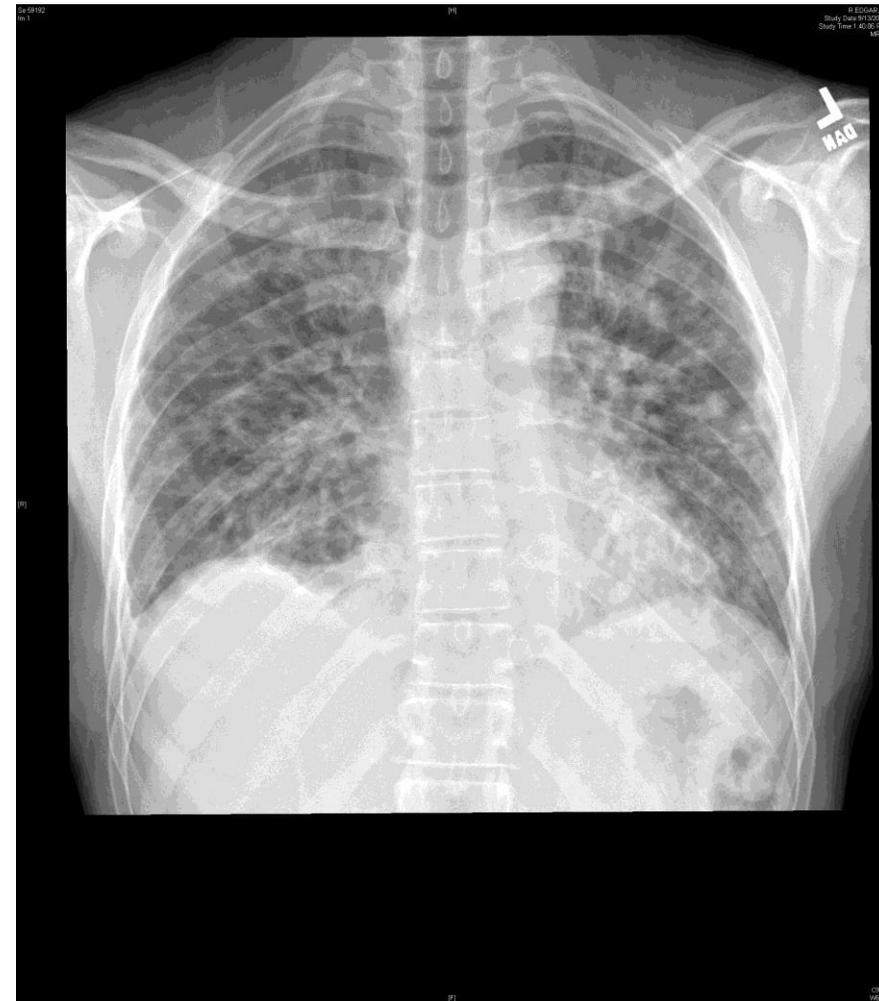
# Barriers to Effective Cancer Management in (HIV-Infected) People in SSA\*

- **Diagnosis**
  - Often delayed
  - Pathology infrastructure
  - Staging resources
- **Co-Morbidities**
  - Effect on diagnosis
  - Effect on treatment tolerance
- **Treatment**
  - Treatment infrastructure
  - Evidence-based standards/Research infrastructure
  - Supportive care
- **Societal/Structural**

\* Varies by country and within countries (e.g., rural vs urban).

# Pulmonary KS on CXR

Could you distinguish this from TB?



# Malawi: Misdiagnosis as TB Delays Cancer Diagnosis

- 34 patients identified between 2010 and 2014; 14 known HIV+
- Most were diagnosed clinically and treated empirically for extrapulmonary TB
- Mean duration of TB treatment – 3.6 months
- Mean delay in cancer diagnosis – 5.4 months
- Adenopathy common, especially neck masses
- 23/34 patients ultimately diagnosed with lymphomas (HD, NHL, Burkitt)

Adapted from: Masamba et al, J Global Oncol 2016; 2:26-29

## Societal/Cultural Challenges

- Who pays for care?
- Time. Travel. Jobs. Child care.
- Coordination of care (referrals; coordination between HIV and cancer care providers)
- Retaining patients in care.

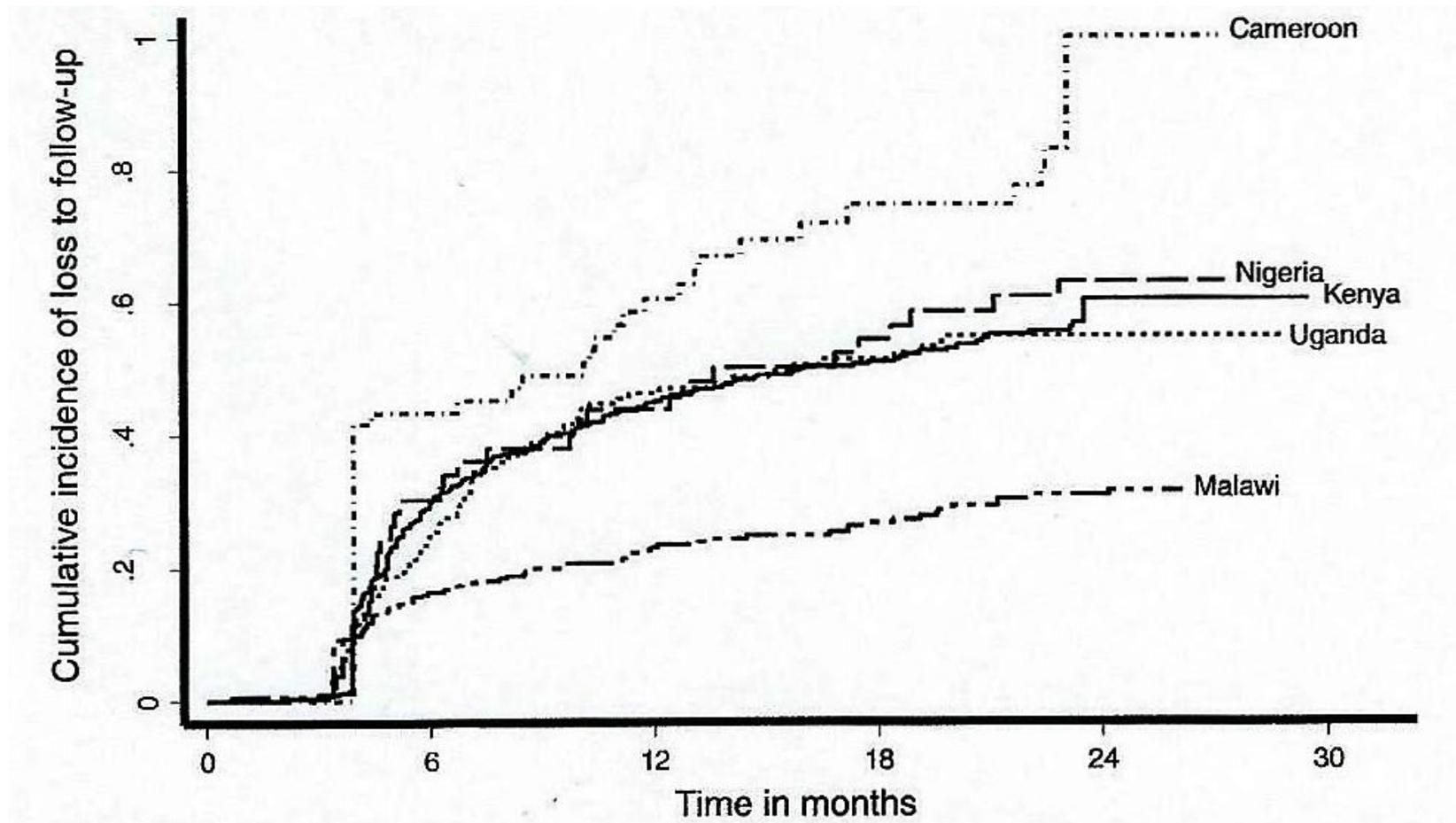
## Botswana: Delayed access to Oncology Services in an area of high HIV prevalence, despite universal access to free health care and high ART coverage

Cancer site/histology	Median days from cancer symptom onset to cancer care enrollment
Lymphoma (NHL or HD)	284
Kaposi sarcoma	441
Head and Neck	282
Cervix	315
Breast	429
Esophagus	205
Rectum, anus, penis, or other female genital	614
Other	672

Adapted from: Brown et al, Oncologist 2016;21:1-8

# Cumulative incidence of loss to follow-up in HIV-infected patients following diagnosis with KS in 5 countries in SSA.

Freeman et al., BMC Cancer (2016);16:65



# Management of Cancers in HIV-Infected People

## Questions:

- Can HIV-infected people with cancer be safely and effectively treated with the same regimens as HIV-uninfected people?
- Is the answer the same worldwide? If not, what drives differences?
- Should we be concerned about the safety of some “standard” cancer treatments (e.g., use of rituximab in NHL) in areas with high rates of TB, high rates of KSHV seroprevalence, or other co-infections?
- Are there circumstances (medical, economic, social) where less intensive or otherwise modified regimens may be acceptable (or even preferable to) “standard” treatments?

Gopal S, et al. (2016) CHOP Chemotherapy for Aggressive Non-Hodgkin Lymphoma with and without HIV in the Antiretroviral Therapy Era in Malawi. PLoS ONE 11(3): e0150445.

- 58 adults; 37 (64%) HIV+
- Stage III/IV: 35 (60%)
- B Symptoms: 43 (74%)
- PS  $\geq$ 2: 28 (48%)
- 31/37 (84%) HIV+ on ART @ NHL dx for median 9.9 mos
  - 43% had HIV RNA <400 copies/mL
  - Median CD4 = 121 cells/ $\mu$ L
- 50 pts treated: 31/37 HIV+, 19/21 HIV- (others died before tx started)
  - 11/50 started on either pre-phase Prednisone or mini-CHOP
  - No G-CSF available
  - 59% OS at 12 months

Table 2. Treatment course and toxicities during CHOP chemotherapy in Lilongwe, Malawi.

	HIV-positive (n = 31)	HIV-negative (n = 19)	P
Total chemotherapy cycles	150	88	—
Cycles per patient, median (IQR) <sup>a</sup>	6 (4–6)	5 (3–6)	0.59
Days between cycles, median (IQR)	21 (21–27)	21 (20–22)	<b>0.0053</b>
Cycles delayed ≥7 days, n (%) <sup>b</sup>	32/119 (26.9%)	8/69 (11.6%)	<b>0.016</b>
Cyclophosphamide dose per cycle, mg/m <sup>2</sup> , median (IQR) <sup>c</sup>	693.0 (555.6–734.8)	721.4 (576.9–750.0)	<b>0.015</b>
Doxorubicin dose per cycle, mg/m <sup>2</sup> , median (IQR) <sup>d</sup>	48.0 (37.6–49.9)	49.4 (39.3–50.0)	<b>0.042</b>
Received <6 cycles, n (%) <sup>a</sup>	14/30 (46.7%)	11/19 (57.9%)	0.56
Death	7	6	
Progression	1	2	
Toxicity	5	1	
Social	1	2	
Grade 3/4 neutropenia <sup>e</sup>			
Cycles, n (%)	49/140 (35.0%)	13/83 (15.7%)	<b>0.002</b>
Patients, n (%)	21/25 (84.0%)	5/16 (31.2%)	<b>0.001</b>
Grade 3/4 anemia <sup>e</sup>			
Cycles, n (%)	13/140 (8.9%)	6/83 (7.2%)	0.80
Patients, n (%)	7/25 (28.0%)	3/16 (18.8%)	0.71
Grade 3/4 non-hematologic toxicity <sup>e</sup>			
Cycles, n (%)	6/140 (4.3%)	12/83 (14.5%)	<b>0.010</b>
Patients, n (%)	6/25 (24.0%)	8/17 (47.1%)	0.18

IQR = interquartile range.

<sup>a</sup>Includes 49 patients (30 HIV+, 19 HIV-) who completed first-line CHOP or died as of August 31, 2015.

<sup>b</sup>Excludes first treatment cycles.

<sup>c</sup>Excludes 9 missed cyclophosphamide doses due to stock-out (6 HIV-, 3 HIV+).

<sup>d</sup>Excludes 6 missed doxorubicin doses due to stock-out (4 HIV-, 2 HIV+).

<sup>e</sup>Toxicity assessment includes patients and cycles with subsequent follow-up visits making them evaluable for interim toxicity; deaths occurring out of hospital are separately adjudicated (S1 Table) without evaluation for non-fatal interim toxicity.

doi:10.1371/journal.pone.0150445.t002

Gopal S, Fedoriw Y, Kaimila B, Montgomery ND, Kasonkanji E, et al. (2016) CHOP Chemotherapy for Aggressive Non-Hodgkin Lymphoma with and without HIV in the Antiretroviral Therapy Era in Malawi. PLOS ONE 11(3): e0150445. doi:10.1371/journal.pone.0150445

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0150445>

## Conclusions...

- “CHOP can be safe, effective, and feasible for aggressive NHL in Malawi with and without HIV.”
- BUT...
  - 35 Deaths:
    - 23 attributed to NHL (12 HIV+, 11 HIV-)
    - 12 attributed to CHOP (9 HIV+, 3 HIV-)

“Treatment-related mortality occurred primarily in patients with very adverse NHL characteristics, and might be reduced with supportive care refinements.”

## My take-home message...

- CHOP may be a “standard-of-care” for a subset of HIV+ individuals in lower-resource environments.
- High rate of NHL-related deaths on CHOP.
- High number of treatment-related deaths suggest that other (modified) treatment regimens and/or substantial improvements in the supportive care infrastructure may need to be explored for poor-risk subgroups.

# Locally Advanced Cervical Cancer (LACC)

- HIV+ women typically excluded from chemoradiation trials for LACC because of concerns about treatment tolerance
- AMC-081: Feasibility Study of Safety, Toxicity, and Compliance of Concomitant Chemoradiotherapy for HIV-Associated Locally-Advanced Cervical Cancer (M. Einstein, J. Kotzen, N. Ndlovu, et al).
- Planned therapy included EBRT + brachytherapy + weekly cisplatin 40mg/m<sup>2</sup> during EBRT (6 doses) + ART in all.
- 64 women screened; reasons for screen failure included labs and advanced stage found on screening radiographic studies
- 41 women enrolled 6/14-2/16 @ 2 sites Zimbabwe (n=26) and South Africa (Wits, n=15); 39 treated and evaluable.
- Preliminary results to be presented by N. Ndlovu at the 31<sup>st</sup> International Papillomavirus Conference in Cape Town next month

# AMC-081: Tolerance of Cisplatin in Women with CD<sub>4</sub>>200

Total Cisplatin Cycles given at full prescribed dose for 36 women who started at 40 mg/m<sup>2</sup>

# Cisplatin Cycles given at full dose (40 mg/m <sup>2</sup> )	N (number of patients)
5-6	15
4	5
3	8
1-2	8

Total Cisplatin Cycles Completed for 36 women who started at 40 mg/m<sup>2</sup>

Total Cisplatin Cycles Completed	N (number of patients)
6	25
5	7
4	3
3	1

# Preliminary Conclusions

- In appropriately selected HIV+ women with LACC receiving ART, chemoradiotherapy at standard doses can be tolerated.
- Unresolved issues:
  - Tolerance of more intensive therapy (e.g., with consolidation chemotherapy after standard chemo-RT) – to be addressed in AMC-102;
  - Tolerance in more advanced disease (i.e., para aortic LN involvement excluded in AMC-081);
  - Tolerance in women with lower CD counts;
  - Appropriate regimens for women with impaired organ function.

# Kaposi Sarcoma/KSHV: A few important questions (of many)

- When is ART enough? Does adding chemo help in limited-stage KS? (AMC-067/A5264)
- What is the optimal regimen for treatment of advanced, symptomatic KS in SSA? (AMC-066/A5263)
  - Are the optimal KS treatment regimens in SSA the same as those typically used in the U.S. & Europe? (are liposomal anthracyclines necessary?)
  - What are the most cost-effective approaches where resources are limited? (are liposomal anthracyclines necessary?)
  - Are there fundamental biological differences between KS in Africa and KS elsewhere that might influence the approach to therapy? (e.g., greater lytic KSHV replication → role of antiherpesvirus drugs?)
  - What is the best approach to recurrent or refractory disease?
- How can KS tumor burden/extent of disease be accurately quantified?
- Are there interactions between ART and anticancer agents that may affect the efficacy and/or toxicity of HIV and/or cancer treatment?
- Are there opportunities to develop targeted therapy for AIDS/KS in SSA? (AMC-100, oral pomalidomide)
- How can we diagnose, treat and/or prevent KS-IRIS?
- How prevalent are other KSHV-associated diseases in SSA (e.g., MCD, KICS)?

# Summary & Conclusions - I

- SSA bears a disproportionate global share of HIV infections and HIV-associated complications, including cancers.
- As access to ART increases in SSA, causes of death in HIV-infected individuals will likely shift, and cancers will likely increase in importance.
- The burden of cervical cancer and Kaposi sarcoma is disproportionately high in SSA.
- Co-infections that are common in SSA may obscure cancer diagnosis and complicate cancer treatment.

## Summary & Conclusions - II

- Structural barriers exist to accessing cancer care, even when universal access to health care is provided, and follow-up is often poor, impeding knowledge of cancer treatment outcomes. Better integration of HIV and cancer care services and training could facilitate cancer diagnosis & care.
- The current supportive care infrastructure may not be adequate to support the same intensity of treatment that is considered standard in the U.S. and Europe.
- Ultimately, in SSA and elsewhere, the aim should be to “mainstream” the cancer treatment of HIV-infected persons when appropriate, and to consider concurrent HIV infection in much the same way as other non-HIV risks that may influence cancer treatment.