HIV associated HHV-8 Multicentric Castleman Disease

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centre de référence maladies rares CASTLEMAN

MaRIH
Filière de santé Maladies Rares Immuno-Hématologiques

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www.castleman.fr

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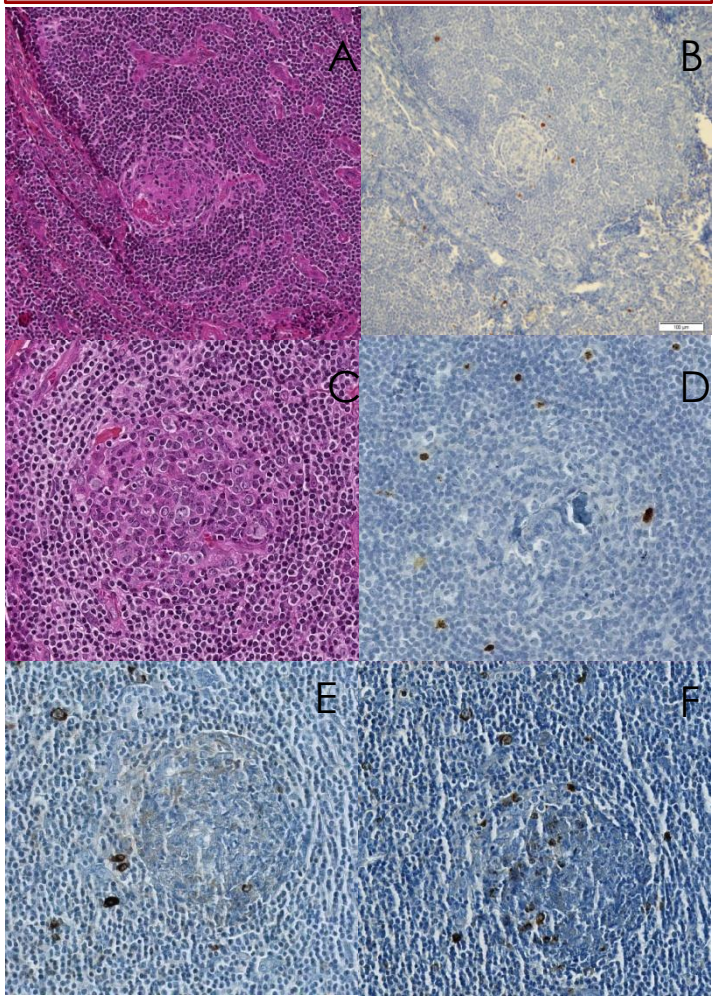
Castleman disease

Common histologic features

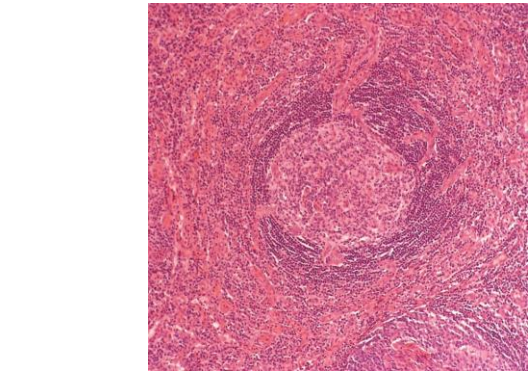


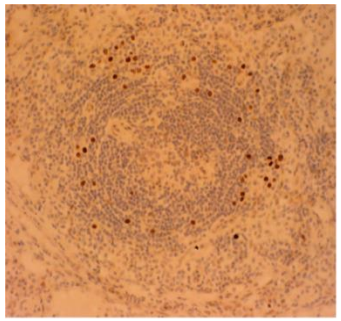
3 Diseases

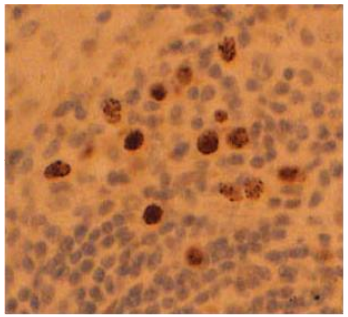
- Unicentric Castleman Disease
  - Usually asymptomatic
  - Mainly hyalino-vascular type
- Idiopathic Castleman Multicentric Disease
  - Systemic symptoms
  - Mainly Plasmacytic type
- **MC Multicentrique associée à HHV-8**
  - The most agressive disease
  - HHV-8 + plasmablastic cells
  - HIV associated but not only

HIV associated Castleman disease

- Looks like lymphoma
- Sometimes spontaneous remissions
- Relapsing disease
- Very agressive course
- Fatal Multi-Organ Failure syndrome
- Histology: Castleman







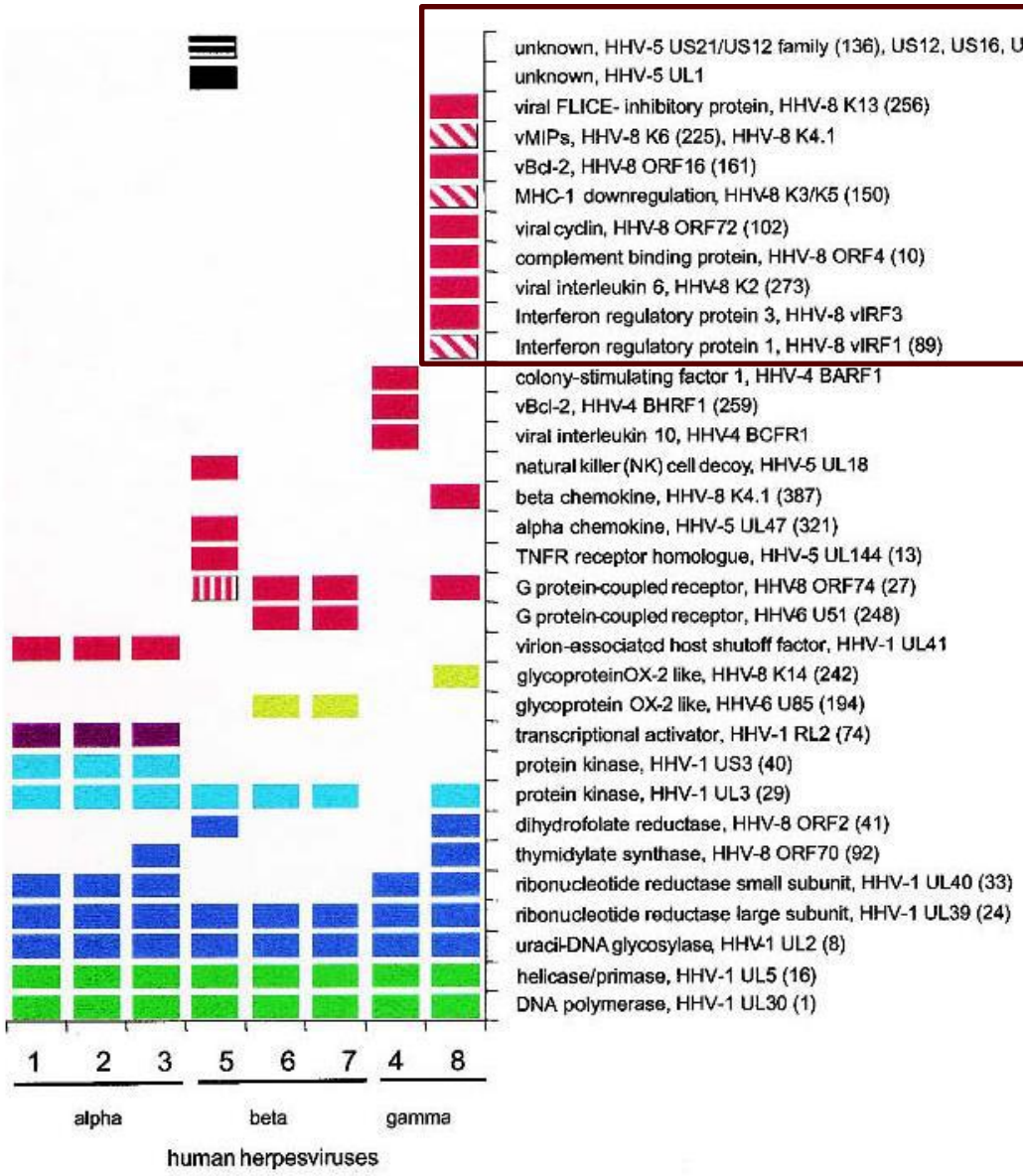
Kaposi's Sarcoma-Associated Herpesvirus-Like DNA Sequences in Multicentric Castleman's Disease

By Jean Soulier, Laurence Grollet, Eric Oksenhendler, Patrice Cacoub, Dominique Cazals-Hatem, Paul Babinet, Marie-Françoise d'Agay, Jean-Pierre Clauvel, Martine Raphael, Laurent Degos, and François Sigaux

Blood, 1995

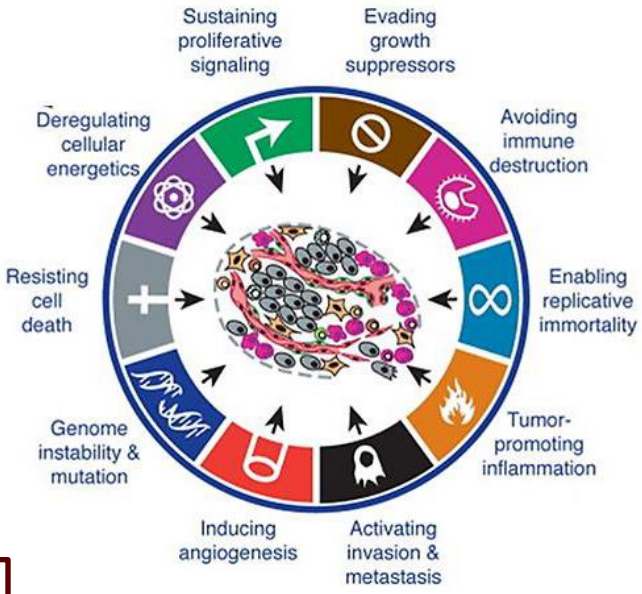
14 out of 14 HIV+ MCD
7 out of 17 HIV- MCD

Success by gene capture : viral homologs of host genes

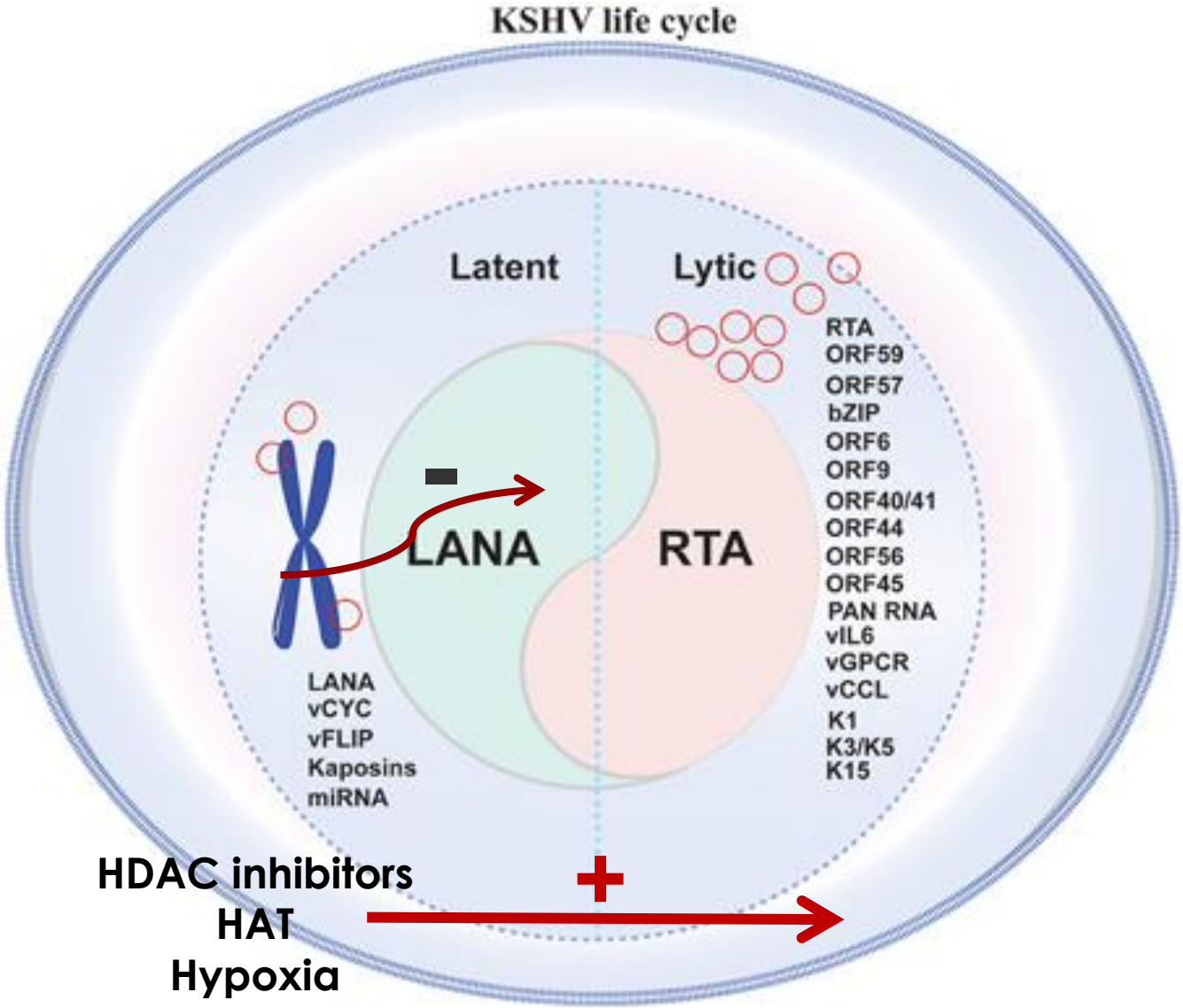


Viral replication and persistence strategies

VIRUS	CANCER	V-ONC	PATHWAYS	CANCER HALLMARK
EBV	BL	EBNA-1		
	NHL, PTLD, NPC	LMP-1	NFkB	
		LMP-2A	PI3K-AKT-mTOR, ERK	
HPV	CxCa, HNCC	E6	p53, mTOR, hTERT	
		E7	Rb	
		E5		
HBV	HCC	HBx	p53, Rb, Wnt, src, DNMTs, ras, PI3K JNK, NF-κB, ERK1/2, TGFβ, HDACs	
HCV	HCC	Core, NS3, Ns5A	p53, PARP, hTERT, TGFβ, HDACs,	
HTLV-1	ATL	Tax	NFkB, CREB, PI3K, DDR	
		HBZ	c-jun, E2F	
KSHV	KS	vFLIP	NFkB	
		LANA	p53, Rb, HIF, Notch, Wnt	
		vGPCR	PI3K-AKT-mTOR, ERK, p38, JNK, NFkB,	
		vIRF-1	αIFN, p53, ATM, Bim	



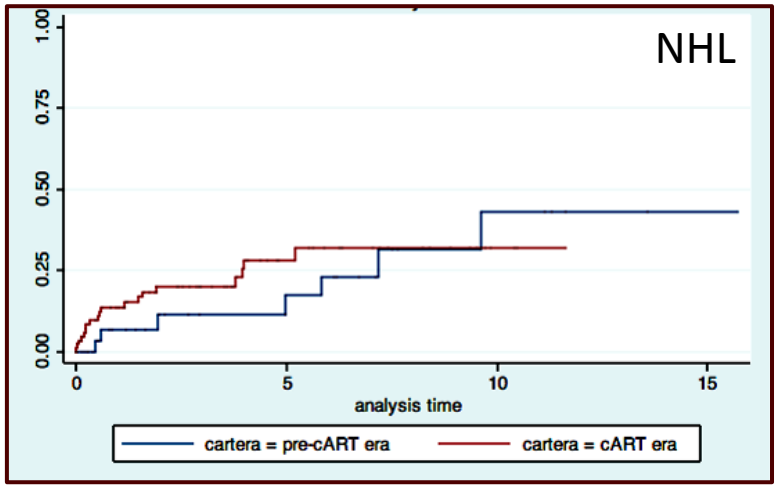
Replication vs persistence: Latent vs lytic viral cycles



HIV+ HHV8+ MCD

	HIV positive
number	176
Sex M / F	145 / 31
Age (median) years	42
Delay for diagnosis (median, months)	4.3
Fever	152 (86%)
Complications	
Splenomegaly	145 (82%)
Edema/Effusion	57(32%)
Lung	61 (35%)
Skin	13 (7%)
Kidney	16 (9%)
Hemophagocytic syndrome	71 (40%)
AIHA	30 (17%)
TAFRO syndrome	0
Kaposi sarcoma	90 (51%)
Leucocytes x10^6/L	4700
Lymphocytes x10^6/L	1150
Hemoglobin g/dL	8.2
Platelets x10^6/L	96000
CRP mg/L	154
Serum albumin g/L	27
Gammaglobulin g/L	24.4
LDH > N	43 (35%)
DAT +	78 (59%)
HHV8-DNA (median, log copies)	5
CD4+ T-cell count (median, x10^6)	182
Plasma HIV-RNA copies < 2 logs	51 (31%)
Follow-up (median, months)	21
Lymphoma during Follow-up	31

Lymphoma Risk

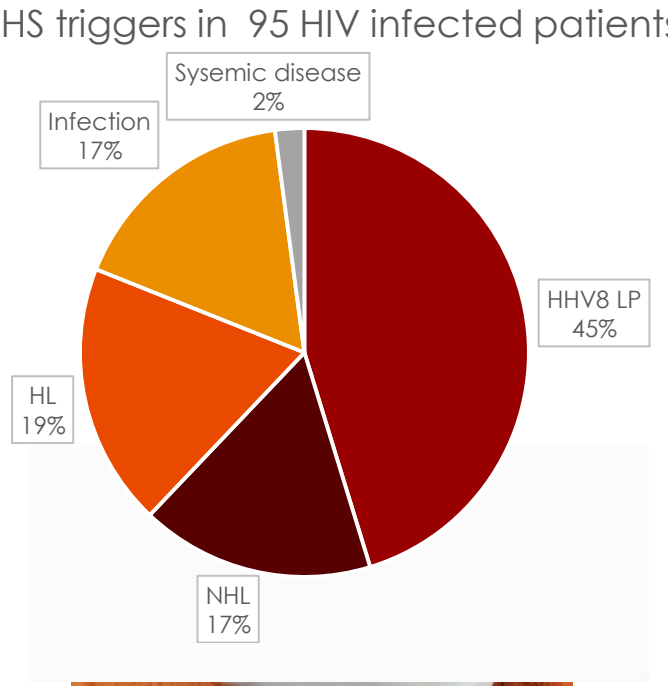


5-year
28% (97-08)
vs
17% (92-96)
p: .46

Oksenhendler et al. Blood 2002

COMPLICATIONS

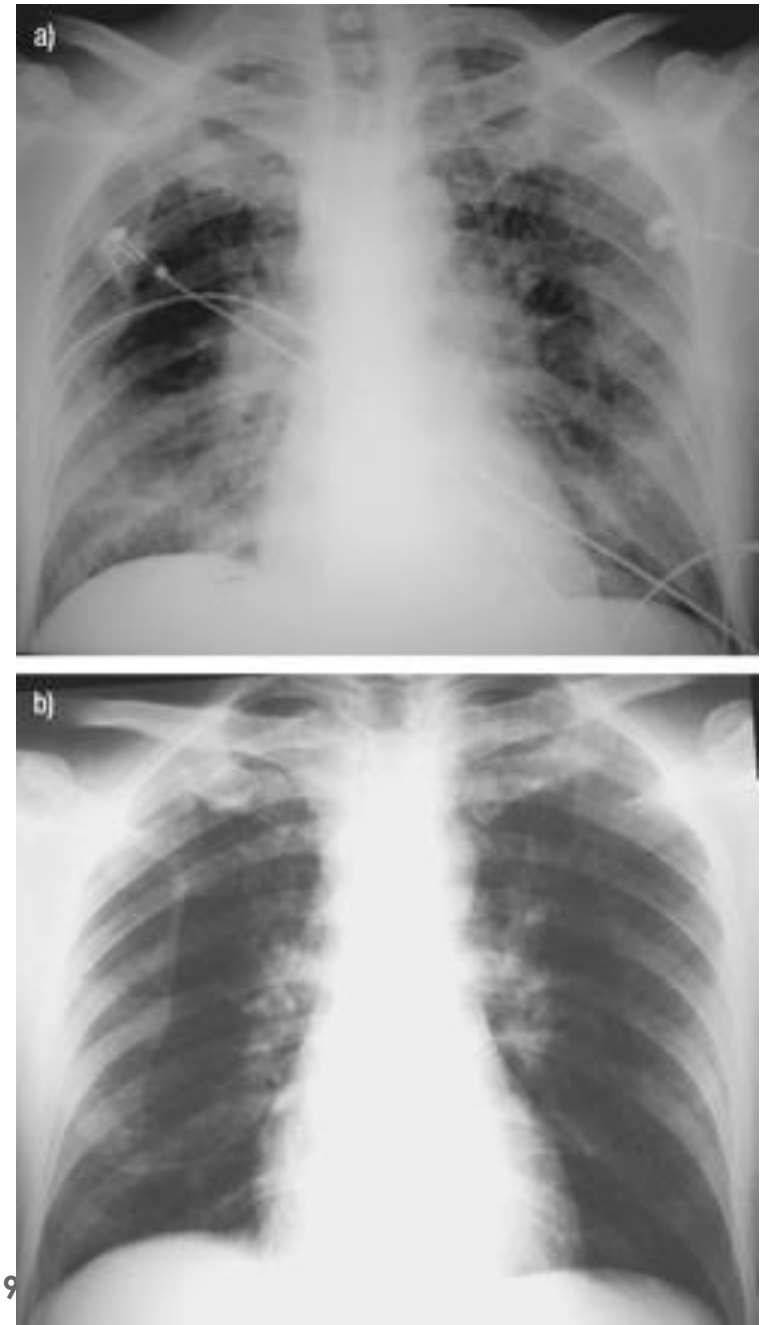
HEMOPHAGOCYTIC SYNDROME



Variable	Odds ratio	95% CI	P-value
Kaposi Sarcoma	19.356	4.574-81.905	< 2e-16
Adenopathy	8.593	1.995-37.01	0.005
Dyspnea	6.746	1.807-25.182	0.006
Lymphocytes<1 G/L	0.14	0.023-0.853	0.038

Galicier 2019

COMPLICATIONS

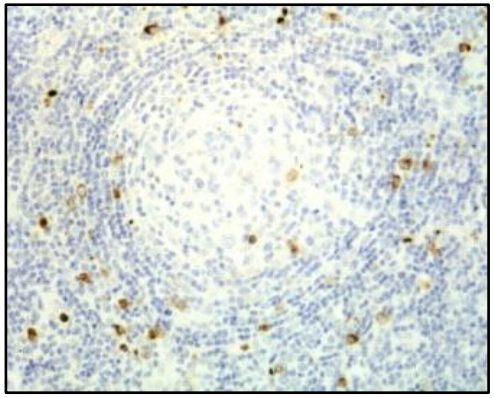


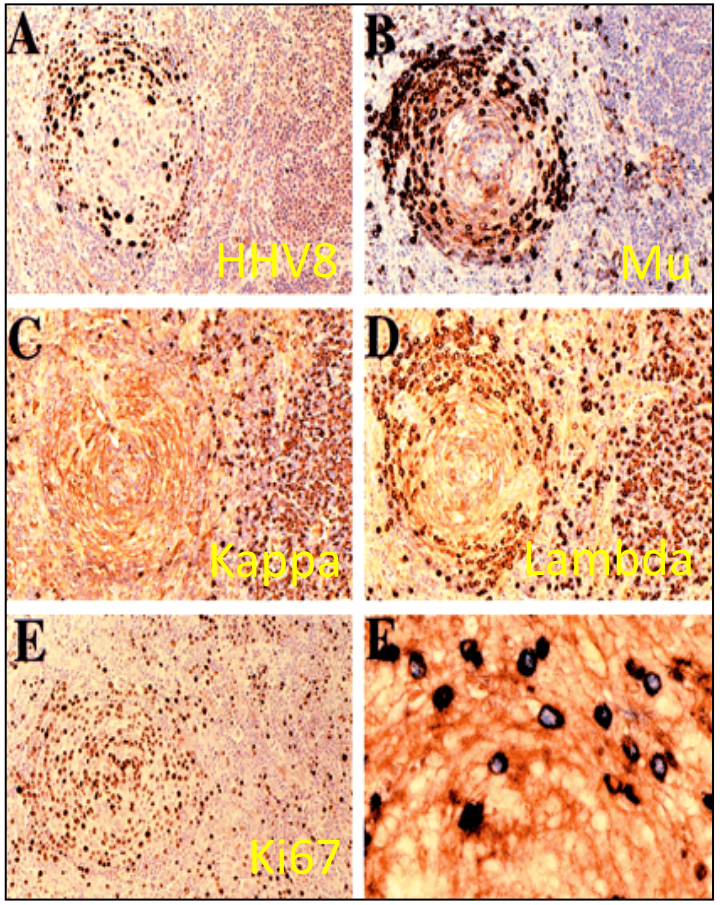
Sometimes…

- Diarrhea
- Autoimmune hemolytic anemia
- Thrombotic Microangiopathy
- Hypoglycemia
- Neuropathy

HHV8 MCD FLARE

- HHV8+ CD20- plasmablastic cells proliferation
- HHV-8 PCR DNA +++ (blood)
- IL6 et IL10 ↗↗
  (Oksenhendler et al. Blood 2000)
- *vIL6* ↗
  (Parravicini et al. Am J Pathol 2000)





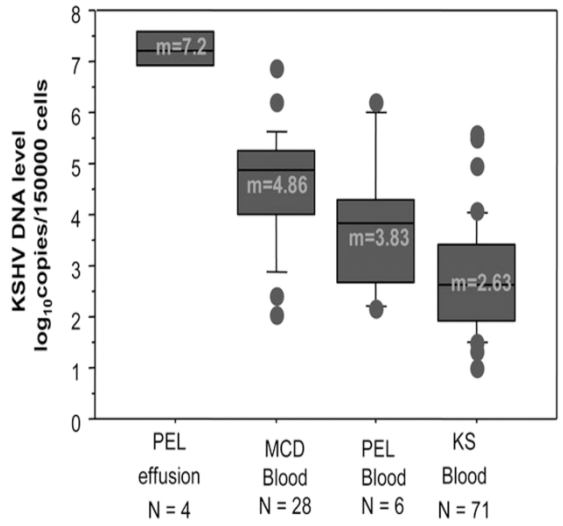
Dupin et al. Blood 2000
Du et al. Blood 2001

HHV8+ lambda+

HHV8 VL as a diagnostic tool

Disease	Patients, no.	Patients with detectable KSHV DNA, no. (%)		Median KSHV-DNA level, log_{10} copies/150,000 cells	
		Active disease	Disease in remission	Patients with active disease	Patients with disease in remission
KS	71	45/48 (94)	1/23 (4)	2.63	1.00
MCD	28	24/24 (100)	0/4 (0)	4.86	1.96
PEL	6	6/6 (100)	NA	3.83	NA

NOTE. KS, Kaposi sarcoma, MCD, multicentric Castleman disease; PEL, primary effusion lymphoma; NA, not applicable.



Marcellin 2007

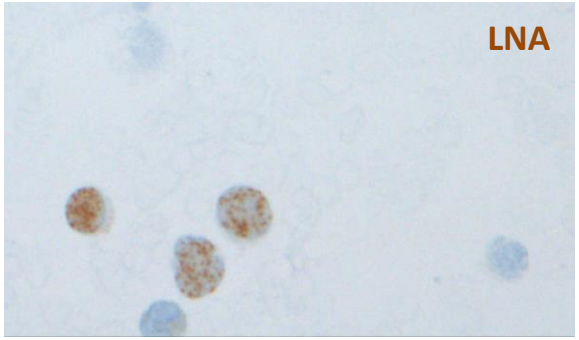
HHV8 PCR > 1000 c/ml >> MCD

Specificity 94%
NPV 97%

Sayer 2016

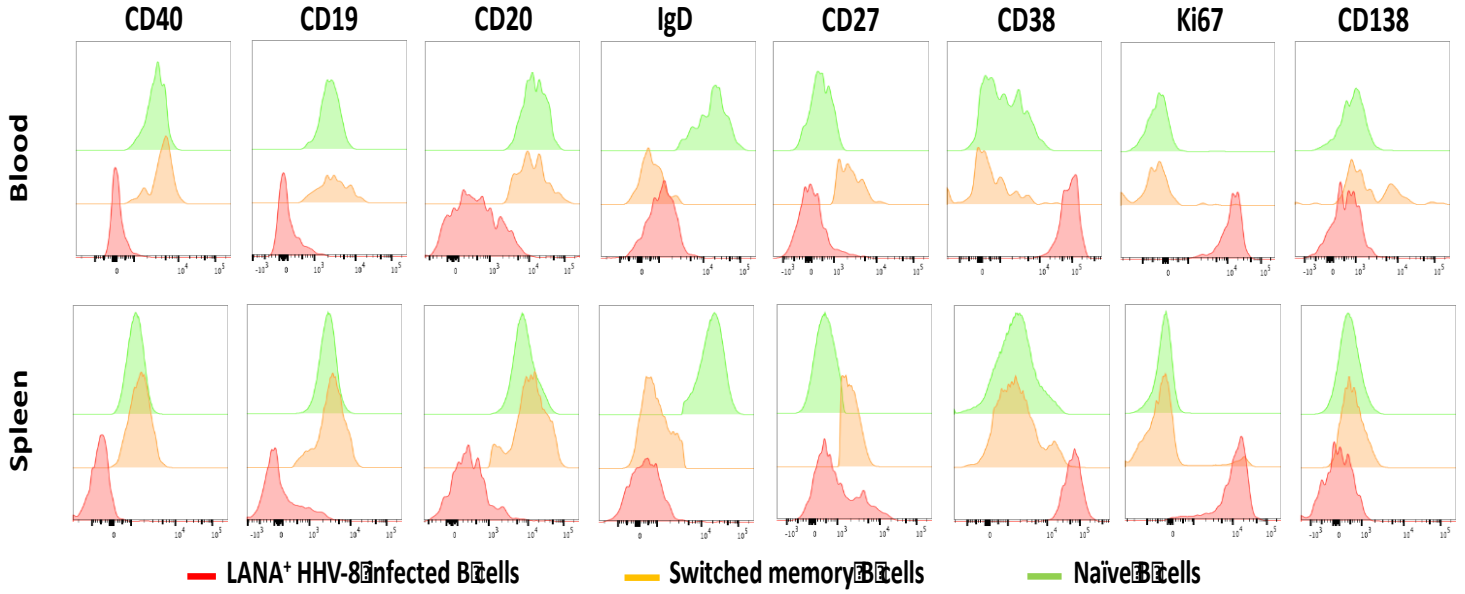
Flow cytometric phenotyping of LNA+ cells

LNA+ λ+ plasmablast-like cells are detectable in the blood of patients with active MCD and HHV-8 PCR>3 log (0.02-6% of PBMC)



LNA staining, blood smear, V. Meignin

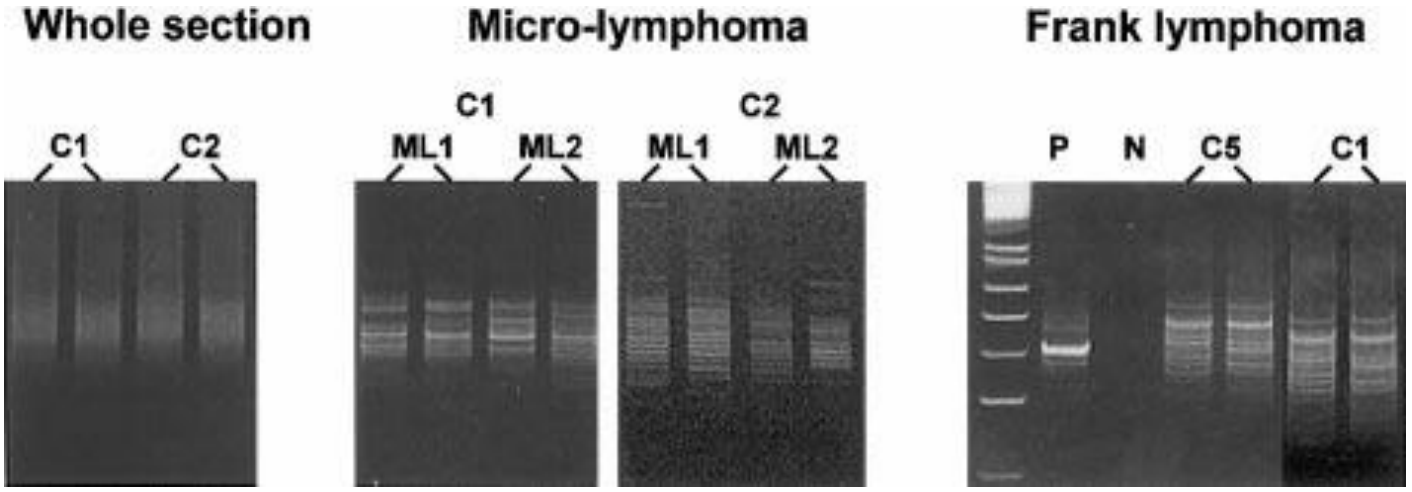
Their phenotype is very similar to lymph node and splenic LNA+ cells



Sbihi et al, submitted

The immune paradox of LNA+ cells

LNA+ cells are **polyclonal B cells** despite monotypic restriction



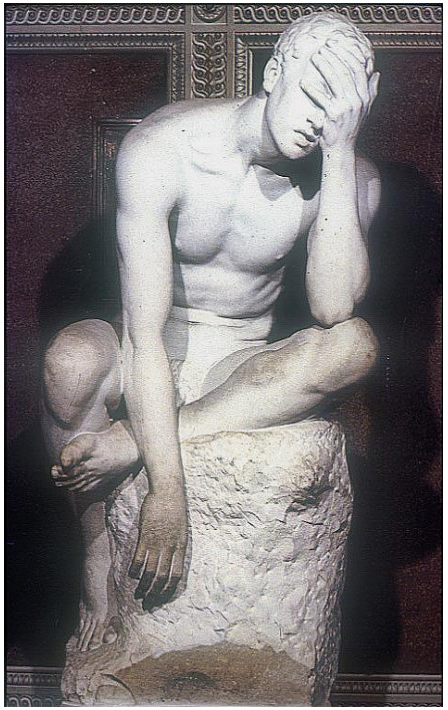
Fr3-JH PCR

LNA+ cells show « **no** » **somatic hypermutations (0-3 changes)** despite a PB-like phenotype

Du et al, Blood 2001

HIV + HHV8+ MCD

- Monotypic IgM lambda cells
  … but polyclonal
- Plasmacytic differenciation
  … But unmutated naive B cells
- Proliferation
  … and replication



Etoposide

Is highly effective

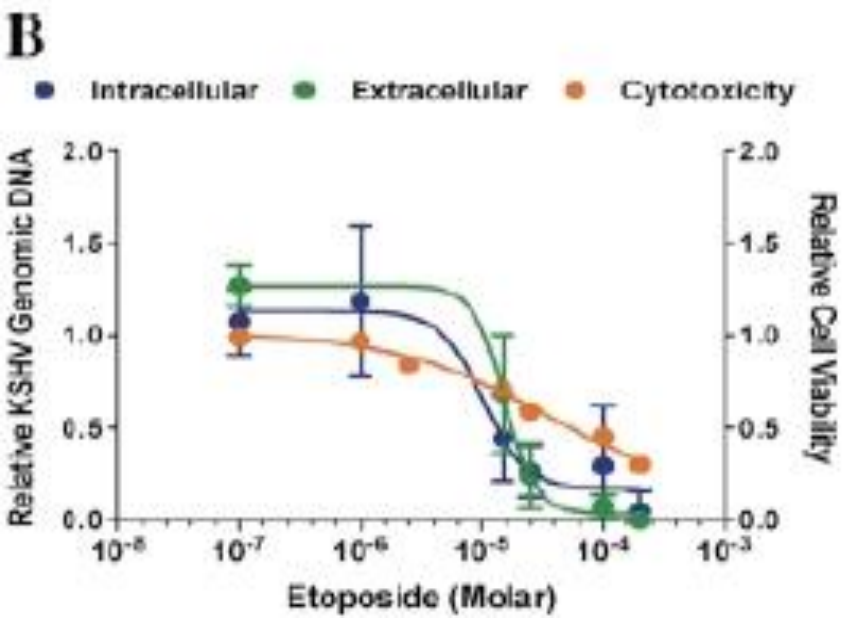
FLARE TREATMENT

150 mg/m² IV,
then 100 mg/m² orally /week

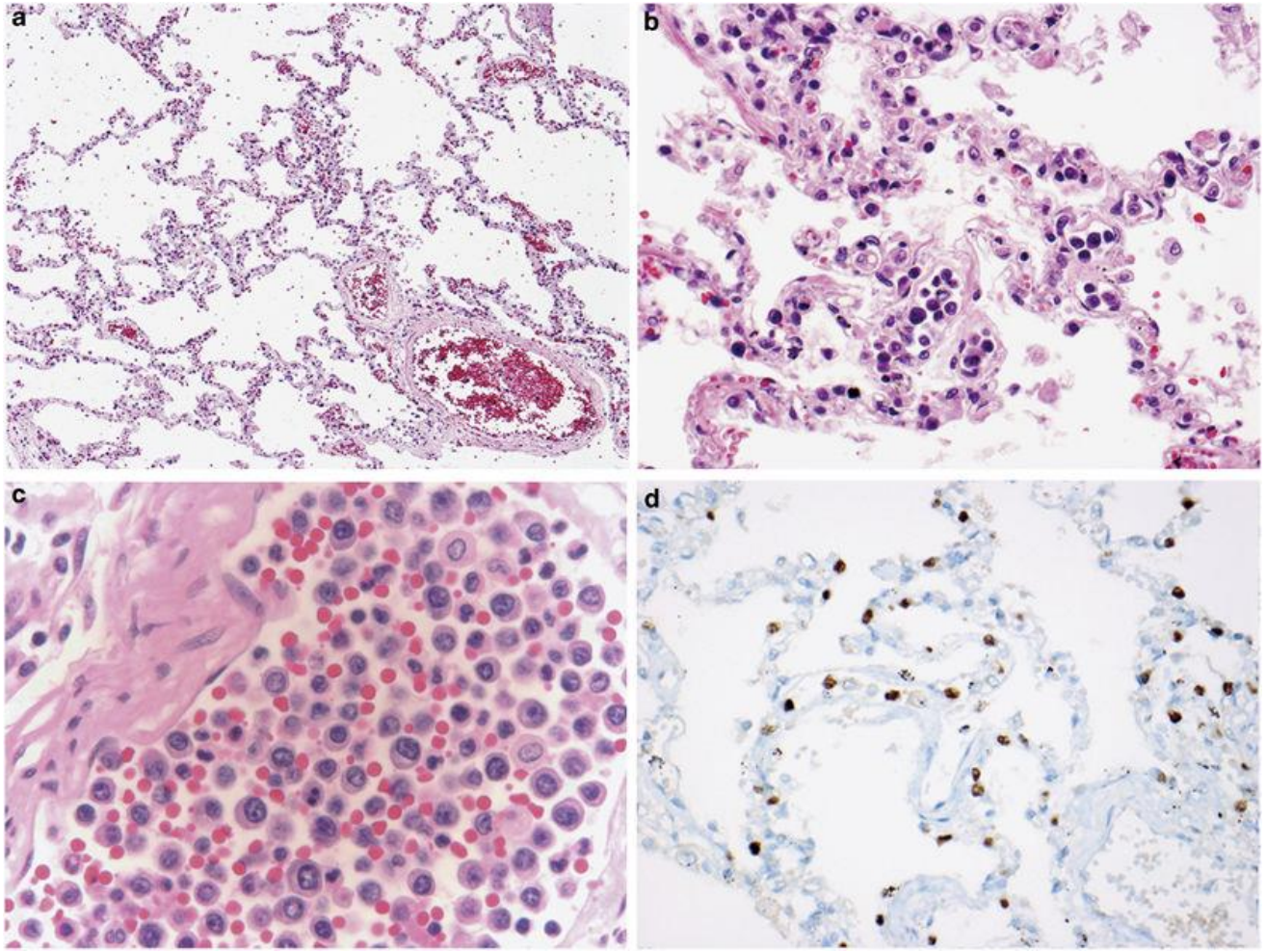
* Rapid control of the flare (42-48h)

* Mild Hematotoxicity

* Oncogenicity limits long-term use



Intravascular HHV8 DLBCL



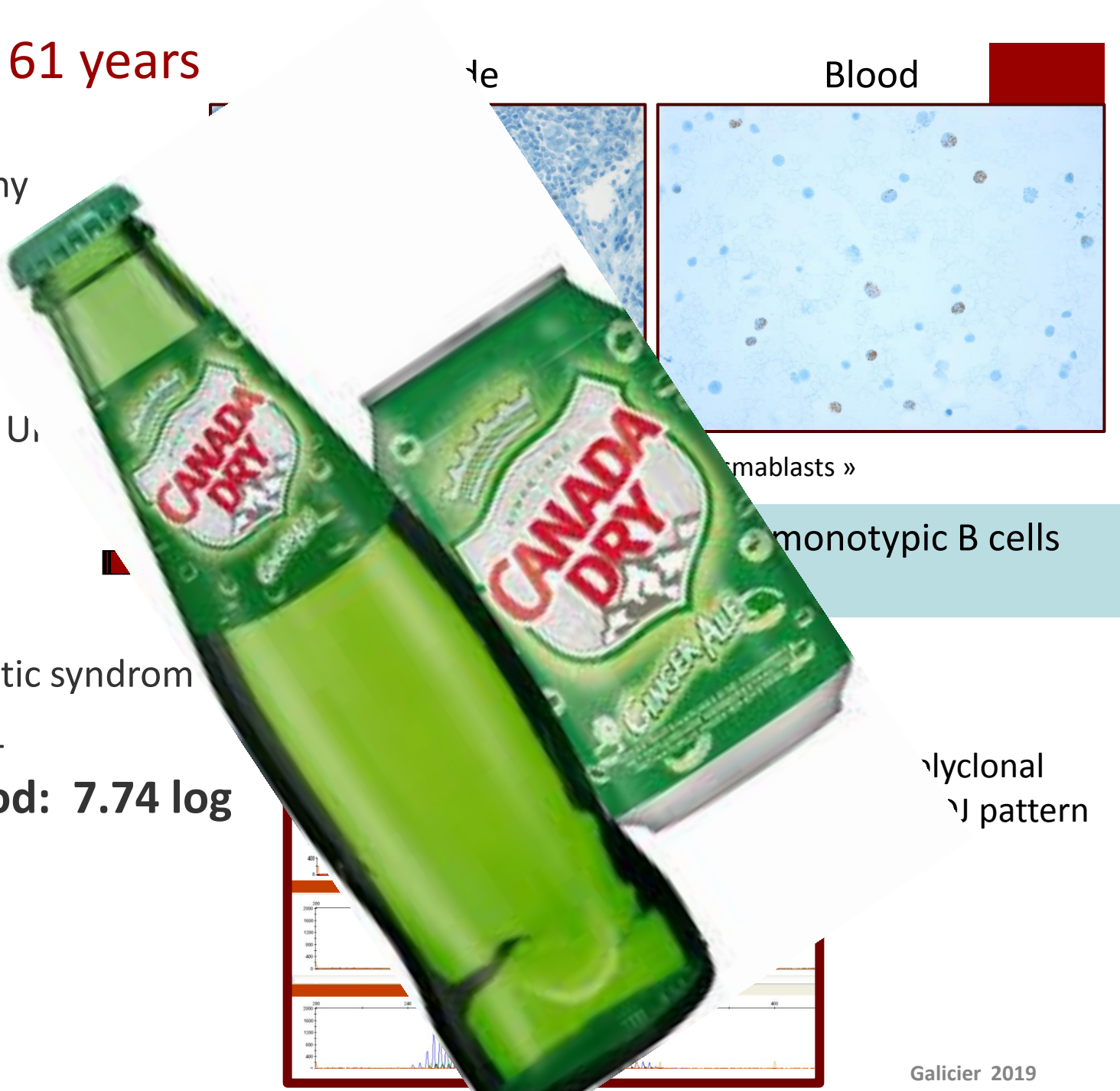
IgM lambda

EBER négatif

Ferry Modern Pathol 2009

Male, HIV+, 61 years

- Fever
- Polyadenopathy
- Splenomegaly
- Dyspnea
- Edema
- Intensive Care U



- Hemophagocytic syndrom
- CRP: 188 mg/L
- **HHV8 / blood: 7.74 log**

Primary Effusion Lymphoma

1186 THE NEW ENGLAND JOURNAL OF MEDICINE May 4, 1995

KAPOSI'S SARCOMA–ASSOCIATED HERPESVIRUS-LIKE DNA SEQUENCES IN AIDS-RELATED BODY-CAVITY–BASED LYMPHOMAS

ETHEL CESARMAN, M.D., PH.D., YUAN CHANG, M.D., PATRICK S. MOORE, M.D., JONATHAN W. SAID, M.D., AND DANIEL M. KNOWLES, M.D.

Table 1. Results of Screening for KSHV Sequences by Southern Blot Hybridization and PCR.

Diagnoses	No. of Neoplasms	No. Positive for KSHV		Percent Positive
		Southern blot	PCR	
In patients without AIDS				
Chronic lymphocytic leukemia or small lymphocytic lymphoma	8	0	0	0
Monocytoid B-cell lymphoma	2	0	0	0
Follicular lymphoma	12	0	0	0
Diffuse large-cell lymphoma	27	0	0	0
Small-noncleaved-cell lymphoma (Burkitt's and non-Burkitt's)	14	0	0	0
Lymphoblastic lymphoma	4	0	0	0
Anaplastic large-cell lymphoma	13	0	0	0
Plasmacytoma or multiple myeloma	11	0	0	0
Hairy-cell leukemia	3	0	0	0
Acute lymphoblastic leukemia	4	0	0	0
Cutaneous T-cell lymphoma	8	0	0	0
Peripheral T-cell lymphoma	10	0	0	0
Adult T-cell leukemia or lymphoma	5	0	0	0
Hodgkin's disease	7	0	0	0
Post-transplantation lymphoproliferative disorder	23	0	0	0
Subtotal	151	0	0	0
In patients with AIDS				
Diffuse large-cell lymphoma	12	0	0	0
Immunoblastic plasmacytoid lymphoma	8	0	0	0
Small-noncleaved-cell lymphoma (Burkitt's and non-Burkitt's)	9	0	0	0
Peripheral T-cell lymphoma	1	0	0	0
Anaplastic large-cell lymphoma	1	0	0	0
Body-cavity–based lymphoma	8	6*	8	100
Hodgkin's disease	3	0	0	0
Subtotal	42	6	8	19
All patients	193	6	8	4

*Only six of eight neoplasms were examined by Southern blot hybridization because of insufficient DNA in two cases; all six neoplasms tested were positive for KSHV sequences.

Table 2. Clinical Characteristics of Eight Homosexual Men with AIDS-Related Body-Cavity–Based Lymphomas.

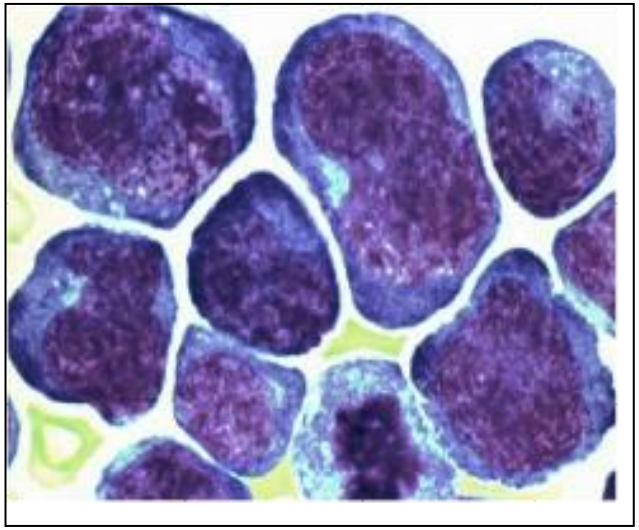
Patient No.	Age (yr)	Site of Lymphoma	Other Tumors	Outcome	Reference
1	46	Peritoneum	None	Died of lymphoma 12 days after diagnosis	Chadburn et al.[20]
2	31	Pleura	None	Died of HIV-associated meningoencephalitis 7 mo after lymphoma diagnosis	Knowles et al.[14]
3	40	Pleura	Kaposi's sarcoma and submandibular-gland lymphoma	Died 5 mo after initial lymphoma, 10 days after diagnosis of pleural effusion	Knowles et al.[14]
4	35	Peritoneum	None	Died of lymphoma 1 mo after diagnosis	Walts et al.[15]
5	38	Pericardium	None	Died of lymphoma 5 mo after diagnosis	
6	58	Pleura	None	Died of lymphoma 14 mo after diagnosis	
7	30	Pericardium	None	Died by suicide while recovering from pericardiectomy	Walts et al.[15]
8	32	Pleura	Kaposi's sarcoma	Died of disseminated Kaposi's sarcoma 4 mo after lymphoma diagnosis	Walts et al.[15]

8 out of 42 HIV+ NHL

0 out of 151 HIV- NHL

Primary Effusion Lymphoma & « solid » PEL

- **Ascite** ou **Pleurésie** ou **Péricardite**
- Atteinte extra-cavitaire pas si rare
- Mauvais pronostic: médiane OS < 12 mois



- **Grandes cellules B** immunoblastiques/anaplasiques post-Gc
- Phénotype « non-B non-T »: CD30+ CD138+ HLA-DR+
  Expression aberrante de marqueurs T
- **HHV8+ 100%, EBV coinfection > 80%**
- Caryotype complexe

Lymphome des séreuses n=51

Characteristics	All patients ($n = 51$)	Classic group ($n = 34$)	Extracavitary group ($n = 17$)
Demographic characteristics			
Sex male, *n* (%)	47 (92)	31 (91)	16 (94)
Median age, years (IQR)	45 (39–53)	45 (40–54)	41 (36–48)
HIV characteristics			
Mode of HIV transmission, *n* (%)			
Sexual	45 (88)	30 (88)	15 (88)
IVDU	5 (10)	3 (9)	2 (12)
Unknown	1 (2)	1 (3)	0
Median HIV duration, years (IQR)	8 (1.5–15.7)	4 (1–12)	10 (8–16)
Prior AIDS, *n* (%)	33 (64.7)	24 (70.6)	9 (53)
cART at diagnosis, *n* (%)	35 (68.6)	24 (70.6)	11 (64.7)
Median cART duration, months (IQR)	40 (18–63.4)	30 (12.3–52.6)	62 (49.3–123)
Undetectable plasma HIV-RNA, *n* (%)	25 (49)	16 (47)	9 (53)
CD4 cell count			
Median, $\times 10^6$ L^{-1}, median (IQR)	204 (90–370)	185 (90–343)	207 (103–377)
Nadir, $\times 10^6$ mL^{-1}, median (IQR)	99 (45–180)	99 (56–145)	159 (35–228)
KS, *n* (%)	25 (49)	19 (56)	6 (35.3)
Castleman disease, *n* (%)	18 (35.3)	11 (32.3)	7 (41)
PEL characteristics			
IPI > 2, *n* (%)	34 (67)	25 (80)	9 (53)
PS > 2, *n* (%)	29 (57)	18 (53)	11 (65)
LDH > normal, *n* (%)	26 (52)	16 (48.5)	10 (59)
ICU stay, *n* (%)	14 (29)	10 (32)	4 (23.5)
EBV + PEL, *n* (%)	34 (66.6)	24 (70.6)	10 (59)
CR, *n* (%)	28 (56)	21 (63.6)	7 (41)
Treatment			
Standard chemo, *n* (%)	45 (88.2)	28 (82.3)	17 (100)
With HD-MTX, *n* (%)	32 (62.7)	23 (67.6)	9 (53)
Without HD-MTX, *n* (%)	13 (25.5)	5 (14.7)	8 (47)
Low dose/no chemo, *n* (%)	6 (11.7)	6 (17.6)	0 (0)

Guillet 2016

Rituximab

Long term Control

- **Allows long term remission**

	n	Patients	One year-EFS	KS flare
Bower et al.	20	1st line	**92%**	**4 / 11**
ANRS 117 CastlemaB trial	24	Chemo-dependant	**71%**	**8 / 12**

Bower et al.
Ann Int Med 2007
Gérard et al.
J Clin Oncol 2007

- **Dramatic reduction of lymphoma risk**

R+ :LNH : 1-> 4.2 / 1,000 pt.y.
R- :LNH : 17-> 69.6 / 1,000 pt.y.
15 /16 HHV8+

NHL probability at 5 year (%)
R+ : 3 (0-20)
R- : 31 (19-47)

HR: .09
(95%CI, .01-.70)

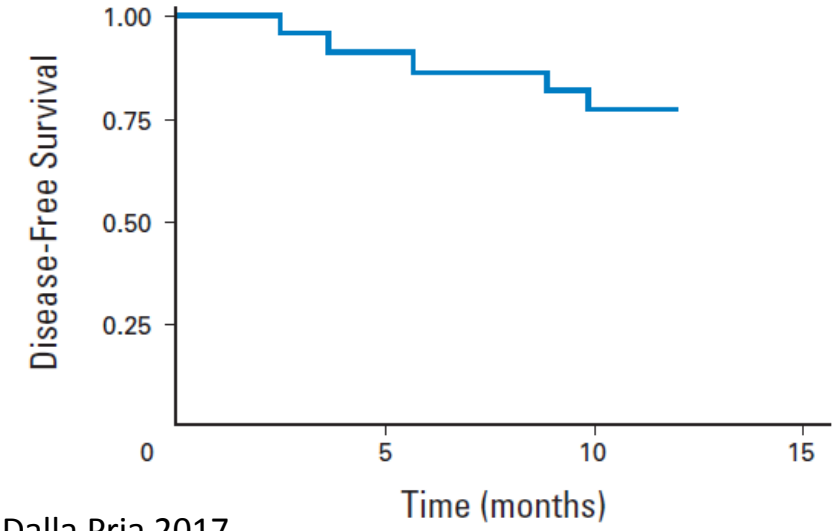
Gérard et al. Blood 2012

- **3 major side effects**
  - Infection in the most immunocompromised patients (< 50 CD4/mm3)
  - MCD flare (D8-D15)
  - Kaposi sarcoma flare

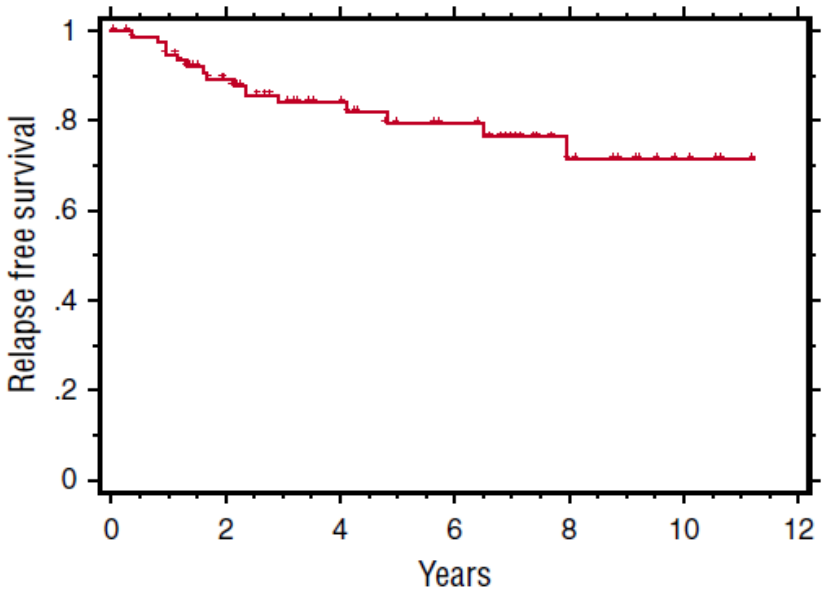
Relapse

- Relapse rate at 5 year: 18%
- No clear predictive factor of relapse

Gérard 2007



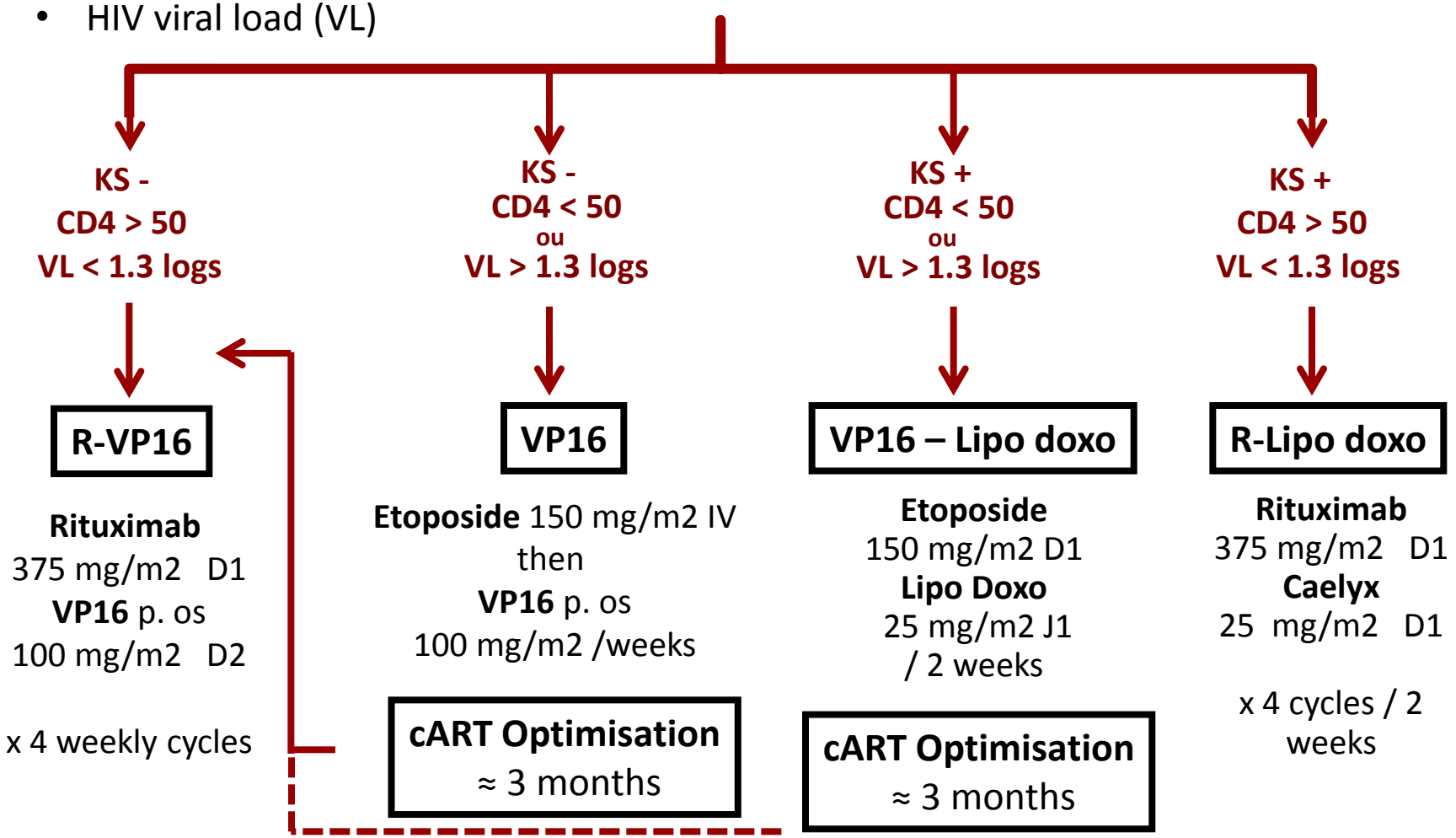
Dalla Pria 2017



Galicier 2019

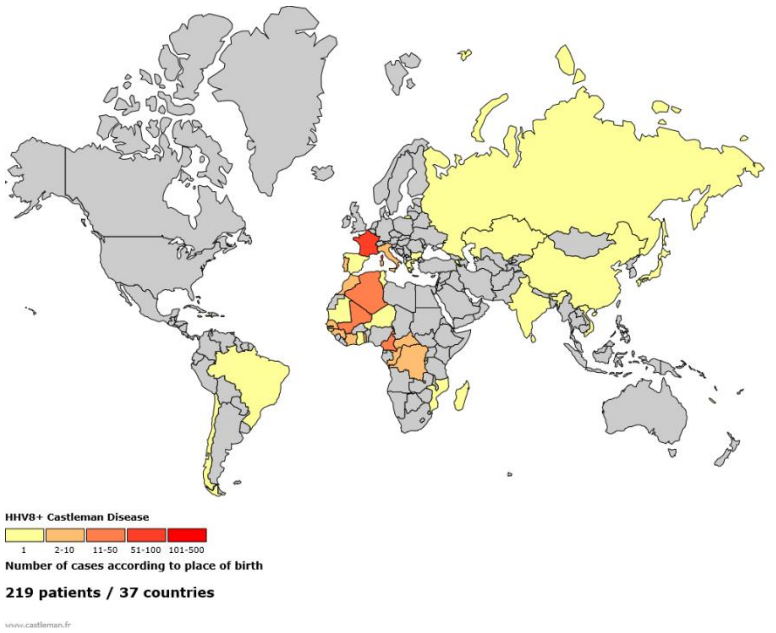
Therapeutic strategy

- **Etoposide and Rituximab combination**
- **Adaptated to:**
  - Active Kaposi Sarcoma
  - Immunodeficiency (CD4)
  - HIV viral load (VL)



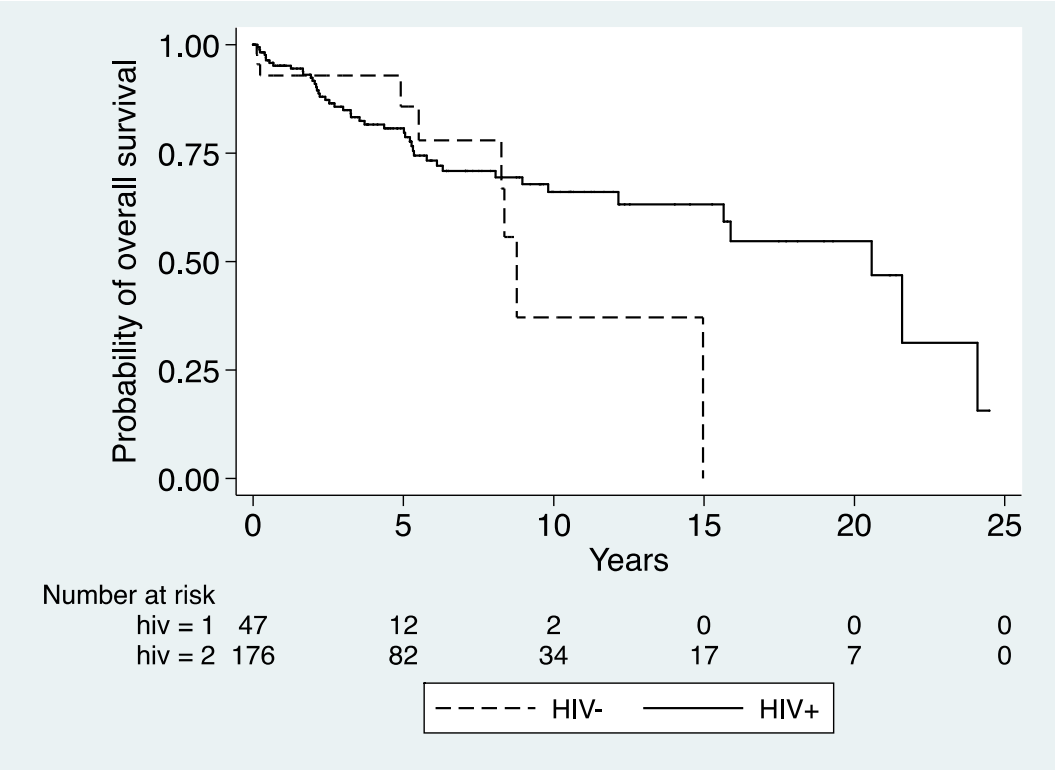
HIV - HHV-8+ MCD

	HIV positive	HIV negative
number	176	47
Sex M / F	145 / 31	34 / 13
Age (median) years	42	64
Fever	152 (86%)	36 (77%)
Complications		
Splenomegaly	145 (82%)	29 (62%)
Edema/Effusion	57(32%)	28 (60%)
Lung	61 (35%)	15 (32%)
Skin	13 (7%)	6 (13%)
Kidney	16 (9%)	7 (15%)
Hemophagocytic syndrome	71 (40%)	14 (30%)
AIHA	30 (17%)	10 (22%)
TAFRO syndrome	0	0
Kaposi sarcoma	90 (51%)	19 (40%)
Hemoglobin g/dL	8.2	9.1
Platelets x10^6/L	96000	148000
CRP mg/L	154	111
Serum albumin g/L	27	30.2
Gammaglobulin g/L	24.4	23
Monoclonal gammapathy	33 (25%)	17 (42%)
Ferritin > 5N	45 (58%)	13 (37%)
DAT +	78 (59%)	26 (72%)
HHV8-DNA (median, log copies)	5	5.4
CD4+ T-cell count (median, x10^6)	182	649
Follow-up (median, months)	21	54
Lymphoma during Follow-up	31	5
Deaths	45 (25.5%)	9 (19%)



Dossier et al. Clin Infect Dis 2013
Oksenhendler et al. BJH 2017

Overall Survival



5-year OS
HIV- : 85.7% (95%CI: 61,3- 95,3)
HIV+ : 80,7% (95%CI: 73 – 86,4)
NS

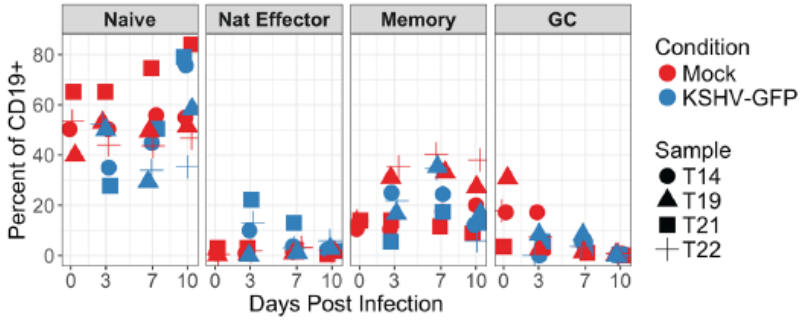
Median Age at diagnosis
HIV- : 64 years
HIV+ : 42 years

Unanswered questions

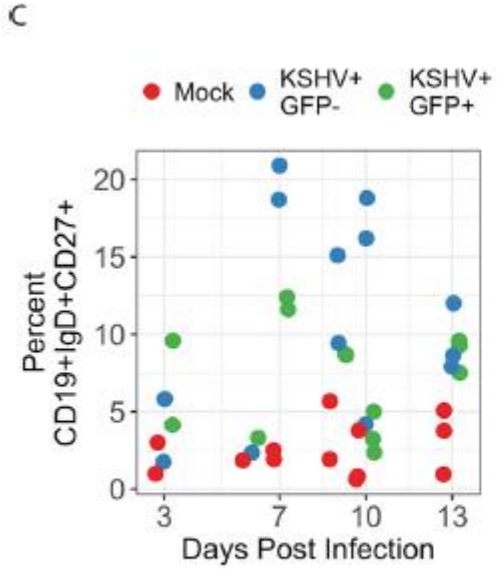
- **A unique lymphoproliferative disorder**
  - Viro-induced
  - Polyclonal despite IgM lambda restriction
  - Unmutated despite plasmacytic differenciation

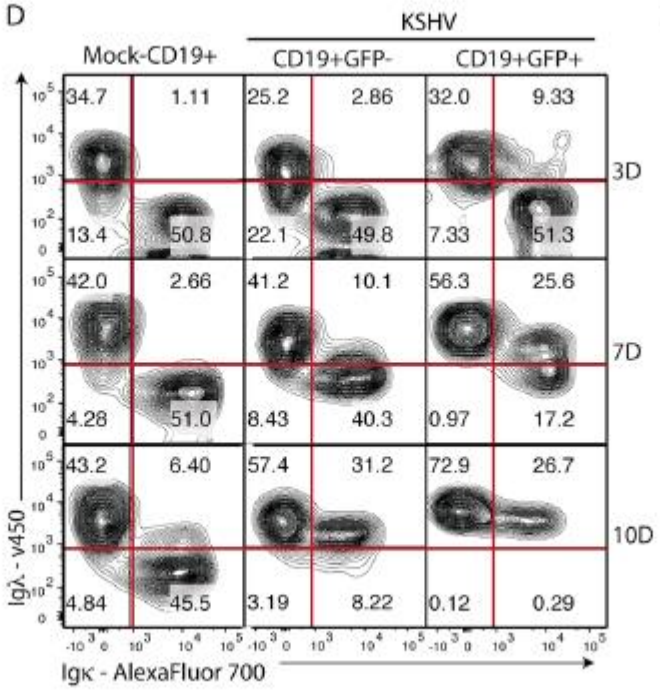
How HHV8 force naive B cells to Lambda restriction and plasmacytic differenciation ?

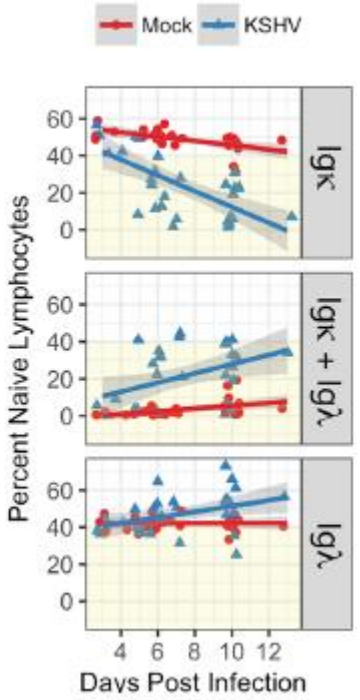
HHV8 Primary infection



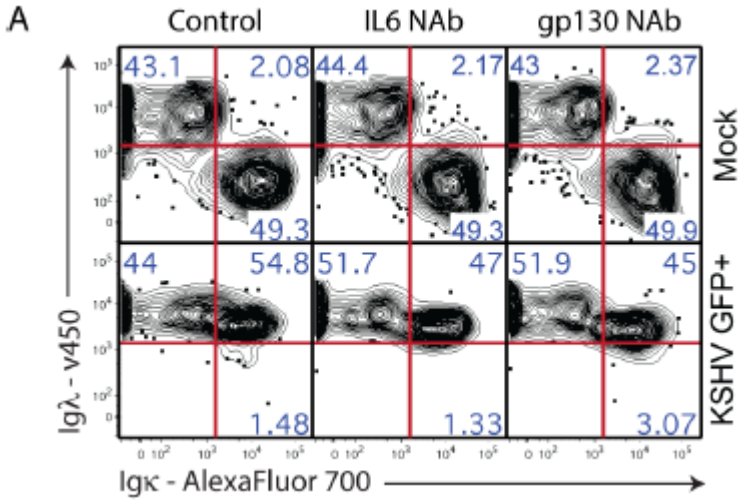
Totonchy Plos Pathol. 2018

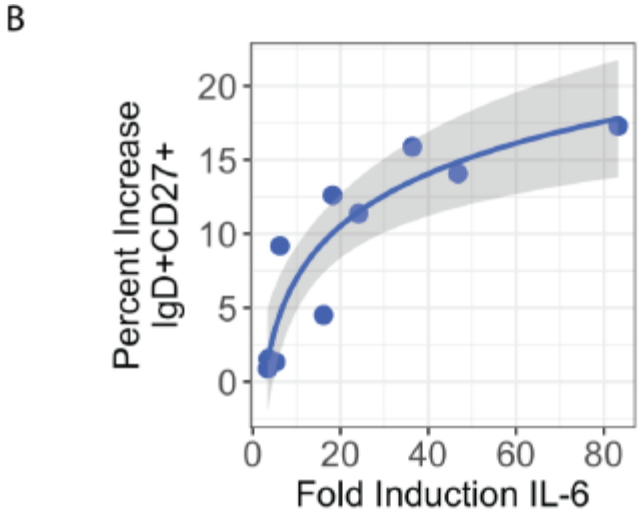


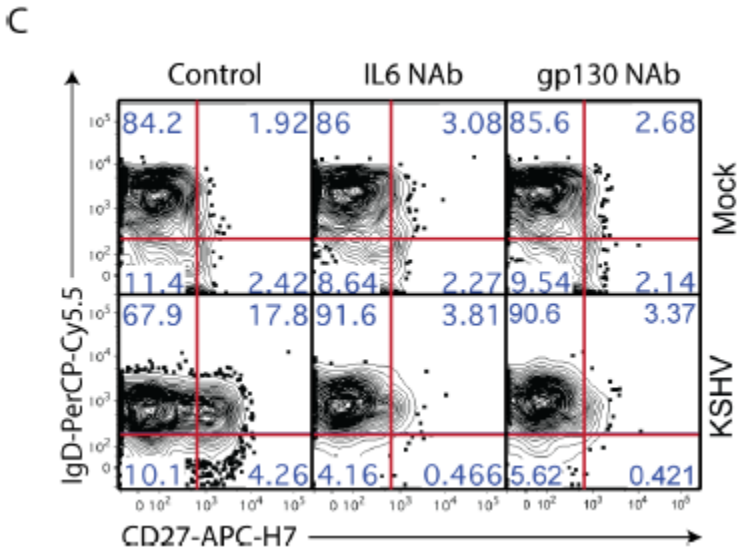




L'IL6 modifie le phénotype mais pas la recombinaison V(D)J



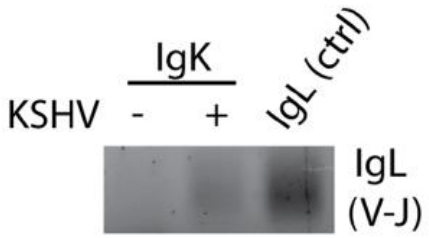




Oksenhendler 2018

HHV8 manipule la recombinaison V(D)J *via* RAG

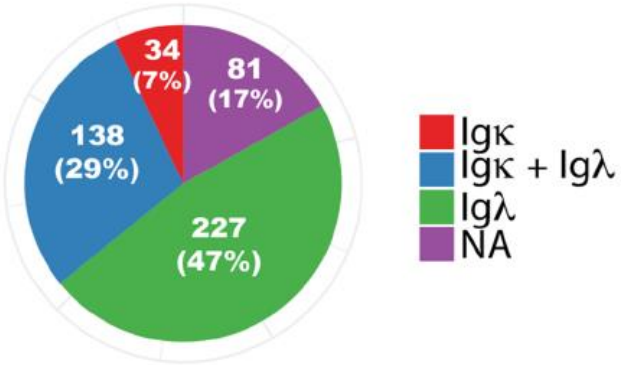
A



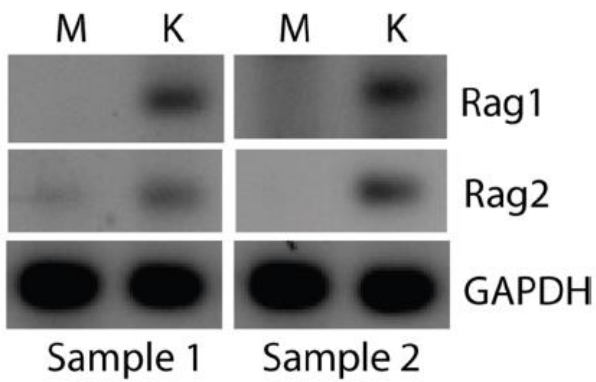
B

	S1	S2	S3
Control IgL	79 %	54 %	81 %
KSHV IgK → IgL	32 %	50 %	87 %

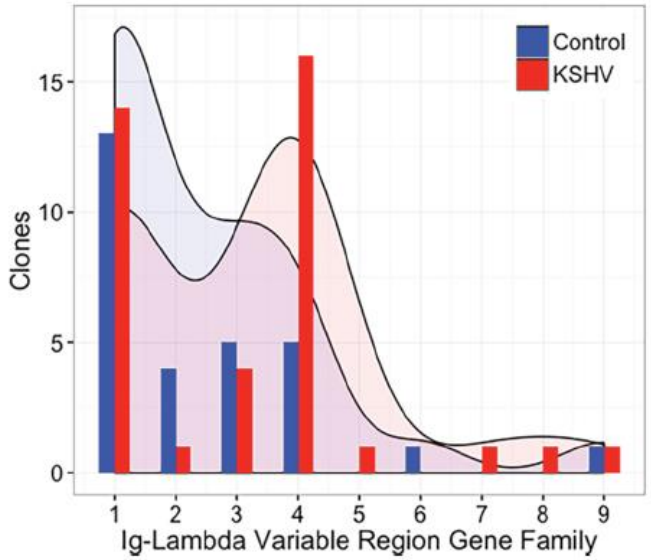
C



D



E



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  - Viro-induced
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Do Castleman histologic features still the gold standard for diagnosis ?

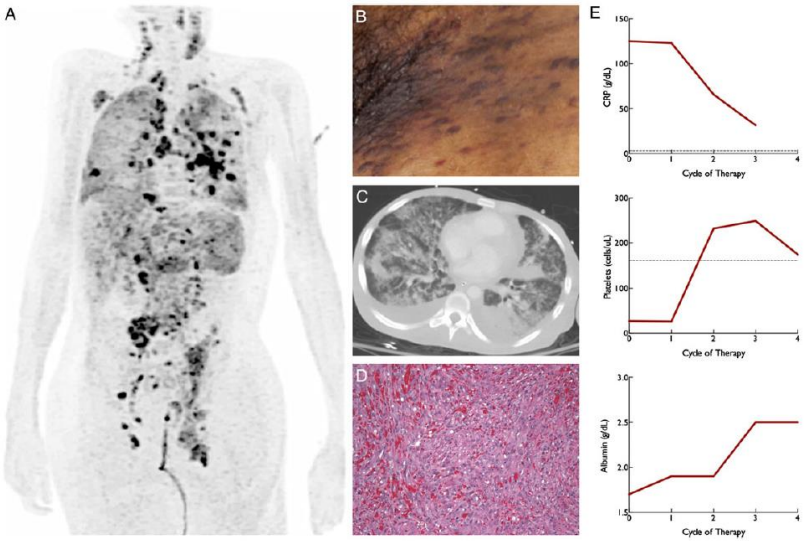
KSHV Inflammatory Cytokine Syndrome

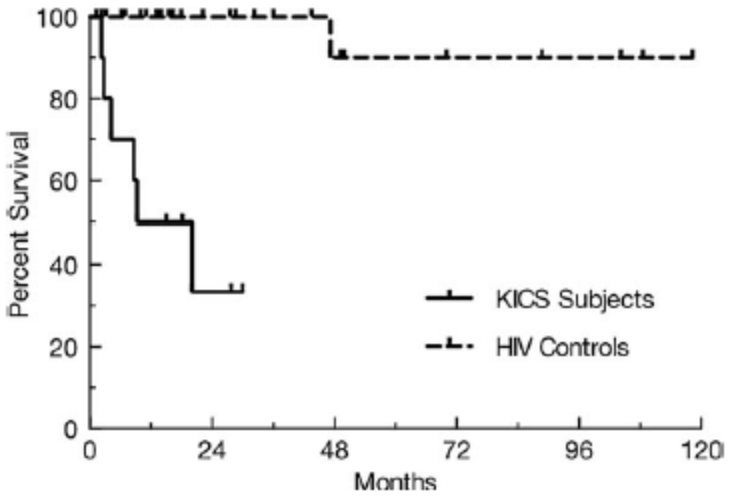
Table 1. Working Case Definition of KSHV-inflammatory Cytokine Syndrome (KICS)

1. Clinical manifestations	
a. Symptoms	b. Laboratory abnormalities
Fever	Anemia
Fatigue	Thrombocytopenia
Edema	Hypoalbuminemia
Cachexia	Hyponatremia
Respiratory symptoms	c. Radiographic abnormalities
Gastrointestinal disturbance	Lymphadenopathy
Athralgia and myalgia	Splenomegaly
Altered mental state	Hepatomegaly
Neuropathy with or without pain	Body cavity effusions
2. Evidence of systemic inflammation	
Elevated C-reactive protein (>3 g/dL)	
3. Evidence of KSHV viral activity	
Elevated KSHV viral load in plasma (>1000 copies/mL) or peripheral blood mononuclear cells (>100 copies/10^6 cells)	
4. No evidence of KSHV-associated multicentric Castleman disease	
Exclusion of MCD requires histopathologic assessment of lymphadenopathy if present.	

The working case definition of KICS requires the presence of *at least 2* clinical manifestations drawn from *at least 2 categories* (1a, b, and c), together with each of the criteria in 2, 3, and 4.

Abbreviations: KSHV, Kaposi sarcoma herpesvirus; MCD, multicentric Castleman disease.





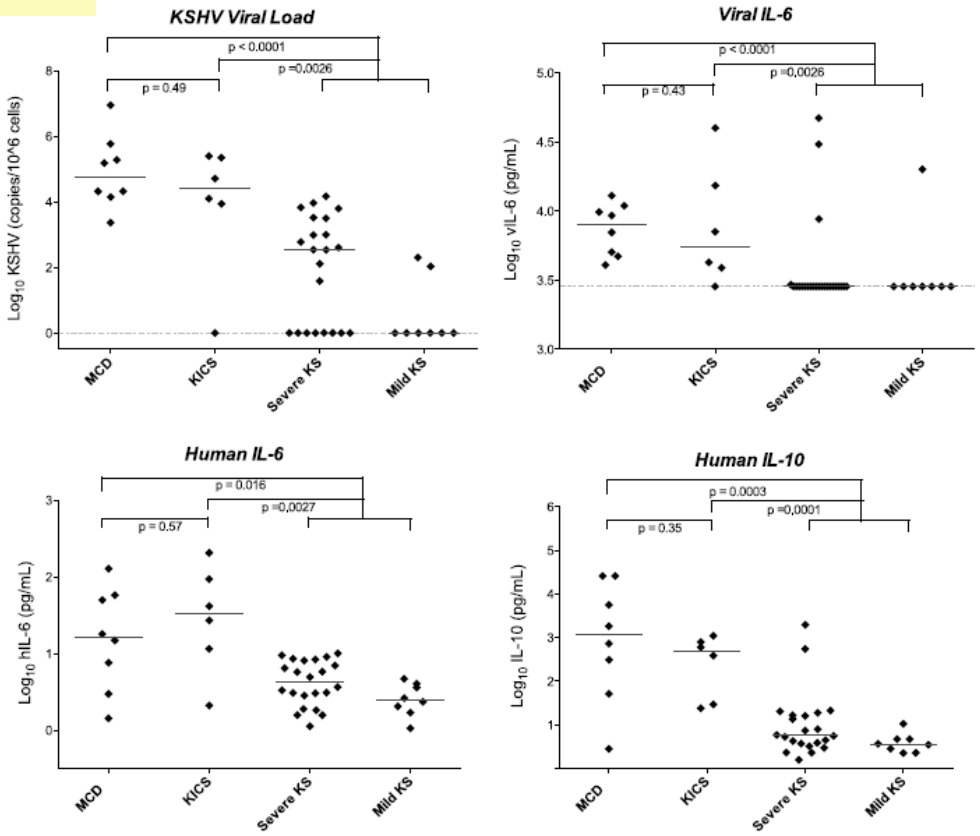
Polizzotto 2012

KICS vs MCD

Latency-associated nuclear antigen staining for KSHV was performed in all cases and nuclear stain was present in the spindle cell proliferation and rare mononuclear cells only. Bone marrow biopsies in 8 subjects demonstrated nonspecific changes characterized increased cellularity with reactive plasmacytosis and scattered KSHV-infected plasma cells, similar to findings previously reported [16].

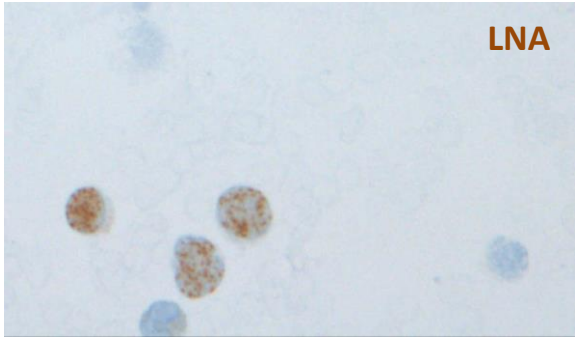
Polizzotto 2012

Galicier 2019



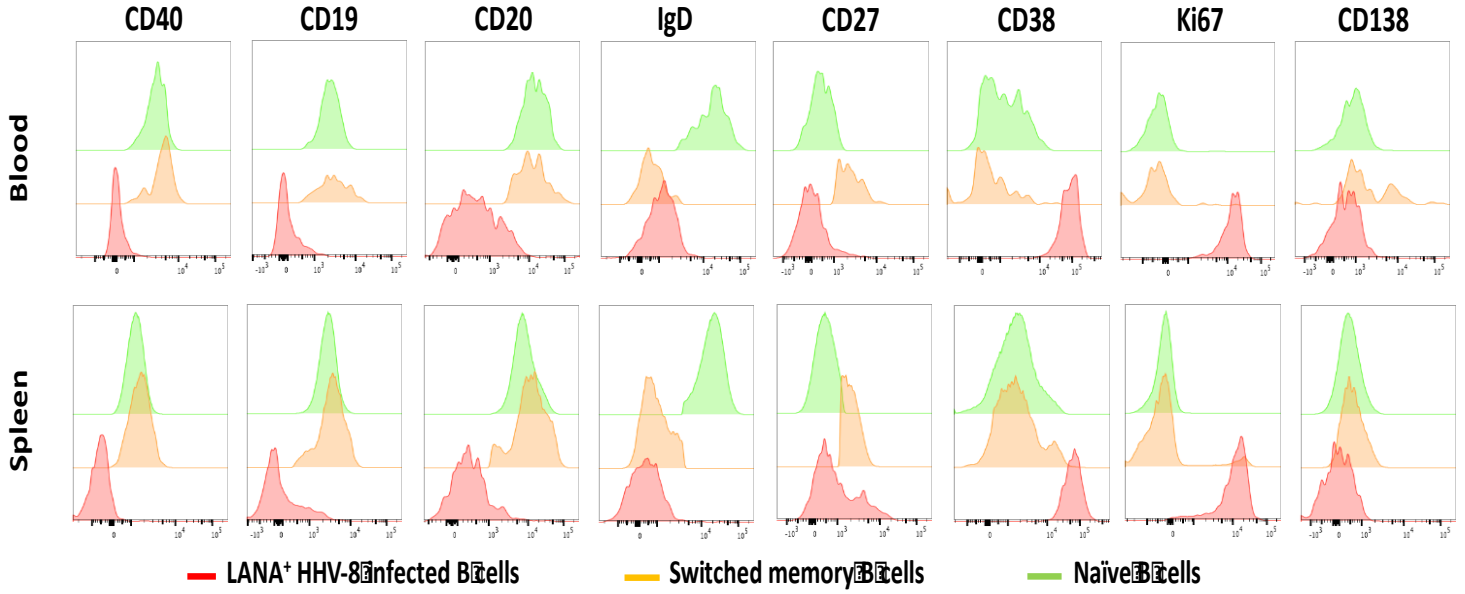
Flow cytometric phenotyping of LNA+ cells

LNA+ λ+ plasmablast-like cells are detectable in the blood of patients with active MCD and HHV-8 PCR>3 log (0.02-6% of PBMC)



LNA staining, blood smear, V. Meignin

Their phenotype is very similar to lymph node and splenic LNA+ cells



Sbihi et al, submitted

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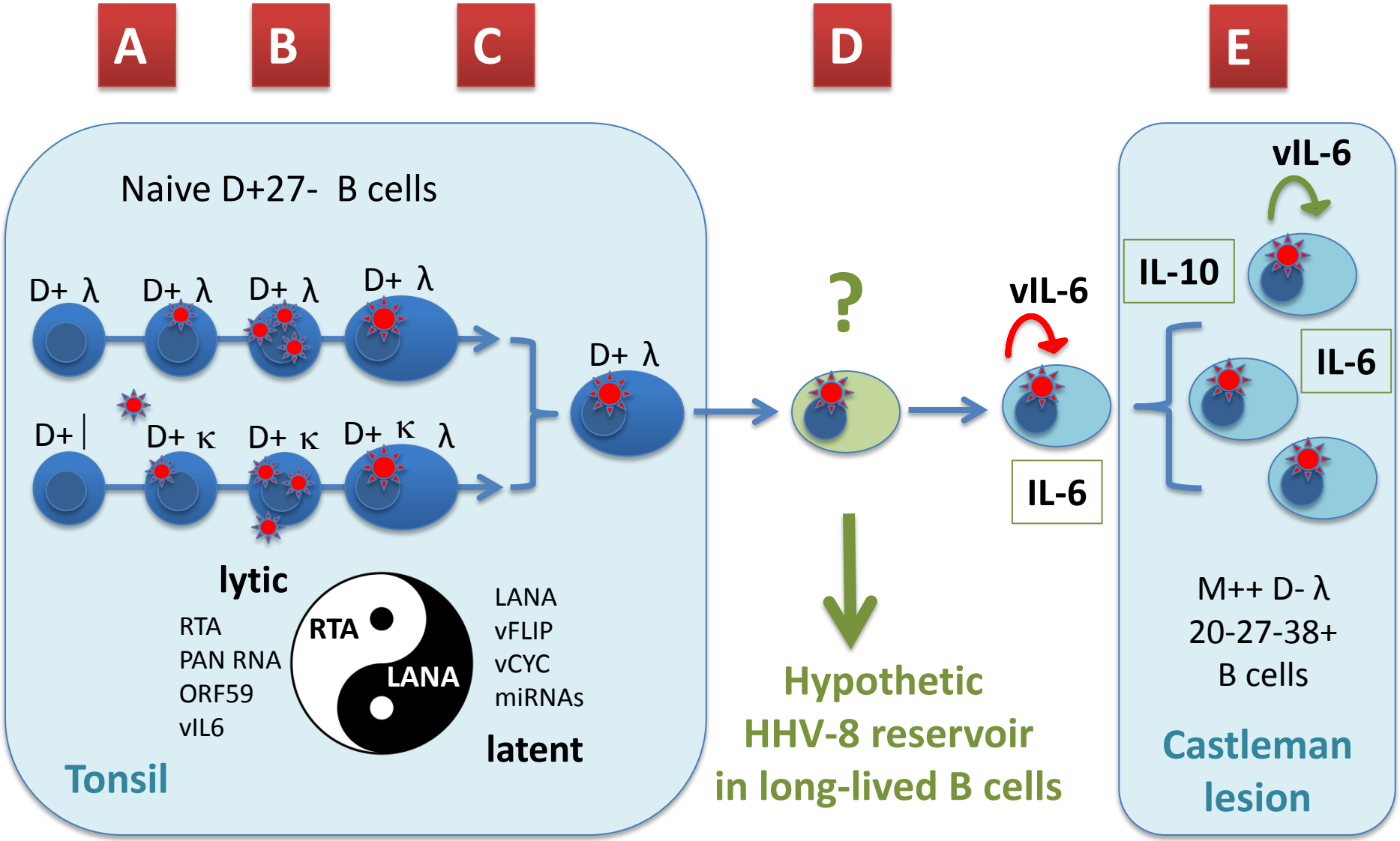
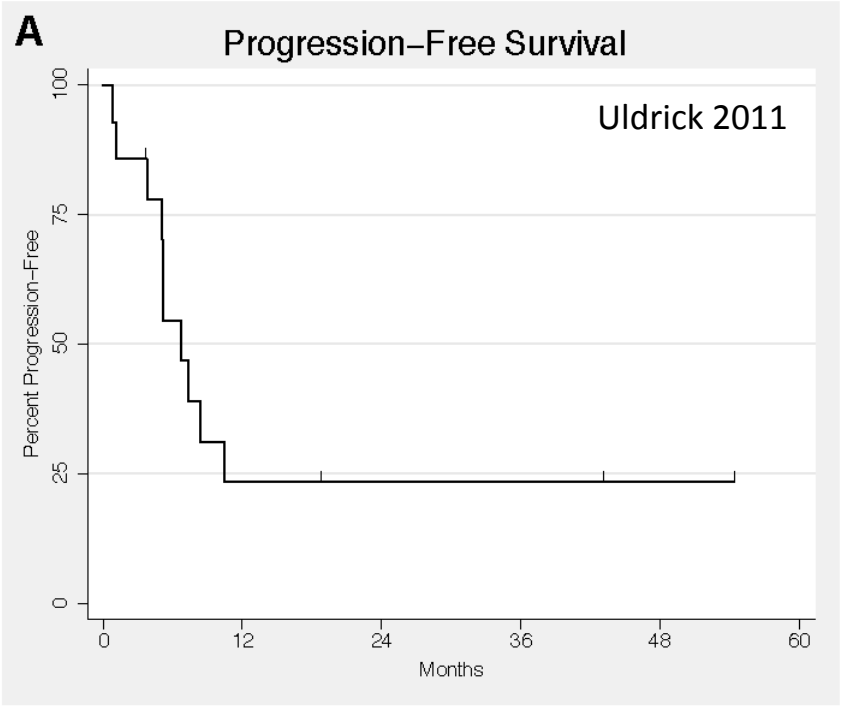
- **Rituximab responsive disease.**
  - Depiste absence of CD20 expression on HHV8+ « visible » B cells
  - Relapse may occur

Where is the real target of rituximab ?
Role of HHV8 lytic phase?


A
B
C
D
E
Naive D+27- B cells
D+ λ
D+ λ
D+ λ
D+ λ
D+
D+ κ
D+ κ
D+ κ λ
D+ λ
lytic
RTA
PAN RNA
ORF59
vIL6
RTA
LANA
LANA
vFLIP
vCYC
miRNAs
latent
Tonsil
?
Hypothetic
HHV-8 reservoir
in long-lived B cells
vIL-6
IL-6
vIL-6
IL-10
IL-6
M++ D- λ
20-27-38+
B cells
Castleman
lesion

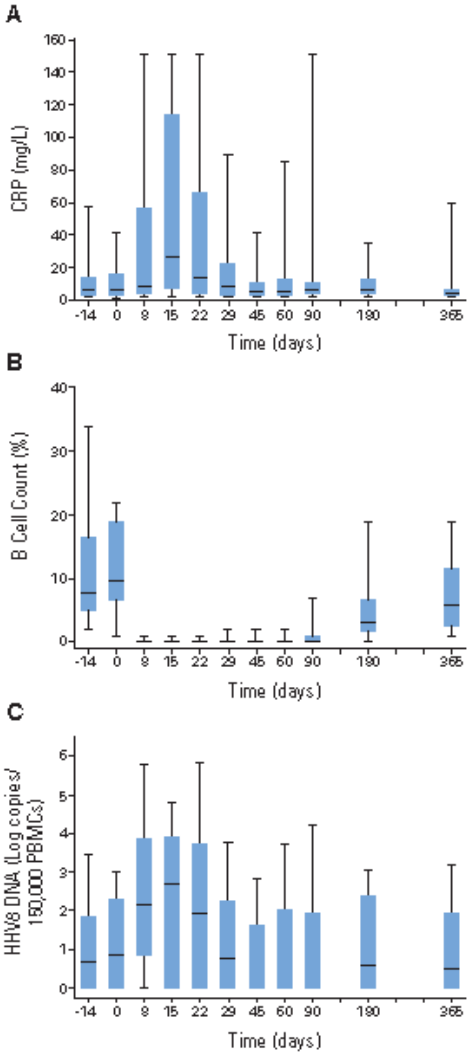
AZT + Ganciclovir

Response category	Best response	No. (%)
Clinical response	Complete response	7 (50)
	Symptom-free disease	3 (21)
	Partial response	2 (14)
	Major clinical response	12 (86)
	Stable disease	2 (14)
Biochemical response	Complete response	3 (21)
	Partial response	4 (29)
	Major biochemical response	7 (50)
	Stable disease	6 (43)
	Progressive disease	1 (7)



A place for antiviral therapy?

CastlemaB



Galicier 2019

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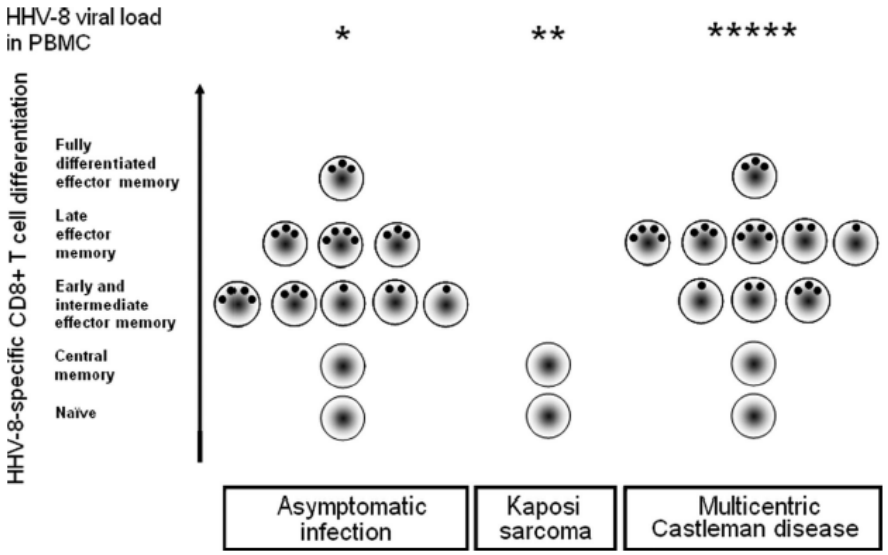
- **May occur in patients with good control of HIV replication**

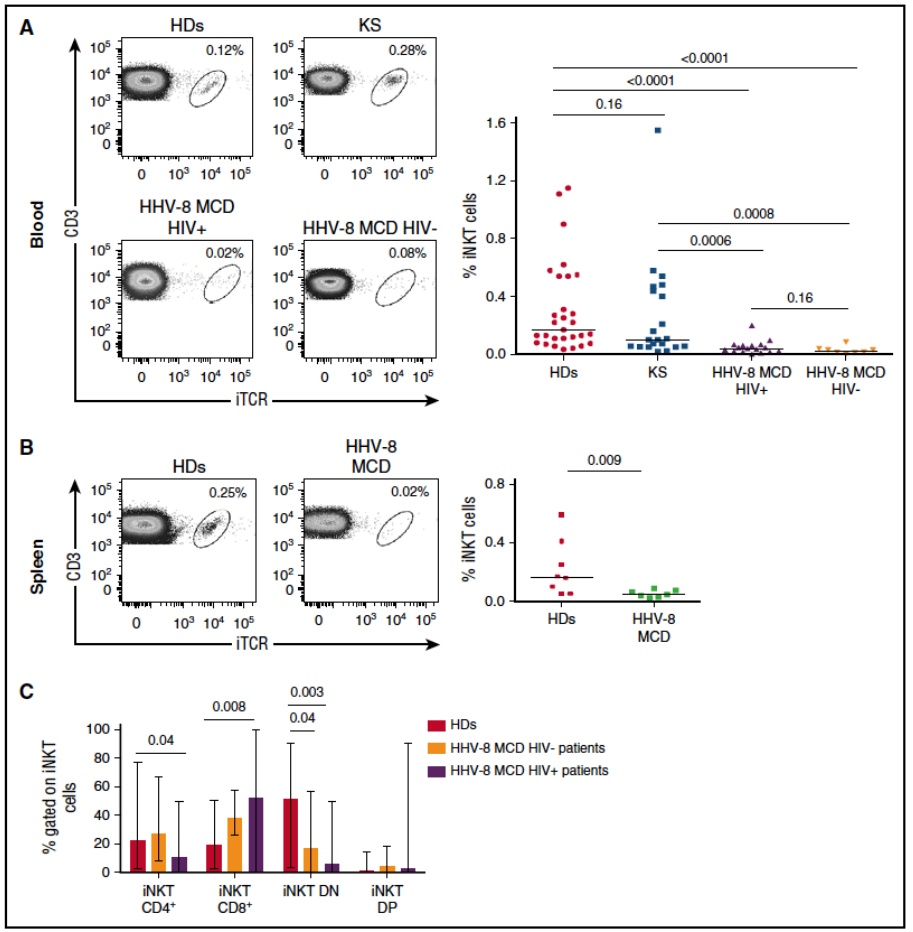
Wich immune system defects allow HHV8 related disease?

Rôle du déficit immunitaire ?

Pas de déficit T CD8 cytotoxique



Déficit i NKT?



Guihot 2008
Sbihi 2017

Les principaux messages …

- Penser à HHV8
  - Fièvre, cytopénie,
  - signes respiratoires
  - Syndrome oedemateux, anasarche
  - CRP
  - Hypergammaglobulinémie
  - Coombs positif
- Traitement rapidement efficace
  - VP16
  - Rituximab
  - Eviter les Corticoïdes (surtout si Kaposi)
- Kaposi et lymphoprolifération HHV8
  - Physiopathologies différentes
  - Traitement parfois difficile.
  - Contrôle de l'infection HIV requise

- **Et beaucoup de questions!**

www.castleman.fr

Conclusions

Thanks!

National reference center

Eric Oksenhendler

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Guislaine Carcelain

Statistician

Laurence Gerard

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Claire Fieschi

Marion Malphettes

Jehanne Fadlallah

Antoine Dossier

Rémi Bertinchamps

And all the others!

Castleman Disease Collaborative Network

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