Professor Mark Bower
Chelsea and Westminster Hospital, London

COMPETING INTEREST OF FINANCIAL VALUE £1,000:

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Mark Bower</td>
<td>Professor Bower has received speaker fees from Gilead, Janssen, ViiV and advisory board fees from Galen</td>
</tr>
</tbody>
</table>

Date: April 2012
KS: Do we still need chemotherapy?

Kaposi sarcoma timelines

1872 Moritz Kaposi describes skin sarcoma
First century (1872-1972)

1895  Heinrich Koebner coins term “Kaposi’s sarcoma”
1962  Cases of endemic KS reported in Africa
1969  KS reported following renal allograft
1972  Herpes virus particles seen by electron microscopy in KS lesions
Cases of PCP in 1981

5 June

One month later.....KS

The New York Times

RARE CANCER SEEN IN 41 HOMOSEXUALS
By Lawrence K Altman
3 July 1981
Rock Hudson died October 1985.... and everyone took notice of AIDS

1993 Tom Hanks gets KS
Early therapies for KS (1980s)

Interferon alpha
Thalidomide
Retinoids
Vincristine/bleomycin (non-myelotoxic chemotherapy)
Liposomal anthracyclines: early 1990s

Initial market was AIDS-KS where no new anti-cancer agents are ever now tested and no new licenses since!

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Interval</th>
<th>Patients</th>
<th>Response rate</th>
<th>Median response duration</th>
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</thead>
<tbody>
<tr>
<td>Daunoxome</td>
<td>40 mg/m²</td>
<td>14 d</td>
<td>116</td>
<td>25%</td>
<td>3.8 m</td>
</tr>
<tr>
<td>Caelyx</td>
<td>20 mg/m²</td>
<td>14 d</td>
<td>133</td>
<td>46%</td>
<td>3.0 m</td>
</tr>
<tr>
<td>Caelyx</td>
<td>20 mg/m²</td>
<td>21 d</td>
<td>121</td>
<td>58%</td>
<td>5.0 m</td>
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</tbody>
</table>
### Phase III trials of liposomal anthracyclines

<table>
<thead>
<tr>
<th></th>
<th>Gill et al.</th>
<th>Stewart et al.</th>
<th>Northfelt et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daunoxome</td>
<td>Caelyx</td>
<td>Caelyx</td>
</tr>
<tr>
<td>n</td>
<td>116</td>
<td>121</td>
<td>133</td>
</tr>
<tr>
<td>RR</td>
<td>25%</td>
<td>59%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>ABV</td>
<td>BV</td>
<td>ABV</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>120</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>23%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;NS</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Liposomal anthracyclines

- Higher response rates
- Higher overall survival
- Lower toxicity

Liposomal anthracyclines gold standard first line chemotherapy for KS
Ulcerating KS treated with liposomal anthracycline

Pulmonary KS treated with liposomal anthracycline
Emergence of HAART in 1996

KS incidence rates 1992-6 vs 1997-9

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted incidence rate per 1000 per year (No.)</th>
<th>Rate ratio (RR) for 1997 through 1999 versus 1992 through 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1992 through 1995</td>
<td>1997 through 1999</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>22.7 (53)</td>
<td>7.7 (7)</td>
</tr>
<tr>
<td>Aquitaine</td>
<td>18.5 (170)</td>
<td>3.3 (18)</td>
</tr>
<tr>
<td>ASD</td>
<td>15.1 (527)</td>
<td>5.5 (115)</td>
</tr>
<tr>
<td>CASCADE</td>
<td>10.4 (149)</td>
<td>3.1 (6)</td>
</tr>
<tr>
<td>DMI-2</td>
<td>15.5 (150)</td>
<td>0.1 (5)</td>
</tr>
<tr>
<td>HERS</td>
<td>0.4 (1)</td>
<td>0.0 (6)</td>
</tr>
<tr>
<td>HOPS</td>
<td>21.0 (104)</td>
<td>9.4 (29)</td>
</tr>
<tr>
<td>MACS</td>
<td>29.3 (189)</td>
<td>4.2 (7)</td>
</tr>
<tr>
<td>MHCS</td>
<td>0.7 (2)</td>
<td>0.0 (6)</td>
</tr>
<tr>
<td>RHIHP</td>
<td>0.3 (1)</td>
<td>0.0 (6)</td>
</tr>
<tr>
<td>SFCCC</td>
<td>37.3 (37)</td>
<td>8.6 (1)</td>
</tr>
<tr>
<td>ALL STUDIES</td>
<td>15.2 (1489)</td>
<td>4.9 (190)</td>
</tr>
</tbody>
</table>
Falling incidence of KS in EuroSIDA

Test for trend (Poisson regression), 0.61; 95% CI, 0.57 to 0.65; P < 0.0001

HAART prevents KS

AIDS 2003, 17: 17
HAART prolongs treatment-free interval in KS

AIDS 2009, 23:1701–6

HAART alone causes regression of KS

80% don’t need any other treatment for T0 stage KS over 10 years of follow-up

AIDS 2009, 23:1701–6
HAART healing KS (3m apart)

Improving outcomes in KS

JCO 2005, 23:1253
Effects of HAART on KS

- Reduces incidence
- Increases progression free survival
- Cause regression of KS
- Improves overall survival

So why do we need chemo?
# KS Staging

<table>
<thead>
<tr>
<th>TIS Staging of KS</th>
<th>Good risk (all of the following)</th>
<th>Poor risk (any of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T) Tumour</td>
<td>Confined to skin, lymph nodes or minimal oral disease</td>
<td>Tumour-associated oedema or ulceration Extensive oral KS KS in non-nodal viscera</td>
</tr>
<tr>
<td>(I) Immune Status</td>
<td>CD4 count &gt;150/mm$^3$</td>
<td>CD4 &lt;150/mm$^3$</td>
</tr>
</tbody>
</table>

## KS Associated Oedema (T1)

![Images showing KS associated oedema](image_url)
KS ulceration / extensive oral disease (T1)

KS visceral (T1)
BHIVA guidelines 2008

**Early – stage KS (T0 stage)**
HAART (level evidence III B)

**Advanced KS (T1 stage)**
HAART and liposomal anthracycline (either DuanoXome 40mg/m² every 14 days or Caelyx 20mg/m² every 21 days) Level of evidence 1B A

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**CWH cohort HAART era (1996-2012)**

521 First diagnosis KS
490 (94%) Male, 30 Female, 1 M2F
86/521 (17%) Black African
Median age 38 years (range:16-71)
Median CD4 168 /mm³ (range: 0-1200)
**Staging (CWH post-HAART cohort)**

<table>
<thead>
<tr>
<th></th>
<th>T0</th>
<th>I0</th>
<th>T0 = 342 (66%)</th>
<th>I0 = 257 (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 I0</td>
<td>189 (36%)</td>
<td>153 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 I0</td>
<td>68 (13%)</td>
<td>T1 = 177 (34%)</td>
<td>I1 = 262 (50%)</td>
<td></td>
</tr>
<tr>
<td>T1 I1</td>
<td>109 (21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival**

Log rank p<0.0001

![Graph showing cumulative survival over years for T0 and T1 stages, with labels T0 stage n=342 and T1 stage n=176.]
T1 stage KS (34%)

- Oedema/ulceration: 70/520 (13%)
- Extensive oral: 71/520 (13%)
- Visceral: 75/520 (14%)
  - Pulmonary: 46/520 (9%)
  - Gastrointestinal: 39/520 (7%)

Cumulative Survival

No extensive oral KS n=439
Extensive oral KS n=71

P=0.51
Cumulative Survival

**No oedema/ulceration**
n=450

**Oedema/Ulceration**
n=70

P=0.12

**Visceral KS**
n=75

**No visceral KS**
n=445

p<0.0001
RCT: HAART vs HAART & Chemo

112 HAART naive patients with KS
Excluded symptomatic visceral KS and fungating KS (deemed to require immediate chemo)
3TC, D4T, NVP ± ABV chemotherapy

Mosam et al. JAIDS 2012 epub

RCT: HAART vs HAART & Chemo

89% T1

54% I1 (CD4 <150/mm³)
42% S1

Mosam et al. JAIDS 2012 epub
RCT: HAART vs HAART & Chemo

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Response rate</th>
<th>1yr PFS</th>
<th>1yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAART alone</td>
<td>59</td>
<td>39%</td>
<td>31%</td>
<td>78%</td>
</tr>
<tr>
<td>HAART and chemo</td>
<td>53</td>
<td>66%</td>
<td>56%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>P=0.005</td>
<td>P=0.006</td>
<td>P=NS</td>
<td></td>
</tr>
</tbody>
</table>

Mosam et al. JAIDS 2012 epub

KS: Do we still need chemotherapy?

1. ACTG stage T1 disease
**IRIS KS**

Progressive KS in naïve patient following start of HAART

<table>
<thead>
<tr>
<th></th>
<th>Pre-ART</th>
<th>12 weeks following ART</th>
<th>24 weeks following ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>CWH</td>
<td>10/150</td>
<td>(7%)</td>
<td>(Bower 2005)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>8/69</td>
<td>(12%)</td>
<td>(Letang 2010)</td>
</tr>
<tr>
<td>Chicago</td>
<td>12/41</td>
<td>(29%)</td>
<td>(Achenberg 2012)</td>
</tr>
</tbody>
</table>

**Risk factors for IRIS KS**

Meta-analysis of 4 cohorts:
- 40/204 (20%) in African cohorts
- 18/213 (8%) in CWH cohort (excludes T1 stage)

Independent risk factors for IRIS KS:
- High VL, Low CD4, T1 disease, African cohort
How to define IRIS KS

1. Immunology (CD4 rising, VL falling/undetectable)

2. Timing (on HAART ≥1 months)

3. Progression of KS (ACTG definition)
   - ≥25% rise in bidimensional diameter of index lesions
   - New KS lesions
   - ≥25% flat lesions becoming raised
   - New KS associated oedema

KS: Do we still need chemotherapy?

2. Management of IRIS KS

   Addition of chemotherapy to HAART
Rituximab related progression of KS

KS in fully suppressed patients

521 KS newly diagnosed in post HAART era
80 (15%) established on HAART >3months
32 (6%) undetectable viral load
20 (4%) undetectable viral load & CD4 >350/mm³
KS in suppressed patients

4% **new** KS diagnosed in patients with CD4>350 & undetectable viral load

In addition many patients with recurrent KS despite CD4>350 & undetectable viral load

KS: Do we still need chemotherapy?

3. Management of KS in fully suppressed patients

Addition of chemotherapy to HAART
KS: Do we still need chemotherapy?

Chemotherapy is effective
Minimal toxicity
No cumulative cardiotoxicity
No prolonged effect on CD4 cell count

KS: Role of chemotherapy

1. ACTG stage T1 disease
2. Management of IRIS KS
3. Management of KS in fully suppressed patients
St. Peregrine

Born in 1260 at Forlì, Italy. He was cured of cancer of leg, after he received a vision of Christ on the cross reaching out to touch his diseased limb. He died in 1345 and was canonized in 1726.