18th Annual Conference of the British HIV Association (BHIVA)

Professor Mark Bower

Chelsea and Westminster Hospital, London

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Professor Mark Bower:	Professor Bower has received speaker fees from Gilead, Janssen, ViiV and advisory board fees from Galen
Date	**April 2012**

18-20 April 2012, The International Convention Centre, Birmingham

KS: Do we still need chemotherapy?

Kaposi sarcoma timelines

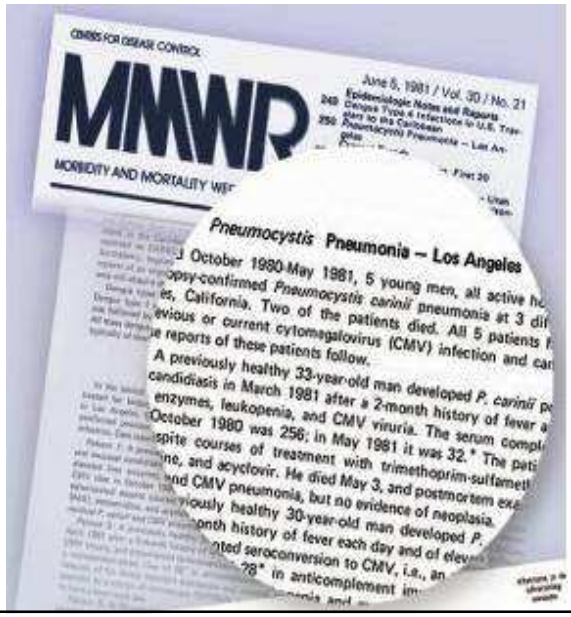
1872 Moritz Kaposi describes skin sarcoma

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

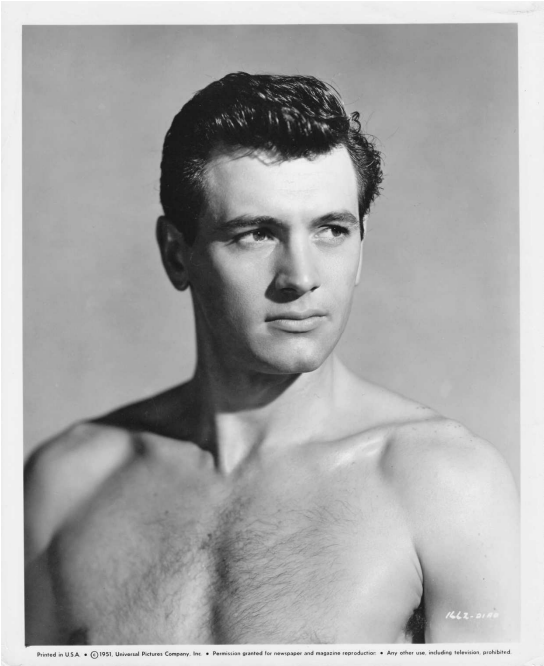
RARE CANCER SEEN IN 41 HOMOSEXUALS

By Lawrence K Altman

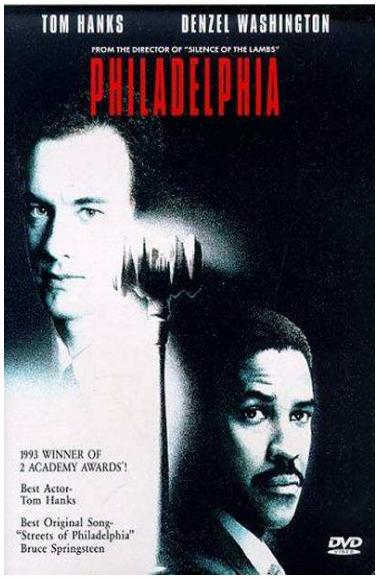
3 July 1981

Rock Hudson
died October 1985....

and everyone took notice of AIDS



1993 Tom Hanks gets KS



KS lesions

Early therapies for KS (1980s)

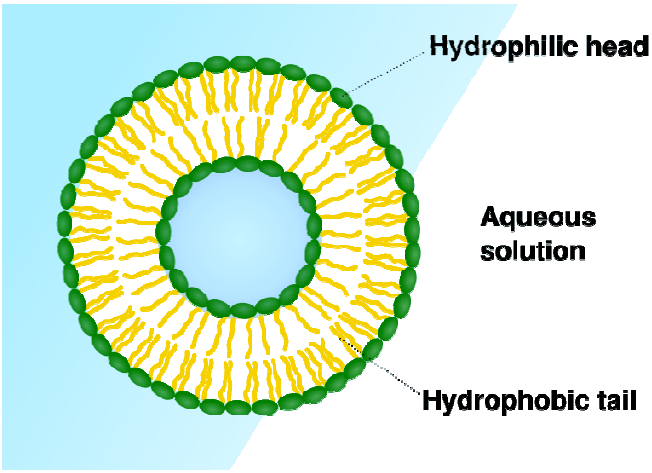
Interferon alpha

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!

Phase III RCTs of liposomal anthracyclines

	Dose	Interval	Patients	Response rate	Median response duration
Daunoxome	40 mg/m^2	14 d	116	25%	3.8 m
Caelyx	20 mg/m^2	14 d	133	46%	3.0 m
Caelyx	20 mg/m^2	21 d	121	58%	5.0 m

Phase III trials of liposomal anthracyclines

	Gill et al.			Stewart et al.			Northfelt et al.		
	Daunoxome	ABV	*p*	Caelyx	BV	*p*	Caelyx	ABV	*p*
n	116	111		121	120		133	125	
RR	25%	28%	NS	59%	23%	<0.001	46%	25%	<0.001

Liposomal anthracyclines

Higher response rates

Higher overall survival

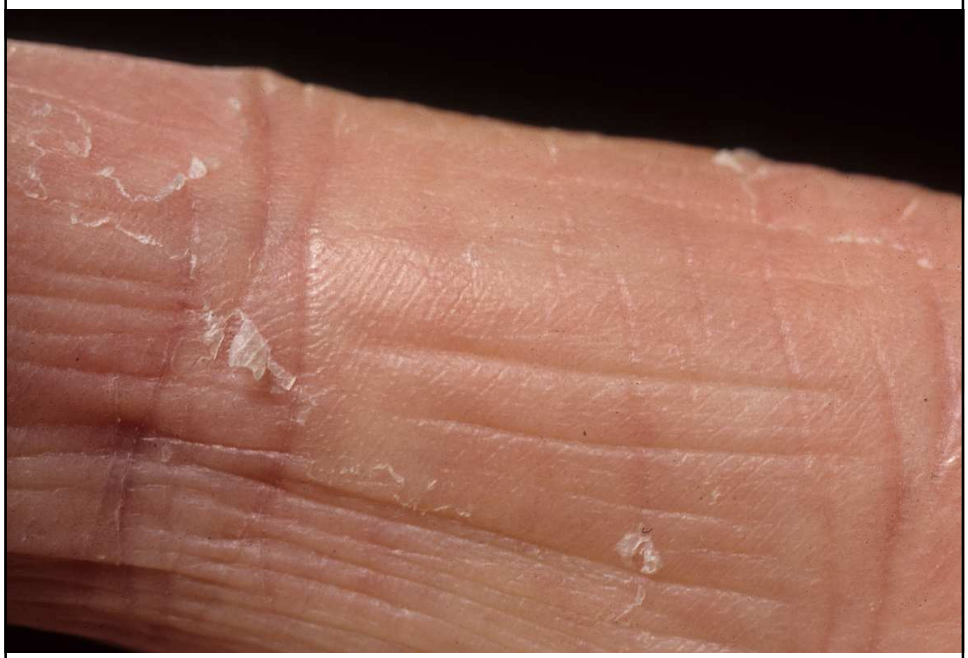
Lower toxicity

Liposomal anthracyclines gold standard first line chemotherapy for KS

Ulcerating KS treated with liposomal anthracycline



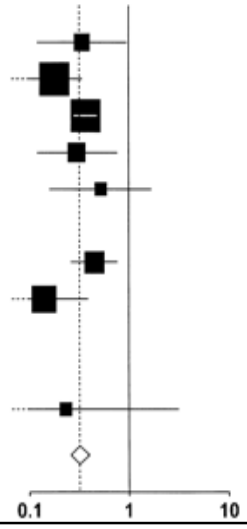

Pulmonary KS treated with liposomal anthracycline



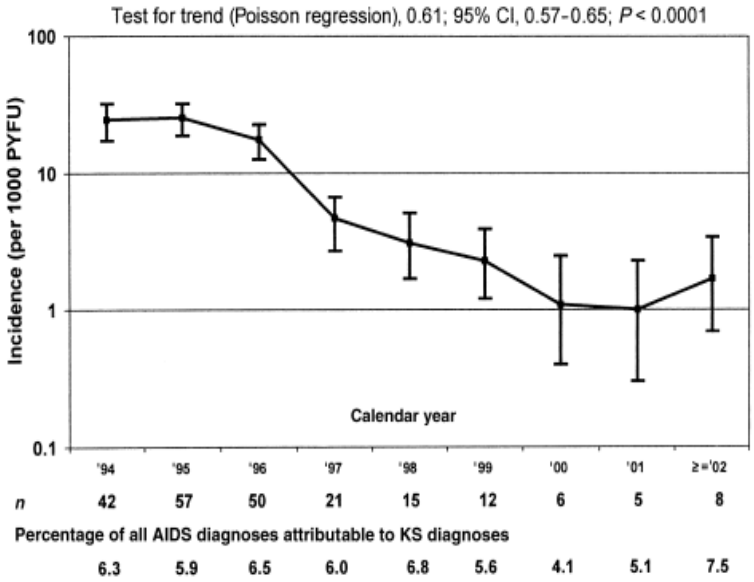
Emergence of HAART in 1996

KS incidence rates 1992-6 vs 1997-9

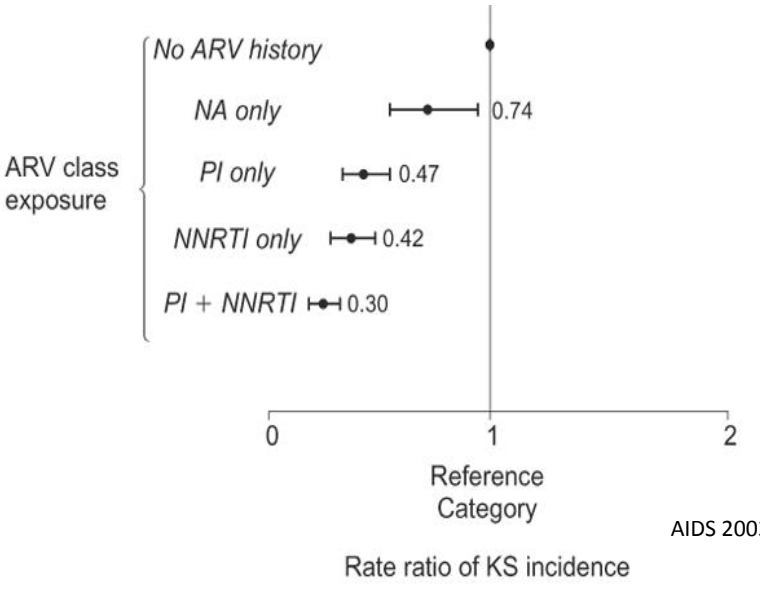
Study	Adjusted incidence rate per 1000 per year (No.) 1992 through 1996	1997 through 1999	Rate ratio (RR) for 1997 through 1999 versus 1992 through 1996 RR (SE)	RR (99% CI)
Amsterdam	22.7 (53)	7.7 (7)	0.34 (0.14)	
Aquitaine	18.5 (170)	3.3 (18)	0.18 (0.04)	
ASD	15.1 (627)	5.5 (115)	0.37 (0.04)	
CASCADE	10.4 (149)	3.1 (8)	0.30 (0.11)	
DMI-2	15.5 (156)	8.1 (5)	0.52 (0.24)	
HERS	0.4 (1)	0.0 (0)	0.00	
HOPS	21.0 (104)	9.4 (29)	0.45 (0.09)	
MACS	29.3 (189)	4.2 (7)	0.14 (0.06)	
MHCS	0.7 (2)	0.0 (0)	0.00	
RHIHP	0.3 (1)	0.0 (0)	0.00	
SFCCC	37.3 (37)	8.6 (1)	0.23 (0.23)	
ALL STUDIES	**15.2 (1489)**	**4.9 (190)**	**0.32 (0.03)**	



Falling incidence of KS in EuroSIDA

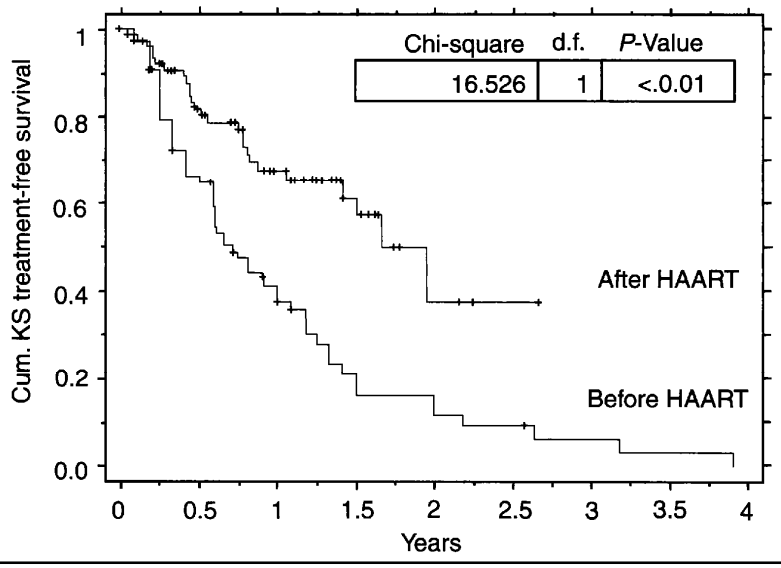


HAART prevents KS

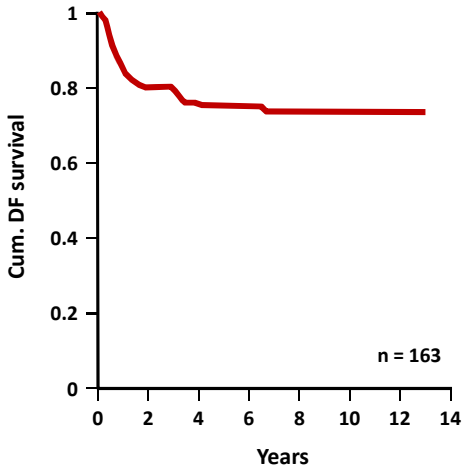


AIDS 2003, 17: 17

HAART prolongs treatment-free interval in KS



HAART alone causes regression of KS

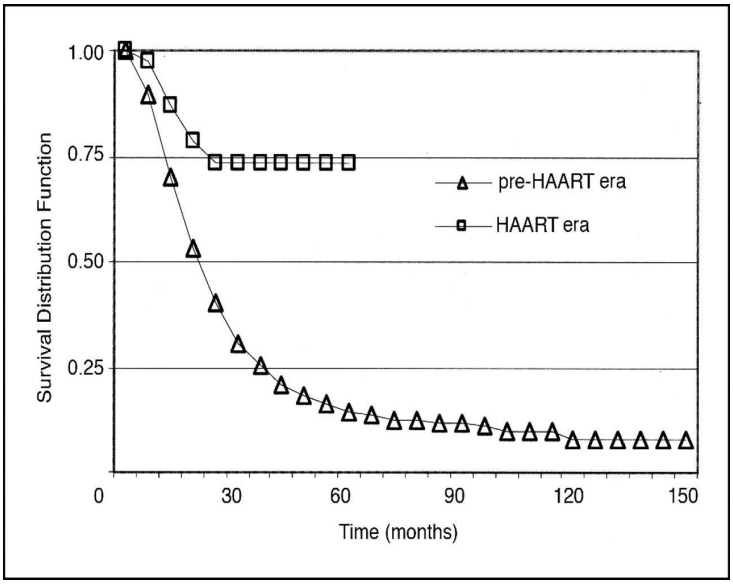


80% don't need any other treatment for T0 stage KS over 10 years of follow-up

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

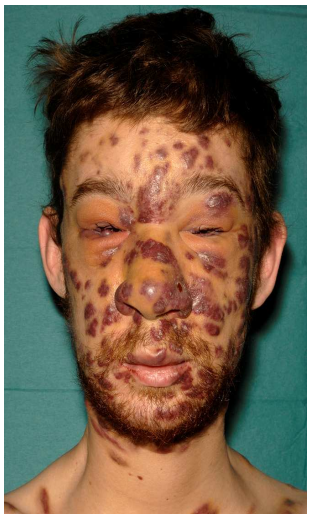
Improves overall survival

So why do we need chemo?

KS staging

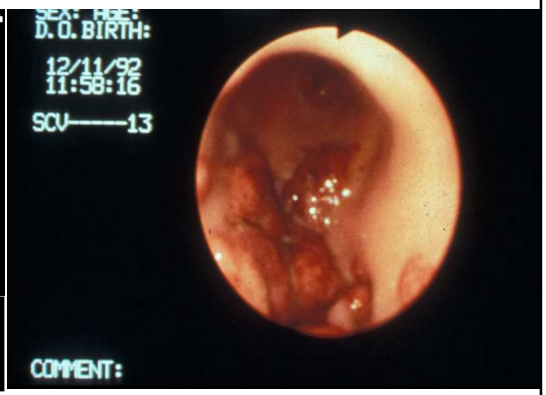
TIS Staging of KS	Good risk (all of the following)	Poor risk (any of the following)
(T) Tumour	Confined to skin, lymph nodes or minimal oral disease	Tumour-associated oedema or ulceration Extensive oral KS KS in non-nodal viscera
(I) Immune Status	CD4 count >150/mm^3	CD4 <150/mm^3

KS associated oedema (T1)


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/m^2 every 14 days or Caelyx 20mg/m^2 every 21 days) Level of evidence 1B A

CWH cohort HAART era (1996-2012)

521 First diagnosis KS

490 (94%) Male, 30 Female, 1 M2F

86/521 (17%) Black African

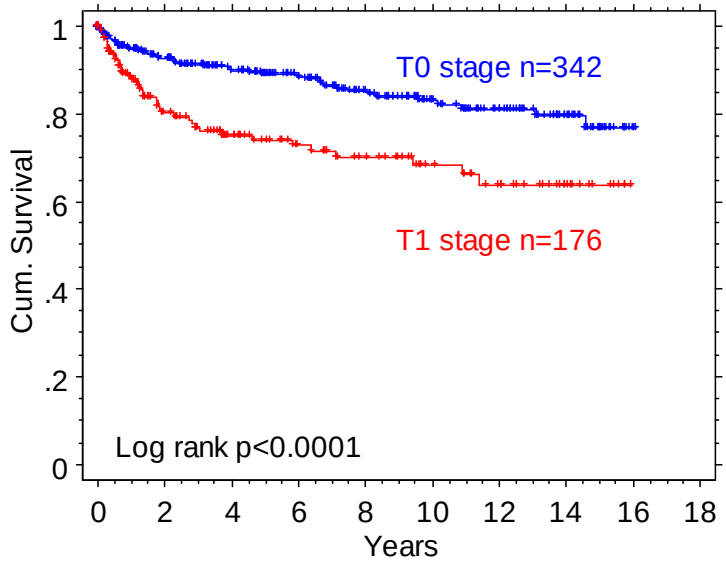
Median age 38 years (range:16-71)

Median CD4 168 /mm^3 (range: 0-1200)

Staging (CWH post-HAART cohort)

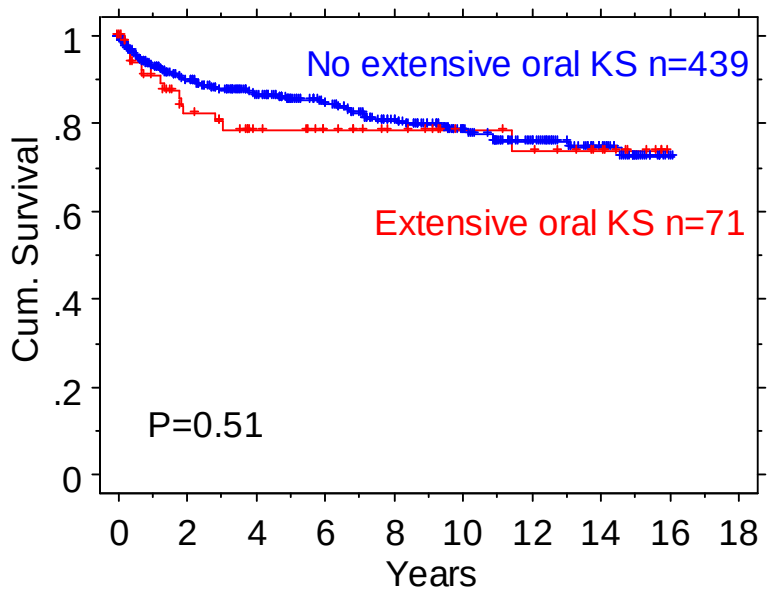
T0 I0	189 (36%)	T0 =342 (66%)	I0 = 257 (50%)
T0 I1	153 (29%)		
T1 I0	68 (13%)	T1 = 177 (34%)	I1 = 262 (50%)
T1 I1	109 (21%)		

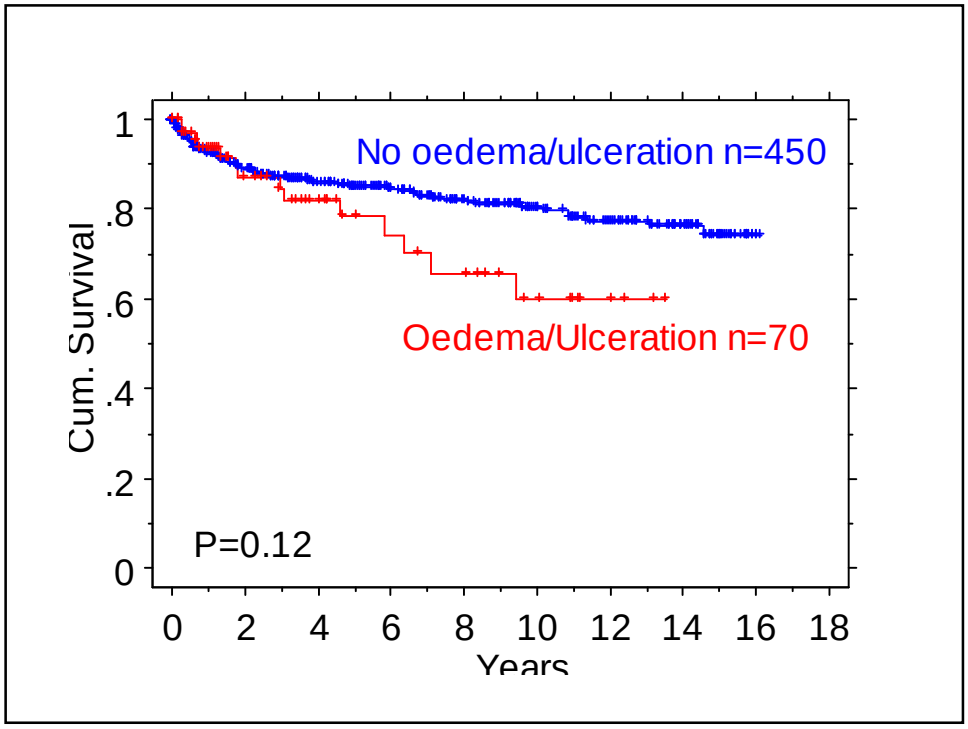
Overall survival

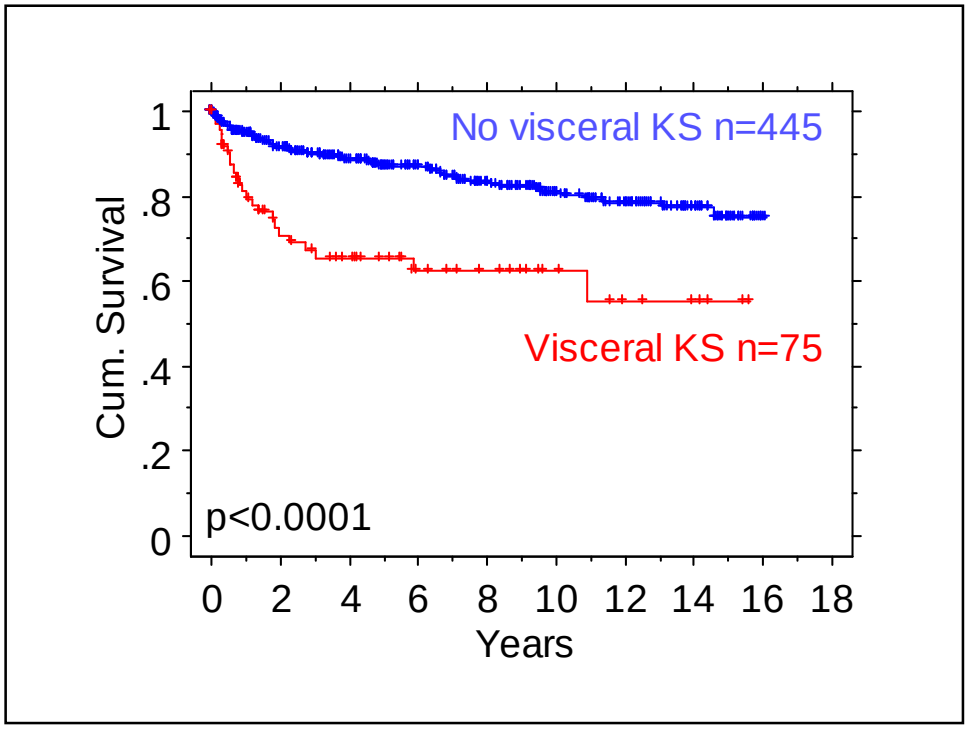


T1 stage KS (34%)

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




No oedema/ulceration n=450
Oedema/Ulceration n=70
P=0.12
Cum. Survival
1
.8
.6
.4
.2
0
0 2 4 6 8 10 12 14 16 18
Years


No visceral KS n=445
Visceral KS n=75
p<0.0001
Cum. Survival
1
.8
.6
.4
.2
0
0 2 4 6 8 10 12 14 16 18
Years

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/mm^3)

42% S1

Mosam et al. JAIDS 2012 epub

RCT: HAART vs HAART & Chemo

	n	Response rate	1yr PFS	1yr OS
HAART alone	59	39%	31%	78%
HAART and chemo	53	66%	56%	74%
		P=0.005	P=0.006	P=NS

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

CWH	10/150 (7%)	(Bower 2005)
Mozambique	8/69 (12%)	(Letang 2010)
Chicago	12/41 (29%)	(Achenberg 2012)

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 ≥1months)

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/mm^3

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.