Lymphomes et infection par le VIH
Etat des lieux

Caroline Besson

Cohorte LYMPHOVIR ANRS CO16

- **Cohorte observationelle**

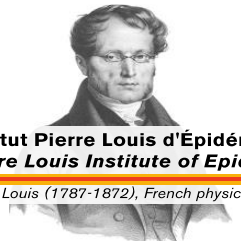
  (CB, D Costagliola, M Genin, R Lancar)

- Adultes infectés par le VIH atteints de LH ou LNH

- Peuvent être coinfectés par VHB / VHC

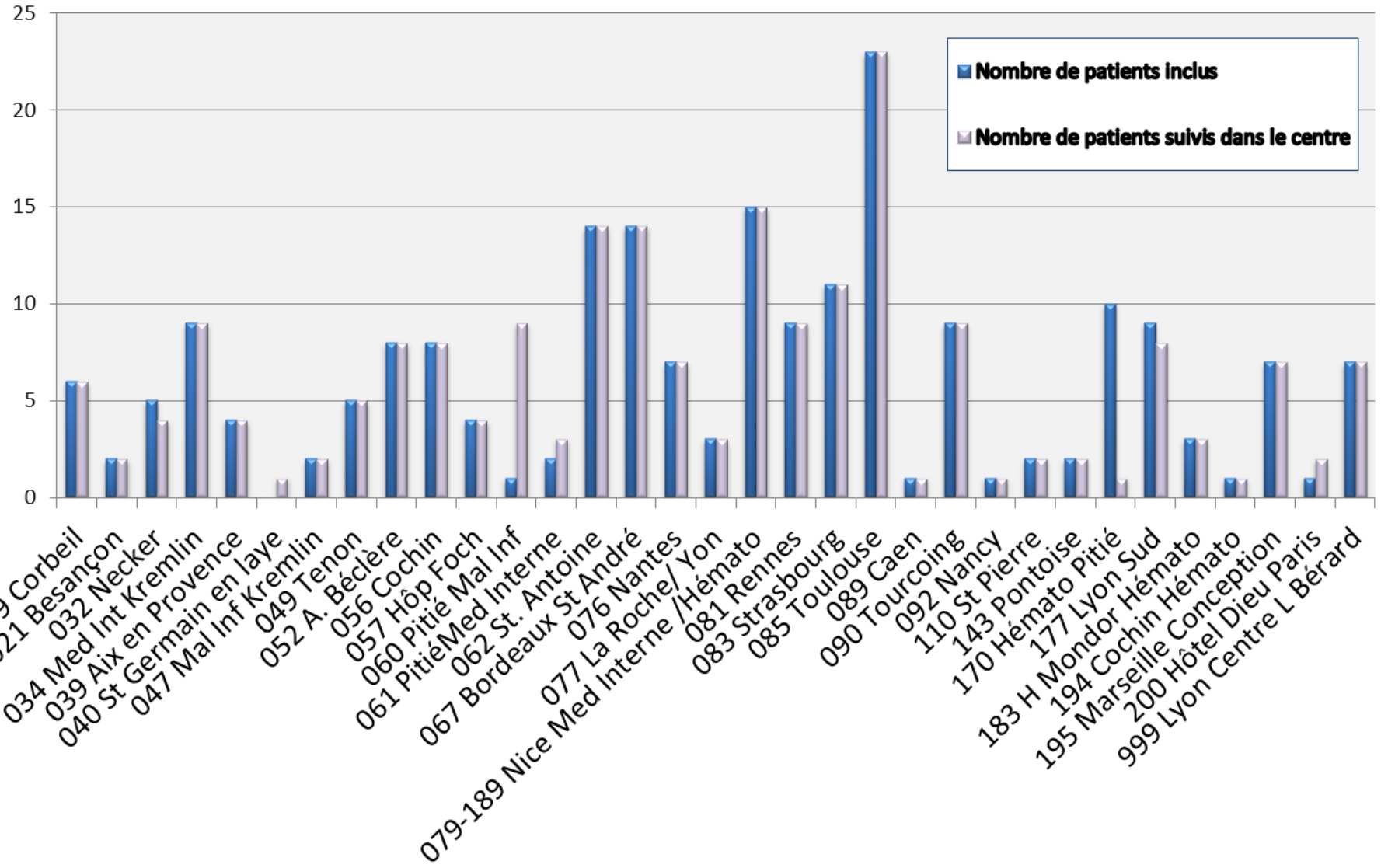
- **Biothèque, tissuthèque** (Y Taoufik, H Chavez, S Prevot)

- **Etudes ancillaires** : Immuno (G Carcelain), EBV (P Morand)

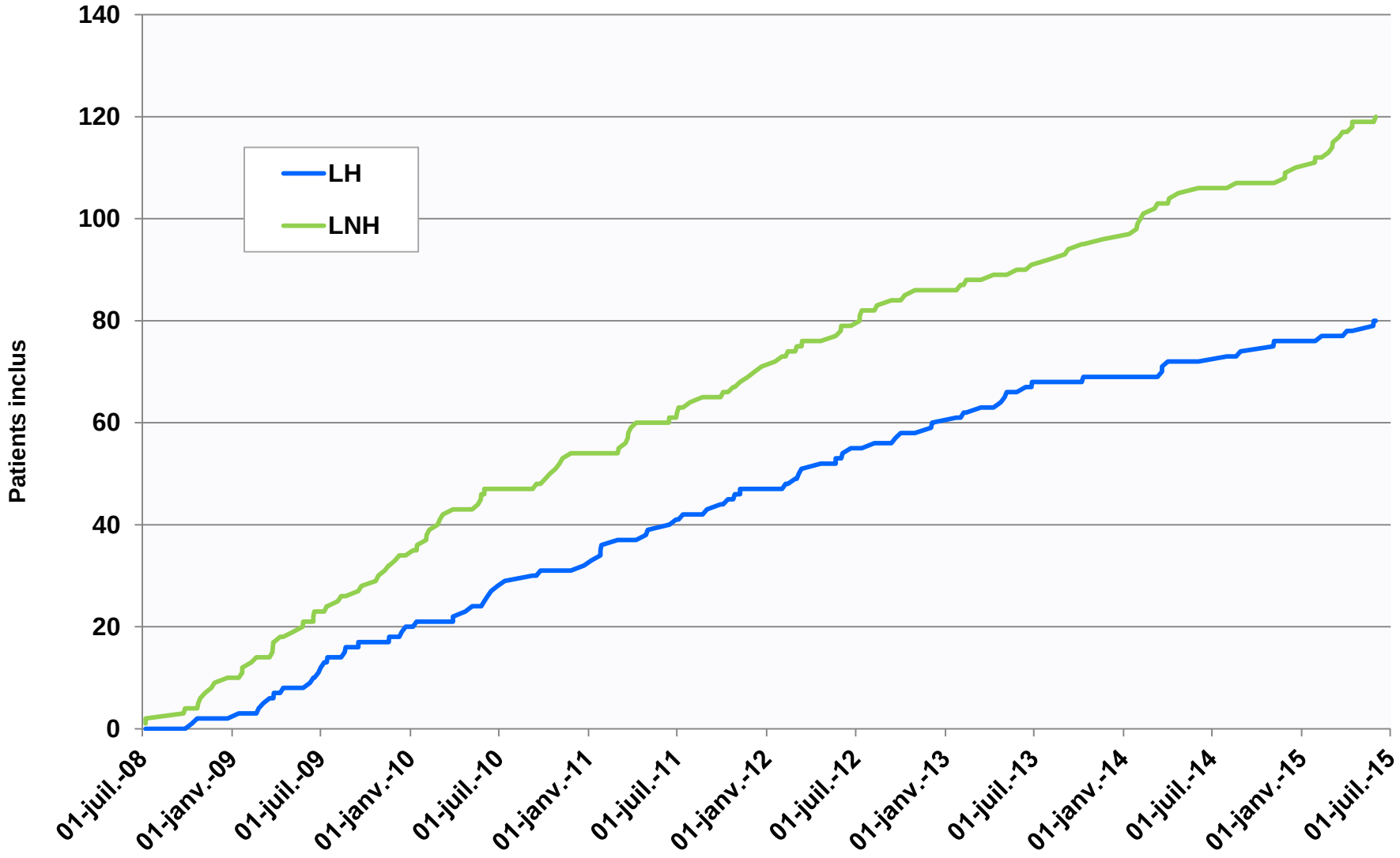


Inclusions par centre

au 1er juin 2015



Cohorte ANRS CO16 LYMPHOVIR :
Courbe des inclusions LH et LNH



Classification et épidémiologie

Classification

OMS 2008

Lymphomes survenant chez le sujet immunocompétent

- Lymphome à grandes cellules B (DLBCL)
- Lymphome de Burkitt
- Lymphome de Hodgkin
- Autres lymphomes (LZM, …)

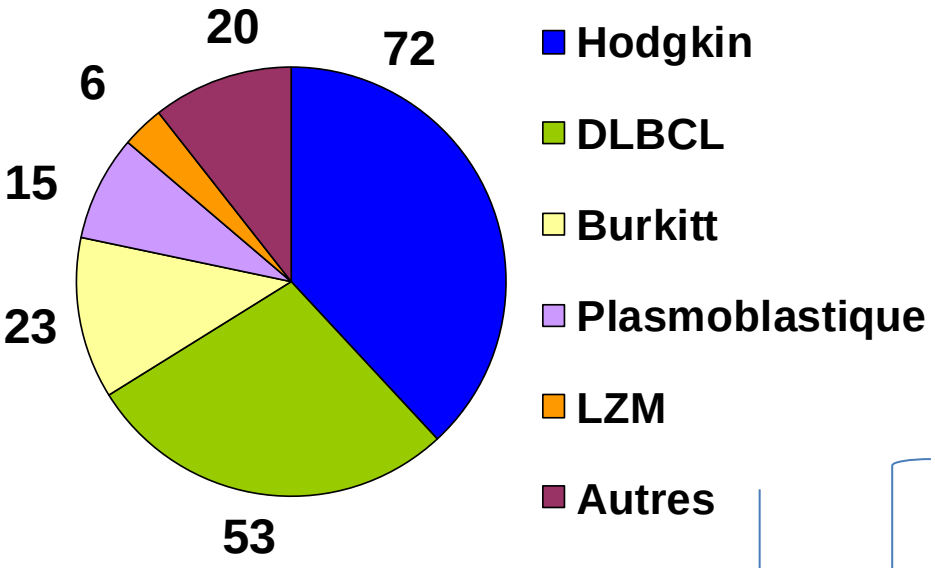
Lymphomes survenant spécifiquement au cours de l'infection VIH

- Lymphome plasmoblastique
- Lymphome des séreuses
- Lymphome lié à la maladie de Castleman

Lymphomes associés aux déficits immunitaires

- PTLD- like

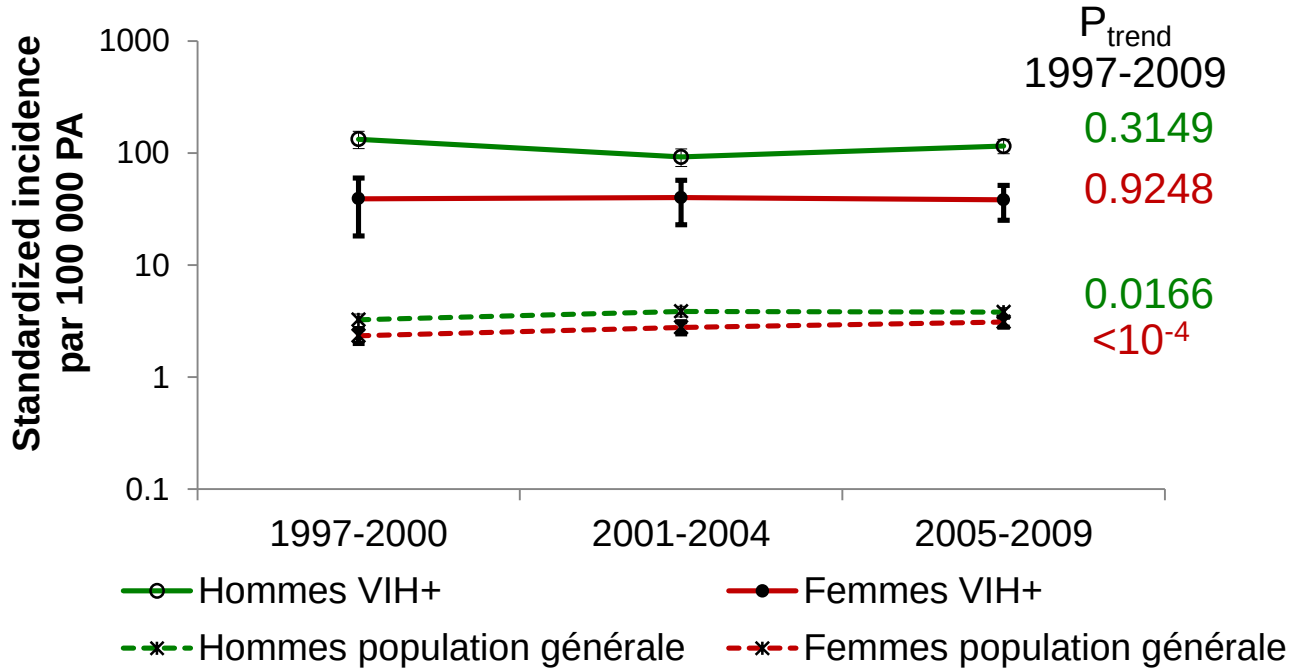
Distribution par sous-types histologiques



Besson et al, EHA 2013

LNH	
LNH T	4
Autres LNH B	
LNH séreuses	3
PTLD like	2
Autres LNH B	11

Hodgkin's Lymphoma

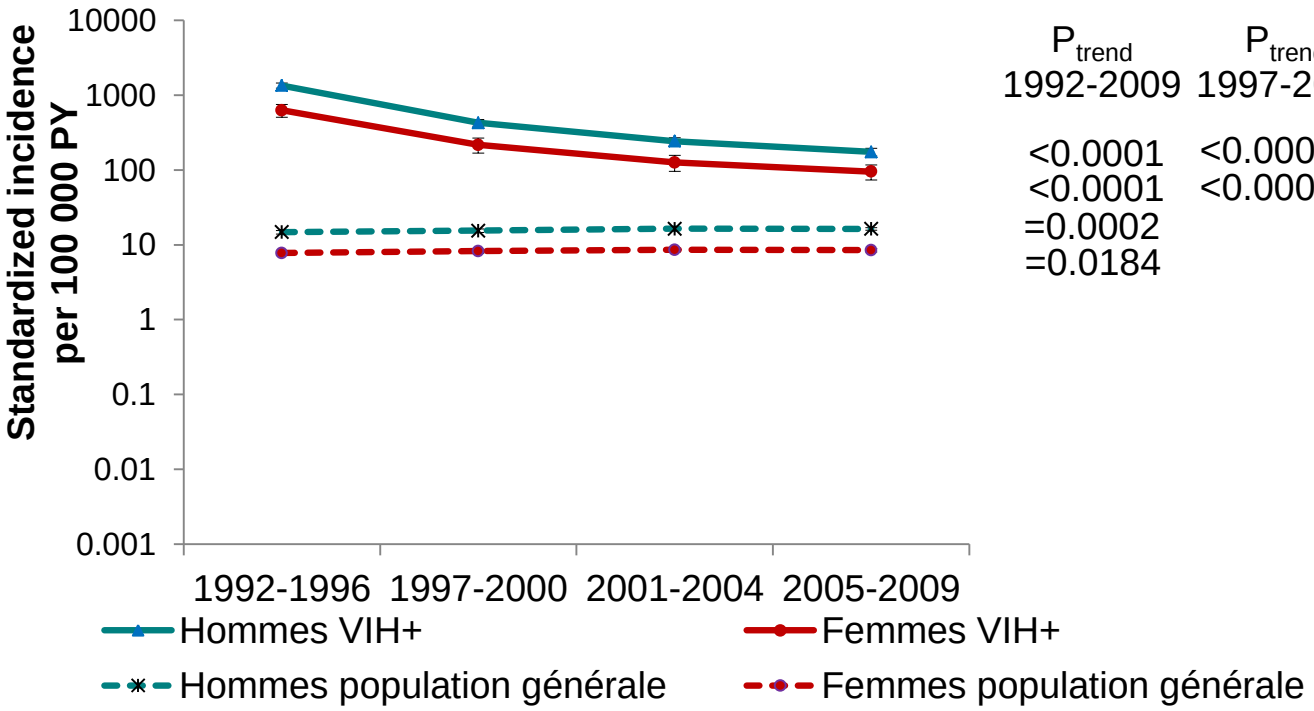


SIR (95% CI) HIV+ / general population

	1997-2000	2001-2004	2005-2009
Men	**39 (33-46)**	**24 (20-29)**	**31 (27-36)**
Women	**15 (9-25)**	**14 (9-22)**	**15 (10-20)**

Hleyhel 2014

Non Hodgkin Lymphoma



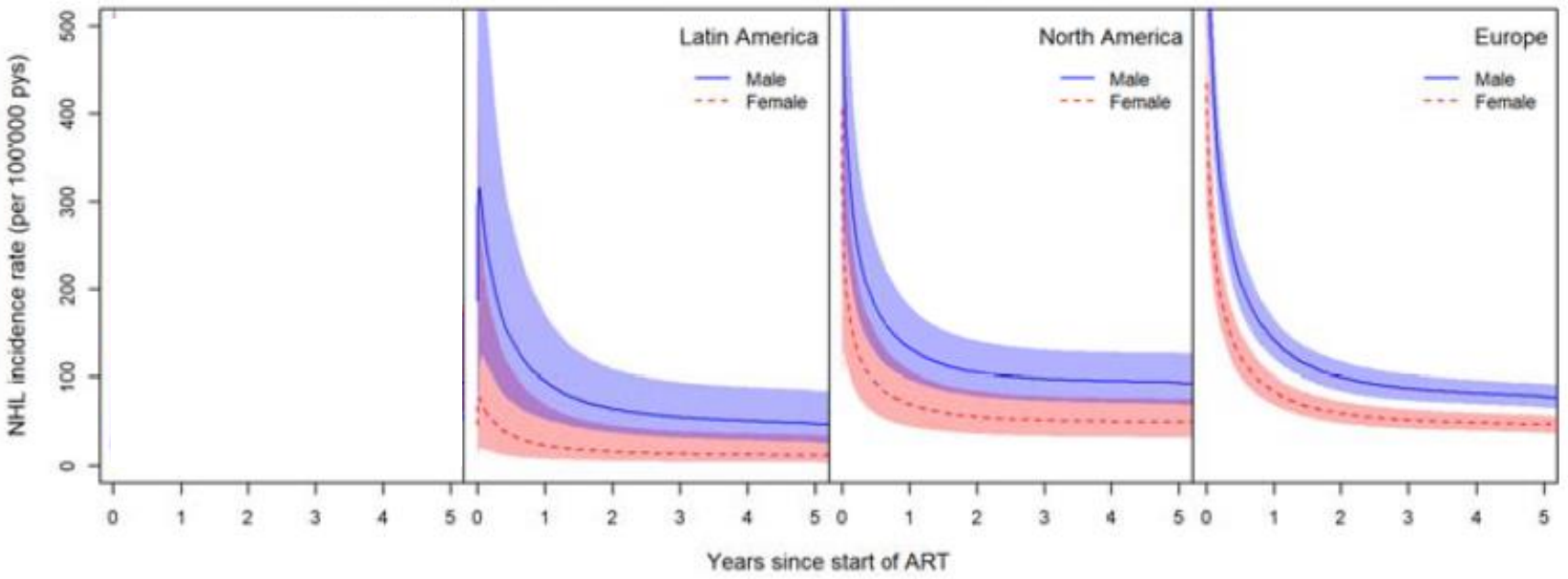
	P_{trend} 1992-2009	P_{trend} 1997-2009
Hommes VIH+	<0.0001	<0.0001
Femmes VIH+	<0.0001	<0.0001
Hommes population générale	=0.0002	
Femmes population générale	=0.0184	

SIR (95%CI) HIV+ / general population

	1992-1996	1997-2000	2001-2004	2005-2009
Hommes	**118**	**34**	**15**	**9**
Femmes	**113**	**34**	**16**	**10**

Lleyel M, CID 2013

Lymphomes et VIH : Incidence



Group authorship: The AIDS-defining Cancer Project Working Group of IeDEA and COHERE in EuroCoord*

Figure 1: NHL incidence rates by time since ART start in men and women across regions. Incidence rates are predicted for adults with a current CD4 cell count of 450 cells/µl who started an NNRTI-based first-line ART regimen between 2008-2014

AIDS, Publish Ahead of Print

Table 2: Crude and adjusted hazard ratios for the regional effect of sex and current CD4 cell count on the risk of developing NHL in adults who started ART.

	Latin America HR (95% CI)	North America HR (95% CI)	Europe HR (95% CI)
Sex			
Men	1.00	1.00	1.00
Women (crude)	0.23 (0.08 - 0.64)	0.52 (0.36 - 0.75)	0.54 (0.47 - 0.63)
Women (adjusted*)	0.24 (0.09 - 0.67)	0.52 (0.36 - 0.76)	0.59 (0.51 - 0.69)
Current CD4 cell count			
Per 100 cells/µl increase (crude)	0.66 (0.54 - 0.80)	0.66 (0.61 - 0.71)	0.71 (0.69 - 0.73)
Per 100 cells/µl increase (adjusted**)	0.66 (0.55 - 0.80)	0.65 (0.60 - 0.71)	0.72 (0.69 - 0.74)

Table 3: Crude and adjusted hazard ratios for the effect of exposure group and drug use on the risk of developing NHL in adults who started ART, restricted to North America, Latin America, and Europe.

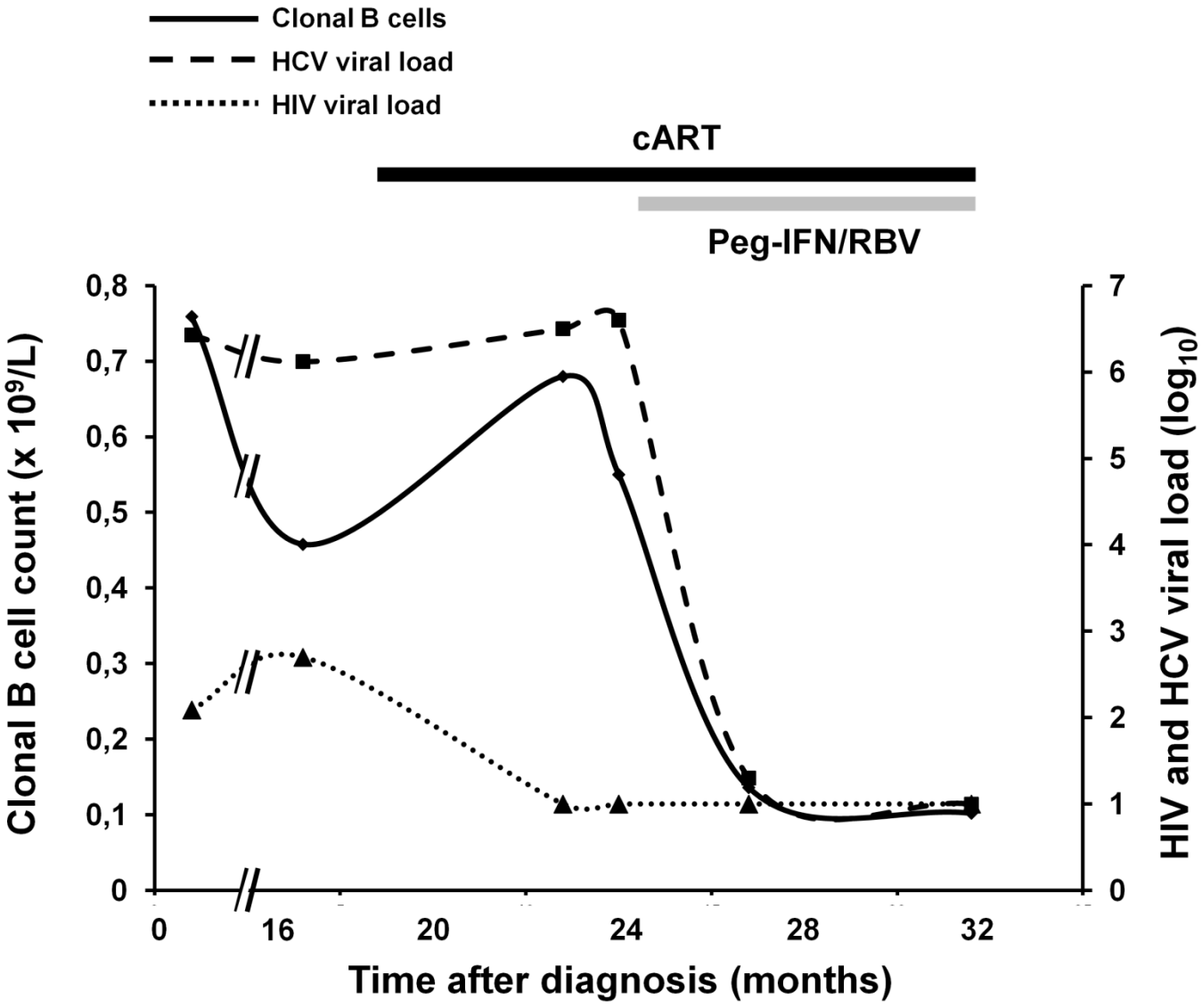
	Crude HR (95% CI)	Adjusted* HR (95% CI)
Exposure group		
Women	0.52 (0.44 - 0.61)	0.66 (0.57 - 0.78)
Heterosexual men	1.00	1.00
MSM	0.95 (0.84 - 1.07)	1.30 (1.14 - 1.48)
PWID		
No	1.00	1.00
Yes	0.98 (0.84 - 1.16)	0.94 (0.79 - 1.12)

Characteristics of B-Cell Lymphomas in HIV/HCV-Coinfected Patients During the Combined Antiretroviral Therapy Era: An ANRS CO16 LYMPHOVIR Cohort Study

Benjamin Terrier, MD, PhD, Dominique Costagliola, MD, PhD,†‡§ Sophie Prevot, MD, PhD,‖¶ Houria Chavez, MD, PhD,#** Pascale Missy,‡§ Patricia Rince, MD,¶# Regis Costello, MD, PhD,†† Lelia Escaut, MD,‡‡ Jean Gabarre, MD,§§ Bertrand Joly, MD,‖‖ Lorraine Letranchant, MD, PhD,¶¶ Steven Le Gouill, MD, PhD,## Pascale Morineau-Le Houssine, MD,*** Anne Simon, MD,† Danielle Canioni, MD, PhD,††† Olivier Hermine, MD, PhD,‡‡‡ Patrice Cacoub, MD, PhD,* Yassine Taoufik, MD, PhD,¶#** Martine Raphael, MD, PhD,¶#§§§ and Caroline Besson, MD, PhD¶#***

J Acquir Immune Defic Syndr • Volume 63, Number 2, June 1, 2013

Lymphome de la zone marginale splénique VIH+



B Terrier, .. Besson, J Acquir Immune Defic Syndr. 2013

Annals of Internal Medicine

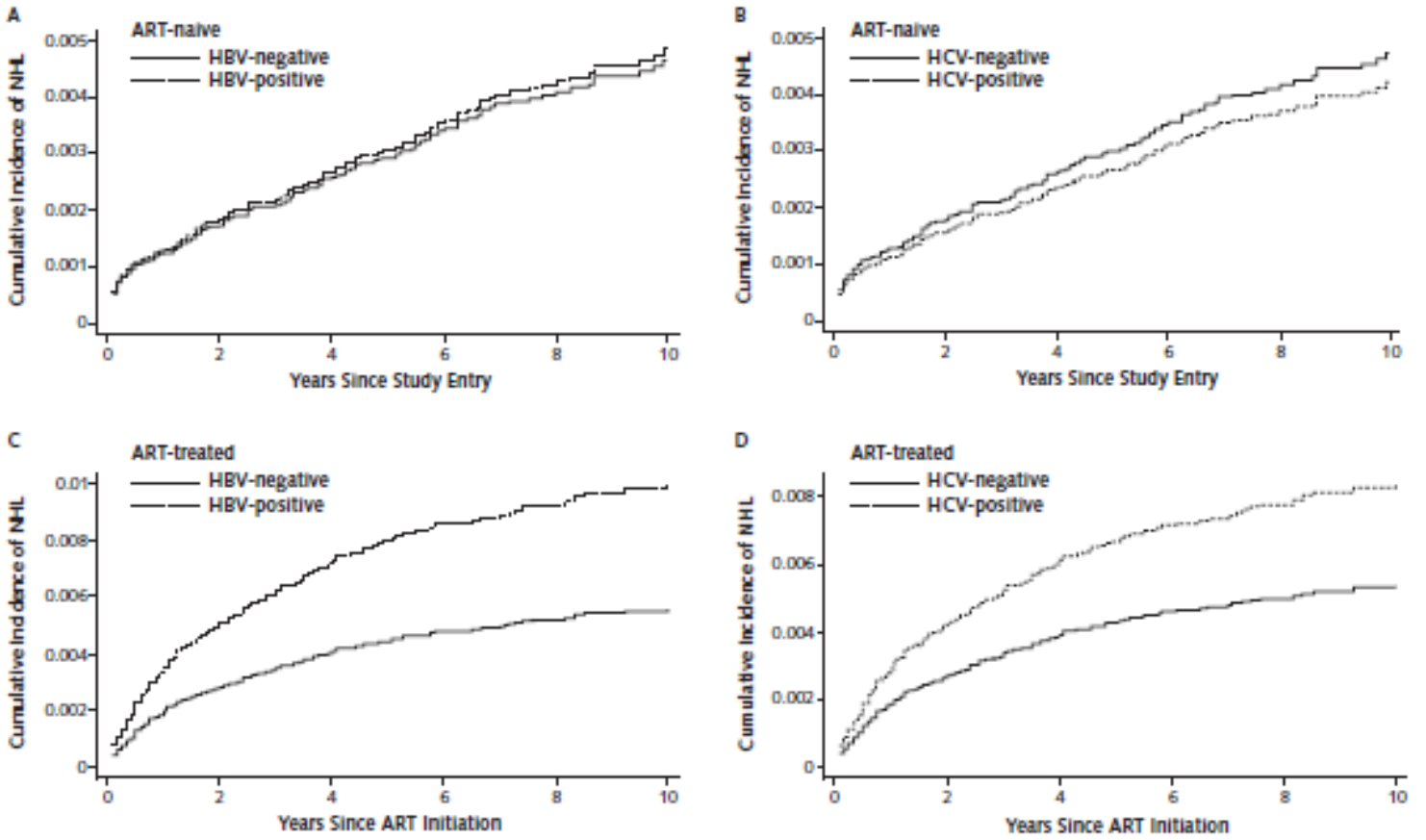
ORIGINAL RESEARCH

Chronic Hepatitis B and C Virus Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients

A Cohort Study

Qing Wang, PhD; Andrea De Luca, MD; Colette Smith, PhD; Robert Zangerle, MD; Helen Sambatakou, MD; Fabrice Bonnet, MD, PhD; Colette Smit, MD, PhD; Philipp Schommers, MD; Alicia Thornton, PhD; Juan Berenguer, MD, PhD; Lars Peters, MD; Vincenzo Spagnuolo, MD; Adriana Ammassari, MD; Andrea Antinori, MD; Eugenia Quiros Roldan, MD, PhD; Cristina Mussini, MD; Jose M. Miro, MD, PhD; Deborah Konopnicki, MD, PhD; Jan Fehr, MD; Maria A. Campbell, MMA; Monique Termote, MSc; and Heiner C. Bucher, MD, MPH; on behalf of The Hepatitis Coinfection and Non Hodgkin Lymphoma project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord*

Figure 2. NHL event-free survival in ART-naive and ART-treated HIV-infected patients, by chronic HBV and HCV infection status at baseline.



ART = antiretroviral therapy; HBV = hepatitis B virus; HCV = hepatitis C virus; NHL = non-Hodgkin lymphoma.

Variable	Hazard Ratio for NHL (95% CI)	
ART-treated patients (*n* = 40 219)		
Adjusted for baseline covariates*†		
Chronic HBV infection	1.73 (1.08–2.80)	1.74 (1.08–2.82)
Chronic HCV infection	1.76 (1.23–2.51)	1.73 (1.21–2.46)

Prevalence of HBV and/or HCV infection among HIV-infected patients with lymphoma enrolled in the Lymphovir-ANRS-CO16 cohort in comparison with HIV-infected patients followed in the French hospital database on HIV (FHDH-ANRS-CO4 cohort

	HCV seropositivy					Chronic HBV infection			
	N	n	%	OR, 95% CI	p-value	N	%	OR, 95% CI	p-value
FHDH	48186	6891	(14)	ref	ref	3558	(7)	ref	ref
NHL	110	29	(26)	2.15 [1.35-3.32]	<0.001	5	(5)	0.60 [0.19-1.45]	0.26
DLBCL	52	17	(33)	2.91 [1.53-5.34]	<0.001	2	(4)	0.51 [0.06-1.95]	0.34
HL	69	9	(13)	0.90 [0.39-1.82]	0.77	10	(14)	2.16 [1.00-4.27]	0.02

Caractéristiques des lymphomes les plus fréquents

Présentation initiale

	LH N=72	DLBCL N=53	Burkitt N=25
Age méd, Q1-Q3	44 (37-49)	51 (45-59)	50 (38-58)
Sexe-ratio F/H	10 / 62	6 / 47	3 / 22
Durée VIH mois méd, Q1-Q3	**149** **(59-227)**	**161** **(50-268)**	**42** **(10-138)**
Stade SIDA	17	24	11
Naifs de cART	1	5	4
CD4 au diagnostic /mm^3, méd, Q1-Q3	396 (151-543)	261 (120-410)	234 (122-387)
CV au diagnostic copies/ml, méd, Q1-Q3	**<50** **(<50-75)**	**<50** **(<50-29154)**	**3094** **(50-81000)**

MAJOR ARTICLE HIV/AIDS

High Risk Features Contrast With Favorable Outcomes in HIV-associated Hodgkin Lymphoma in the Modern cART Era, ANRS CO16 LYMPHOVIR Cohort

Caroline Besson,[1,2] Remi Lancar,[3,4] Sophie Prevot,[1,5] Pauline Brice,[6] Marie-Caroline Meyohas,[7] Bruno Marchou,[8] Jean Gabarre,[9] Fabrice Bonnet,[10] Cécile Goujard,[1,2] Olivier Lambotte,[1,2] François Boué,[1,11] Nicolas Mounier,[12] Marialuisa Partisani,[13] Francois Raffi,[14] Régis Costello,[15] Houria Hendel-Chavez,[1] Michele Algarte-Genin,[3,4] Selma Trabelsi,[3,4] Lucie Marchand,[16] Martine Raphael,[1] Yassine Taoufik,[1,17] and Dominique Costagliola[3,4]

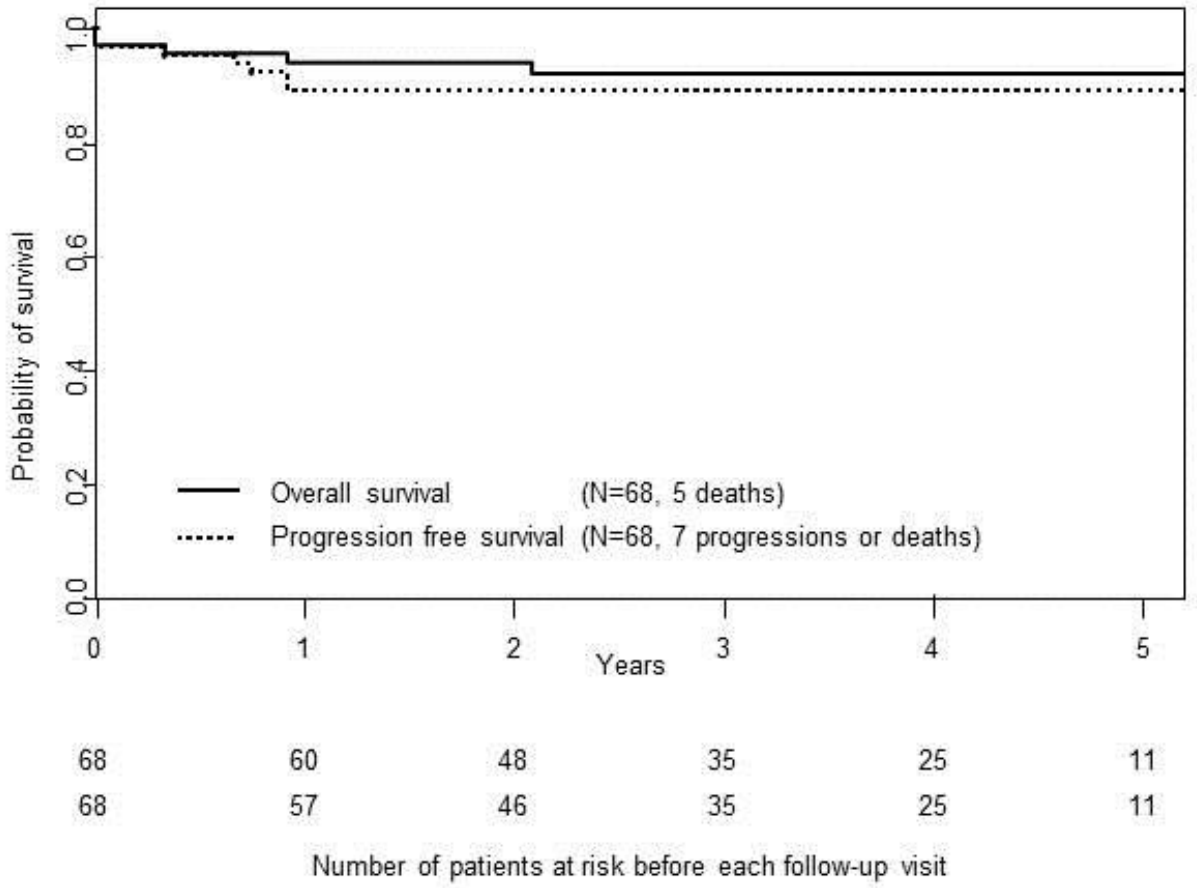
Lymphomes de Hodgkin

Facteurs pronostiques, survie sans progression

	N=68	Evènements (n)	RR	IC 95 %	p-value
Sexe					0.94
F	9	1	1		
M	59	6	0.92	[0.11 ; 7.68]	
Age, ans					**0.05**
<45	**38**	**1**	**1**		
≥45	**30**	**6**	**8.07**	**[0.97 ; 67.03]**	
Stade					0.77
I-II	16	1	1		
III	20	2	1.54	[0.14 ; 17.00]	
IV	32	4	2.09	[0.23 ; 18.72]	
IPS					0.33
0-2	19	1	1		
3-7	41	6	2.88	[0.35 ; 23.90]	
CD4, /µL					0.58
> 200	42	4	1		
≤200	22	3	1.50	[0.30 ; 6.80]	

Besson et al, CID 2015

Lymphomes de Hodgkin, évolution



2 years OS : 0.94 ; 95%CI=[0.88 , 1]
2 year PFS : 0.89 ; 95%CI=[0.82 , 0.97]

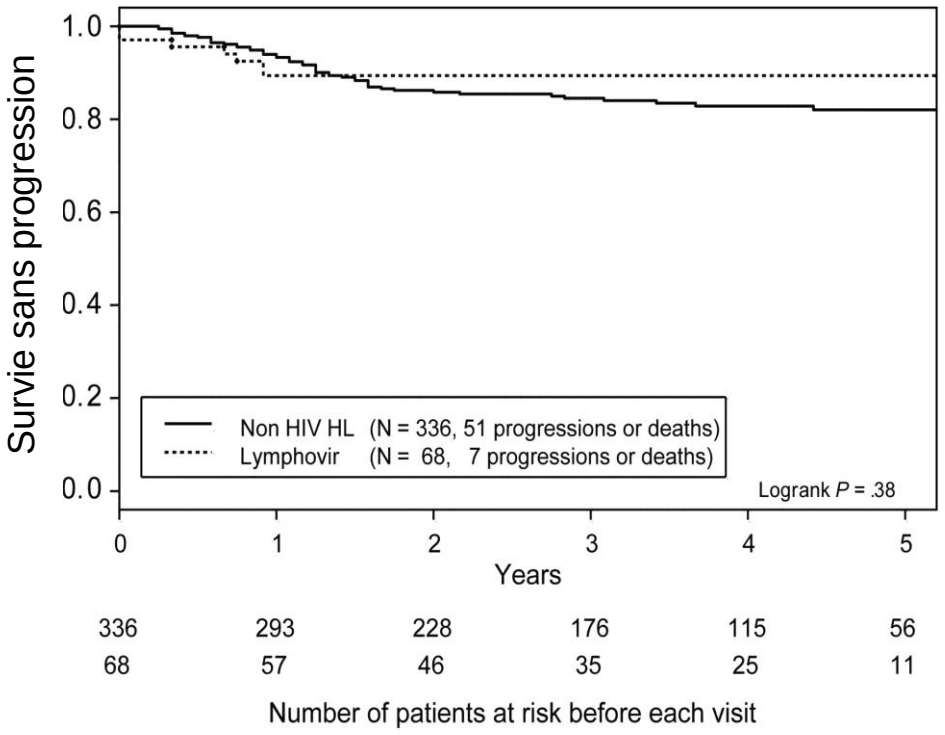
Besson et al, CID 2015

Median follow-up: 38 months (IQR : 31)

Lymphomes de Hodgkin

Caractéristiques et évolution après ABVD

	VIH+ N=68	VIH- N=336	p
Hommes	87%	52%	**<0.0001**
Age, Médiane	44 ans	29	**<0.0001**
Durée d'infection	13 ans	/	
CD4/mm3	387	/	
cART	96%	/	
Histologie			**<0.0001**
SN	21%	81%	
CM	79%	16%	
Stade			**<0.0001**
I-II	24%	62%	
III-IV	76%	38%	
IPS			**<0.0001**
0-2	**32%**	**74%**	
3-7	**68%**	**26%**	



2 year PFS : 0.89 ; 95%CI=[0.82 , 0.97]

C Besson et al. Clin Infect Dis. 2015

VOLUME 30 · NUMBER 33 · NOVEMBER 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

HIV Status Does Not Influence Outcome in Patients With Classical Hodgkin Lymphoma Treated With Chemotherapy Using Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine in the Highly Active Antiretroviral Therapy Era

Silvia Montoto, Kate Shaw, Jessica Okosun, Shreyans Gandhi, Paul Fields, Andrew Wilson, Milensu Shanyinde, Kate Cwynarski, Robert Marcus, Johannes de Vos, Anna Marie Young, Melinda Tenant-Flowers, Chloe Orkin, Margaret Johnson, Daniella Chilton, John G. Gribben, and Mark Bower

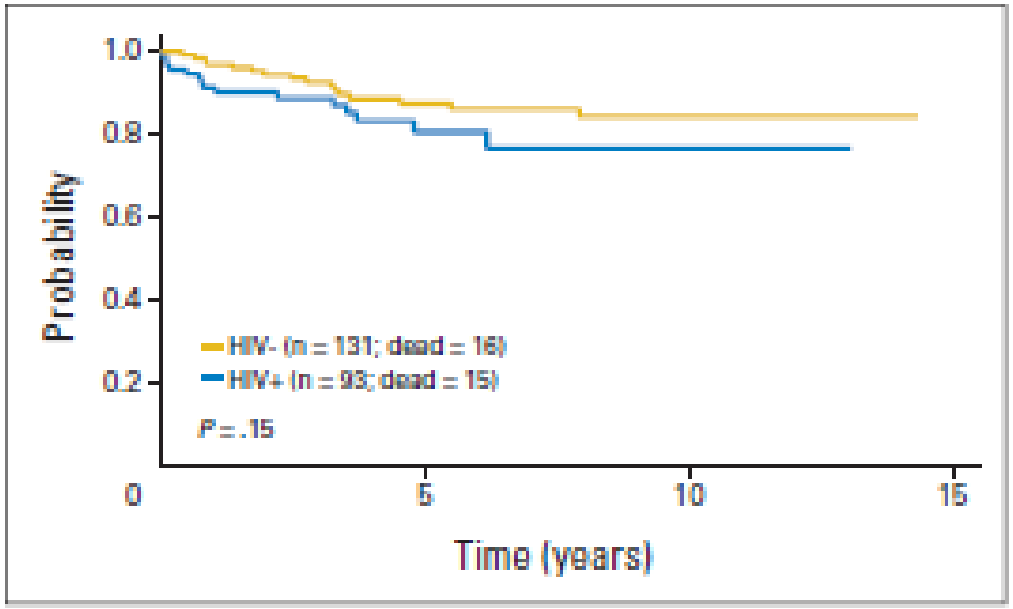


Fig 1. Overall survival according to HIV status.

Demographic or Clinical Characteristic	HIV-Positive Patients (n = 93) No.	%	HIV-Negative Patients (n = 131) No.	%	P
Male	83	89	75	57	< .001
Age, years					
Median	41		31		
Range	26-73		16-70		
≥ 45	31	33	26	20	.03
Histologic subtype					< .001
Nodular sclerosis	15	16	100	76	
Mixed cellularity	51	55	27	21	
Lymphocyte depleted	3	3	1	1	
Unknown	24	26	3	2	
"B" symptoms	75	81	52	40	< .001
WBC, × 10^9/L					
Median	4.3		9.5		
Range	0.3-14.1		2-39		
≥ 15	0	0	22	17	< .001
Lymphocyte count, × 10^9/L					
Median	0.9		1.5		
Range	0.09-3.1		0.1-3.9		
< 0.6	64	68	6	5	< .001
Hemoglobin, g/dL					
Median	10.9		12.2		
Range	4.1-15.3		2.2-16.6		
< 10.5	41	44	27	21	< .001
Albumin, g/L					
Median	33		42		
Range	10-49		21-54		
< 40	73	79	48	37	< .001
Bone marrow involvement	42	45	5	4	< .001
Spleen involvement	23	25	7	5	< .001
Lung involvement	5	5	11	8	.4
Liver involvement	17	18	15	11	.2
Stage					< .001
I	6	6	14	11	
II	13	14	72	55	
III	24	26	18	14	
IV	50	54	27	21	
International Prognostic Score					< .001
0-2	29	31	92	70	
3-7	63	68	34	26	
Unknown	1		5	4)	

Lymphomes de Hodgkin
Approches thérapeutiques

Essai Pilote associant AVD et Brentuximab Vedotin pour le traitement du Lymphome de Hodgkin de stade III-IV associé au VIH

CBesson, N Mounier en France

Paul G. Rubinstein, Chair
Ariela Noy, Co-Chair

Brentuximab vedotin with AVD shows safety, in the absence of strong CYP3A4 inhibitors, in newly diagnosed HIV-associated Hodgkin lymphoma

Paul G. Rubinstein[a,b], Page C. Moore[c], Michelle A. Rudek[d], David H. Henry[e], Juan C. Ramos[f], Lee Ratner[g], Erin Reid[h], Elad Sharon[i], Ariela Noy[j], for the AIDS Malignancy Consortium (AMC)

Table 2. Grade 3/4/5 treatment-related adverse events for all cycles at the patient level.

Adverse event	Grade 3	Grade 4/5[a]
Hematological adverse events		0%
Lymphocyte decrease	1 (16%)	
Neutrophil decrease	1 (16%)	
Non-hematolgical adverse events		0%
Diarrhea	1 (16%)	
Lung infection	1 (16%)	
Peripheral motor neuropathy[b]	2 (33%)	
Peripheral sensory neuropathy[b]	1 (16%)	

[a]No grade 4/5 adverse events were identified.
[b]One patient experienced both a Grade 3 peripheral motor and sensory neuropathy.

AIDS 2018, **32**:605–611

Case Report

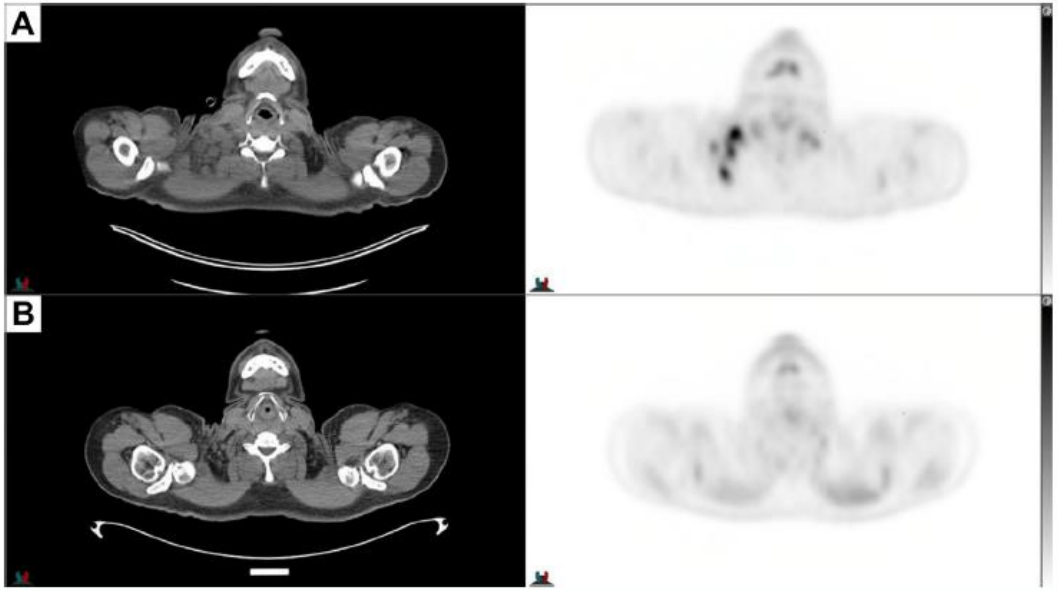
HIV-related Refractory Hodgkin Lymphoma: A Case Report of Complete Response to Nivolumab

Elaine Chang,[1,2] Gustavo Rivero,[1,3] Niraj R. Patel,[4,5] Elizabeth Y. Chiao,[2,6] Syeling Lai,[8,9] Kelash Bajaj,[1] John E. Mbue,[7] Sarvari V. Yellapragada[1,3]

Clinical Practice Points

- We present a case of a veteran with well-controlled human immunodeficiency virus (HIV) infection and primary refractory classical Hodgkin lymphoma (HL) who, after multiple prior lines of therapy, received nivolumab with a complete response. He also developed autoimmune diabetes mellitus after 6 months of nivolumab.
- HIV-associated HL is currently treated under the same algorithm as HL in the general population, but its unique biology, particularly the near-universal association with Epstein-Barr virus, regardless of histology, suggests that immunotherapy may have an important role in the management of this disease.
- Most clinical trials highlighting checkpoint inhibitors have excluded HIV-infected patients. More prospective data is clearly needed to delineate the risks and benefits of immunotherapy in this population with increased autoimmunity at baseline.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 18, No. 2, e143-6



Lymphomes diffus à grandes cellules B

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

Caroline Besson[a,b,c], Remi Lancar[d], Sophie Prevot[e,f], Michele Algarte-Genin[d], Pierre Delobel[g], Fabrice Bonnet[h], Marie-Caroline Meyohas[i], Marialuisa Partisani[j], Lucie Oberic[k,l], Jean Gabarre[m], Cécile Goujard[e,n], François Boue[e,o], Paul Coppo[p], Regis Costello[q], Houria Hendel-Chavez[r], Nawel Mekerri[d], Gabriella Dos Santos[d], Christian Recher[k,l], Richard Delarue[s], Rene-Olivier Casasnovas[t], Yassine Taoufik[e,r], Nicolas Mounier[u], Dominique Costagliola[d], the ANRS-CO16 LYMPHOVIR Cohort

Lymphomes non Hodgkiniens à grandes cellules B : Facteurs pronostiques et causes de décès

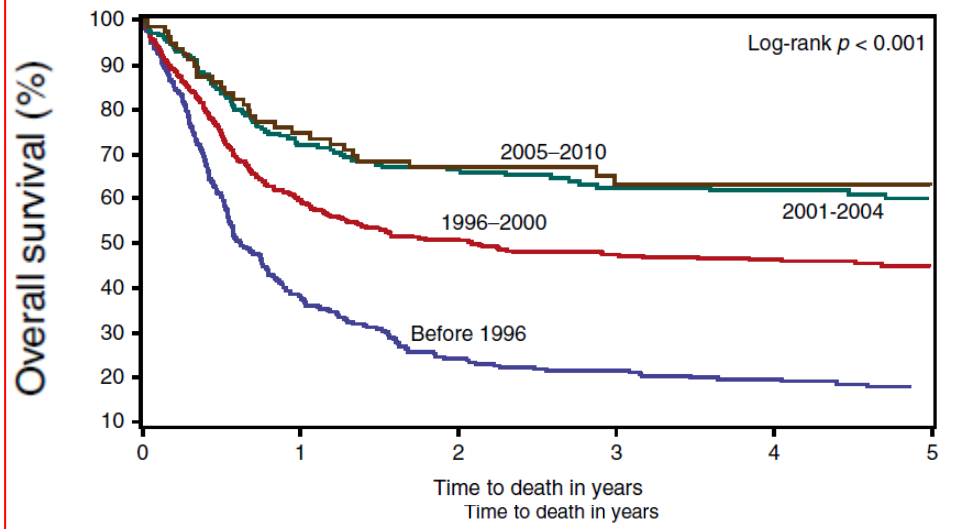
	N	Event	RR	P
Age, ans				0,55
≤60	41	12	1	
>60	11	4	1,41	
CD4/mm3				0,62
≥200	29	10	1	
<200	21	5	0,76	
Rituximab				**0,11**
Non	18	7	1	
Oui	34	9	0,43	
LDH				**0,25**
≤seuil	25	6	1	
>seuil	25	10	1,81	
ECOG				**0,02**
0-1	**34**	**7**	**1**	
2-3-4	**18**	**9**	**3,31**	
Stade				**0,06**
1-2	8	0		
3-4	41	15		
aaIPI				**0,05**
0-1	**20**	**3**	**1**	
2-3	**27**	**12**	**3,50**	

Délai depuis l'inclusion	Causes de décès
< 5 mois	-**complications infectieuses (n=5)** -embolie pulmonaire (n=1) -arrêt cardiaque (n=1)
5 à 11 mois	- **progressions (n=10)** -complication infectieuse (n=1)
>12 mois	-progression (n=5) -complications infectieuses (n=1) -leucémie aigüe (n=2) -autre cancer (n=1)

C Besson et al. AIDS. 2017

Lymphomes non Hodgkiniens à grandes cellules B : Evolution de la survie au cours du temps

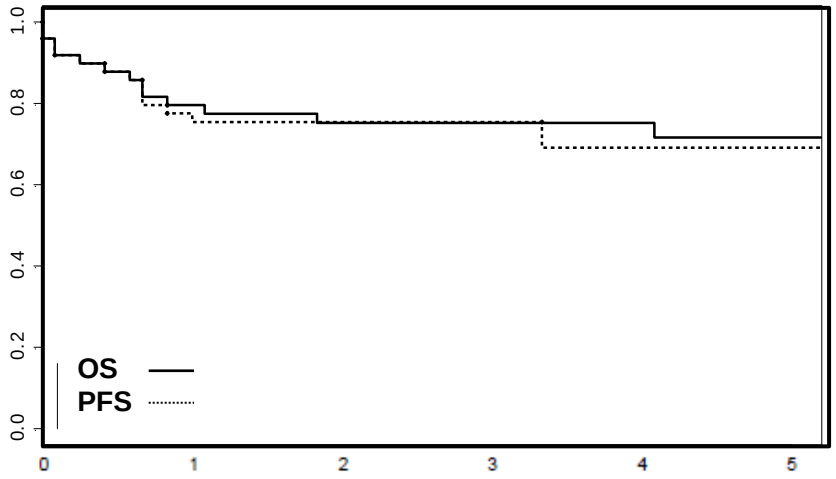
Méta-analyse



Number at risk:						
2005–2010	80	59	50	33	24	13
2001–2004	220	135	114	88	80	63
1996–2000	443	248	200	175	125	80
Before 1996	281	104	64	57	49	43

Survie globale de patients VIH en fonction du temps *(Barta SK, 2015)*

Lymphovir (2008-2015)



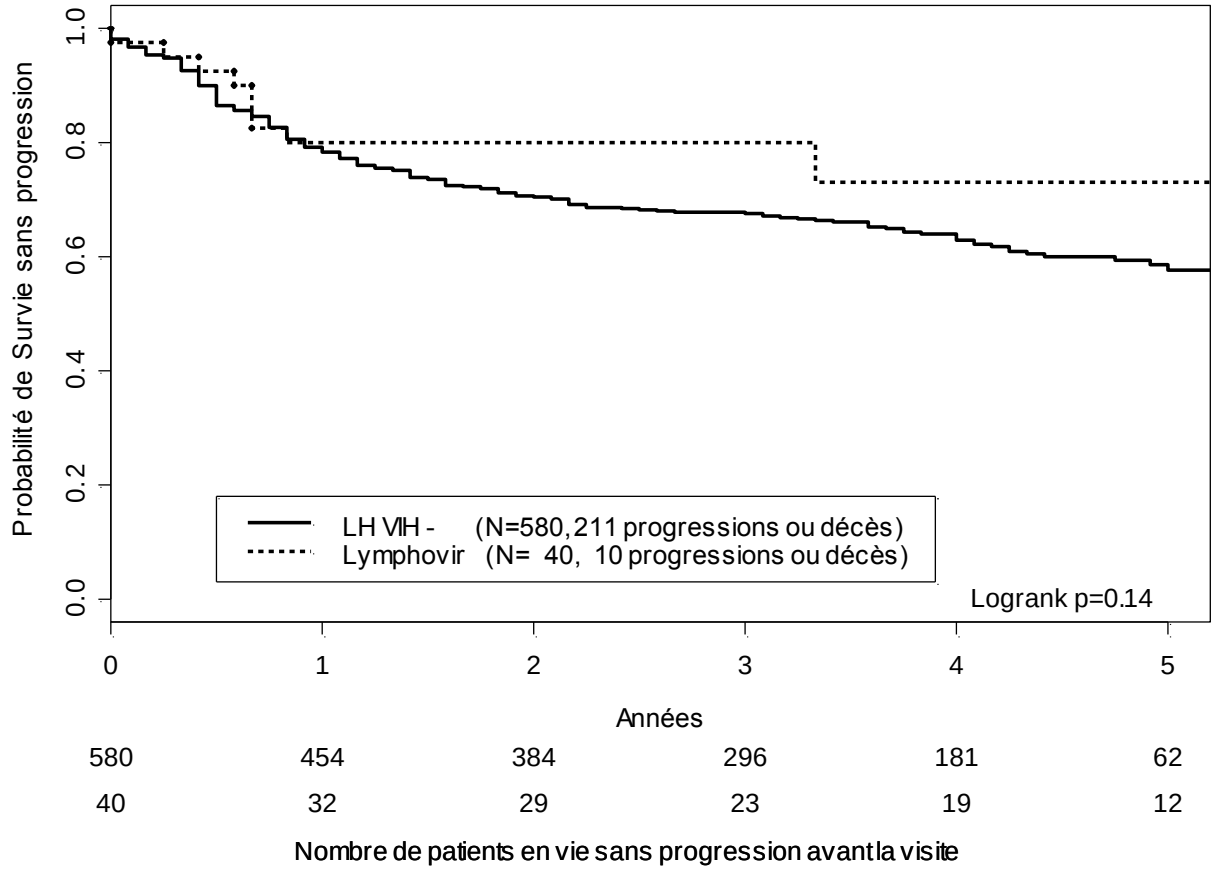
49	37	30	26	21	14	
49	36	30	26	19	14	

Nombre de patients en vie et nombre de patients en vie sans progression avant la visite

Survie globale à 2 ans : 0.75 [0.64, 0.88]
Médiane de suivi : 39 mois

C Besson et al. AIDS. 2017

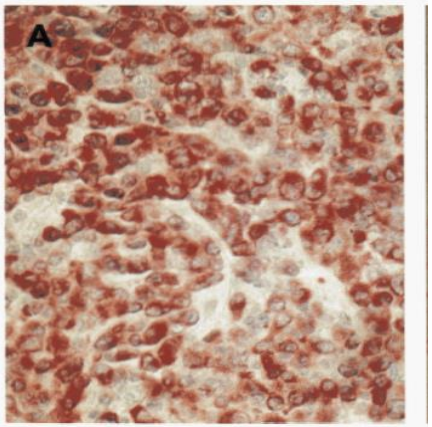
Comparaison des patients de Lymphovir et de 3 essais LYSA traités par R-CHOP

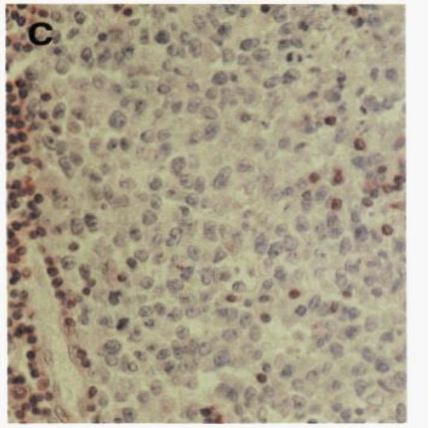


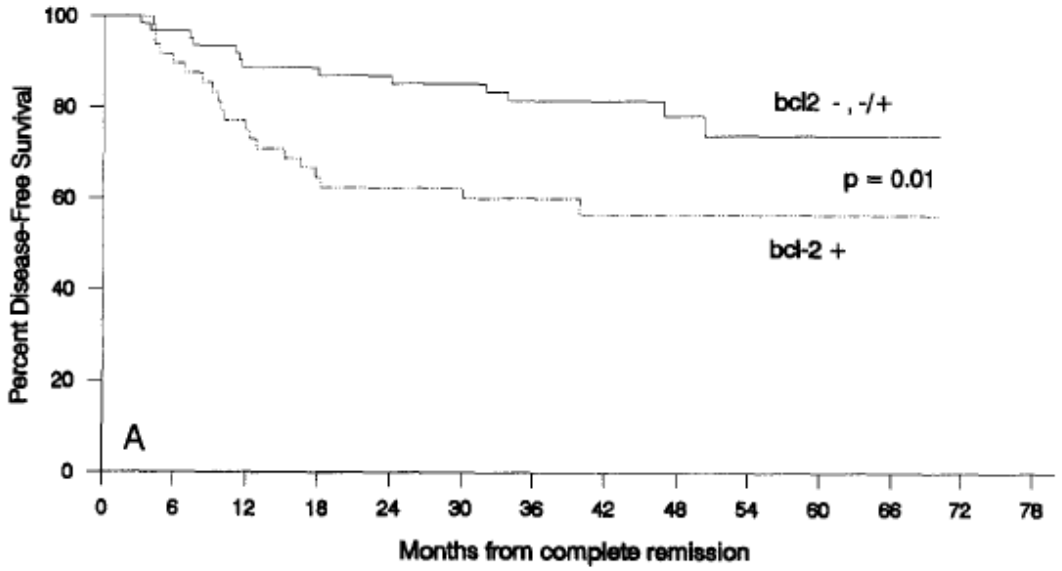
C Besson et al. AIDS. 2017

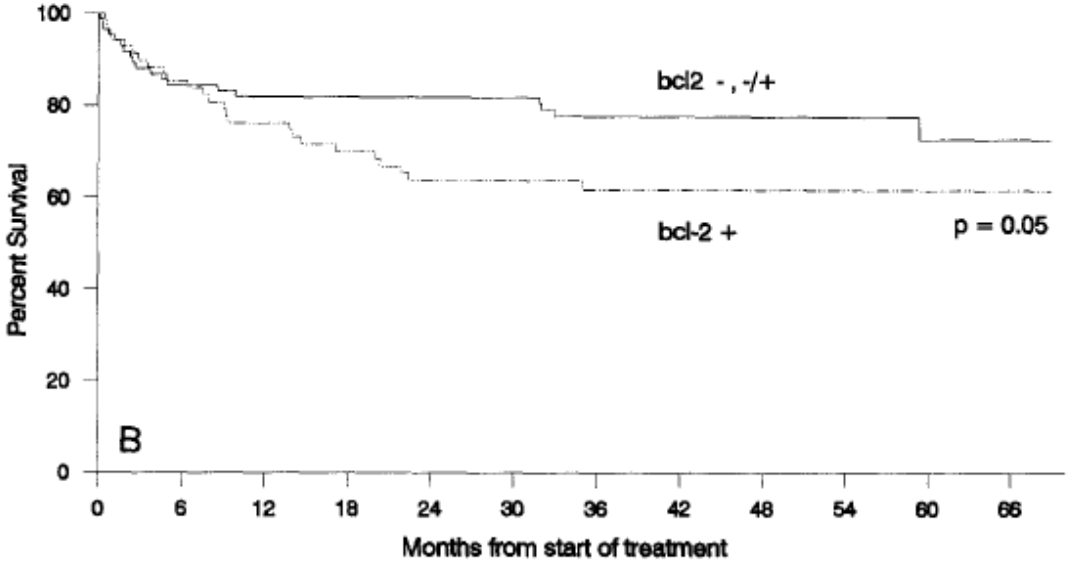
Prognostic Significance of bcl-2 Protein Expression in Aggressive Non-Hodgkin's Lymphoma

By Olivier Hermine, Corinne Haioun, Eric Lepage, Marie-Françoise d'Agay, Josette Briere, Caroline Lavignac, Georges Fillet, Gilles Salles, Jean-Pierre Marolleau, Jacques Diebold, Felix Reyes, Philippe Gaulard, for t





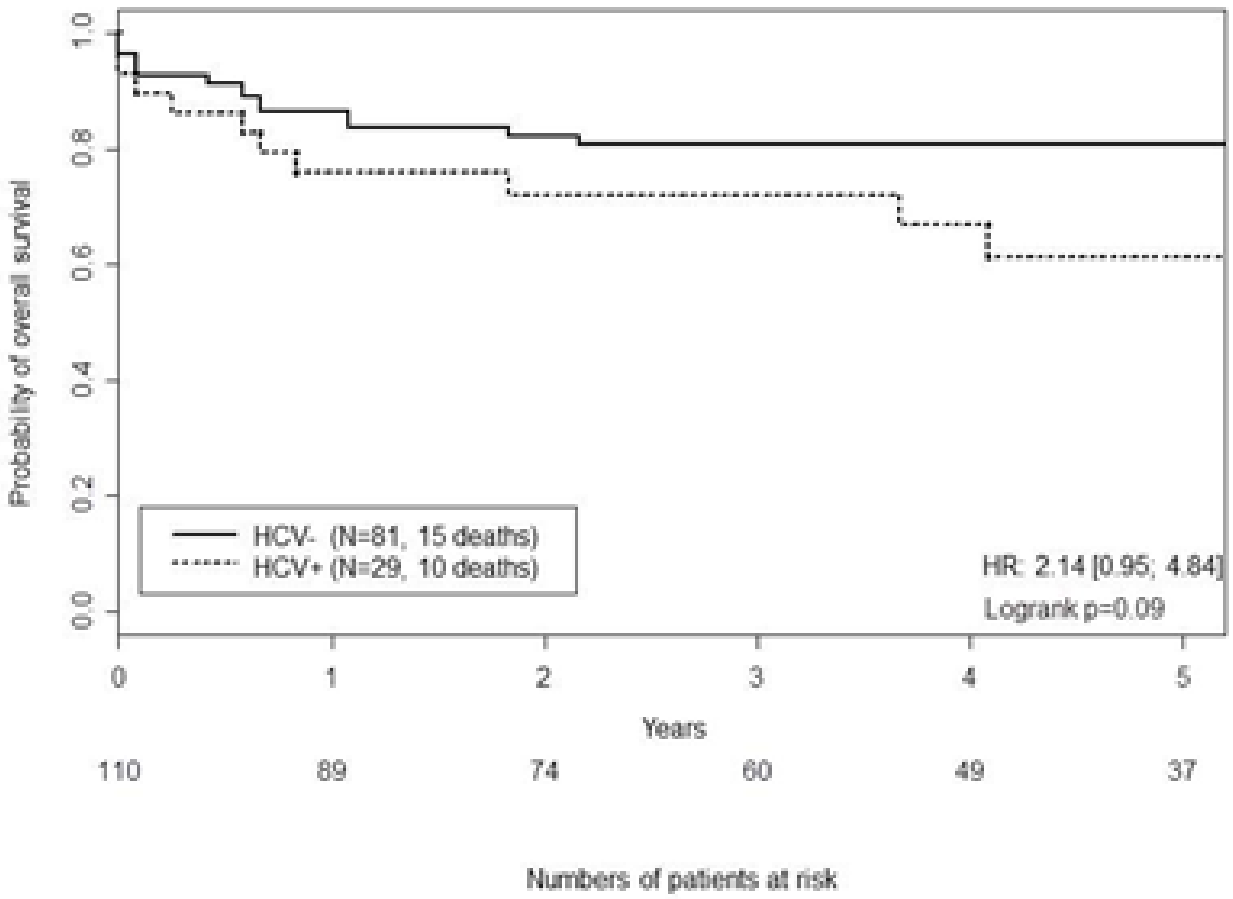




Blood, Vol 87, No 1 (January 1), 1996: pp 265-272

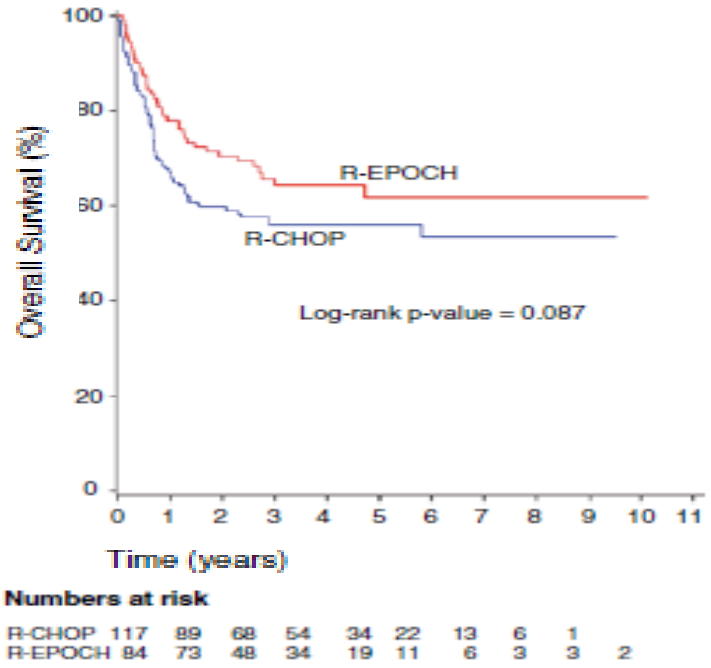
Overall survival of NHL among LYMPHOVIR-ANRS-CO16 patients according to HCV antibody status

Figure 1



Lymphomes non Hodgkiniens à grandes cellules B : Perspectives thérapeutiques

- Rôle d'une pré-phase pour les plus fragiles ?
- Antiviraux si VHC+
- Autres chimiothérapies pour les bcl-2 plus ?



Barta. 2014

- Thérapies ciblées ?

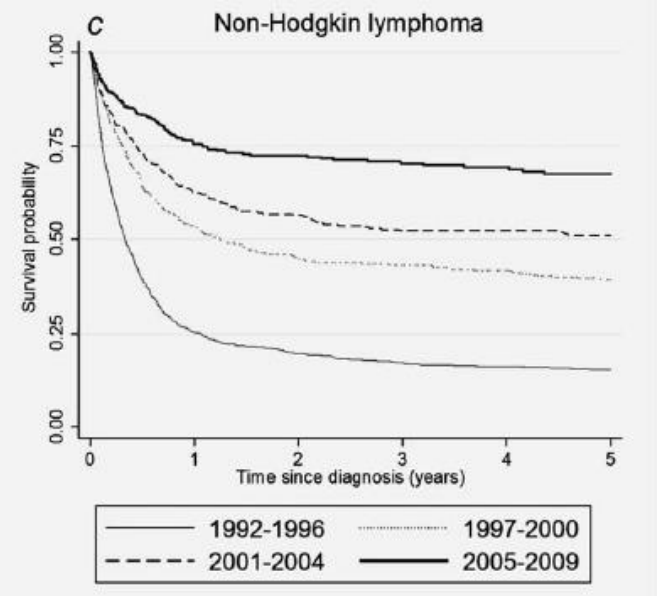
Conclusion

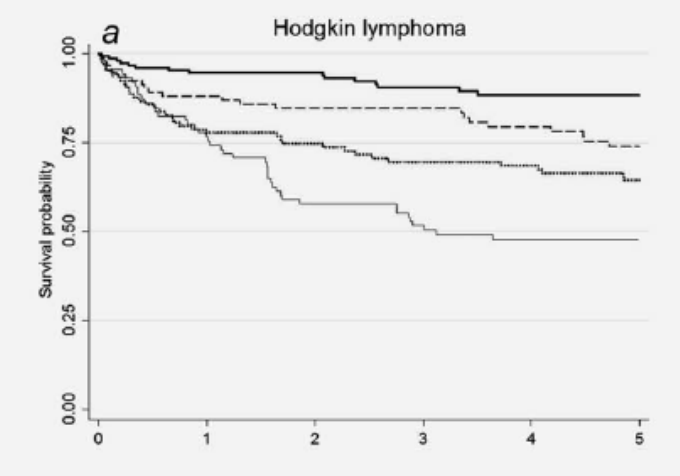
- Proportion croissante de **lymphomes de Hodgkin** (42%)
  Excellent pronostic sous ABVD

- **Lymphomes non Hodgkiniens**, prédominance de DLBCL,
  Evolution comparable aux patients non VIH sous R-CHOP

- Rôle des **coinfections virales** : EBV et VHC, autres ?

- **Inclusions dans essais en population générale ?**





Merci

Dominique Costagliola et son équipe
Michèle Génin, Rémi Lancar

Martine Raphaël, Sophie Prevot et anatomo-pathologistes
Houria Chavez et Yassine Taoufik

Nicolas Noel, Olivier Lambotte, Cécile Goujard, François Boué
Laure Philippe, Loic Vasseur

Nicolas Mounier, Paul Rubinstein, Ariela Noy, Elad Sharon
Ombeline Verité et l'équipe du LYSARC

Cliniciens et TEC des centres investigateurs

Patients participants