



Lymphoproliférations et Infection HIV

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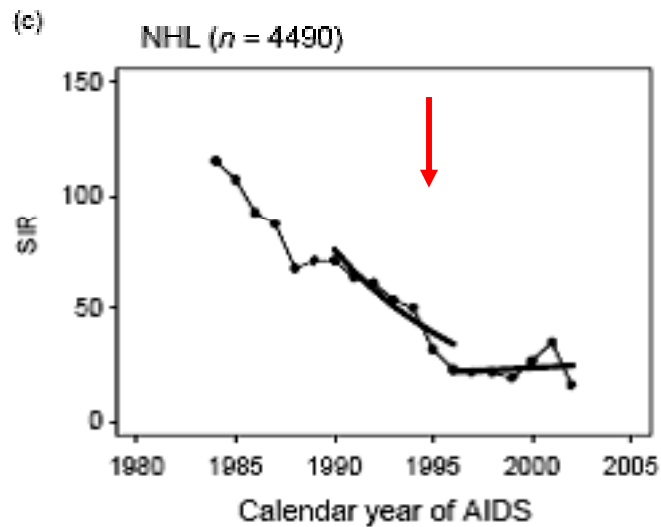


Lymphomes et Infection HIV

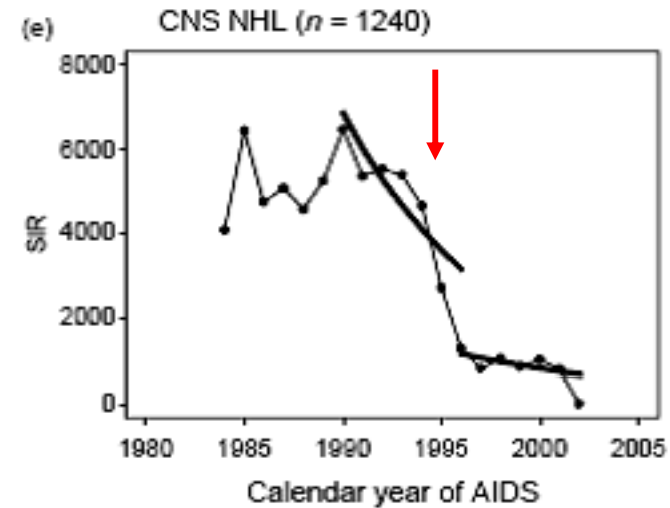
- **Epidémiologie**
- Présentation clinique
- Thérapeutique
- Cas particuliers

Evolution du risque de lymphome / HIVneg 1984-2002

Lymphomes systémiques



Lymphomes cérébraux






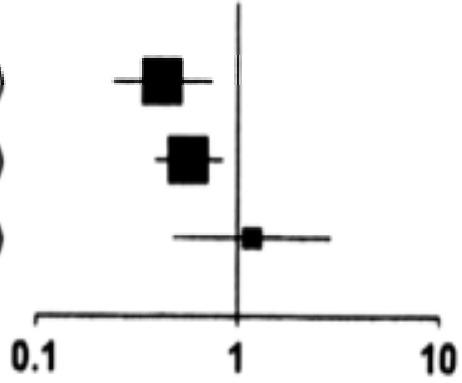
SIR	79.8	53.2	22.6	SIR	5000	4850	1020
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N= 37,428
Pts stade SIDA

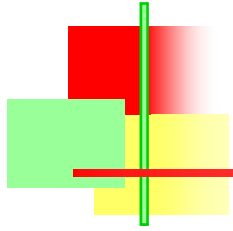
Non-Hodgkin 's Lymphoma

International Collaboration on HIV and Cancer,

CANCER TYPE	Adjusted incidence rate per 1000 per year (No.)		Rate ratio (RR) for 1997 through 1999 versus 1992 through 1996	
	1992 through 1996	1997 through 1999	RR (SE)	RR (99% CI)
Cerebral lymphoma	1.7 (138)	0.7 (24)	0.42 (0.09)	
Immunoblastic lymphoma	3.0 (246)	1.7 (54)	0.57 (0.09)	
Burkitt's lymphoma	0.3 (26)	0.4 (13)	1.18 (0.41)	

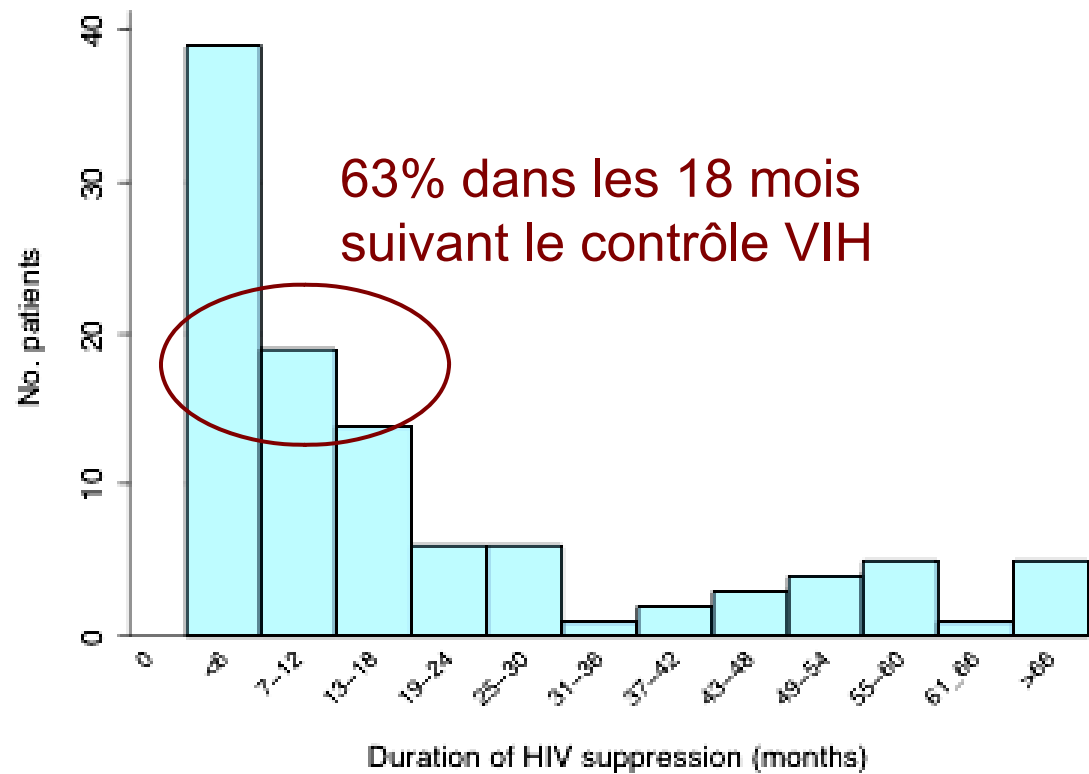


JNCI 2000



LNH %o patients à charge virale indétectable

N = 107 / 345



Saint-Louis 1997-2007

Patients traités: Place croissante des LNH

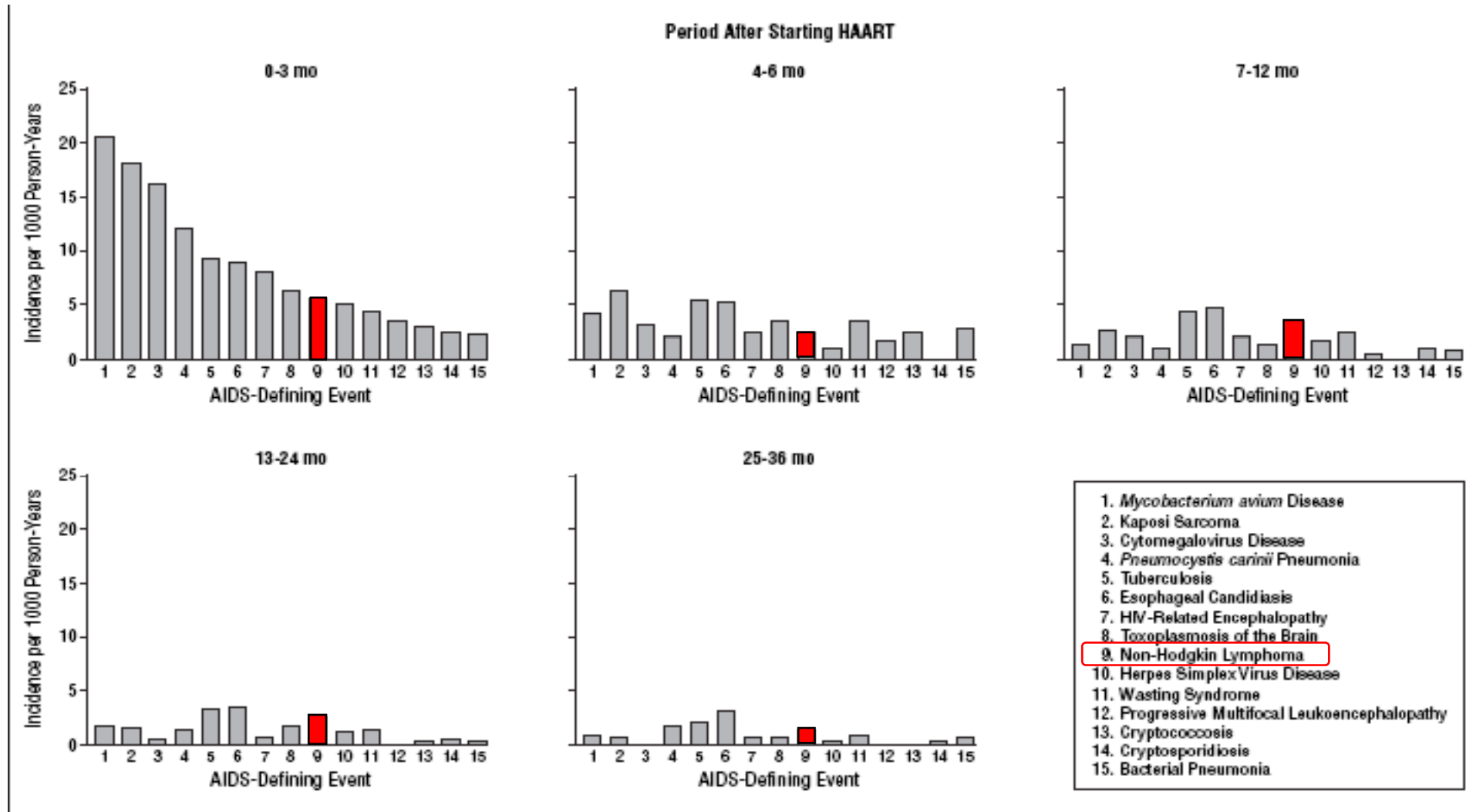
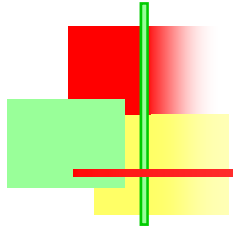


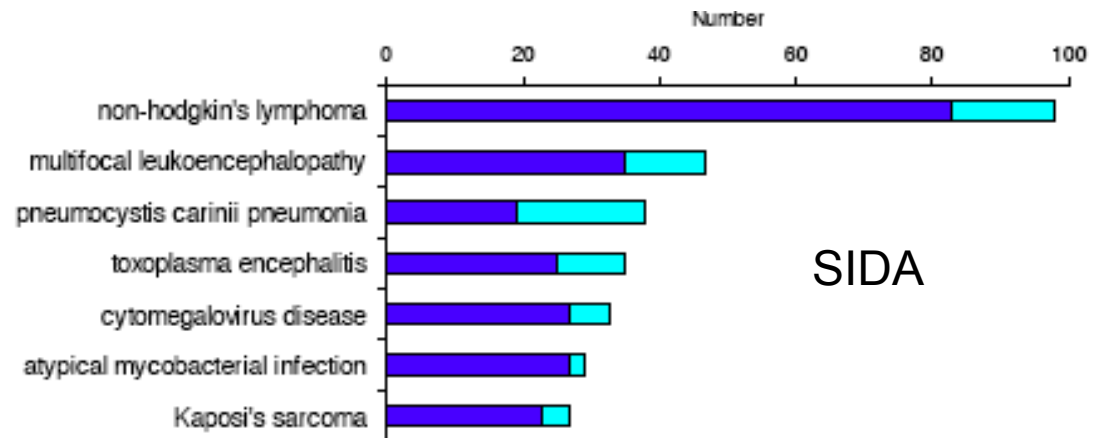
Figure 1. Incidences of 15 AIDS-defining events in 5 time periods after initiation of highly active antiretroviral therapy (HAART).

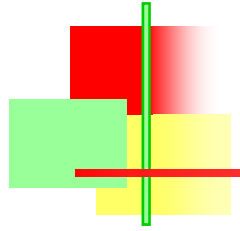


Lymphome : cause majeure de décès

SIDA (337)	36% ➤	➔ LNH (98)
Cancer	16% ▼	➔ MdH (8)
VHC	11% ▼	
CardioVasc	9% ▼	
Suicide	5% ▼	
Infection	5% ➤	

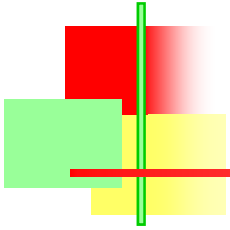
Enquête « Mortalité 2005 »
340 centres (78 000 pts) - 989 décès



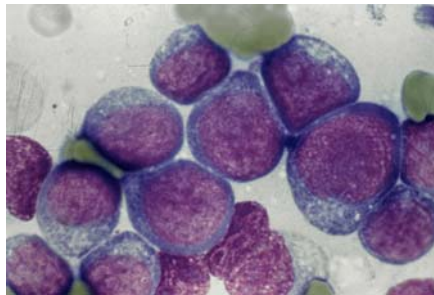
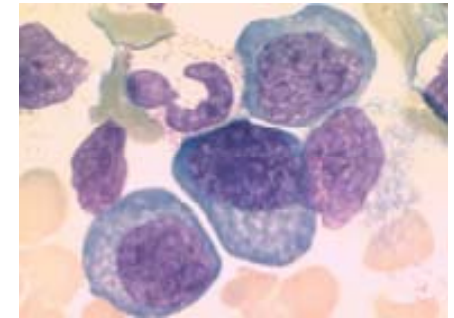
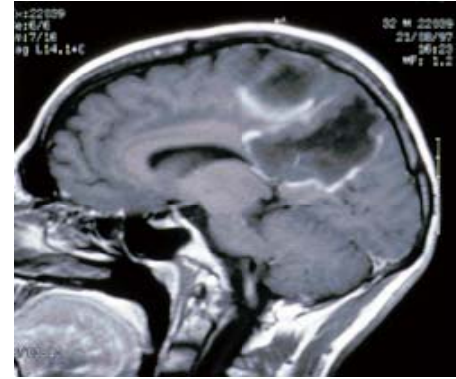
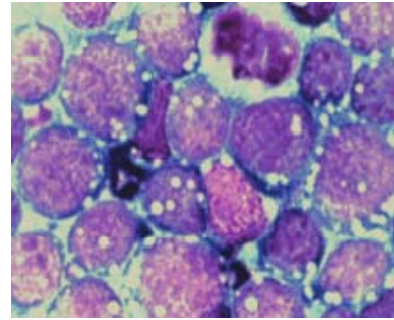
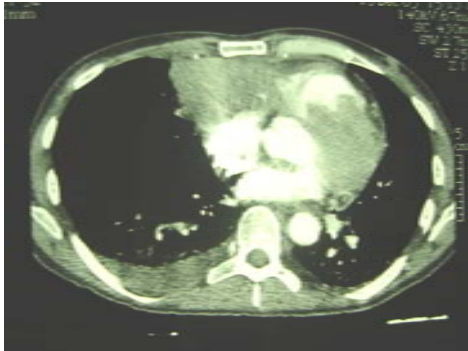


Lymphomes et infection HIV

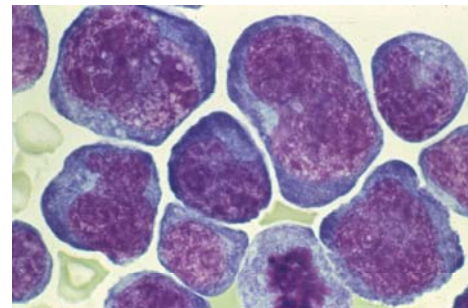
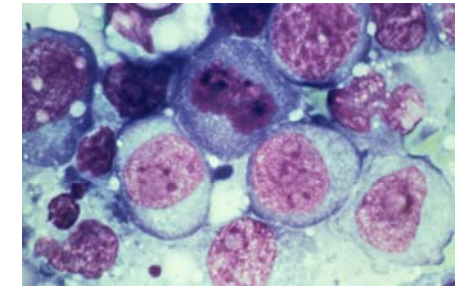
- Epidémiologie
- **Présentation clinique**
- Thérapeutique
- Cas particuliers



CLINIQUE



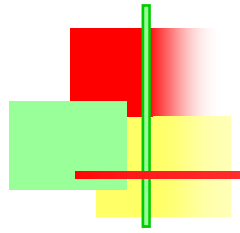
POLYMORPHE!





En résumé

	LPC	BGC	Btt t 8;14	MdH	HHV8	
					Castleman	Séreuse
CD4	<100	200	/	/	/	/
Fièvre	-	+/-	+/-	+++	+++	++
Masse Tumorale	Cerveau	GG, Extra Nodal	+++ LDH ↑↑	Moelle+ Foie > GG	GG, rate	Séreuse MAIS PEL solid
Neuro	exclusif	rare	+++ Houppes	jamais	non	non
Risque	Engage- ment	Compres°	Lyse Compres°	SAM	SAM	SAM



Lymphomes et Infection HIV

- Epidémiologie
- Présentation clinique
- **Thérapeutique**
- Cas particuliers

Low-dose vs standard mBACOD

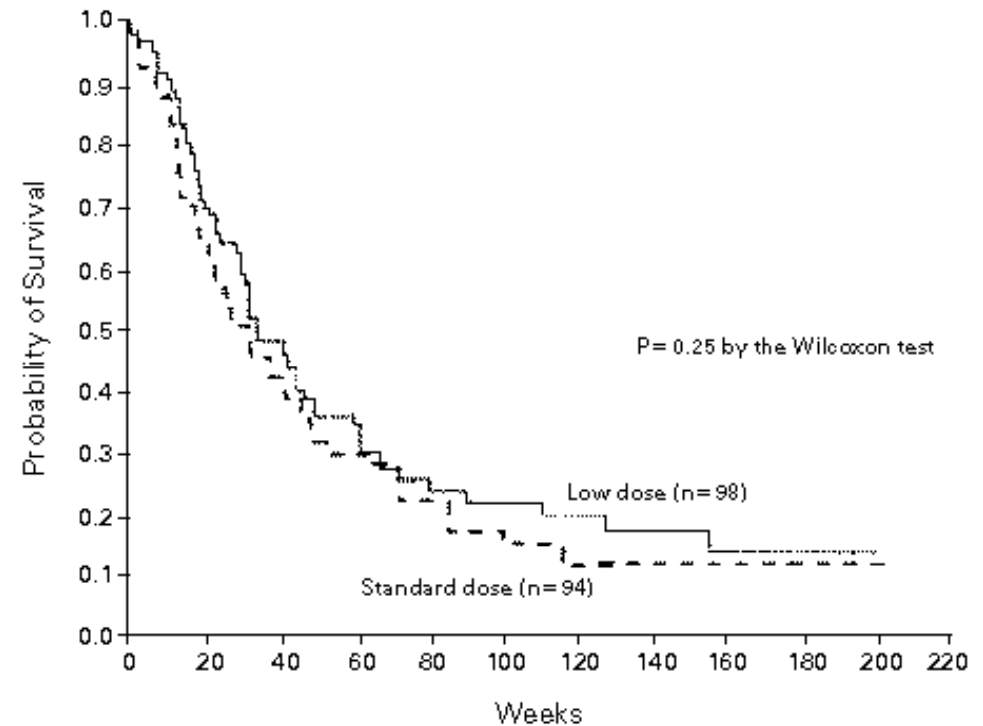
98 vs 94 patients

CR: 41% vs 52%

Survie médiane

35 sem vs 31 sem

« low-dose » fait *aussi mal*
que « standard »

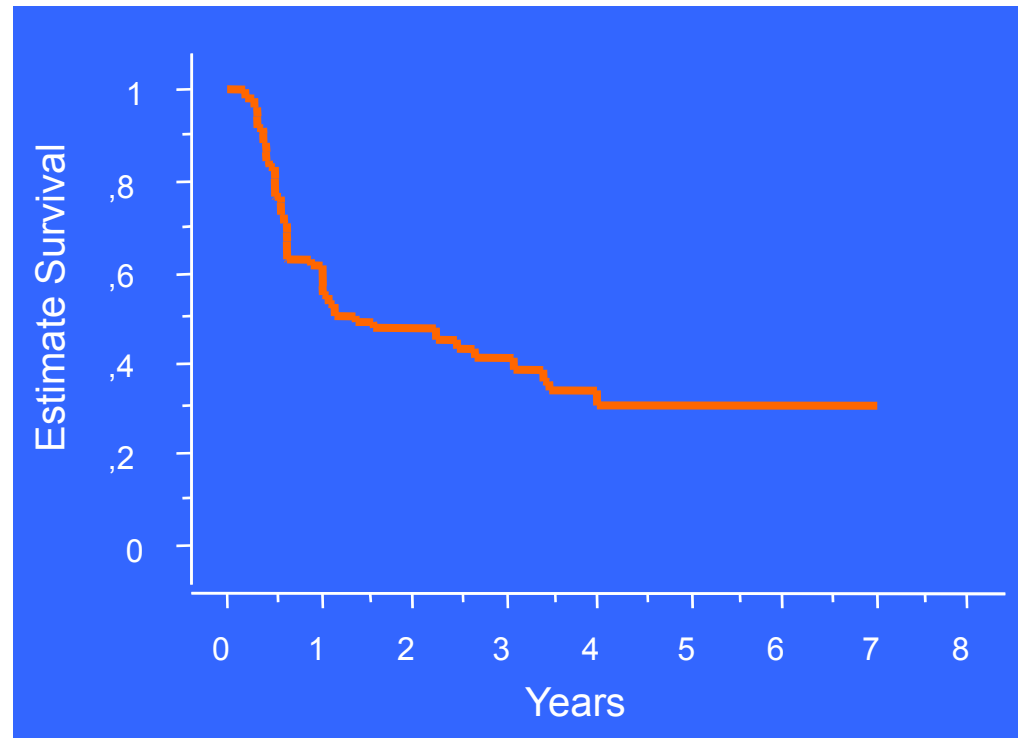


L Kaplan 1996



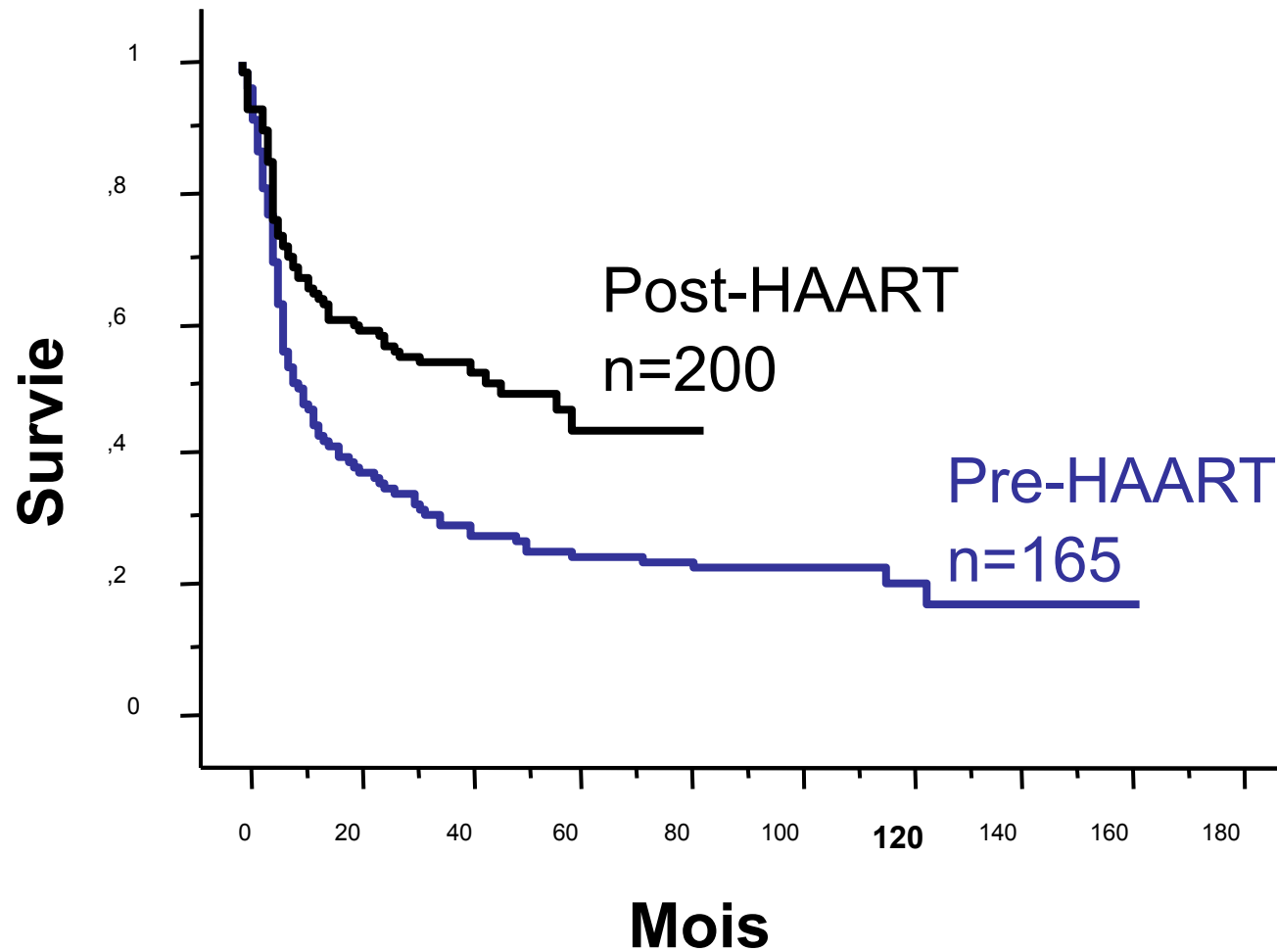
LNHIV-91 survie (CD4 > 100, n = 52)

- Follow-up median :
70 mois (30 à 88)
- Décès : 34 (LNH: 21)
- **Survie à 2 ans :**
47.3 % (33.3 - 61.3%)
- Plateau à 4 ans :
33.6 % (19.8 - 47.4%)



LNH et infection HIV (90-96 / 96-03)

Survie globale - St-Louis



$P = 0.0001$

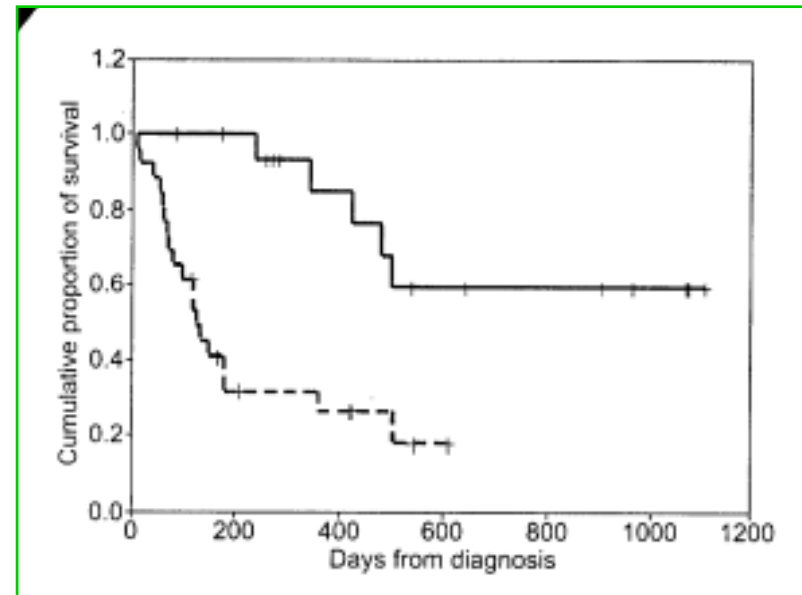
Lymphomes et infection HIV

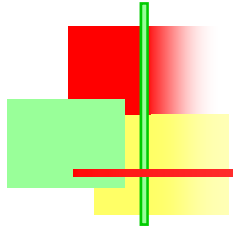
Place des antirétroviraux

- Améliorent la survie
- Doivent être maintenus
- Interactions (RTV)
- Suspensions ?

NON !

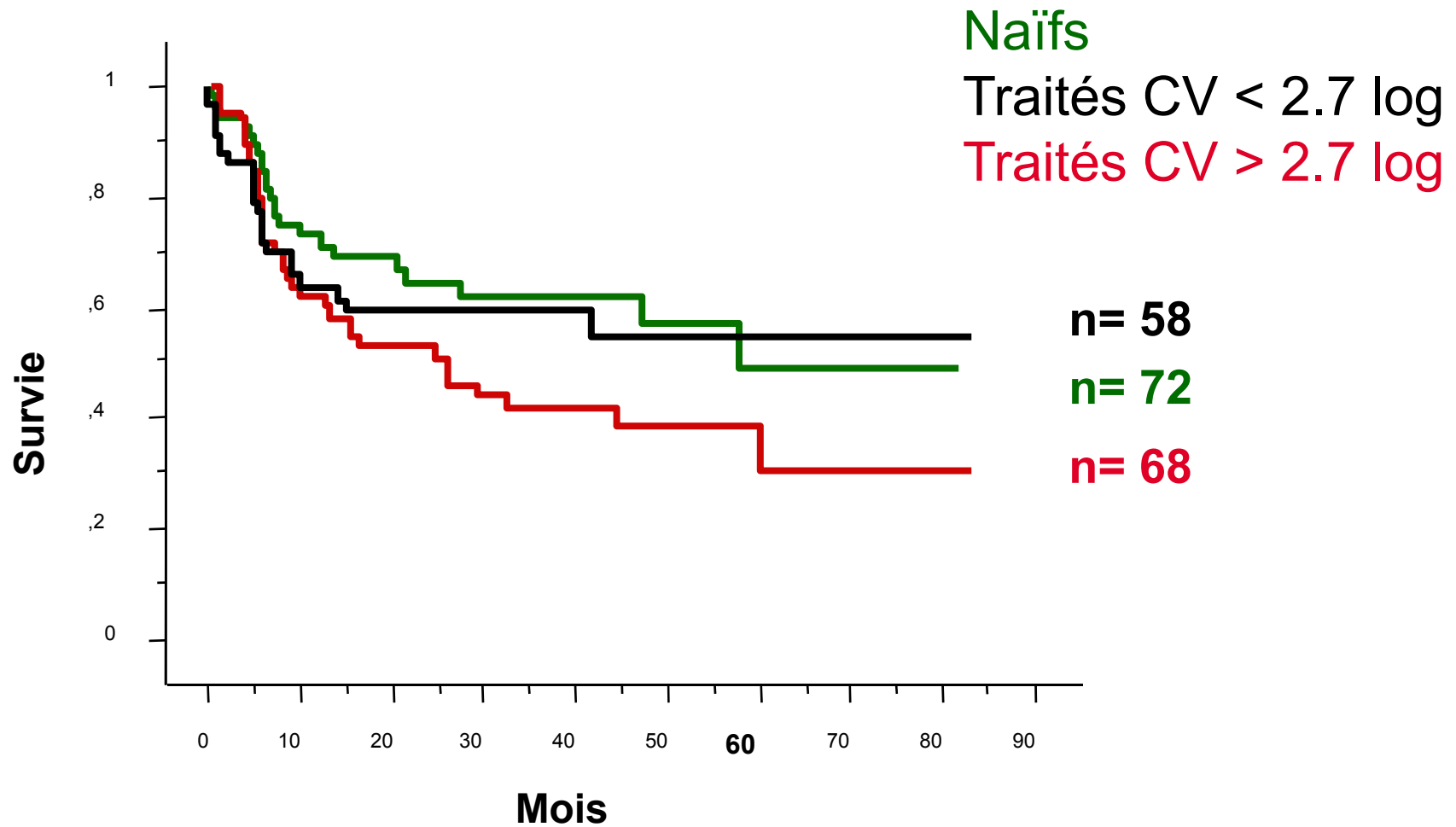
A Antinori, 2001

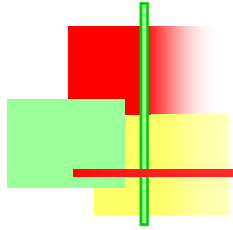




LNH et infection HIV (6/96 - 10/03)

Survie globale - St-Louis





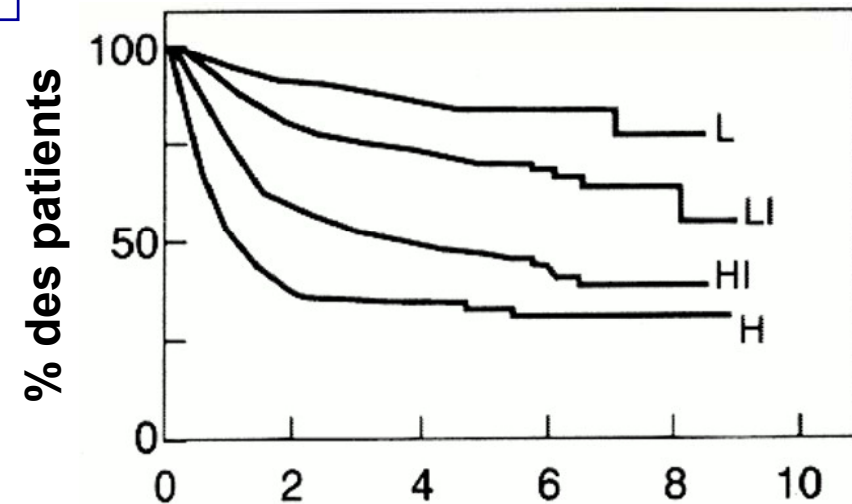
Facteurs pronostiques

IPI (International Prognostic Index)

- Critères :
- Age > 60 ans
 - Stade Ann Arbor III ou IV
 - LDH supérieures à la normale
 - Plus d'un site extra-ganglionnaire
 - ECOG ≥ 2

		Défavorables
Âge du patient	≤ 60 ans	> 60 ans
Indice d'activité ECOG	0-1	≥ 2
Stade d'Ann Arbor	I-II	III-IV
Taux des LDH	Normal	> Normal
Nombre de localisations extra ganglionnaires	0-1	2 ou plus

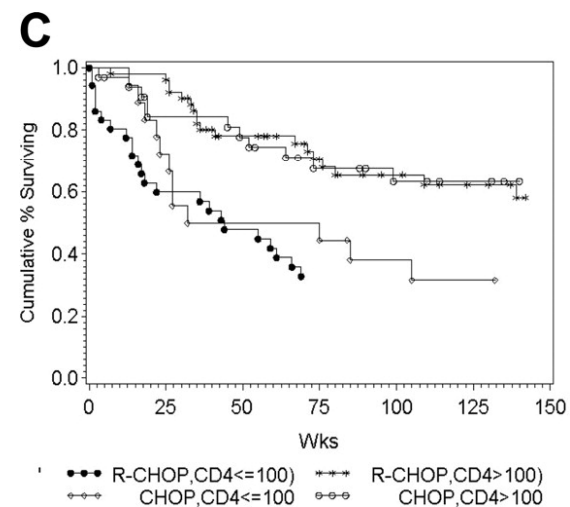
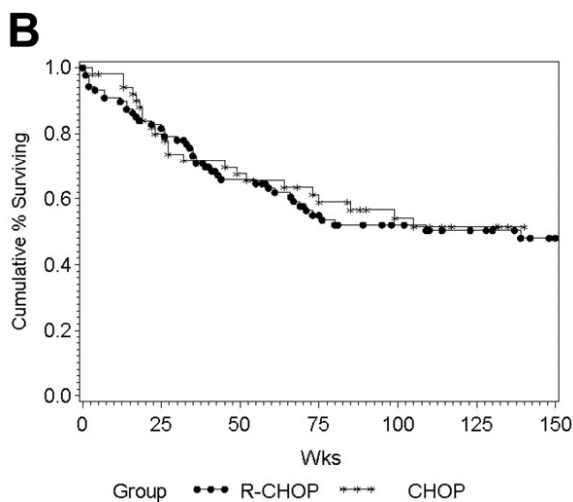
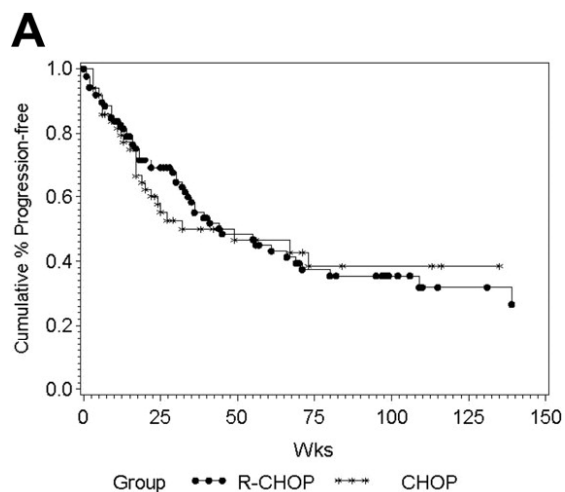
Survie globale



Combinaisons anti-CD20 / chimiothérapie

Essai comparatif R-CHOP (n=99) vs CHOP (n=50)

- Médiane CD4 = 133 /mm³
- R-CHOP -> décès par infection: **14% vs 2% (p=.02)**
- > survie médiane identique: 138 vs 121 sem.



R-CHOP

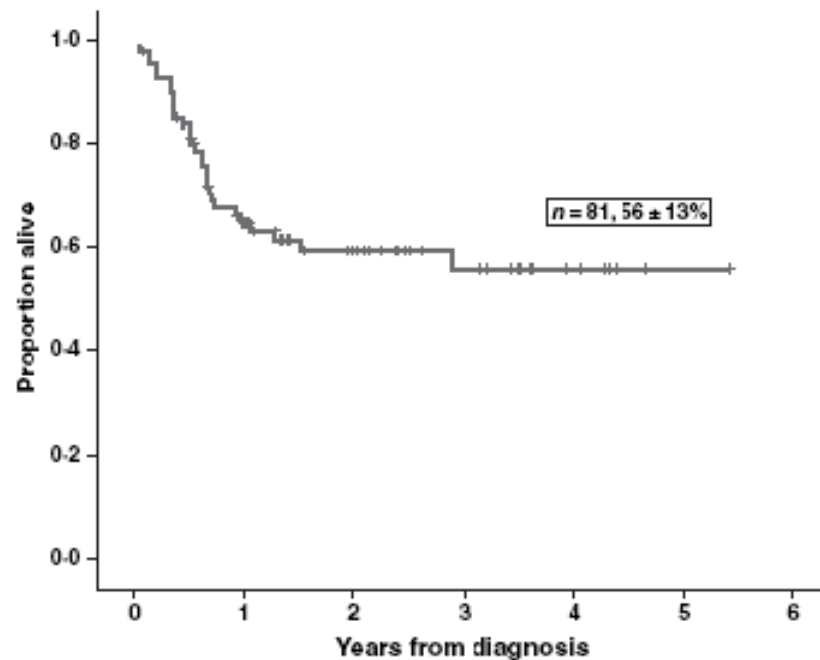
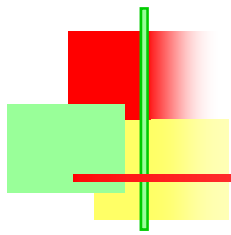


Fig 3. Overall survival for the 81 patients from the series.

Characteristic	n	%
Sex		
Male	66	82
Female	15	18
Risk activity for HIV infection		
IV drug use ⁺	29	36
Heterosexual	25	31
Homosexual/bisexual	24	29
Unknown	3	4
Prior opportunistic infections	38	47
Prior neoplasia	3	4
NHL as first HIV-associated event	40	49
Prior HAART [†]		
Yes	32	44
No	41	56
CD4 lymphocyte count [‡] ($10^9/l$)		
>0.2	35	44
0.1–0.199	20	25
0.050–0.099	9	11
<0.050	16	20
HIV viral load <50 copies/ml [‡]	22	28
ECOG status [‡]		
0–2	65	81
3	15	19
B symptoms	43	53
Extranodal involvement (organ)	54	67
1	32	59
2	16	30
≥3	6	11
Ann Arbor stage		
I/II	24	30
III/IV	57	70
IPI score		
0–1 (low)	26	32
2 (intermediate-low)	19	23
3 (intermediate-high)	20	25
4–5 (high)	16	20



R-CHOP

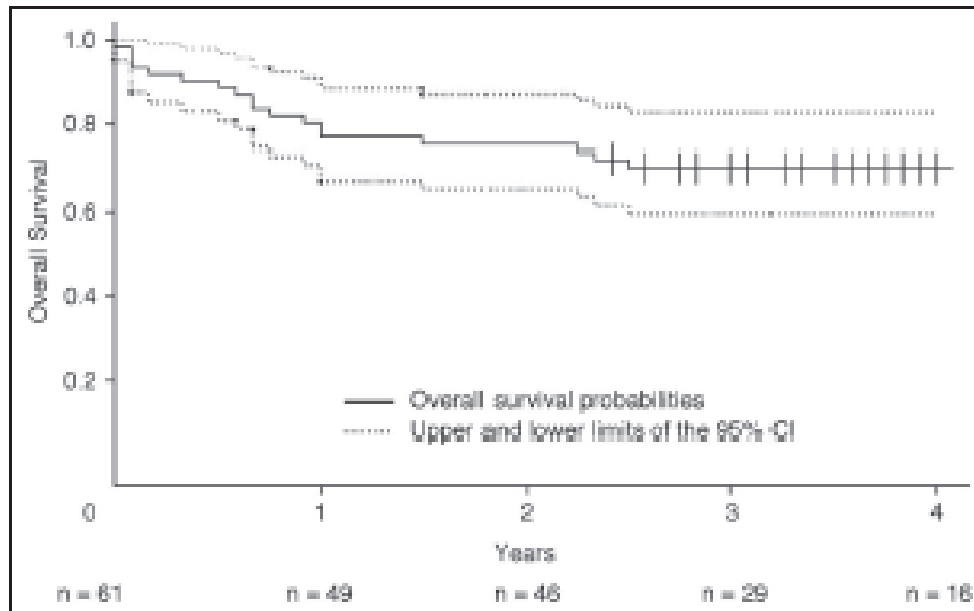
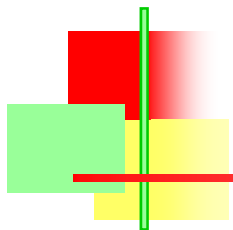


Fig 1. Overall survival.

Characteristic	All Patients (n = 61)	Assessable Patients (n = 52)
Age, years		
Median	41	40
Interquartile range	35-51	34-51
Sex		
Male	55	49
Female	6	3
Prior opportunistic infection	13	9
CD4+ lymphocyte count		
Median/ μ L	172	160
Interquartile range	104-346	112-446
No. of patients with		
< 200 CD4/ μ L	31	26
< 100 CD4/ μ L	12	9
Prior HAART		
Yes	36	21
No	25	31
Histology		
DLBCL	42	36
c-BL	6	6
s-BL	10	9
IBL	2	1
Plasmablastic	1	0
Stage		
I, IE, II	19	18
III/IV	42	34
ECOG status		
0-1	31	28
?	27	23
IPI		
0-1	31	28
2	27	23
3	2	0



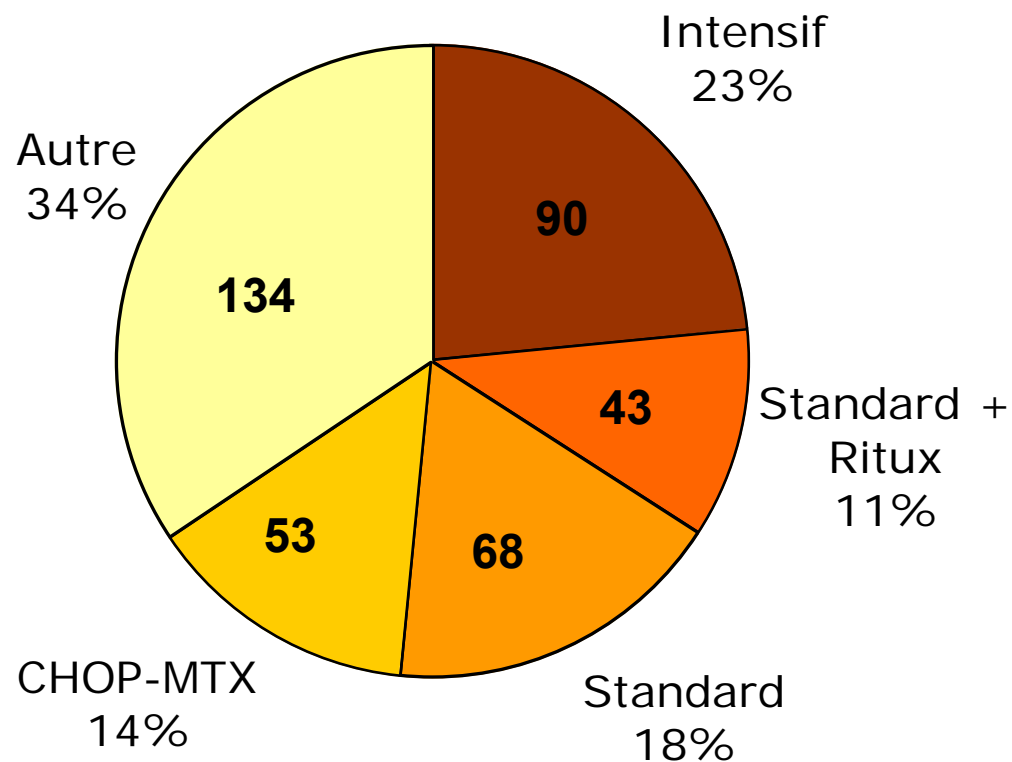
Saint-Louis 1996-2008

N = 388

Intensif	ACVBP
Std + Ritux	R-CHOP
Std	CHOP
CHOP-MTX	CHOP-MTX

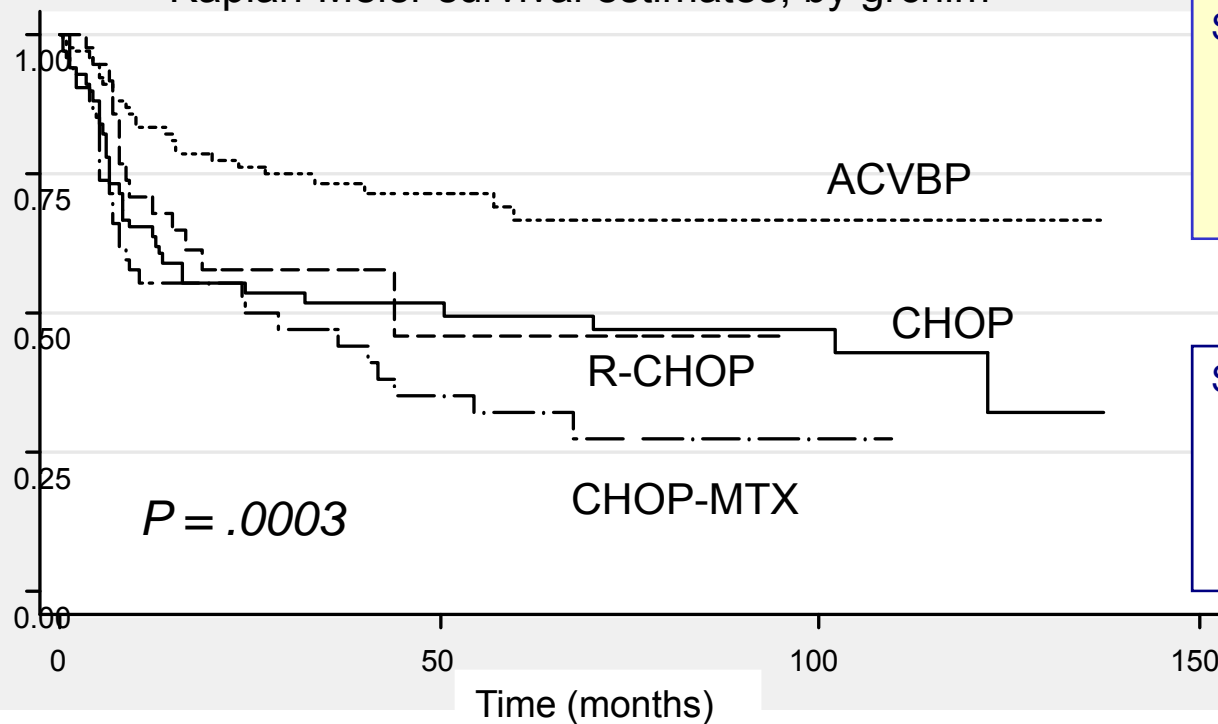
Autre

COPADEM	80
Divers	54



Survie globale en fonction du TT (OS)

Kaplan-Meier survival estimates, by grchim

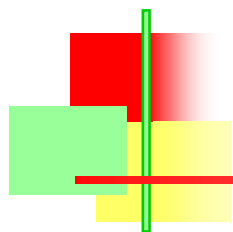


Survie à 2 ans :

ACVBP	76% [66-84]
R-CHOP	58% [39-72]
CHOP	55% [42-66]
CHOP-MTX	53% [38-66]

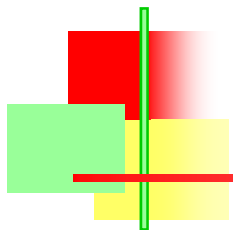
Survie à 4 ans :

ACVBP	71% [60-80]
R-CHOP	46% [21-68]
CHOP	52% [42-66]
CHOP-MTX	53% [39-63]

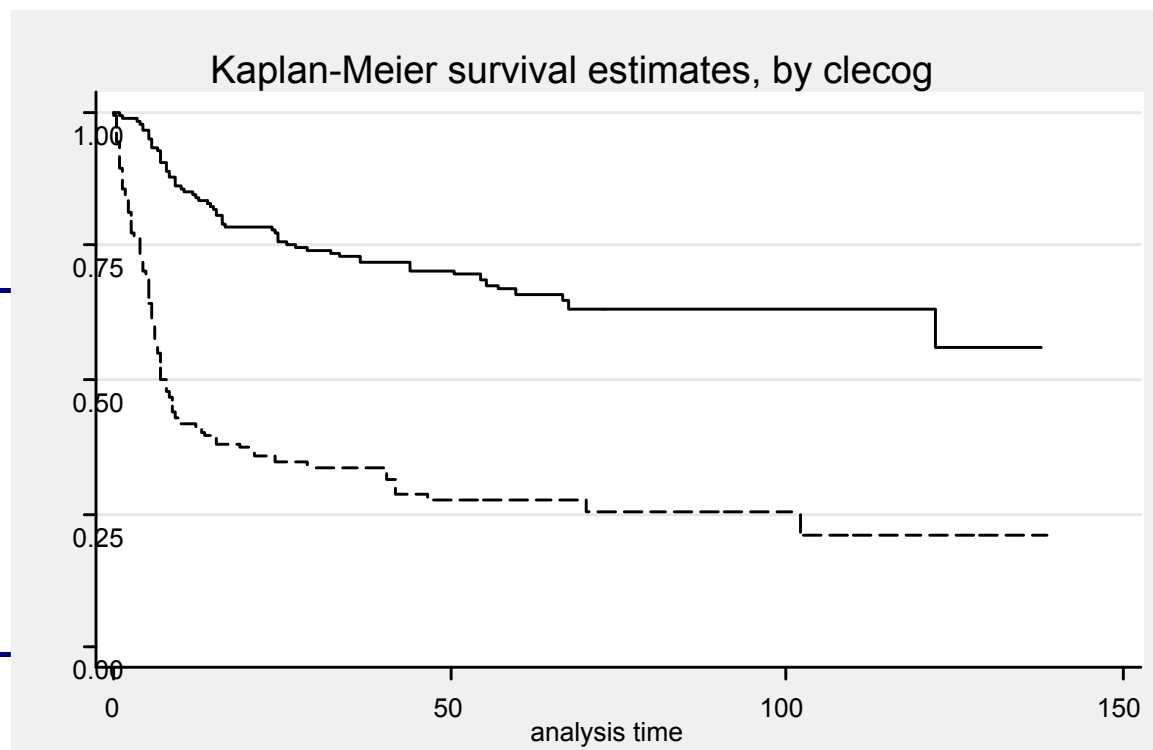


Description populations en fonction du TT

	ACVPB (n = 90)	R-CHOP (n = 43)	CHOP (n = 68)	<i>P</i>
CD4	254 [4-1290]	167[12-805]	140[2-686]	.001
CD4 ≤ 200	34 (51%)	24 (56%)	44 (65%)	
CD4 ≤ 100	13 (14%)	11 (26%)	25 (37%)	
Gpe ARV				.16
cART det.	28 (31%)	13 (30%)	25 (37%)	
cART indet.	23 (43%)	18 (42%)	24 (35%)	
naïfs	39 (43%)	12 (28%)	19 (28%)	
ECOG ≥ 3	17 (19%)	20 (48%)	30 (45%)	<10 ⁻³
IPI ≥ 3	30 (33%)	24 (57%)	33 (49%)	.02



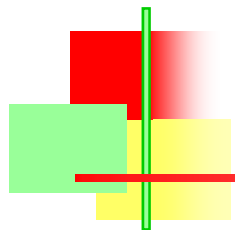
Facteurs pronostiques de survie



CD4 \leq 100
Gpe ARV
ECOG \geq 3
IPI \geq 3
Chimio

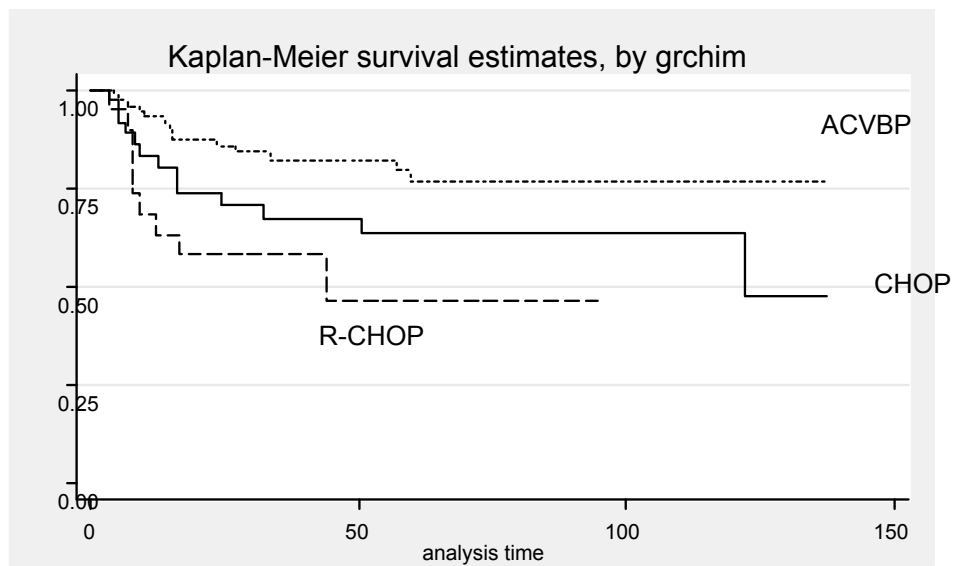
P

.27
.13
 10^{-3}
.04
.08

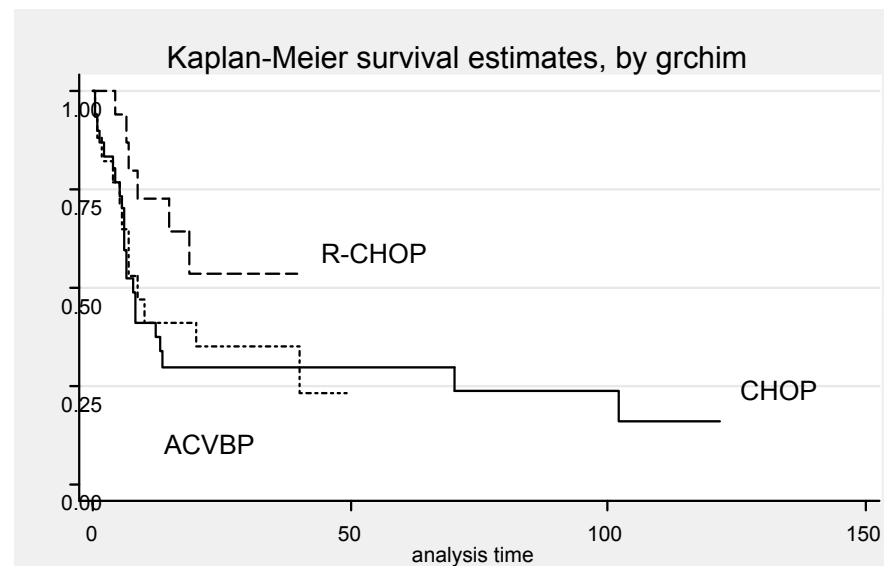


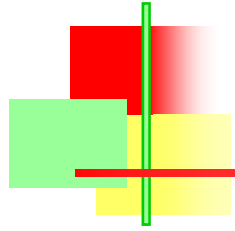
Proposition Thérapeutique

ECOG 0-2



ECOG 3-4



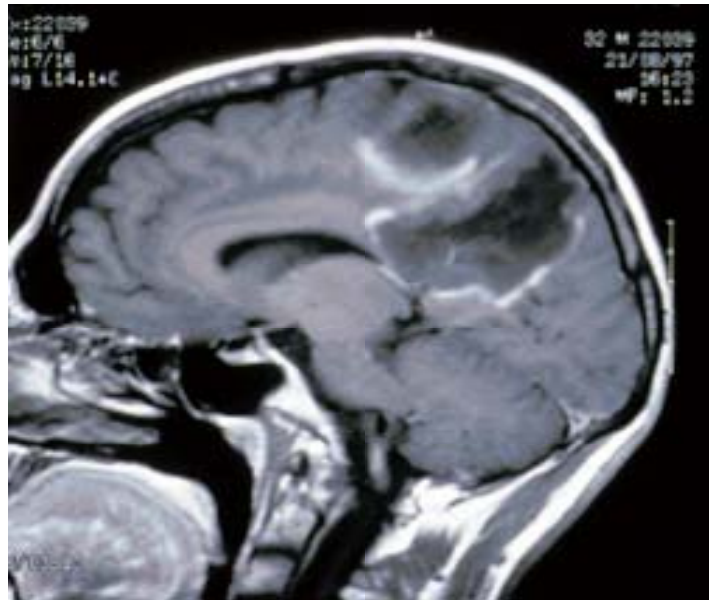


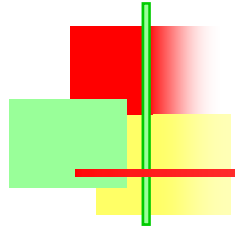
Cas particuliers

- Lymphome primitif cérébral
- LAL3 - Burkitt
- Burkitt - non-Burkitt - Burkitt
- Lymphoproliférations associés à HHV8
 - *lymphome des séreuses*
 - *Maladie de Castleman*
 - *lymphome associé à une maladie de Castleman*
- Maladie de Hodgkin

Lymphome primitif cérébral

- Déficit immunitaire sévère (CD4 < 50 /mm³)
- Diagnostic difficile
- Grandes cellules immunoblastiques B
- EBV > 90%

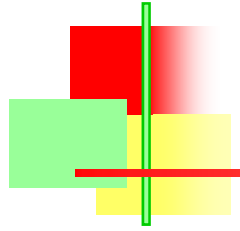




Lymphome primitif cérébral et infection HIV

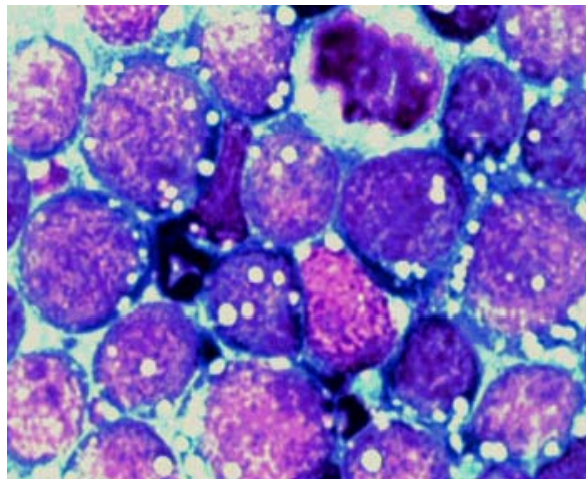
Traitement

- HAART
- Corticothérapie à forte dose
- Mono-chimiothérapie
 - methotrexate
 - aracytine
- Poly-chimiothérapie
 - CHOP-MTX
- Radiothérapie ?
 - encéphale < 20 Gy
 - surdosage sur la lésion



LAL3 - Burkitt

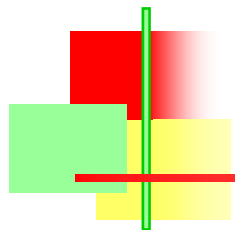
- Atteinte médullaire et neurologique
- Syndrome de lyse
- **Urgence** diagnostique et thérapeutique
- **Chimiothérapie intensive**





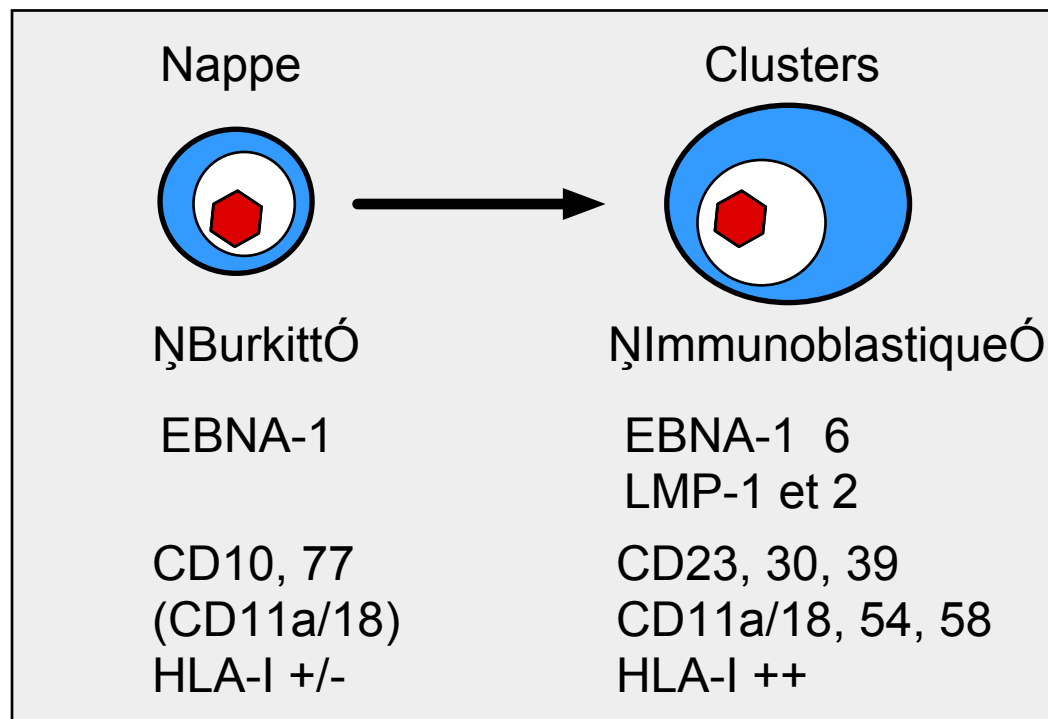
Burkitt - non-Burkitt - Burkitt

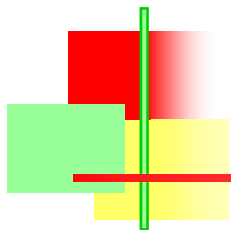
- Présentation clinique suggérant un Burkitt
- Le plus souvent déficit immunitaire sévère
- Grandes cellules parfois à différenciation plasmocytaire
- Le plus souvent EBV+
- Translocation du Burkitt (8;14) (8;22) (2;8)
 - ***Anomalies cytogénétiques surajoutées***
- -> *Traiter comme un Burkitt ?*



Les « Burkitt - non-Burkitt - Burkitt »

- Rôle du déficit immunitaire dans l'expression
- clinique
- morphologique
- virologique
- immunologique

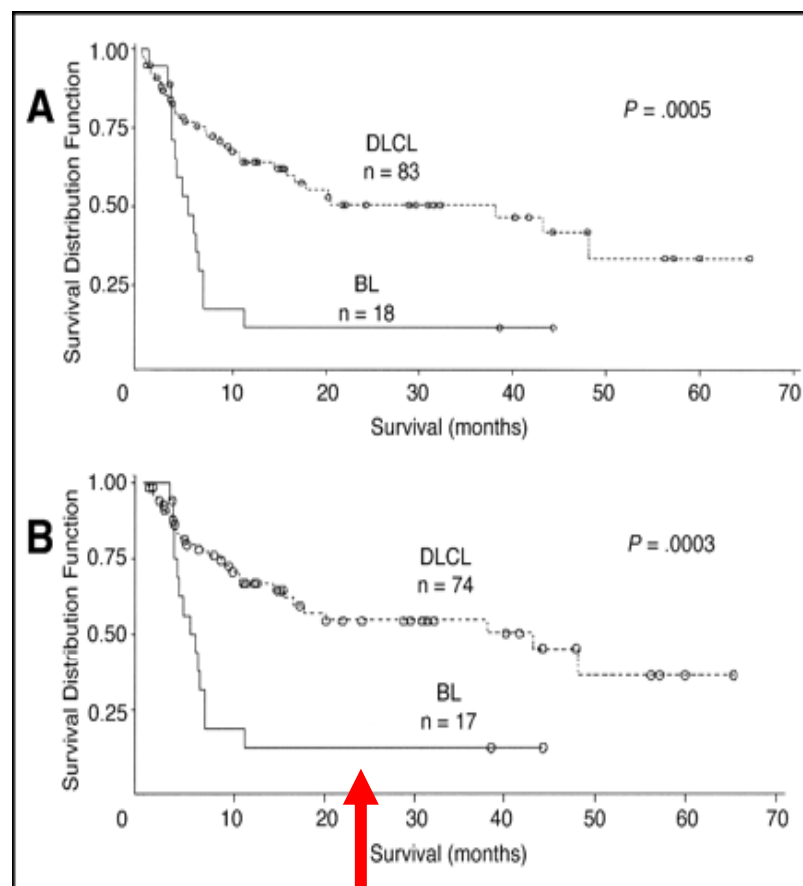
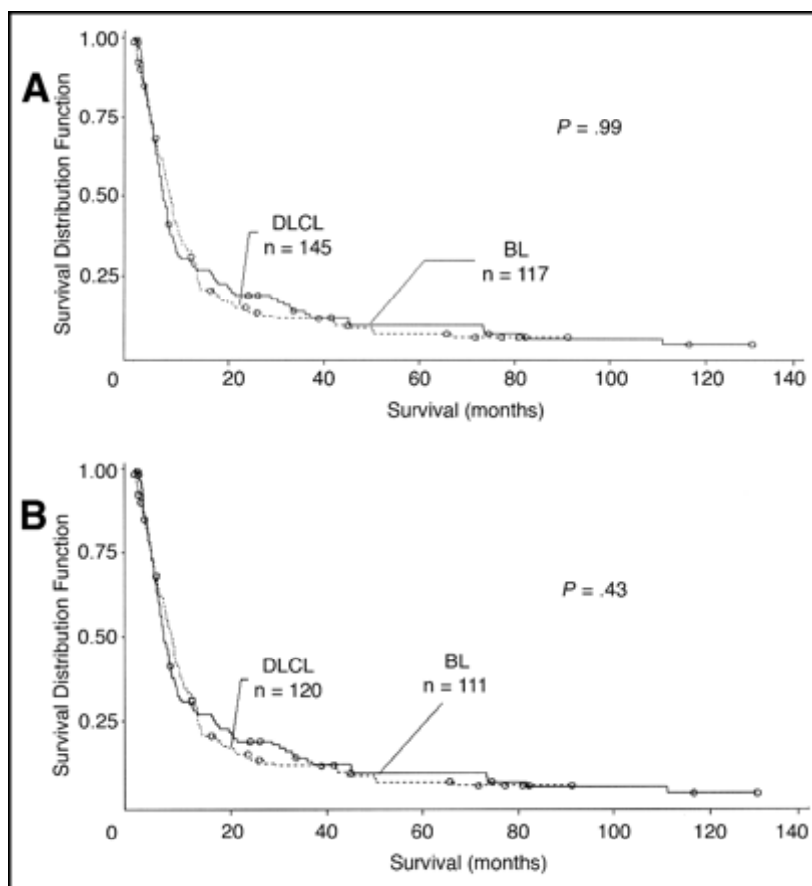




Burkitt ... le pronostic sous HAART

Pre HAART

Post HAART



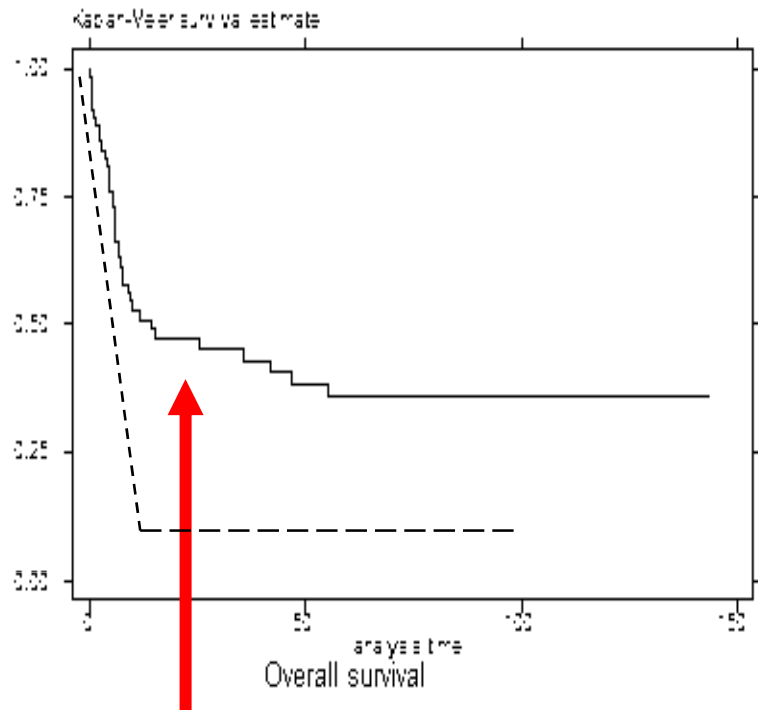
2 ans

Kaplan 2005

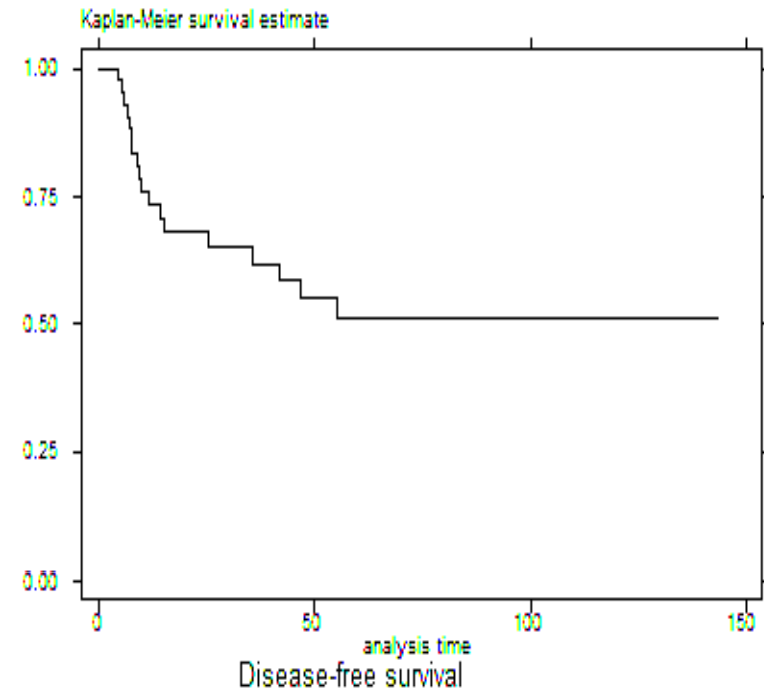
LMB 86 - Burkitt stade IV - n = 63

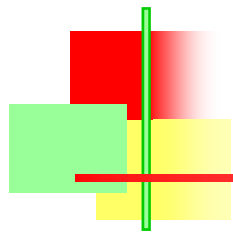
2-year overall survival : 47%

2-year estimate DFS: 67.8 %

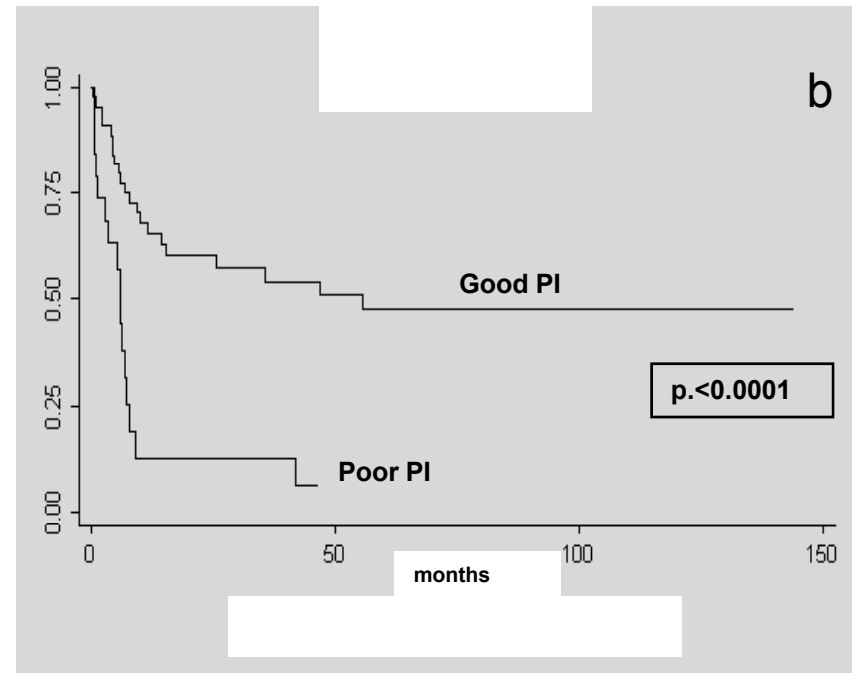
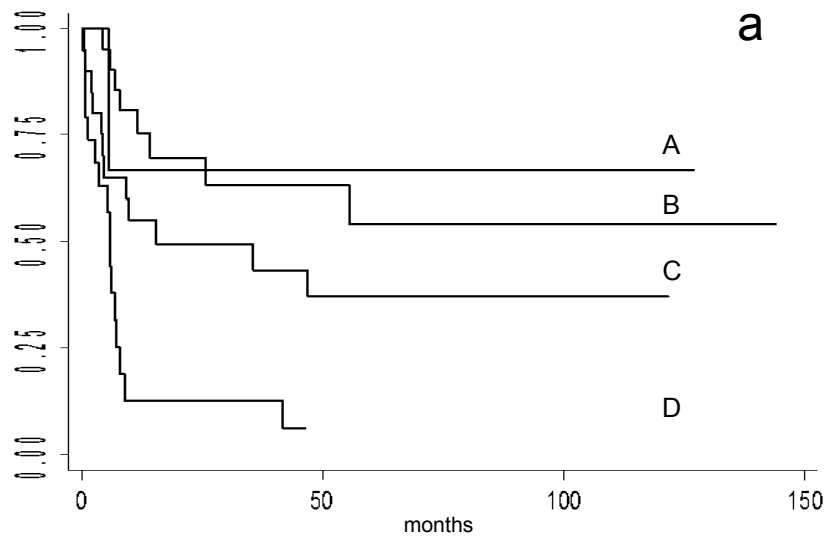


2 ans





Burkitt - facteurs pronostic

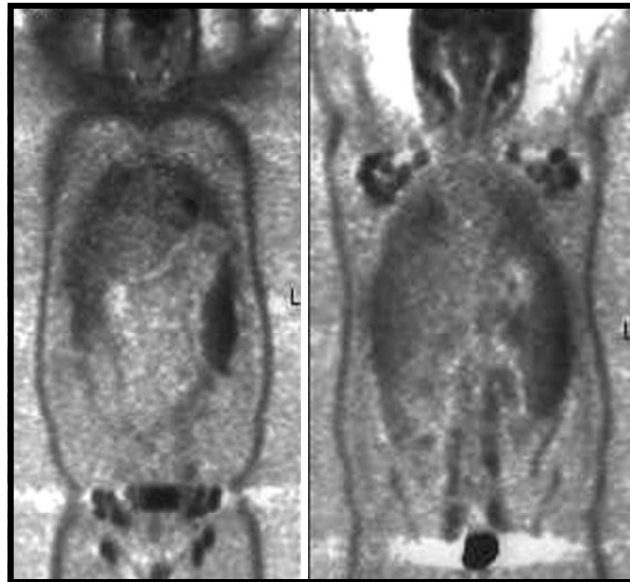


CD4 < 200/mm³ ECOG > 2

Castleman: diagnostic

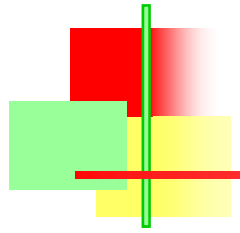
Symptômes

- * Symptômes "B"
- * Polyadénopathies
- * Splénomégalie
- * Symptômes Respiratoires
- * Œdèmes
- * Sd sec
- * Coma
- * **Kaposi**



Biologie

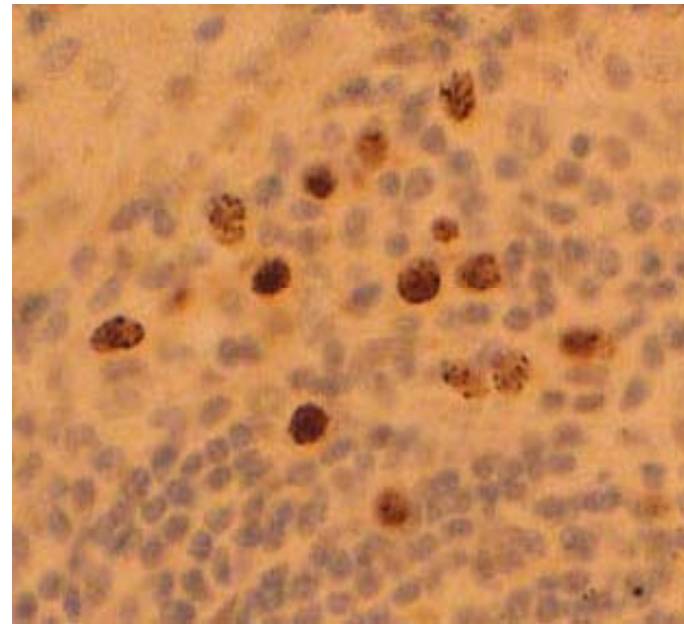
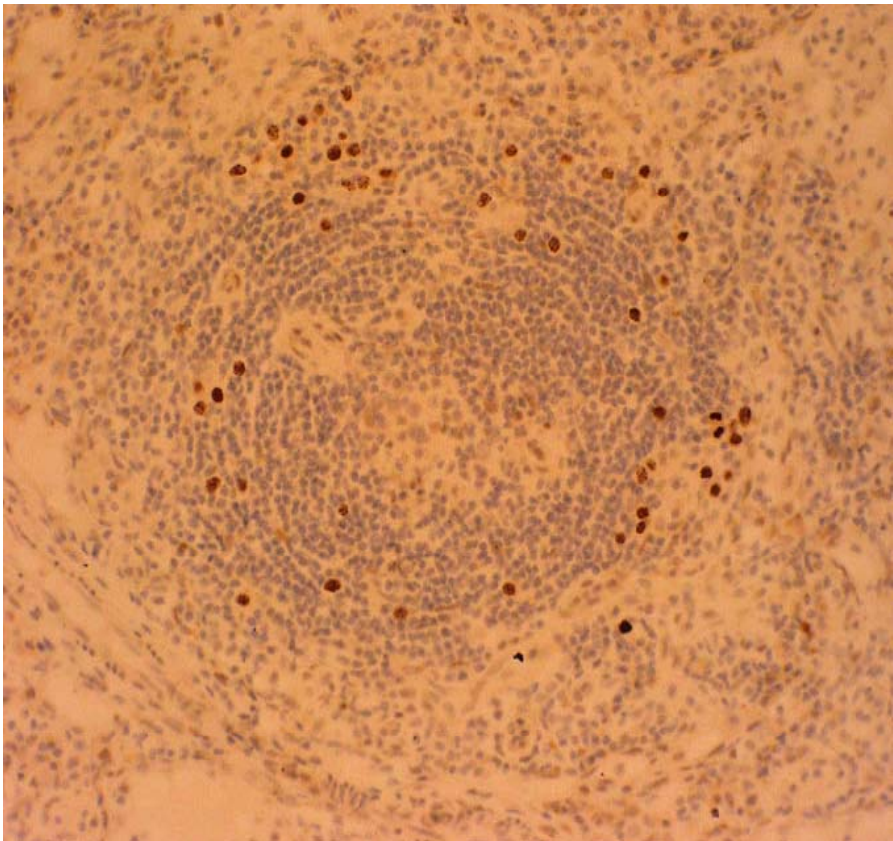
- * Cytopénies
- * CRP très élevée
- * Gammaglobuline > 20g/l
- * Albumine < 30g/l
- * Cholestase
- * TP allongé
- * Test de Coombs Direct +
- * **DNA-HHV8 / PBMCs**
+++



MCM: diagnostic

« Plasmablastes » KSHV/HHV8 +

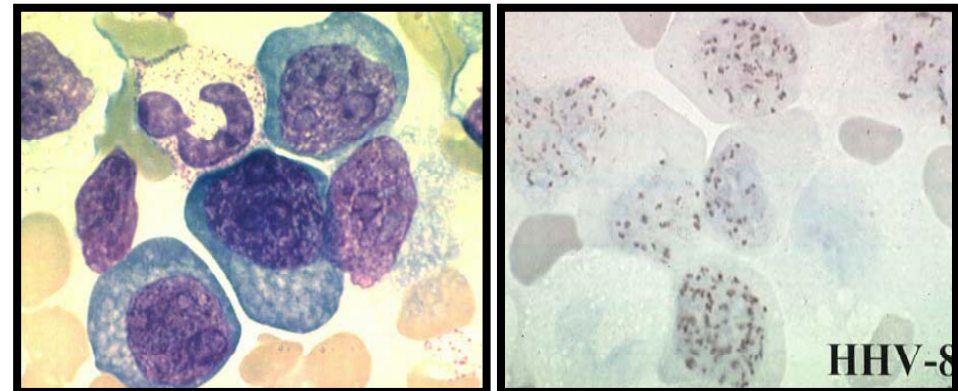
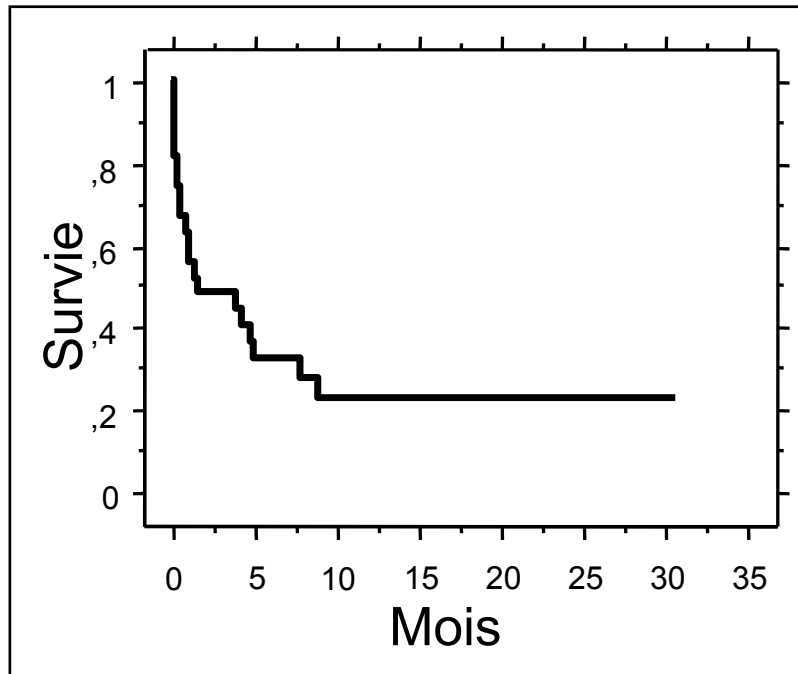
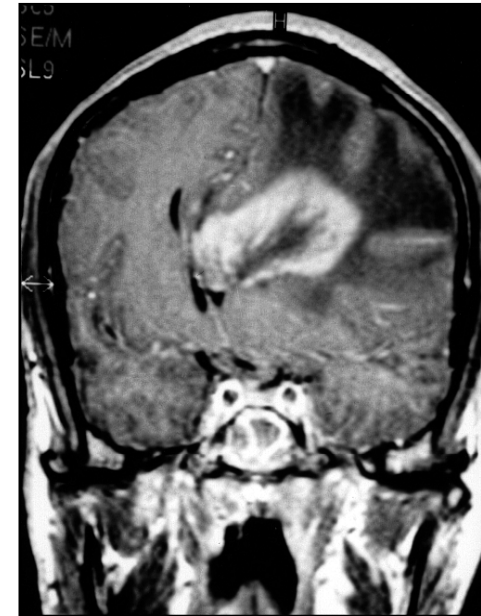
IHC (LNA moAb)



LNH sur une cohorte MCM-HIV (n= 27/ 77)

histologie: 29 LNH / 27 pts

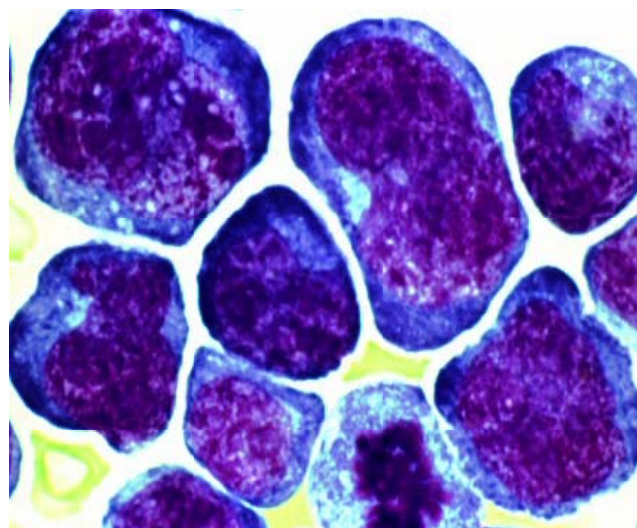
- PEL 5
- « PEL-like » 10
- Plasmablastique 14



Primary Effusion Lymphoma (PEL)

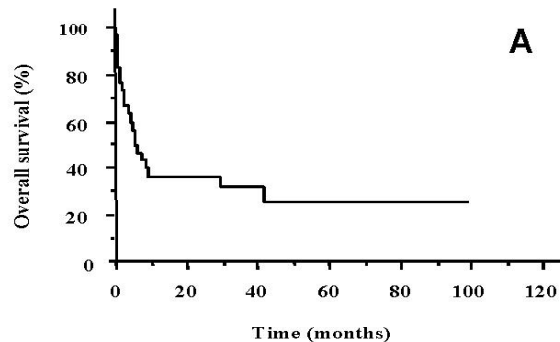
Lymphome des séreuses : 2-4% des LNH HIV

- rare – terrain HIV ou sujets âgés
- « phase liquide »: ascite, pleurésie, péricardite
- Atteinte extra-séreuse fréquente
- Grandes cellules B immunoblastique/anaplasique
- phénotype activé non-B non-T
CD30+ CD38+ HLA-DR+
- HHV8+ 100%, coinfection EBV > 80%
- Anomalies caryotypiques complexes non récurrentes



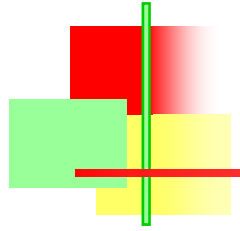
PEL: pronostic sur patients 30 HIV+

E. Boulanger 2005



Atcd KS: 20
 Atcd MCD: 10
 Lésions extraséreuses: 12

		<i>RR</i>	<i>p</i>
PS > 2	63%	4.83	0.005
Alb < 30 g/l	70%	4.10	0.02
EBV+	71.5%		0.23
CD4 < 100	47%		0.87
HAART+	57%	0.39	0.036
VL < 200	42%		0.15
HD-MTX	43%	0.30	0.01



Maladie de Hodgkin

- Incidence accrue (x 5-10) **En augmentation?**
- **Incidence dépendante des CD4**
- Médiane des CD4 au diagnostic $\approx 200 /\text{mm}^3$

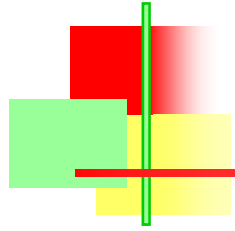
- Association à l' **EBV: 100%** vs 50%
- **Cellularité mixte: 60%** vs 20%
- **Stade IV: 60%** vs 15%
- Assez mauvais pronostic

Lymphome de Hodgkin

L'incidence du Lymphome de Hodgkin ne diminue pas ...

Table 2. Observed and Expected Number of Cancers, Standardized Incidence Ratios, and 95% Confidence Intervals Among HIV-Seropositive Men in the French Hospital Database From 1992 to 1995 (pre-HAART period) and From 1996 to 1999 (HAART period)

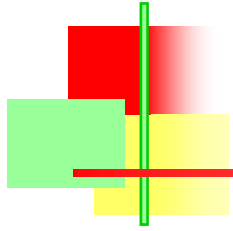
Cancer Site	ICD IX	Pre-HAART Period: 1992-1995				HAART Period: 1996-1999			
		Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Oral cavity†	140-149	44	15.63	2.82	2.05-3.78	27	28.98	0.93	0.61-1.36
Esophagus	150	1	4.56	0.22	0.00-1.22	5	8.63	0.58	0.19-1.35
Stomach	151	18	3.74	4.81	2.85-7.61	8	6.71	1.19	0.51-2.35
Colon, rectum, anus	153, 154	25	14.14	1.77	1.14-2.61	30	25.89	1.16	0.78-1.65
Pancreas	157	5	1.80	—†	—	3	3.40	—	—
Larynx	161	4	4.83	0.83	0.22-2.12	9	8.98	1.00	0.46-1.90
Lung	162	22	19.40	1.13	0.71-1.72	77	36.31	2.12	1.67-2.65
Melanoma	172	8	3.99	2.01	0.86-3.95	7	6.35	1.10	0.44-2.27
Prostate	185	2	6.72	0.30	0.03-1.07	7	13.39	0.52	0.21-1.08
Bladder	188	6	5.06	1.19	0.43-2.58	6	9.57	0.63	0.23-1.36
Kidney	189	3	3.17	0.95	0.19-2.77	13	5.95	2.18	1.16-3.74
Brain and CNS	191, 192	14	4.72	2.97	1.62-4.98	8	7.61	1.05	0.54-2.24
Thyroid	193	0	2.42	—	—	4	3.65	—	—
Hodgkin's disease	201	58	2.55	22.75	17.27-29.40	101	3.19	31.66	25.79-38.47
Multiple myeloma	203	3	0.75	—	—	4	1.41	—	—
Leukemias	204-208	13	2.30	—	—	23	3.68	—	—
All sites		226	95.78	2.36	2.09-2.69	332	173.70	1.91	1.71-2.13



Maladie de Hodgkin et Infection HIV (96 - 03)

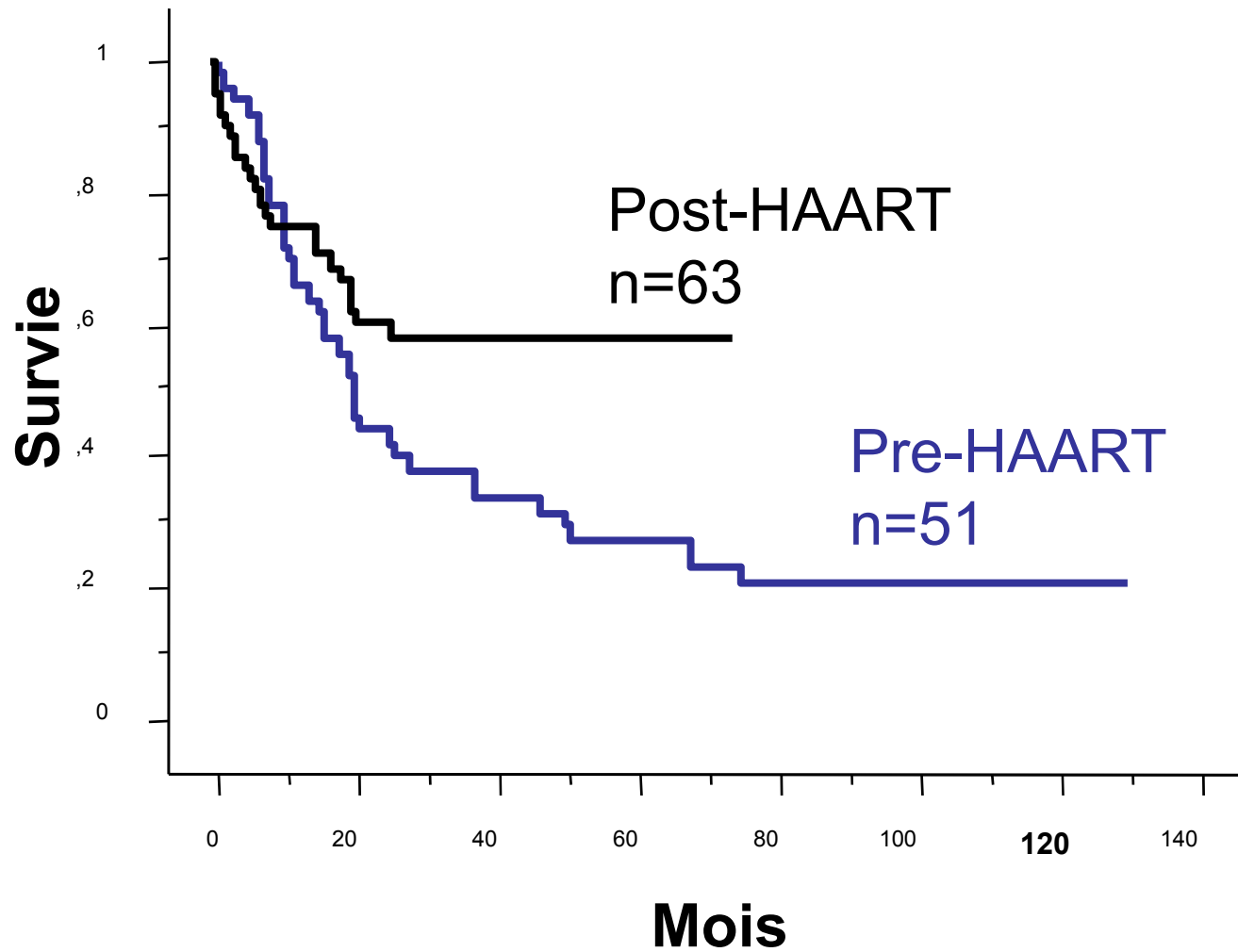
Saint-Louis

	90 – 96 n = 51	96 – 03 n = 63
CD4 médiane	171	201
HIV-RNA <2.7 log	-	45 %
Stade IV	64 %	58 %

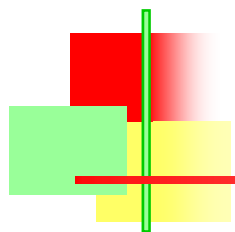


MdH et infection HIV (90-96 / 96-03)

Survie globale - St-Louis



$P = 0.02$

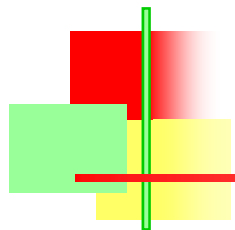


Maladie de Hodgkin et infection HIV

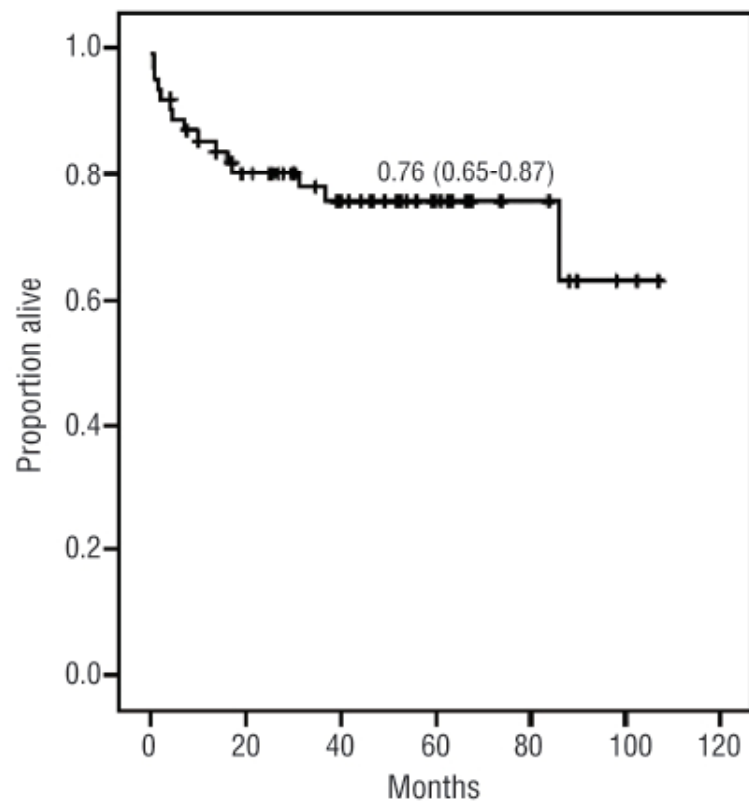
Traitement

Protocole	n	HAART	St III-IV	CR	OS À 2 ans	DFS À 2 ans
EBV	17	Non	88%	53%	11mo	-
EBVP	35	Non	83%	74%	16mo	53%
Stfd V	59	Oui	71%	81%	68%	70%
VEBEP	28	Oui	68%	75%	86%	90%

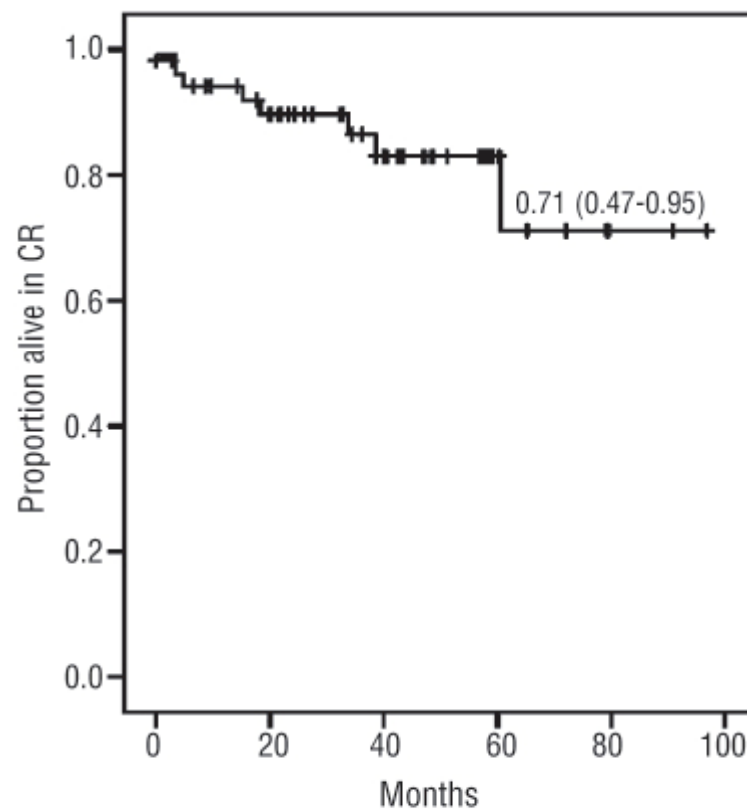
Tirelli ASH 2005



ABVD – traitement de référence

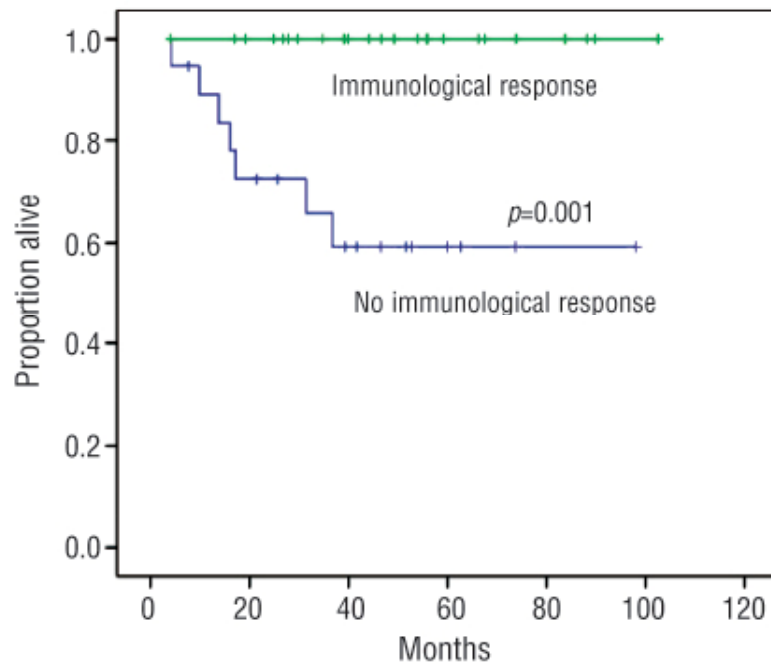


OS n = 62

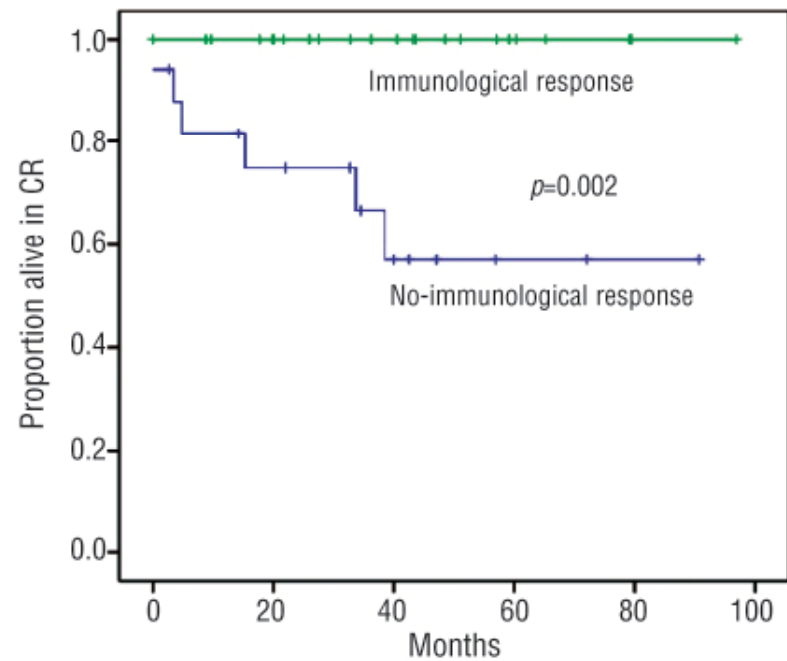


EFS n = 54

De l'importance de contrôler la charge virale HIV.....

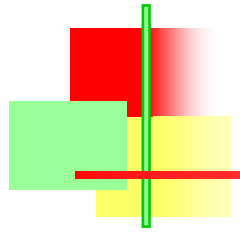


OS



EFS

En fonction de la réponse immunologique



Pour conclure

- Diminution mais persistance de l'incidence
- « Des » lymphomes, « des » traitements
- Chimiothérapie intensive + HAART
- Prise en charge en milieu spécialisé