# Malignancies in HIV


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# Outline

- General background

- Today I will break it down:
  - Basic facts
  - Clinical challenges in ADM and non-ADM
  - Management

- Please feel free to interrupt….

# ADM and NADM

**AIDS-defining malignancies (ADM)**

- **Kaposi's sarcoma**
- **Non-Hodgkin lymphoma**
- **Primary CNS lymphoma**
- Cervical cancer

**Non-AIDS defining malignancies (NADM)**

- **Anal cancer**
- **Hodgkin disease**
- Hepatoma
- Testicular cancer
- Lung cancer
- SCC conjunctiva, mucous membranes
- Many other sites..

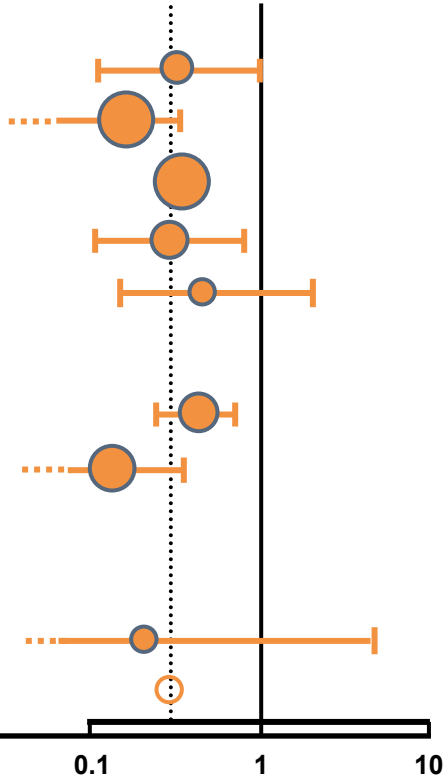
# Malignancies in HIV-infected individuals: clinical situations

- ADM
  - Associated with low CD4
  - Much commoner in HIV
- Non-ADM
  - Associated with less pronounced immune dysfunction
  - Associated with additional contributory factors that may be increased in HIV-infected patients

# Incidence of KS has decreased since introduction of ART

## International Collaboration on HIV and Cancer

| STUDY | Adjusted incidence rate per 1000 per year (No.) 1992–1996 | 1997–1999 | Rate ratio (RR) for 1997–1999 versus 1992–1996 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) | |




International Collaboration on HIV and Cancer. J Nat Canc Instit 2000;92:1823–1830.

# Incidence of NHL has decreased since introduction of ART

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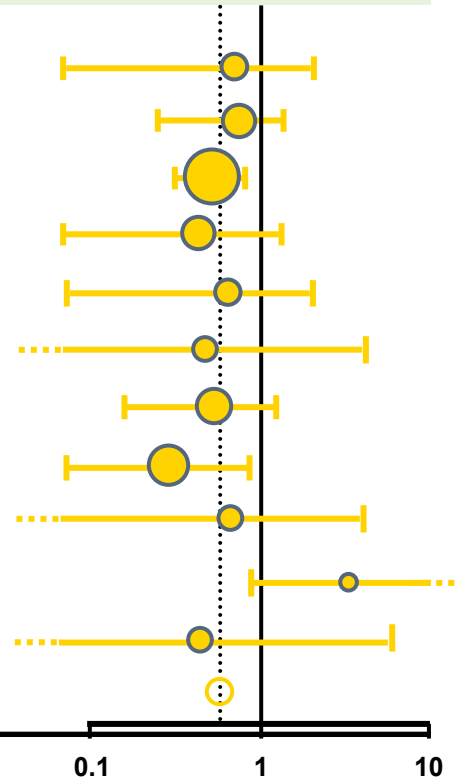
| STUDY | Adjusted incidence rate per 1000 per year (No.) 1992–1996 | 1997–1999 | Rate ratio (RR) for 1997–1999 versus 1992–1996 RR (SE) | RR (99%CI) |
|---|---|---|---|---|
| Amsterdam | 6.6 (16) | 4.2 (4) | 0.64 (0.36) | |
| Aquitaine | 5.1 (50) | 3.8 (20) | 0.73 (0.20) | |
| ASD | 6.0 (247) | 3.3 (70) | 0.55 (0.07) | |
| CASCADE | 4.0 (58) | 1.8 (5) | 0.45 (0.21) | |
| DMI-2 | 8.3 (84) | 5.1 (3) | 0.61 (0.36) | |
| HERS | 2.7 (6) | 1.4 (2) | 0.52 (0.44) | |
| HOPS | 7.2 (37) | 3.8 (12) | 0.53 (0.18) | |
| MACS | 13.1 (86) | 4.2 (8) | 0.32 (0.12) | |
| MHCS | 5.7 (16) | 3.7 (2) | 0.65 (0.49) | |
| RHIHP | 2.8 (10) | 9.3 (7) | 3.30 (1.65) | |
| SFCCC | 12.9 (13) | 6.2 (1) | 0.48 (0.50) | |
| ALL STUDIES | 6.2 (623) | 3.6 (134) | 0.58 (0.06) | |

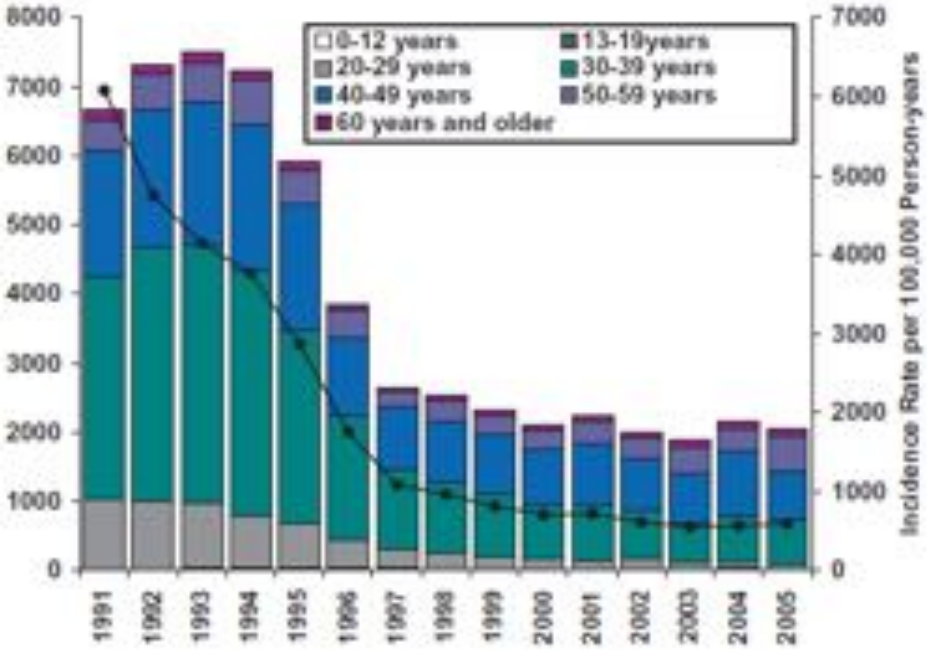



International Collaboration on HIV and Cancer. J Nat Canc Instit 2000;92:1823–1830.

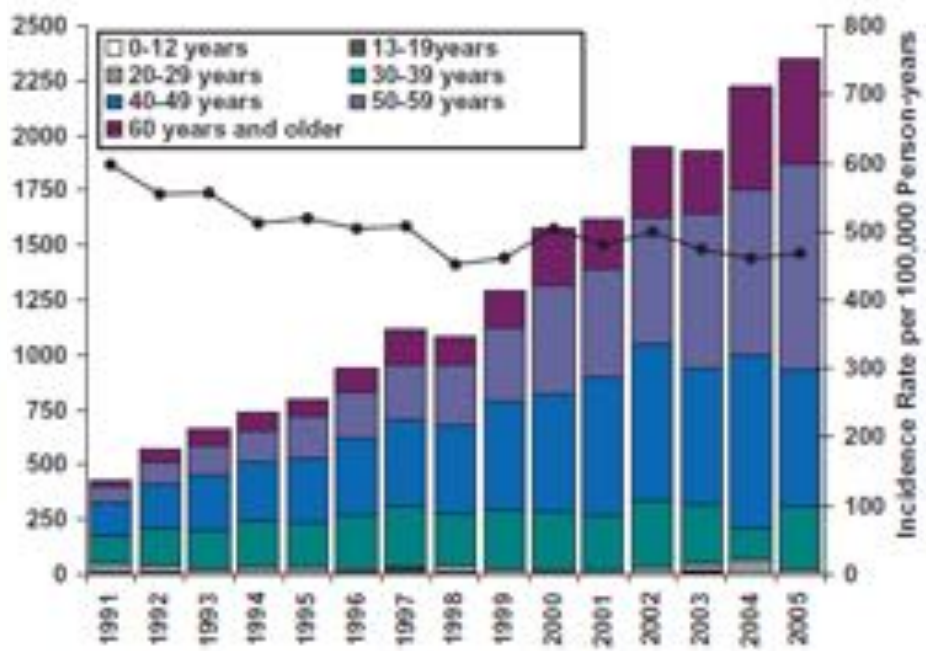
# But with decreasing ADM one sees increasing NADM ( USA 1991-2005)

HIV-AIDS cancer match study USA

**AIDS-defining malignancy**

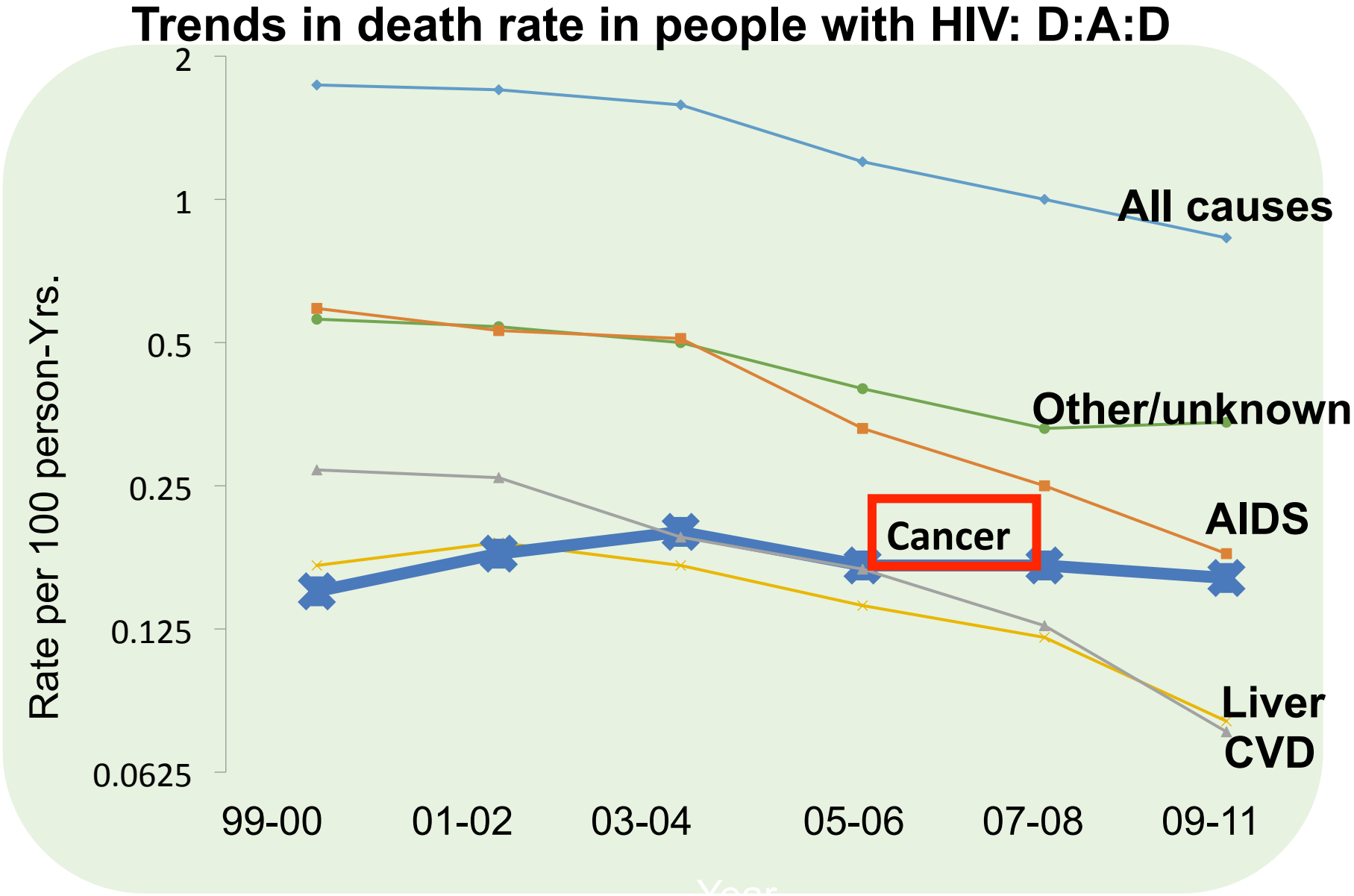



**Non-AIDS-defining malignancy**



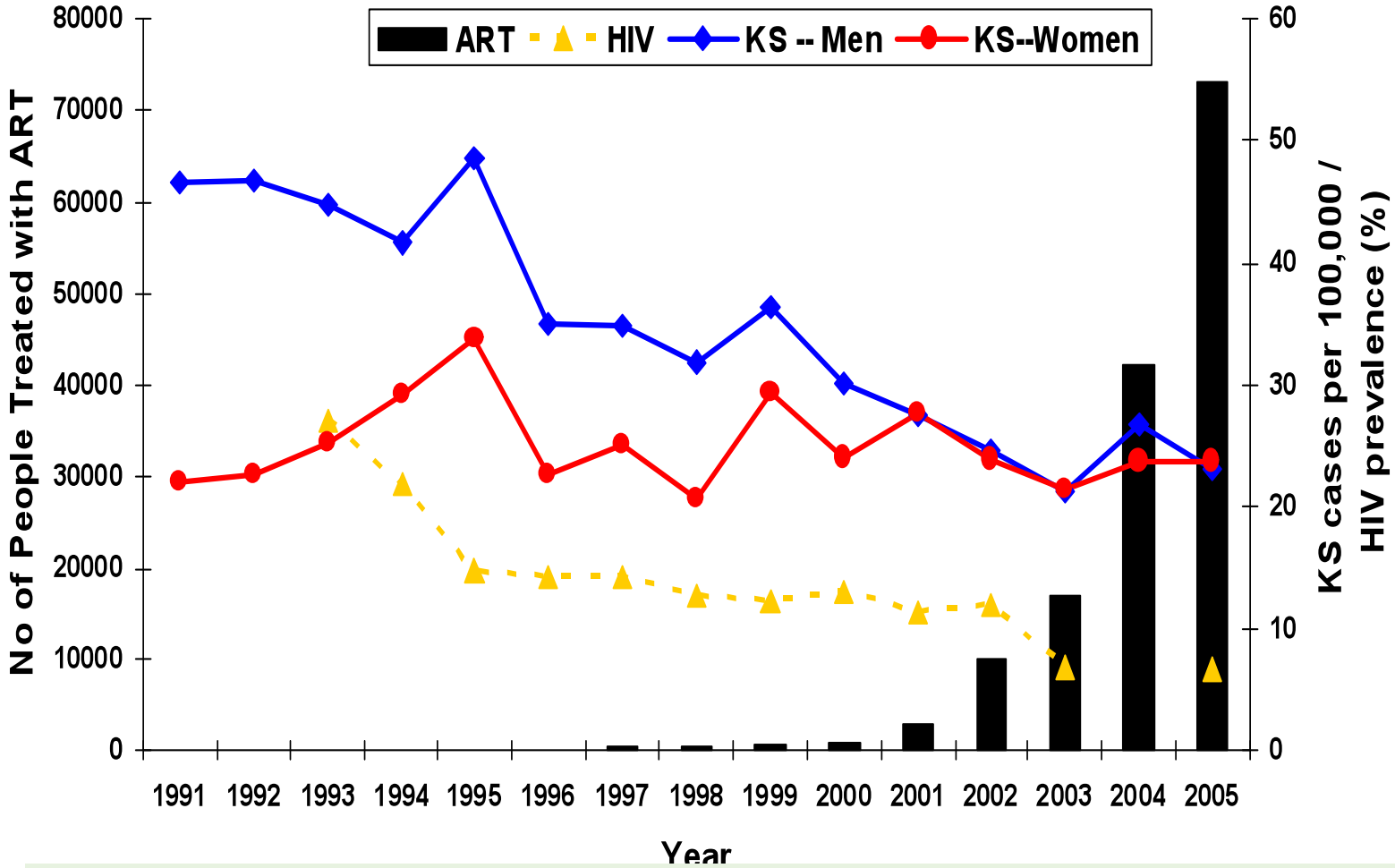

Shiels et al. 2010

# So overall the ⇧NADM is has balanced the ⇩ADM…




Smith C et.al: Washington IAS 2012

# Also not necessarily matched in endemic areas..




No change in KS incidence in Uganda despite over 100,000 persons started on HAART

Adapted from C Casper 2009

# NADM as well as ADM are more common in HIV-infected patients

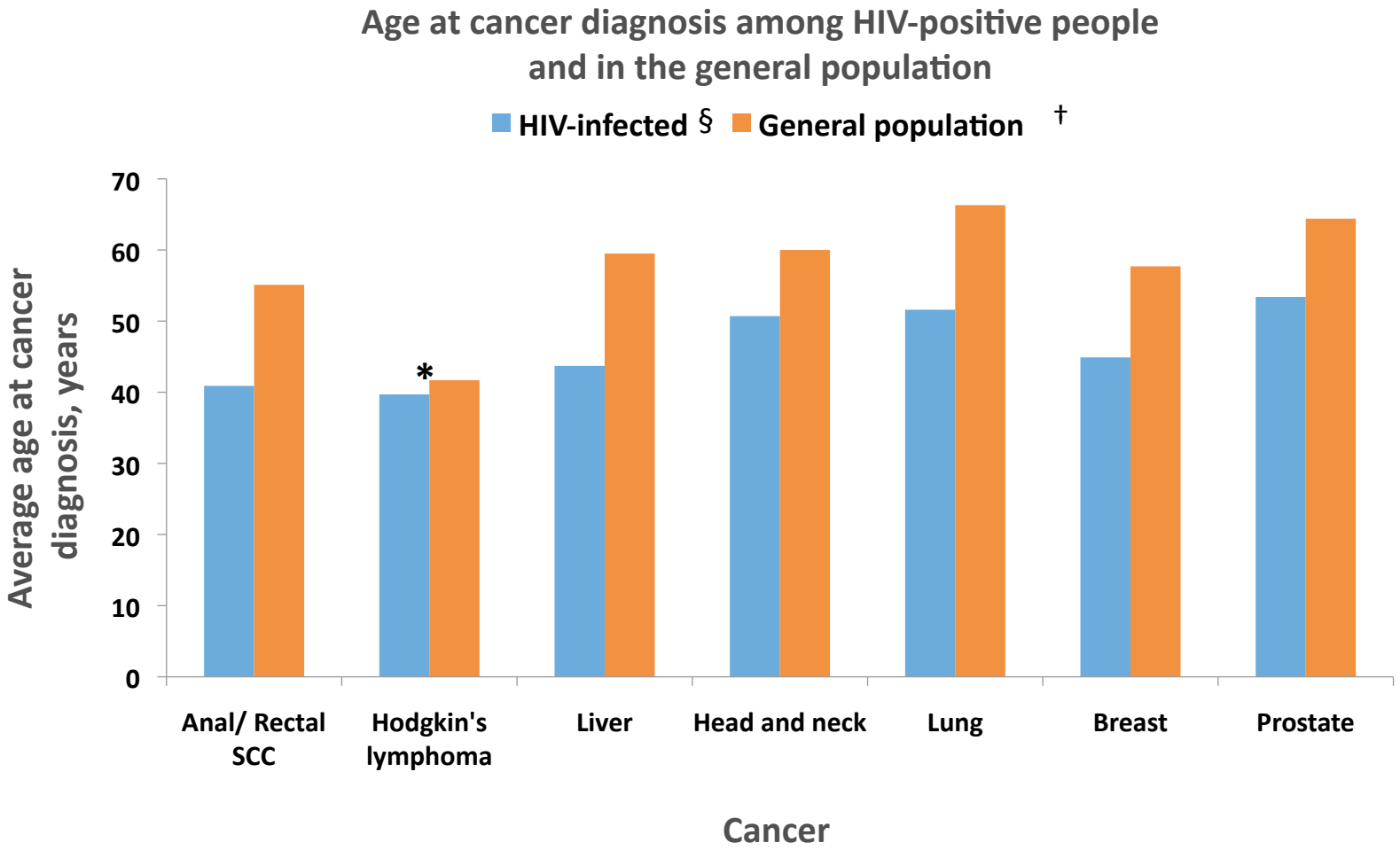
**Retrospective analysis of Kaiser Permanente database, 1996–2008[2]**

| | HIV-infected (n = 20,775) | | HIV-uninfected (n = 215,158) | | Adjusted RR* (95% CI) |
|---|---|---|---|---|---|
| | n | Rate/100,000 p/y | n | Rate/100,000 p/y | |
| Anal | 86 | 96 | 18 | 2 | 55.7 (33.2–93.4) |
| Hodgkin's lymphoma | 52 | 58 | 32 | 3 | 18.7 (11.8–29.5) |
| Liver | 24 | 27 | 110 | 10 | 1.8 (1.1–2.8) |
| Oral/pharyngeal | 26 | 29 | 183 | 16 | 1.4 (0.9–2.1) |
| Lung | 56 | 62 | 380 | 34 | 1.2 (0.9–1.6) |

*Adjusted for age, sex, smoking, overweight, alcohol/drug abuse, viral hepatitis.

Adapted from Silverberg M, et al. Cancer Epidemiol Biomarkers Prev . 2011;20:2551–2559.

# NADM are diagnosed at a younger age in HIV infection




* Difference between groups not statistically significant at p <0.05.

§ HIV-infected patients recruited from Ponce Clinic, 2000–2007 (n=8,300)

† General population refers to age-, race-, and sex-matched cases from the Atlanta SEER database.

Adapted from Nguyen ML, et al. IAC 2010. Oral Presentation WEAB0105.

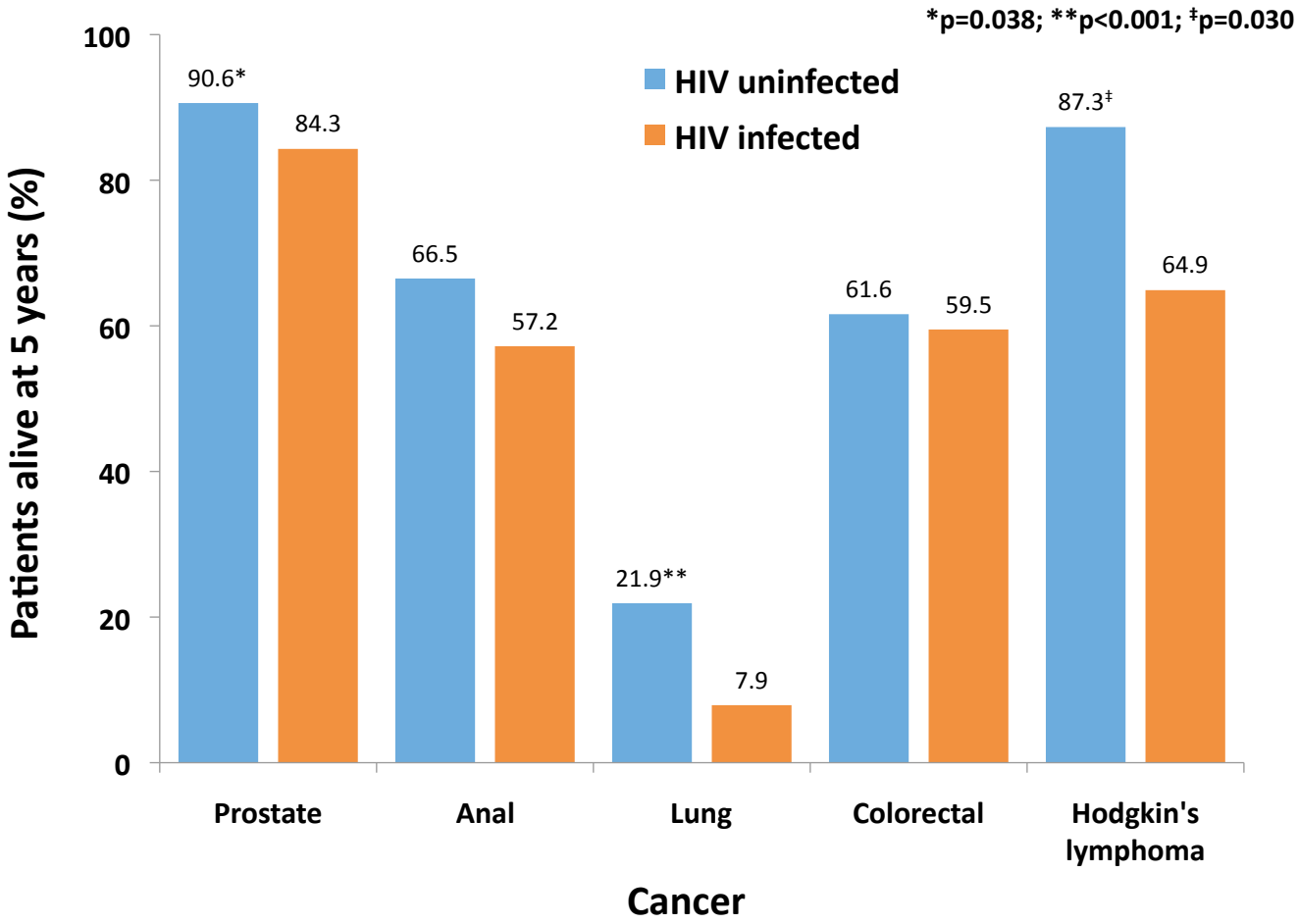
# And are also more aggressive/ more advanced…

## Hodgkin's disease – presentation: UK

| | HIV –ve | HIV +ve | P |
|---|---|---|---|
| **Male %** | 57 | 89 | <0.001 |
| **Age (median)** | 31 | 41 | <0.03 |
| **B-symptoms %** | 40 | 81 | <0.001 |
| **WCC >15 %** | 17 | 0 | <0.001 |
| **Lymphocytes <0.6 %** | 5 | 68 | <0.001 |
| **Hb <10.5 g/l %** | 21 | 44 | <0.001 |
| **Albumin <40 g/l %** | 37 | 79 | <0.001 |
| **Bone marrow involvement %** | 4 | 45 | <0.001 |
| **Stage III-IV %** | 35 | 80 | <0.001 |
| **IPS ≥3 %** | 26 | 68 | <0.001 |

Montoto BHIVA 2012

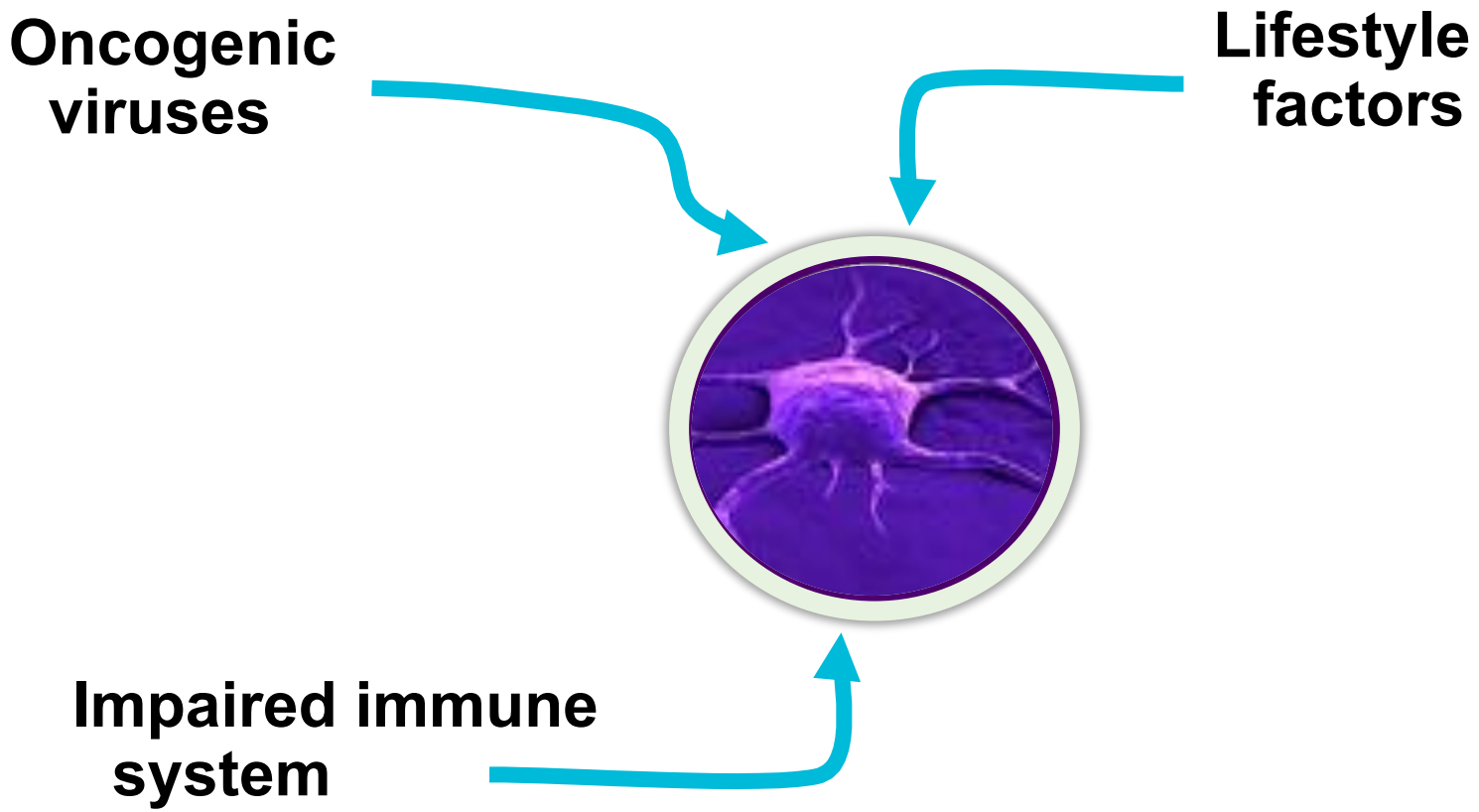
# And have a reduced survival




22,081 HIV-infected and 230,069 age- and sex-matched HIV-uninfected individuals between 1996–2009 who were enrolled in Kaiser Permanente California.

Adapted from Silverberg M, et al. CROI 2012. Poster Presentation 903.

# Risk factors for cancer in HIV




Adapted from Hensel M, et al. Dtsch Arztebl Int. 2010;107:117–122.

# Oncogenic viruses

| AIDS-Defining | Oncogenic virus |
|---|---|
| • Kaposi's Sarcoma | HHV-8 |
| • Non-Hodgkin's Lymphoma | EBV, HHV-8 |
| • PCNSL | EBV |
| • Invasive Cervical Carcinoma | HPV |

| **Non-AIDS Defining (e.g.)** | |
|---|---|
| • **Anogenital cancers** | **HPV** |
| • **Hodgkin's Disease** | **EBV** |
| • **Leiomyosarcoma (pediatric)** | **EBV** |
| • **Squamous Conjunctival Carcinoma oesophagus, larynx, lip** | **HPV** |
| • **Hepatoma** | **HBV, HCV** |

# Impaired immune system – overall death rate from ADM ***and*** NADM ↑ ↓ with CD4 counts

**Mortality rates by CD4 count in individuals with ADM and non-ADM**

| Latest CD4 count (/µL) | Person-years (py) | Non-ADM | | ADM | |
|---|---|---|---|---|---|
| | | Rate (/1000py) (n) | Relative risk* (p) | Rate (/1000py) (n) | Relative risk* (p) |
| **<50** | 2335 | 6.0 (14) | 15 (<0.001) | 20.1 (47) | 175 (<0.001) |
| **50–99** | 2295 | 9.6 (22) | 19 (<0.001) | 4.8 (11) | 41 (<0.001) |
| **100–199** | 8097 | 6.8 (55) | 10 (<0.001) | 2.8 (23) | 24 (<0.001) |
| **200–349** | 21,048 | 2.0 (43) | 3 (<0.001) | 0.7 (14) | 6 (<0.001) |
| **350–499** | 24,052 | 1.1 (27) | 2 (0.03) | 0.3 (7) | 3 (0.09) |
| **500+** | 46,903 | 0.6 (27) | 1 (–) | 0.1 (5) | 1 (–) |

*Adjusted for cohort, age, gender, smoking status, weight, transmission group, ethnicity, prior non-fatal non-neoplastic AIDS, HCV and HBV status, cART exposure, and latest HIV-RNA level

D'Arminio Monforte A, *et al.* CROI 2007;Abstract 84.

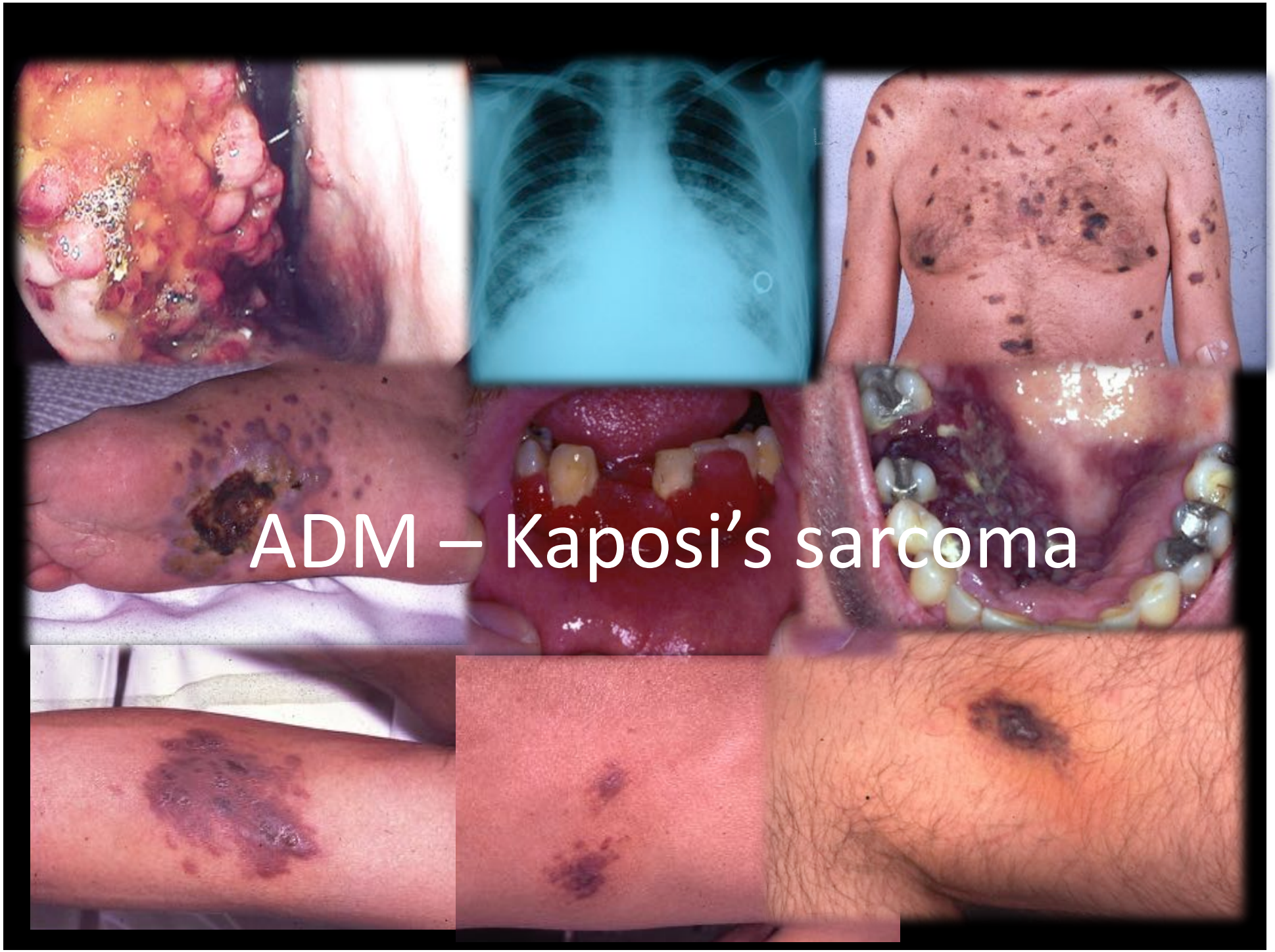
# CD4 count at which malignancy occurs varies by ADM and non-ADM and infective agent

| | | Median CD4 range at diagnosis | Infective factor/co-factor |
|---|---|---|---|
| NHL: | Burkitt's | 350–500 | EBV |
| | Diffuse large B-cell | 10–150 | EBV |
| | PCNSL | 10–50 | EBV |
| KS | | 100–200 | HHV-8 |
| Hodgkin's lymphoma | | 100–500 | EBV |
| Castleman's disease | | 100-300 | HHV-8 |

Personal communication on file. Dr Edmund Willkins, 2008.

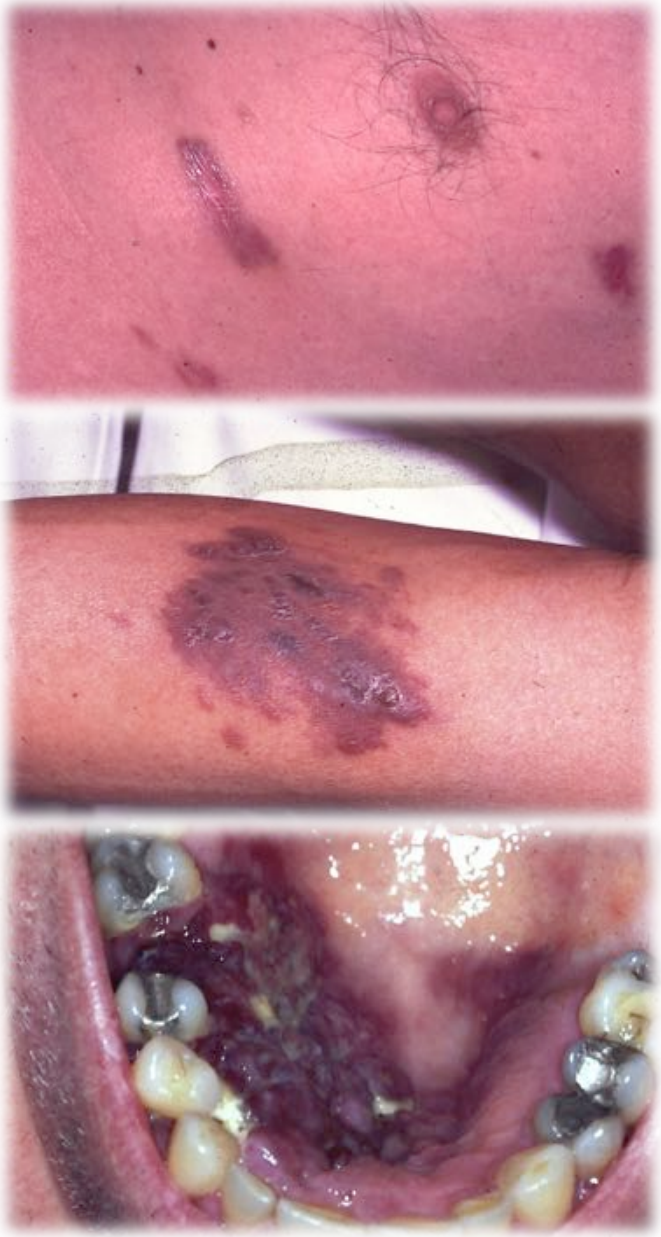
# And carcinogens play a part…

- Infected tissues may be more sensitive to effects from environmental carcinogens
- Tobacco used more frequently in HIV patients
  - 1.5-3x
  - Known carcinogen for H/N, lung cancers
  - Even after controlling for smoking status increased risk observed: lung
- Often more advanced at presentation


ADM – Kaposi’s sarcoma

# Patient 1

- 51y old MSM
- Admitted with PCP
  - LOW for 4 months
  - Oesophageal candidiasis
  - CD4 102, VL 430,923
- Responded to IV Co-trimoxazole and steroids
- Noticed to have purple spots on trunk:
  - Non-tender, non-pruritic
  - Also lump in the roof of his mouth with loosening teeth



# What is the diagnosis?

- TB
- Kaposi's sarcoma
- Bacillary angiomatosis
- Purpura fulminans
- Other

Audience vote

# How would you manage this patient?

- Watch and wait till visceral
- Start ART
- Start chemotherapy
- Start ART and chemotherapy
- Other

Audience vote

# Modified ACTG staging – KS

| TIS Staging of KS | Good risk (all of the following) | Poor risk (any of the following) |
|---|---|---|
| (T) Tumour | Confined to skin, lymph nodes<br>or minimal oral disease | Tumour-associated oedema or ulceration<br>Extensive oral KS<br>Gastrointestinal KS<br>KS in other non-nodal viscera |
| (I) Immune Status | CD4 count > 150/mm$^3$ | **CD4 < 150/mm$^3$** |
| (S) Systemic illness | Karnovsky performance status > 70 | Karnovsky performance status < 70<br>**Or other HIV related illness** |

**T0: 5y survival with ART treatment alone 92%**
**T1: survival with ART and chemotherapy 85%**

Krown SE, Metroka C, Wernz JC. J Clin Oncol 1989;7(9):1201–1207.

British HIV Association. HIV Medicine 2008;9:336–388.

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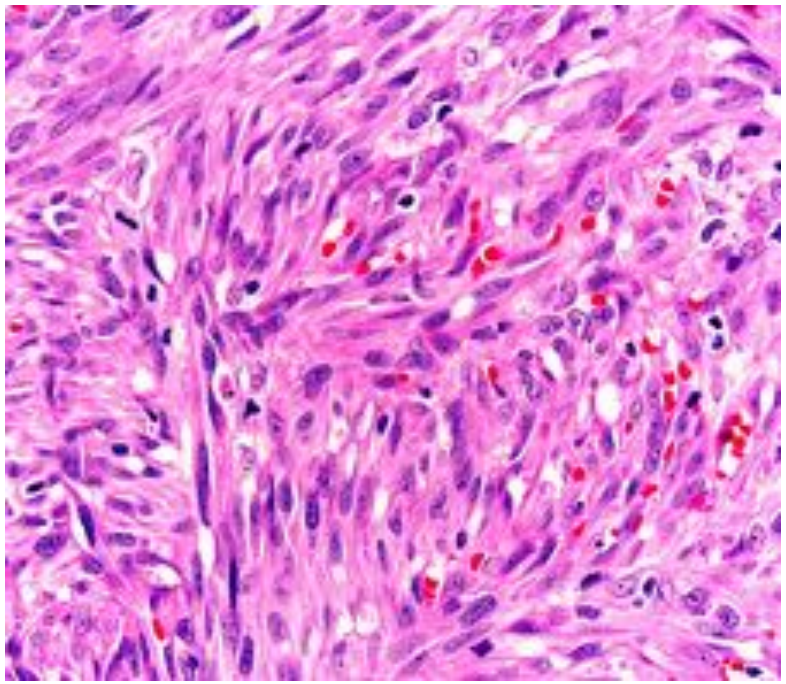
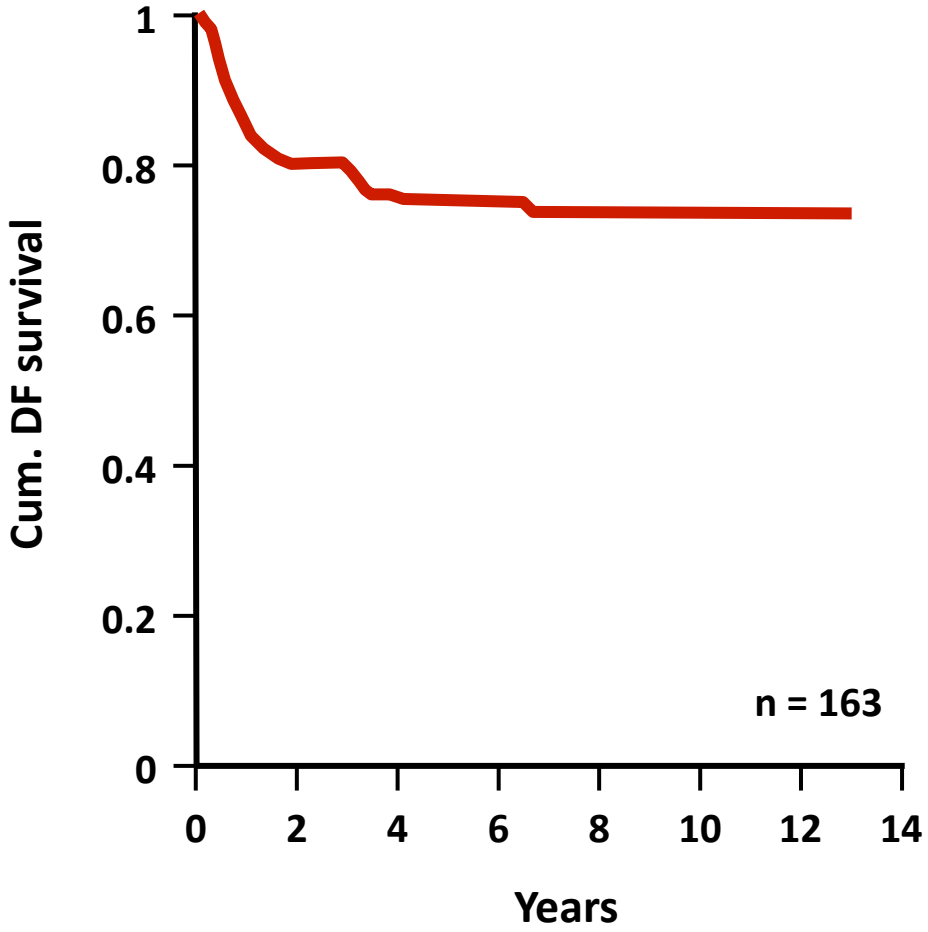
British HIV Association. HIV Medicine 2008;9:336–388.

# Management of KS

1. Early stage disease:
    - ART alone



# HAART alone for KS (T0)




- Starts ATAZ/r and TDF/FTC
  - Over 12w CD4 increases to 326 cells/mL and VL fall to 256 c/ml
- 80% don't need any other treatment for KS over 10 years of follow-up
- Initial CXR clear
  - No evidence of visceral disease

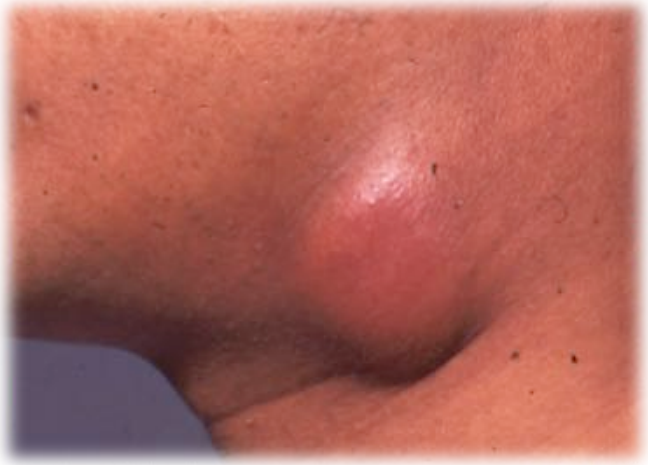
*AIDS* 2009;23 (13):1701–6

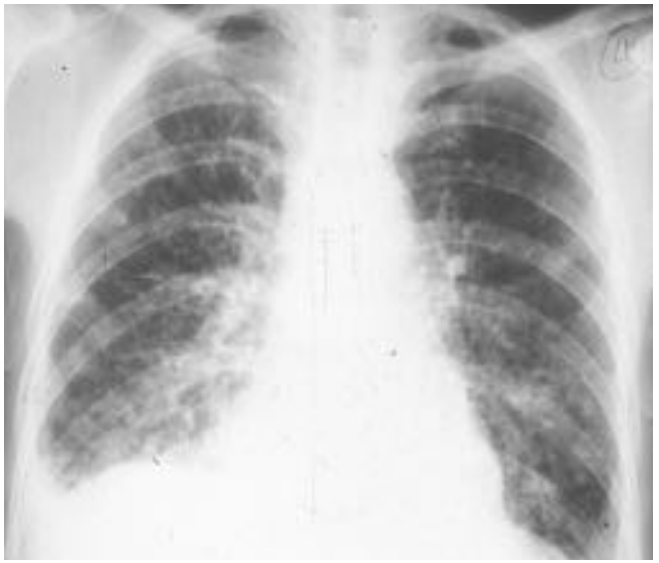
# Clinical challenges with KS

A. Diagnosing visceral disease
B. Optimal treatment when progression despite ART
C. Relapsing cutaneous disease despite good CD4
D. KS IRIS
E. Additional HHV-8 related disease

# A. Diagnosing visceral disease: patient 1

- No improvement in lesions
- Increasing breathlessness
  - Had stopped co-trimoxazole when CD4 >200 cells/mL
  - **Develops large cervical LN**
  - **CXR becomes abnormal**





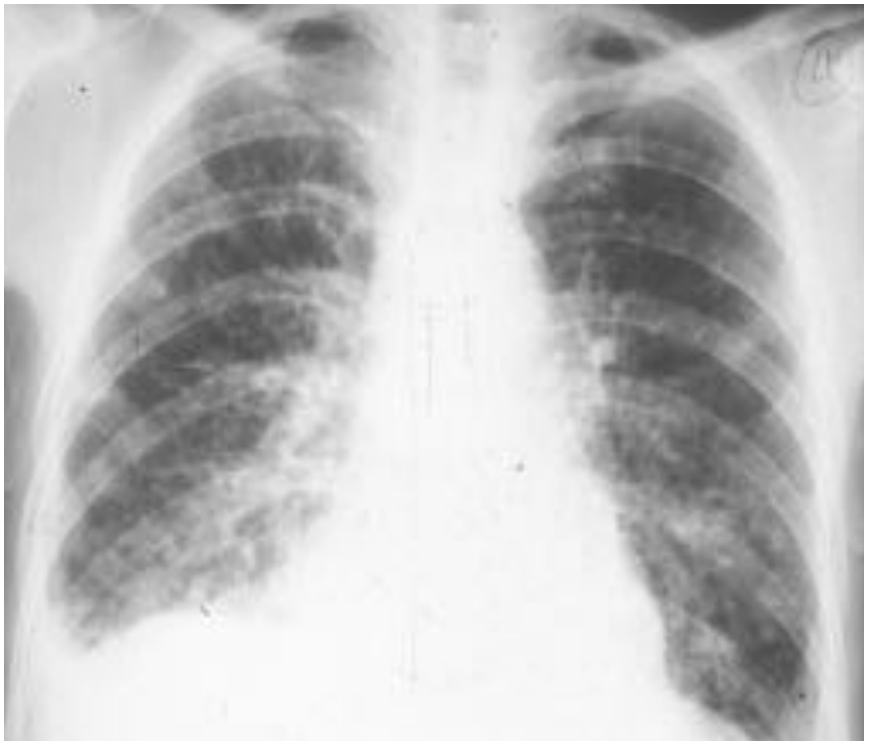
# What is the likely cause?

- Visceral KS
- PCP
- TB
- Cryptococcal infection
- Histoplasmosis
- Other

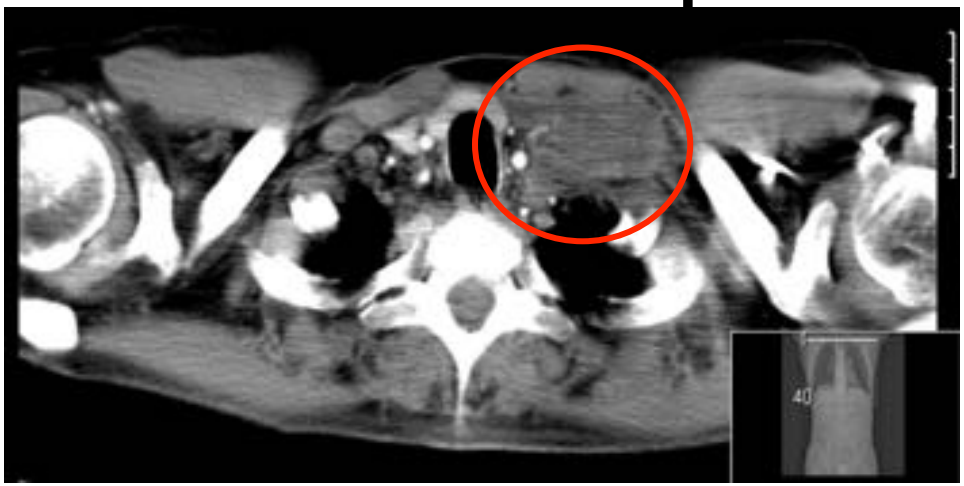
Audience vote

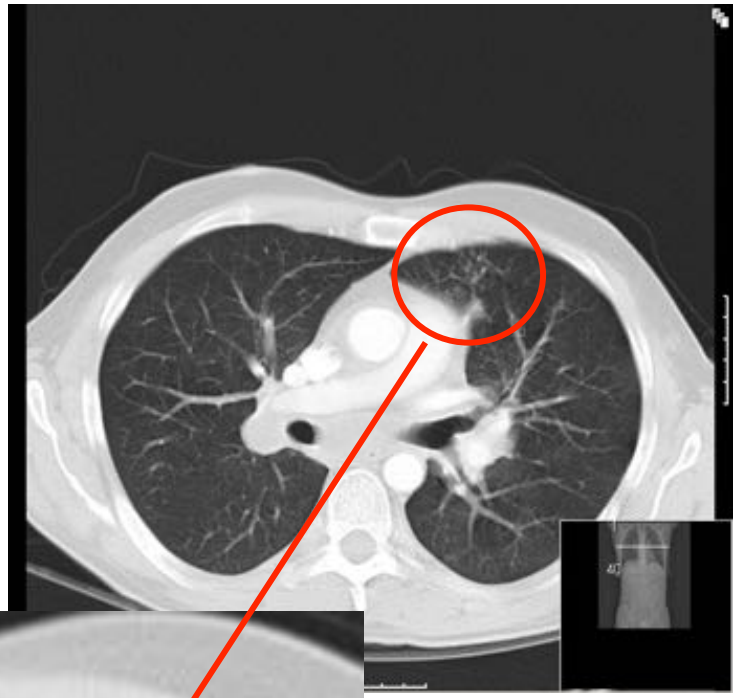
# Patient 1 – progress

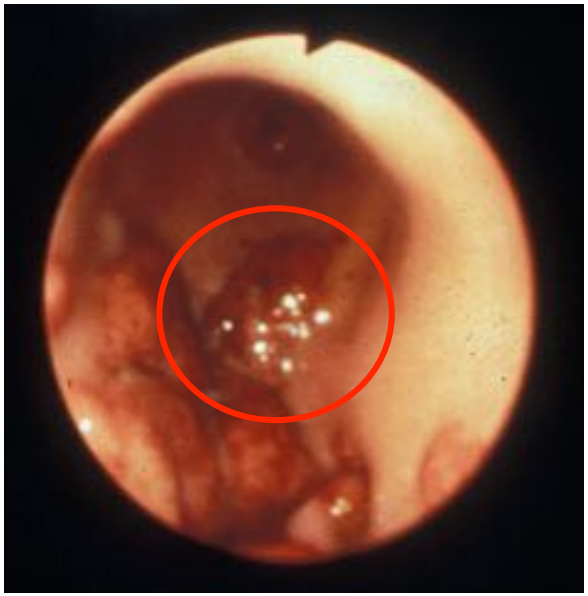
- Started IV co-trimoxazole and steroids
- CT scan thorax and abdomen
- LN biopsy and bronchoscopy
- Continued ART

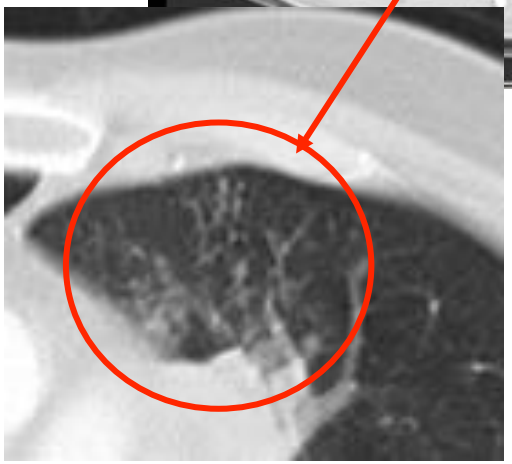


# A. Diagnosing visceral disease - patient 1



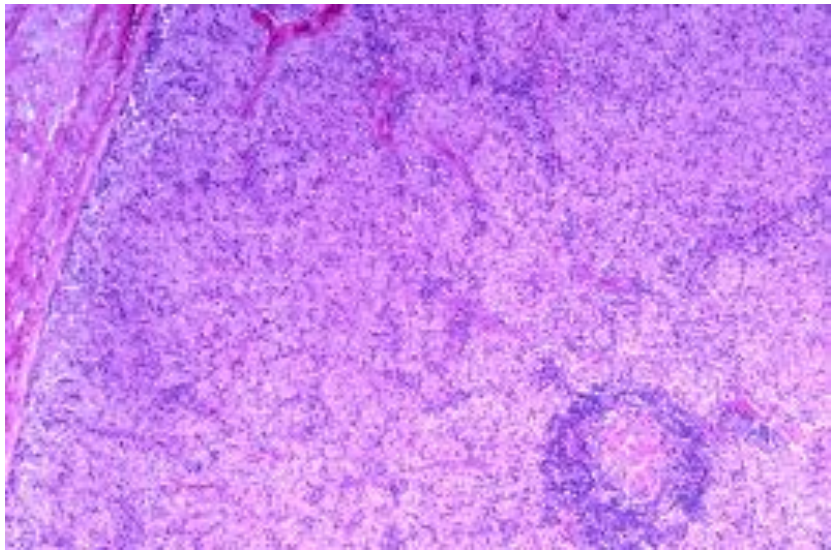


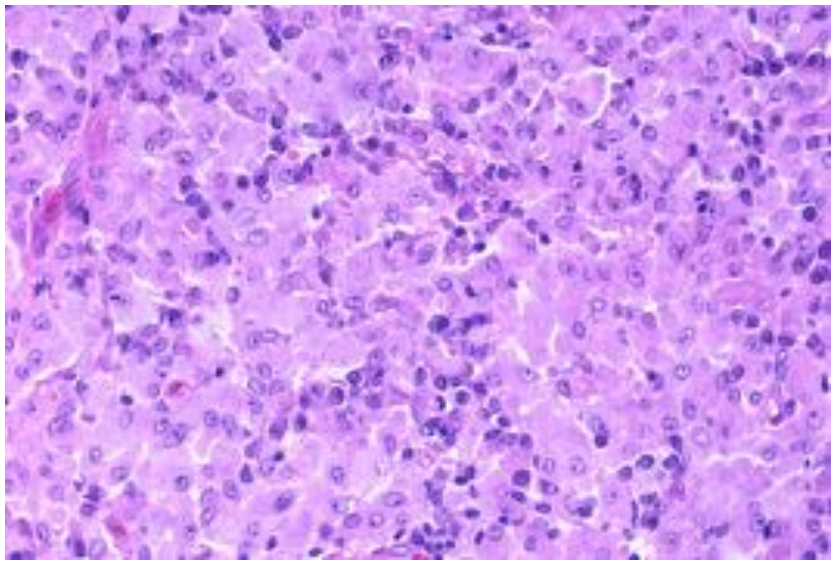




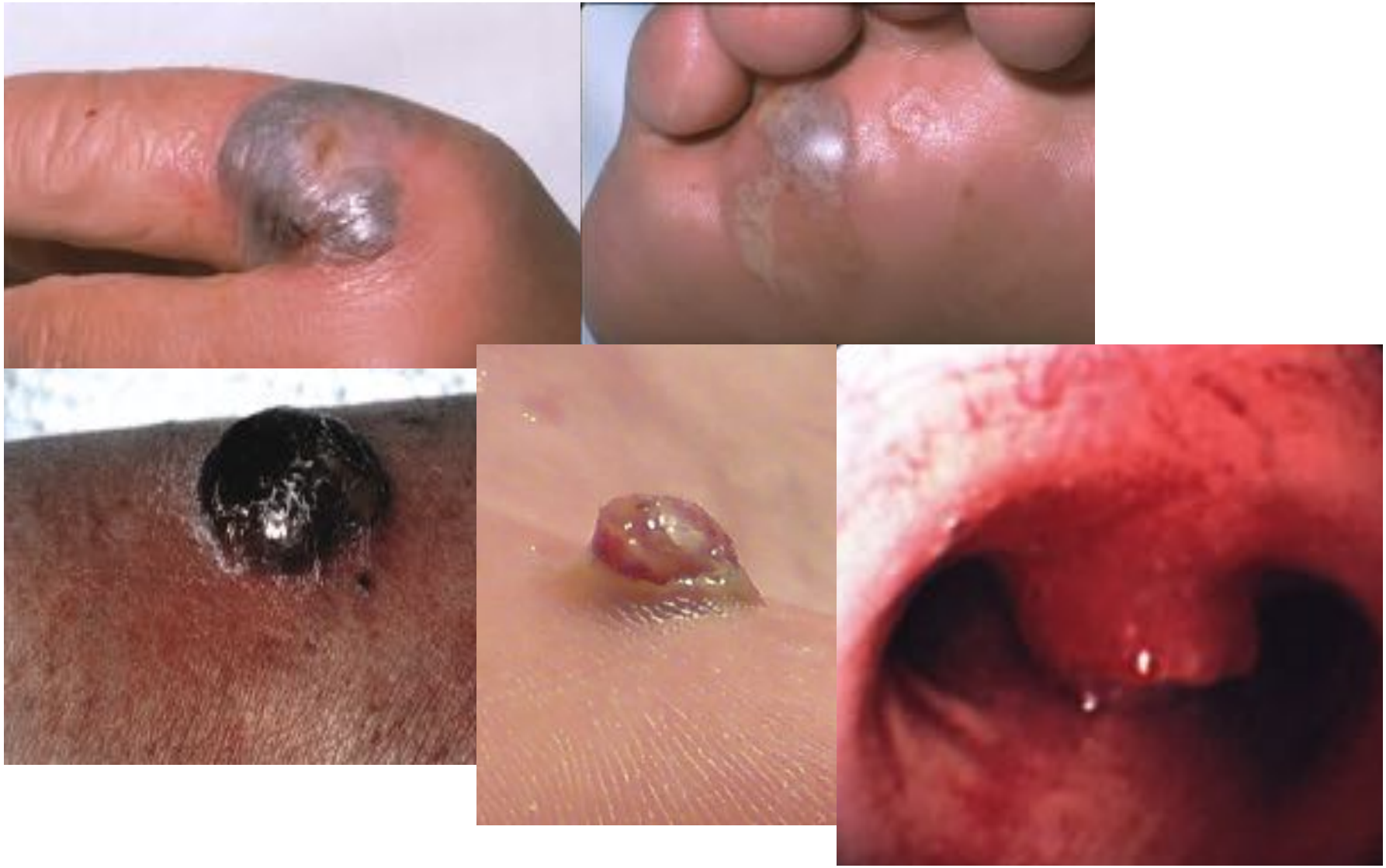
# Patient 1 – LN biopsy

- LN biopsy shows caseating granulomata
- Starts:
  - Rifampicin
  - Isoniazid
  - Ethambutol
  - Pyrazinamide
- Symptoms, radiology improve
- **But cutaneous KS progresses**



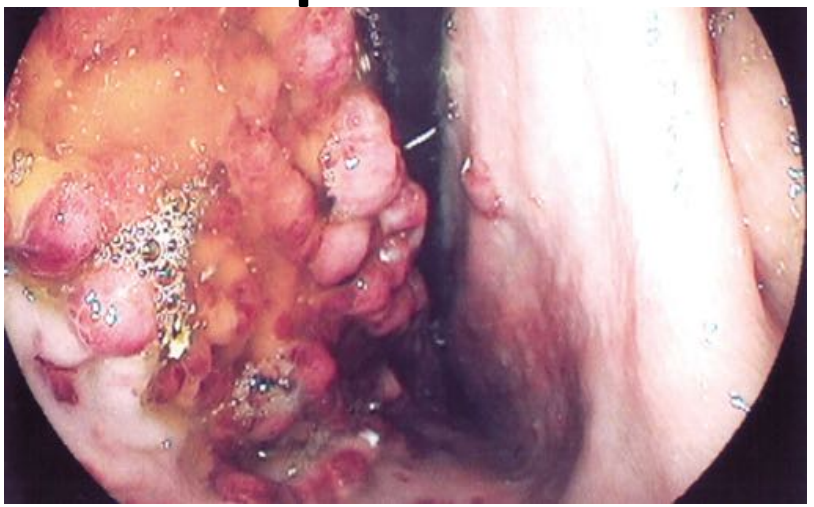


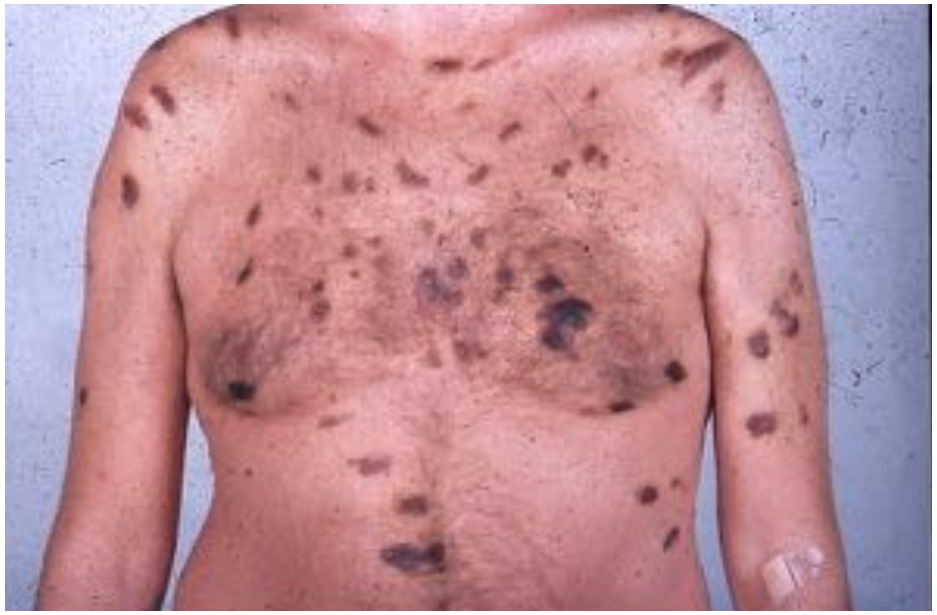
# Not all disease that looks like KS is KS: biopsy may be required!

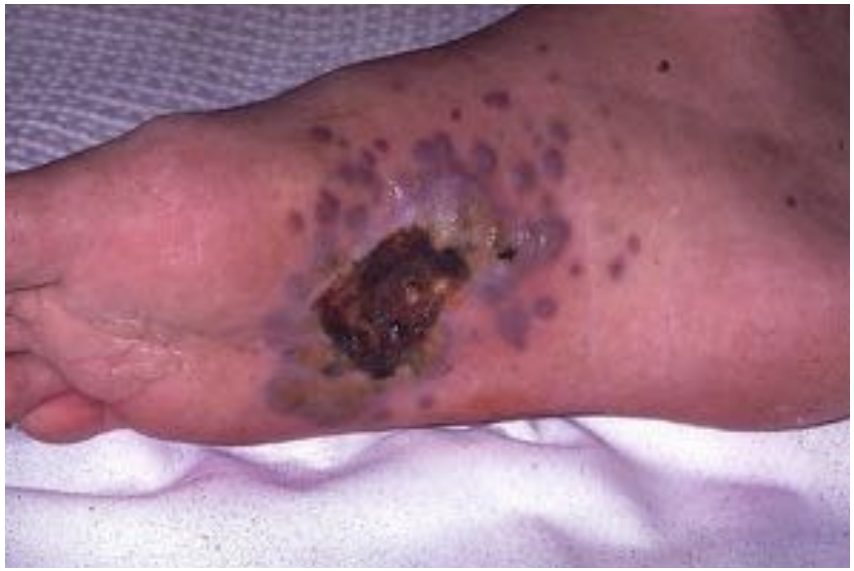


# B. Optimal treatment when progression despite ART – patient 1

- 4m later
  - CD4 225, VL <40
  - Cutaneous HS progressed
  - Haemetemesis, Hb 9,0







# How would you manage?

- Switch ART
- Give chemotherapy (what do you have)
- Arrange radiotherapy (where)
- Other

Audience vote

# Management of KS

1. Early stage disease:
   - ART alone
2. Late stage disease:
   - First line: ART and
     - Liposomal anthracycline
     - (Or if unavailable - Vincristine and bleomycin)
   - Second line:
     - Paclitaxel

# Treatment of KS when T1 disease or progression with ARV: liposomal anthrocyclines

## Mainly pre-ART

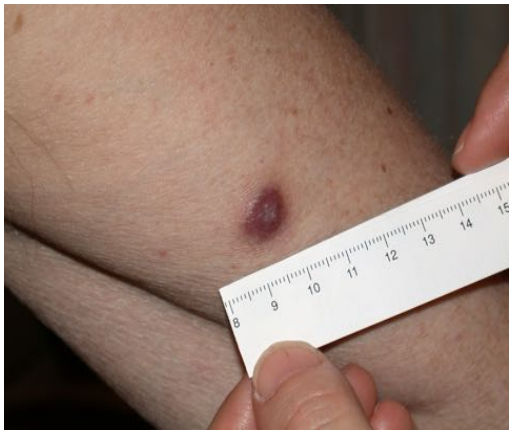
| | Stewart et al[2] | | | Northfelt[3] | | |
|---|---|---|---|---|---|---|
| | LD | BV | p= | LD | ABV | p= |
| n= | 121 | 120 | | 133 | 125 | |
| CR + PR | 59% | 23% | < 0.001 | 46% | 25% | < 0.001 |

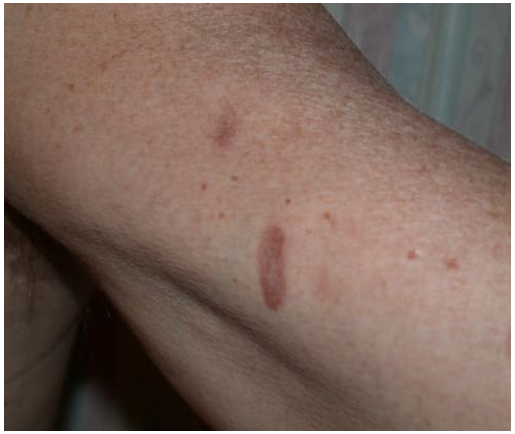
CR = complete response: PR = partial response
A = doxorubicin, B = bleomycin, V = vincristine
LD = liposomal doxorubicin


1. Gill PS, Wernz J, Scadden DT, *et al*. J Clin Oncol 1996;14:2353–2364.
2. Northfelt DW, Dezube BJ, Thommes JA, *et al*. J Clin Oncol 1998;16:2445–2451.
3. Stewart S, Jablonowski H, Goebel FD *et al*. J Clin Oncol 1998;16:683–691.

# Patient 1 – progress

- No improvement KS lesions after 4m
  - Started liposomal doxorubicin
  - Completed 6 courses
  - Flattening of all lesions
- CD4 156, VL <50 copies/mL
- TB responded
  - TB treatment stopped after 6m





# Treatment of KS with Paclitaxel

- Indication:
  - Failure to respond to cyclical course of liposomal doxorubicin or early relapse
- Response rates with HAART for refractory KS have been 56–71%
- Toxicity greater: bone marrow suppression, vomiting, alopecia
- Requires pre-infusional steroids

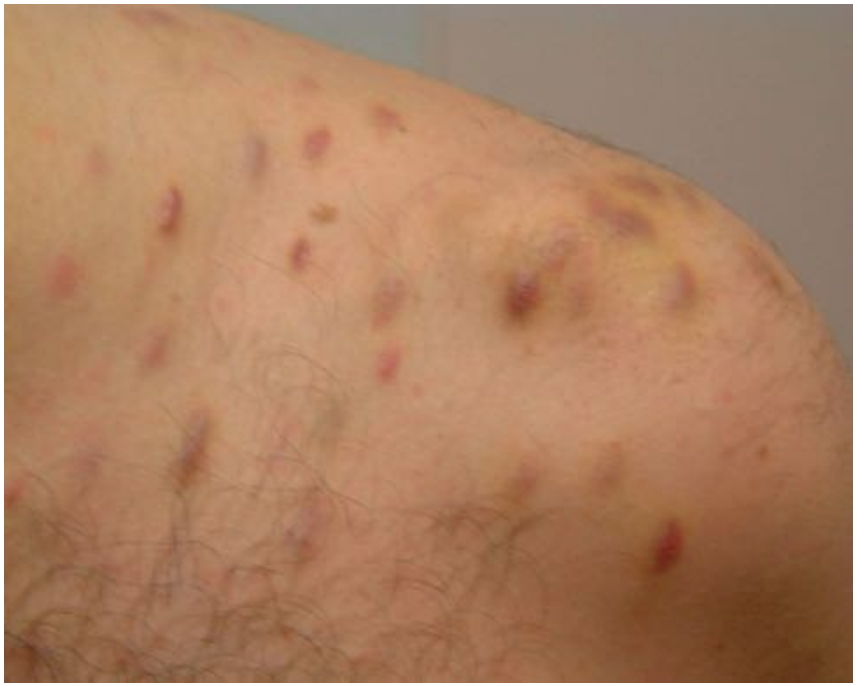
British HIV Association. HIV Medicine 2008;9:336–388.

# Under study

- Bevacizumab (humanized anti-VEGF-A monoclonal antibody)
- COL-3 (MMP Inhibitor)
- Irinotecan (CPT-11) (semi-synthetic camptothecin derivative)
- **Interferon alpha**
- IL12
- **Thalidomide**

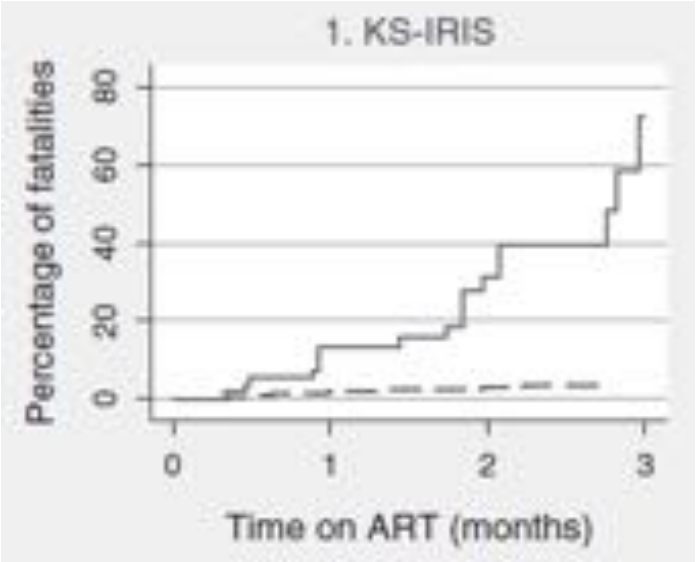
# C. Relapsing cutaneous disease despite good CD4

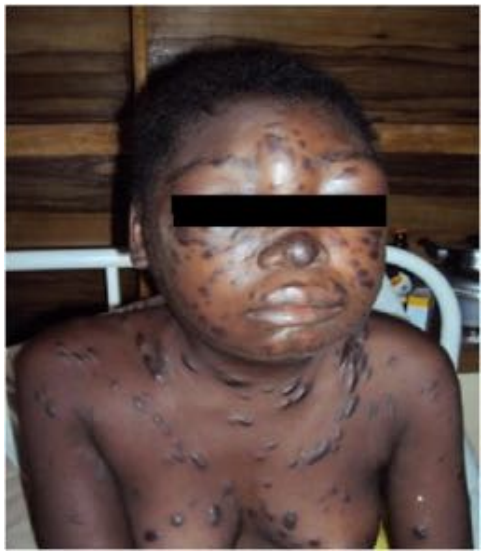
- 38y old MSM
- Diagnosed 2004
  - PCP, cutaneous KS
- Responded to HIV treatment
  - CD4 756 , VL <40 c/ml
- Multiple relapses
  - Numerous S-DOX, paclitaxel courses
- Usually indolent course
- Most relapses occur within 1st year



# D. KS immune reconstitution

- KS-IRS associated with:
  - Receiving ART alone
  - T1 disease
  - High HIV VL
  - High HHV8 VL
  - African cohorts
  - > risk of death
- Treatment
  - Judicious steroids

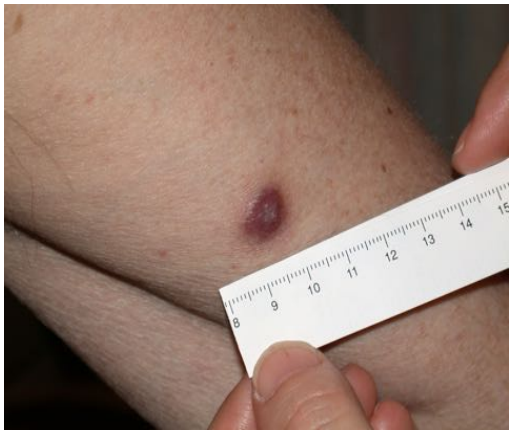


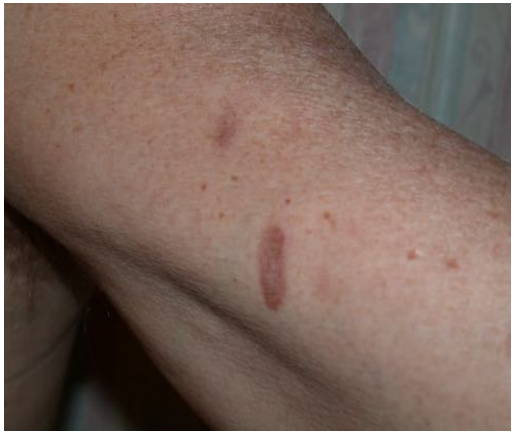



# Patient 1 – progress

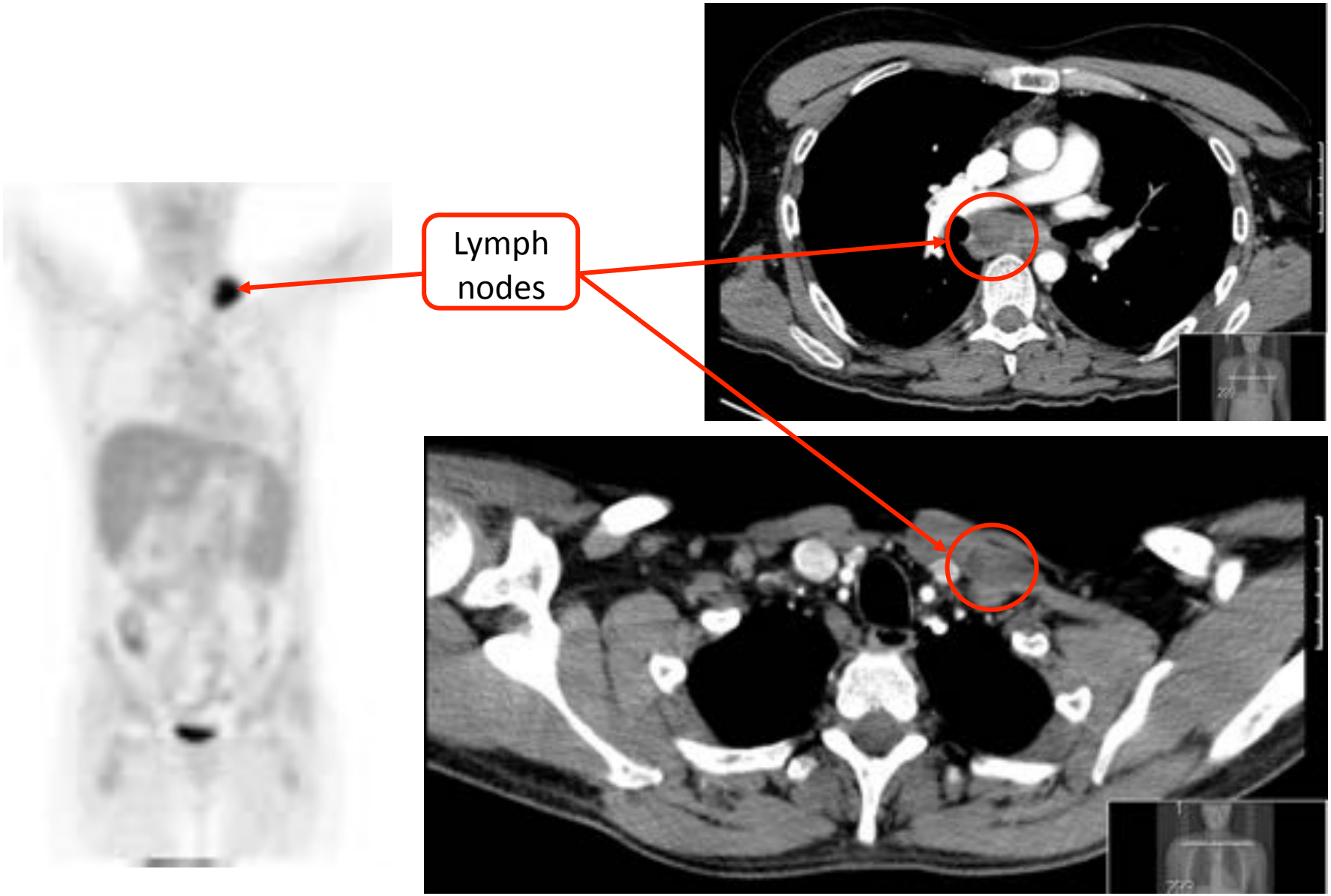
- No improvement KS lesions after 4m
  - Started liposomal doxorubicin
  - Completed 6 courses
  - Flattening of all lesions
- CD4 156, VL <50 copies/mL
- TB responded
  - TB treatment stopped after 6m

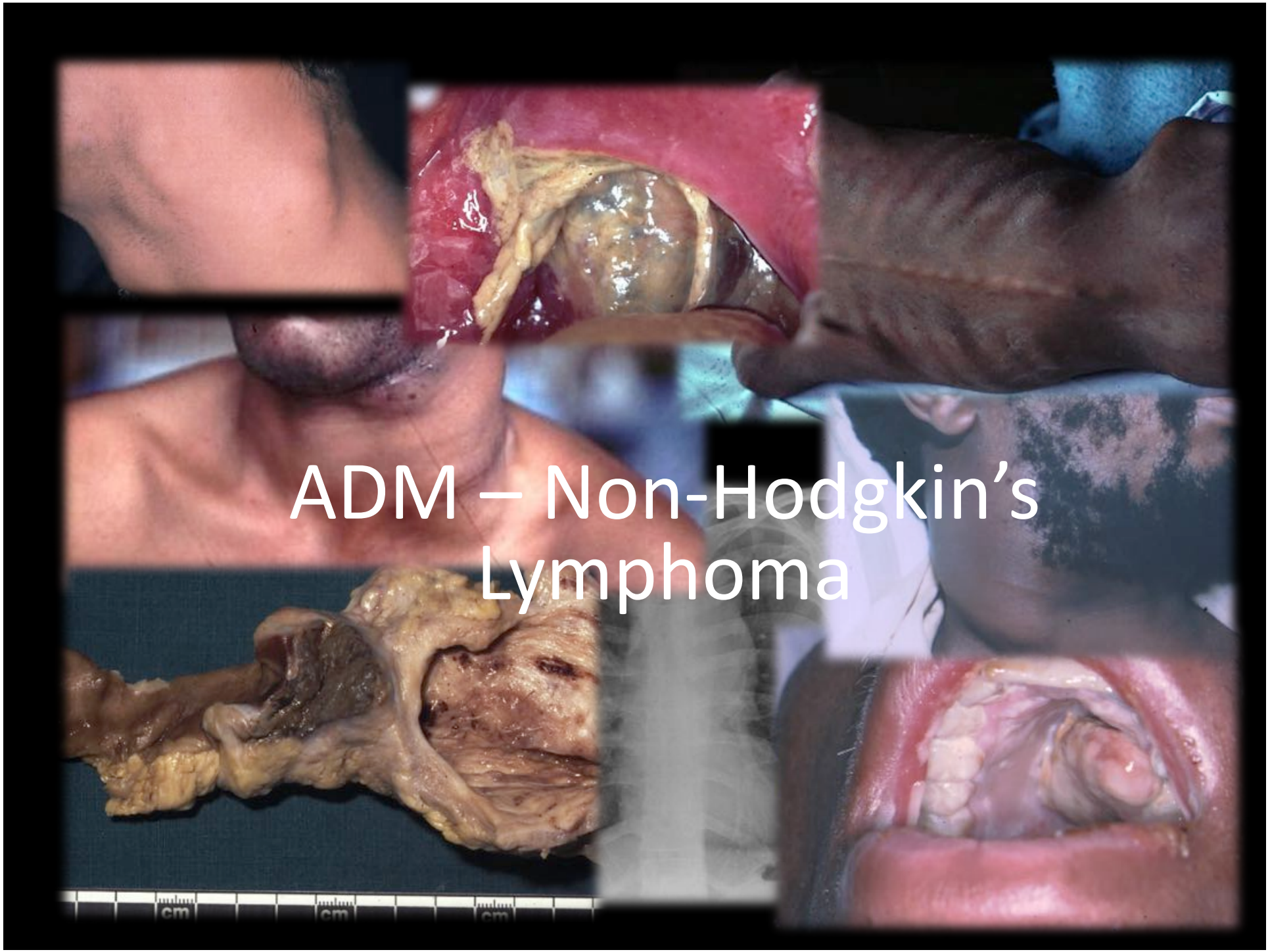
- **Increase in left-sided lymphadenopathy**





# MR and PET Imaging



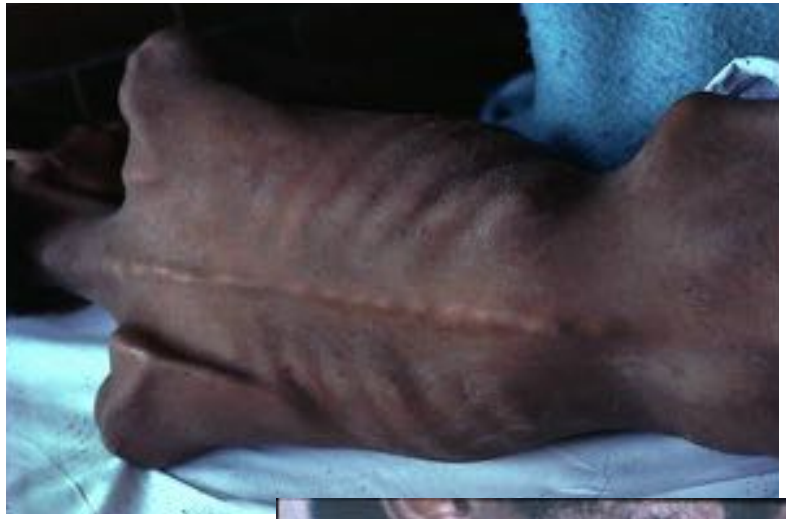

ADM – Non-Hodgkin's Lymphoma

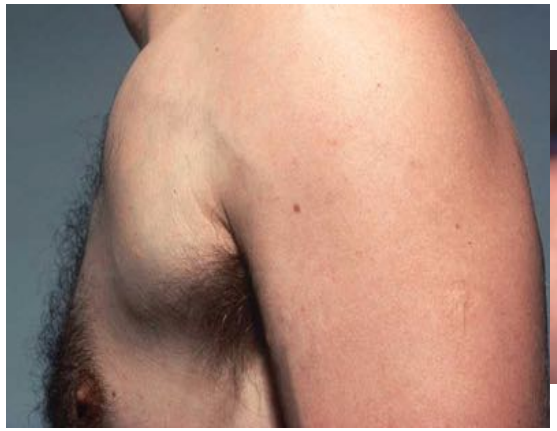
# Biopsy = Non-Hodgkin's lymphoma

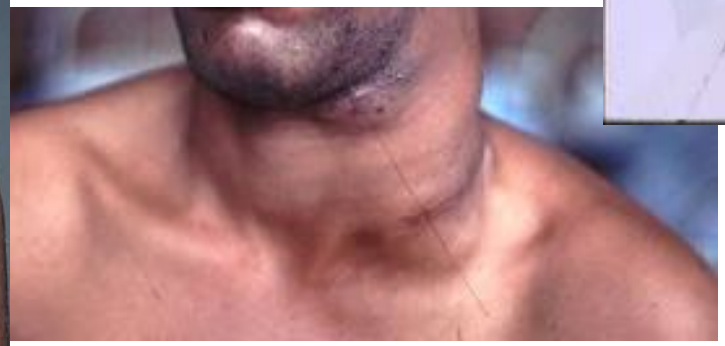
- Individuals with HIV are at increased risk
- Second most common malignancy in HIV
- Several pathological types
  - Differ in prognosis, treatment and association with CD4 count
- Prognosis improved with additional HAART and approaching that seen in HIV-negative persons
- HIV-related primary effusion lymphoma (PEL) is rare

# Presentation of NHL: nodal 50%

- Majority of patients present with:
  - Type B symptoms – fevers, sweats and weight loss
  - Lymphadenopathy which may be generalised or localised

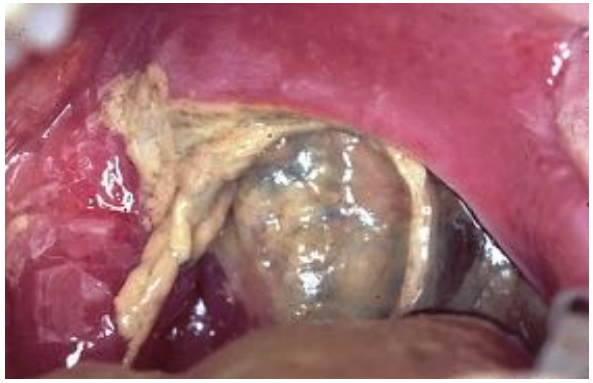


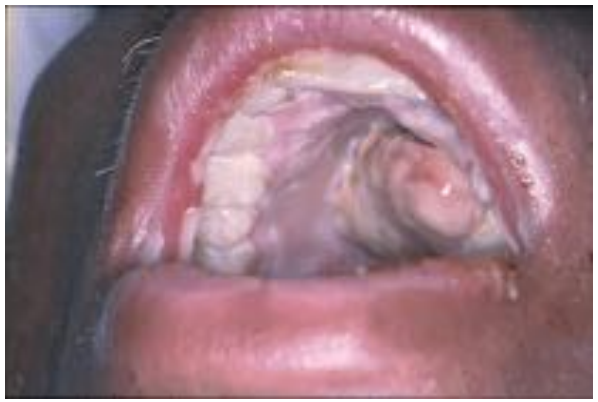


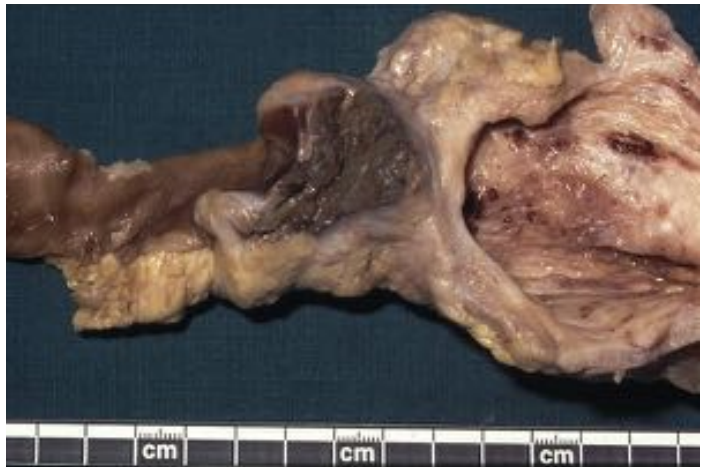


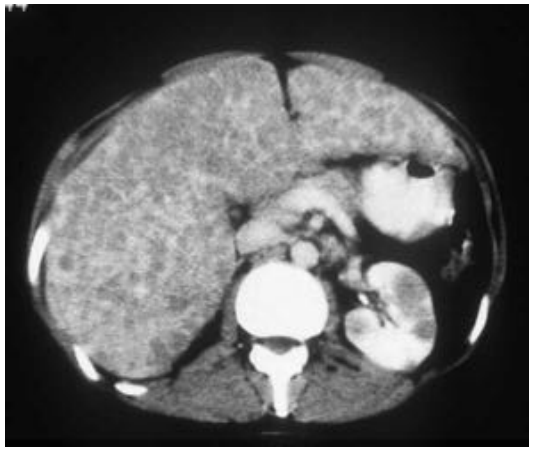
# GI presentation – 30%

- Extra-nodal disease is common
- Sites of extra-nodal involvement include:
  - Oral cavity
  - Liver, spleen
  - GI tract (ileum)



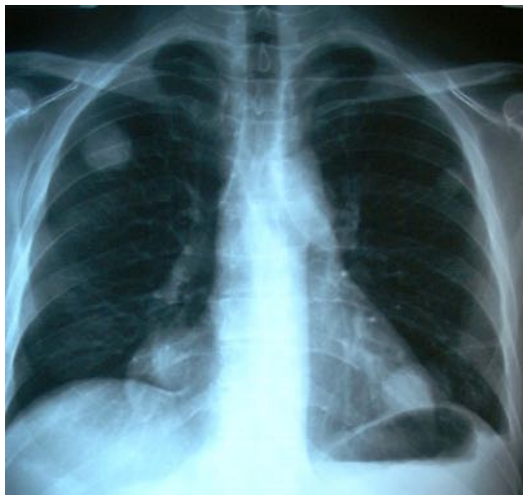


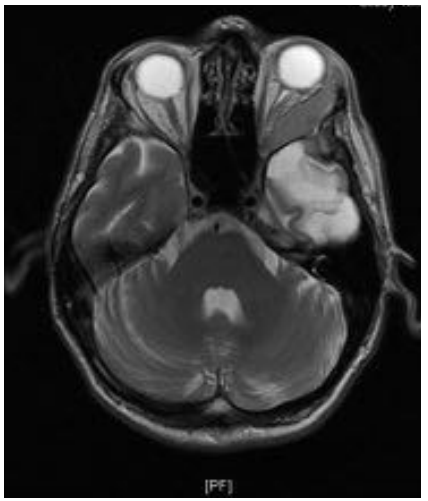


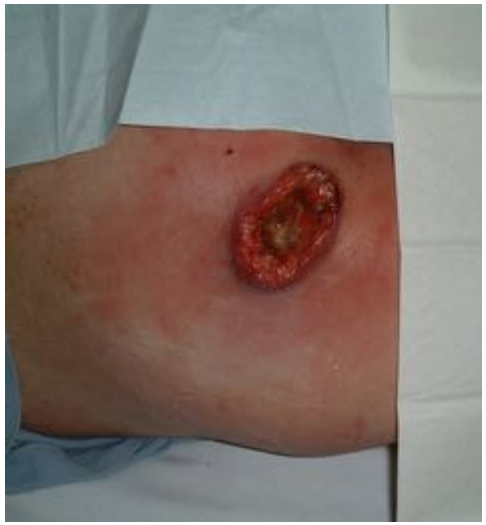



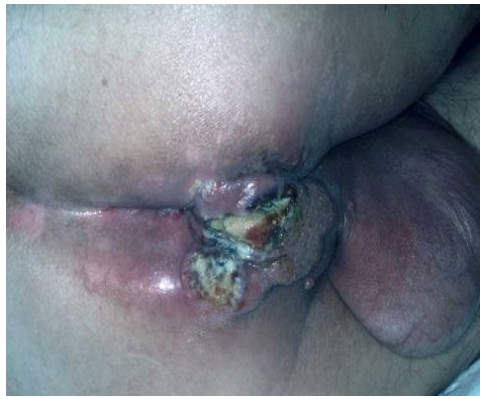
# Other extra-nodal presentation – 20%

- Other sites
  - Pulmonary
  - Brain
  - Skin
  - Salivary glands

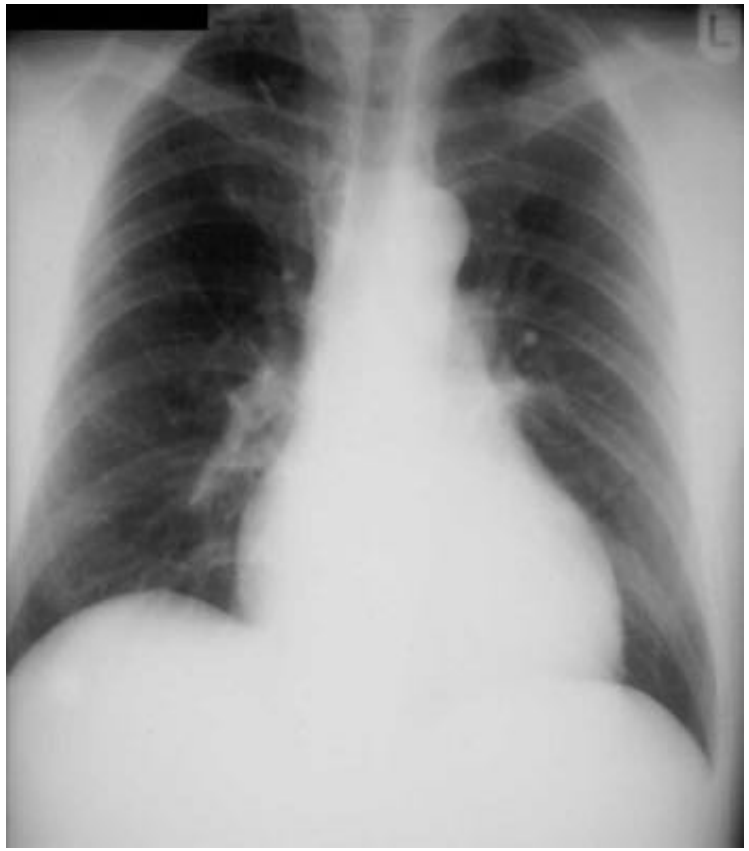


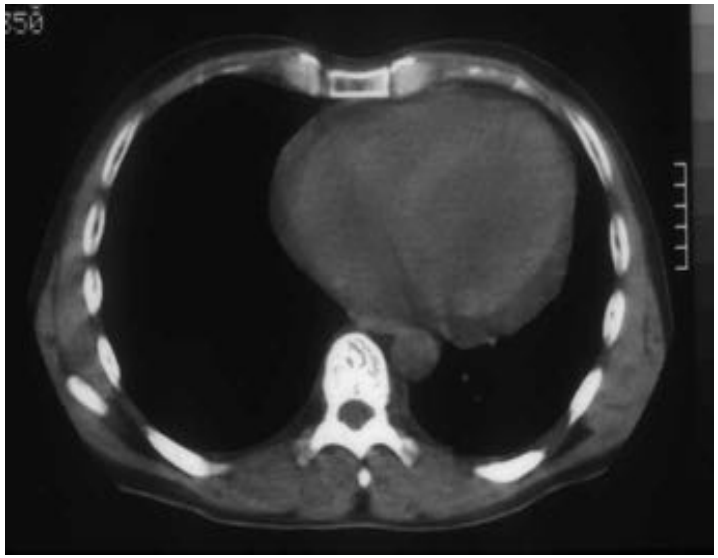


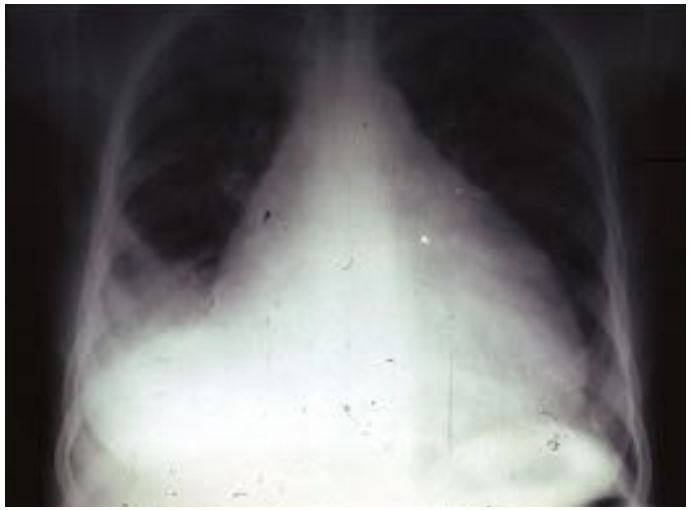




# Primary effusion lymphoma – 1%







# Clinical challenges with NHL

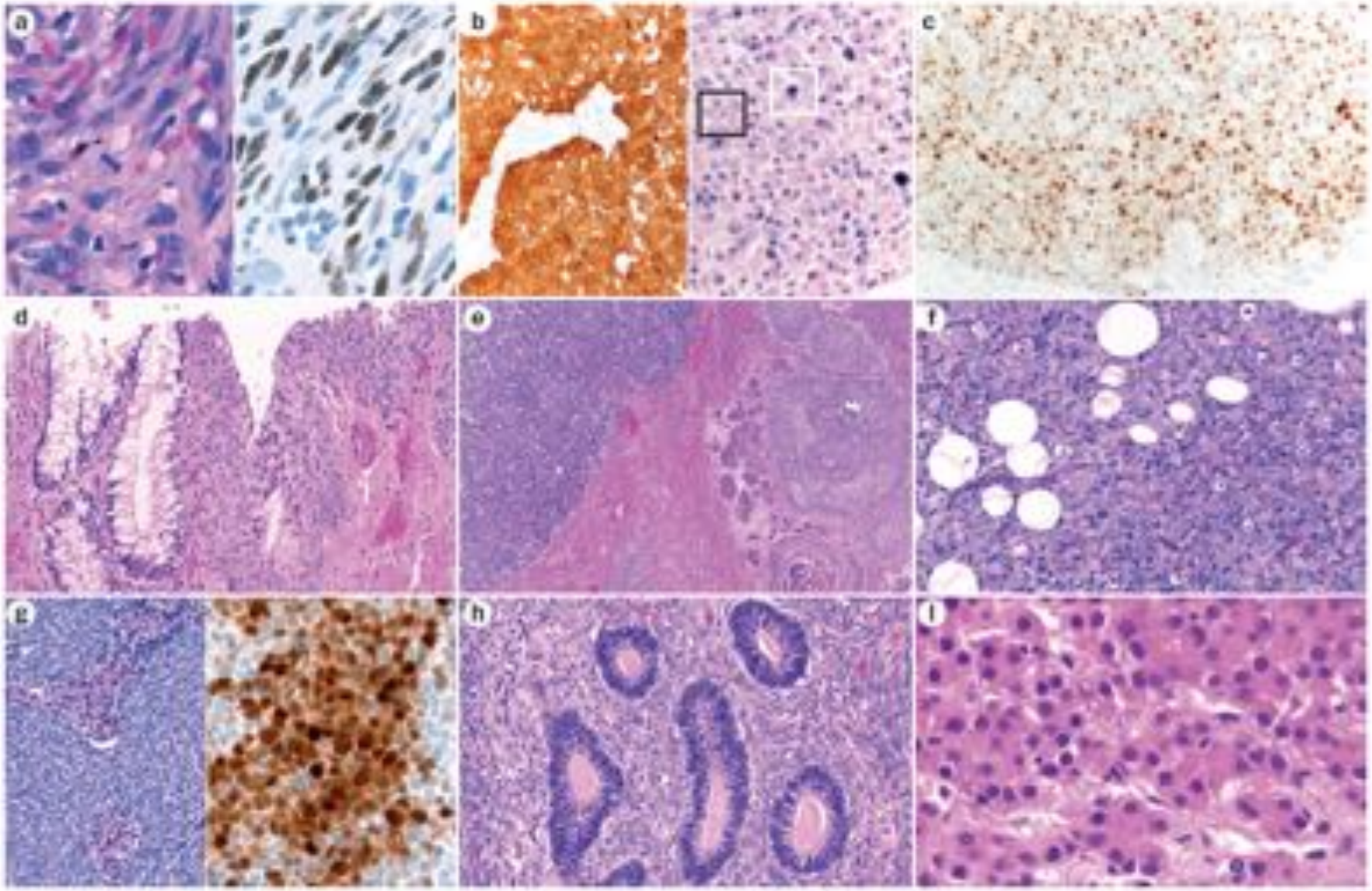
A. Diagnosis – especially when extra-nodal
B. Deciding optimal treatment
C. Awareness of drug-drug interactions
D. Salvage treatment

# Diagnosis/investigation of NHL

| Summary of baseline investigations |
| --- |
| **Initial diagnostic histology:**<br>**Usually lymph node biopsy – confirmation by tissue biopsy critical** |
| Lumbar puncture (not always indicated):<br>CSF for protein, glucose, and cytology<br>(intrathecal chemotherapy can be administered with the staging lumbar puncture) |
| **Bone marrow**<br>**Biopsy and aspirate** |
| **Neck-chest-abdomen-pelvis CT scan with contrast (unless contra-indicated)** |
| Specific investigations<br>Magnetic resonance imaging (MRI), Positron Emission Tomography (PET) scan, CSF for EBV (PCNSL) |

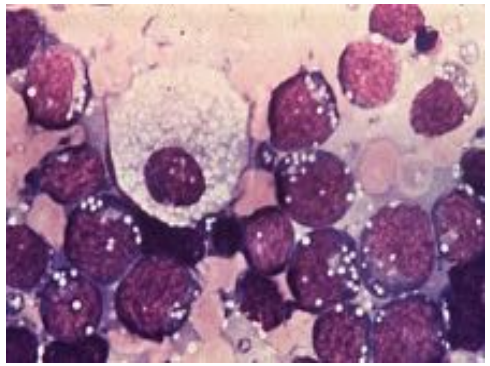
British HIV Association. HIV Medicine 2008;9:336–388.

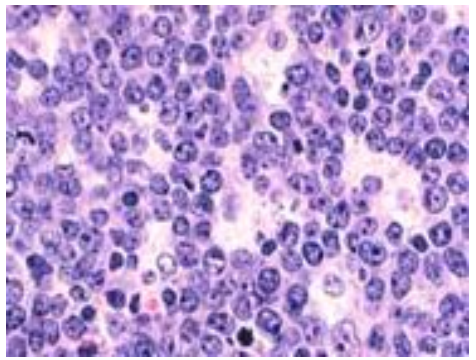
# A. Diagnosis – biopsy is critical..



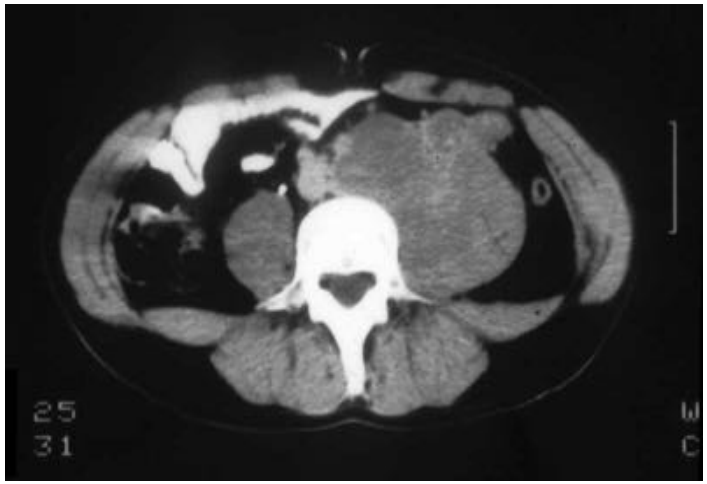
# Different types of NHL

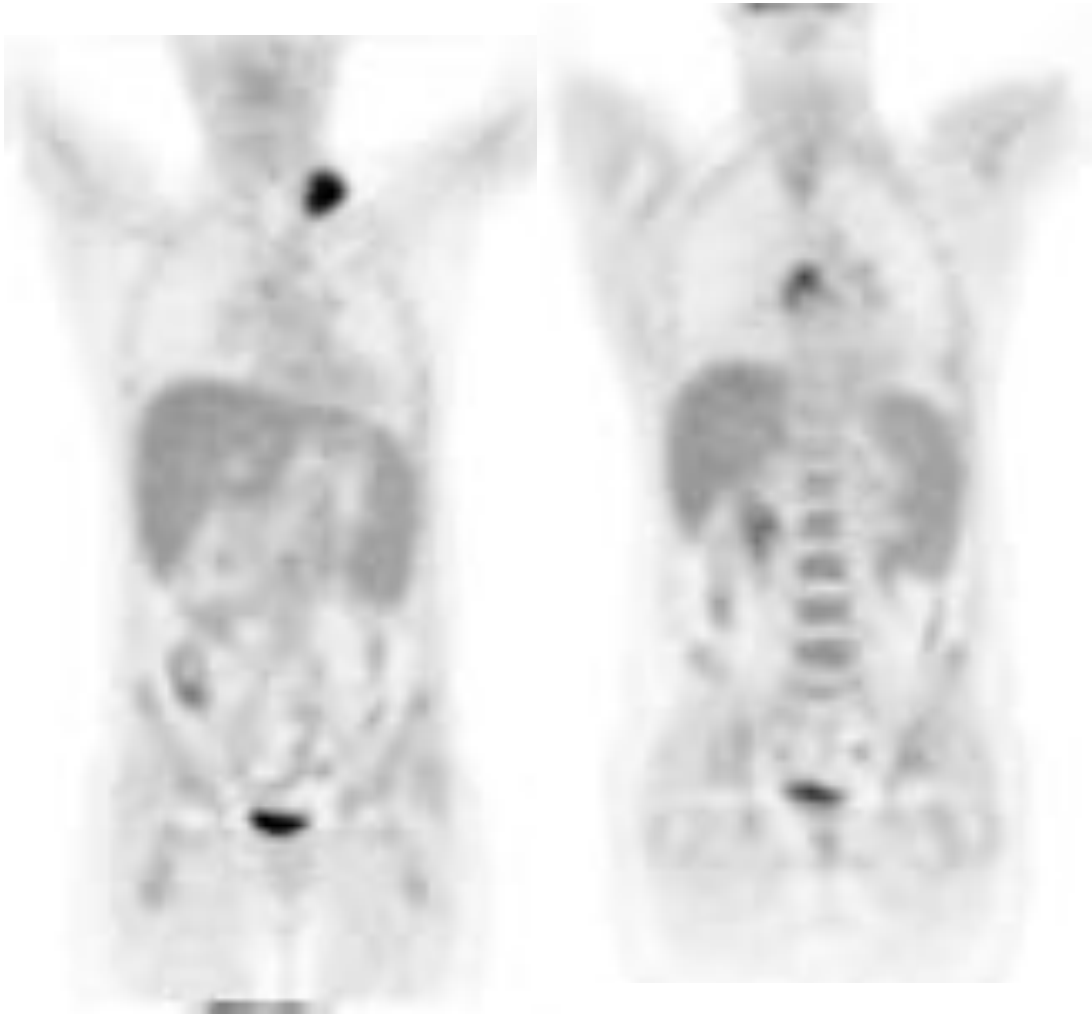
| Lymphoma type | % | Comments |
|---|---|---|
| Burkitt's | 25 | Higher CD4, cMYC translocation |
| Diffuse large B-cell (DLBCL) | 70 | Centroblastic |
| Immunoblastic | 5 | Associated with PCNSL |
| Primary effusion | 1 | Rare, HHV8 |
| Peripheral T-cell | 1 | Rare |





# Diagnosis – imaging



# Staging/prognosis of NHL

| Ann Arbor classification/Cotswolds modification |
| --- |
| Stage I Involvement of a single lymph node group or lymphoid structure |
| Stage II Involvement of 2 or more lymph node groups on the same side of the diaphragm |
| Stage III Involvement of lymph node groups on both sides of the diaphragm |
| Stage IV Involvement of extra-nodal site(s) beyond those designated 'E' |
| X: Bulky disease: > 10 cm or > 1/3 widening of the mediastinum at T5-6 |
| E: Extra-nodal extension contiguous or proximal to known nodal site of disease or single isolated site of extra-nodal disease |
| A/B: Absence/presence of B symptoms (weight loss > 10%, fever, drenching night sweats) |

British HIV Association. HIV Medicine 2008;9:336–388.

# Staging/prognosis of NHL

- Short-term survival approaching immunocompetent patients
- Poor prognosis for PEL and Burkitt's lymphoma or when CNS involvement
- Rituximab effective
  - Improving response rates
  - Fewer lymphoma-related deaths
- Place of bone marrow transplant not elucidated (when in CR, first relapse, or refractory disease?)

British HIV Association. HIV Medicine 2008;9:336–388.

# Our patient 1

- CT/PET:
  - Left sided supraclavicular mass
  - Mediastinal mass, splenomegaly
- Bone marrow clear
- CSF cytology clear
- No type B symptoms: fever, loss of weight or night sweats
- **Stage 3a**

# How would you manage ART?

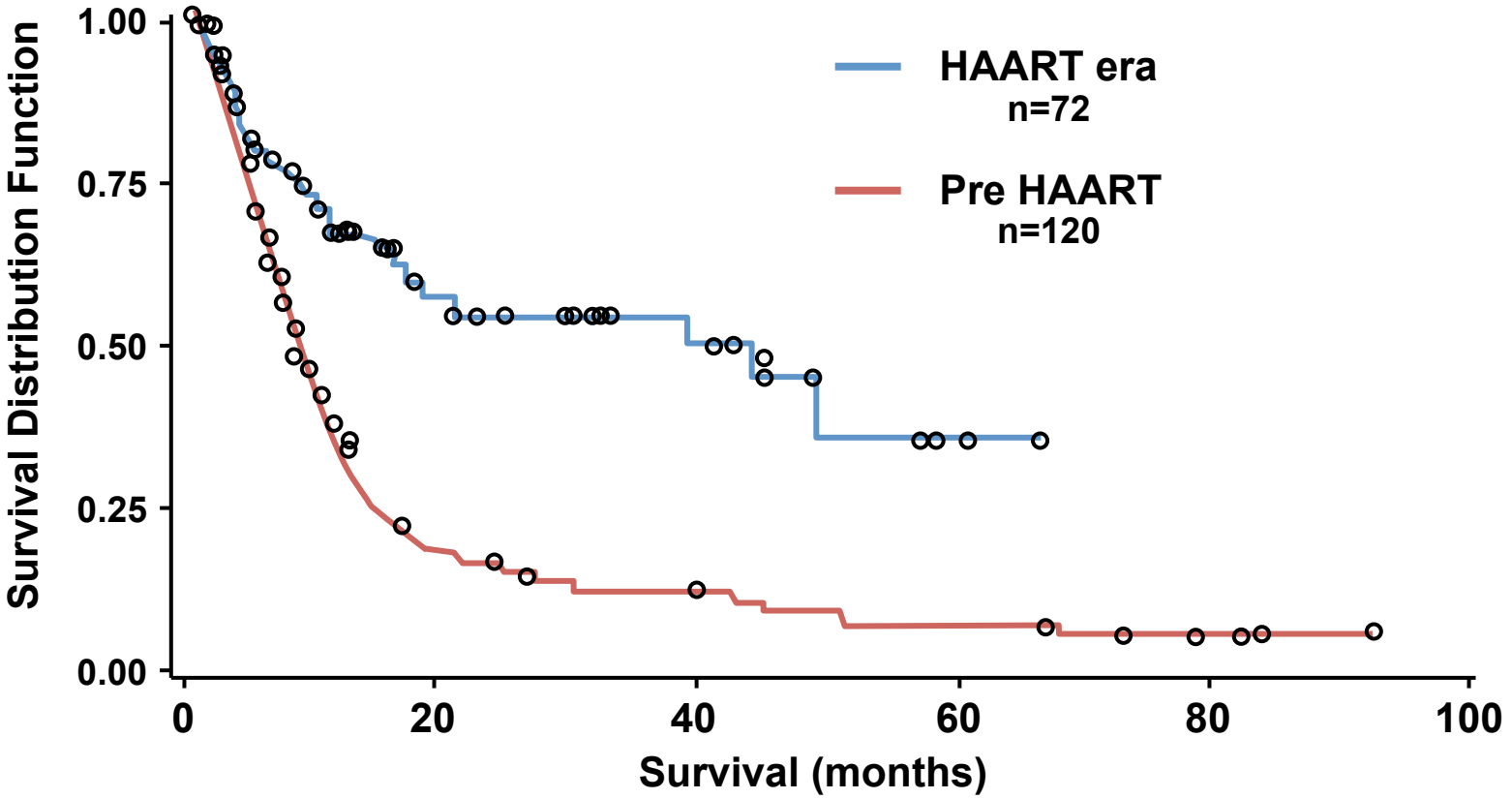
- Stop until finished chemotherapy
- Continue with ATAZ/r and TDF/FTC
- Switch to new combination
- Other

Audience vote

# Supportive care in NHL treatment

- Start/continue ART
  - Use TDF/FTC or ABC/3TC backed regimens
  - Use INI (raltegravir or dolutegravir) or other 3rd agent not involved with CYP3A4
- Prophylaxis for:
  - Tumour lysis
  - PCP, fungal infection (fluconazole)
  - Consider also for herpes and MAI

# Median survival of patients with DLCL




**The overall median survival time improved from 8.3 months in the pre-HAART era to 43.2 months in the HAART era (p=0.0005)**

Adapted from Lim ST, et al. *J Clin Oncol*. 2005, 23:8477–8482.

# B. Optimal treatment: Diffuse Large B-cell Lymphoma (DLBCL)

Trials evaluating chemotherapy combinations in DLBCL

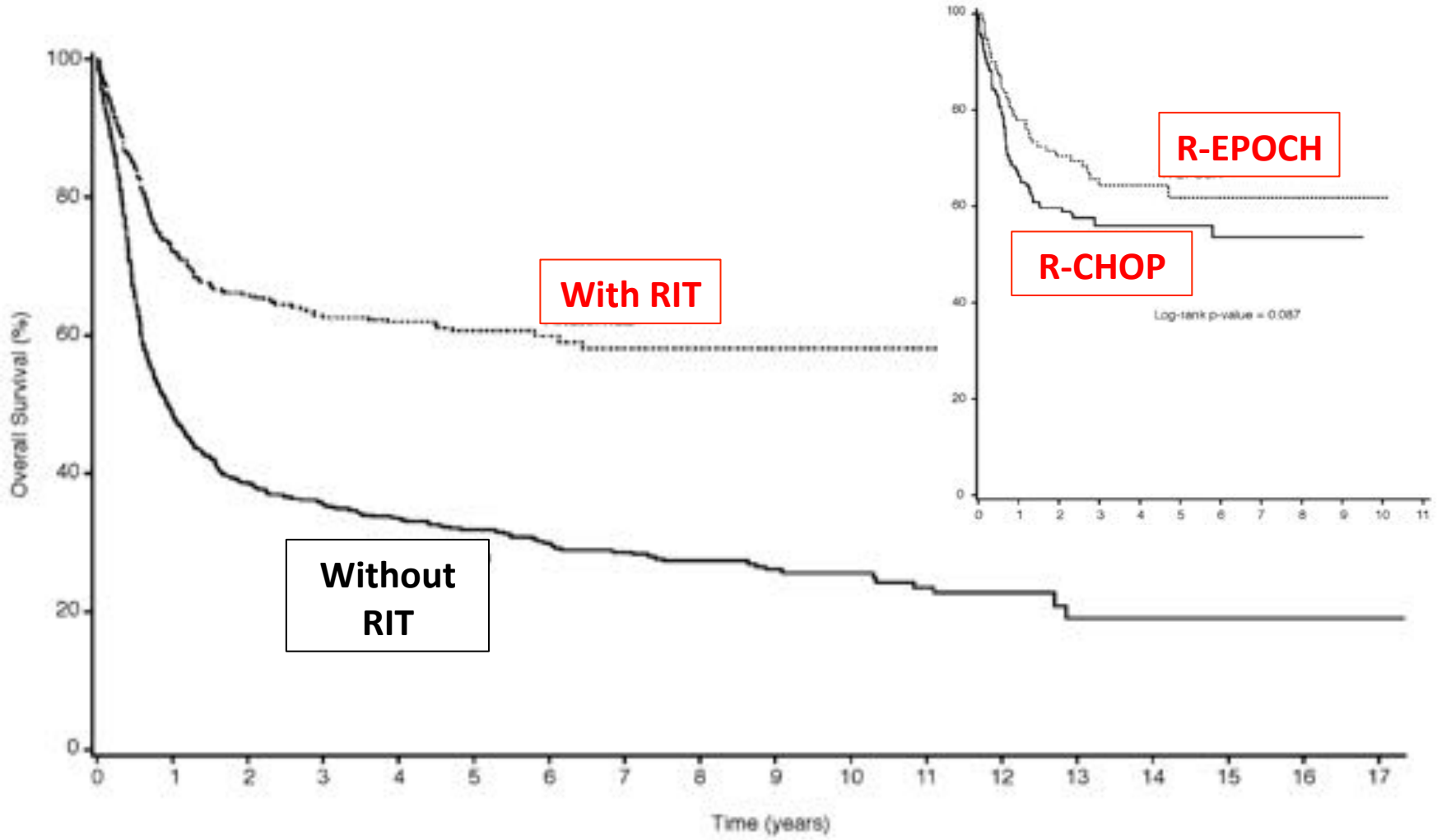
| Chemotherapy regimen | n= | IPI score 2/3 (%) | % Complete response (CR) |
|---|---|---|---|
| da – EPOCH[1] | 39 | 59 | 74 |
| da – EPOCH[1] (sequential rituximab) * | 54 | 64 | 53 |
| da – EPOCH[1] – rituximab * | 51 | 69 | 69 |
| CHOP[2] ** | 50 | 53 | 47 |
| CHOP – rituximab[2] ** | 99 | | 58 |
| CHOP – rituximab[3] | 52 | | 77 |
| CDE (historical controls)[3] | | | 45 |
| CDE – rituximab[3] | 74 | | 70 |

* Randomised trial EPOCH with or without rituximab

** Randomised trial CHOP with or without rituximab

1. Levine A, *et al*. Curr Opin Oncol 2008;20(5):522–528.
2. Kaplan L, *et al.* Blood 2005;106(5):1638–1543.
3. Spina M, *et al.* Blood 2005 105: 1891-1897.

# Rituximab effect on DLBCL treatment



# C. Drug-drug interactions - DLCBL

| R-CHOP | PI | NVP | RAL | MVC |
|---|---|---|---|---|
| **C**yclophosphamide* | ■ / □ | ■ | - | - |
| Vincristine** **O** | ■ / □ | □ | - | - |
| Doxorubicin† **H** | ♦ / ◊ | ◊ | - | - |
| Prednisolone¶ **P** | ■ / □ | □ | ◊ | ♦ |
| Rituximab§ | - | - | - | - |

■ / □ Potential interaction – may require close monitoring, alteration of drug dosage/schedule

♦ / ◊ No clinically significant interaction expected

– Data not available

Empty symbols indicate that the combination has not been studied and an interaction has been predicted based on metabolic profiles of the drugs.

*For IDV, NFV, NVP – data based on studied interactions.

**For IDV, LPV, NFV, ritonavir – data based on studied interactions.

†For IDV, NFV, SQV – data based on studied interactions.

¶For FPV, LPV, NFV, ritonavir data based on studied interactions.

§The concomitant administration of rituximab with HAART is contentious and data from further clinical trials are awaited.

HIV Drug Interactions. Available at: http://www.hiv-druginteractions.org. Accessed August 2010

§Bower M, et al. *HIV Medicine* 2008, 9;336–988

# Drug-drug interactions - Burkitt's

| Options | PI | NNRTI | RAL | MVC |
|---|---|---|---|---|
| **Cyclophosphamine*** | ■ / □ | ■ / □ | – | – |
| **Vincristine**** | ■ / □ | ■ / □ | – | – |
| **Doxorubicin†** | ◆ / ◇ | ◆ / ◇ | – | – |
| **Methotrexate** | – | – | – | – |
| **Ifosfamide** | – | – | – | – |
| **Cytarabine** | ◇ | ◇ | – | – |
| **Etosposide** | □ | □ | – | – |

■ / □ Potential interaction – may require close monitoring, alteration of drug dosage/schedule

◆ / ◇ No clinically significant interaction expected

– Data not available

Empty symbols indicate that the combination has not been studied and an interaction has been predicted based on metabolic profiles of the drugs.

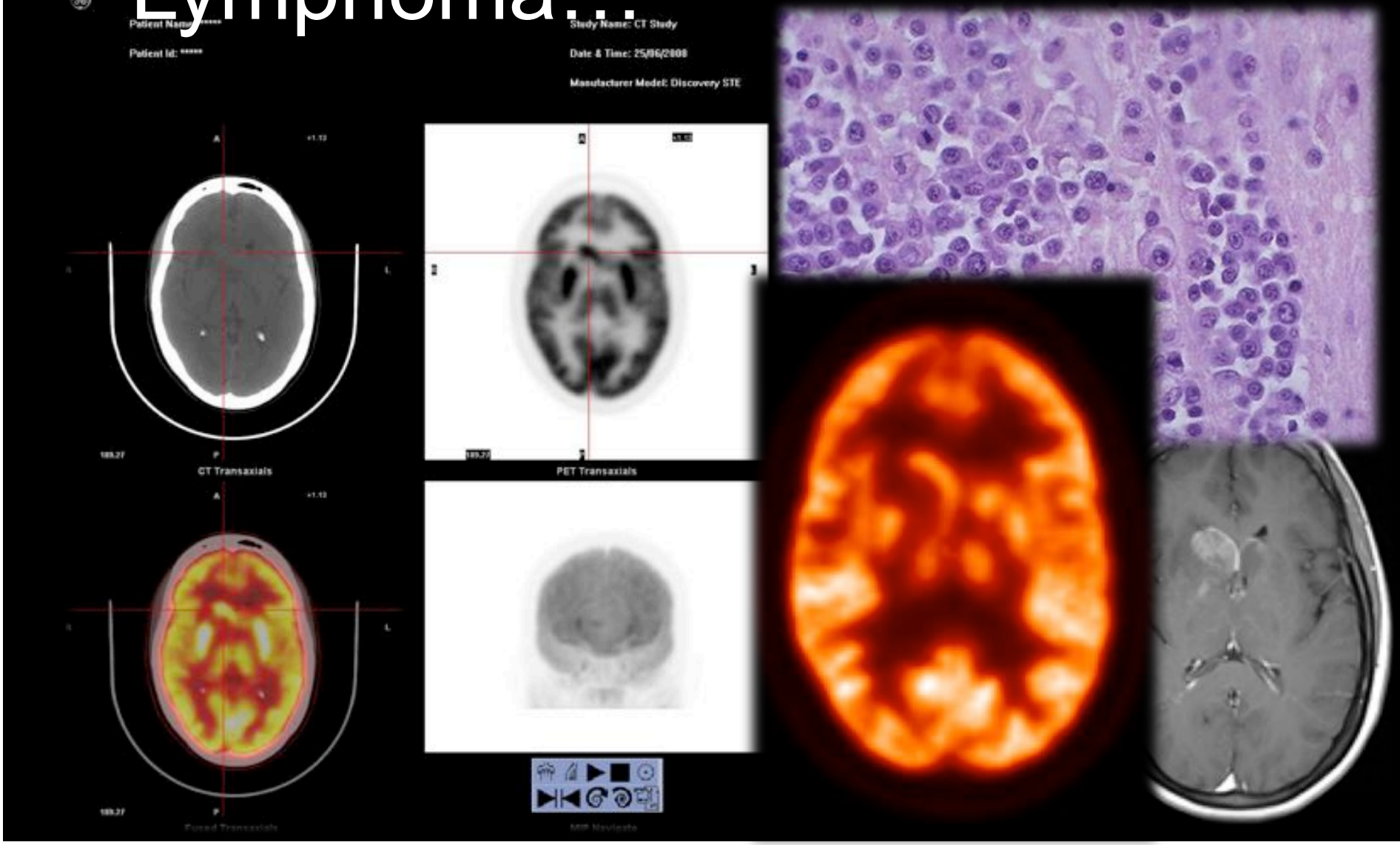
*For IDV, NFV, NVP – data based on studied interactions.

**For IDV, LPV, NFV, ritonavir – data based on studied interactions.

†For IDV, NFV, SQV – data based on studied interactions.

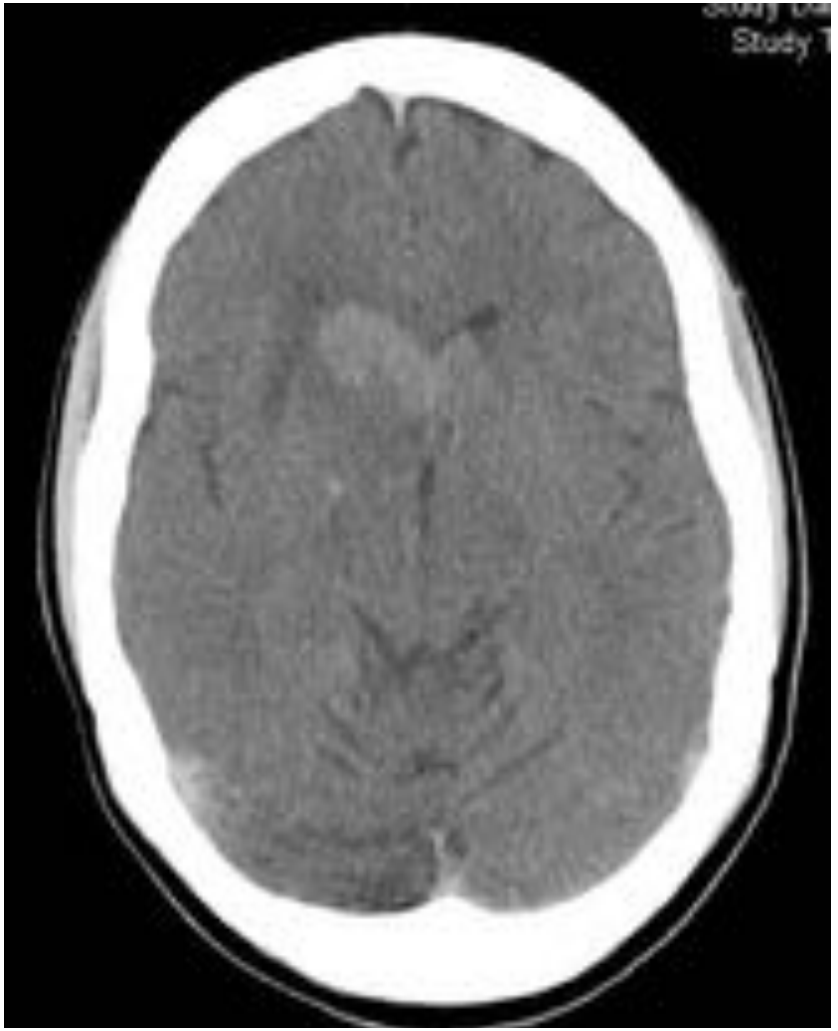
HIV Drug Interactions. Available at: http://www.hiv-druginteractions.org. Accessed August 2010.

# ADM - Primary CNS Lymphoma…



# Patient 2

- 28y old female SSA
- Presented with infected son; known +ve
  - Cutaneous KS
  - Mild hemiparesis
  - CD4 27
  - CSF: LC 24, protein 0.8, CRAG -ve
- No improvement with 2w anti-toxoplasma Rt
- CSF:
  - EBV +ve
- PET scan
- Brain Bx

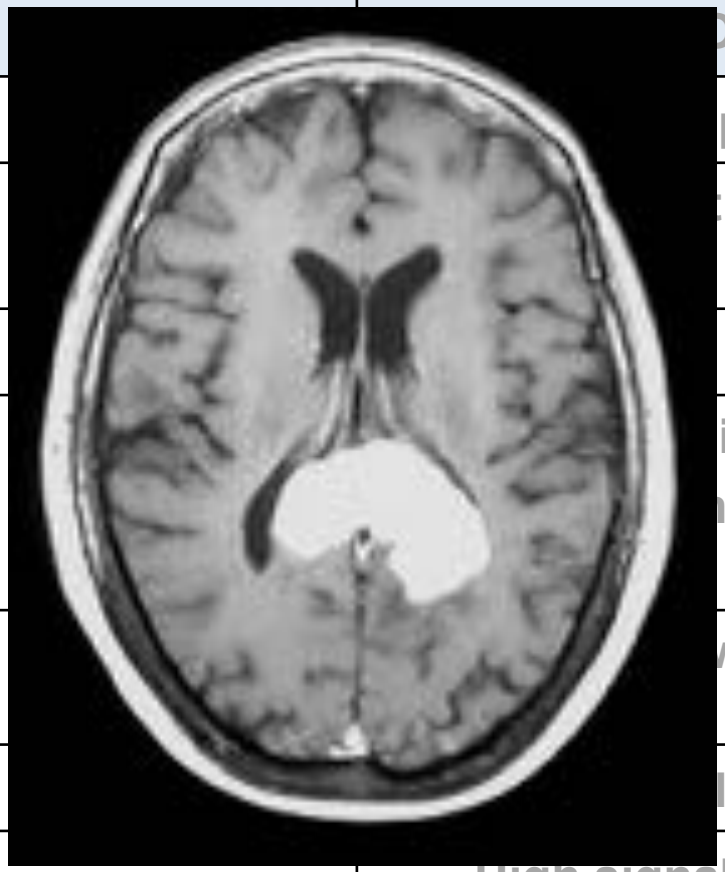


# Clinical challenges with PCNSL

A. Diagnosing cause
B. Improving treatment
C. Improving prognosis

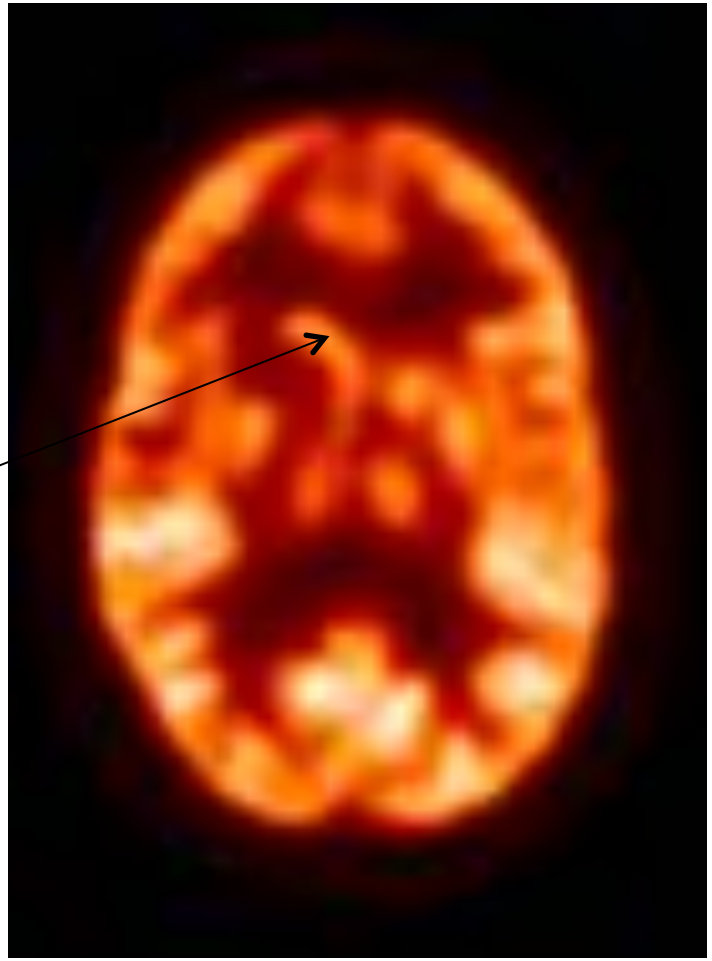
# A. Diagnosis – imaging

| MR FEATURES | | | |
|---|---|---|---|
| | PCNSL | | OSIS |
| Number | Single-few | | ple |
| Enhancement | Prominent<br>Homogeneous | | |
| Oedema | Mild-moderate | | |
| Location | Periventricular | | ia |
| | Anywhere | | white |
| MR T1 | Low to isodense | | |
| MR T2 | Variable | | High signal |



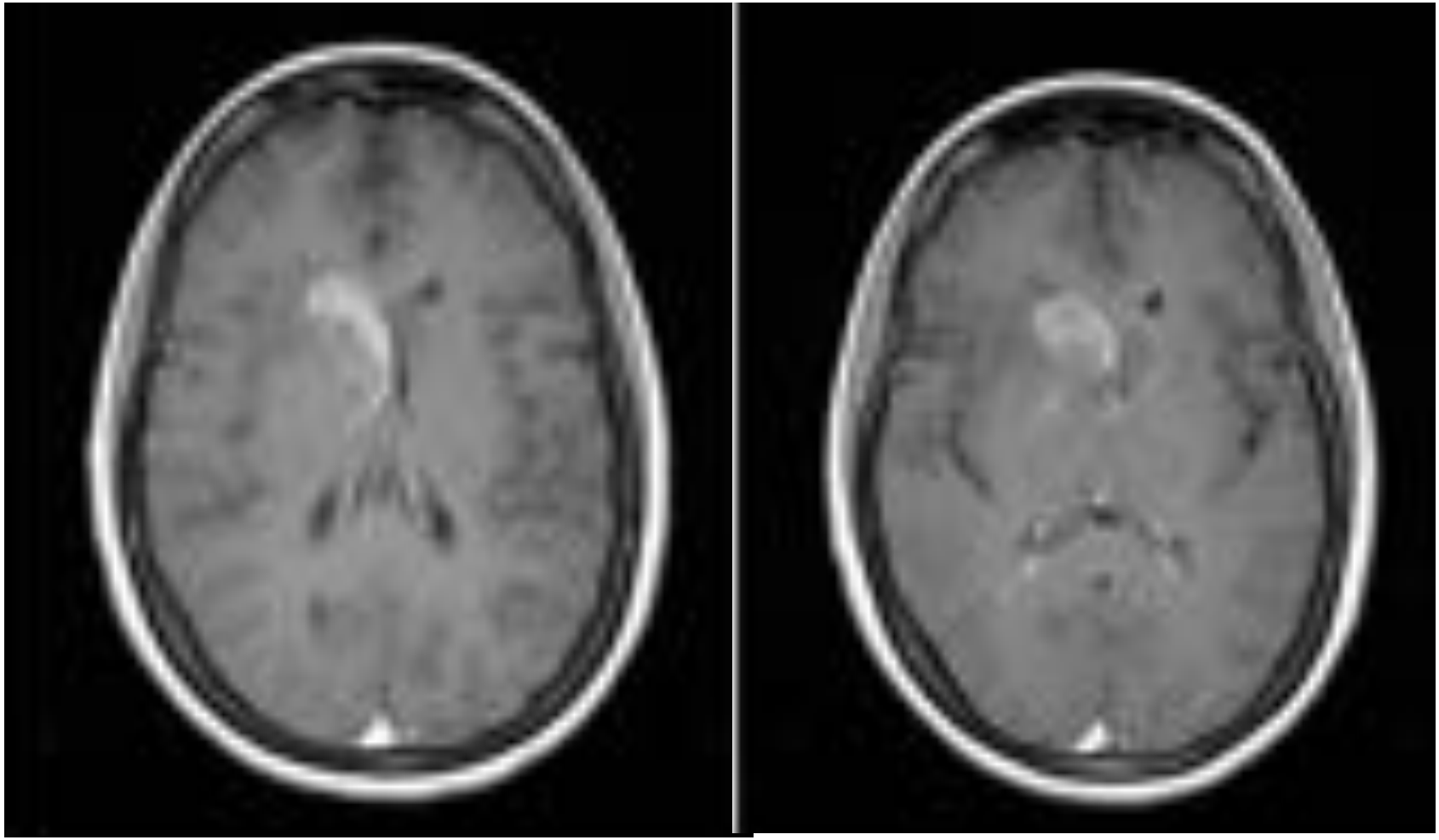
# Additional imaging

- CT body (diagnosis)
- USS testes
- 201 Thallium SPECT
- 18FDG-PET (positron emission scanning):
  - Lesions show increased uptake
  - Toxoplasmosis lesions are metabolically inactive



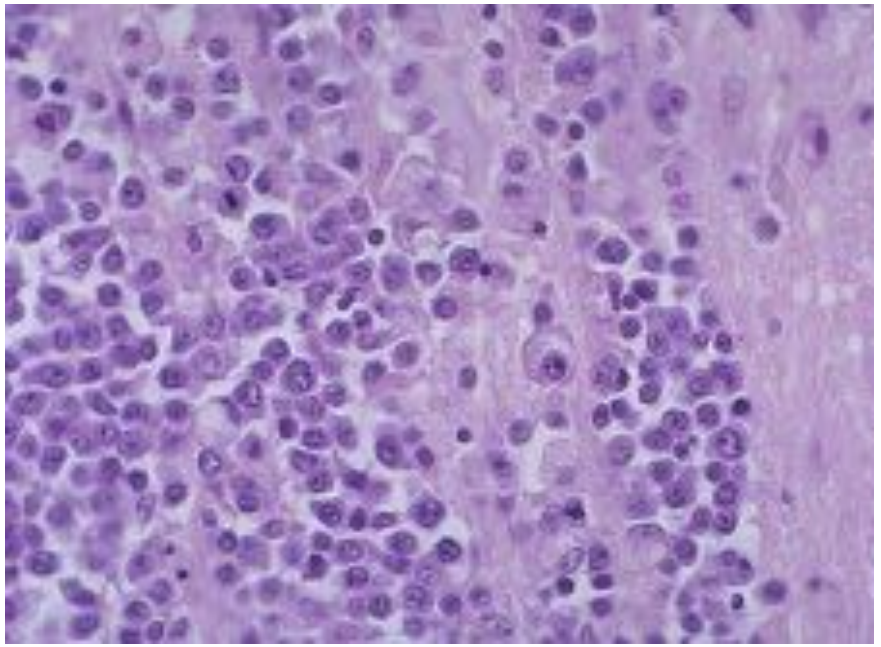
$^{18}$FDG-PET

# After 2w toxoplasma treatment – no improvement



# A. Diagnosis: CSF & biopsy

- AIDS-defining cancer
- CSF (if safe):
  - Often shows raised protein
  - Approximately 20% have abnormal cytology with malignant cells
  - **EBV DNA +ve in >90% with > 90% specificity**



- Biopsy:
  - With the exception of those who are terminally ill, a pathologic diagnosis **is required**

# B. Treatment: high-dose Methotrexate

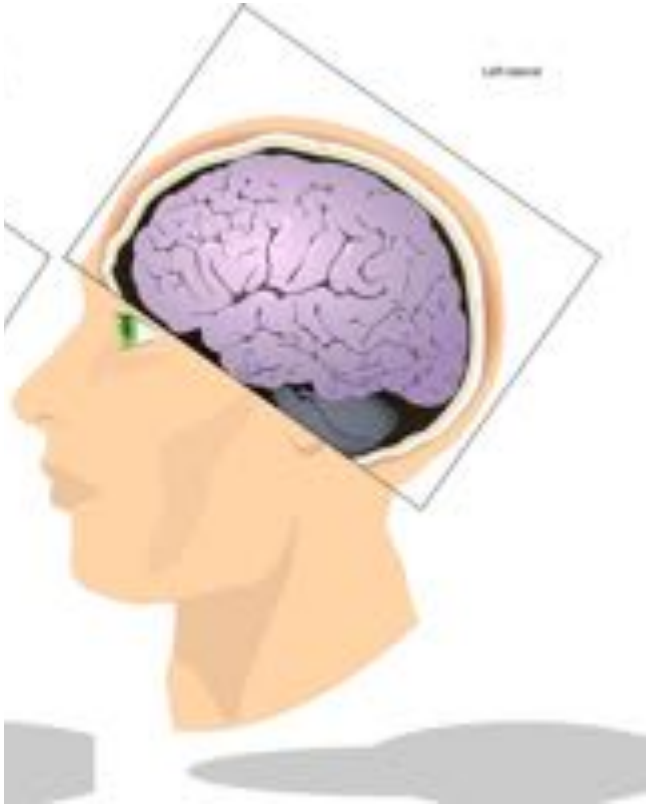
- A central place of high-dose IV MTX in HIV-related PCNSL therapy is supported by:
  - Data in HIV-negative PCNSL
  - Better survival with chemotherapy than radiotherapy in non comparative studies
  - Relatively low neurotoxicity compared to radiotherapy
  - Relatively good tolerability compared to chemotherapy with multiple agents
  - Relapse rare if HAART options available
- Place of Rituximab in addition to high-dose MTX under study

# B. Treatment – HAART/prognosis

- Consistent but slight improvement in overall survival in HAART era
  - median 32d (5-315d) vs. 48d (15-1136d)
- Benefit restricted to patients:
  - Not on HAART at diagnosis of PCNSL
  - Receive additional chemotherapy or radiotherapy
    - Lower rate of relapse
    - Enhanced rate of remission
- Spontaneous remissions have rarely been reported with HAART alone

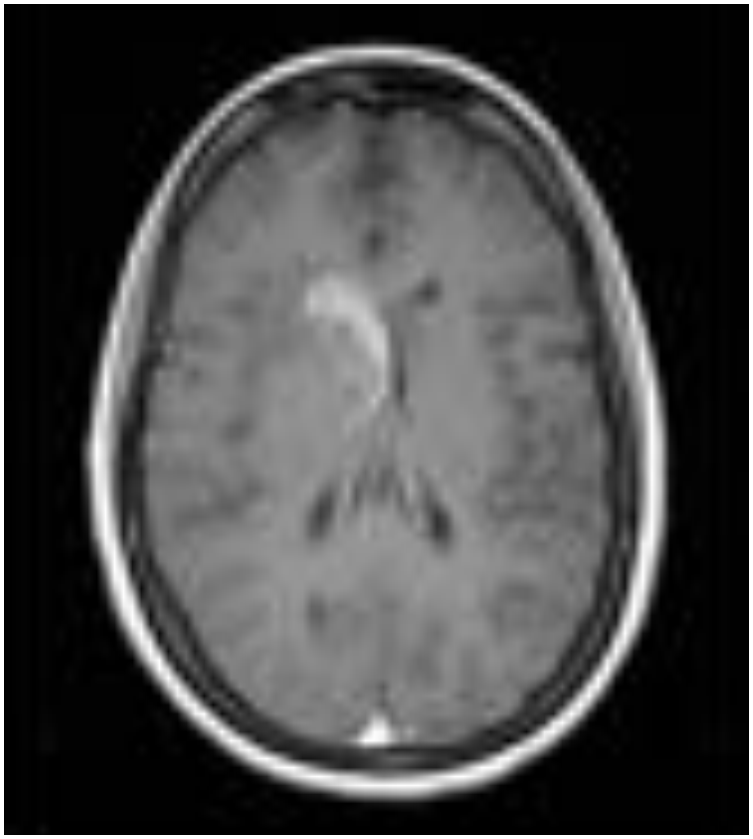
# B. Treatment - radiotherapy

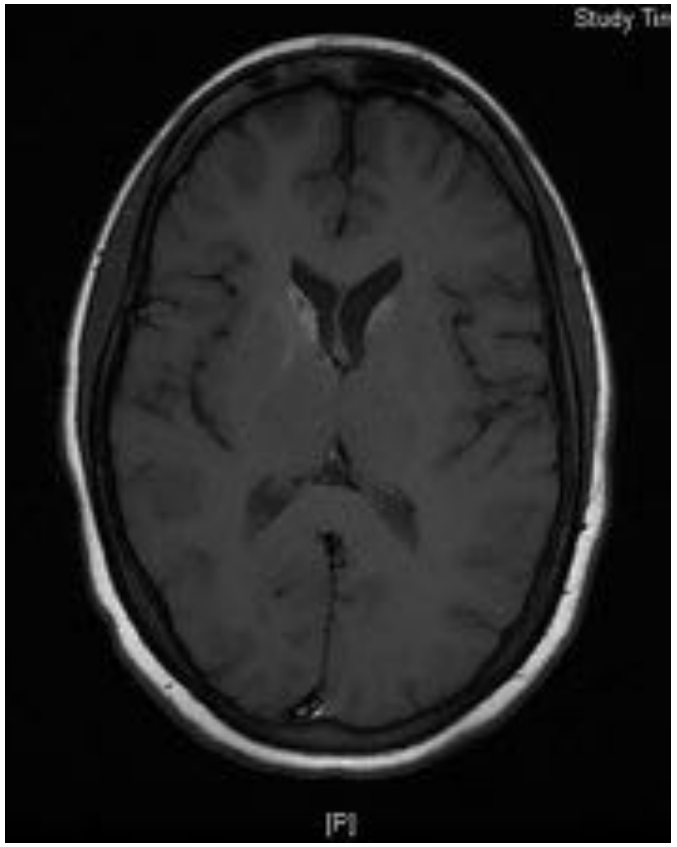
- Use whole brain radiotherapy for symptom control or as alternative to first-line treatment if risk of toxicity from high-dose IV agents unacceptable



# 3m post methotrexate and ART

- She is given high-dose IV methotrexate and her HAART is optimised





# Patient progress..

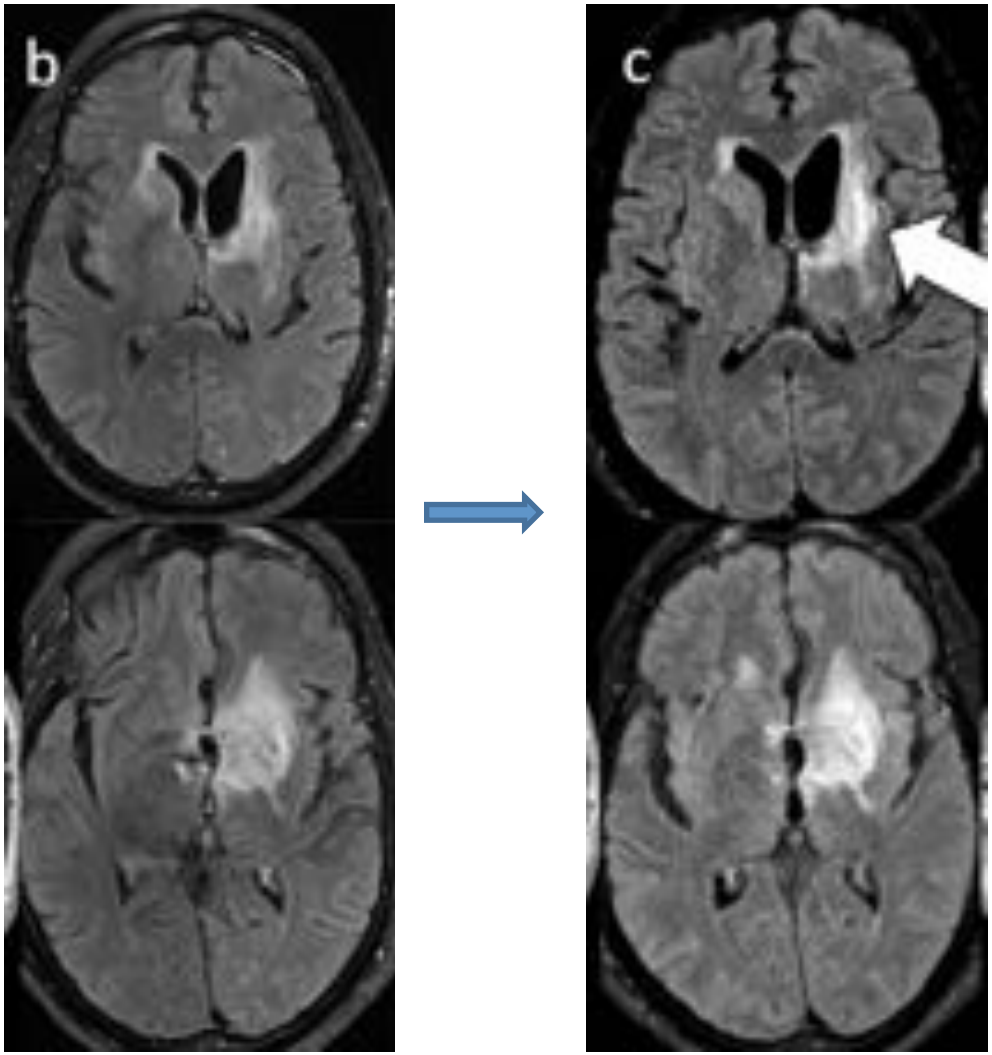
- Amazing
  - Slight hemiparesis but functioning normally

- CD4 >400 cells/µl VL <40 c/ml

- Now 4y since diagnosis
- Discharged by oncologist

# Be alert - paradoxical reaction can occur in PCNSL

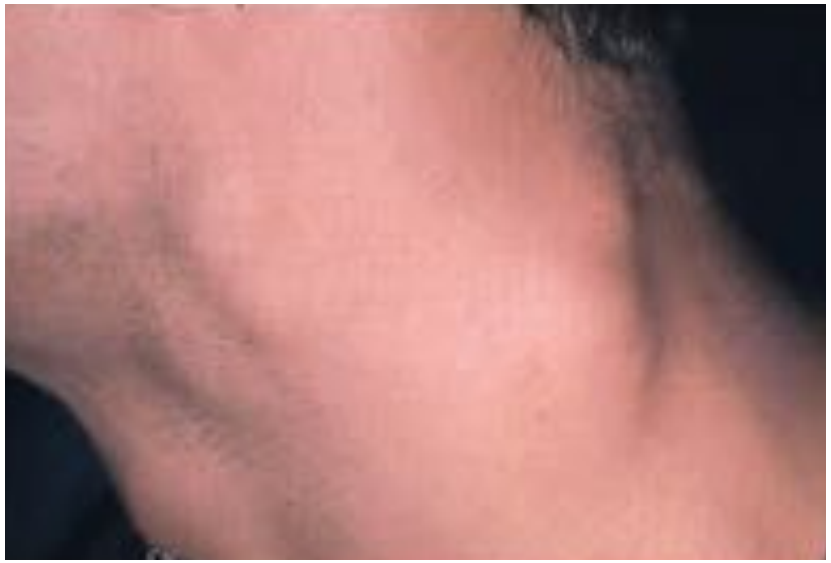
- Diagnosis PCNSL
  - Treatment methotrexate and rituximab
  - Responded well
- After 3rd cycle of R-M deteriorated and intubated
- Responded after high-dose steroids
  - Returned to baseline function
  - CD4 271



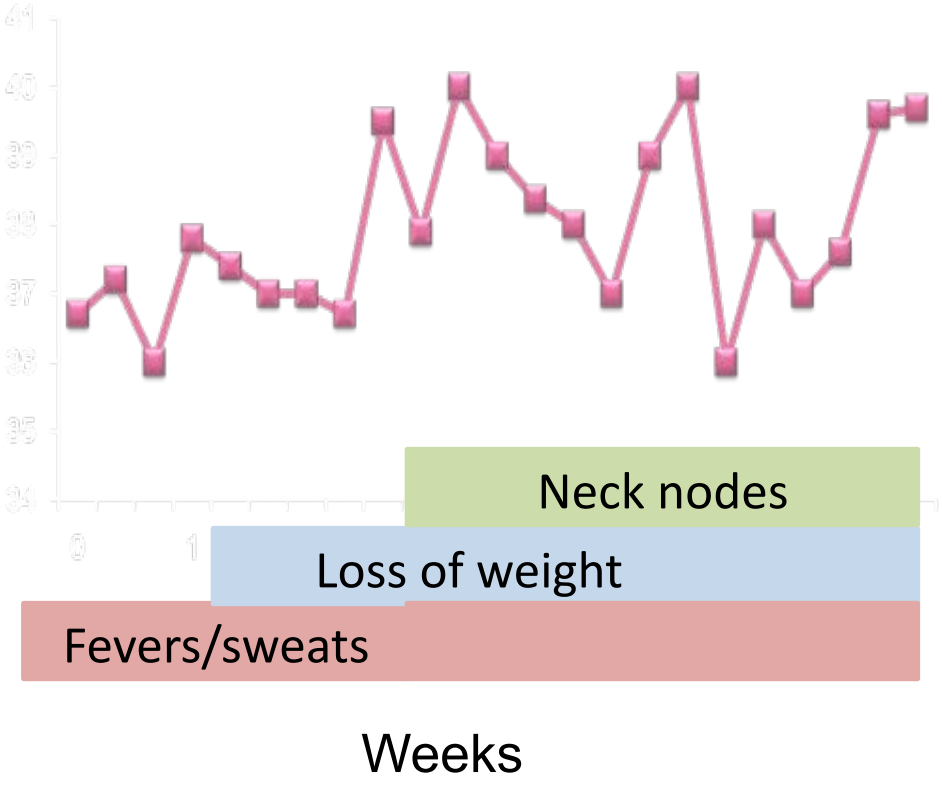
# NADM – Hodgkin´s Lymphoma and anal cancer

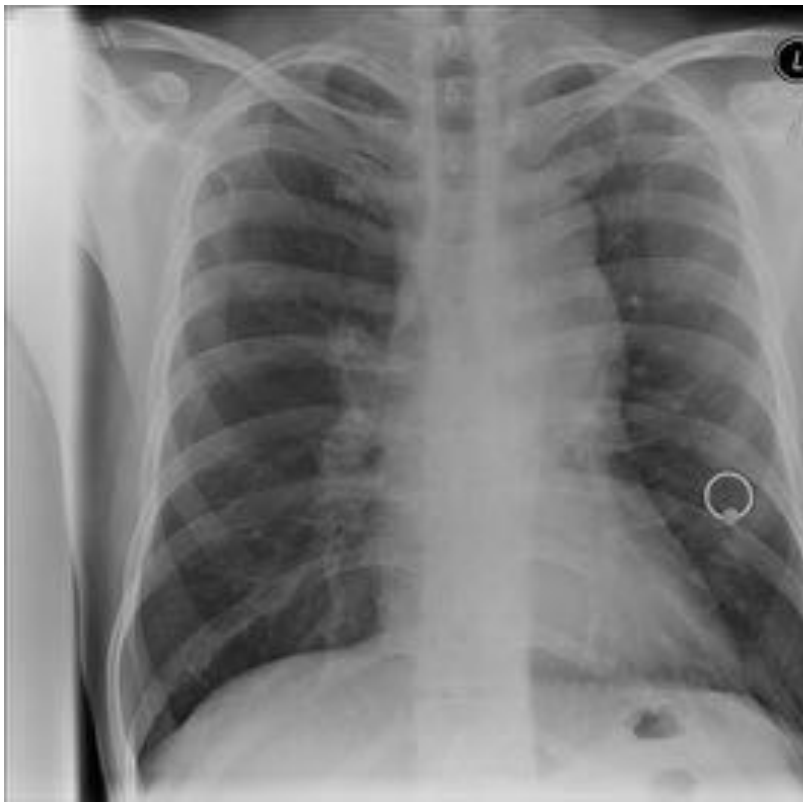
# Patient 3

- 37y-old White French born ex-IDU for 8y
- Lived in Spain till 2005, travelled Asia/Europe ++
- PMH – pulmonary TB 1998, HCV +ve (RNA –ve)
- Presented with 6w history of fever, sweats, loss of weight
- Non-adherent to medication
- HIV+ve, CD4 180 cells/mm3, VL 295,000 c/ml
- On methadone



# Chronology of symptoms



# Hodgkin lymphoma

- Commoner in PLWH x10–20
- Post-cART rates for CR/overall survival/disease-free survival same as for HIV-negative patient
- Increased incidence with CD4 <200 cells/ml, and CD4 count may fall 1 year pre-HL diagnosis
- EBV-driven

# Clinical challenges with Hodgkin disease

A. Not missing the diagnosis , especially when extra-nodal
B. Deciding optimal treatment
C. Awareness of drug-drug interactions
D. Salvage treatment

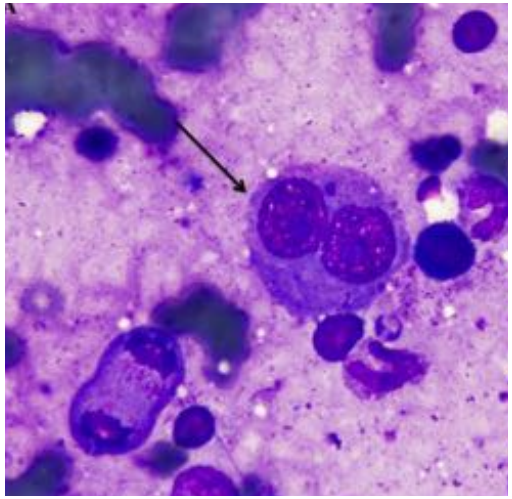
# A. Not missing the diagnosis - differential diagnosis for patient

- Fever/weight loss:
  - Opportunistic infections:
    - Mycobacterial (MAI and MTB )
    - NHL
    - Castleman's disease
    - Syphilis

- Lymphadenopathy:
  - NHL
  - TB, mycobacterium avium intracellulare (MAI), or another atypical mycobacteria
    - +/- IRIS
  - Castleman's disease
  - Reactive lymphadenopathy

# A. Not missing the diagnosis

- 90% have ‘B’ symptoms
- 74–92% have advanced stages of disease
- Frequent involvement of extra-nodal sites:
  - Bone marrow (40–50%)
  - Liver (15–40%) and spleen (20%)
- HIV-HL tends to develop as an earlier manifestation of HIV
- Higher CD4



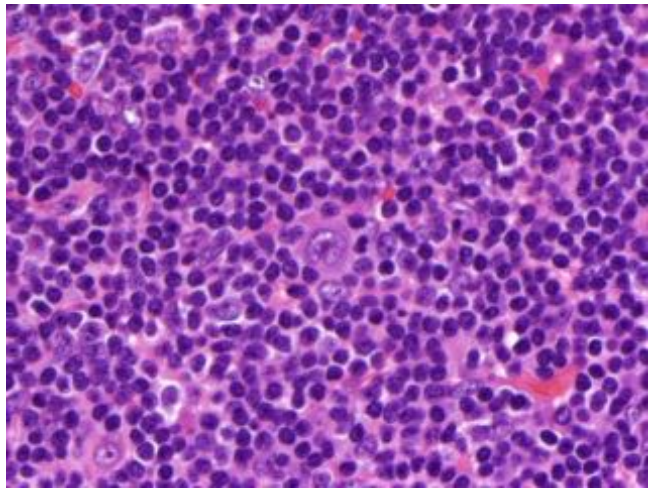
# Diagnosis/investigation of Hodgkin's disease

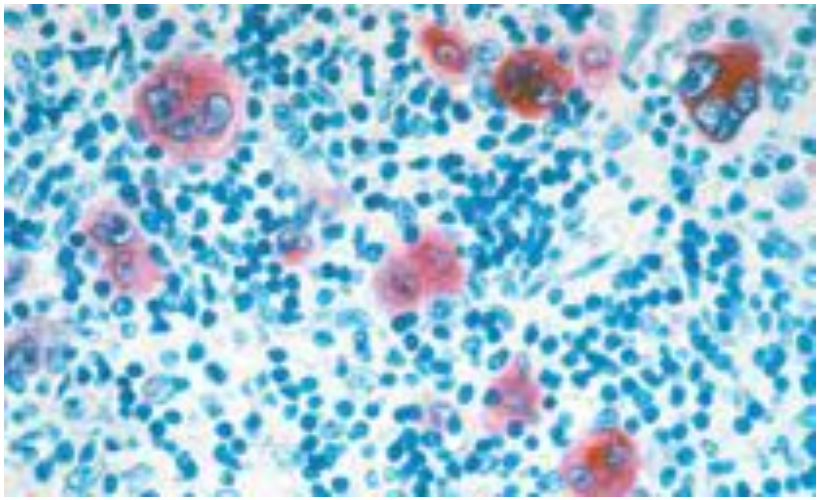
| Summary of baseline investigations |
| --- |
| **Initial diagnostic histology:**<br>**Usually lymph node biopsy – confirmation by tissue biopsy critical** |
| **Lumbar puncture:**<br>**CSF for protein, glucose, and cytology**<br>**(intrathecal chemotherapy can be administered with the staging lumbar puncture)** |
| **Bone marrow**<br>**Biopsy and aspirate in all patients (higher incidence of BM involvement in HIV-infected patients)** |
| **Neck-chest-abdomen-pelvis CT scan with contrast** |
| Specific investigations<br>MRI, PET scan |

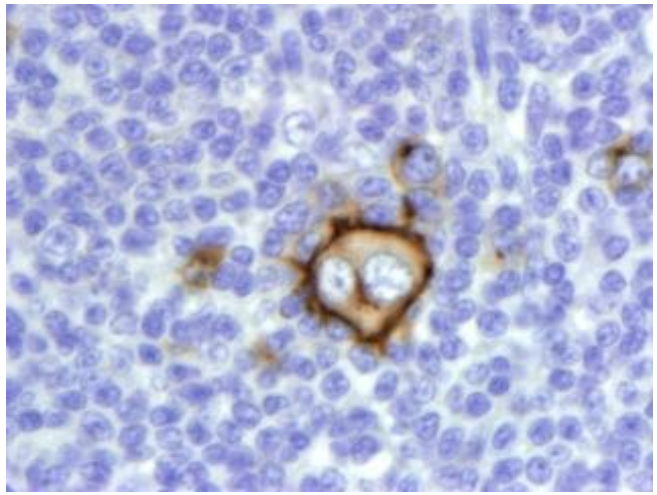
British HIV Association. HIV Medicine 2008;9:336–388.

# A. Diagnosing Cause: histology

- Increased nodular sclerosis and decreased mixed cellularity
- Reed-Sternberg cell
- EBV association







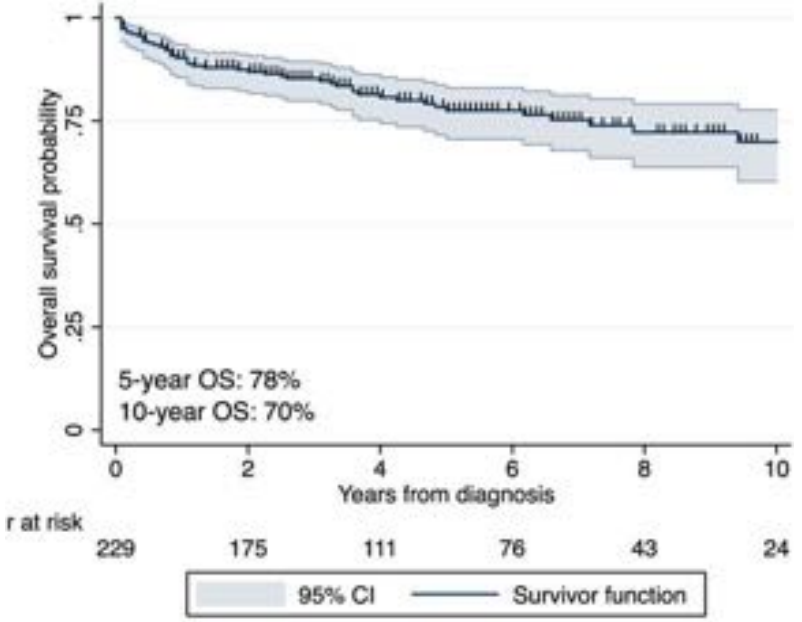
# Staging/prognosis of Hodgkin's disease

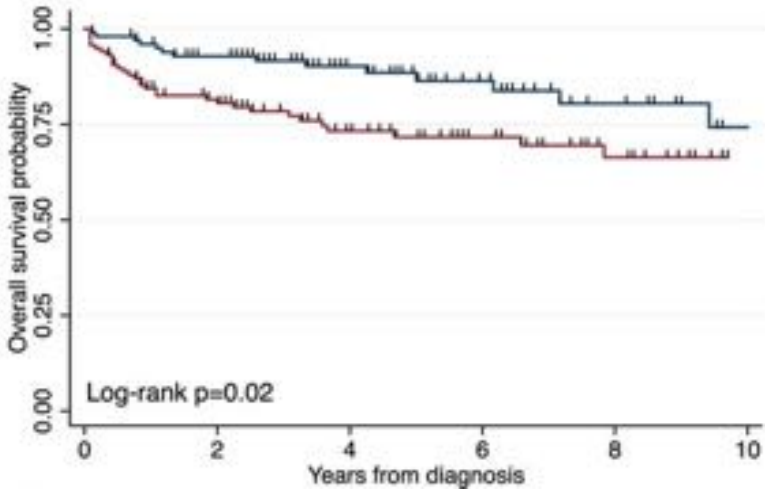
| Ann Arbor classification/Cotswolds modification |
|---|
| Stage I Involvement of a single lymph node group or lymphoid structure |
| Stage II Involvement of 2 or more lymph node groups on the same side of the diaphragm |
| Stage III Involvement of lymph node groups on both sides of the diaphragm |
| Stage IV Involvement of extra-nodal site(s) beyond those designated 'E' |
| X: Bulky disease: > 10 cm or > 1/3 widening of the mediastinum at T5–6 |
| E: Extra-nodal extension contiguous or proximal to known nodal site of disease or single isolated site of extra-nodal disease |
| A/B: Absence/presence of B symptoms (weight loss > 10%, fever, drenching night sweats) |

British HIV Association. HIV Medicine 2008;9:336–388.

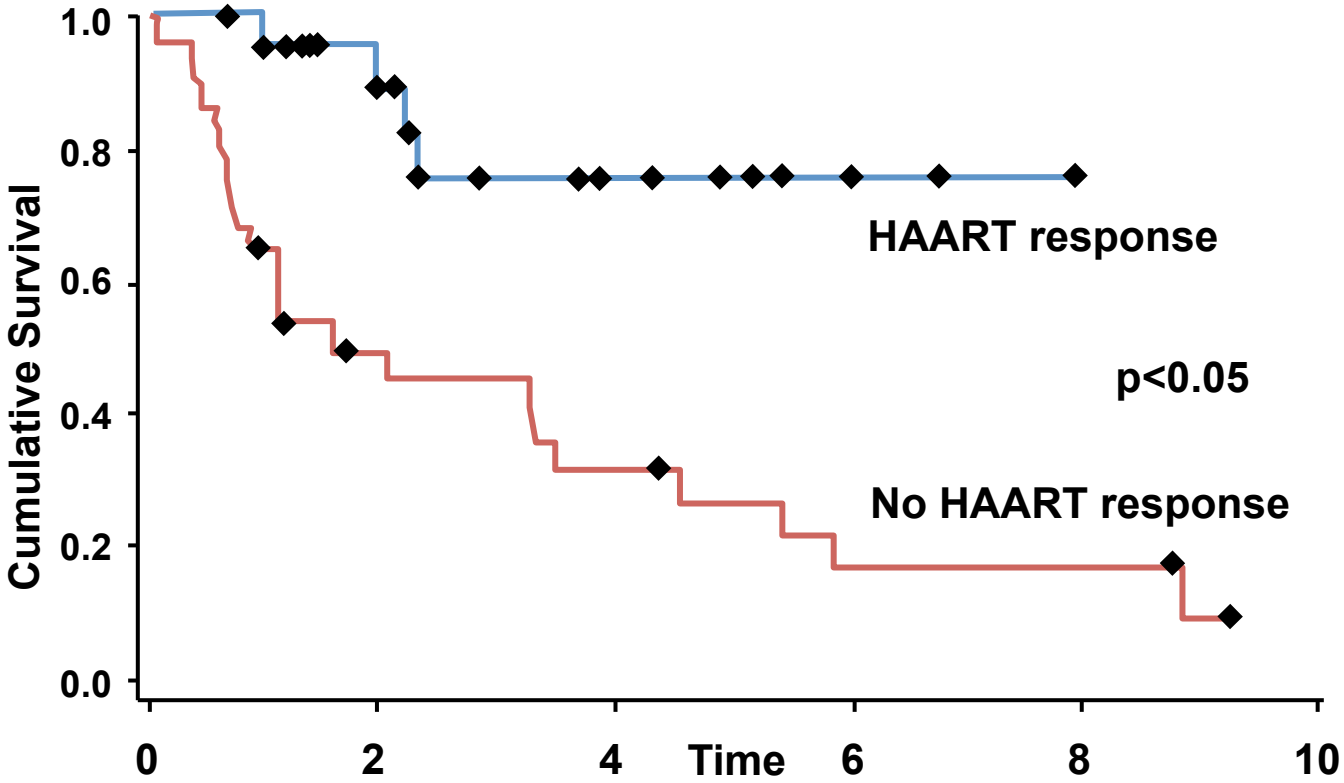
# Deciding optimal treatment ART and ABVD

- Good prognosis associated with:
  - Mixed cellularity subtype
  - Absence of extra-nodal involvement,
  - Absence of B symptoms
  - Prior use of HAART
- Overall and complete response rates to ABVD were 91% and 83%,
  - IPS and CD4 associated



# Cumulative survival of HD patients who respond to HAART




**Median survival was 18.6 months in patients without HAART response, but was not reached in patients that responded to HAART (89% overall survival at 24 months vs. 44%)**

Hoffmann C, et al. *Br J Haem* 2004, 125:455–62.

# Awareness of drug-drug interactions
# ABVD-HAART interactions

| ABVD | PI | NNRTI | RAL | MVC |
|---|---|---|---|---|
| **Doxorubicin** | ■ | ■ | ■ | ■ |
| **Bleomycin** | – | – | – | – |
| **Vinblastine** | ■ | ■ | ■ | – |
| **Dacarbazine** | – | – | – | – |

■ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

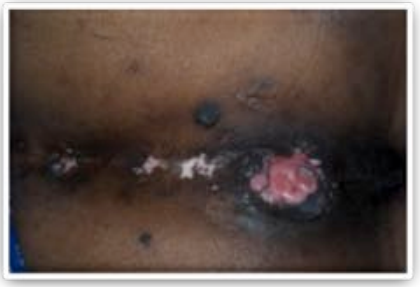
■ No clinically significant interaction expected

HIV Drug Interactions. Available at: http://www.hiv-druginteractions.org/ (accessed April 2010).

# Anal cancer

Diagnosis/Investigation of Anal Cancer[2]

- Twice as common in HIV-infected men who have sex with men (MSM) :
  - Baseline and nadir CD4 count <200
  - Older age
  - RR 37 for HIV-infected men and 6.8 for women
- Diagnosis:
  - Biopsy essential
  - Majority squamous cell carcinomas
  - Relationship and benefits of screening uncertain



1. Silverberg M, *et al.* 17th CROI 2010. Presentation 28; 2. British HIV Association. *HIV Medicine* 2008;9:336–388.

# Clinical challenges with anal cancer

A. Not attributing cause to another diagnosis
B. Deciding optimal treatment
C. Place of vaccine

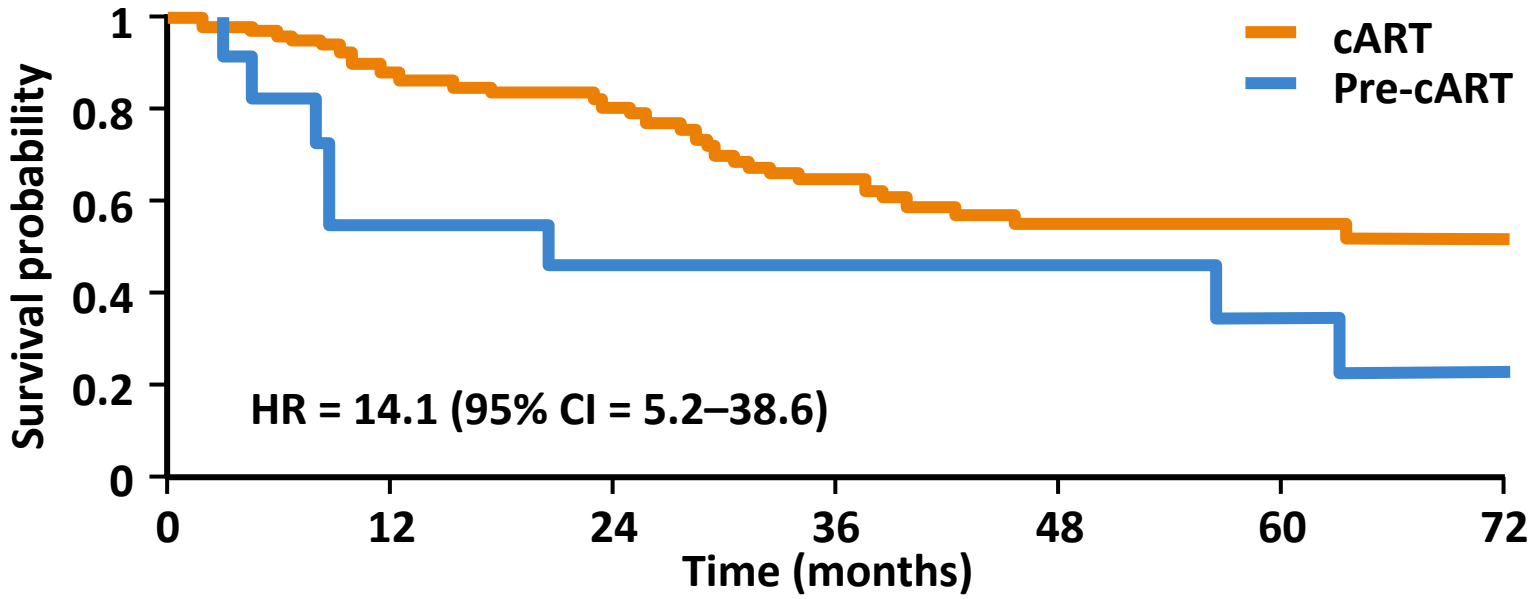
# A. Not attributing cause to another diagnosis

- Bleeding – present in half and usually 1st sign
- Mass – wart like or ulcerative
- Itching – more common with AIN
- Pain – present in one third usually post defaecation
- Change in bowel habit
- Localised inguinal lymphadenopathy

# Anal Cancer Survival has improved significantly

**Stage distribution & 5-year relative survival by stage at diagnosis (1999–2006), all races, both sexes**

| Age | Stage distribution(%) | 5-yr relative survival (%) |
|---|---|---|
| Localised (confined to primary site) | 50 | 80.1 |
| Regional (spread to regional LN) | 29 | 59.8 |
| Distant (cancer has metastasized) | 12 | 30.5 |
| Unknown (unstaged) | 9 | 56.0 |



# B. Deciding optimal treatment

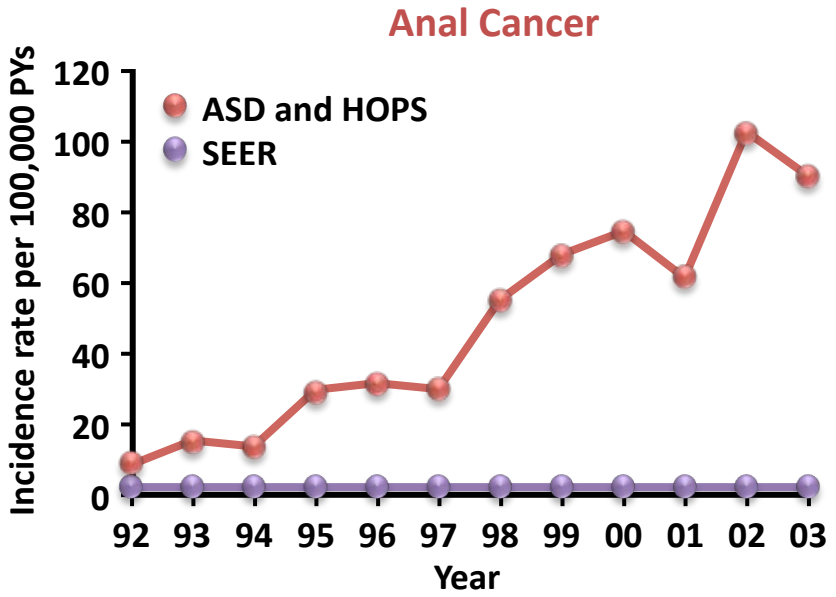
| Primary tumor | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ (Bowen's disease), high grade- squamous intraepithelial lesion (HISL), AIN II-III |
| T1 | Tumor 2 cm or less |
| T2 | Tumor more than 2 cm but no more than 5 cm |
| T3 | Tumor more than 5 cm |
| T4 | Tumor of any size invades adjacent organ(s), eg, vagina, urethra, bladder (direct invasion) of rectal wall, peri-rectal skin, subcutaneous tissue, or sphincter muscle is not classified as T4 |

| Regional lymph nodes (N) | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in peri-rectal lymph node(s) |
| N2 | Metastasis in unilateral internal iliac and/or inguinal lymph nodes |
| N3 | Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes |
| **Distant metastases (M)** | |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

- Treatment:
  - **Chemoradiotherapy:**
    - **5FU and mitomycin**
  - Surgical excision required if:
    - Small lesions, persistent or recurrent tumour after chemoradiotherapy

# C. Place of Vaccine

| HPV Type | Approximate Disease Burden |
|---|---|
| 16 and 18 | 70% of cervical cancer<br>70% of anal cancer, AIN<br>Targeted in both quadrivalent and bivalent vaccines |
| 6, 11, 16, and 18 | 35%–50% of all CIN 1<br>90% of genital warts<br>Targeted in quadrivalent vaccine |




ASD = Adult & Adolescent Spectrum of Disease Study
HOPS = HIV Outpatient Study
SEER = Surveillance, Epidemiology, & End Results*

**Available HPV vaccines target types common to oncogenesis of all genital sites.**

**Vaccine should logically prevent anal outcomes.**


1. Patel *Ann Int Med* 2008*; Chiao *CID* 2006; Palefsky *J AIDS* 2001; Bower *J AIDS* 2004; Witkin *JID* 2004.
2. Munoz *NEJM* 2003; Palefsky J*AIDS* 1998

# Summary

- Most HIV-infected MSM have HPV infection
- Most of these patients have abnormal cytology
- Most patients with abnormal cytology have abnormal biopsies
- Sensitivity/specificity cytology = cervical screening
- Most patients with early AIN progress to AIN 3
- AIN 3 rarely regresses
- AIN 3 progresses to SCC
- SCC worse prognosis
- Vaccine has a place.

# Outline

- Differing knowledge and differing requirements…
- Today I will break it down:
  - Basic facts
  - Clinical challenges in ADM and non-ADM
  - Management
- Hopefully you have interrupted….

# Thank you

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