Kaposi Sarcoma and HIV-associated Lymphoproliferative Disorders

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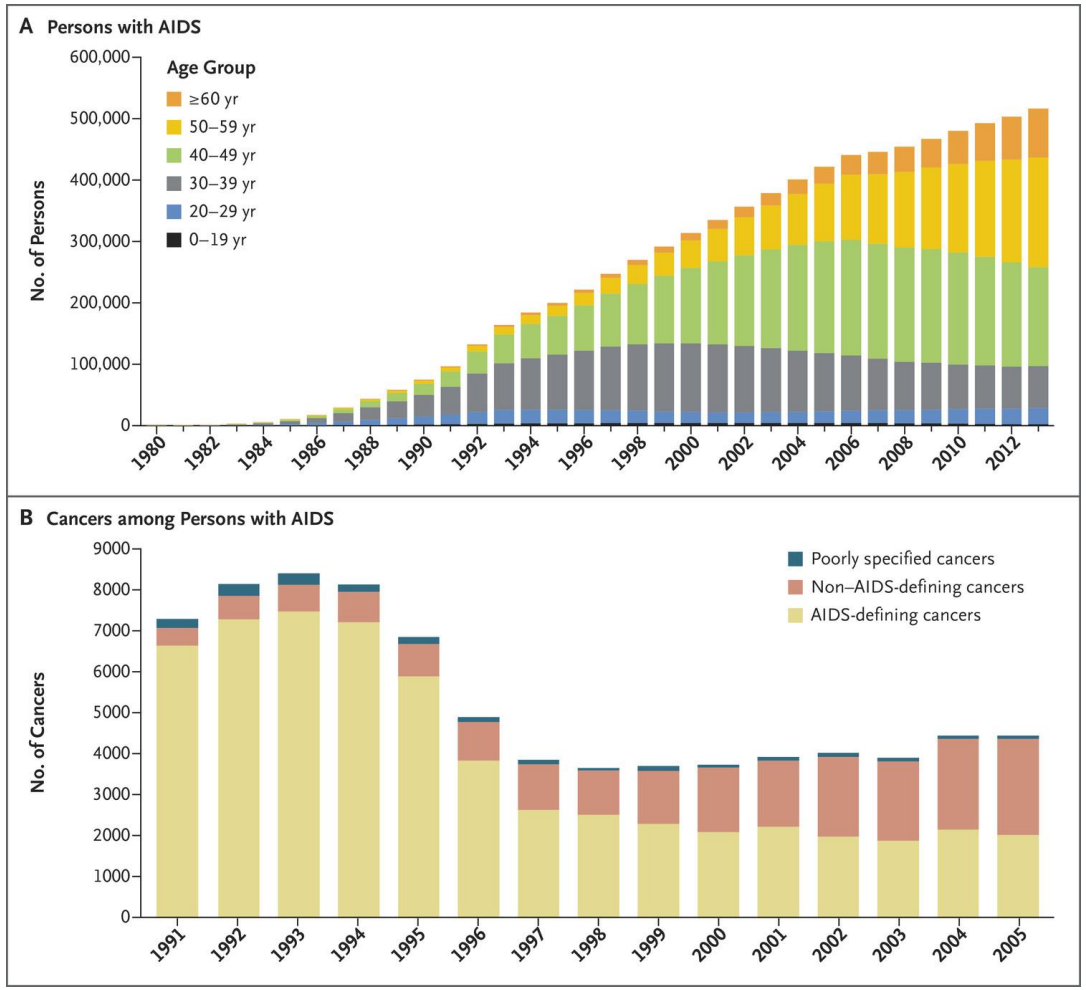
SA HIV Clinicians Society Conference 2018

24-27 October

Groote Schuur Hospital

Kaposi Sarcoma

Trends in AIDS and in Cancers among Persons with AIDS.

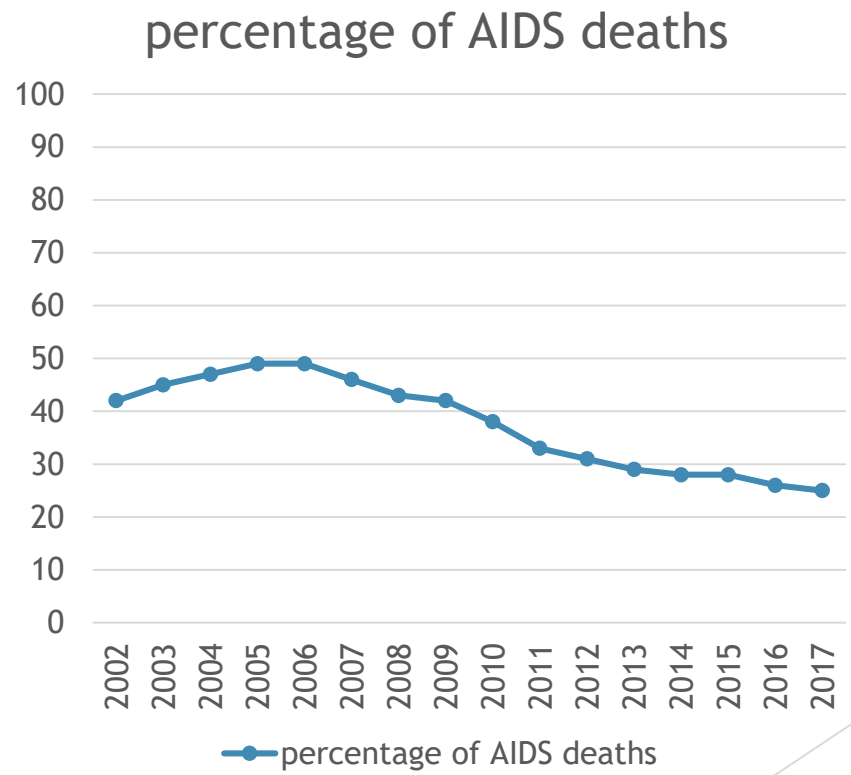


R Yarchoan, TS Uldrick. N Engl J Med 2018;378:1029-1041.

The NEW ENGLAND JOURNAL of MEDICINE

Stats SA Midyear population estimates 2017

- SA population 56.52 million
- HIV prevalence 12.6%
- 7.06 million HIV positive
- SA has largest no of PLWA and largest ART program worldwide
- Sept 2016: universal ART eligibility



Stats SA midyear statistical release P0302 accessed online 9 August 2018; Cornell et al JIAS 2017

Incidence of Kaposi Sarcoma in South Africa

South African National Cancer Registry 2014

- Pathology-based registry
- Within top 10 cancers for males and females
- 3rd commonest cancer in Black men
- 5th commonest cancer in Black women

From CANSA factsheets accessed online

Comparison of KS risk in HIV+ve adults across 5 continents: A Multiregional Multicohort Study

- KS incidence rates per 100000 person-years in adults who started ART after 1995
  - South Africa 280 (95% CI 238-328)
  - Latin America 244 (203-295)
  - North America 237 (207-271)
  - Europe 180 (172-190)
  - Asia-Pacific 52 (19-137)
- Risk 6X more in MSM
- Risk 5X higher in SA women than European women

AIDS-defining Cancer Project Working Group for IeDEA and COHERE in Eurocord, Clin Infec Diseases 2017

Risk Factors for KS

21 European Cohort studies

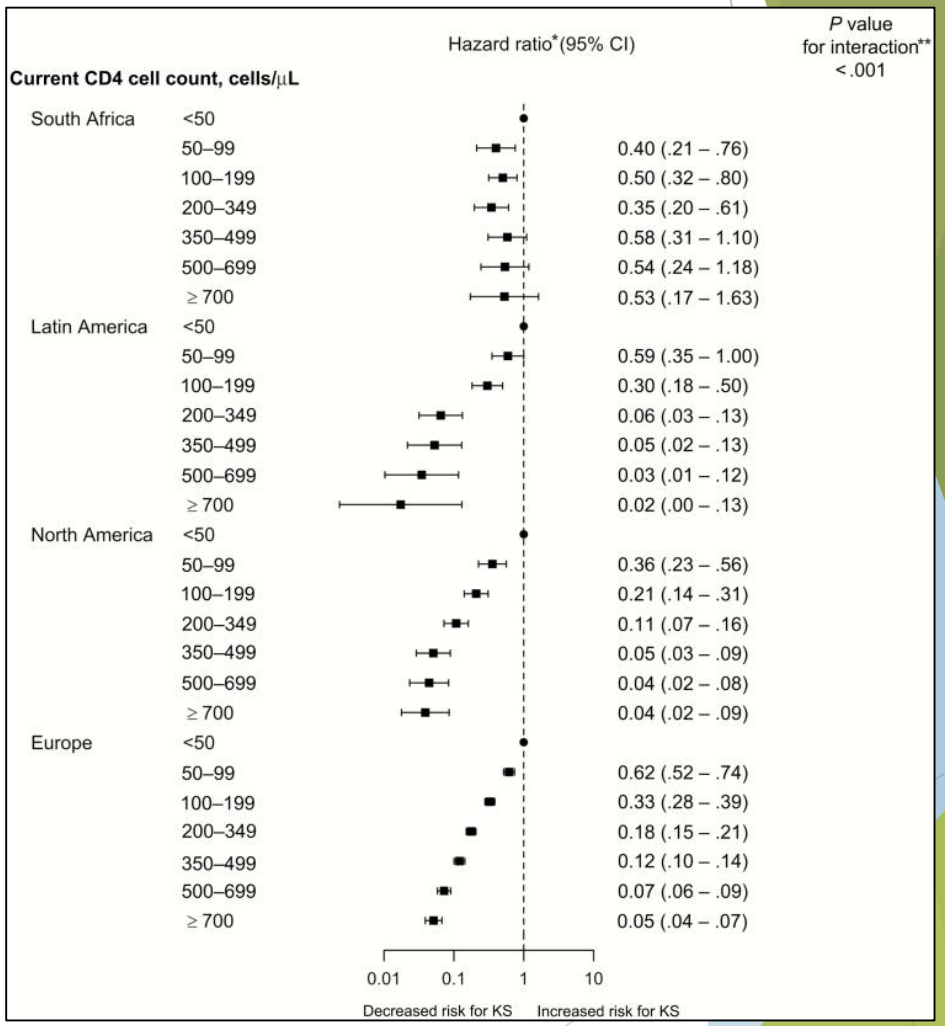
- Incidence highest 6 months after starting ART
- Low CD4 counts
- Elevated viral load is a later risk factor

6 Southern African Cohorts IeDEA-SA database

- Risk increased with age
- Low CD4 counts
- Adults, Male sex
- Starting ART at WHO stage IV

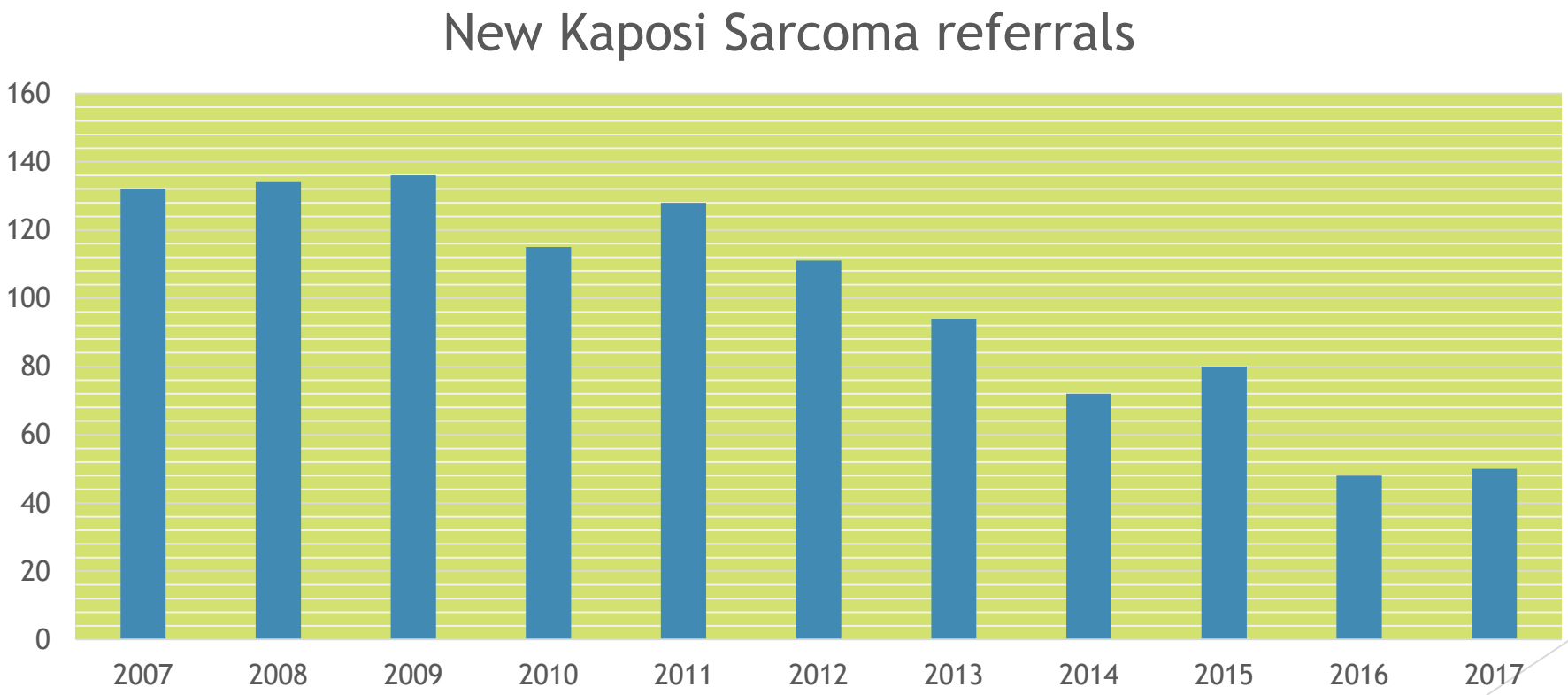
Wyss et al COHERE in Eurocord, Clin Infec Dis 2016; Rohner et al, J Aquir Immune Defic Syndr 2014

Comparison of KS risk in HIV+ve adults across 5 continents: A Multiregional Multicohort Study

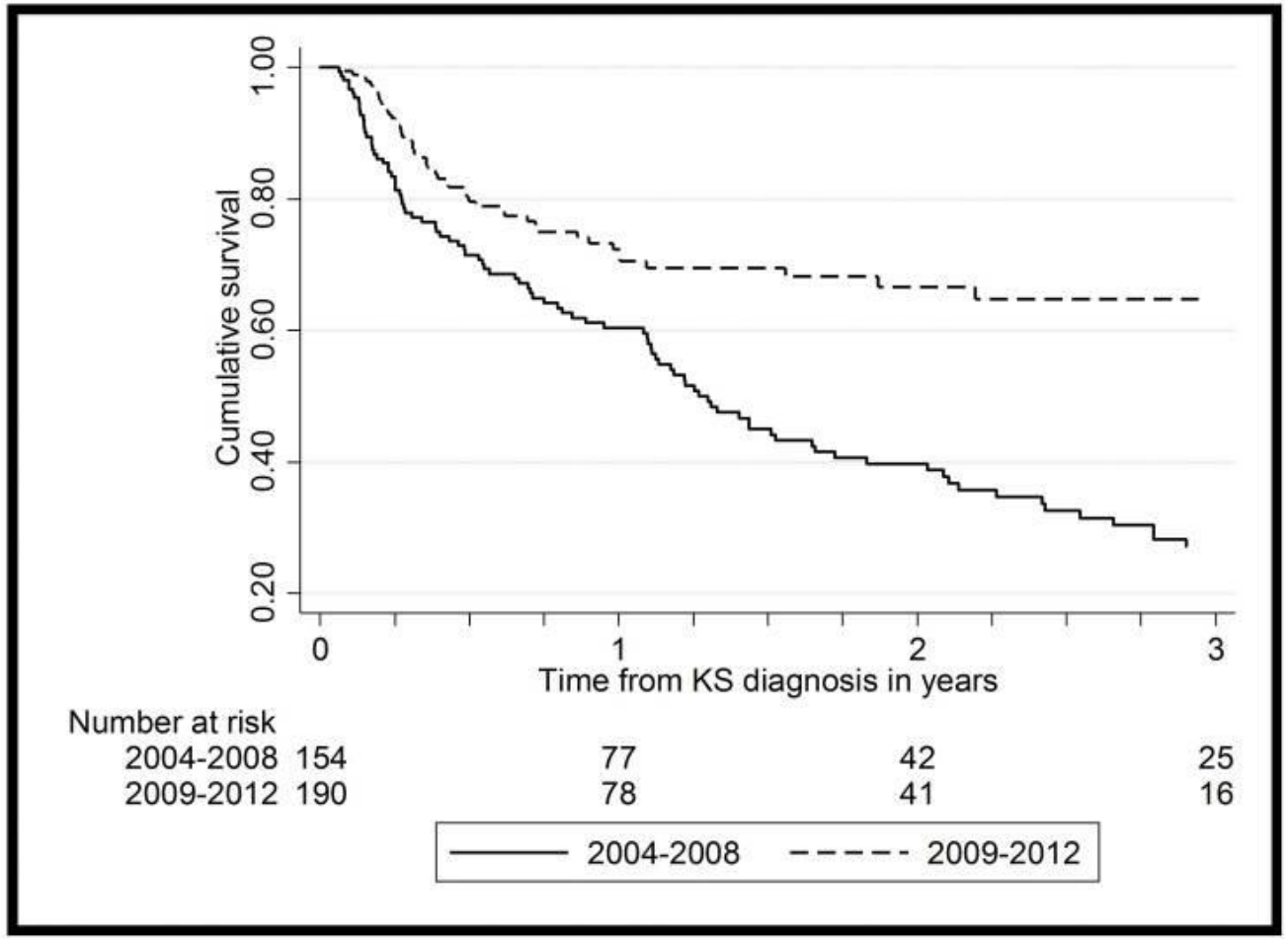


From: AIDS-defining Cancer Project Working Group for IeDEA and COHERE in Eurocord, Clin Infec Dis 2017

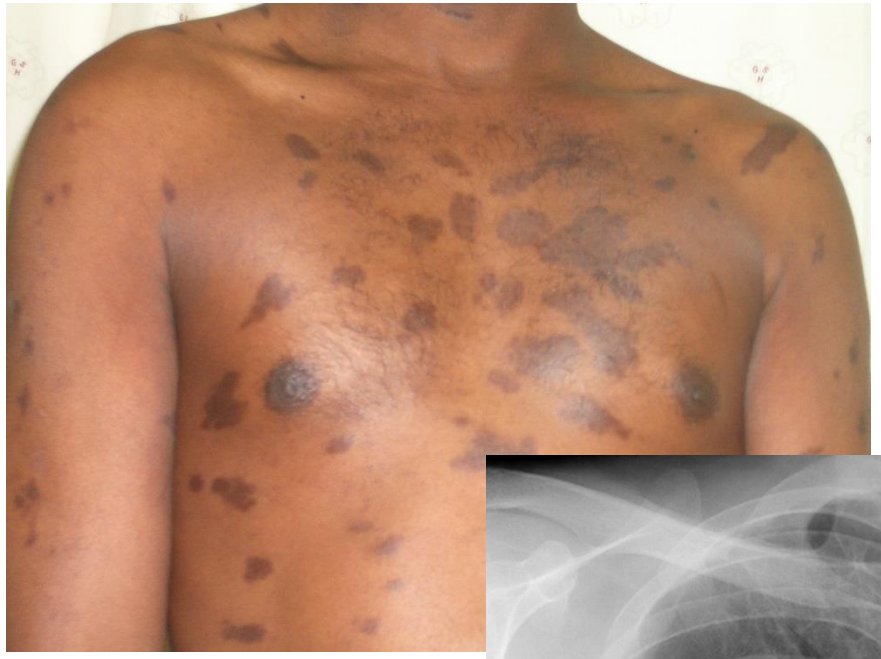
Declining incidence of Kaposi Sarcoma at GSH Oncology

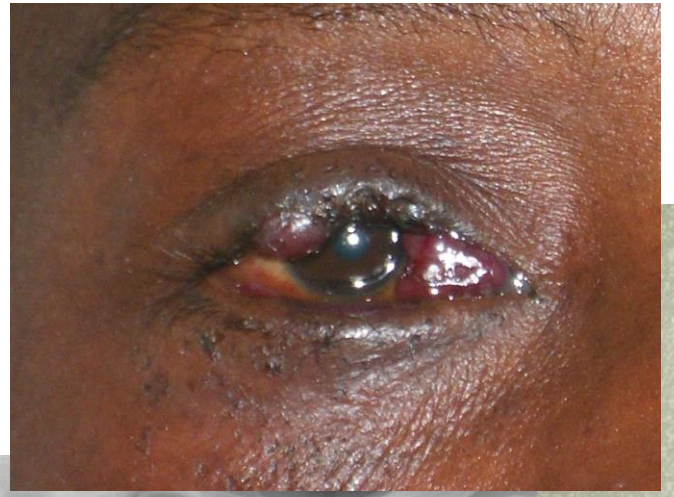


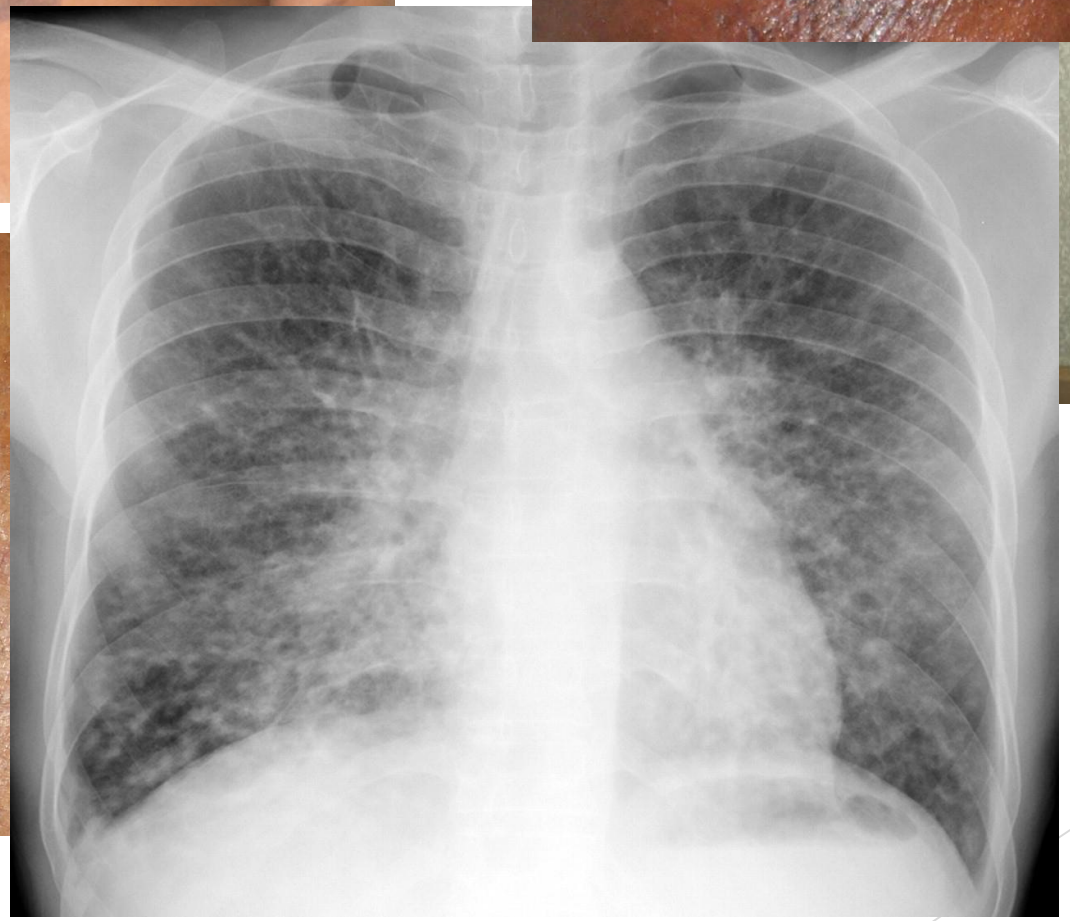
From Sengayi et al: Survival changes over time in AIDS-KS patients treated at SBAH

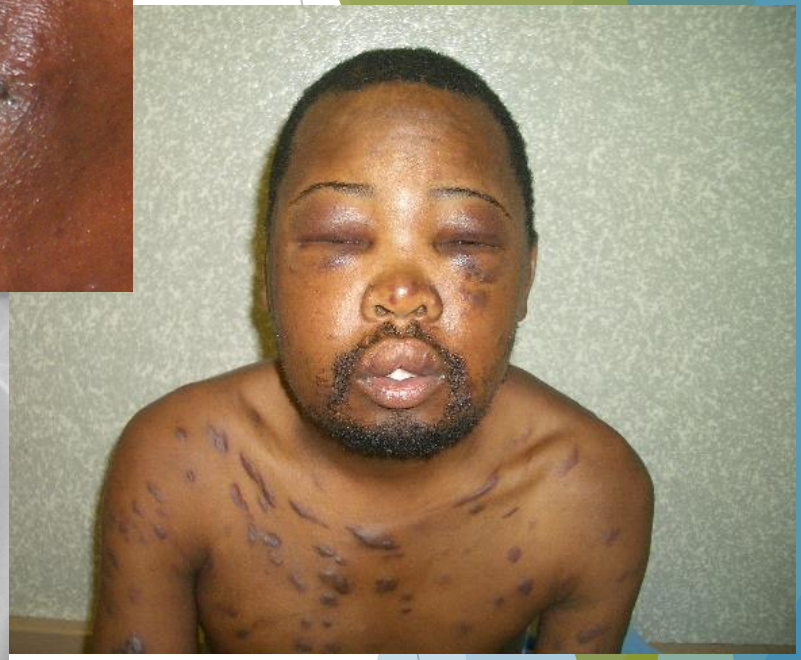


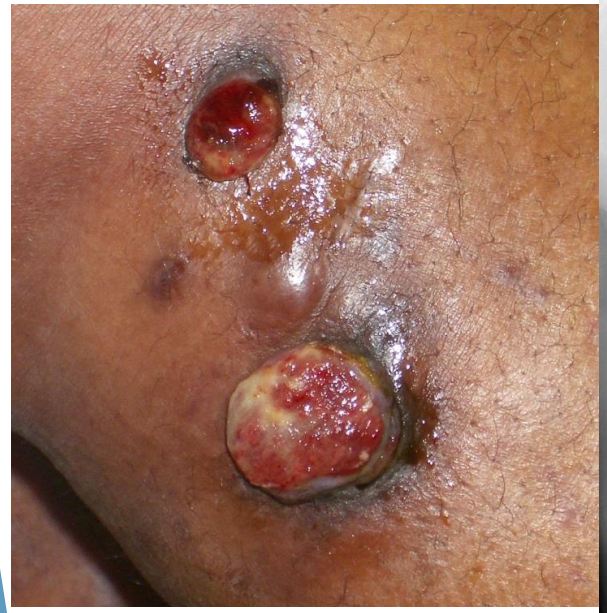
Sengayi M; Kielkowski D et al S Afr Med J 2017 107(10):871-876

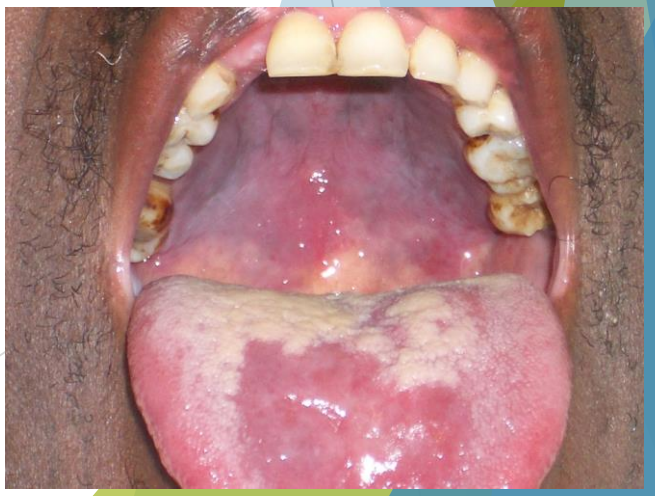












Presenting Symptoms

- Cutaneous lesions: patch, plaque, nodule, fungating, ulcerated
- Mucosal lesions: oral, eye, nasal
- Lymphoedema: legs, genitalia, face, arms
- Lymphadenopathy
  - Kaposi Sarcoma
  - TB or other infections
  - Lymphoma
  - Multicentric Castleman Disease
- Visceral involvement
  - Pulmonary
  - Gastrointestinal
  - Other organs: liver, spleen, etc

KS IRIS

Within 3 months of initiating ART:

- Unexpected progression of pre-existing KS lesions
- New KS lesions
- Involvement of new sites
- Atypical clinical, histologic or radiologic findings
- Rapid onset

With suppressed viral load

Incidence 2.5 times higher in African vs European cohorts

Letang et al, AIDS 2013

Kaposi Sarcoma

- Angiogenic, inflammatory tumor of endothelial cells
- Caused by KSHV/HHV8
  - Gamma-2-herpesvirus closely related to EBV
  - 6 subtypes and 13 variants
  - Also causes Castleman's and Primary Effusion Lymphoma
- Seroprevalence of KSHV parallels KS incidence
  - US and Europe <10%
  - Sub Sahara Africa ~50%
  - South African studies: 35-49%

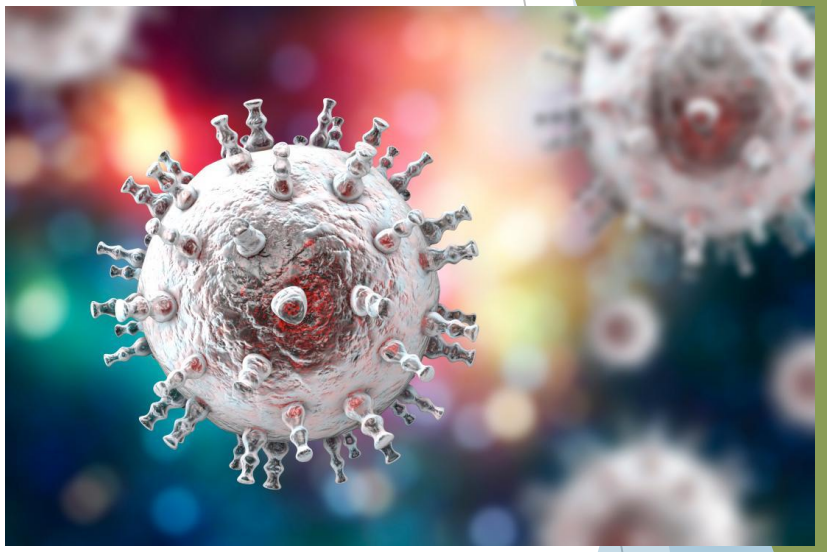
Thomas F Schulz and Ethel Cesarman

"Kaposi sarcoma is an unusual tumour. Several of its features suggest that unlike other cancers, it may not result from a transformation event that results in autonomously growing tumour cells, but represents the combined effects of a virus with angiogenic properties and local or systemic inflammation"

From: Kaposi sarcoma-associated Herpesvirus: mechanisms of oncogenesis. Curr Opin Virol 2015

Horenstein et al, J Cutan Path 2008; Magri et al, J Med Virol 2009; Maskew et al Infec Dis and Cancer 2011; Malope-Kgokong et al Infec Dis and Cancer 2010; Isaacs et al J Med Virol 2016

KSHV / HHV-8



- Virus is latent in majority of infected cells
  - Viral genome maintained in extrachromosomal episome within the nucleus
  - evades immune detection
- Spontaneously enters lytic cycle
  - Expression of viral replicative and structural genes
  - Cell lysis and release of progeny virions capable of infecting more cells
- KSHV gene products
  - Latent genes promote cell proliferation eg LANA1 and 2
  - Lytic genes provide paracrine signals to adjacent latently-infected cells eg **KSHV G-protein coupled receptor**
- HIV transactivating protein upregulates HIV gene expression resulting in cytokine, growth factor and adhesion molecule production and angiogenesis

Horenstein et al, J Cut Path 2008; Wood and Fellar, Can Cell Int,2008

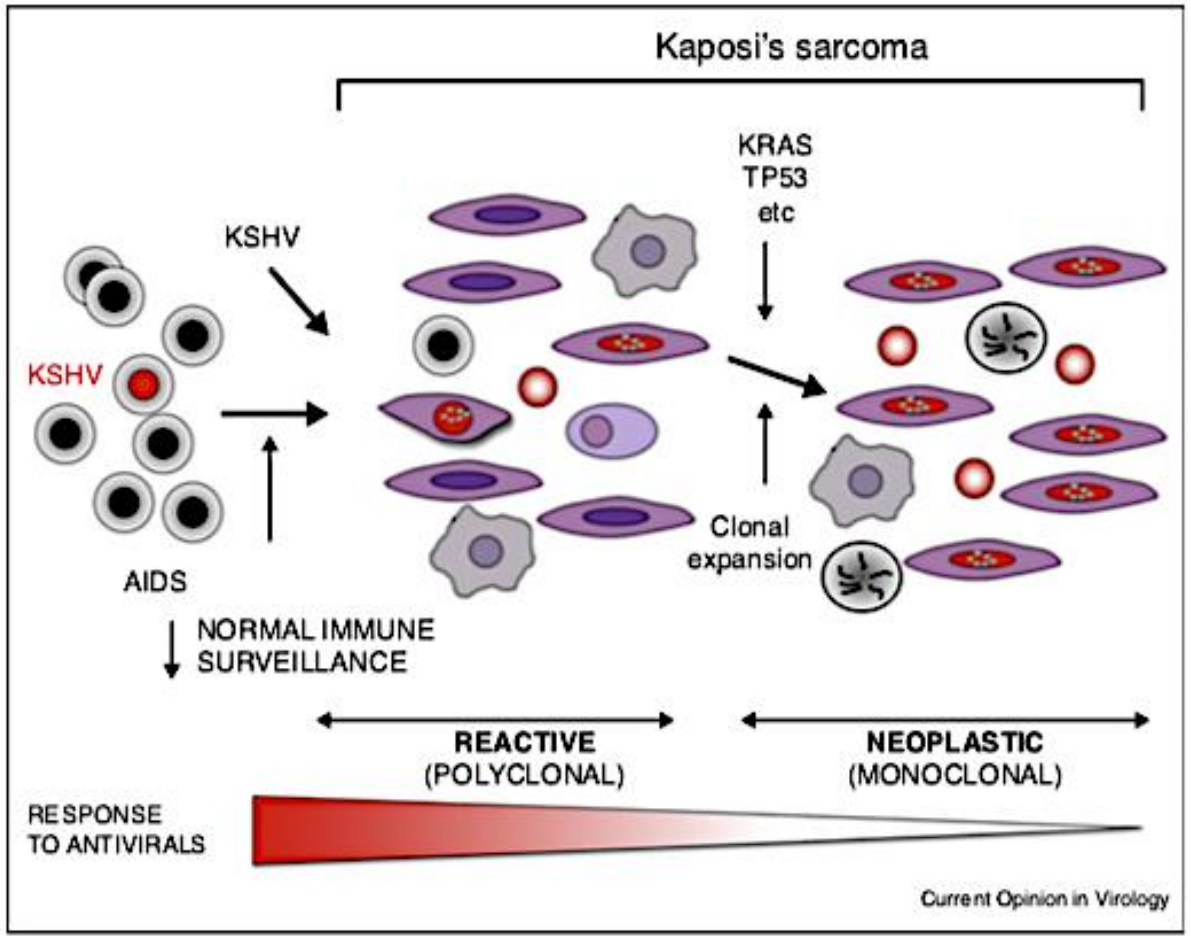
Available online at www.sciencedirect.com

ScienceDirect

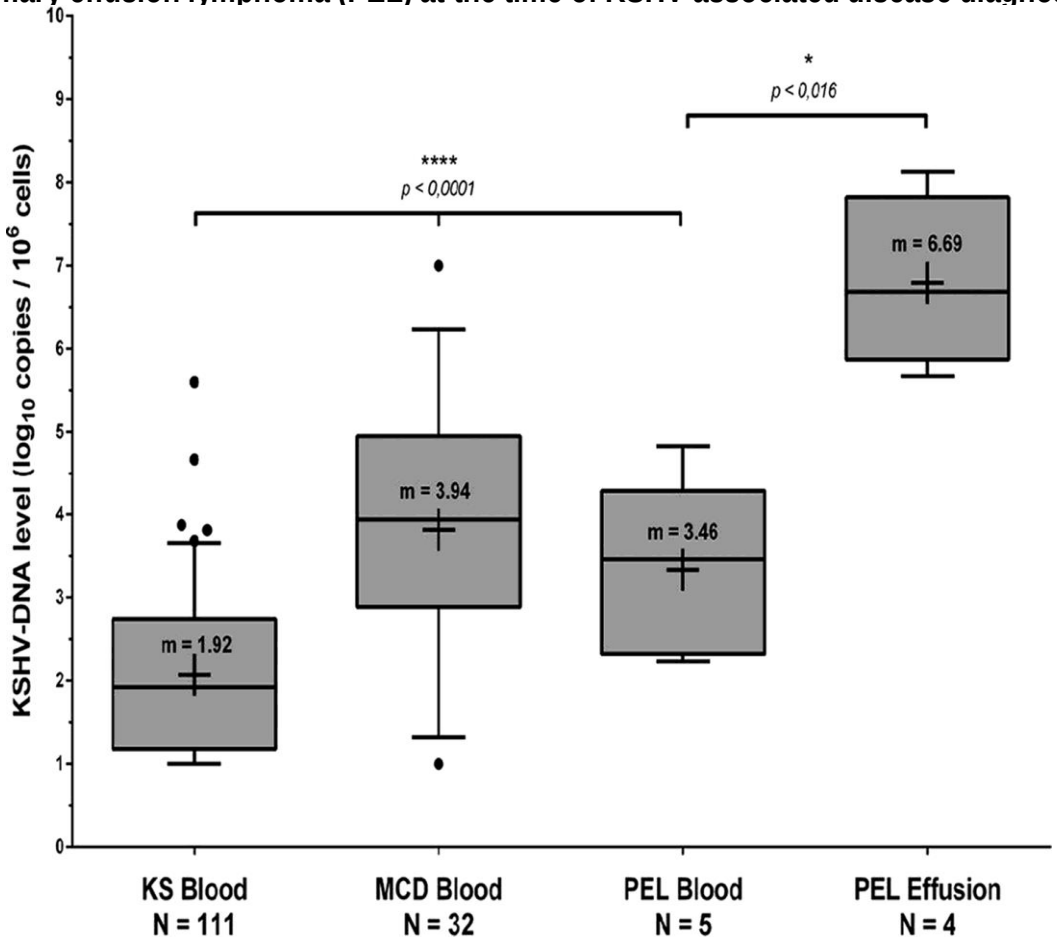
Current Opinion in Virology

Kaposi Sarcoma-associated Herpesvirus: mechanisms of oncogenesis

Thomas F Schulz[1,2] and Ethel Cesarman[3]



Levels of Kaposi's sarcoma-associated herpesvirus (KSHV) in whole-blood and effusion fluid samples from patients with Kaposi's sarcoma (KS), Castleman multicentric disease (MCD), and primary effusion lymphoma (PEL) at the time of KSHV-associated disease diagnosis.



Aude Jary et al. J. Clin. Microbiol. 2018; doi:10.1128/JCM.00569-18

- Broccolo et al (J Clin Vir 2016): plasma HHV8 viral load correlated with response to treatment
- Jary et al(J Clin Micro 2018): KSHV viral load useful for diagnosis and monitoring of KSHV-associated diseases

Cancer Epidemiology 56 (2018) 133–139

Contents lists available at ScienceDirect

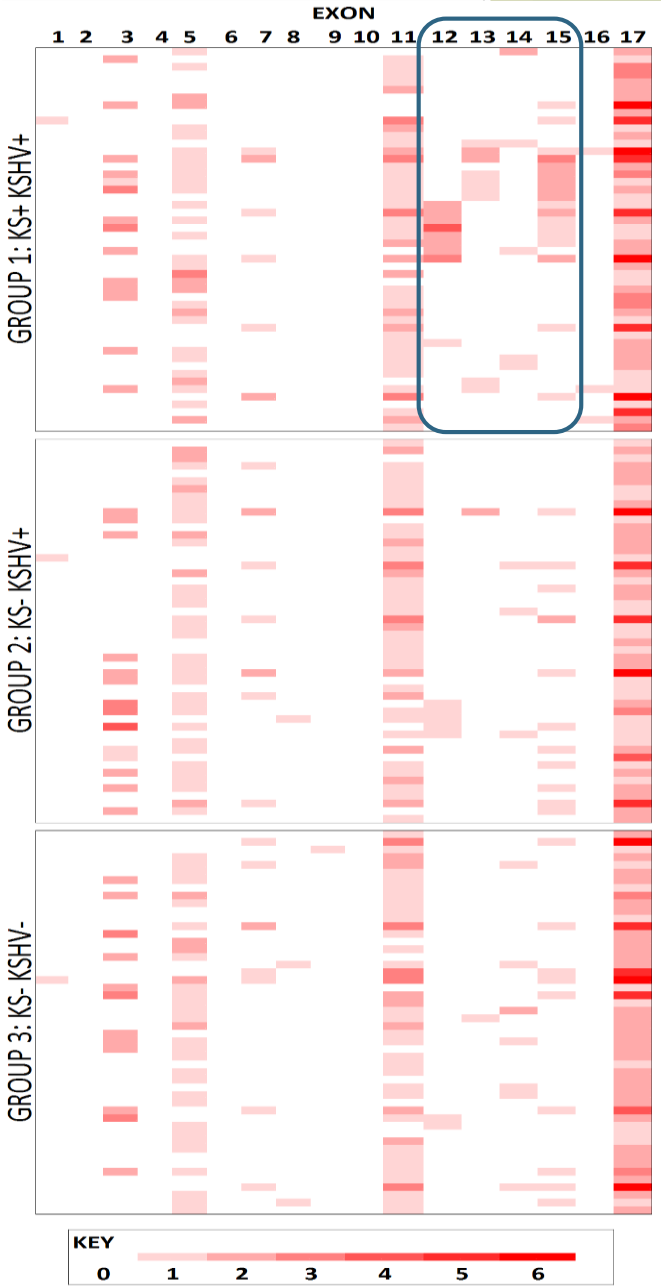
Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

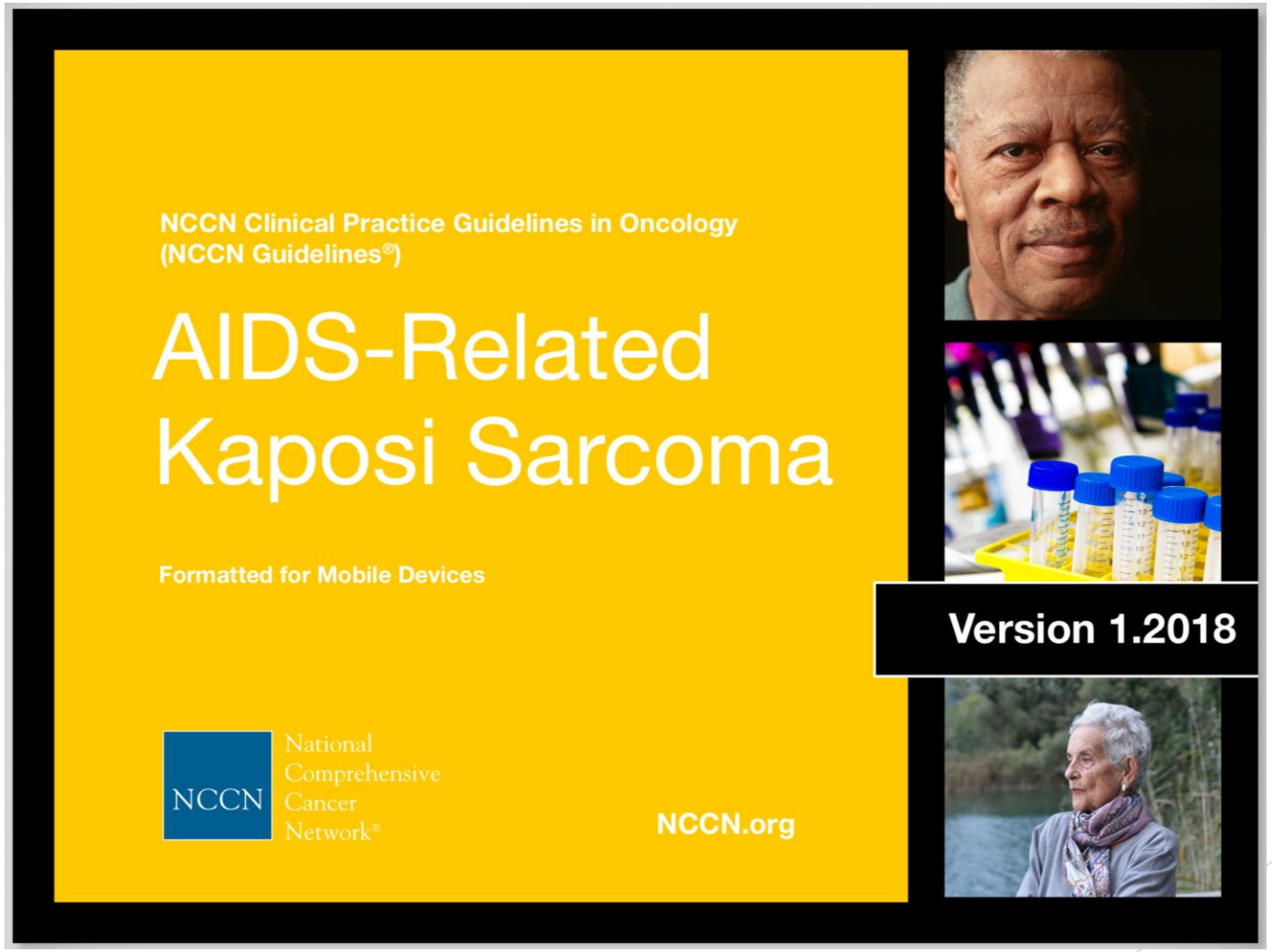
EPHA2 sequence variants are associated with susceptibility to Kaposi's sarcoma-associated herpesvirus infection and Kaposi's sarcoma prevalence in HIV-infected patients

Melissa J. Blumenthal[a,b], Charlotte Schutz[b,c], Graeme Meintjes[b,c], Zainab Mohamed[d], Marc Mendelson[e], Jon M. Ambler[f], Denise Whitby[g], Romel D. Mackelprang[h], Sinead Carse[a,b], Arieh A. Katz[a,b], Georgia Schäfer[a,b,*]

- Is there a genetic susceptibility to develop KS?
- EPHA2: Eph receptor A2 protein tyrosine Kinase receptor
  - host receptor for entry of KSHV into endothelial cells
  - Implicated in oncogenesis in various cancers
- 3 HIV+ cohorts: KS+KSHV+; KS-KSHV+ and KS-KSHV-
  - Extract DNA from peripheral blood and sequence the EPHA2 coding region
  - 31.6% of KS negative cohort was KSHV positive
- Variation across EPHA2 coding region associated with KS particularly in protein tyrosine kinase domain (exons 12-15)



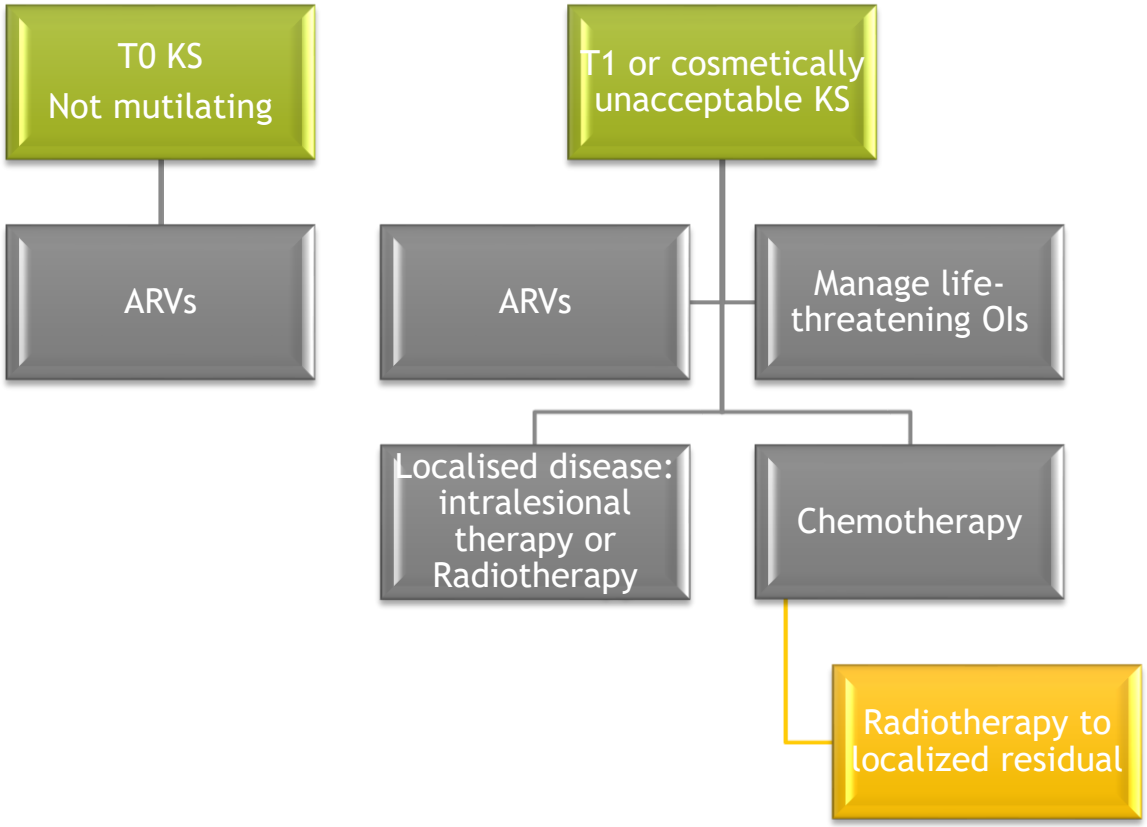
Treatment of Kaposi Sarcoma



AIDS Clinical Trials Group Staging

	Good risk (all of the following)	**Poor risk** (any of the following)
Tumour (T)	T0 skin and/or lymph nodes and/or minimal oral disease	T1 oedema or ulceration extensive oral KS visceral KS (non- nodal)
~~**Immune system (I)**~~	~~I0~~ ~~CD4 ≥ 200 (150)~~	~~I1~~ ~~CD4 < 200 (150)~~
Systemic illness (S)	S0 no opportunistic infections or thrush no B-symptoms KPS ≥ 70	S1 opportunistic infections, B-symptoms or other HIV-related illnesses KPS < 70

Basic Treatment Algorithm for KS



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
AIDS-Related Kaposi Sarcoma

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PRINCIPLES AND GOALS OF THERAPY

PRINCIPLES OF THERAPY:

- Individual KS lesions may be distinct clones that arise due to the common risk factors of immunosuppression and persistent HHV-8 infection as opposed to metastases. Treatment of existing disease therefore may not prevent occurrence of future lesions.

- Reconstitution of immune function, maintenance of viral suppression, and avoidance of additional immunosuppression are critical to prevention of additional KS lesions and maintenance of response to therapy. For AIDS-related KS, it is important to work with an HIV specialist to optimize suppression of HIV and reconstitution of immune function with ART. Important examples of iatrogenic immunosuppression, which may promote KS, include not only systemic but local glucocorticoids (ie, inhaled, topical, intra-articular). Note that KS may flare in a remote location from the site of local glucocorticoids. Patients requiring rituximab for treatment of NHL with coexisting KS or multicentric Castleman's disease may develop flares of KS or incident KS. This may be mitigated by use of concurrent chemotherapy active against both KS and disease for which rituximab is prescribed (ie, doxorubicin).

- Persons with AIDS-related KS, especially those with advanced immunosuppression, are at increased risk of opportunistic infections (OIs), marrow suppression with neutropenic fever, or thrombocytopenic bleeding and should be monitored closely. It is important to collaborate with an HIV specialist to ensure adequate OI prophylaxis appropriate to CD4+ T-cell count (which may temporarily decrease with cytotoxic chemotherapy). Growth factor support may be needed to facilitate systemic therapy.

- Lymphedema and soft tissue infections: KS is often complicated by lymphedema with increased risk of cellulitis and deep tissue infections in affected limbs. Risk of severe lymphedema and delayed wound healing may be increased after radiation. Refer to a lymphedema specialist. In the setting of advanced cutaneous disease, radiation should be reserved for circumstances when systemic therapy is not feasible with the goal of palliation or short-term disease management until systemic therapy may be delivered. Note that treatment responses may be delayed in the context of significant lymphedema.

GOALS OF THERAPY:

- Patients with limited cutaneous disease that is asymptomatic and cosmetically acceptable may be observed while continuing ART with optimization of immune function and HIV viral suppression as above. Remissions or stable disease may occur with ART and optimization of immune function and HIV viral suppression alone.

- Patients with symptomatic or cosmetically unacceptable disease should use the most minimally invasive and least toxic therapy to control disease. A limited number of cycles of systemic therapy (eg, 3–6) may be sufficient for those initiating or re-initiating ART.

- Patients with advanced symptomatic cutaneous, visceral, nodal, or oral disease should be treated with systemic therapy with the goal of reducing or reversing symptoms, lymphedema, or threat to organ function. Complete remissions are rare.
  - Treatment is typically continued until unacceptable toxicity or plateau in response; maintenance therapy beyond 2 cycles of systemic therapy after determination of plateau is not recommended. If response is then clinically acceptable, patients may be observed on ART alone. Otherwise, alternative therapy should be initiated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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AIDS-Related Kaposi Sarcoma

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SYSTEMIC THERAPY[a]

First-line systemic therapy options

- Liposomal doxorubicin[1,b] (preferred)
  - 20 mg/m² IV every 3 weeks
- Paclitaxel[2]
  - 100 mg/m² IV every 2 weeks (premedication with dexamethasone 10 mg at time of administration is acceptable for prevention of hypersensitivity reaction)

Relapsed/refractory systemic therapy[c] options (advanced cutaneous, oral, visceral, or nodal disease)

If tolerated and durable response (≥3 months) to first-line systemic therapy → Repeat of first-line systemic therapy or Alternate first-line systemic therapy → Progression

If no response to first-line systemic therapy → Alternate first-line systemic therapy[d] → Progression

- Subsequent systemic therapy options for relapsed/refractory therapy
  - Preferred regimen:
    - ◊ Pomalidomide[3]
      - – 5 mg/d orally for 21 days of each 28-day cycle
  - Other regimens (in alphabetical order):
    - ◊ Bevacizumab[4]
      - – 15 mg/kg IV on days 1 and 8 and then every 3 weeks
    - ◊ Etoposide[5]
      - – 50 mg/d orally for 7 days of each 21-day cycle
    - ◊ Gemcitabine[6]
      - – 1000 mg IV every 2 weeks
    - ◊ Imatinib[7]
      - – 400 mg/d orally
    - ◊ Interferon alfa-2b[8]
      - – 1 million International Units SC daily
    - ◊ Nab-paclitaxel[9]
      - – 100 mg IV days 1, 8, and 15 of each 28-day cycle
    - ◊ Thalidomide[10]
      - – 200 mg/d orally (starting dose, titrated to effect and tolerability)
    - ◊ Vinorelbine[11]
      - – 30 mg/m² every 2 weeks

[a]See references for regimens on KS-D 2 of 2.
[b]Due to risk of cardiotoxicity, perform echocardiogram prior to initial and repeat course of liposomal doxorubicin and limit lifetime dose to 400–450 mg/m².
[c]Consider repeating any prior systemic therapy that was tolerated and resulted in a durable response.
[d]If both first-line options have already been given, the patient should proceed to the subsequent systemic therapy options.

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Table 4 Combination Chemotherapy for treatment of AIDS–KS

Reference	Regimen	Patients (N)	Response rate (%)
Northfelt[19]	Doxorubicin 20 mg/m^2 Bleomycin 10 mg/m^2 Vincristine 1 mg every 2 weeks	125	25
Stewart[a 53]	Bleomycin 15 UI/m^2 Vincristine 2 mg every 3 weeks	120	23
Gill[21]	Doxorubicin 10 mg/m^2 Bleomycin 15 UI Vincristine 1 mg every 2 weeks	111	28
Gill[70]	Doxorubicin 20 mg/m^2 Bleomycin 10 mg/m^2 Vincristine 1.4 mg/m^2 every 2 weeks	61	88
Laubestein[71]	Doxorubicin 40 mg/m^2 Bleomycin 15 UI/m^2 Vinblastine 6 mg/m^2 every 28 days	31	84

None of the studies cited above was controlled for the use of HAART in addition to chemotherapy.
[a] Limited number of cycles (six).

Table 2 Liposomal anthracyclines for the treatment of AIDS–KS

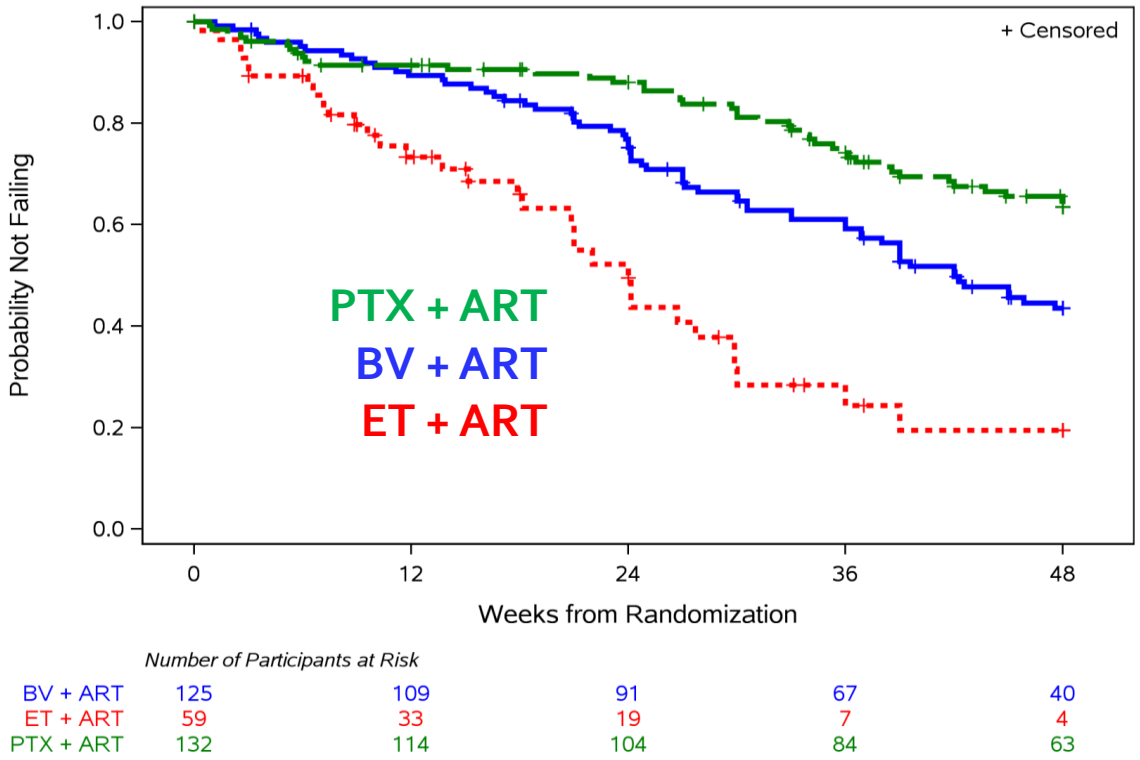
Reference	Regimen	Patients (N)	Response rate (%)
Martín-Carbonero[a 58]	Liposomal doxorubicin 20 mg/m^2 every 3 weeks	13	76
Tulpule[c 60]	Liposomal daunorubicin 60 mg/m^2 every 2 weeks	53	59
Northfelt[19]	Liposomal doxorubicin 20 mg/m^2 every 2 weeks	133	46
Stewart[b 53]	Liposomal doxorubicin 20 mg/m^2 every 3 weeks	121	59
Girard[62]	Liposomal daunorubicin 40 mg/m^2 every 2 weeks	30	73
Gill[21]	Liposomal daunorubicin 40 mg/m^2 every 2 weeks	116	25

[a] Only in this study all patients had used HAART in addition to chemotherapy.
[b] Limited number of cycles (six).
[c] Complete or partial resolution of pulmonary symptom (shortness of breath) in patients with pulmonary AIDS–KS.

A5263/AMC-066 A Randomized Comparison of Three Chemotherapy Regimens as an Adjunct to Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource-Limited Settings

Progression-free survival by treatment group

(numbers of participants as of the time of the last DSMB review prior to arm closure)



Number of Participants at Risk

BV + ART	125	109	91	67	40
ET + ART	59	33	19	7	4
PTX + ART	132	114	104	84	63

63%

43%

19%

-20% PFS difference

- CI for difference excludes zero difference
- Prediction showed low chance of showing NI and current result unlikely to change
- Ad-hoc summary showed better response with PTX as second-line therapy than BV

-39.4% PFS difference

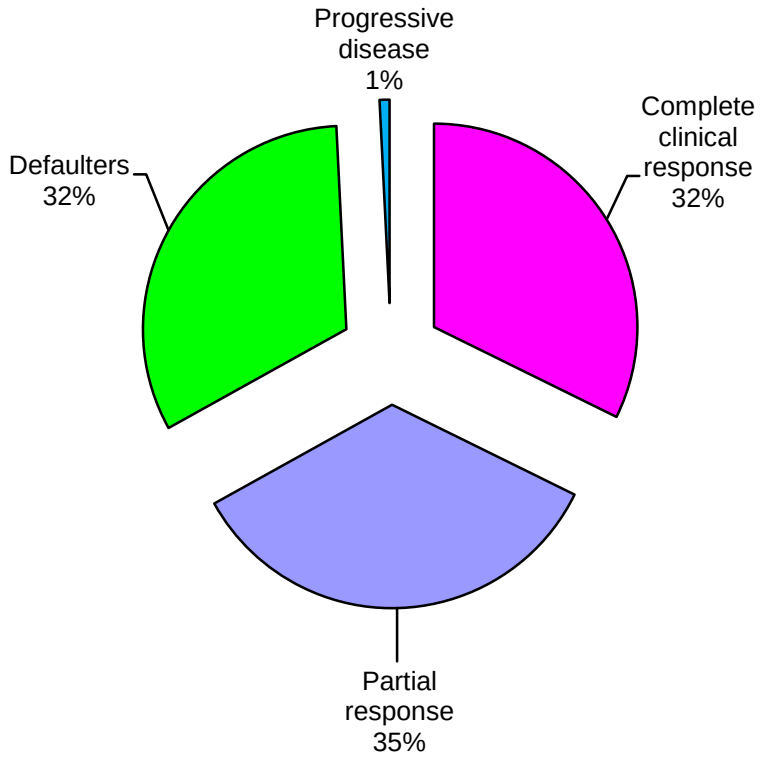
- More than -25% team threshold
- Consistent trend over time that ET worse than PTX
- CI for difference almost excludes zero difference
- Prediction showed low chance of showing NI

Margaret Borok and Susan Krown for AMC: abstract presented at the 22nd International AIDS Conference July 2018

Review of patients with Epidemic Kaposi Sarcoma seen over a 2-year period (2013-2014) at Groote Schuur Hospital.

Njiraini PN, Mohamed Z (MMed unpublished data)

- 166 cases identified
  - 38 excluded from analysis due to no chemo or concomitant MCD
  - 58% male
  - Median age 36.5 yrs (18-63)
  - 87.5% Black African (9.4% mixed race)
  - 10.2% not South African
  - 96.9% on ARVs
- 73% clinical diagnosis (no histology)
- Median CD4 164 (1-700)
- Concurrent TB: 31.3%
  - (20.3% history of TB)



67% Overall response to chemo (BV)
Median cycle of response = 7

SURVEILLANCE

- For patients not requiring active therapy and with no signs of progression
  - Every 3 months for year 1, then every 4-6 months for year 2, then every 6-12 months thereafter
    - ◊ History and physical exam
      - – including history of additional immunosuppression such as transplant/glucocorticoids
      - – including complete skin and oral exams, and documentation of edema
    - ◊ CBC, differential, comprehensive metabolic panel, T-cell subsets (CD4+ T-cell count), and HIV viral load
    - ◊ Assess ART compliance

- Photography of oral, conjunctival, and cutaneous lesions (with reference unit of measure in picture) for documentation of extent of disease if change in disease is noted

- If signs and symptoms concerning for visceral involvement or prior to new therapy if progression/refractory disease
  - Stool hemoccult
  - Chest x-ray or chest CT with contrast
  - EGD/colonoscopy
  - Bronchoscopy

- As KSHV is not eradicated with treatment of KS, the risk for future KS persists even after complete remission. Optimization and monitoring of HIV control and immune function is important to minimize this risk. This risk depends on immune function and generally decreases with immune reconstitution. However, KS can persist, relapse, or present even in the setting of normal values of T-cell subsets. Less frequent (every 6–12 mo) oncology monitoring may be appropriate for selected patients with undetectable HIV viral loads, normal T-cell subsets, and stable KS for 2 or more years as long as the patient has regular follow-up with an HIV provider.

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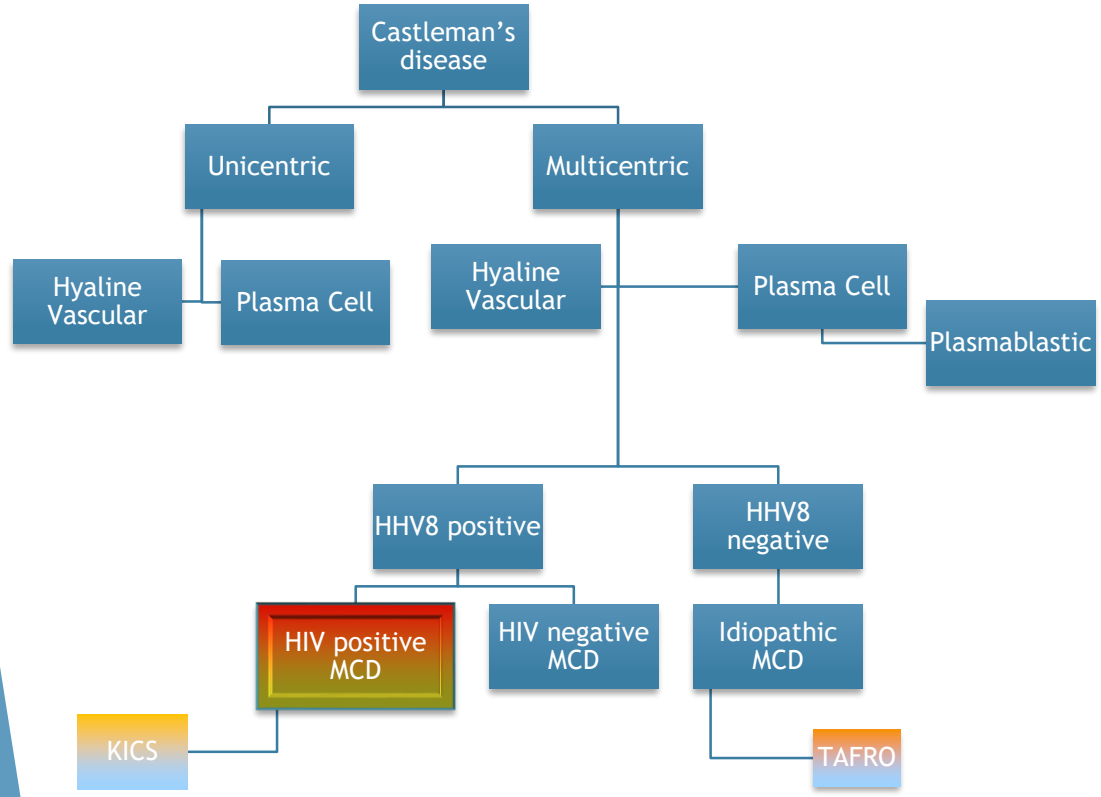
Radiotherapy

- For localised disease
- Longer course fractionated RT better response and longer control than single fraction 8Gy
- 40Gy 83% CR vs 8Gy 50% CR
- But can repeat single fraction
- Side-effects: skin reaction, lymphoedema, mucositis

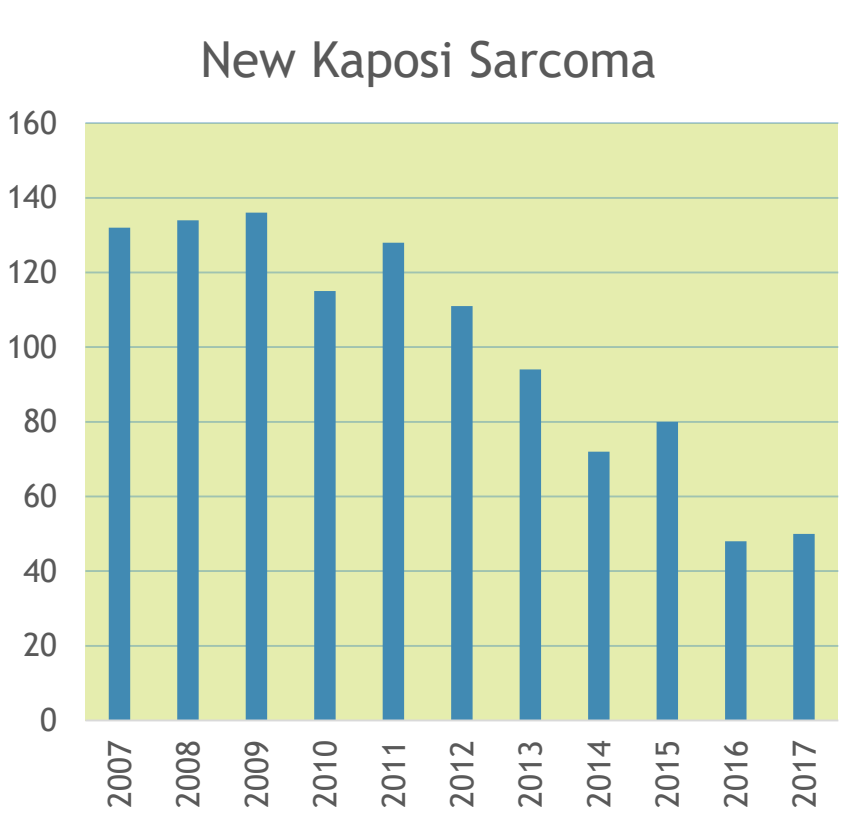
HIV-associated Lymphoproliferative Disorders

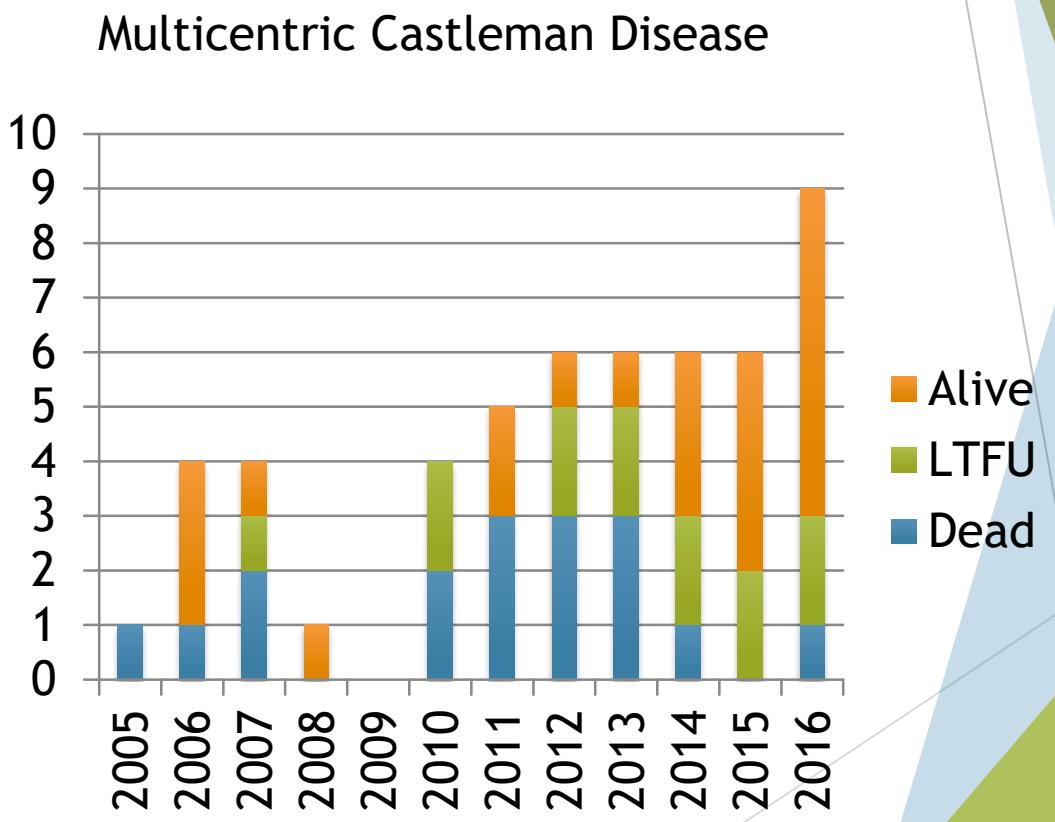
Multicentric Castleman's disease



- Lymphoproliferative disorder associated with HHV8
- "Waxing and waning" acute febrile illness characterized by lymphadenopathy, splenomegaly and anaemia
- Excess IL6 production results in constitutional symptoms and biochemical and haematological abnormalities
- Hyaline vascular, plasma cell and mixed variants
- CD20+ve, HHV8

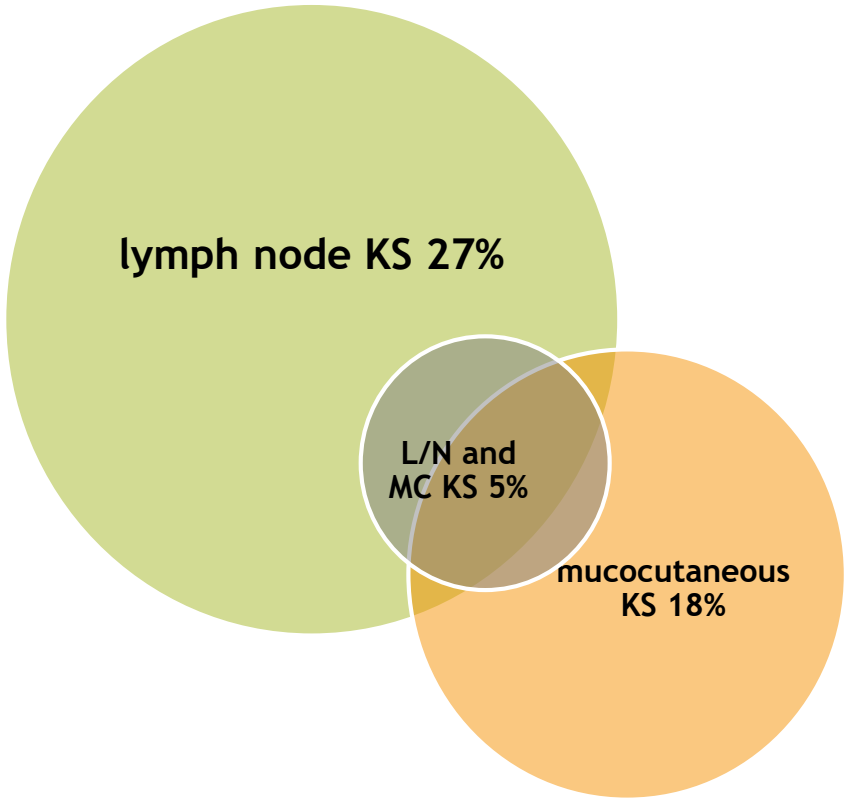
Changing trends of KS and MCD at GSH Oncology



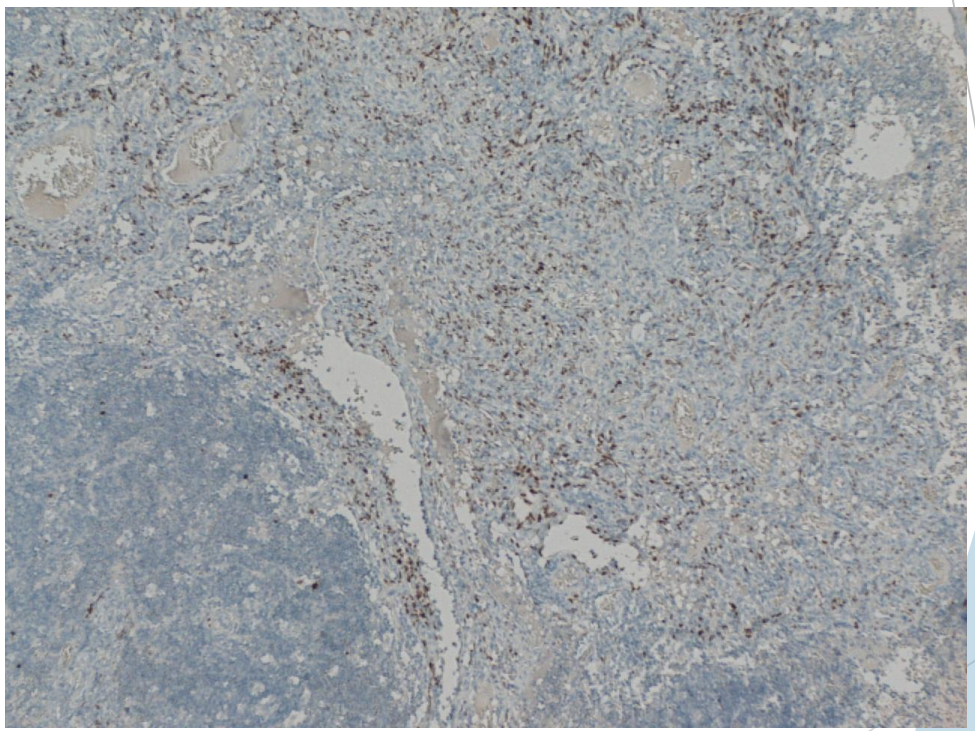


GSH data

Simultaneous KS + MCD



HHV8 stain



Slide provided courtesy of Dr D Chetty NHLS GSH

Multicentric Castleman's disease

- Gerard et al (Blood 2012):
  - 113 patients (1996-2011), 42 % had Ritux
  - Rituximab associated with 11 fold decrease in risk of developing NHL
- Bower et al (JCO 2011):
  - 61 patients since 2000, 49 received Rituximab +/- Etoposide
  - OS 90% at 5 years vs 42% without Rituximab
- Pria et al (Blood 2017):
  - 84 patients treated with Rituximab-based therapy
  - 5 year relapse-free survival 82%
  - Median time to relapse 30 months

- Treatment in resource-limited setting
  - ARVs
  - Supportive therapy
  - 6-8 cycles CHOP
  - Severe cytokine-induced cytopaenias: weekly Etoposide 100mg/m^2 until counts improve. Follow with CHOP
  - Rituximab not available for MCD in state sector
- NCCN guidelines
  - Active disease but no organ failure: Rituximab +/- liposomal doxorubicin +/- prednisone OR Zidovudine + ganciclovir/valganciclovir
  - Combination therapy +/- Rituximab (CHOP, CVAD, CVP, lipos doxo)

Lurain et al (Hematol Oncol Clin N Am 2018): Treatment of Kaposi Sarcoma Herpesvirus-Associated Multicentric Castleman Disease

Table 1
Treatments for Kaposi sarcoma herpesvirus–associated multicentric Castleman disease

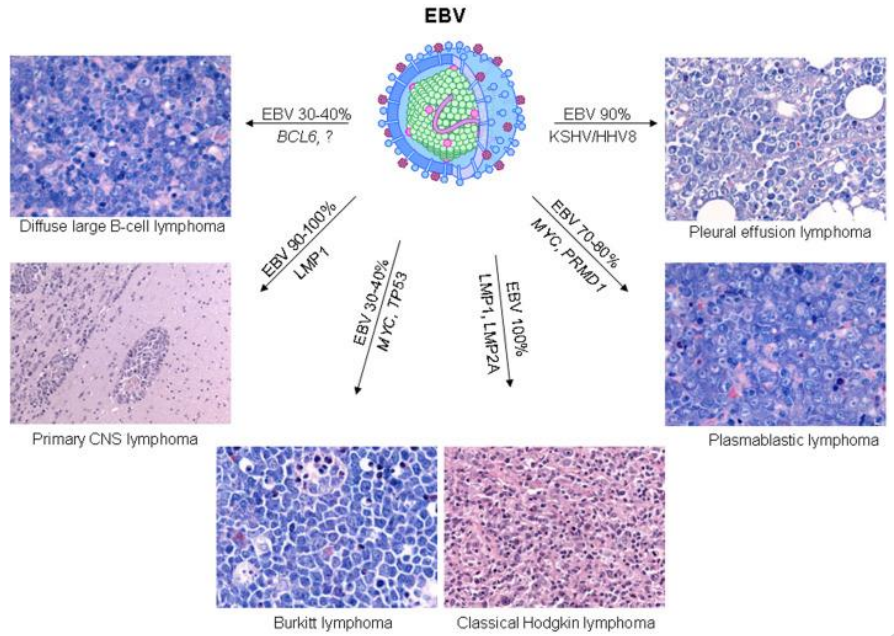
Therapy	Dose	Mechanism of Action	When to Use
Rituximab	375 mg/m^2 weekly ×4 wk	Depletes IL-6–secreting CD20$^+$ B cells	Mild symptomatic disease
Rituximab + liposomal doxorubicin	Rituximab 375 mg/m^2 + liposomal doxorubicin 20 mg/m^2 every 3 wk until response plateau	Addition of cytotoxic chemotherapy to treat CD20$^-$ MCD plasmablasts and KS spindle cells	Aggressive disease and/or concurrent KS
Rituximab + etoposide	Rituximab 375 mg/m^2 + etoposide 100 mg/m^2 IV weekly ×4 wk	Addition of cytotoxic chemotherapy to treat CD20$^-$ MCD plasmablasts	Aggressive disease
AZT + valganciclovir	Zidovidine 600 mg PO every 6 h + valganciclovir 900 mg PO every 12 h, d 1–7 of 21-d cycle	Virus-activated cytotoxic therapy	Mild disease with concurrent KS and/or patients allergic to rituximab

HIV-associated lymphomas

- AIDS-defining lymphomas are defined as aggressive B-cell non-Hodgkin's lymphomas arising in patients who have HIV
  - Burkitt's
  - Diffuse Large B-cell
  - Primary CNS
  - Plasmablastic
  - Primary Effusion Lymphoma
- HIV also increases the risk of classic Hodgkin lymphoma but this is not "AIDS-defining"

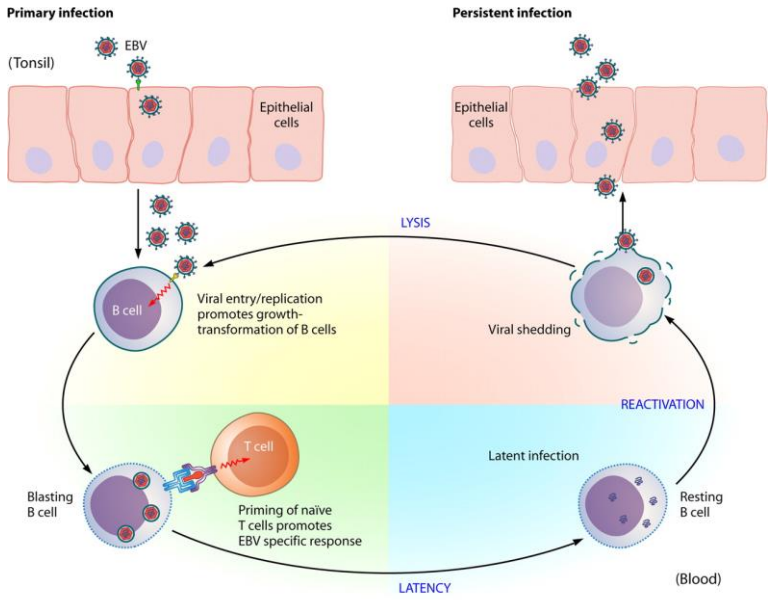
EBV

- Non EBV-related lymphoproliferative disorders
  - KSHV-related Multicentric Castleman's disease
  - Primary Effusion lymphoma



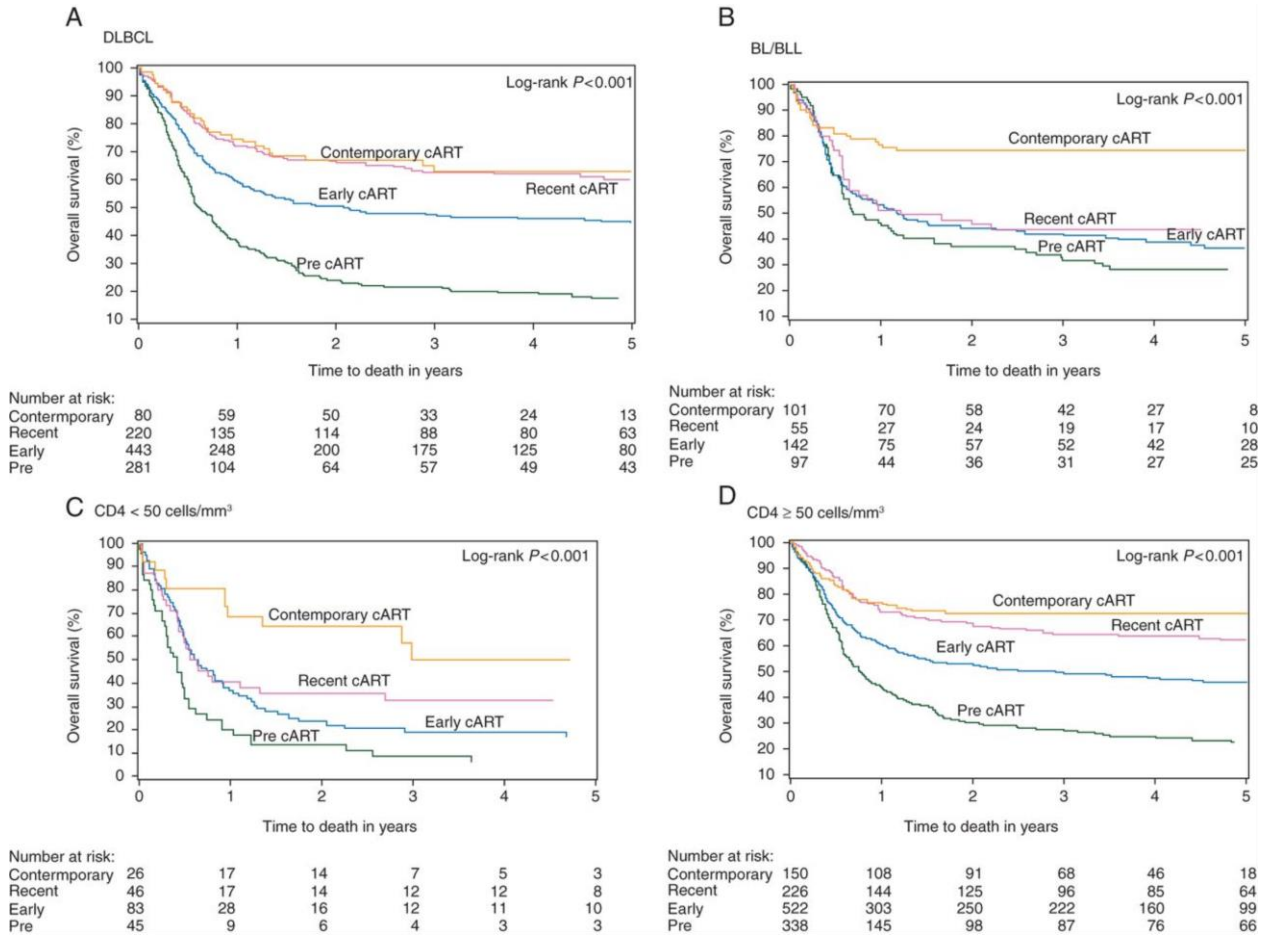
EBV-associated Lymphomas

- EBV-associated lymphomas are heterogeneous in terms of pathology, pathogenic pathways and cellular derivation
- Pathogenesis
  - Impaired immune surveillance, loss of EBV-specific T-cell response
  - Chronic B-cell activation
  - Viral cooperation
  - Genetic alterations
- High incidence of lymphomas in HIV persist despite immune reconstitution due to ART



Carbone et al, Curr opin Hiv AIDS 2017; Gloghini et al, Sem Cancer Biol 2013

- Systematic review of 19 studies
- A significant improvement in CR rate and survival seen with more effective HIV therapy



SK Barta et al: Changes in the influence of lymphoma- and HIV-specific factors on outcomes in AIDS-related non-Hodgkin lymphoma

Ann Oncol. 2015;26(5):958-966. doi:10.1093/annonc/mdv036

Workup

- Excision biopsy with immunophenotyping to establish diagnosis

- B-symptoms, comorbidities, meds, ARVs
- Physical exam, PS

- FBC&diff, CUE, LDH, LFT, uric acid, CMP
- Hep B, CD4, Viral load

- PET-CT or CT neck, chest, pelvis
- BMAT
- Lumbar puncture in selected cases
- ECHO or ERNA

Diffuse Large B-cell lymphoma

- Immunohistochemistry:
  - Pan-B markers +ve (CD19, CD20, CD22, CD79a)
  - 30-60% CD10+
  - 60-90% BCL6+
  - 35-65% IRF4/MUM1+
  - Ki67>40%
  - 20-30% BCL2+
- Cell of origin (COO): germinal centre B (GCB) vs activated B-cell (ABC)

- Treatment: R-EPOCH vs R-CHOP

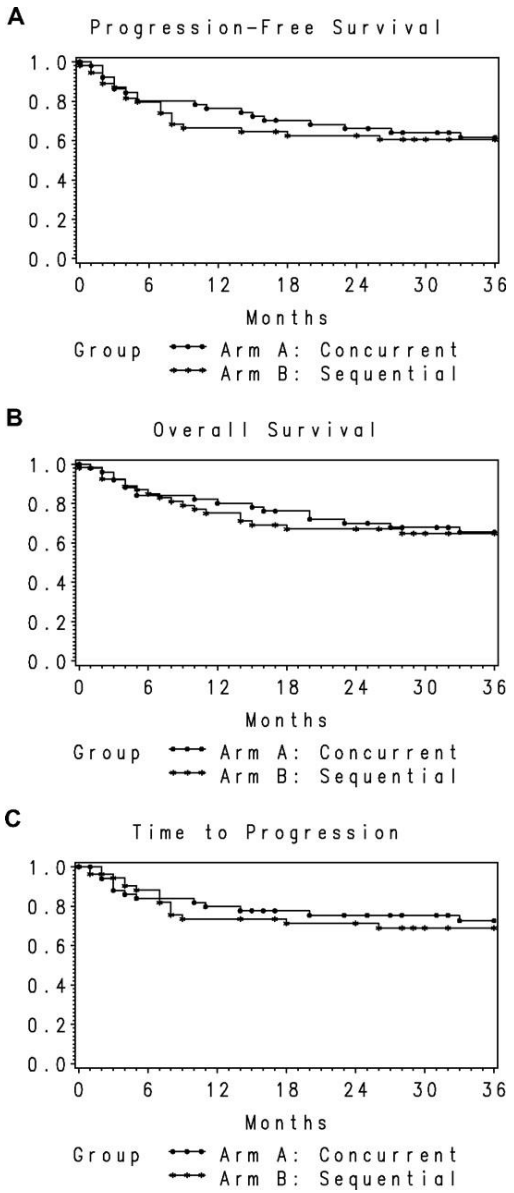
Treatment of HIV-related DLBCL

- Spina and Tirelli (Cancer in AIDs 2005): noted that Rituximab improved outcome in HIV-related lymphomas but should be used cautiously in patients with CD4 count <50

- Sparano et al (Blood 2010): concurrent vs sequential Rituximab plus infusional EPOCH
  - 106 patients enrolled, both arms experimental
  - 2-year PFS 66% for concurrent vs 63% for sequential Rituximab

PFS, overall survival, and TTP for the study population.

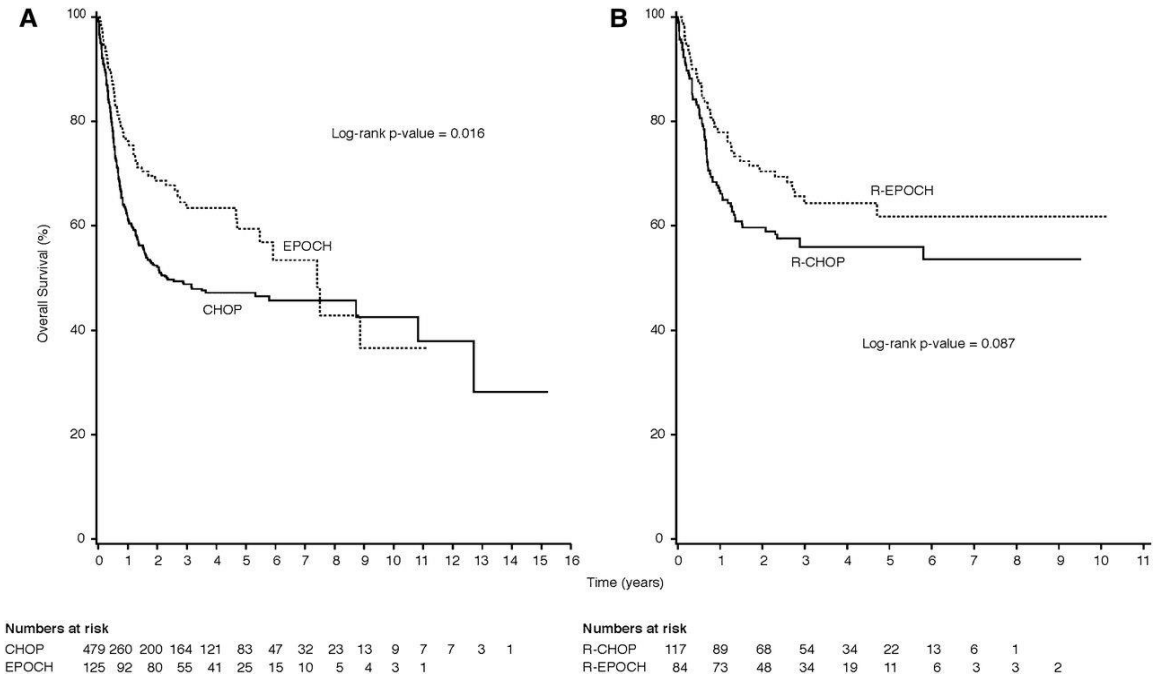
- Sparano et al (Blood 2010): concurrent Rituximab and infusional EPOCH is effective for HIV-associated lymphoma
  - Patients who had not been established on ARVs deferred treatment until completion of R-EPOCH
  - Rituximab given with each cycle or weeklyX6 after 6 cycles of EPOCH
  - 96 hour continuous infusion of Etoposide, Doxorubicin and Vincristine and 5 days oral Prednisone plus bolus cyclophosphamide on day 5
  - Filgrastim from day 6 until neutrophil recovery
  - Prophylactic Bactrim, fluconazole, ciproflox
  - All patients need a port
  - AEs: 43% grade 3-4 neutropenia, 16% febrile neutropenia and 27% infection in concurrent arm



Joseph A. Sparano et al. Blood 2010;115:3008-3016

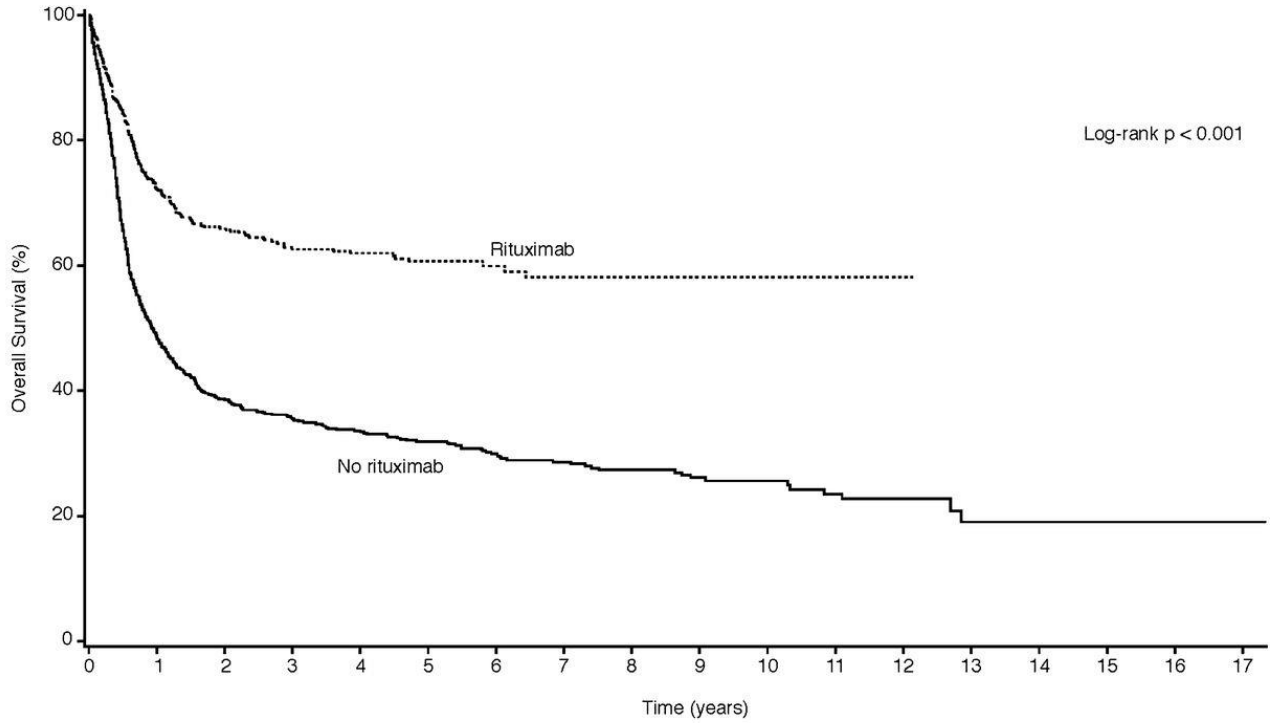
Kaplan-Meier plots comparing OS for HIV-positive patients with DLBCL treated with EPOCH vs CHOP and R-EPOCH vs R-CHOP.

- Barta 2013 (Blood 2013): pooled analysis of 1546 patients from 19 trials
  - Rituximab associated with higher CR rate
  - Infusional EPOCH resulted in better OS in DLBCL (HR 0.33, 95% CI 0.11-0.85 p=0.31)
  - R-EPOCH better OS than R-CHOP but borderline statistically significant
  - Concurrent ART associated with better CR rates



Stefan K. Barta et al. Blood 2013;122:3251-3262

Kaplan-Meier plots comparing the OS for HIV-positive patients with DLBCL treated with rituximab-containing regimens vs non–rituximab-containing regimens.

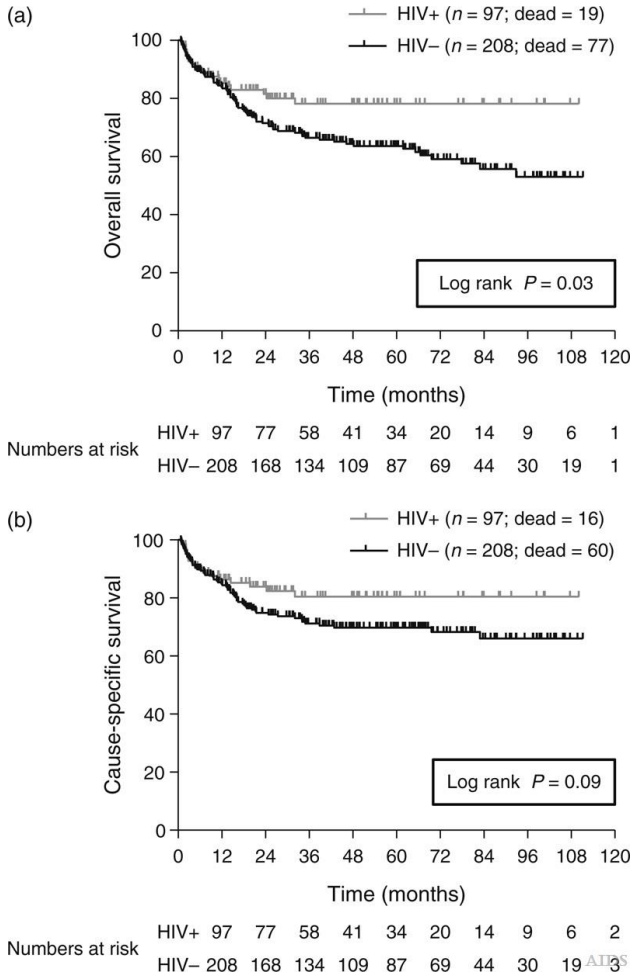


Numbers at risk

No rituximab	954	446	340	296	235	177	119	97	75	55	40	30	17	9	6	4	2	1
Rituximab	542	353	292	222	171	101	73	52	35	23	1 0	4	2	1				

Stefan K. Barta et al. Blood 2013;122:3251-3262

- Coutinho et al (AIDS 2014): Outcome with RCHOP in ART era
  - 97 HIV+ compared to 208 HIV-ve patients
  - HIV+ patients with DLBCL had more B-symptoms and extranodal disease than HIV-ve
  - HIV+ patients had significantly longer 5yr DFS: 94% in HIV+ vs 77% in HIV-ve (p=0.03)
  - Lymphoma-related factors (IPI) and complete response rate were predictive of survival



Kaplan–Meyer curves for overall survival and cause-specific survival for patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP according to HIV status. (a) HIV-positive patients (grey line) with DLBCL treated with R-CHOP achieved significantly better overall survival compared with HIV-negative patients (black line;P=0.03); (b) There are no significant differences in cause-specific survival according to HIV status (P=0.09).

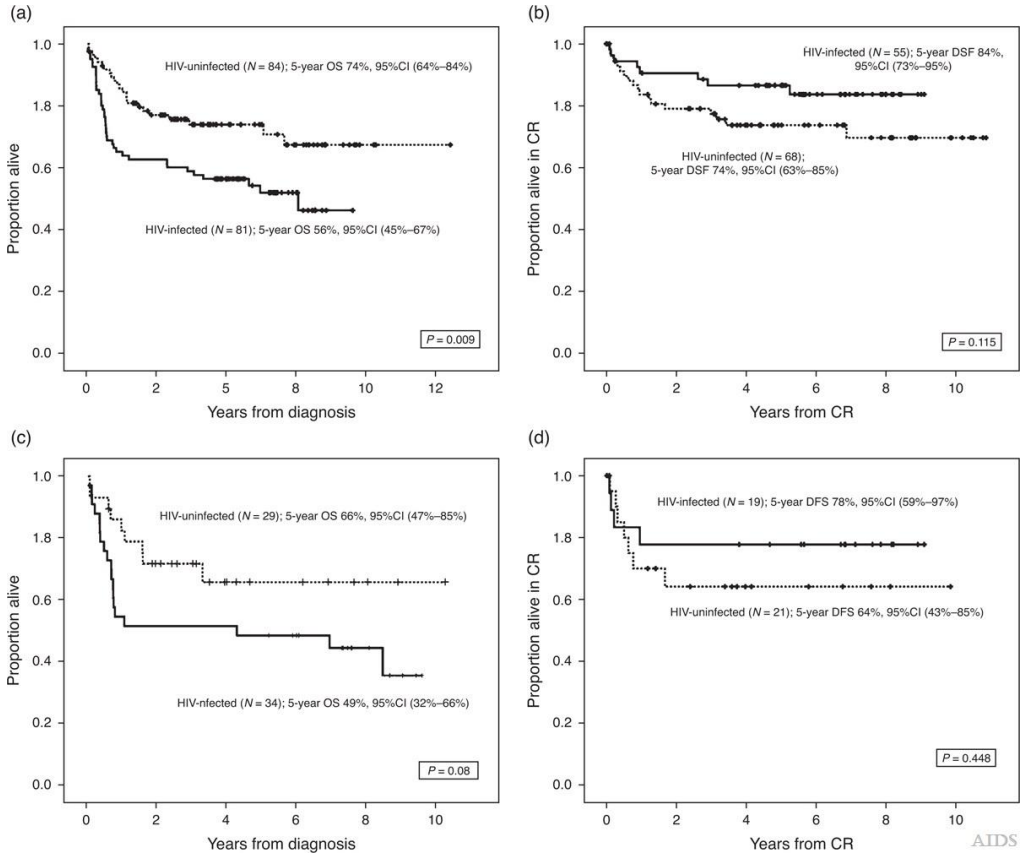
HIV status does not impair the outcome of patients diagnosed with diffuse large B-cell lymphoma treated with R-CHOP in the cART era

Coutinho, Rita; Pria, Alessia D.; Gandhi, Shreyans; Bailey, Katharine; Fields, Paul; Cwynarski, Kate; Wilson, Andrew; Papanastasopoulos, Panagiotis; Tenant-Flowers, Melinda; Webb, Andrew; Burns, Fiona; Marcus, Robert E.; Orkin, Chloe; Montoto, Silvia; Bower, Mark

AIDS28(5):689-697, March 13th, 2014.

doi: 10.1097/QAD.0000000000000133

- Baptista et al (AIDS 2015): Clinical features and outcome with RCHOP in ART era
  - 81 HIV+ compared to 84 HIV-ve patients
  - HIV+ patients with DLBCL had worse PS, more B-symptoms and higher stage than HIV-ve
  - Prior AIDs-defining illness is the strongest negative predictive factor for OS
  - CR rate and 5yr DFS similar but OS worse in HIV+ compared to HIV-ve



Kaplan–Meier plots comparing overall survival and disease-free survival in HIV-infected vs. HIV-uninfected patients with diffuse large B-cell lymphoma treated with R-CHOP.(a) OS of the whole series of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (b) DFS of the whole series of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (c) OS of the subgroups with high IPI scores (3–5) of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. (d) DFS of the subgroups with high IPI scores (3–5) of HIV-infected vs. HIV-uninfected patients with DLBCL treated with R-CHOP. CI, confidence interval; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; IPI, international prognostic index; OS, overall survival.

HIV-infection impact on clinical-biological features and outcome of diffuse large B-cell lymphoma treated with R-CHOP in the combination antiretroviral therapy era

Baptista, Maria Joao; Garcia, Olga; Morgades, Mireia; Gonzalez-Barca, Eva; Miralles, Pilar; Lopez-Guillermo, Armando; Abella, Eugenia; Moreno, Miriam; Sancho, Juan-Manuel; Feliu, Evarist; Ribera, Josep-Maria; Navarro, Jose-Tomas

AIDS29(7):811-818, April 24th, 2015.

doi: 10.1097/QAD.0000000000000624

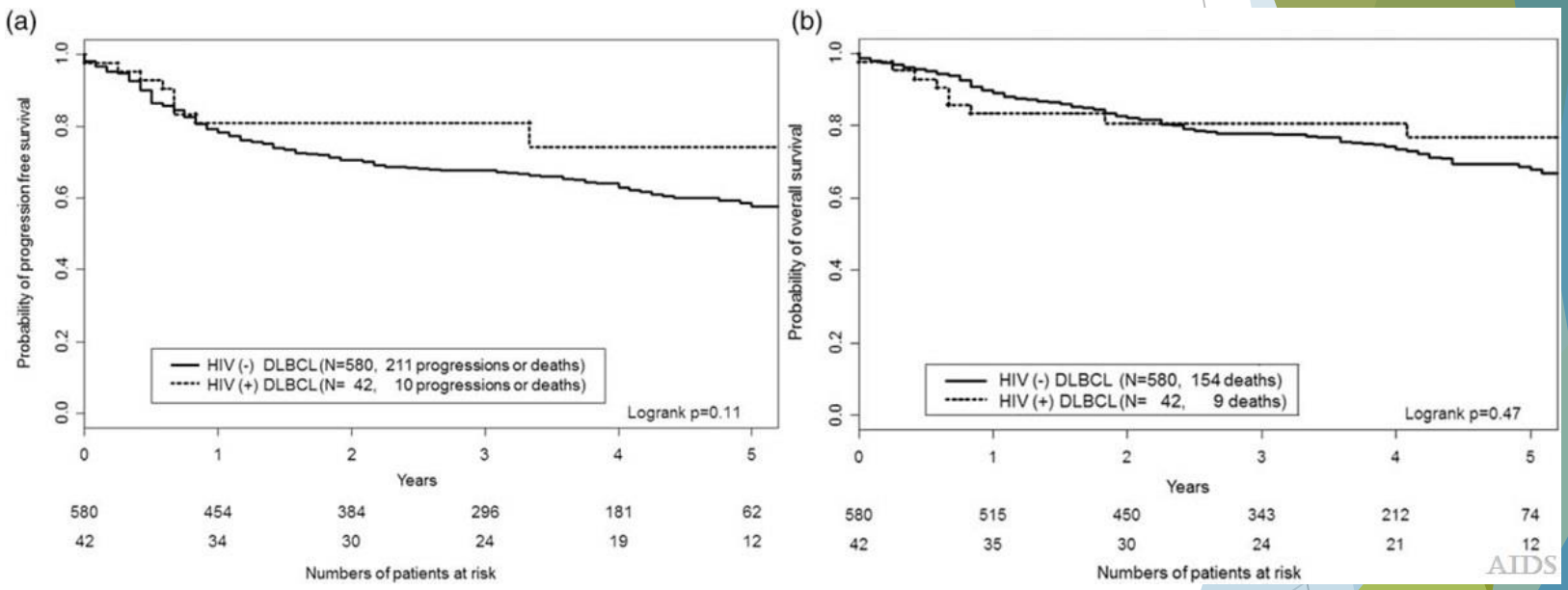
- Besson et al (AIDS 2017): Outcome in modern ARV era
  - 52 HIV+ DLBCL had same PFS after RCHOP as HIV-ve cohort. 2yr OS and PFS 75%
  - Factors associated with progression or death: poor PS, more than 1 EN site and high IPI

Outcomes for HIV-associated diffuse large B-cell lymphoma in the modern combined antiretroviral therapy era

Besson, Caroline; Lancar, Remi; Prevot, Sophie; Algarte-Genin, Michele; Delobel, Pierre; Bonnet, Fabrice; Meyohas, Marie-Caroline; Partisani, Marialuisa; Oberic, Lucie; Gabarre, Jean; Goujard, Cécile; Boue, François; Coppo, Paul; Costello, Regis; Hendel-Chavez, Houria; Mekerri, Nawel; Dos Santos, Gabriella; Recher, Christian; Delarue, Richard; Casasnovas, Rene-Olivier; Taoufik, Yassine; Mounier, Nicolas; Costagliola, Dominique; the ANRS-CO16 LYMPHOVIR Cohort

AIDS31(18):2493-2501, November 28, 2017.

doi: 10.1097/QAD.0000000000001652



Progression-free (a) and overall (b) survival among patients with systemic diffuse large B-cell lymphoma treated with R-CHOP, according to HIV status.(a) Two-year progression-free survival among HIV-negative patients: 0.71; 95% confidence interval (0.67, 0.74); 2-year progression-free survival among HIV-positive patients: 0.81; 95% confidence interval (0.70, 0.94). (b) Two-year overall survival among HIV-negative patients: 0.83; 95% confidence interval (0.80, 0.86); 2-year overall survival among HIV-positive patients: 0.81; 95% confidence interval (0.69, 0.94). Median follow-up of Lymphovir and LYSA patients: 40 months. Median follow-up of Lymphoma Study Association patients: 40 months; interquartile range: 27–53. CI, confidence interval; DLBCL, diffuse large B-cell lymphoma.

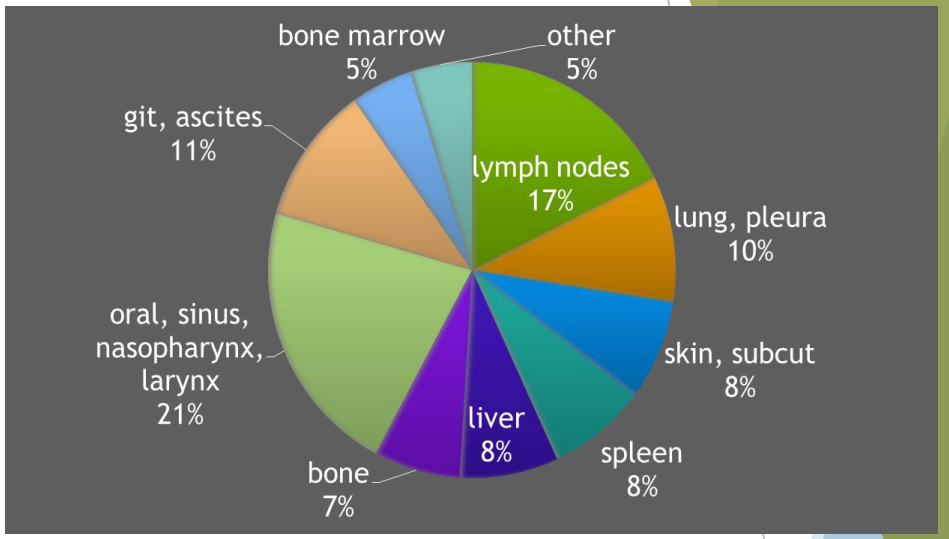
Prognostic factors

- As summarized from the 5 studies cited above
  - International Prognostic Index
  - Prior AIDs-defining illness
  - Complete response rate
    - Use of Rituximab
    - Concurrent ARVs
- Cingolani et al (Plos 1 2017): Survival and predictors of death in people with HIV-associated lymphoma compared to those in the general population
  - Older age and high IPI associated with increased risk of death
  - Female sex associated with reduced risk of death
  - “In NHL HIV was no longer an independent predictor of death after controlling for Rituximab use and IPI”

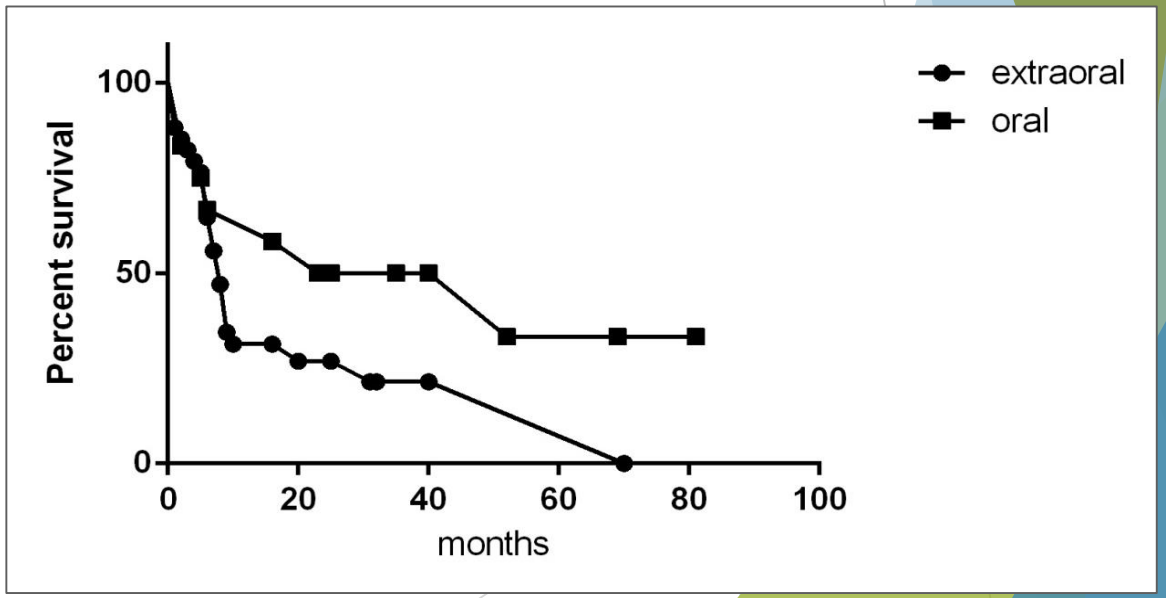
High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations

- Present with poor prognostic indicators eg high LDH, high IPI, BM and CNS involvement
- Inferior outcomes with standard R-CHOP
- Suggested treatment regimens:
  - DA-EPOCH-R
  - RHyperCVAD
  - R-CODOX-RM-IVAC

Plasmablastic lymphoma



- Immunophenotype
  - Positive: CD 138, CD 38, IRF4/MUM1, Ki 67>90%
  - Negative: CD20, CD45, PAX5
- Allie et al (Oral Oncology 2017)
  - Plasmablastic lymphoma is the commonest head and neck lymphoma diagnosed in HIV-positive patients at Wits
  - 1993-2012: 56% PBL, 43.9% DLBCL and 25% BL
- GSH data presented 2013
  - 46 HIV positive PBL seen from 2004-2012
  - Median OS St 1-2 (oral) 30 months vs 8 months for extraoral disease



Plasmablastic lymphoma treatment

- Loghavi et al (J Hematol Oncol 2015): clinicopathologic analysis of 61 patients
  - 20 patients were HIV positive (11 HIV status unknown)
  - Patients who received CHOP had better OS than hyperCVAD (p=0.078)
  - Age, stage and EBV positivity were significant prognostic factors
- Pinnix et al (Clin Lymphoma Myeloma Leuk 2016)
  - 10 cases of stage 1 and 2 PBL, 2 HIV-positive
  - Doxorubicin-based chemo and ISRT resulted in 90% 2yr PFS and 100% 2yr OS
- Tchernonog et al (Annals of Oncology 2017): 135 patients, 56 HIV positive
  - Median OS 32 months
  - HIV positive had better OS
  - CR rate same for CHOP vs intensive chemo
  - IPI, chemotherapy and CR rate associated with survival benefit

Hodgkin Lymphoma

- 90% of cases associated with EBV
- Present with more advanced disease, extranodal involvement and bone marrow infiltration
  - L Swart et al GSH cohort 2005-2012: 61% bone marrow infiltration in HIV-positive HL; BMT provided diagnosis of HL in 17%
- Mixed cellularity and lymphocyte-depleted subtypes more common in HIV positive
- ABVD is treatment of choice
  - BEACOPP regimen not recommended due to myelotoxicity
- Adverse reactions due to drug interactions: Vinblastine and boosted PIs lopinavir/ritonavir inhibits CYP3A4
- PET-guided therapy is feasible

Role of Radiotherapy

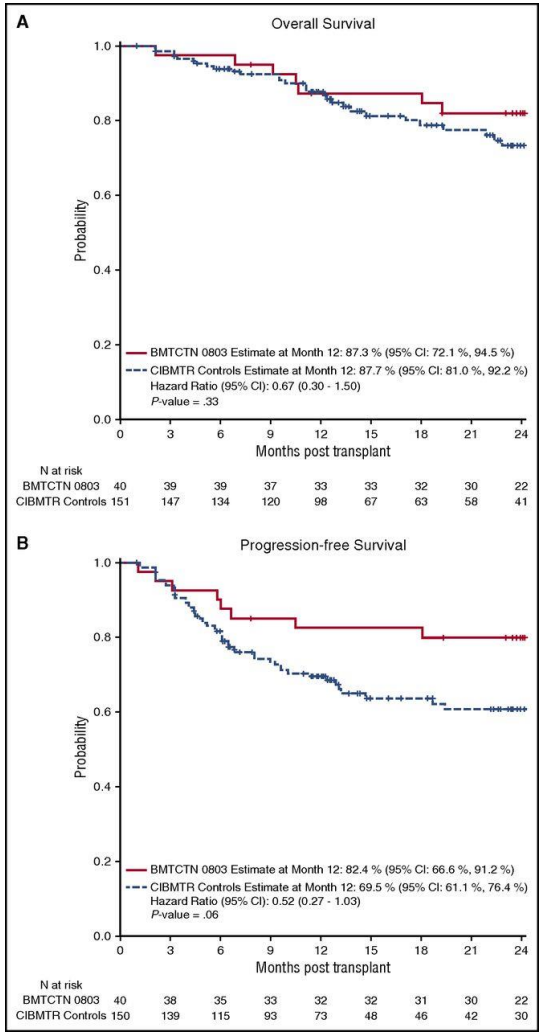
- Follow ILROG guidelines
- Radical: Involved site radiotherapy as consolidation or for previously bulky disease
  - St 1 and 2 DLBCL treated with RCHOP
  - St 1 and 2 PBL treated with CHOP
  - 30-36Gy consolidation if CR after chemotherapy
- Palliative: relapsed or refractory disease
  - 40Gy if localized residual disease post chemo (not for HD salvage therapy)
  - Palliation: 3GyX10 or 4GyX5

Relapsed or refractory disease

- Patients compliant on ARVs with suppressed viral load, good PS, normal cardiac, pulmonary and renal function are considered for high-dose chemo and SCT

- Palliative chemotherapy
- Palliative radiotherapy

OS and PFS for HIV-infected and noninfected patients.



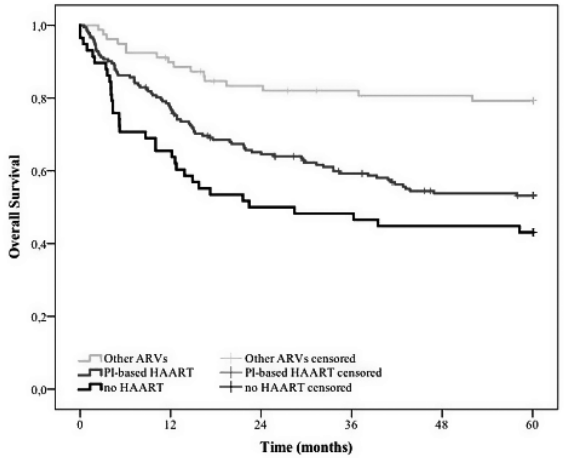
Joseph C. Alvarnas et al. Blood 2017;130:1976-1984

Antiretroviral and chemotherapy drug interactions

- Sombogaard et al (Int J of Clin Pharmacy 2018)
  - PI-based ART in patients receiving chemotherapy for lymphoma results in a lower 1 year survival when compared to NNRTI
  - Trend towards more bone marrow toxicity resulting in treatment delays and dose reductions in patients on PI-based ART
- PI's inhibit CYP3A4 (necessary for metabolizing cytotoxics) resulting in increased drug exposure and toxicity
- PI's include lopinavir/ritonavir (Kaletra), atazanavir etc
- NNRTI's include efavirenze, nevirapine
- Fixed dose combination in SA: tenofovir (NtRTI), emtricitabine (NRTI) and efavirenze (NNRTI)

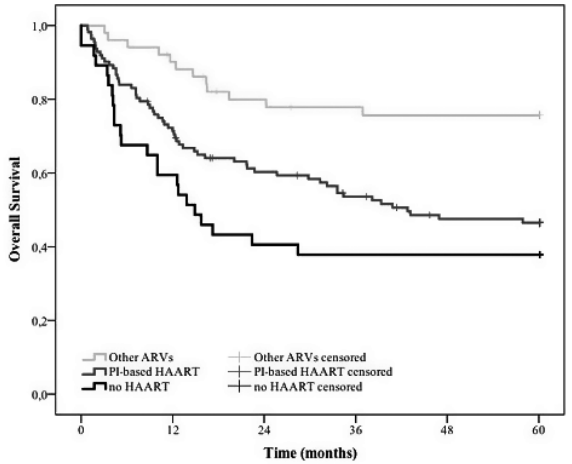
Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study

All patients



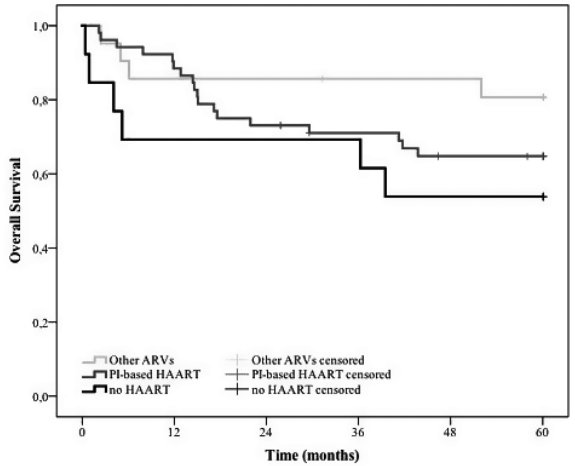
n	336	257	213	195	177	173

Non Hodgkin's lymphoma



n	212	152	120	108	97	96

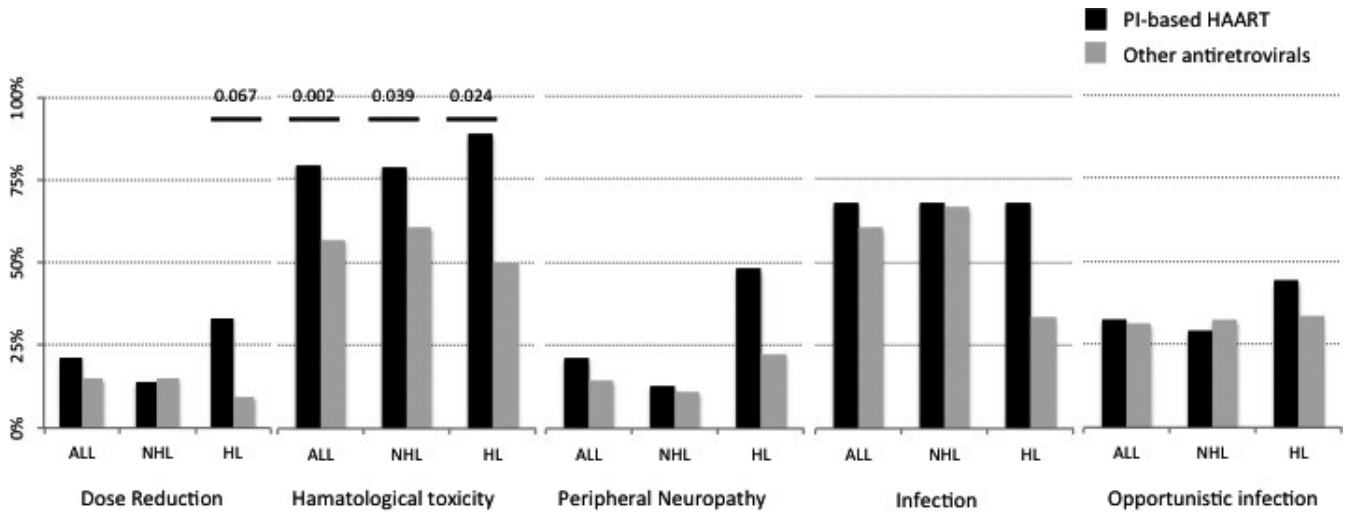
Hodgkin's lymphoma



n	90	76	68	63	57	55

Foca et al HIV Medicine 2018: Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study, First published: 04 June 2018, DOI: (10.1111/hiv.12624)

Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study



Foca et al HIV Medicine 2018: Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study, First published: 04 June 2018, DOI: (10.1111/hiv.12624)

To be or not to be HIV+, that is no longer the question

Stefan K. Barta FOX CHASE CANCER CENTER/TEMPLE UNIVERSITY HEALTH SYSTEM

In this issue of *Blood*, Noy et al report the outcomes of HIV-infected patients with Burkitt lymphoma (BL) treated with a modified cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC)-rituximab regimen that rival outcomes seen in HIV-uninfected patients.[1]

Acknowledgements

Thank you to my colleagues at Dept Radiation Oncology, Haematology and Infectious Diseases Unit Groote Schuur Hospital

Thank you to all the brilliant researchers who have helped to light the way

And thank you to our many brave and wonderful patients

Groote Schuur Hospital