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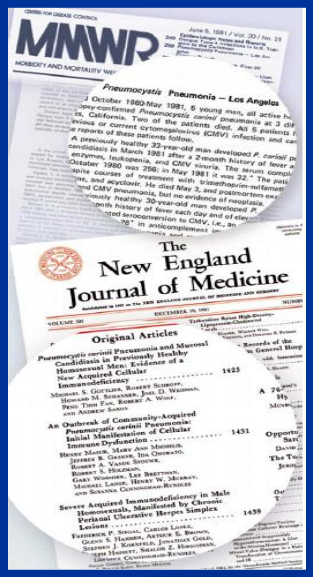
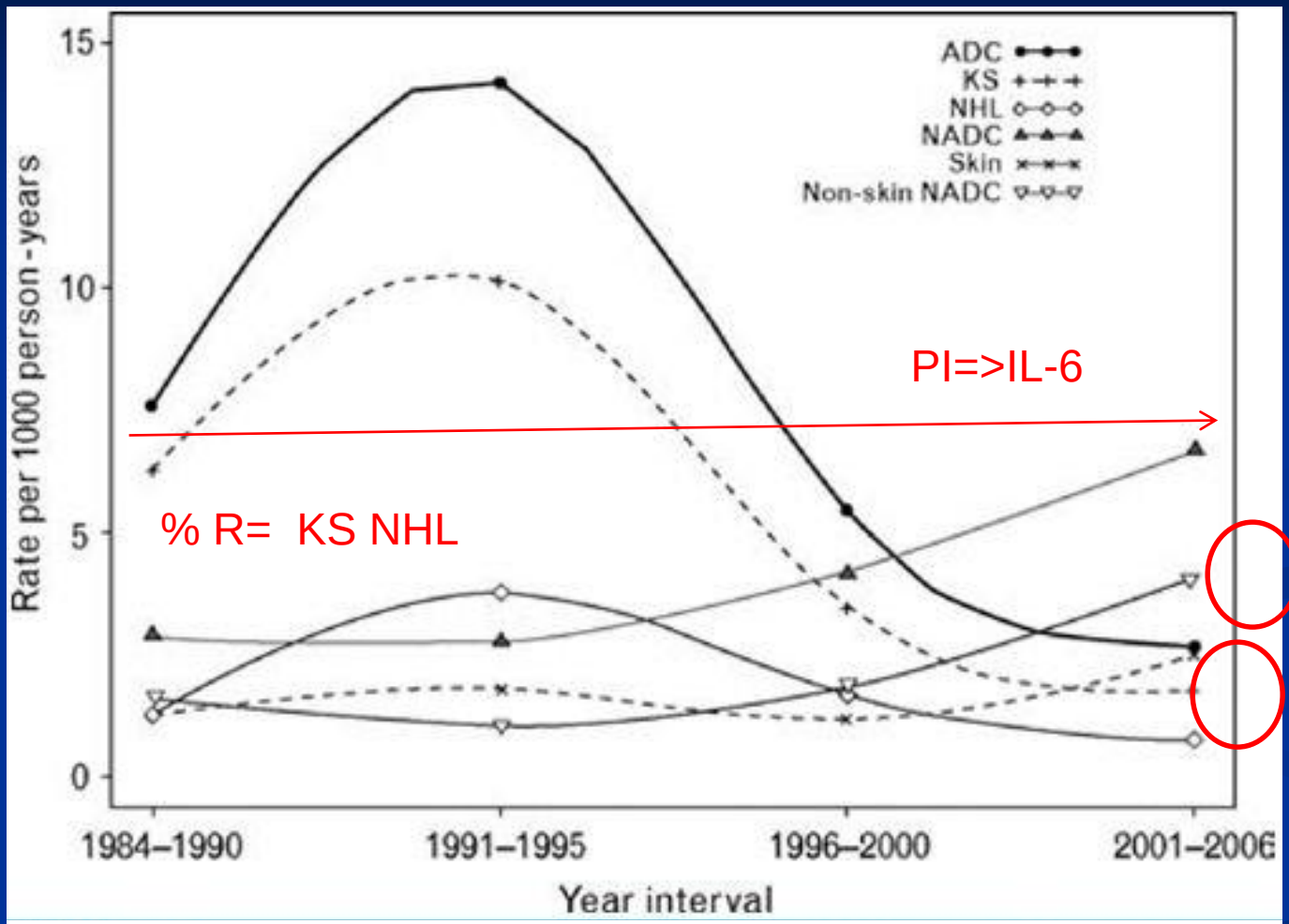
HIV Related Malignancies: Lessons Learned



Dr. Adan Rios
Division of Oncology
Department of Internal Medicine

Cancer, HIV and HAART



J Acquir. Immune. Defic. Syndr. 2015. 68:568-577

Cancer and HIV

- AIDS-defining malignancies
  - Kaposis Sarcoma, NH Lymphoma, Cervical CA
- Malignancies associated with immune dysfunction or chronic inflammation
  - Hodgkin's lymphoma, seminoma, liver cancer
- Malignancies associated with other exposure factors that are increased in HIV
  - Lung cancer smoking
  - Anal cancer HPV
- Other malignancies
  - Melanoma, prostate, colorectal CA

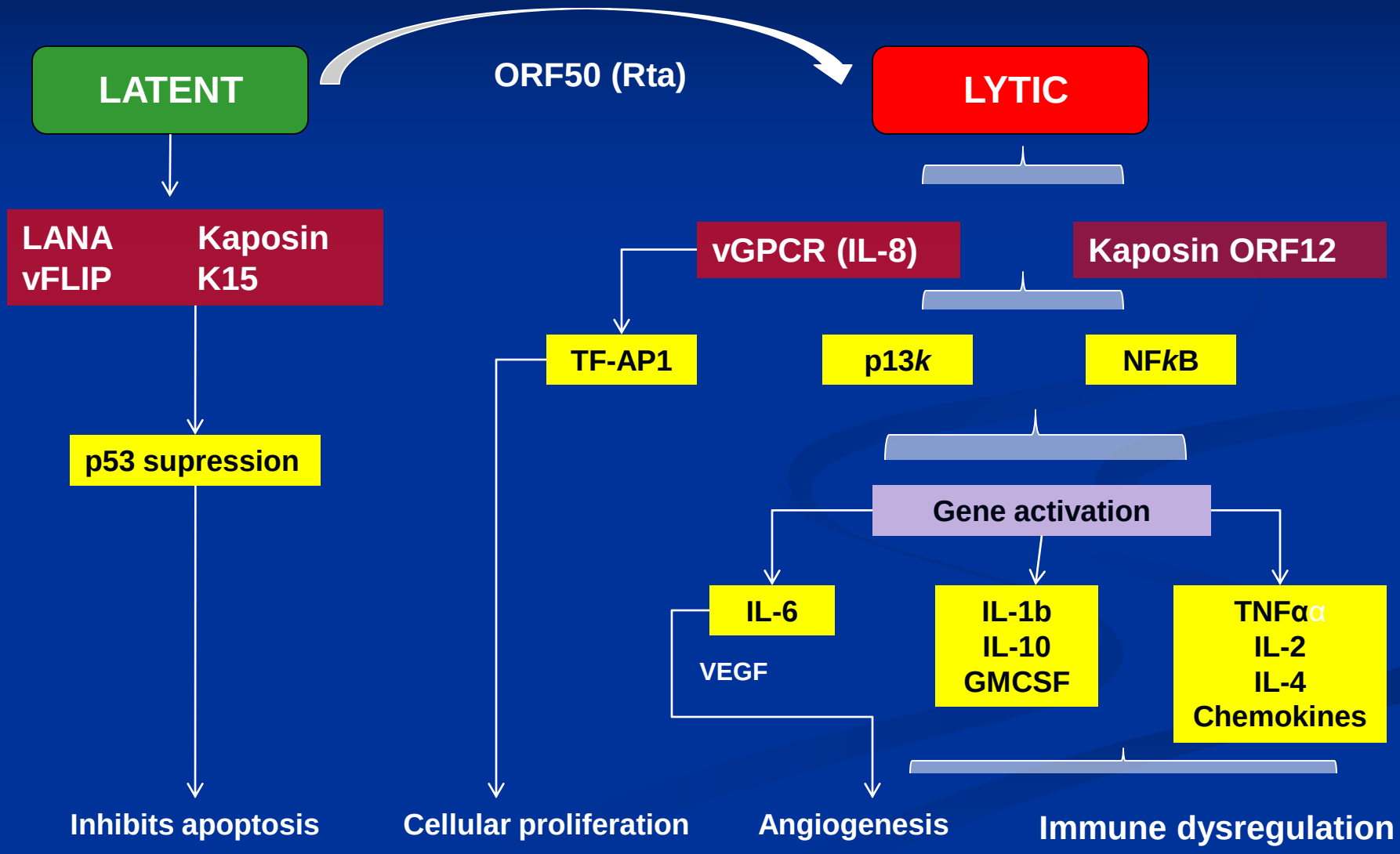
Cancer and HIV
Pathogenesis

- **Immunosupression**
  - Similar risk as seen in transplant recipients.
    - 100-fold increased risk of cancer (renal, SCC, NLH, KS, uterine, cervix, vulva, sarcoma)
  - Loss of immune surveillance
- **Viral mediated carcinogenesis**
  - EBV, HHV-8, HPV
  - Role of HIV genes in oncogenesis remains unclear

AIDS-Associated Malignancies and Oncogenic Viruses

Kaposi's sarcoma	HHV-8
Primary effusion lymphoma	HHV-8 ~ 80%; EBV
Primary CNS lymphoma	EBV >90%
Burkitt's Lymphoma	EBV ~ 50%
Diffuse large B-cell lymphomas	EBV ~ 30-80%
Invasive cervical cancer	HPV
Multicentric Castleman disease	HHV-8
Hodgkin lymphoma	EBV ~70-100%
Nasopharyngeal carcinoma	EBV
Plasmablastic lymphoma (oral cavity)	EBV ~70%
Leiomyosarcoma (in children)	EBV
Anogenital cancers	HPV
Head and Neck cancer	HPV
Hepatocellular carcinoma	Hepatitis B and C
Markel cell tumor	Merkel cell polyomavirus

Human Herpes Virus - 8



HIV Associated Malignancies

NH Lymphomas

Immunosupression
Chronic Antigenic stimulation
Cytokine overproduction

→

B cell expansion (Oligloclonal)

EBV

EBV infection
microRNA155
C-myc gene rearrangement
Bcl-6 gene rearrangement
Ras gene mutations
p53 mutations/deletions

Monoclonal malignant expansion

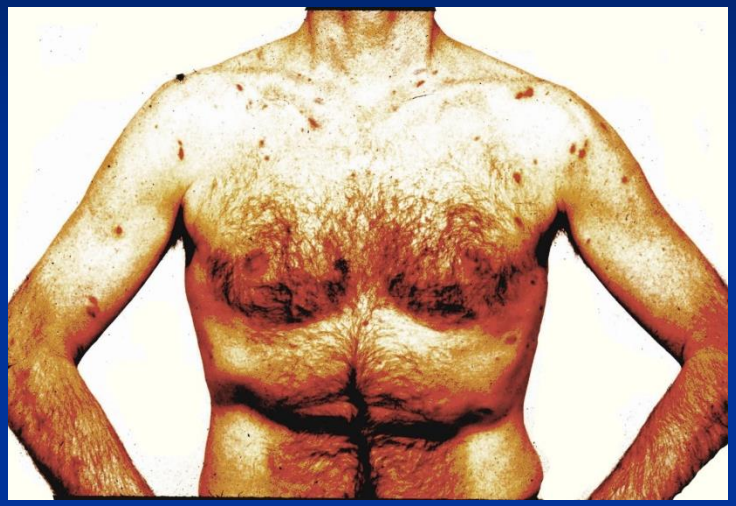
50 % of all ADC.
36% of all deaths: 1996-2006

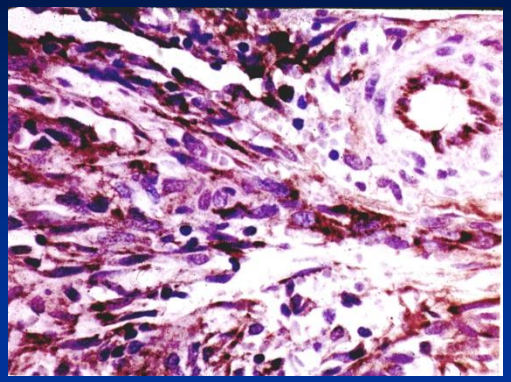
PATHOGENESIS:
Disrupted Immune Surveillance.
Viral Infection
Genetic alterations.
Chronic antigenic stimulation.
Cytokine dysregulation.

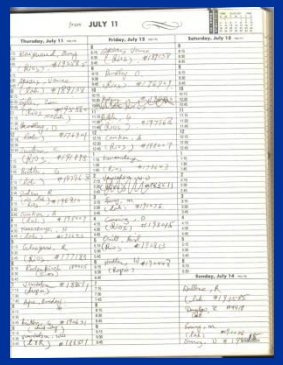
HIV Associated Malignancies

Clinical Aspects

Kaposi Sarcoma

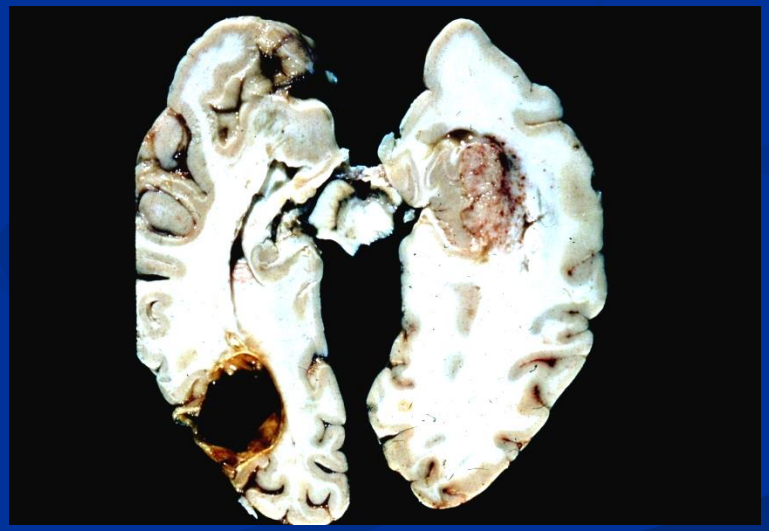






Kaposi Sarcoma

Kaposi Sarcoma does not invade the CNS



Kaposi's Sarcoma in the HAART era

Figure 1: Pretreatment: Typical KS lesions of both legs (A and B: close up)

Doxil 25mg/m2BSA

Taxol 25mg/m2BSA

Every two weeks
for 6-8 Rxs

NEW Rx: Pomalidomide

JCO. 2016 . Vol34:4125-31

Figure 4: Post treatment A: Left leg; B: Right leg: There is significant flattening of KS lesions compared with Figure 1

Endocr. Pract. 2011 Jul-Aug;17(4):e87-91

NHL in the HAART era

	HAART	Non-HAART	P value
Number	198	134	
Mean CD4 count	147	43	0.001
CNS involvement	11%	27%	0.005
Chemotherapy	93%	76%	0.001
CNS prophylaxis	43%	27%	0.004
Complete Remission	68%	26%	0.001
Median survival (mo)	50	5	0.001

Hospital G Maranon. Spain . 2003

Lymphomas in HIV+ patients

- DLBCL :
  Immunoblastic: 90% EBV. PCNSL < incidence due to HAART
  Centroblastic: Germinal vs Non-Germinal

- Burkitt's Lymphoma

- **Classical Hodgkin's Disease:**
- 100% EBV positive

- **Primary Effusion Lymphoma:**
- <5% of all HIV related NHLs
- Null cells

- **Plasmablastic Lymphomas:**
- Common in India.
- Cytoplasmic IgG(Different from PEL).
- 43% outside the oral cavity.
- 50% MYC translocation with low survival (mediam:14 months).

- **Lymphoma arising in Castleman's disease:**
- EBV negative with cytoplasmic IgG lambda (different from PEL)
- Arise from naïve B-cells. PEL from terminally differentiated cells.

Polymorphic B-cell lymphomas: Resemble PTLDs

NHL in the HAART era

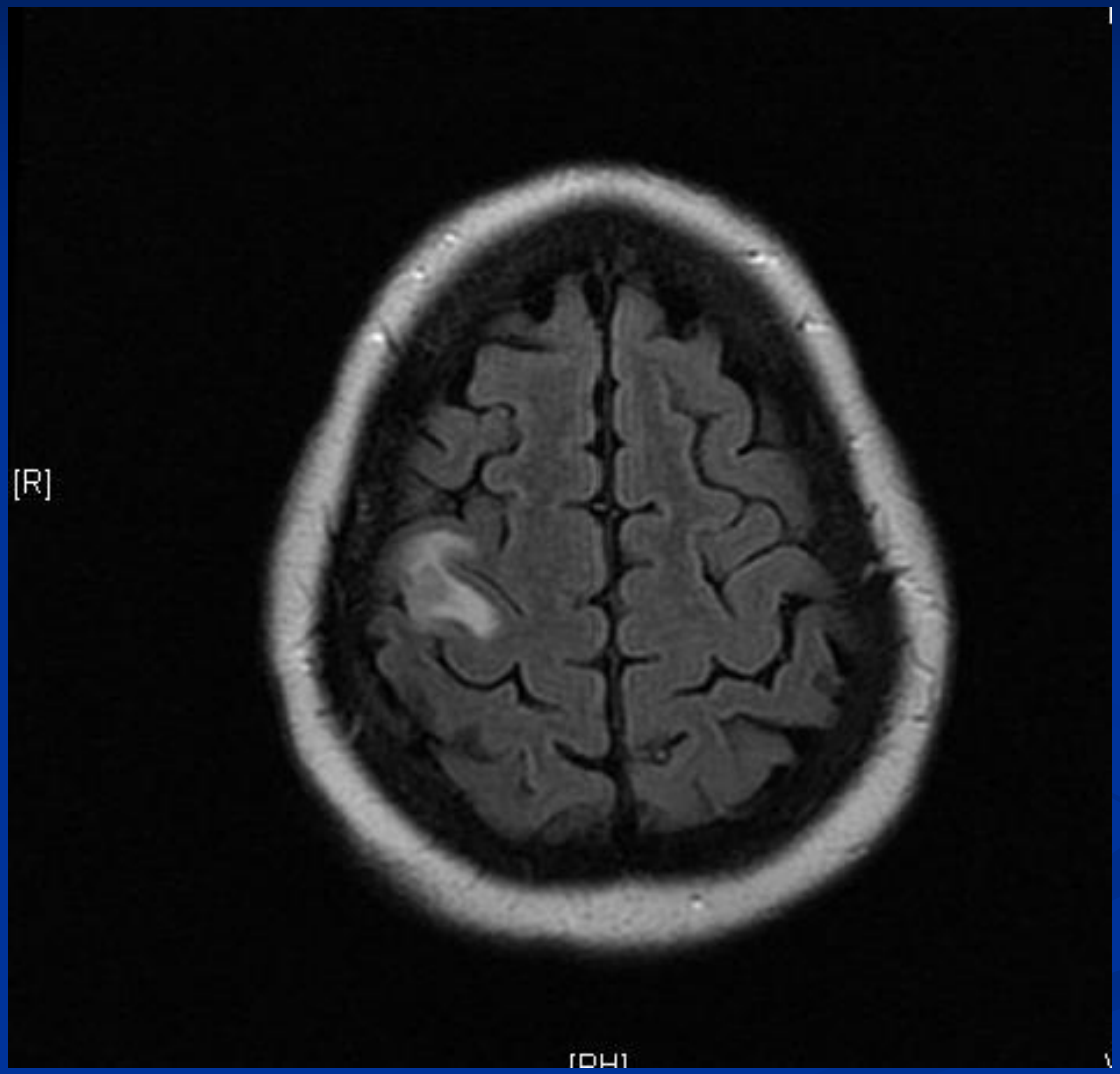
- **Incidence**
  - Decrease PCNSL
  - Decrease immunoblastic lymphoma
  - Burkitt's lymphoma = no change

- **Improved survival**
  - 50% survival at 2 years
    - Pre HAART = 10% at 2 years

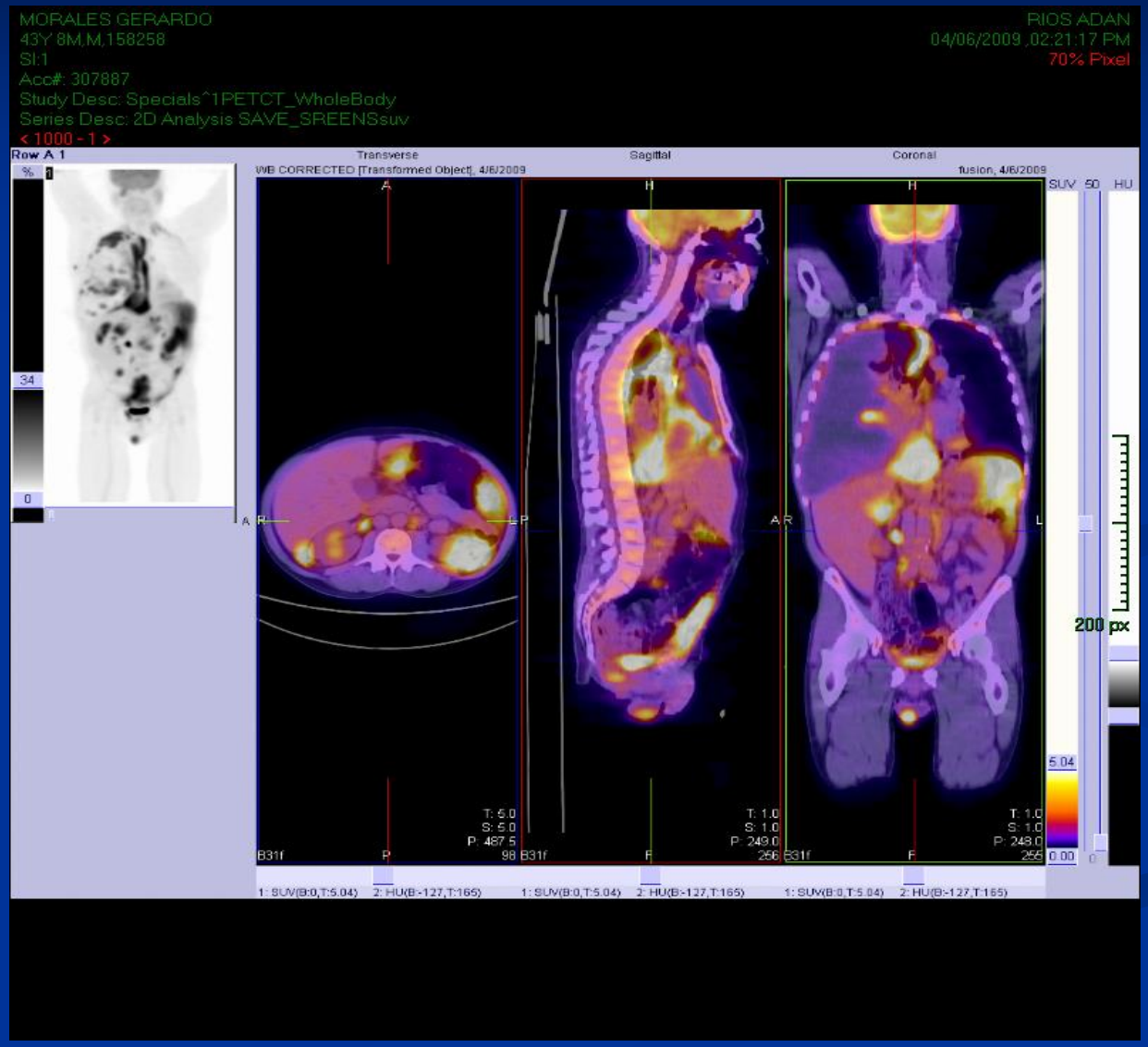
Change in the pathogenesis of NH lymphoma?

- MALT
- PTCL
- Plasmablastic lymphomas of the oral cavity
- PTLD-like

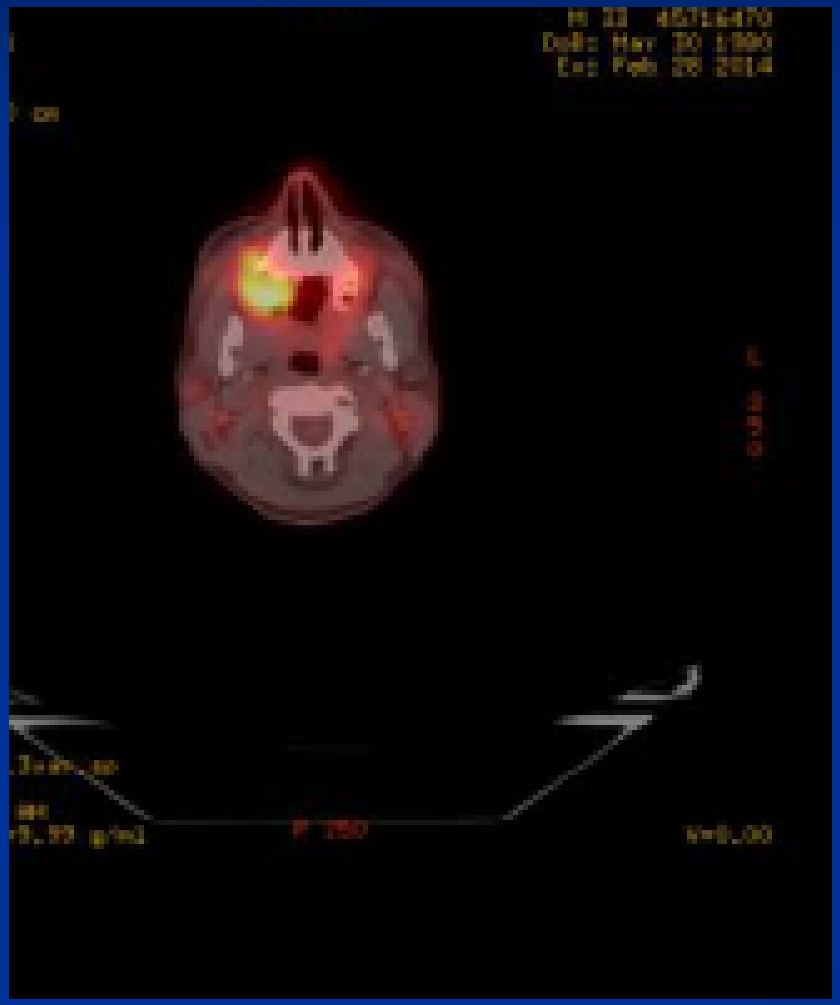
Primary CNS Non-Hodgkin Lymphoma



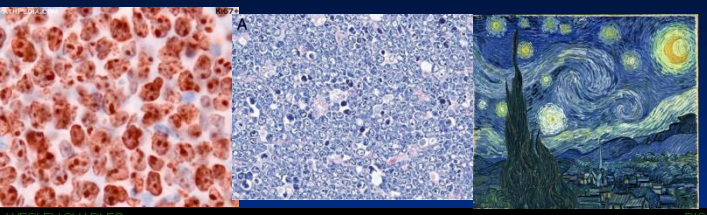
Primary Effusion Lymphoma

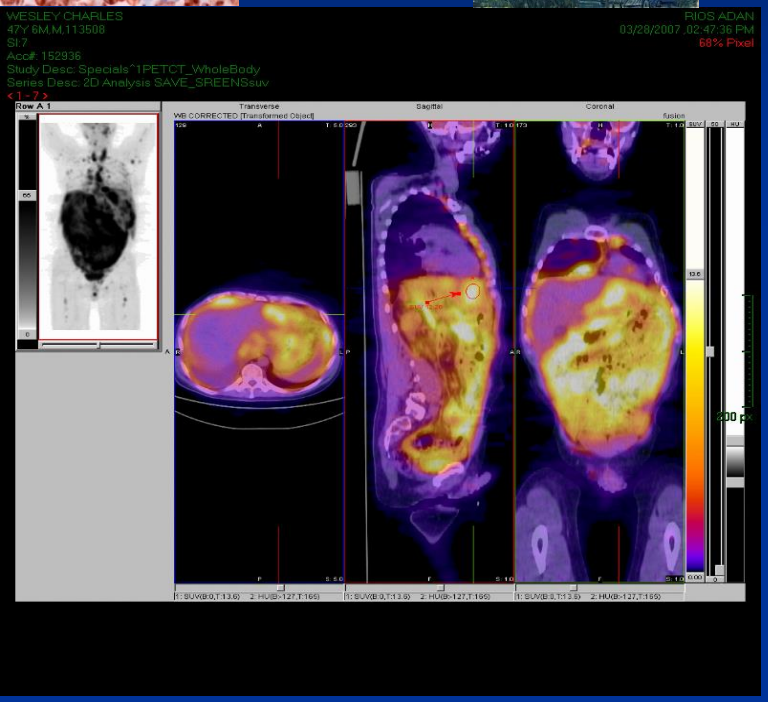


Plasmablastic Lymphoma

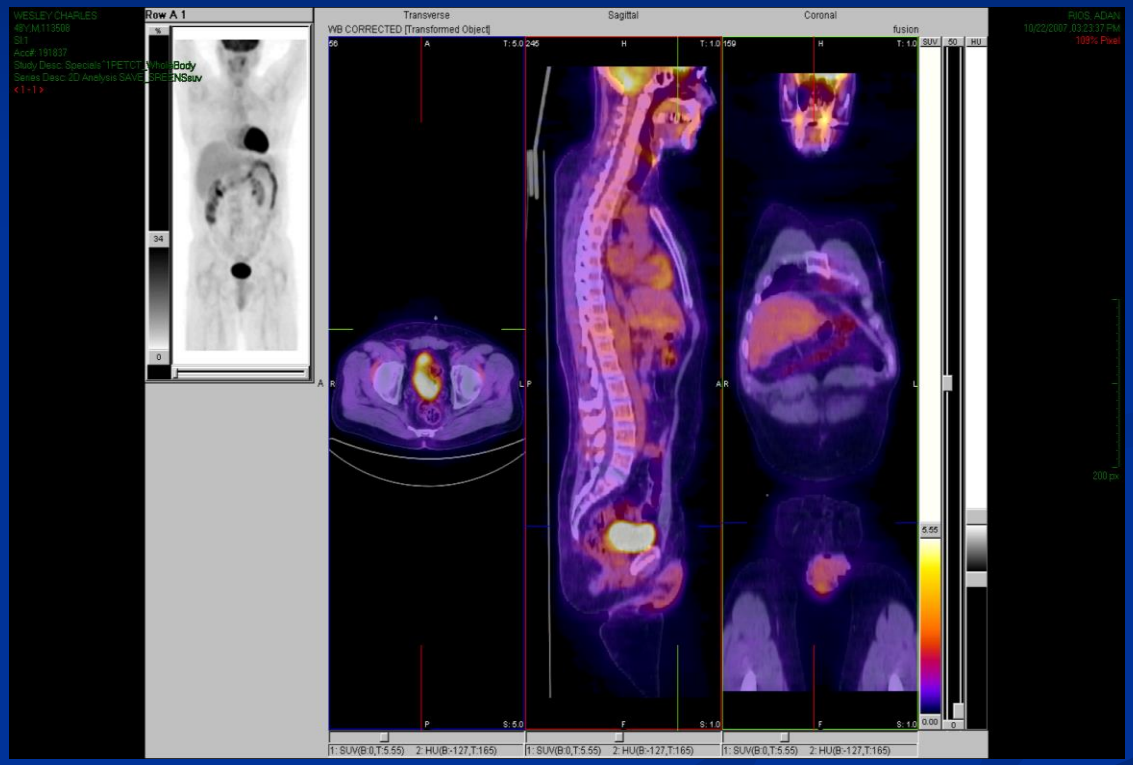


Burkitt's Lymphoma HIV Related





Post Hyper CVAD + Ara-C/Methotrexate-Rituximab



HyperCVAD in Burkitt's

- Hyper-CVAD is an effective regimen for patients with AIDS-associated Burkitt lymphoma/leukemia, with acceptable toxicity. The combination of hyper-CVAD and HAART is associated with long-term survival in patients with the two diseases, which, until recently, were both considered invariably fatal and almost futile to treat medically.

Cortes J, Thomas D, Rios A, Koller C, O'Brien S, Jeha S, Faderl S, Kantarjian H. Cancer. 2002 Mar 1;94(5):1492-9.

Large B Cell Lymphoma Post Q.T.

UTMS-MHH 5 years Experience

Diagnosis	Number
T Cell Lymphoma, NOS	7
T Cell Lymphoma, Angioimmunoblastic	2
T Cell Lymphoma, NK type (nasal)	1

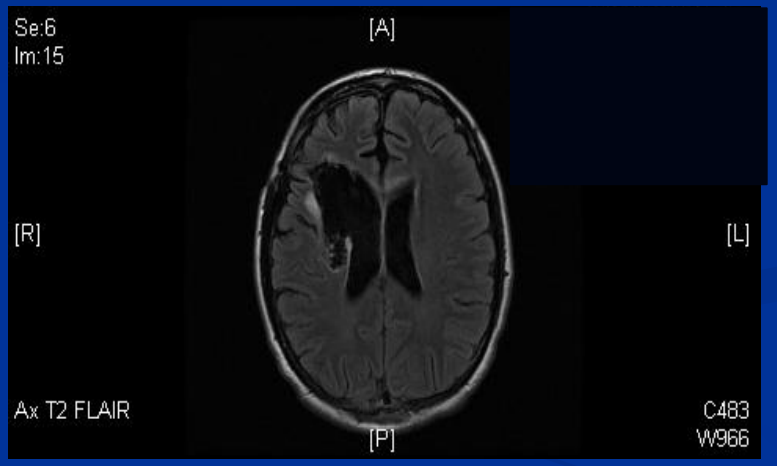
CHOEP
Etop= 100mg/m2 x 3

Pralatrexate + Romidepsin

Blood 2018. 131:397-407

Primary CNS Lymphoma

2008



Steroids+ HD MTX+ HD Rituximab± IFRT

The “one hand” saxophone

Hodgkin's Lymphoma

- Most common non–AIDS-defining malignancy
- Advanced stages
- "B" Symptoms
- Extranodal disease
  - Bone marrow involvement
- Unfavorable cell types
  - Mixed cellularity
  - Lymphocyte depletion
- EBV +
- Increased incidence
  - Risk higher 8-16 times in HIV+ patients

EBV + AZT

Response rate = 53% CR
Median Survival = 11 mo
2 yr DFS = 52%

EBVP

Response rate = 74% CR
3 yr DFS = 53%

ABVD

Response rate = 87% CR
3 yr DFS = 71%

Stanford V Regimen

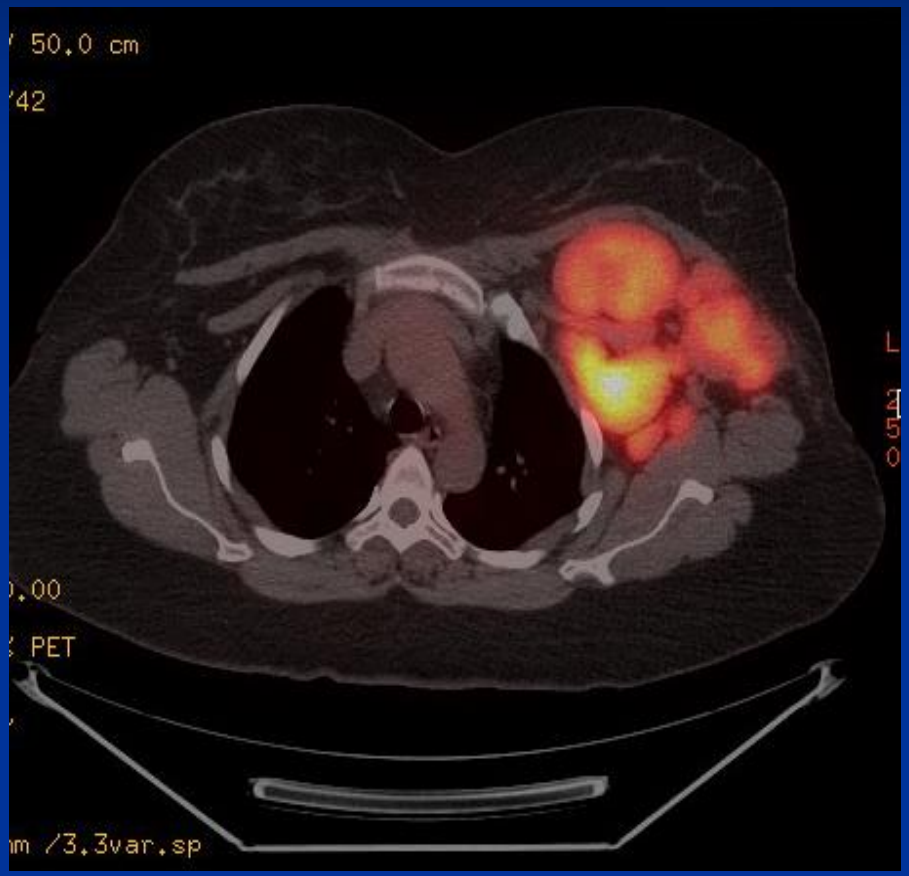
Response rate = 81% CR
3 yr DFS = 51%

BEACOPP

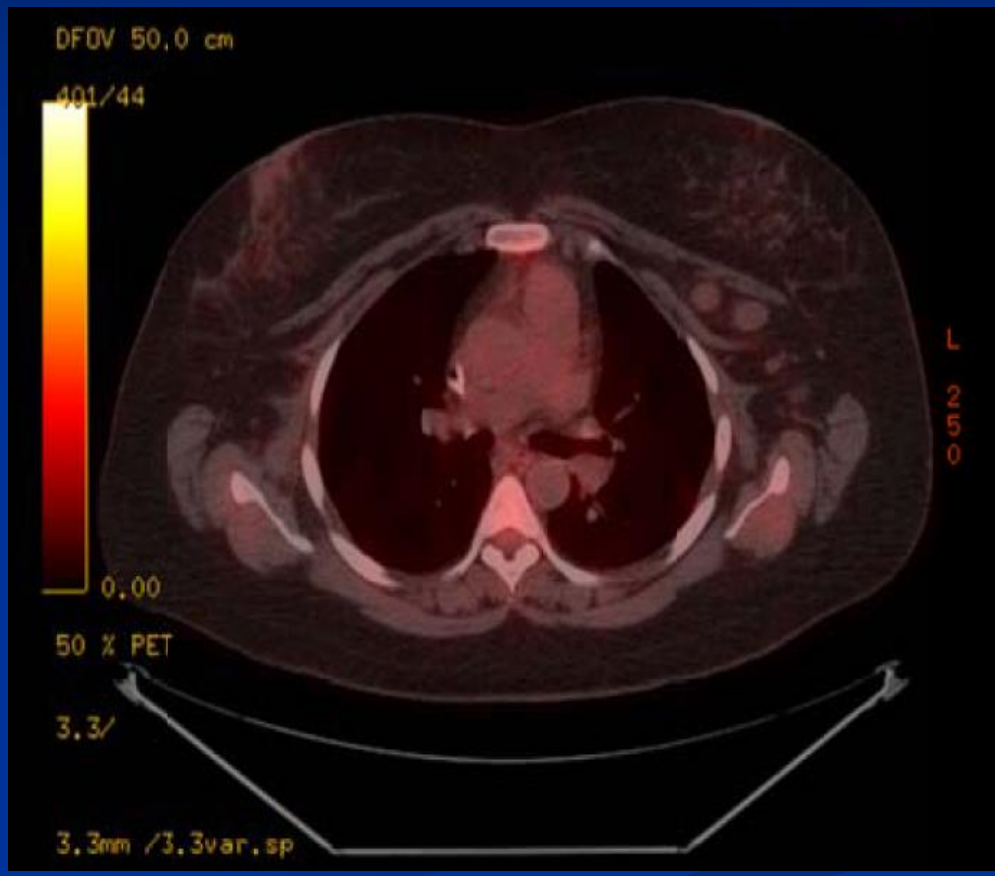
Response rate = 100% CR
5 yr DFS = 70% (calc)

Hodgkin's Disease

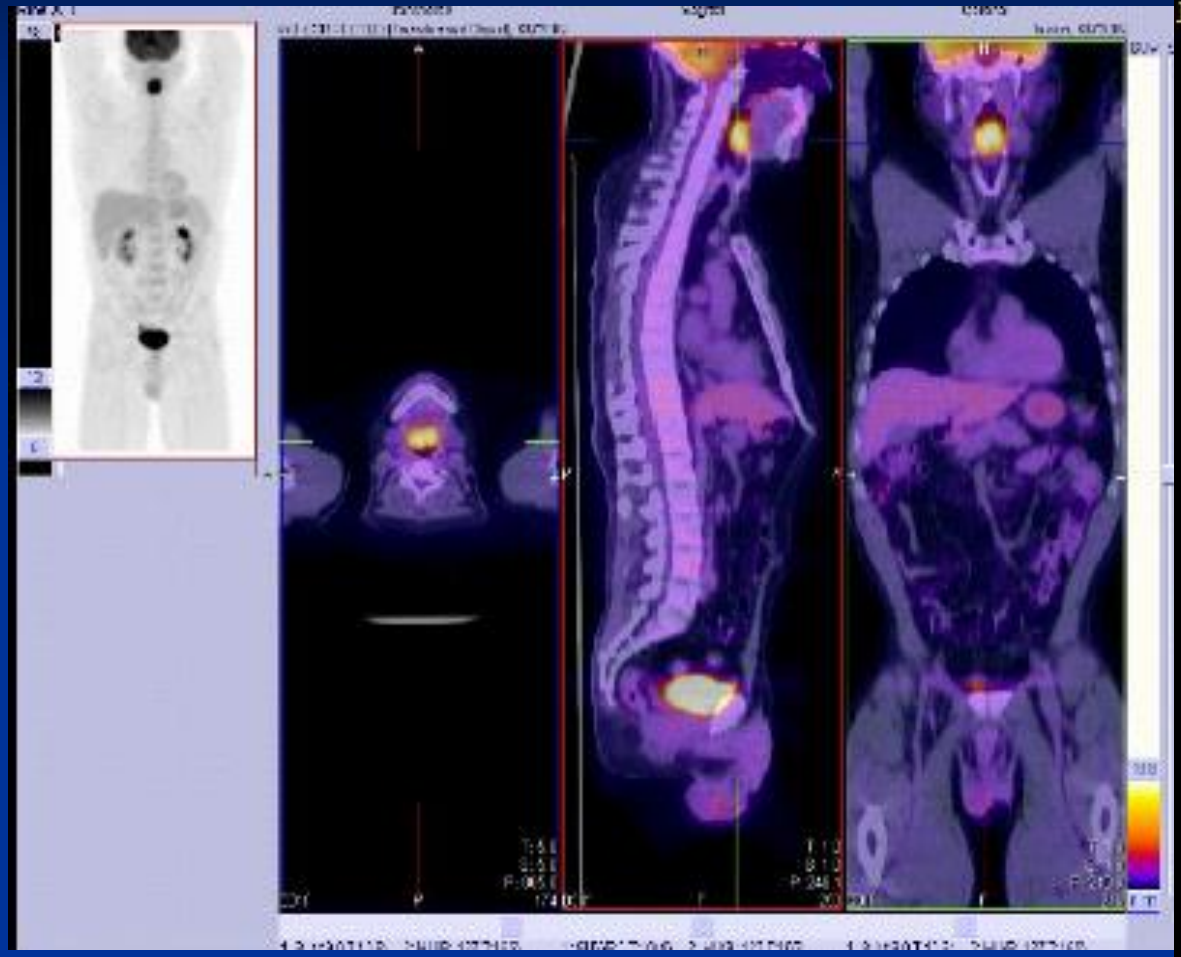
HD NS Pre RX HIV+



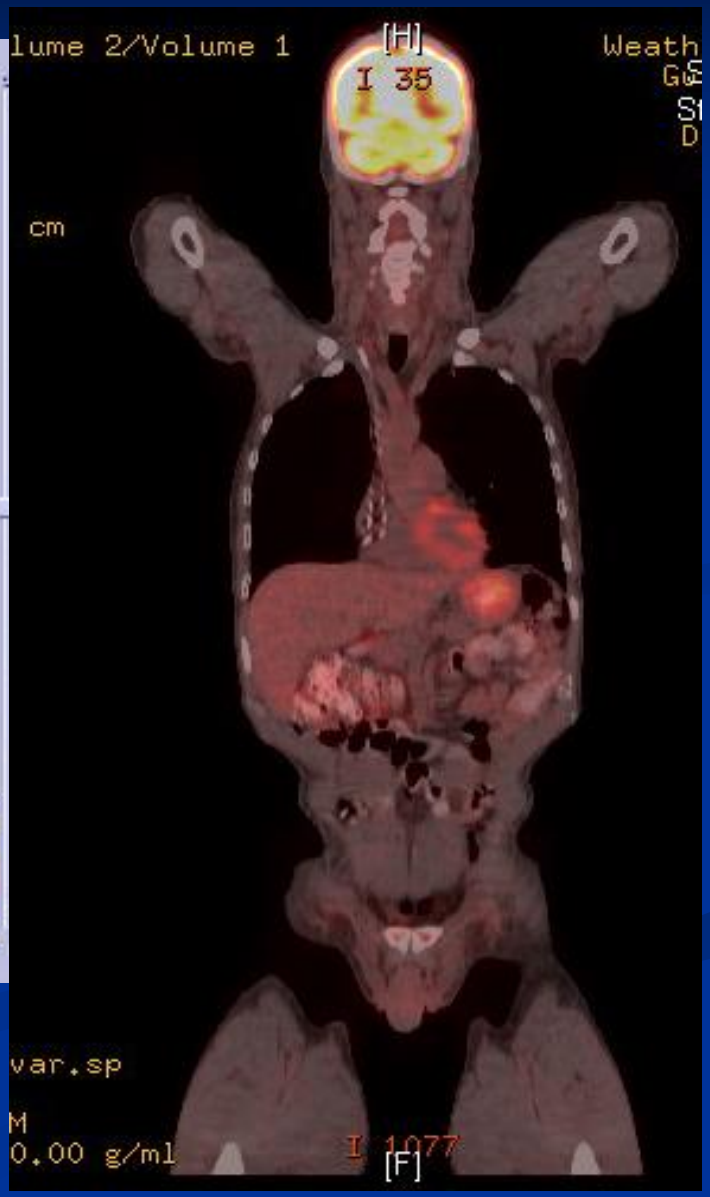
HD NS Post RX HIV+



SCC base of the tongue



SCC Post RX with Chemo XRT



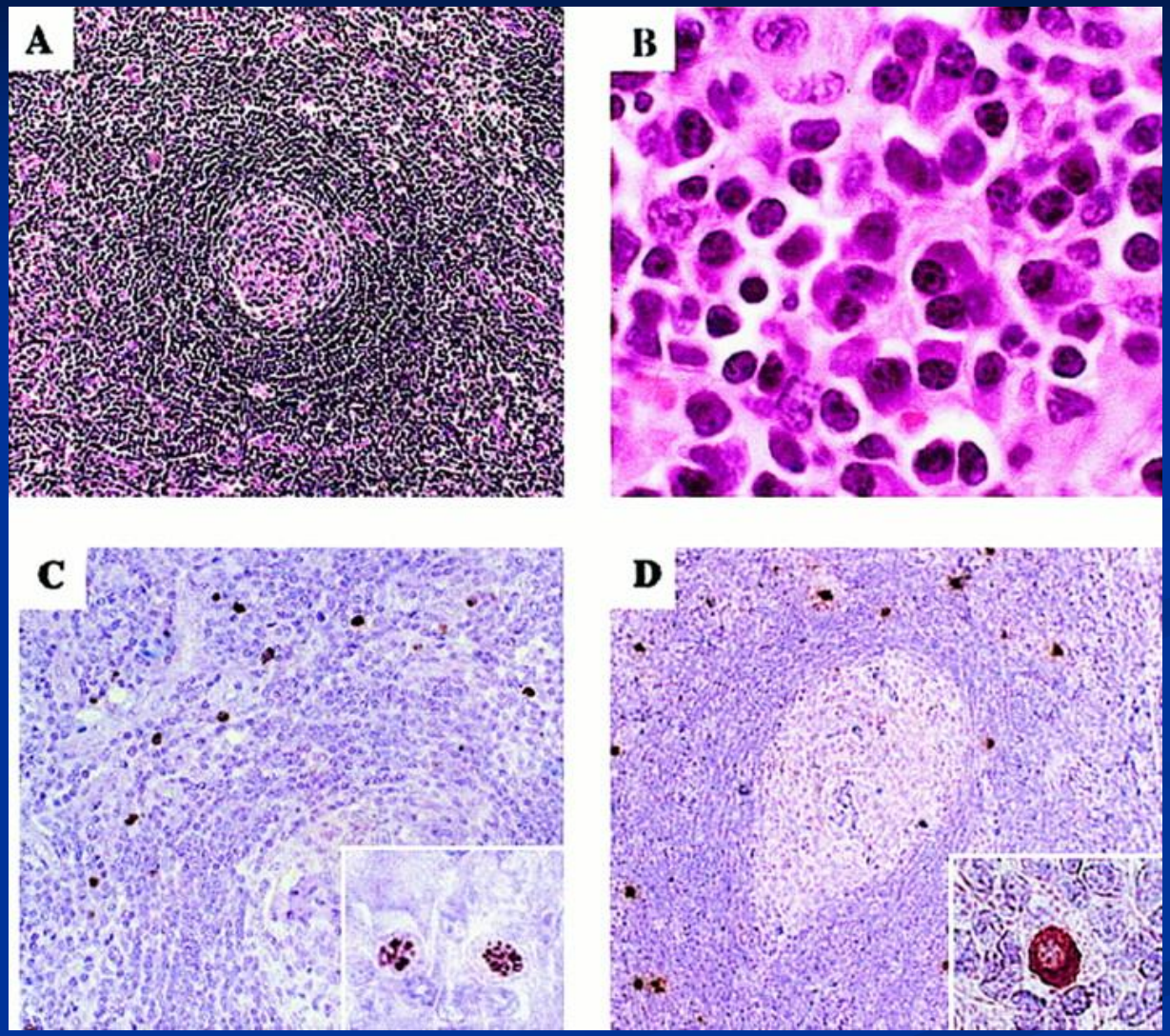
SCC of the Rectum B

POST Q-RT

Cervical Cancer in HIV+ Women

- Younger age than HIV-negative women.
- Cervical cancer is frequently the initial AIDS-defining diagnosis in HIV+ women
- HIV+ women with cervical cancer have higher CD4 count than HIV+ patients with other AIDS-defining illnesses.
- HAART has not decreased the incidence of invasive cervical cancer in infected women
  - Reduction in risk of CIN in HIV infected women has a minimal impact on the overall incidence of cervical cancer
  - HAART may have a positive impact on prognosis.

Castleman's disease



Aoki Y et al. Blood 2001;97:2526-2527

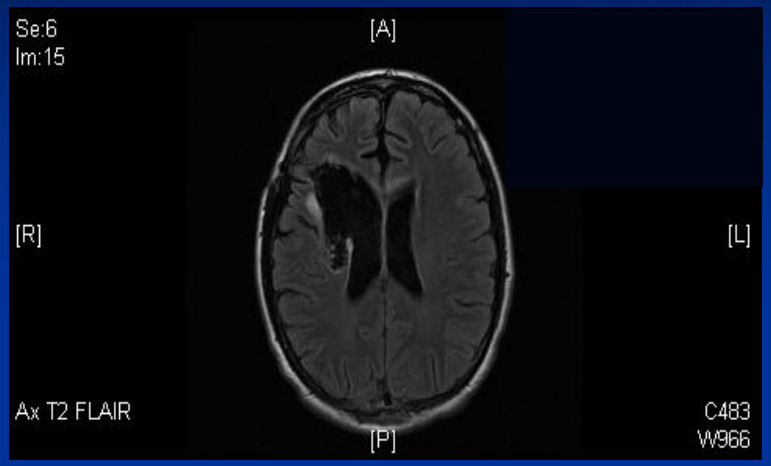
CD Clinical Presentation

- Unexplained fever, malaise.
- Anemia, thrombocytopenia, neutropenia
- Splenomegaly
- Low albumin, edema, Low Na.
- Be particularly alert in patients with K.S.

- Evaluation should include C-Reactive Protein and lymph node biopsy.

Primary CNS Lymphoma

2008



Steroids+ HD MTX+ HD Rituximab+ IFRT

2018

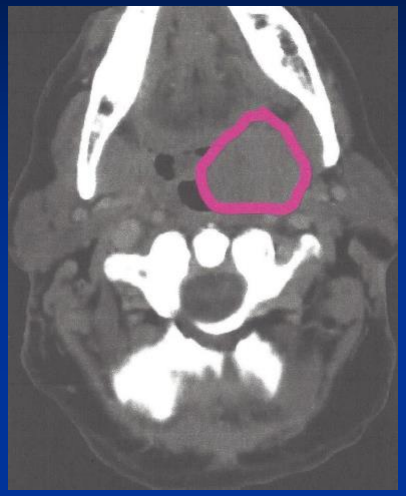
Ckii

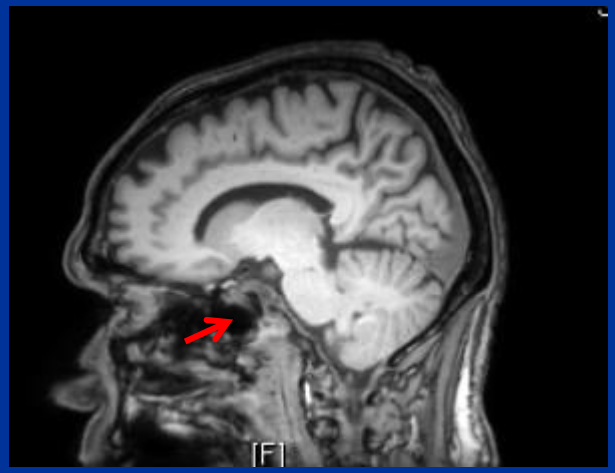
9p24.1/PD-L1/PD—L2 CNA

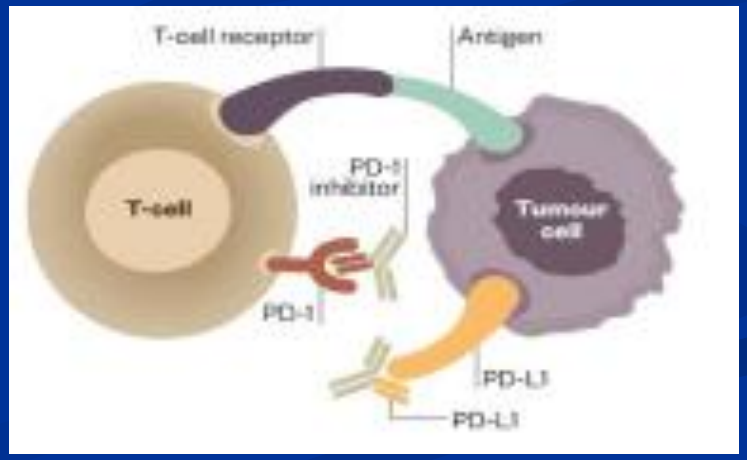
Targetable features of testicular and primary central nervous system lymphomas

Blood .2016. Vol127:869-881

The Future

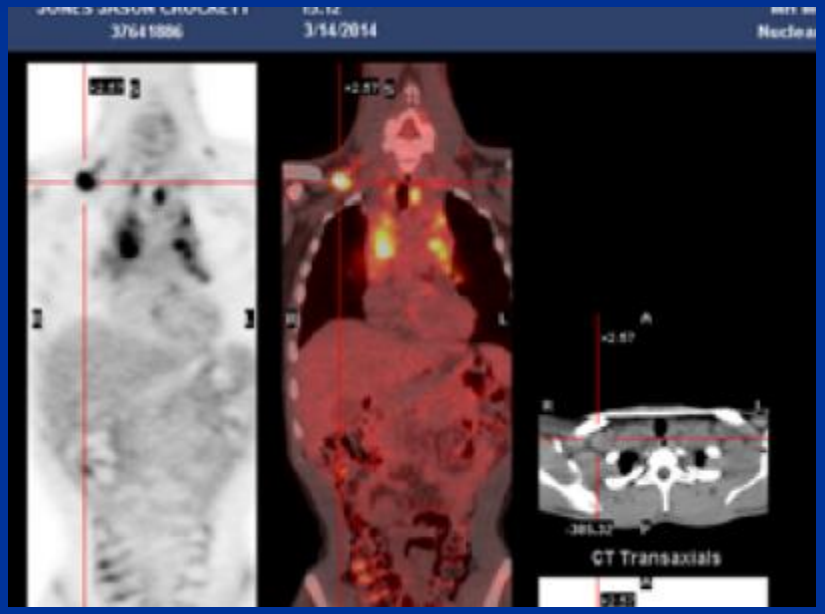




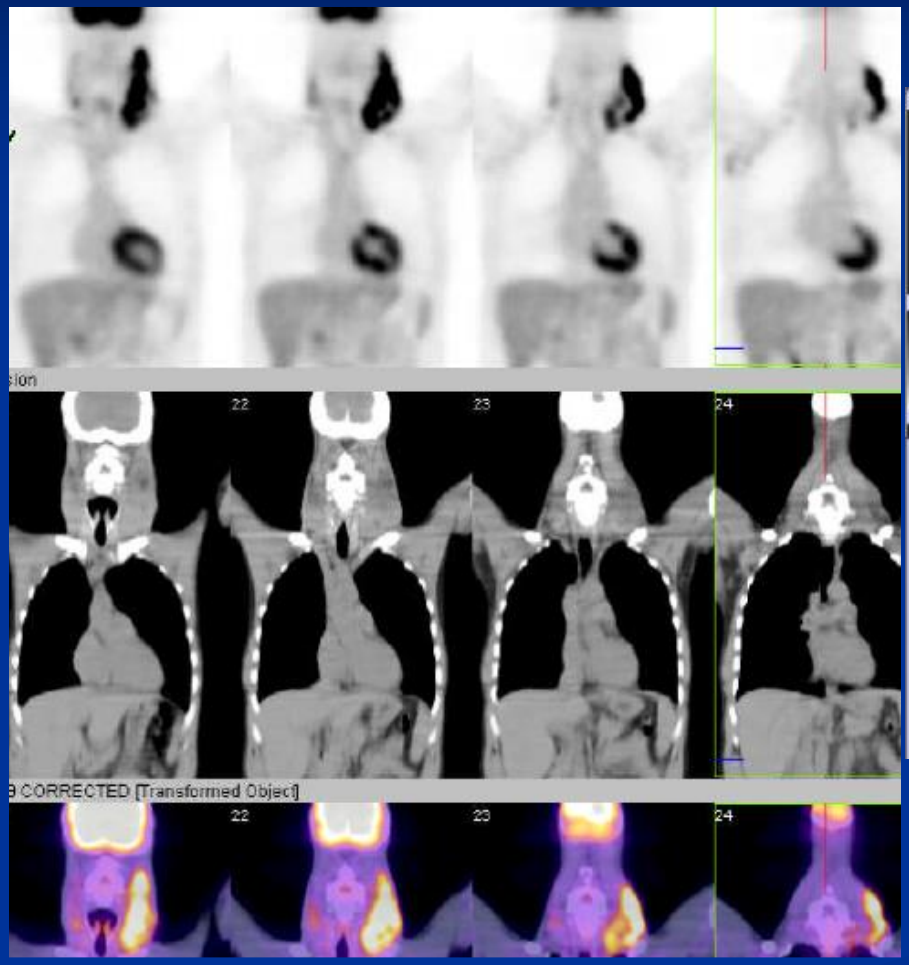


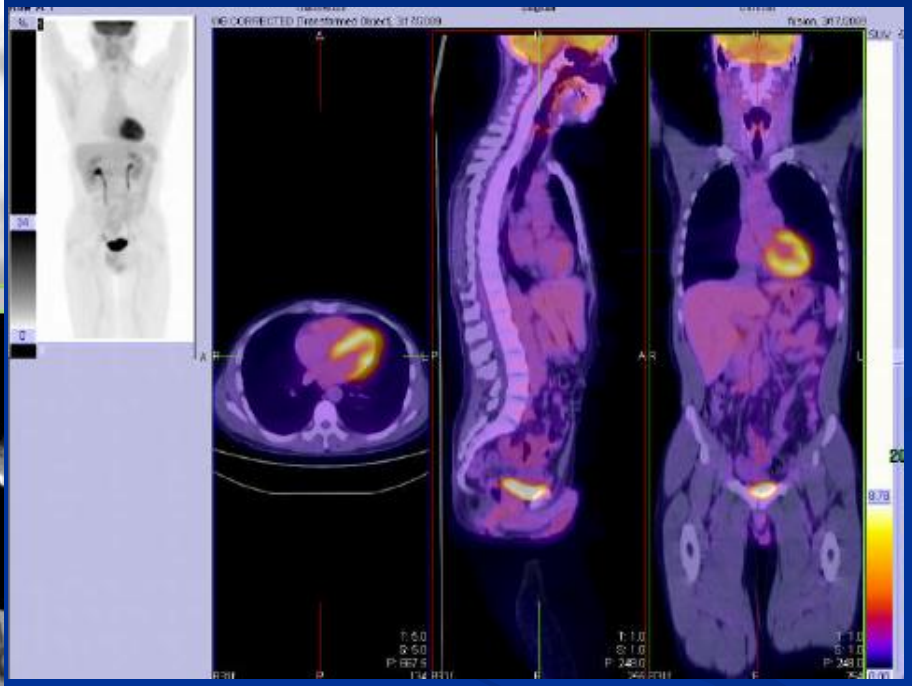
NEJM. 2016; Vol375:1867.

Brentuximab vedotin+Nivolumab in Hodgkin Disease



Plasmacytoid NHL Post HAART Rx





Treatment of Acquired Immunodeficiency Syndrome–Related Kaposi's Sarcoma With Lymphoblastoid Interferon

By Adan Rios, Peter W.A. Mansell, Guy R. Newell, James M. Reuben, Evan M. Hersh, and Jordan U. Gutterman

Virus Research 155 (2011) 189–194

Contents lists available at ScienceDirect

Virus Research

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

Complete inactivation of HIV-1 using photo-labeled non-nucleoside reverse transcriptase inhibitors

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Mark A. Wainberg