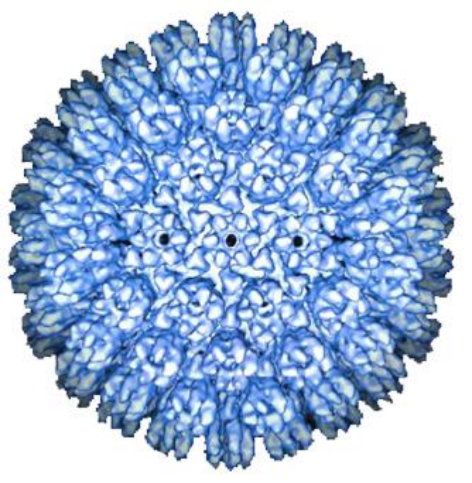
Maladies HHV-8



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Un Réseau membre de la
Filière de Santé Maladies Rares
MARIH

www.castleman.fr

HHV-8 / KSHV

- Découvert en 1994 (Kaposi)

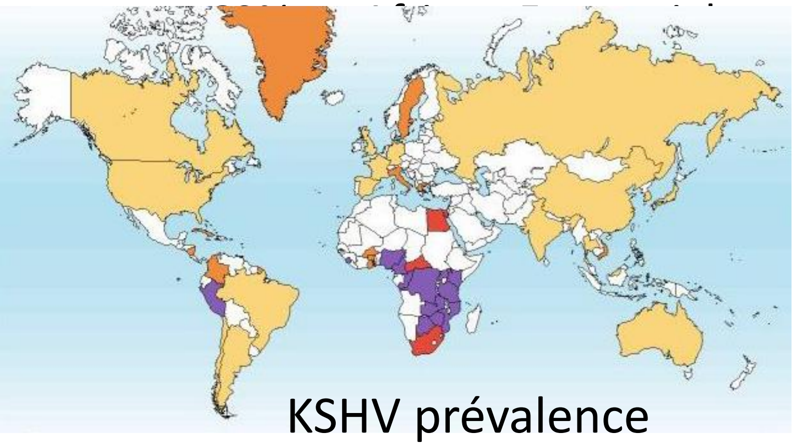
  Representational Difference Analysis

  Chang Y. et al.

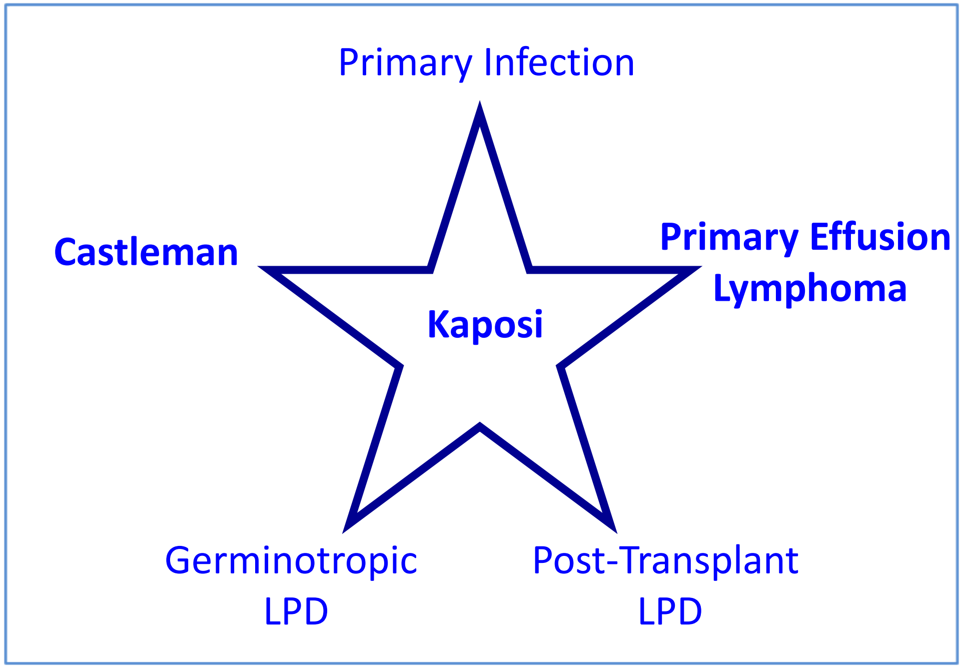
- Séquencé en 1996

  Russo JJ. et al.

- Non ubiquitaire
  - 1-5% pays du « Nord »,



KSHV prévalence



Primary Infection

Castleman

Primary Effusion Lymphoma

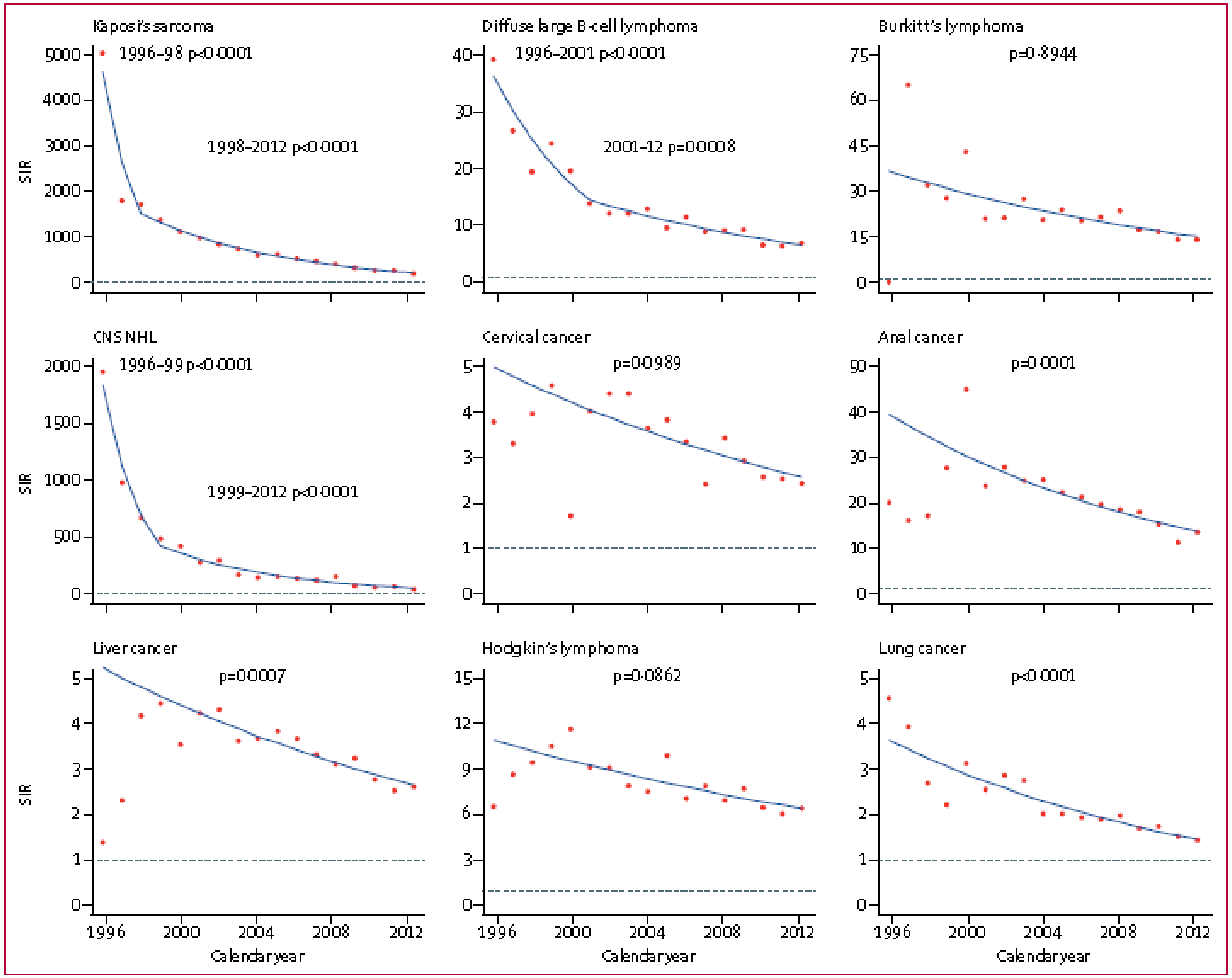
Kaposi

Germinotropic LPD

Post-Transplant LPD

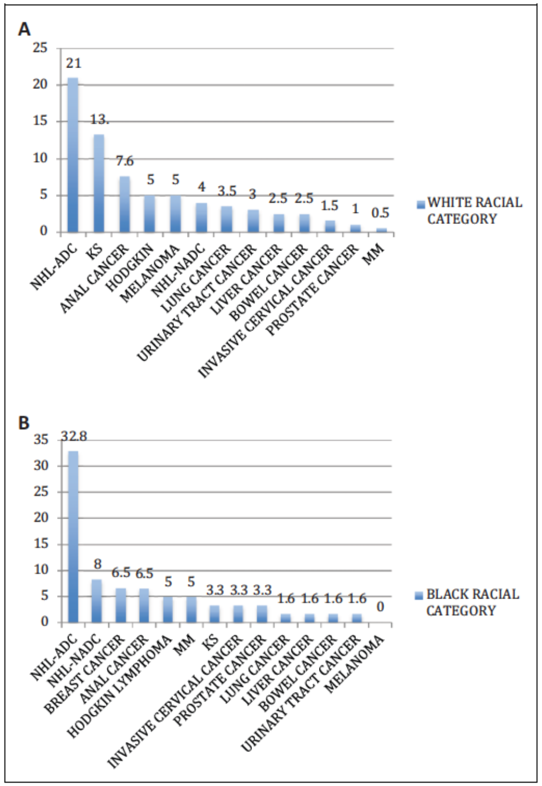
- Transmission Horizontale / salive dans l'enfance puis lors de rapports sexuels

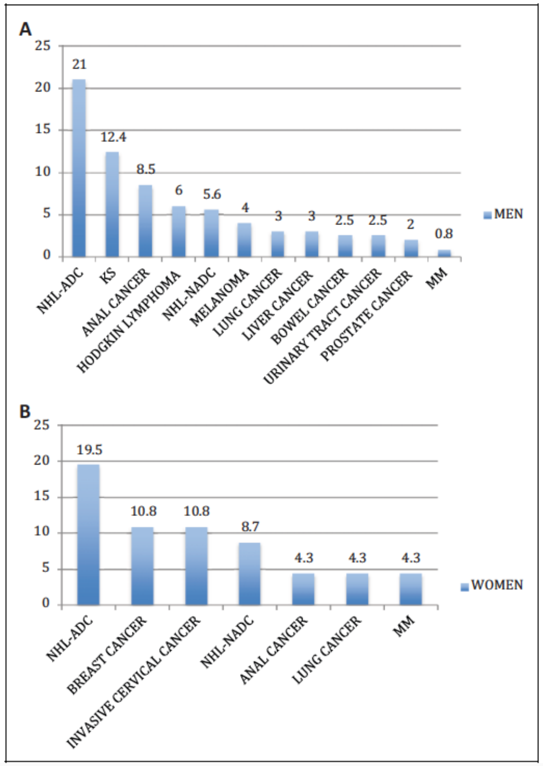
Evolution du risque de cancer 1996-2012

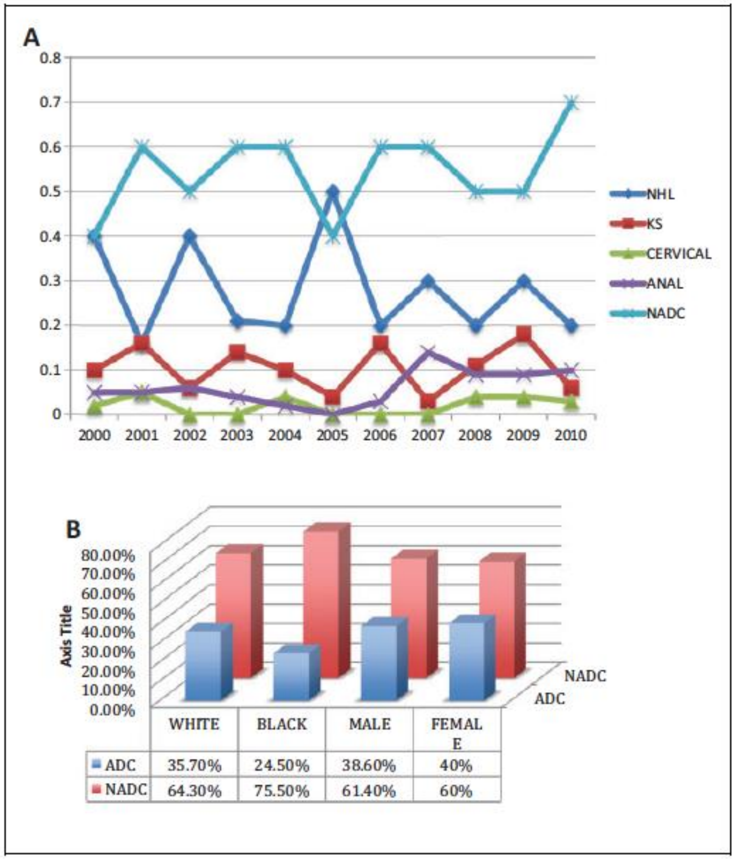


Hernandez ramirez 2017

Prévalence des cancers chez les patient infectés par le VIH: 2000 - 2010 Floride







Homme, blanc, HSH

Rihana 2018

Incidence KS selon le type d'ARV: IP ou non IP

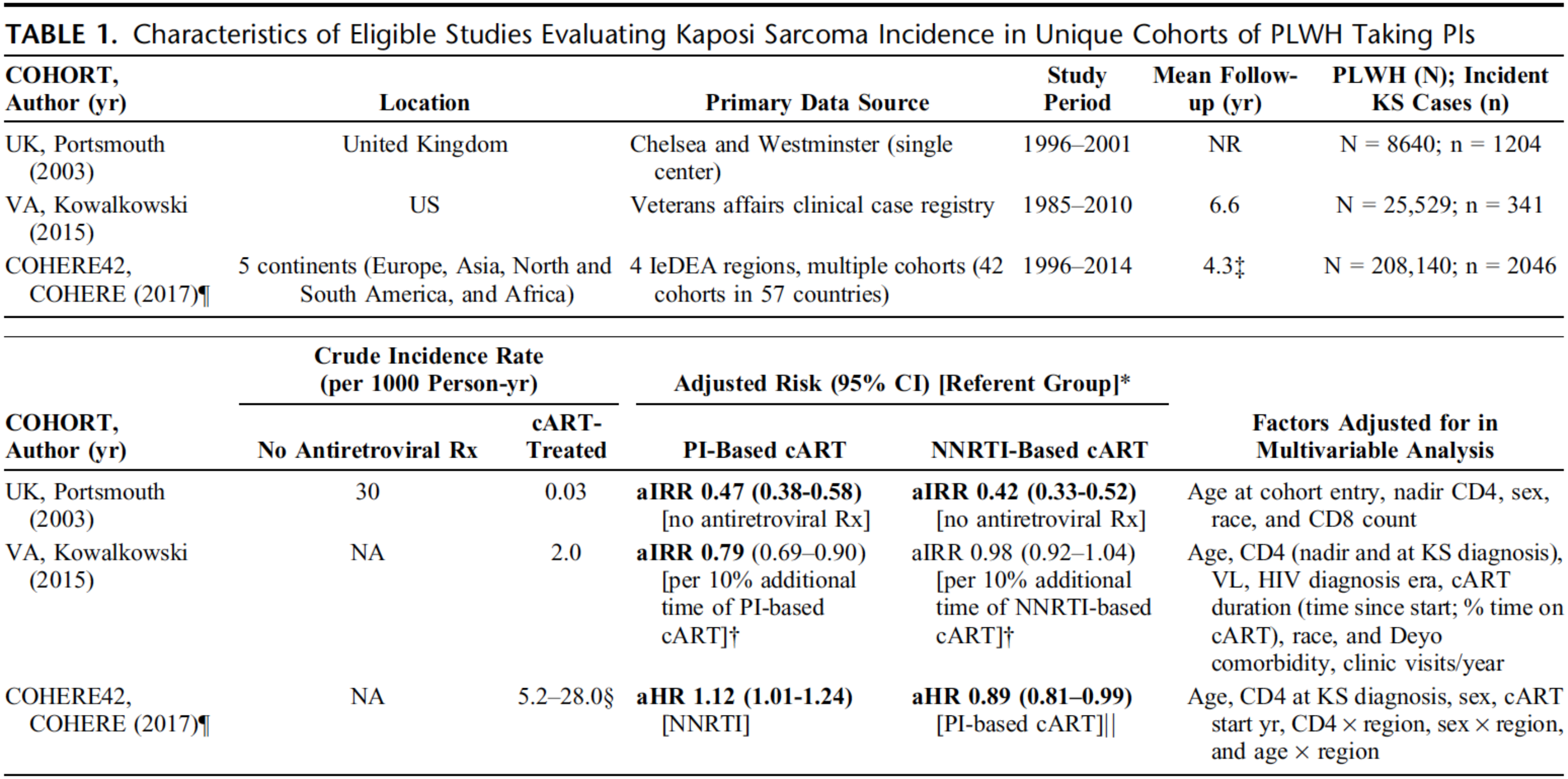


TABLE 1. Characteristics of Eligible Studies Evaluating Kaposi Sarcoma Incidence in Unique Cohorts of PLWH Taking PIs

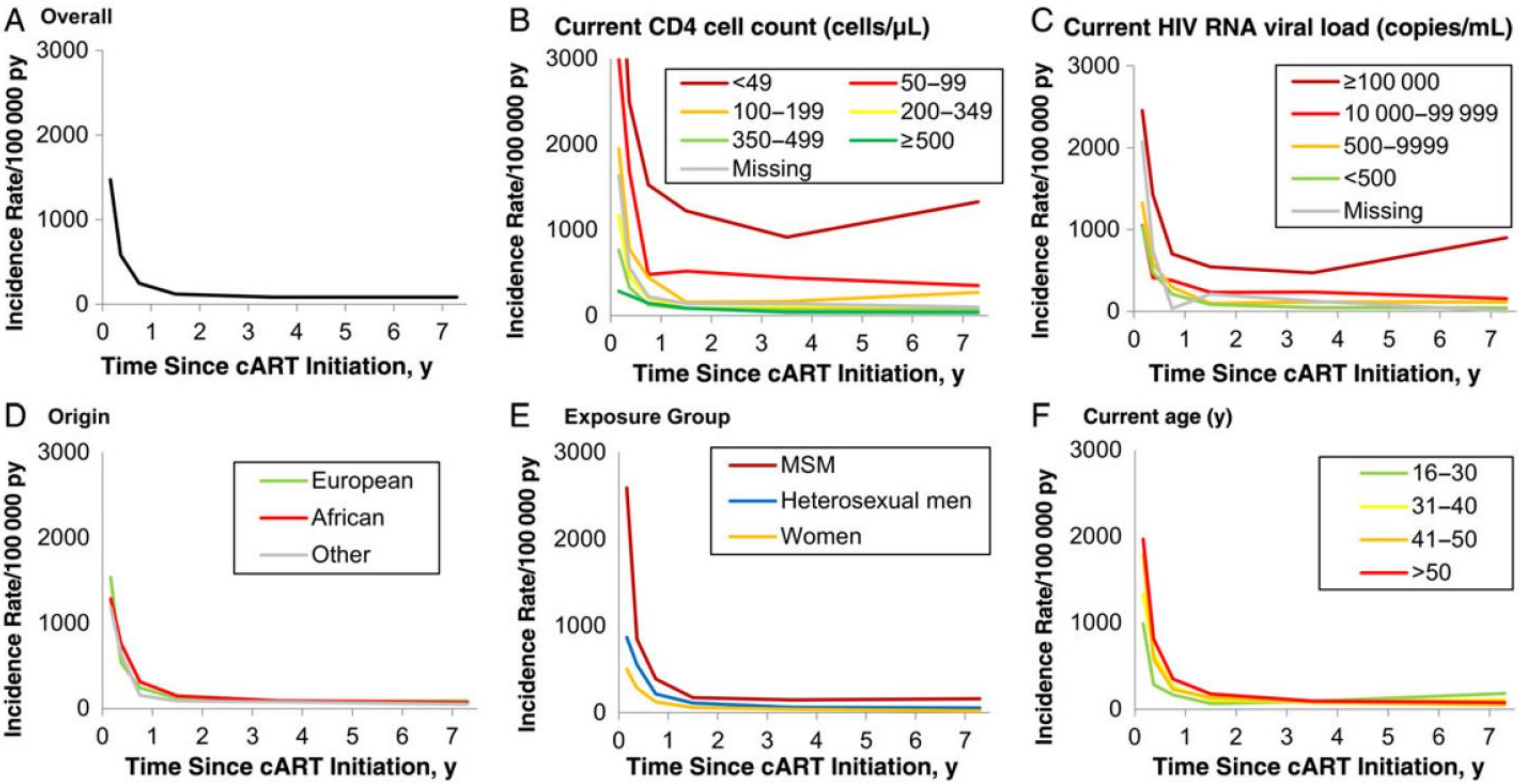
COHORT, Author (yr)	Location	Primary Data Source	Study Period	Mean Follow-up (yr)	PLWH (N); Incident KS Cases (n)
UK, Portsmouth (2003)	United Kingdom	Chelsea and Westminster (single center)	1996–2001	NR	N = 8640; n = 1204
VA, Kowalkowski (2015)	US	Veterans affairs clinical case registry	1985–2010	6.6	N = 25,529; n = 341
COHERE42, COHERE (2017)¶	5 continents (Europe, Asia, North and South America, and Africa)	4 IeDEA regions, multiple cohorts (42 cohorts in 57 countries)	1996–2014	4.3‡	N = 208,140; n = 2046

COHORT, Author (yr)	Crude Incidence Rate (per 1000 Person-yr): No Antiretroviral Rx	Crude Incidence Rate (per 1000 Person-yr): cART-Treated	Adjusted Risk (95% CI) [Referent Group]*: PI-Based cART	Adjusted Risk (95% CI) [Referent Group]*: NNRTI-Based cART	Factors Adjusted for in Multivariable Analysis
UK, Portsmouth (2003)	30	0.03	**aIRR 0.47 (0.38-0.58)** [no antiretroviral Rx]	**aIRR 0.42 (0.33-0.52)** [no antiretroviral Rx]	Age at cohort entry, nadir CD4, sex, race, and CD8 count
VA, Kowalkowski (2015)	NA	2.0	**aIRR 0.79** (0.69–0.90) [per 10% additional time of PI-based cART]†	aIRR 0.98 (0.92–1.04) [per 10% additional time of NNRTI-based cART]†	Age, CD4 (nadir and at KS diagnosis), VL, HIV diagnosis era, cART duration (time since start; % time on cART), race, and Deyo comorbidity, clinic visits/year
COHERE42, COHERE (2017)¶	NA	5.2–28.0§	**aHR 1.12 (1.01-1.24)** [NNRTI]	**aHR 0.89 (0.81–0.99)** [PI-based cART]‖	Age, CD4 at KS diagnosis, sex, cART start yr, CD4 × region, sex × region, and age × region

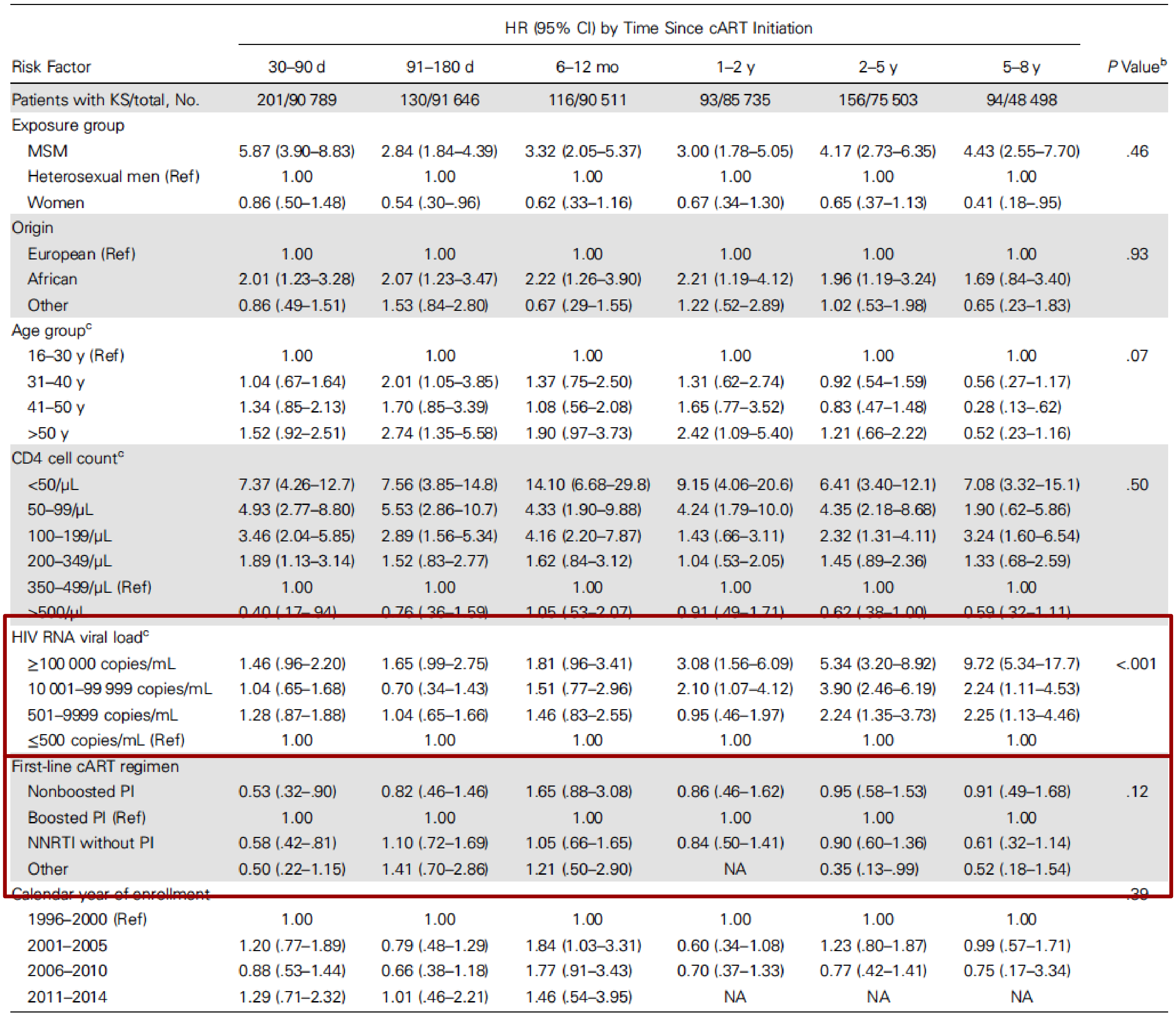
L'important c'est d'être traité.

Chang 2018

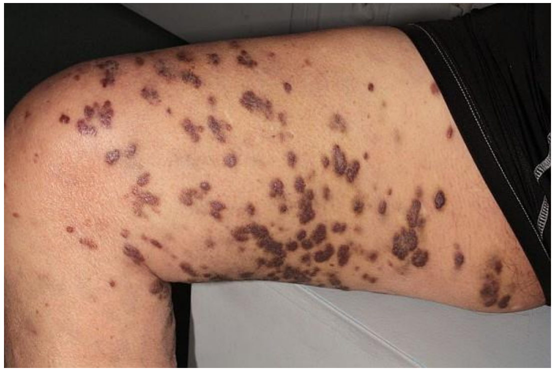
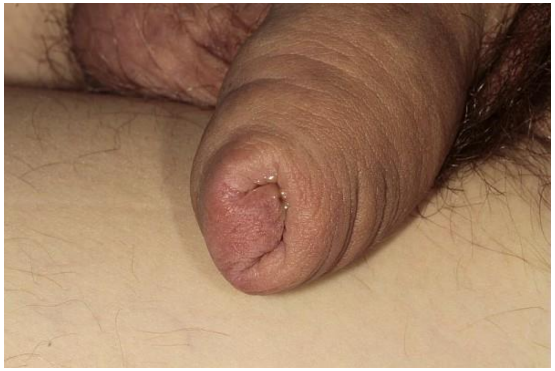
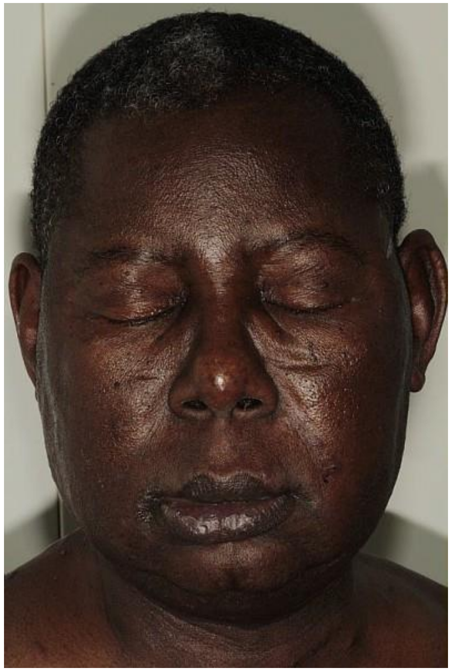
COHERE données 2016: Incidence kaposi sous traitement ARV



Et d'avoir une charge virale contrôlée



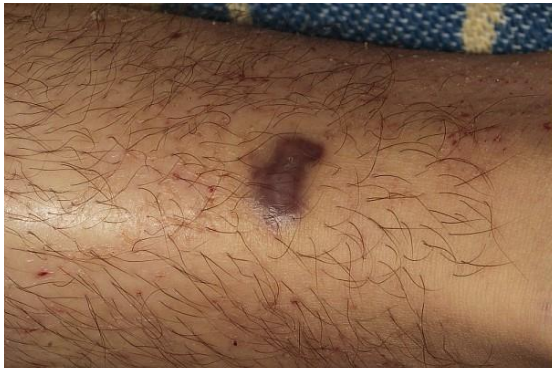
Risk Factor	HR (95% CI) by Time Since cART Initiation 30–90 d	91–180 d	6–12 mo	1–2 y	2–5 y	5–8 y	*P* Value[b]
Patients with KS/total, No.	201/90 789	130/91 646	116/90 511	93/85 735	156/75 503	94/48 498	
Exposure group							
MSM	5.87 (3.90–8.83)	2.84 (1.84–4.39)	3.32 (2.05–5.37)	3.00 (1.78–5.05)	4.17 (2.73–6.35)	4.43 (2.55–7.70)	.46
Heterosexual men (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
Women	0.86 (.50–1.48)	0.54 (.30–.96)	0.62 (.33–1.16)	0.67 (.34–1.30)	0.65 (.37–1.13)	0.41 (.18–.95)	
Origin							
European (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	.93
African	2.01 (1.23–3.28)	2.07 (1.23–3.47)	2.22 (1.26–3.90)	2.21 (1.19–4.12)	1.96 (1.19–3.24)	1.69 (.84–3.40)	
Other	0.86 (.49–1.51)	1.53 (.84–2.80)	0.67 (.29–1.55)	1.22 (.52–2.89)	1.02 (.53–1.98)	0.65 (.23–1.83)	
Age group[c]							
16–30 y (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	.07
31–40 y	1.04 (.67–1.64)	2.01 (1.05–3.85)	1.37 (.75–2.50)	1.31 (.62–2.74)	0.92 (.54–1.59)	0.56 (.27–1.17)	
41–50 y	1.34 (.85–2.13)	1.70 (.85–3.39)	1.08 (.56–2.08)	1.65 (.77–3.52)	0.83 (.47–1.48)	0.28 (.13–.62)	
>50 y	1.52 (.92–2.51)	2.74 (1.35–5.58)	1.90 (.97–3.73)	2.42 (1.09–5.40)	1.21 (.66–2.22)	0.52 (.23–1.16)	
CD4 cell count[c]							
<50/μL	7.37 (4.26–12.7)	7.56 (3.85–14.8)	14.10 (6.68–29.8)	9.15 (4.06–20.6)	6.41 (3.40–12.1)	7.08 (3.32–15.1)	.50
50–99/μL	4.93 (2.77–8.80)	5.53 (2.86–10.7)	4.33 (1.90–9.88)	4.24 (1.79–10.0)	4.35 (2.18–8.68)	1.90 (.62–5.86)	
100–199/μL	3.46 (2.04–5.85)	2.89 (1.56–5.34)	4.16 (2.20–7.87)	1.43 (.66–3.11)	2.32 (1.31–4.11)	3.24 (1.60–6.54)	
200–349/μL	1.89 (1.13–3.14)	1.52 (.83–2.77)	1.62 (.84–3.12)	1.04 (.53–2.05)	1.45 (.89–2.36)	1.33 (.68–2.59)	
350–499/μL (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
≥500/μL	0.40 (.17–.94)	0.76 (.36–1.59)	1.05 (.53–2.07)	0.91 (.49–1.71)	0.62 (.38–1.00)	0.59 (.32–1.11)	
HIV RNA viral load[c]							
≥100 000 copies/mL	1.46 (.96–2.20)	1.65 (.99–2.75)	1.81 (.96–3.41)	3.08 (1.56–6.09)	5.34 (3.20–8.92)	9.72 (5.34–17.7)	<.001
10 001–99 999 copies/mL	1.04 (.65–1.68)	0.70 (.34–1.43)	1.51 (.77–2.96)	2.10 (1.07–4.12)	3.90 (2.46–6.19)	2.24 (1.11–4.53)	
501–9999 copies/mL	1.28 (.87–1.88)	1.04 (.65–1.66)	1.46 (.83–2.55)	0.95 (.46–1.97)	2.24 (1.35–3.73)	2.25 (1.13–4.46)	
≤500 copies/mL (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
First-line cART regimen							
Nonboosted PI	0.53 (.32–.90)	0.82 (.46–1.46)	1.65 (.88–3.08)	0.86 (.46–1.62)	0.95 (.58–1.53)	0.91 (.49–1.68)	.12
Boosted PI (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
NNRTI without PI	0.58 (.42–.81)	1.10 (.72–1.69)	1.05 (.66–1.65)	0.84 (.50–1.41)	0.90 (.60–1.36)	0.61 (.32–1.14)	
Other	0.50 (.22–1.15)	1.41 (.70–2.86)	1.21 (.50–2.90)	NA	0.35 (.13–.99)	0.52 (.18–1.54)	
Calendar year of enrollment							.39
1996–2000 (Ref)	1.00	1.00	1.00	1.00	1.00	1.00	
2001–2005	1.20 (.77–1.89)	0.79 (.48–1.29)	1.84 (1.03–3.31)	0.60 (.34–1.08)	1.23 (.80–1.87)	0.99 (.57–1.71)	
2006–2010	0.88 (.53–1.44)	0.66 (.38–1.18)	1.77 (.91–3.43)	0.70 (.37–1.33)	0.77 (.42–1.41)	0.75 (.17–3.34)	
2011–2014	1.29 (.71–2.32)	1.01 (.46–2.21)	1.46 (.54–3.95)	NA	NA	NA	

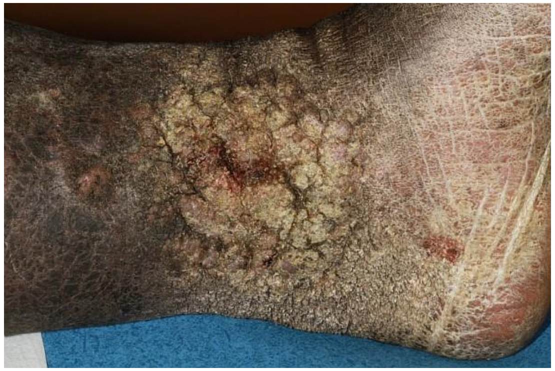
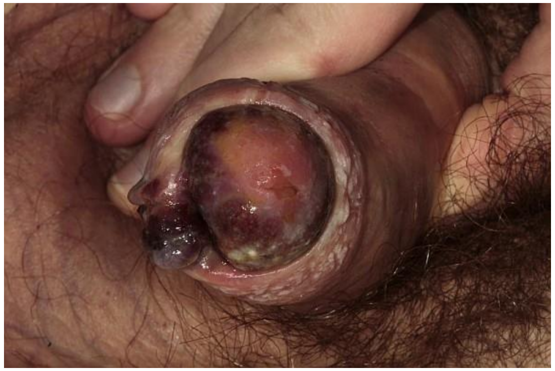




KAPOSI

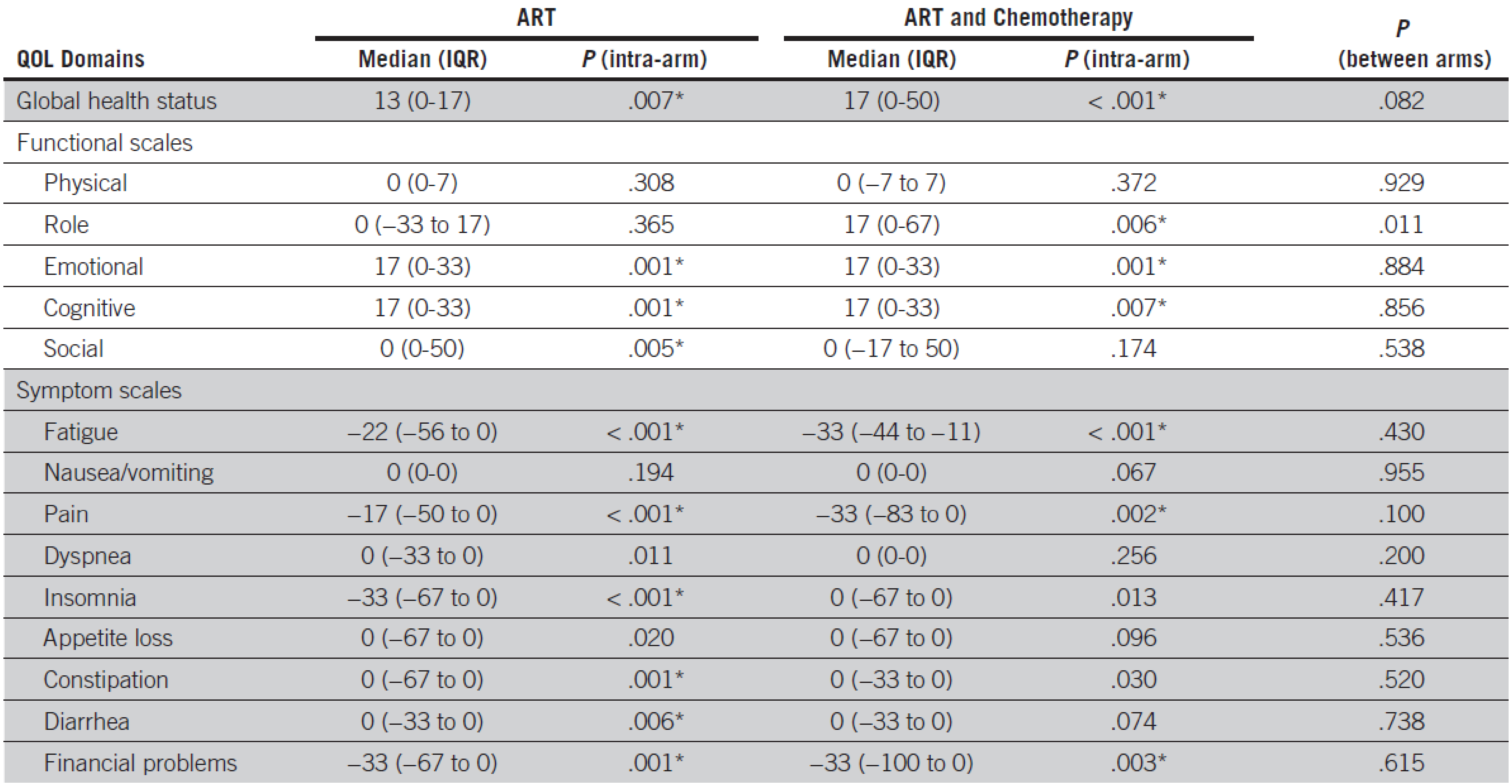
Polymorphe

Infiltration
Violine
Oedeme



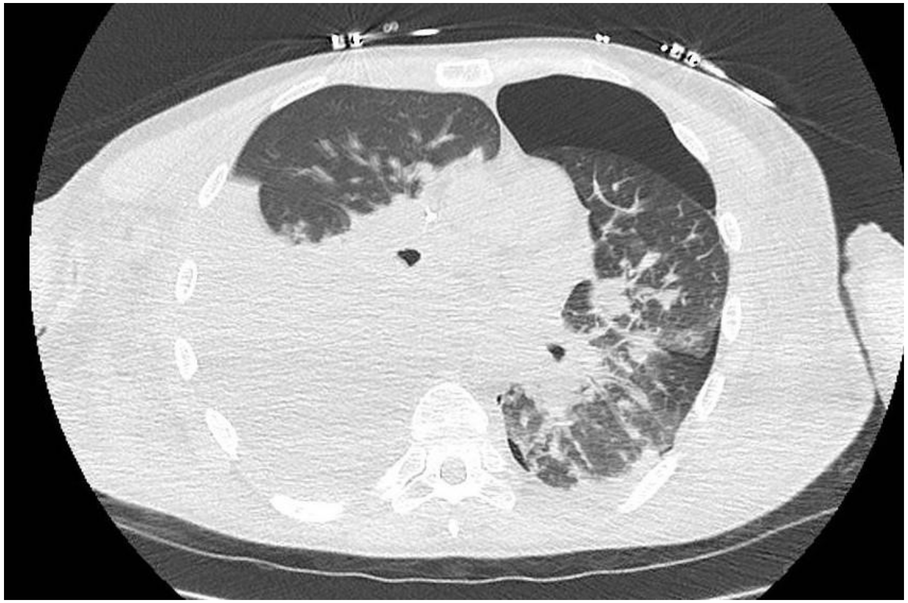



Ne traiter que si nécessaire

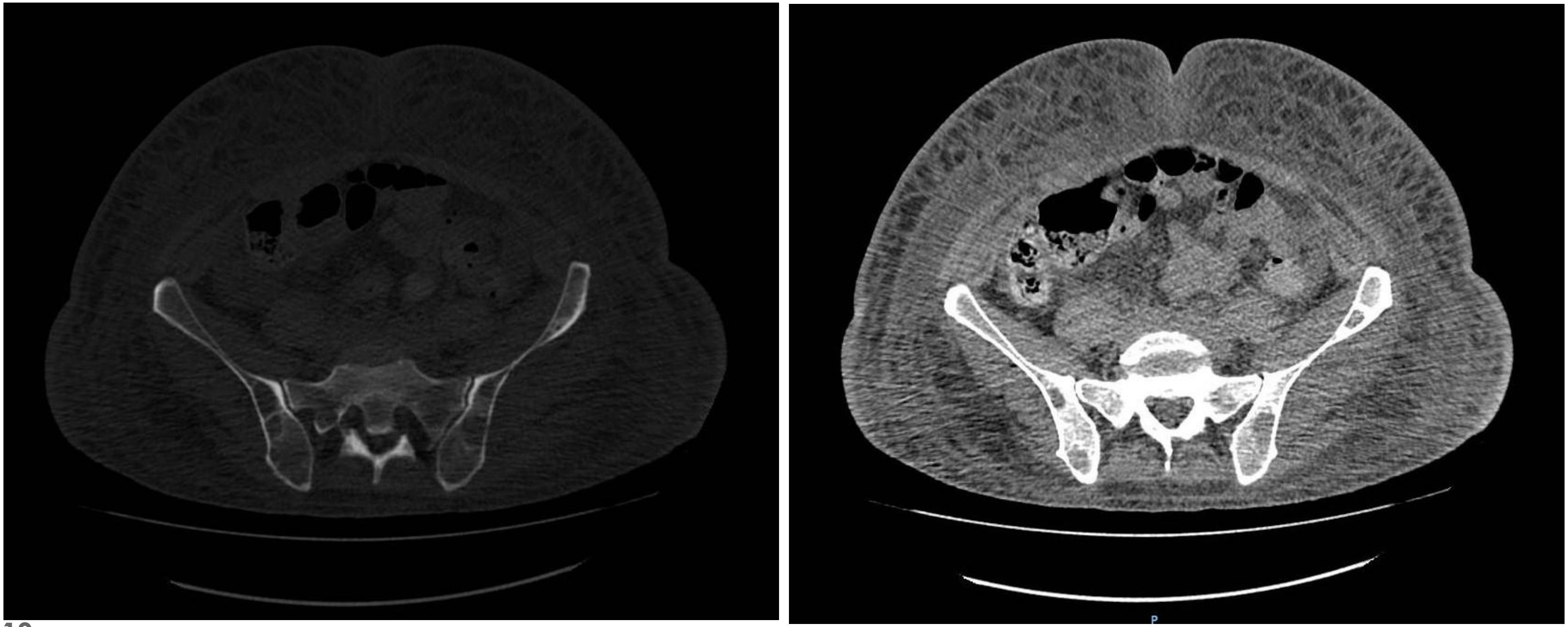


QOL Domains	ART Median (IQR)	ART *P* (intra-arm)	ART and Chemotherapy Median (IQR)	ART and Chemotherapy *P* (intra-arm)	*P* (between arms)
Global health status	13 (0-17)	.007*	17 (0-50)	< .001*	.082
Functional scales					
Physical	0 (0-7)	.308	0 (–7 to 7)	.372	.929
Role	0 (–33 to 17)	.365	17 (0-67)	.006*	.011
Emotional	17 (0-33)	.001*	17 (0-33)	.001*	.884
Cognitive	17 (0-33)	.001*	17 (0-33)	.007*	.856
Social	0 (0-50)	.005*	0 (–17 to 50)	.174	.538
Symptom scales					
Fatigue	–22 (–56 to 0)	< .001*	–33 (–44 to –11)	< .001*	.430
Nausea/vomiting	0 (0-0)	.194	0 (0-0)	.067	.955
Pain	–17 (–50 to 0)	< .001*	–33 (–83 to 0)	.002*	.100
Dyspnea	0 (–33 to 0)	.011	0 (0-0)	.256	.200
Insomnia	–33 (–67 to 0)	< .001*	0 (–67 to 0)	.013	.417
Appetite loss	0 (–67 to 0)	.020	0 (–67 to 0)	.096	.536
Constipation	0 (–67 to 0)	.001*	0 (–33 to 0)	.030	.520
Diarrhea	0 (–33 to 0)	.006*	0 (–33 to 0)	.074	.738
Financial problems	–33 (–67 to 0)	.001*	–33 (–100 to 0)	.003*	.615

Shaik 2018



Atteintes Viscérales



Les traitements

Chimiothérapie:

- **Anthracyclines liposomales**
- **Taxanes**

Radiothérapie formes localisée

Pas sur

- Imids
- Imatinib
- AntiVEGF

Probablement

- Interféron
- Inhibiteur de mTOR

On espère

- Inhibiteur du check-point

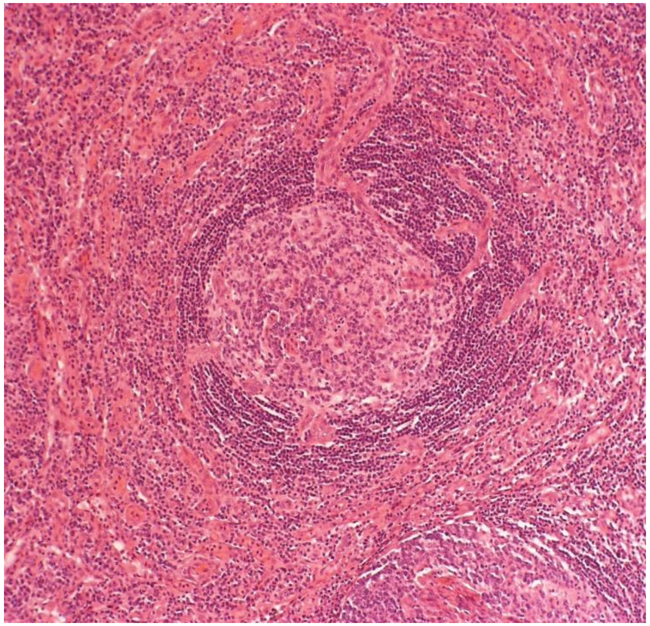
mais….

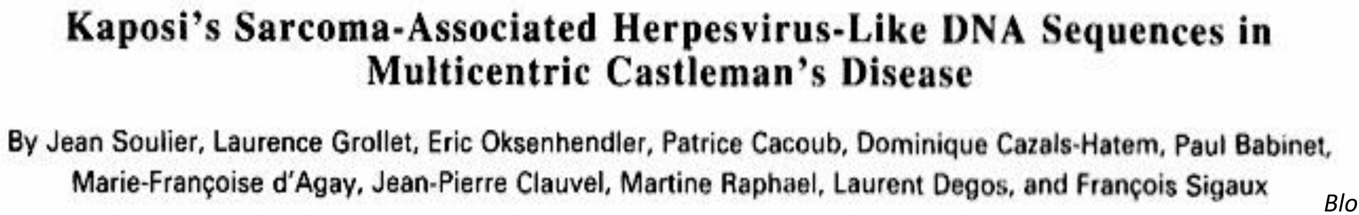
Sous réserve d'un contrôle optimal de la réplication VIH

Maladie de Castleman associée au HIV

Un syndrome lymphoprolifératif bien particulier

- Une présentation clinique évoquant un lymphome
- Aggravation clinique et biologique rapide
- Défaillance multiviscérale fatale possible
- Remissions spontanées possibles (2 à 3 semaines)
- Rechutes quasi constantes
- Histologie: 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

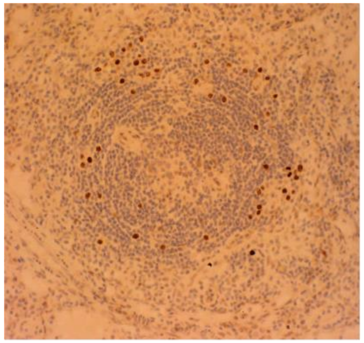
14 out of 14 HIV+ MCD
7 out of 17 HIV- MCD

MCM HHV-8+ HIV +

	HIV positive
number	140
Sex M / F	121 / 19
Age (median) years	41.4
Fever	126(90%)
Complications	
Splenomegaly	113 (81%)
Edema/Effusion	49(35%)
Lung	35 (25%)
Skin	17 (12%)
Kidney	6 (4%)
Hemophagocytic syndrome	56 (40%)
AIHA	8 (13%)
TAFRO syndrome	0
Kaposi sarcoma	79 (56%)
Hemoglobin g/dL	8.1
Platelets x10^6/L	96000
CRP mg/L	159
Serum albumin g/L	27.5
Gammaglobulin g/L	24
DAT + (n=110/26)	50 (46%)
HHV8-DNA (median, log copies)	4.57
CD4+ T-cell count (median, x10^6)	184
Plasma HIV-RNA copies < 2 logs	37 (26%)
Follow-up (median, months)	58
Lymphoma during Follow-up	23
Deaths	61 (44%)

Adultes (HSH, Afrique noire …)
Le plus souvent symptomatique
Syndrome inflammatoire
Cytopénie
Histologie: Plasmablastes LANA (HHV-8) +

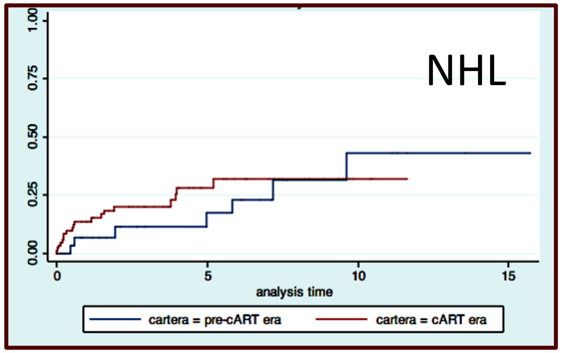
Kaposi
Splénomégalie
Oedèmes / épanchements
AHAI
Hémophagocytose



PCR HHV-8 DNA +++

IHC LANA +++

Risque de Lymphome



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

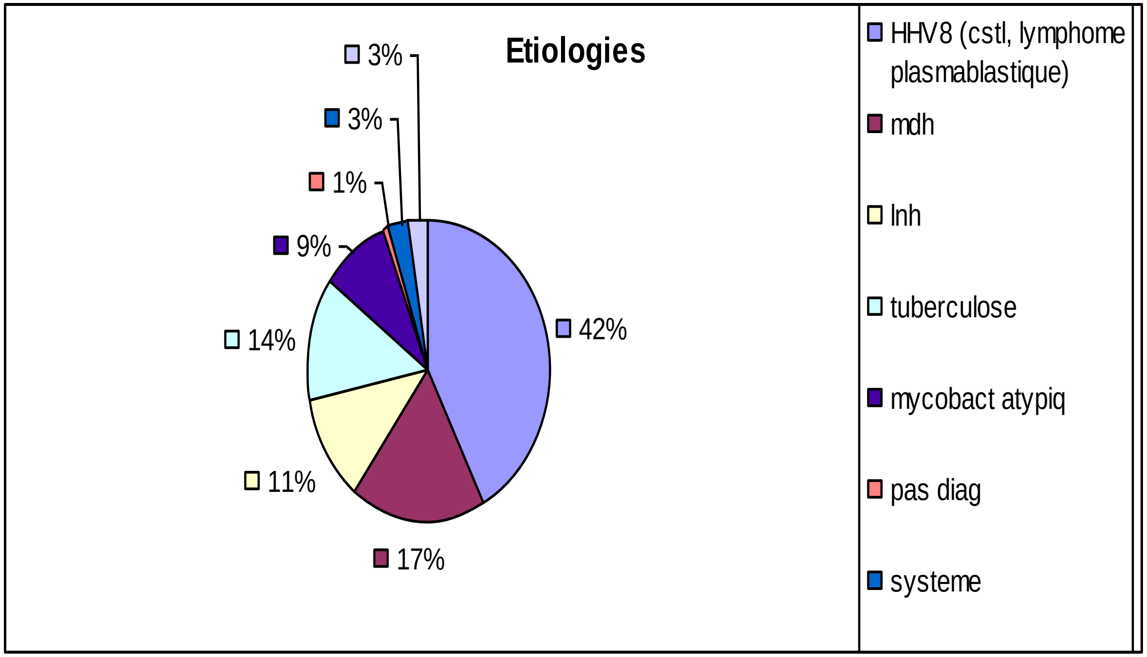
Oksenhendler et al. Blood 2002

COMPLICATIONS

MCM HHV-8+ HIV +

Syndrome hémophagocytaire

Etiologies HIV n= 75

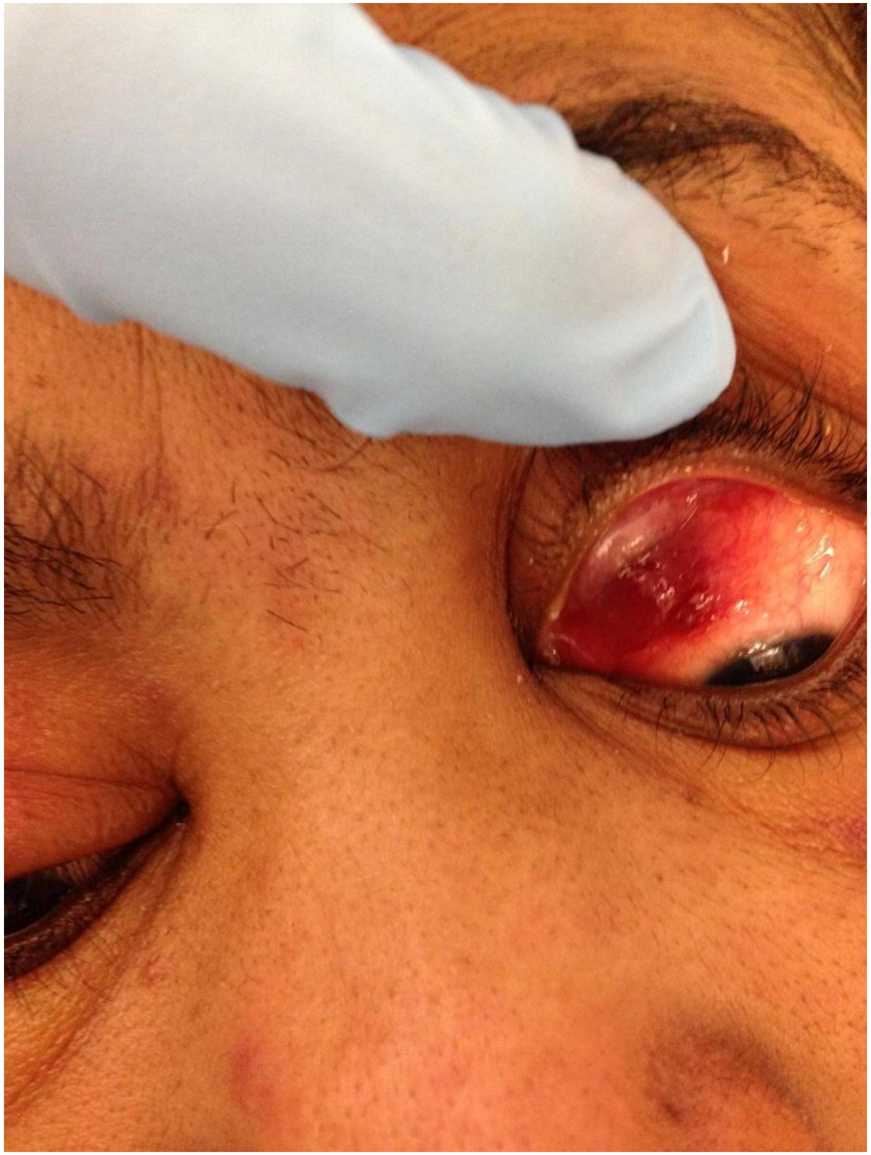


Plus rarement…

- Diarrhée
- AHAI
- MAT (PTT)
- Hypoglycémie
- Neuropathie

Galicier 2018

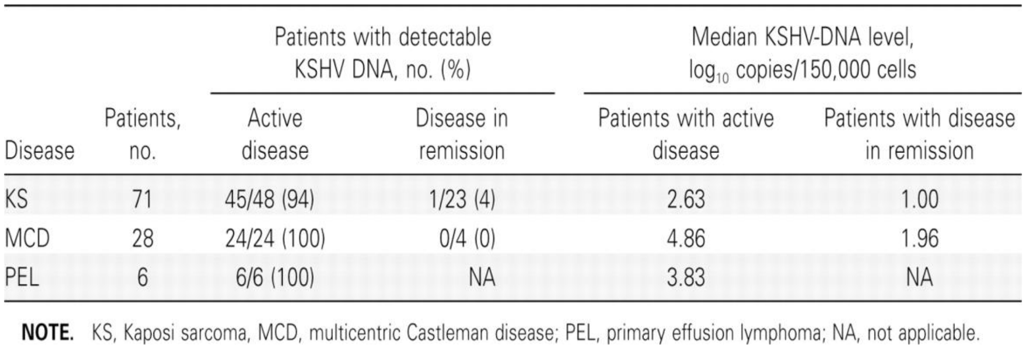
La valeur de l’examen clinique



Oksenhendler 2018

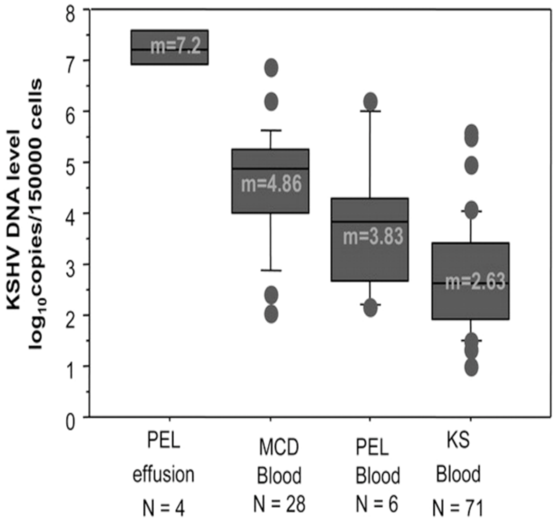
MCM HHV-8+ HIV +

PCR HHV8 outil diagnostic



		Patients with detectable KSHV DNA, no. (%)		Median KSHV-DNA level, $\log_{10}$ copies/150,000 cells	
Disease	Patients, no.	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

PCR HHV8 > 1000 c/ml >> MCD

Spécificité 94%
VPN 97%

Sayer 2016

Etoposide

MCM HHV-8+ HIV +

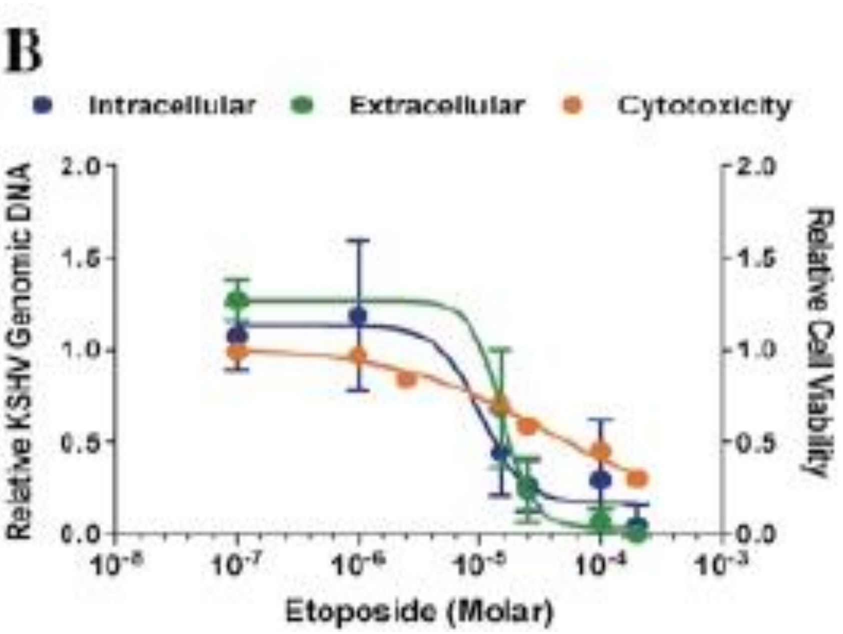
Induit une rémission rapide

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

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

* Mild Hematotoxicity

* Oncogenicity limits long-term use



Rituximab

MCM HHV-8+ HIV +

- Induit une rémission durable

	nb	Patients	EFS à un an	Poussée de KS
Bower et al.	20	Naïfs	**92%**	**4 / 11**
ANRS 117 CastlemaB trial	24	Chimio-dépendants	**71%**	**8 / 12**

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

- Diminue le risque de lymphome

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

Probabilité LNH à 5 ans (%)

R+ : 3 (0-20)
R- : 31 (19-47)

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

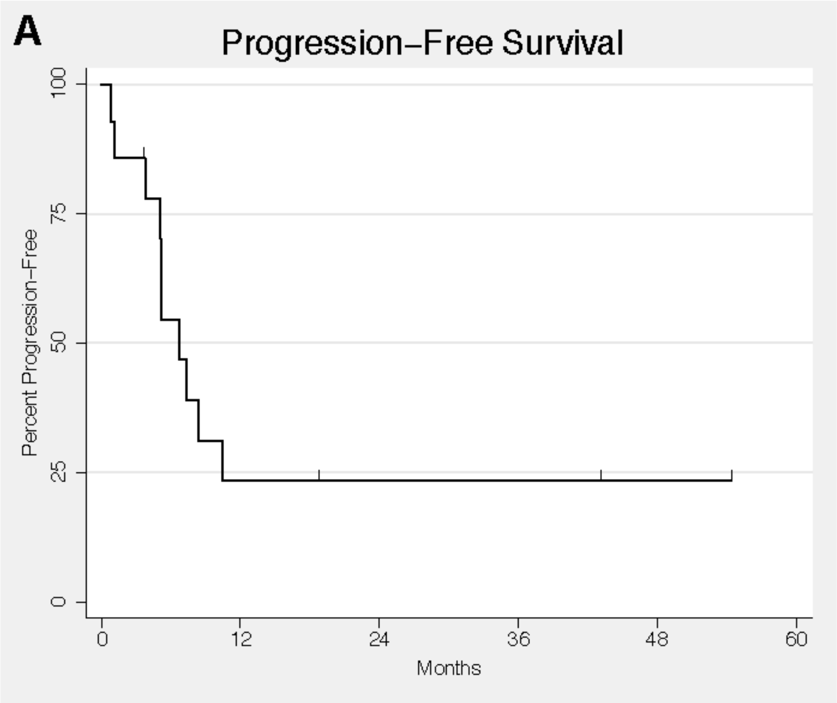
Gérard et al. Blood 2012

- Mais expose à 3 complications potentielles
  - Risque infectieux si déficit immunitaire sévère
  - Poussée de Castleman (flare)
  - Evolutivité du Kaposi

AZT + Ganciclovir

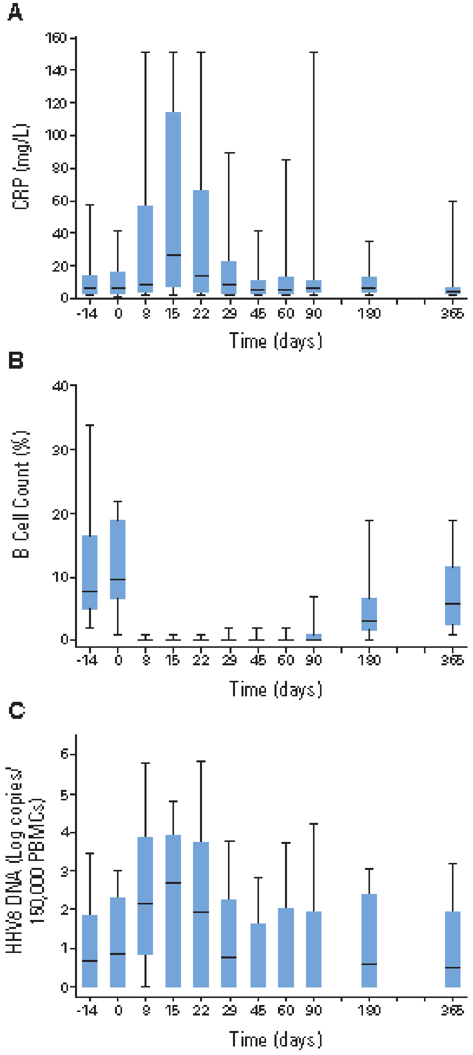
Rôle des antiviraux?

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)



Uldrick 2011

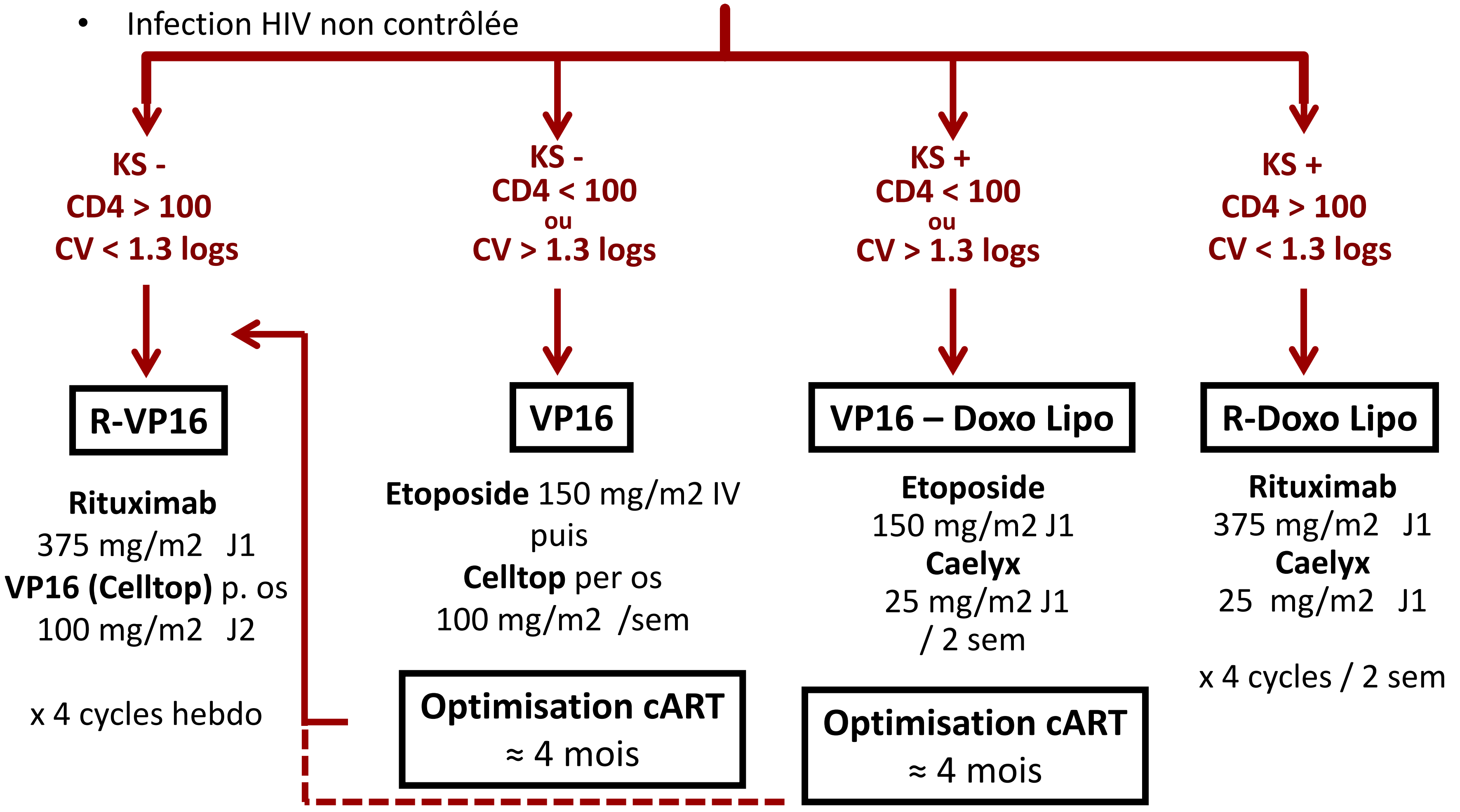
CastlemaB



Traitement

MCM HHV8+ HIV+

- Rituximab et VP16
- A adapter si
  - Sarcome de Kaposi actif ou
  - Déficit immunitaire sévère ou
  - Infection HIV non contrôlée



KS -
CD4 > 100
CV < 1.3 logs

R-VP16

Rituximab
375 mg/m2 J1
VP16 (Celltop) p. os
100 mg/m2 J2

x 4 cycles hebdo

KS -
CD4 < 100
ou
CV > 1.3 logs

VP16

Etoposide 150 mg/m2 IV
puis
Celltop per os
100 mg/m2 /sem

Optimisation cART
≈ 4 mois

KS +
CD4 < 100
ou
CV > 1.3 logs

VP16 – Doxo Lipo

Etoposide
150 mg/m2 J1
Caelyx
25 mg/m2 J1
/ 2 sem

Optimisation cART
≈ 4 mois

KS +
CD4 > 100
CV < 1.3 logs

R-Doxo Lipo

Rituximab
375 mg/m2 J1
Caelyx
25 mg/m2 J1

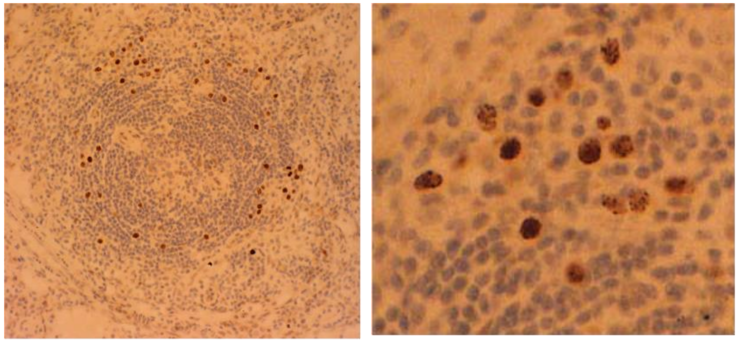
x 4 cycles / 2 sem

Galicier 2018

Physiopathologie

MCM HHV-8+ HIV +

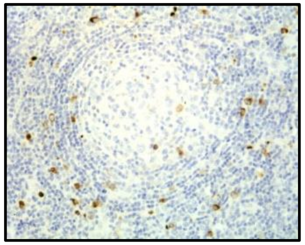
- Prolifération lymphoïde
- Castleman plasmocytaire
- « Plasmablastes » LANA (HHV-8)+

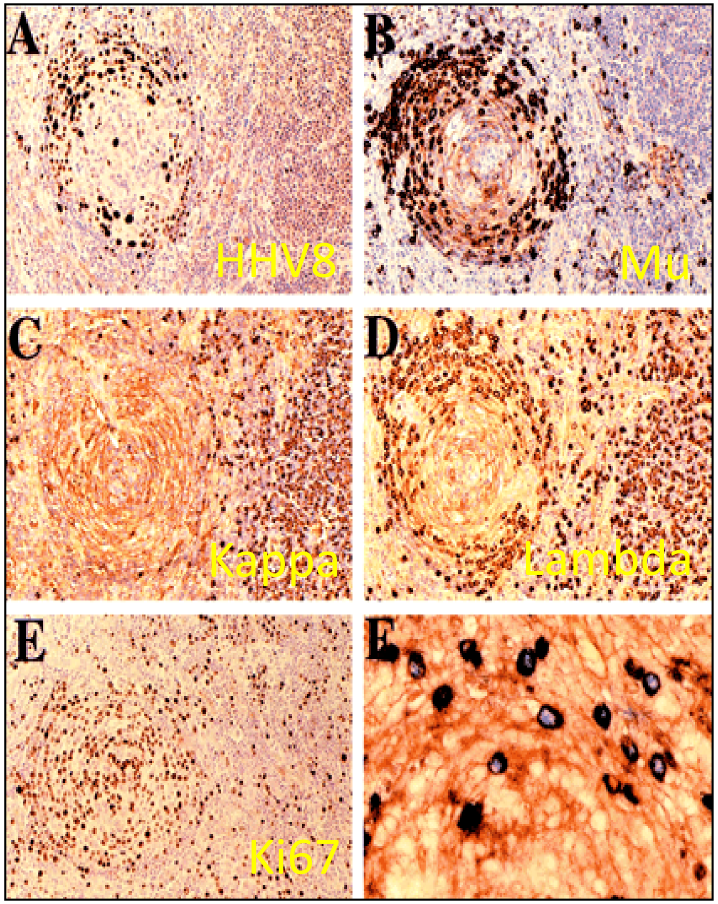


- PCR HHV-8 DNA +++ (sang)
- IL6 et IL10 ↗↗

  (Oksenhendler et al. Blood 2000)
- *vIL6* ↗

  (Parravicini et al. Am J Pathol 2000)




A
HHV8
B
Mu
C
Kappa
D
Lambda
E
Ki67
F

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

HHV8+
lambda+

Physiopathologie

MCM HHV-8+ HIV +

- Prolifération monotypique de cellules IgM lambda

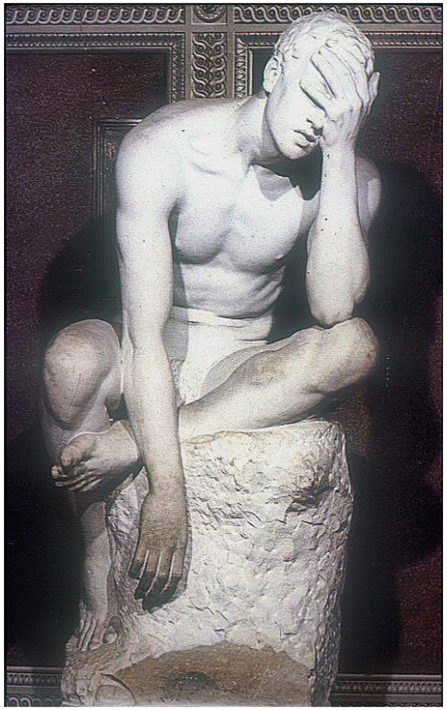
  … polyclonales

- Cellules naïves, non mutées

  … en différenciation plasmocytaire

- Prolifération

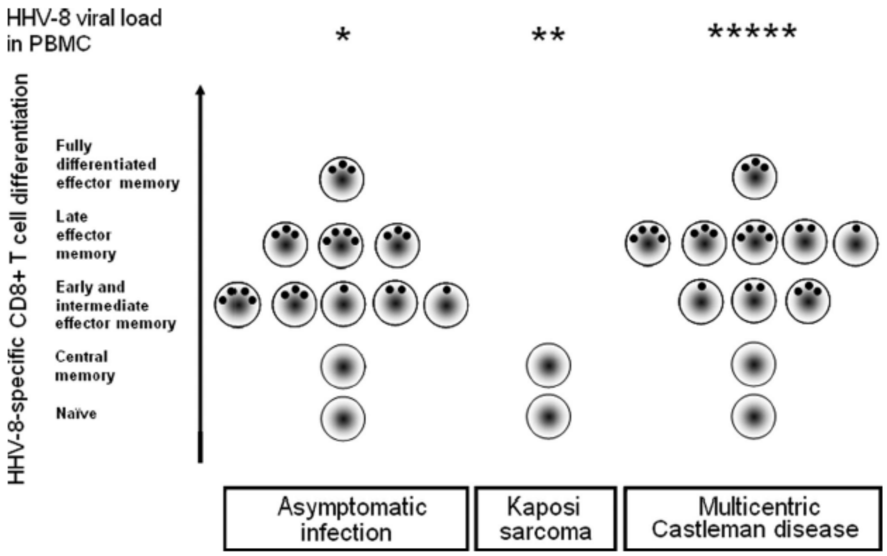
  … et réplication

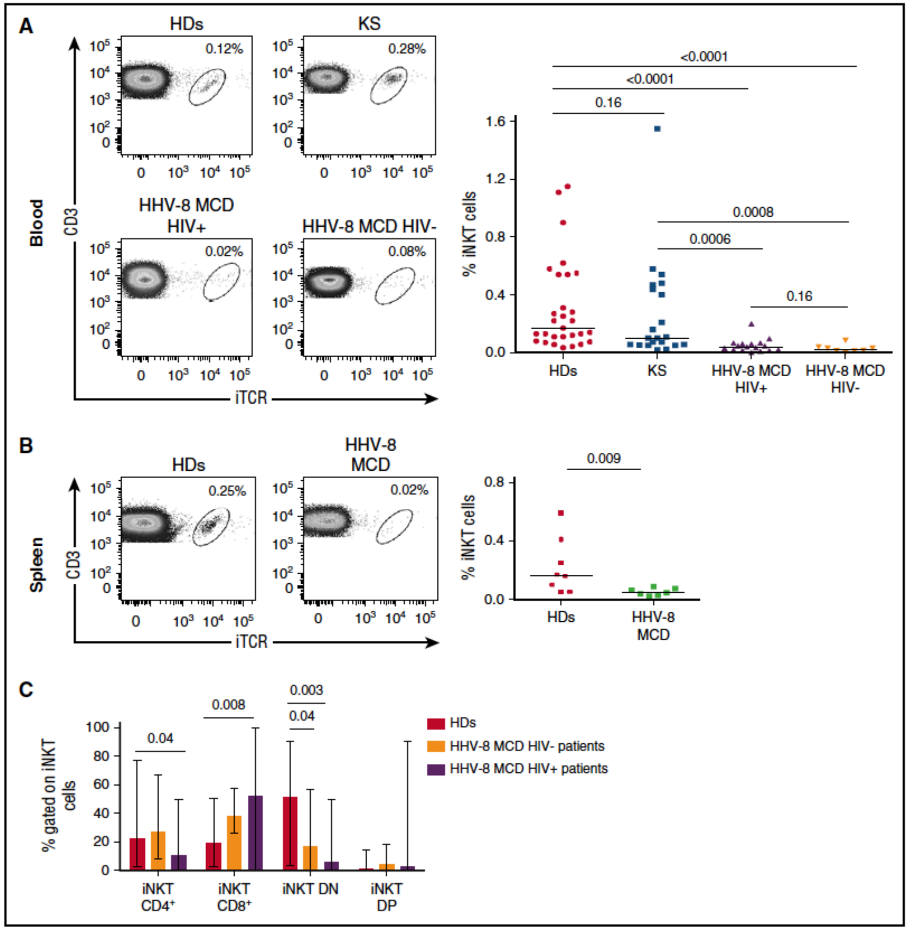


Rôle du déficit immunitaire ?

Pas de déficit T CD8 cytotoxique

Déficit i NKT?


HHV-8 viral load in PBMC
*
**
*****
HHV-8-specific CD8+ T cell differentiation
Fully differentiated effector memory
Late effector memory
Early and intermediate effector memory
Central memory
Naïve
Asymptomatic infection
Kaposi sarcoma
Multicentric Castleman disease



Guihot 2008
Sbihi 2017

Le Spectre
des « Lymphoproliférations associées à HHV-8 »

Maladie de Castleman

- Fière
- Adénopathies
- Splénomégalie

Lymphoprolifération plasmablastique

- Forme « leucémique »
- Forme « solide »
- PCR-HHV8 > 7 logs/mL
- Cellules Mu-Lambda
- Poly- ou Mono-clonale

Lymphome des séreuses

- Sérite
  - Péricardite
  - Ascite
  - Pleurésie

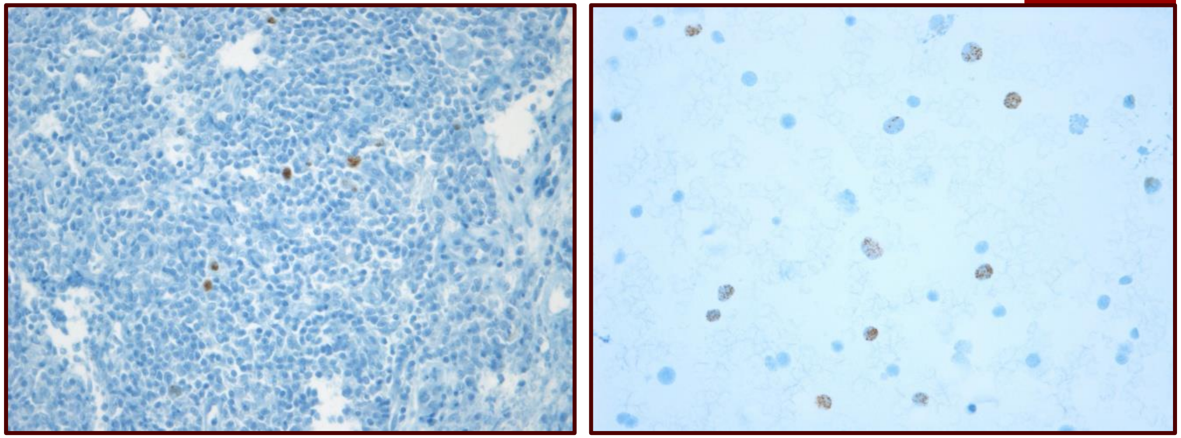
KICS

- Cytopénie
- Grand Sd Inflammatoire
- Pas d'adénopathie
- Souvent KS ++

Homme, 61 ans

- Fièvre
- Polyadénopathie
- Splénomégalie
- Dyspnée
- Oedème

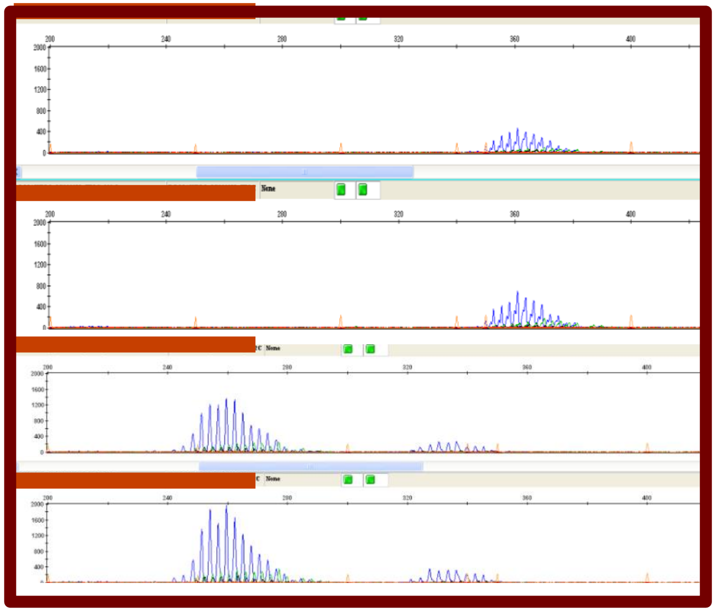
- Leuco: 2,700 /mm3
- Lympho: 580 /mm^3
- Hb: 4.4 g/dL
- Plaquettes: 23,000 /mm^3
- Albumine: 17 g/L
- CRP: 188 mg/L
- HIV+
- CD4: 150 /mm^3
- Plasma HIV-RNA: 5.2 log
- **HHV8 / blood: 7.74 log**


Lymph node

Blood

LANA+ HHV8 infected « plasmablasts »

CD19+ CD38+ IgM lambda+ monotypic B cells
74%



Polyclonal
IgH VDJ pattern

Galicier 2018

KSHV Inflammatory Cytokine Syndrome

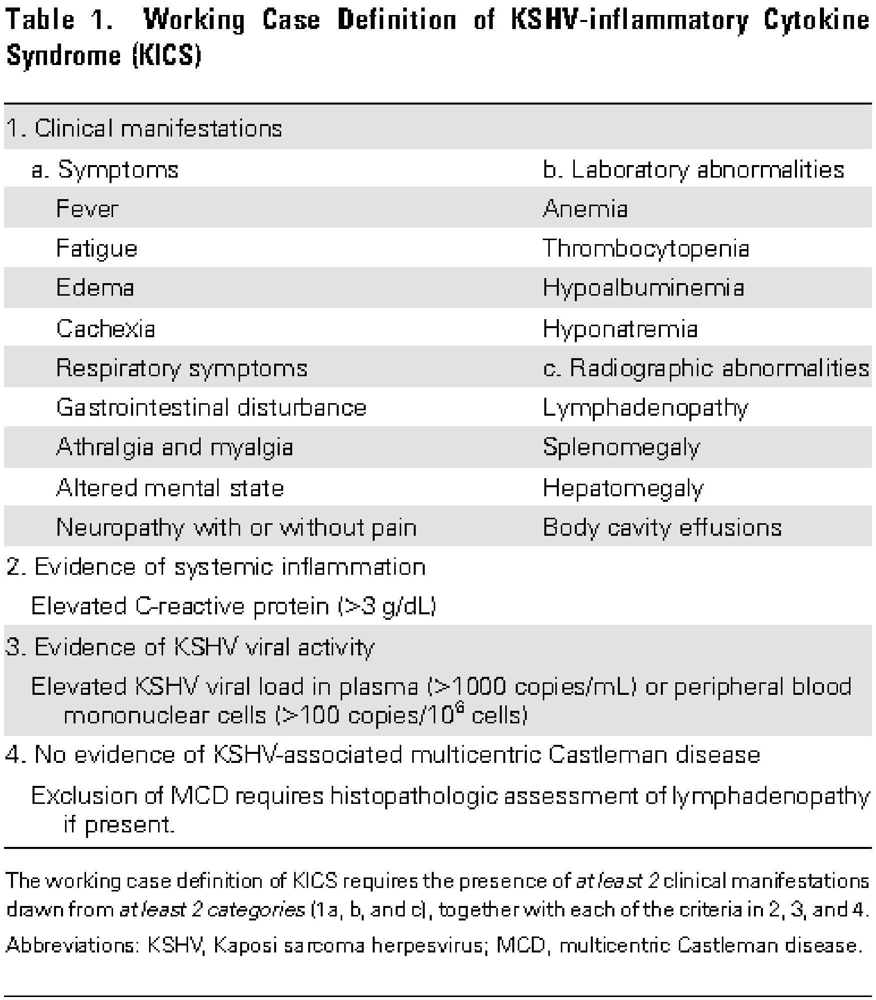
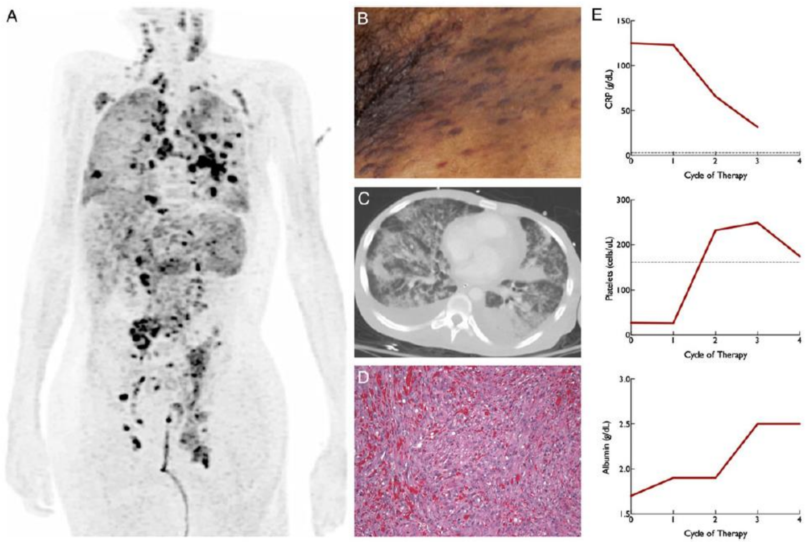


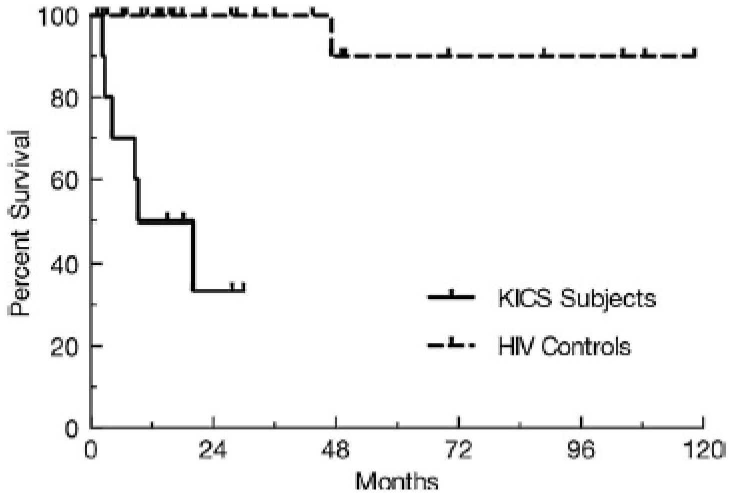
Table 1. Working Case Definition of KSHV-inflammatory Cytokine Syndrome (KICS)

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.

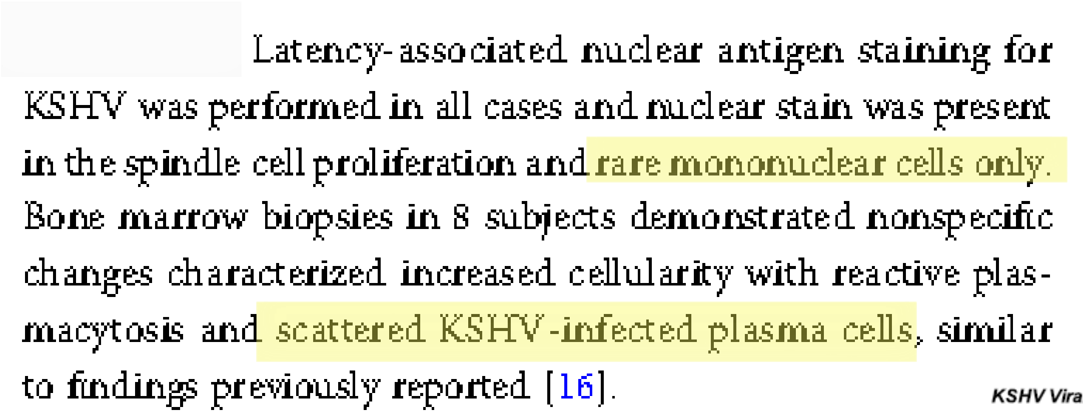




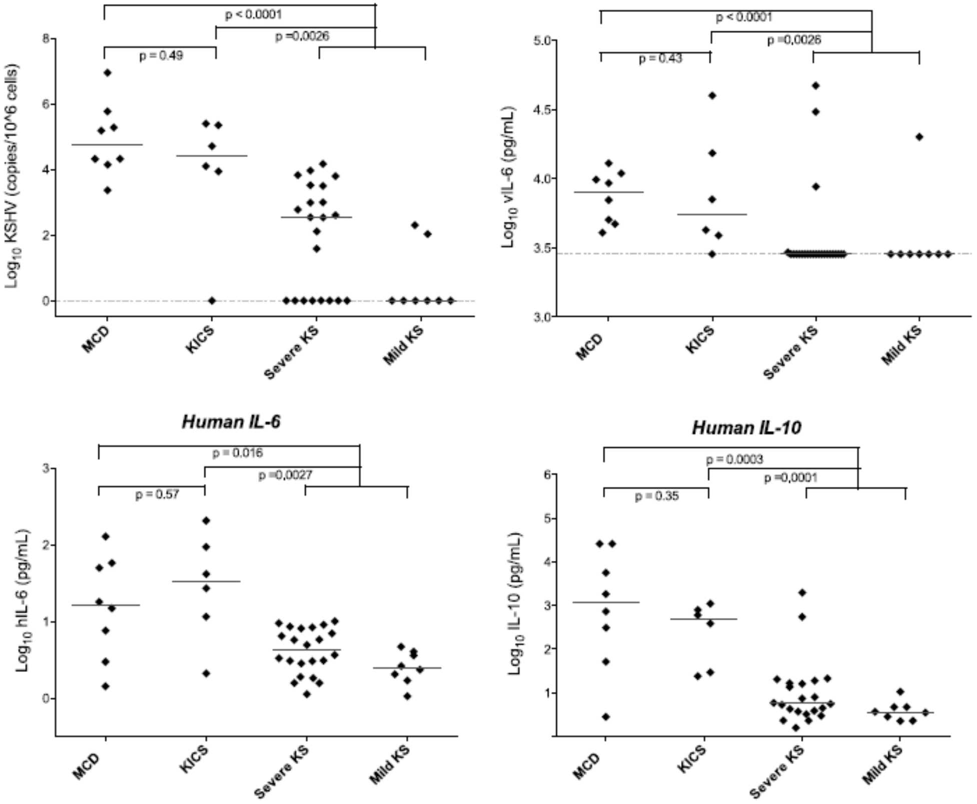
Polizzotto 2012

Galicier 2018

KICS vs MCD



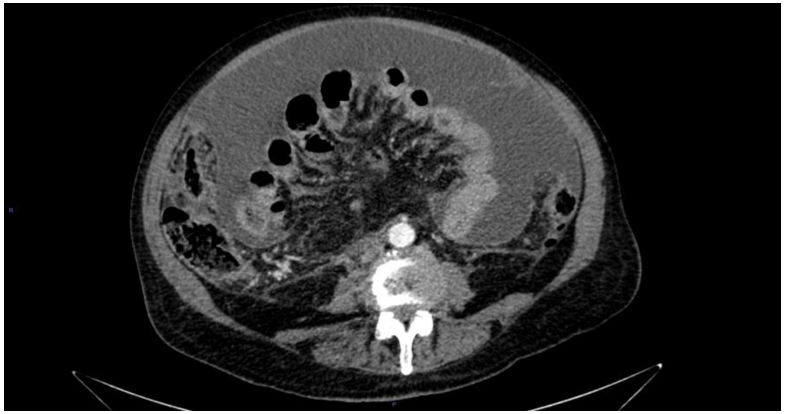
Latency-associated nuclear antigen staining for KSHV was performed in all cases and nuclear stain was present in the spindle cell proliferation and rare mononuclear cells only. Bone marrow biopsies in 8 subjects demonstrated nonspecific changes characterized increased cellularity with reactive plasmacytosis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

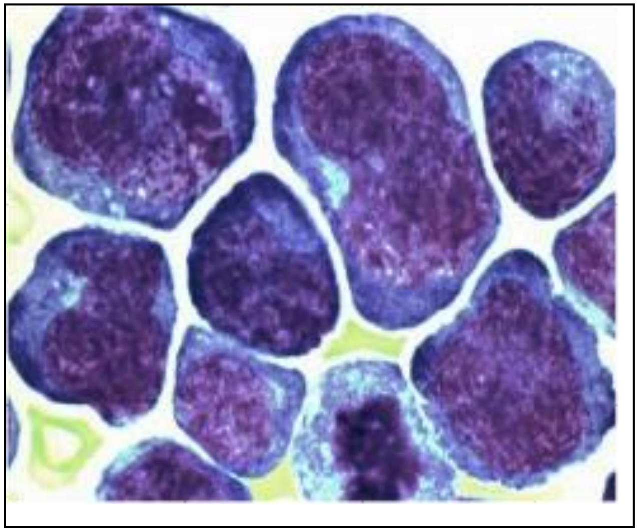


Polizzotto 2012

Primary Effusion Lymphoma & « solid » PEL

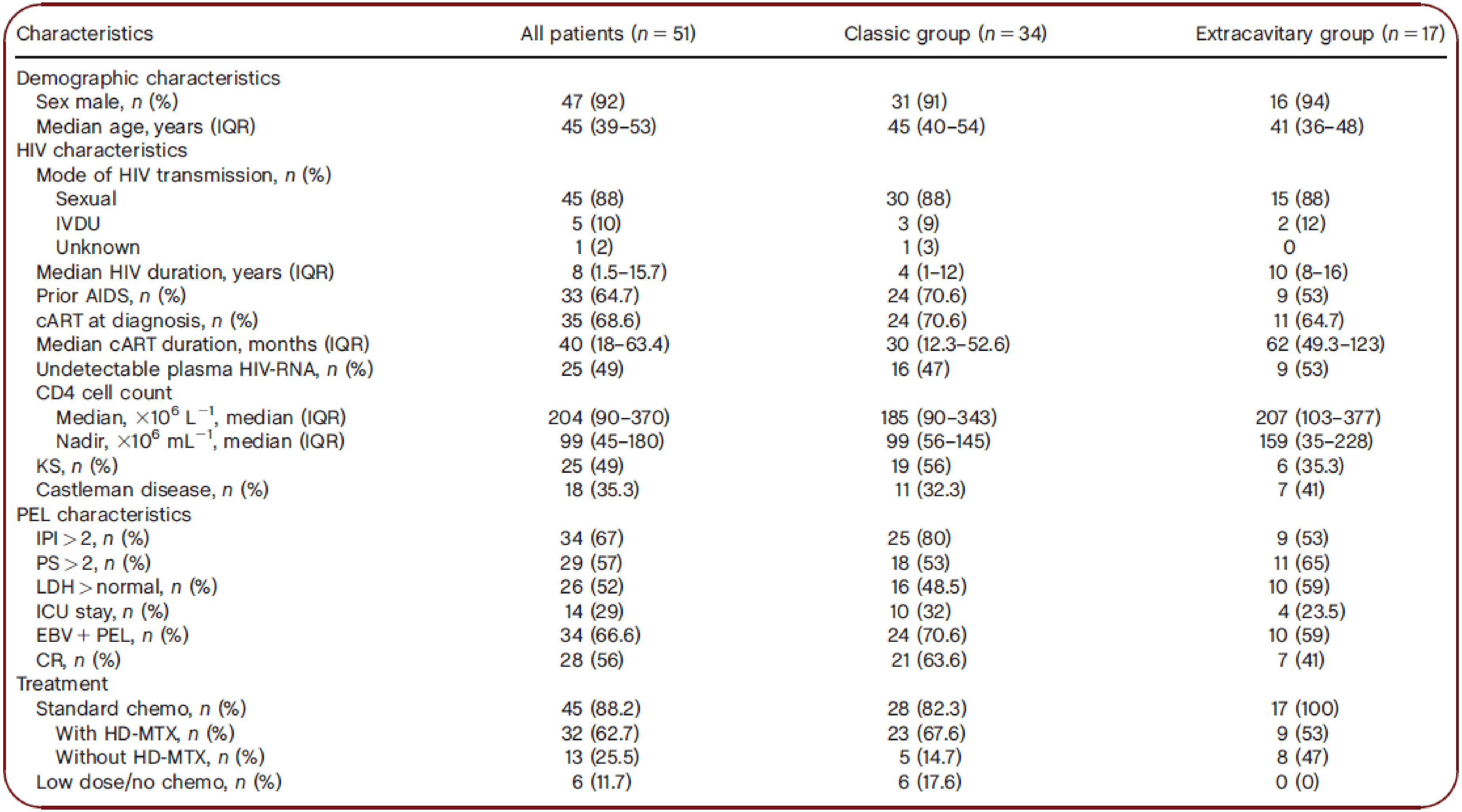
- **Ascite** ou **Pleurésie** ou **Péricardite**
- Atteinte extra-cavitaire pas si rare
- Mauvais pronostic: médiane OS < 12 mois





- **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

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 lymphoproliférations HHV8
  - Physiopathologies différentes
  - Traitement parfois difficile.
  - Contrôle de l'infection HIV requise

Conclusions

www.castleman.fr