Kaposi’s Sarcoma in Africa: Challenges in the Era of Antiretroviral Rollout

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HHV-8 or KSHV

HHV-8

HHV6
HHV7
HHV8
HSV1
HSV2
EHV1
EHV2
EBV
PRV
VZV
HCMV
HVS
Gamma

EBV
HHV7
HHV6
HHV8
HSV1
HSV2
EHV1
EHV2
PRV
VZV
HCMV
HVS
Gamma

Moore, J Virol 1996
Seroprevalence of HHV-8 in HIV-infected persons in the US

% LANA Antibody Positive

HIV Risk Group

- MSM
- Het men
- Transfusion
- Hemophiliacs
- Women
- IVDU

Kedes, Nat Med 1996
Kedes, JAMA 1997
HHV-8 is sexually transmitted in American gay men

Martin et al, 1998
Epidemiologic Associations of HHV-8 and KS

- All persons with KS have evidence of HHV-8 infection
- Incidence of KS in a population is strongly correlated with HHV-8 prevalence
Relationship of KS Incidence to HHV-8 seroprevalence

Whitby et al. JNCI 1998;90:395
Spectrum of KS Pathogenesis

Latent HHV-8 infection → Lytic HHV-8 replication → Multicentric hyperplasia → Malignancy
Response of AIDS-KS to HAART, University of Washington
Declining KS Incidence in High Income Countries

**United States**

**Switzerland**

Estimated HHV-8 Seroprevalence

UNAIDS 2001 HIV
Adult prevalence rate
- 15.0% - 39.0%
- 5.0% - 15.0%
- 1.0% - 5.0%
- 0.5% - 1.0%
- 0.1% - 0.5%
- 0.0% - 0.1%
- not available
"I ask the Congress to commit $15 billion over the next five years, including nearly $10 billion in new money, to turn the tide against AIDS in the most afflicted nations of Africa and the Caribbean."

State of the Union Address
January 29, 2003
Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2009

- **North Africa and the Middle East**
- **East, South and South-East Asia**
- **Europe and Central Asia**
- **Latin America and the Caribbean**
- **Sub-Saharan Africa**

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<thead>
<tr>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Millions</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
<td>0.6</td>
<td>1.2</td>
<td>2.0</td>
<td>3.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

(TOWARDS UNIVERSAL ACCESS: Scaling up priority HIV/AIDS interventions in the health sector 2010)
FIGURE 5.3
Estimated number of adult and child deaths due to AIDS globally, 1990–2007

Source: Data from UNAIDS and WHO, 2008.

This bar indicates the range around the estimate.
Kaposi’s Sarcoma in Africa

• Despite wider availability of antiretroviral therapy in Africa, AIDS-KS remains a significant cause of mortality and morbidity
  – 3rd leading cause of death for people initiating antiretroviral therapy in southern Africa
KS Incidence in Zimbabwe, 1993-98

Chokunonga et al, 2002
## Cancer Distributions in Zimbabwean Men and Women

### Men

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>KAPOSI'S SARCOMA</td>
<td>25.6</td>
</tr>
<tr>
<td>PROSTATE</td>
<td>11.6</td>
</tr>
<tr>
<td>NON-MELANOMA OF SKIN</td>
<td>11.2</td>
</tr>
<tr>
<td>NON-HODGKIN'S LYMPHOMA</td>
<td>9.5</td>
</tr>
<tr>
<td>EYE</td>
<td>5.5</td>
</tr>
<tr>
<td>OESOPHAGUS</td>
<td>4.8</td>
</tr>
<tr>
<td>LIVER</td>
<td>4.5</td>
</tr>
<tr>
<td>LUNG</td>
<td>2.6</td>
</tr>
<tr>
<td>BLADDER</td>
<td>2.5</td>
</tr>
<tr>
<td>COLON</td>
<td>2.2</td>
</tr>
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</table>

### Women

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERVIX UTERI</td>
<td>28.9</td>
</tr>
<tr>
<td>KAPOSI'S SARCOMA</td>
<td>11.9</td>
</tr>
<tr>
<td>BREAST</td>
<td>10.9</td>
</tr>
<tr>
<td>EYE</td>
<td>8.7</td>
</tr>
<tr>
<td>NON-MELANOMA OF SKIN</td>
<td>5.3</td>
</tr>
<tr>
<td>NON-HODGKIN'S LYMPHOMA</td>
<td>3.6</td>
</tr>
<tr>
<td>OVARY</td>
<td>3.2</td>
</tr>
<tr>
<td>LIVER</td>
<td>2.5</td>
</tr>
<tr>
<td>STOMACH</td>
<td>2.1</td>
</tr>
<tr>
<td>CORPUS UTERI</td>
<td>2.2</td>
</tr>
</tbody>
</table>
Age Distributions of Cancers in Zimbabwe

Kaposi’s sarcoma

Breast cancer

Cervical cancer

Prostate cancer

ZIMBABWE NATIONAL CANCER REGISTRY 2005 ANNUAL REPORT
UZCHS-UCD AIDS-KS Collaboration

- 1998-present
- Initial funding from the Fogarty International Center/NIH
- Subsequent support from:
  - NCI
  - NIDCR
  - Michael Gelfand Medical Research Foundation
  - Glaxo Smith Kline
  - Boehringer-Ingelheim
  - Colorado CFAR
  - Abbott Laboratories
Parirenyatwa Hospital KS Clinic

- Referral center for northern 2/3’rds of Zimbabwe
- ~1,200 KS patients seen annually
- 8-10 newly diagnosed cases/wk
- ~85% have advanced disease

M. Borok, personal communication
Olweny et al, WHO QOL in Cancer Study
HHV-8 and HIV-1 Prevalence in Zimbabwean Factory Workers

N = 2,750

HHV-8

HIV-1

Co-infection

Campbell CID, 2009
HIV-1 but not HHV-8 was associated with risk factors for sexually transmitted infections.
Risk of HHV-8 in Zimbabwe Blood Transfusion Service

- N = 1008
- HIV-1 seroprevalence 1%
- HHV-8 seroprevalence 2% (95% CI 0-4%)
- Antibody to HHV-8 not associated with age, African race, gender, HIV-1 infection, or hepatitis B surface antigenemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>KSHV Antibody</th>
<th>Univariate Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>14</td>
<td>812</td>
<td>3.1</td>
<td>0.41, 24</td>
</tr>
<tr>
<td>Women</td>
<td>1</td>
<td>181</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 26</td>
<td>9</td>
<td>458</td>
<td>1.7</td>
<td>0.61, 4.9</td>
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<tr>
<td>&lt; 26</td>
<td>6</td>
<td>532</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black African</td>
<td>15</td>
<td>850</td>
<td>&gt; &gt;&gt;</td>
<td>0.1</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0</td>
<td>139</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>11</td>
<td>6.4</td>
<td>0.77, 52</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>982</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>14</td>
<td>&gt;&gt; &gt;&gt;</td>
<td>0.8</td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>979</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Four Subtypes of HHV-8

Zong et al, 1999
K1 gene and KSHV virulence

- Membrane signaling protein - homologous to EBV LMP-1
- Transforming properties in tissue culture and animal models
- Highly divergent alleles
- A5 allele associated with more advanced KS disease?
Two distinct K1 subtypes are prevalent in Zimbabwean AIDS-KS patients

- 40% infected with subtype A5 phylogenetically homogenous
- 60% were infected with subtype B was phylogenetically diverse

White, JCV 2008
K1 Subtypes in Zimbabwe

- 2 highly divergent K1 alleles in Zimbabwe
- Different distribution of A and B subtypes compared to Uganda
- Greater genetic diversity in subtype B with intratype variants with potential for different biological properties
- Support hypothesis that subtype B is the more ancient African HHV-8 subtype
AIDS-KS Clinical Characteristics and Response to ART
Weeks: 0 100 200 300

AIDS-KS Survival: 0.2 0.4 0.6 0.8 1.0

- Combination Chemo
- Etoposide
- Radiotherapy
- Supportive Care

Olweny et al., 2005
Comparison of AIDS-KS to non-KS AIDS Outcomes after Initiation of ART at Parirenyatwa Hospital

- Pre-treatment CD4+ cells higher in AIDS-KS (mean 196 vs. 92 mm\(^{-3}\); \(P=0.005\))
- Absolute change in CD4+ cells (\(p=0.149\)) and total CD4+ cells (\(p=0.729\)) at 1 year not different
- Loss to care was higher in AIDS-KS patients (38 vs. 16%; \(p=0.016\), HR: 4.11, CI: 1.31-12.92)
- Among AIDS-KS patients those retained in care had higher pre-treatment CD4+ cells than those lost to care (232 vs. 122 cells/mm\(^3\), \(p=0.048\))

Loss to care = failure to attend clinic or refill ARV prescriptions for ≥ 3 months

Nelson et al., manuscript under review
IS HHV-8 Viral Load a Marker of KS Disease Burden and/or KS Clinical Outcomes?
Relationship of Plasma and Cell-Associated HHV-8 DNA

![Graph showing the relationship between Plasma KSHV DNA (copies/mL) and PBMC KSHV DNA (copies/10^5 cells). The graph includes a trend line with an R^2 value of 0.44 and a p-value less than 0.001.](image)

Campbell, CID 2003
Plasma HHV-8 DNA Correlates with AIDS-KS Clinical Disease

Campbell, CID 2003
Greater Plasma HHV-8 DNA in AIDS-KS vs Endemic KS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Endemic KS</th>
<th>AIDS-KS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>KS stage, II/III</td>
<td>14/6</td>
<td>14/6</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>45 (20–72)</td>
<td>34 (23–53)</td>
<td>.05</td>
</tr>
<tr>
<td>No. of men/women(^a)</td>
<td>19/1</td>
<td>16/4</td>
<td>.34</td>
</tr>
<tr>
<td>No. of CD4(^+) lymphocytes/mm(^3)</td>
<td>564 (87–878)</td>
<td>162 (50–778)</td>
<td>.002</td>
</tr>
<tr>
<td>PBMC KSHV DNA load, copies/10(^5)cells</td>
<td>19.6 (&lt;0.35–840)</td>
<td>2.8 (&lt;0.35–73,891)</td>
<td>.40</td>
</tr>
<tr>
<td>Plasma KSHV DNA load, copies/mL</td>
<td>&lt;30 (&lt;30–436)</td>
<td>41 (&lt;30–11,231)</td>
<td>.04</td>
</tr>
<tr>
<td>Plasma KSHV DNA prevalence, %(^a)</td>
<td>20</td>
<td>50</td>
<td>.10</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (range), except where indicated. P was determined by the Wilcoxon signed-rank test. KSHV, Kaposi sarcoma–associated herpesvirus.

\(^a\) Fisher’s exact test.
Plasma HHV-8 DNA Not Associated with CD4 Count
Summary

- HHV-8 viremia common in Zimbabwean AIDS-KS patients
- Magnitude of plasma and PBMC HHV-8 DNA associated with KS tumor burden but not with a marker of HIV-1 immunosuppression
- Does plasma or PBMC HHV-8 DNA concentration predict clinical outcomes?
- Could changes in plasma or PBMC DNA serve as surrogate marker for response to treatment?
Single arm pilot study

Planned sample size = 90; 89% power to detect 0.5 log_{10} copy/mL difference plasma HHV-8 DNA

Treatment with ZDV/3TC/ABC (Trizivir) for 96 wks

Chemotherapy and/or radiation therapy provided as part of routine clinical care

Pretreatment KS clinical stage was assessed by both Krigel (Stage II, III or IV) and ACTG criteria (T0 or T1)
Results

• 91% reported at least 90% adherence with ART at 48 wks
• 50% received adjunctive chemotherapy
• 24% received adjunctive radiotherapy
• 14% discontinued study participation or were lost-to-follow-up
• 16% died; odds of death greater during the first 48 wks (OR= 4.67; P=0.01)
Survival after ART Initiation

- **Study Group**

- **1994-2001 (no ART)**
  - Olweny et al., 2005

- **HR 0.78 (95% CI 0.73, 0.84; P<0.0001)**

Borok, CID 2010
Clinical Tumor Response to ART

At 96 weeks:
- 19% Partial Response
- 49% stable KS

Borok, CID 2010
# Causes of Early and Late Mortality

<table>
<thead>
<tr>
<th>Event</th>
<th>Study week</th>
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<tbody>
<tr>
<td></td>
<td>0–24</td>
</tr>
<tr>
<td>Death, by cause</td>
<td></td>
</tr>
<tr>
<td>Infectious disease</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>5</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcal meningitis</td>
<td>1</td>
</tr>
<tr>
<td>KS progression</td>
<td>0</td>
</tr>
<tr>
<td>All deaths</td>
<td>7</td>
</tr>
<tr>
<td>Premature discontinuation from the study</td>
<td></td>
</tr>
<tr>
<td>Moved from Harare, Zimbabwe, area</td>
<td>3</td>
</tr>
<tr>
<td>Missed 3 consecutive visits</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
</tr>
<tr>
<td>Receipt of chemotherapy</td>
<td>15</td>
</tr>
</tbody>
</table>

Borok, CID 2010
Changes in Plasma and PBMC HHV-8 DNA after Initiation of ART
Correlates of Survival and Tumor Response

Univariate Odds Ratio

- Female gender
- Age > 45 years
- Baseline BMI < median
- KS Stage IV (Krigel)
- KS Stage T1 (ACTG)
- KS QOL score > median
- Hemoglobin < 9.5 g/dL
- Absolute neutrophil count
  - Baseline < 1,500 mm$^3$
  - Follow-up < 750 mm$^3$
- Adjunctive Chemotherapy
- Adjunctive Radiation Therapy
- CD4+ lymphocytes
  - Baseline > median
  - Change > median
- Baseline plasma HIV-1 RNA < median
- Antiretroviral virological failure
- Baseline plasma HHV-8 DNA < median
- Baseline PBMC HHV-8 DNA < median

Borok, CID 2010
Randomized comparison of switching to 3TC/ABC + LPV/r for refractory AIDS-KS in patients with VL <400 c/mL (96 weeks)*

<table>
<thead>
<tr>
<th></th>
<th>ABC/3TC/ZDV</th>
<th>ABC/3TC + LPV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects in Arm</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Adherence &gt;95%</td>
<td>10 (91%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>CD4+ lymphocytes (mm-3)</td>
<td>Entry</td>
<td>363 (218 – 616)</td>
</tr>
<tr>
<td></td>
<td>96 weeks</td>
<td>486 (276 – 968)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>470 (118 – 649)</td>
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<tr>
<td>Plasma HIV-1 RNA &lt;400 copies/mL</td>
<td>Entry</td>
<td>11 (100%)</td>
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<td>96 weeks</td>
<td>9 (82%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 (83%)</td>
</tr>
<tr>
<td>96 week KS Tumor Response</td>
<td>Complete</td>
<td>1 (9%)</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>5 (45%)</td>
</tr>
<tr>
<td></td>
<td>No change</td>
<td>3 (27%)</td>
</tr>
<tr>
<td></td>
<td>Progression</td>
<td>2 (18%)</td>
</tr>
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</table>

*Borok, World AIDS 2010*  
*Median pre-randomization ART duration 173 weeks*
Summary

• ART improved AIDS-KS survival in Zimbabwe
• Complete clinical response was not observed in first 96 weeks of follow-up
• Partial clinical response occurred in a minority of participants
• Combined use of ART and chemotherapy need further study
• High plasma HHV-8 DNA was associated with increased risk of death and decreased odds of clinical tumor response during antiretroviral therapy
Future Directions

• A5263/AMC 066 - Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

• A5264/AMC067 - Randomized Evaluation of Antiretroviral Therapy Alone or with Delayed Chemotherapy versus Antiretroviral Therapy with Immediate Adjunctive Chemotherapy for Treatment of Limited Stage AIDS-KS in Resource-Limited Settings (REACT-KS)
Ongoing RCTs of Chemotherapy for AIDS-KS

**A5264**

- **N = 468**
- Limited Stage AIDS-KS

**Arm 1A**
- Antiretroviral Therapy

**Arm 1B**
- Antiretroviral Therapy + Etoposide

- **Post-week 96**

**Arm 2A**
- Antiretroviral Therapy + Etoposide

- **Post-week 96**

**Step 2**

**Step 3**

**A5263**

- **N = 706**
- Advanced Stage AIDS KS

**Arm 1A**
- Antiretrovirals + Etoposide

**Arm 1B**
- Antiretrovirals + Bleomycin + Vincristine

**Arm 1C**
- Antiretrovirals + paclitaxel

**Step 1**

**Step 2A**
- Second course of up to 6 cycles of the same chemotherapy utilized in Step 1

**Step 2B**
- Randomly assigned alternative study-provided chemotherapy regimen.

**Step 2A fails**
Strategies to Improve KS Outcomes (SIKO)

• Current treatment of KS in Zimbabwe is largely through referral centers

• Goal:
  – Develop evidence-based, cost-efficient approaches to improve detection and management of KS in low resource environments
  – Evaluate the implementation of these approaches in primary care settings in urban and rural communities in Zimbabwe
SIKO Intervention

HIV-infected Patients undergoing evaluation for initiation of antiretroviral therapy

Kaposi Sarcoma Standardized Evaluation every year

No Suspected KS → Further evaluations and initiation of ART per local guidelines

Suspected KS → Determine KS Stage

Stage T0 → Initiate ART

Stage T1

Reevaluate at 3 months

KS lesions regressed or stable → Continue ART

KS lesion progression

1. Bx skin lesion
2. Photograph lesions
3. Specialist consultations

Develop treatment plan for chemotherapy and palliative care as appropriate
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