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# Maladie de Hodgkin et infection VIH

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# Plan

- Epidémiologie
- Physiopathologie
- Facteurs pronostiques
- Attitudes thérapeutiques
- Perspectives

# Epidémiologie (1)

- Selon l'OMS 2007:
  - 33,2 millions de personnes porteurs du virus VIH
  - 2,5 millions de nouveaux cas de VIH en 2007
  - 62 000 nouveaux cas /an dans le monde de maladie de Hodgkin
- Incidence relative de la maladie de Hodgkin est 7 fois supérieure dans la population VIH (*Rapezzi, 2001*)
- 2 périodes:
  - Pré trithérapie antirétrovirale (Avant 1996)
  - Post trithérapie antirétrovirale (Après 1996)

# Epidémiologie (3)

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

# Epidémiologie (4)

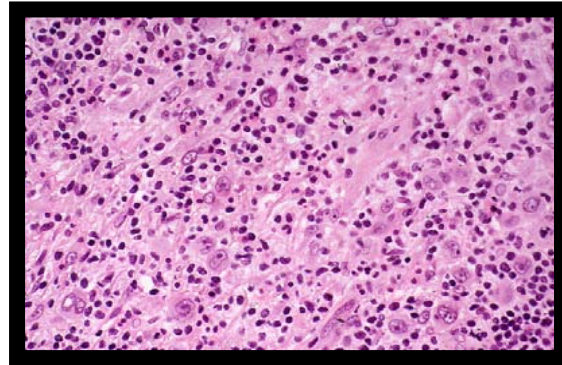
Table 2. Risk of cancer among people with AIDS in the United States, 1980–2002.<sup>a</sup>

Cancer type	No. cases (%)			SIR (95%CI)		
	1980–1989	1990–1995	1996–2002	1980–1989	1990–1995	1996–2002
AIDS related						
Kaposi sarcoma	2733 (63.9)	4637 (53.0)	494 (30.0)	52 900* (50 900–54 900)	22 100* (21 400–22 700)	3640* (3330–3980)
Non-Hodgkin lymphoma <sup>b</sup>	1115 (26.1)	2852 (32.6)	560 (34.0)	79.8* (75.2–84.6)	53.2* (51.2–55.2)	22.6* (20.8–24.6)
Burkitt NHL	38 (0.9)	88 (1.1)	39 (2.4)	57.4* (40.6–78.8)	52.8* (42.4–65.1)	49.5* (35.2–67.7)
Diffuse large B-cell NHL	485 (11.9)	1258 (14.4)	266 (16.2)	98.1* (89.6–107.3)	64.0* (60.5–67.6)	29.6* (26.1–33.3)
Immunoblastic NHL	208 (5.1)	451 (5.4)	44 (2.7)	140.5* (122.0–160.9)	94.9* (86.4–104.1)	59.5* (43.2–79.9)
Other/unspecified NHL	592 (14.5)	1506 (17.2)	255 (15.5)	70.8* (65.2–76.7)	46.6* (44.3–49.0)	17.1* (15.0–19.3)
CNS NHL	264 (6.5)	868 (10.4)	115 (7.0)	5000* (4410–5640)	4850* (4530–5180)	1020* (838–1220)
Cervix	10 (0.2)	34 (0.4)	30 (1.8)	7.7* (3.7–14.1)	4.2* (2.9–5.8)	5.3* (3.6–7.6)
Hodgkin lymphoma	24 (0.6)	77 (0.9)	72 (4.4)	7.0* (4.5–10.4)	8.1* (5.4–10.1)	13.6* (10.6–17.1)
Myeloma	4 (0.1)	15 (0.2)	11 (0.7)	2.7 (0.7–7.0)	2.2* (1.2–3.6)	2.2* (1.1–3.9)
Lymphocytic leukemia	1 (0.0)	7 (0.1)	1 (0.1)	1.2 (0.0–6.9)	2.7* (1.1–5.6)	0.7 (0.0–4.1)

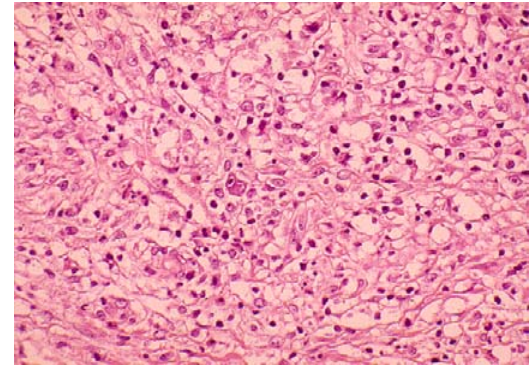
# Physiopathologie (1)

## *Anatomopathologie différente*

- Prédominance de 2 types anatomopathologiques:
  - Cellularité mixte (a)
  - Déplétion lymphoïde (b)
- Type cellulaire riche en cellules de Reed Sternberg



a



b

# Physiopathologie (2)

## *Rôle de EBV*

- 40% des maladies de Hodgkin VIH -
- 80 à 100% des maladies de Hodgkin VIH +  
(*Tirelli, 1995 ; Herndier, 1993*)
- Association à 2 types d'anatomopathologie riches en cellules de Reed Sternberg:
  - Cellularité mixte
  - Déplétion lymphoïde
- Cellules de Reed Sternberg infectées par EBV exprime LMP-1

# Physiopathologie (3)

## Rôle de EBV

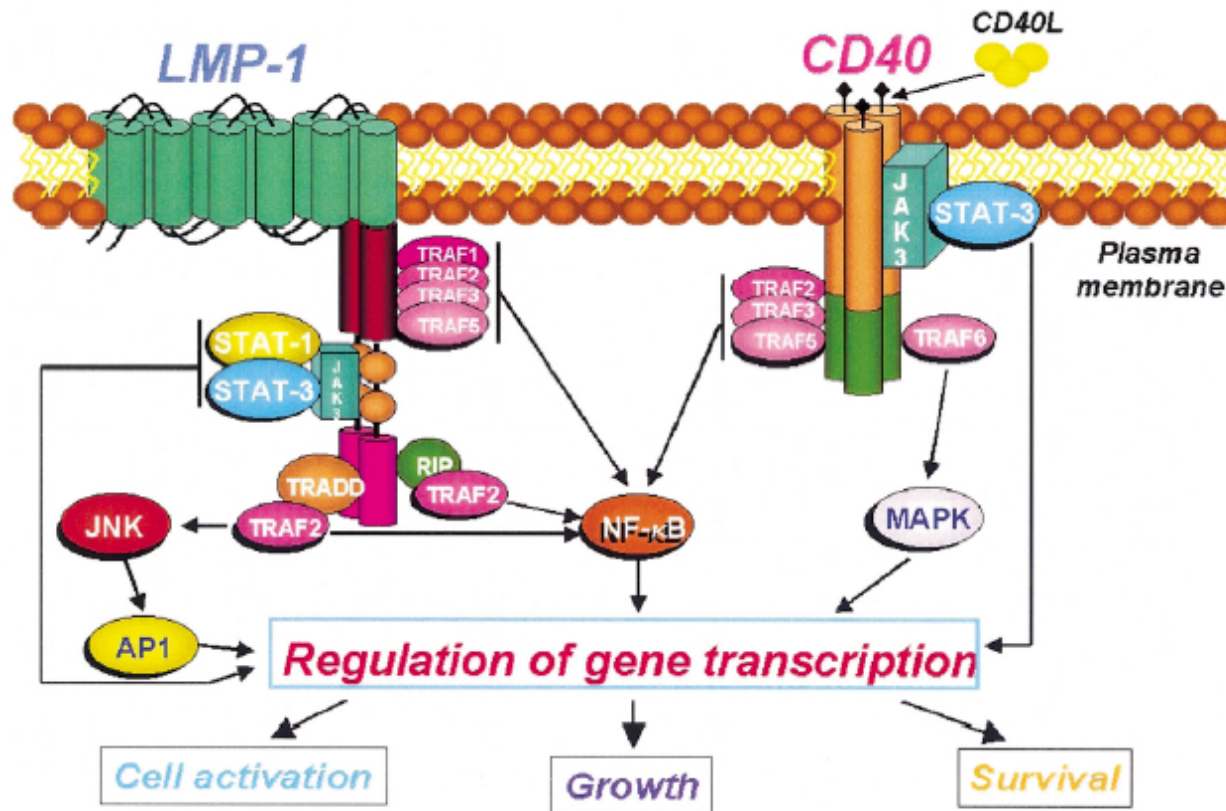


Fig. 1. Schematic representation of the known signalling pathways activated by the EBV-encoded LMP-1 in comparison with those activated by CD40 triggering.

# Physiopathologie (4)

## *Rôle de l'immunodépression ?*

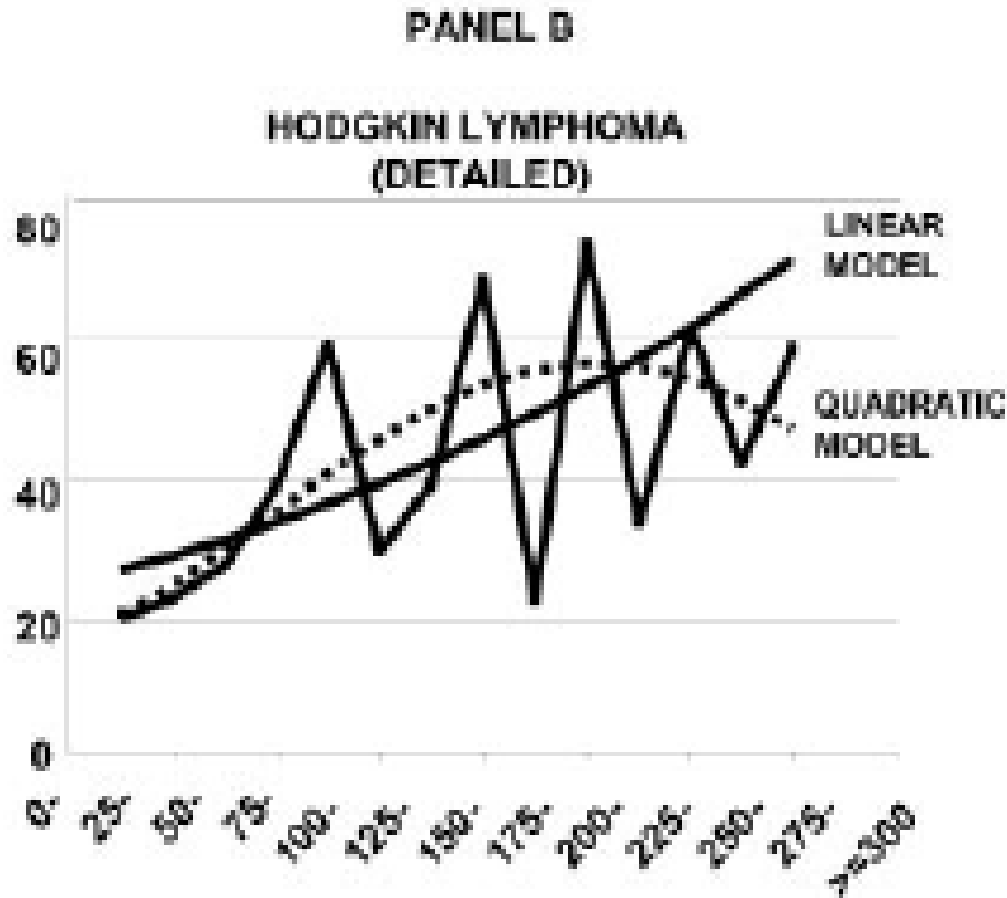
**Table 1. Incidence rates and standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) of Hodgkin lymphoma, 4 through 27 months after AIDS onset**

Category	No. of cases	Person-years at risk	Incidence per 10 <sup>5</sup> py's	Adjusted RR (95% CI)	Adjusted P	Expected cases*	SIR (95% CI)*
All	173	477 368	36.2	—		18.2	9.4 (8.0-10.9)
CD4 cells/ $\mu$ L					.002†		
0-49	17	81 977	20.7	0.46 (0.24-0.86)		3.0	5.3 (3.0-8.6)
50-99	16	49 388	32.4	0.70 (0.37-1.33)		1.8	8.2 (4.6-13.5)
100-149	24	53 652	44.7	0.97 (0.55-1.73)		2.0	12.0 (7.7-17.9)
150-199	41	76 306	53.7	1.18 (0.71-1.97)		2.8	14.5 (10.4-19.6)
200 or more	23	48 767	47.2	1.00		1.8	12.6 (8.0-18.9)
Missing	52	167 277	31.1	0.79 (0.46-1.35)		6.7	7.8 (5.8-10.2)

Augmentation de l'incidence pour une immunodépression modérée

# Physiopathologie (5)

## *Rôle de l'immunodépression ?*



Pic d'incidence  
Autour de 225-249  
CD4/mm<sup>3</sup>

Hypothèse:  
Intervention de  
L'environnement  
Cellulaire?

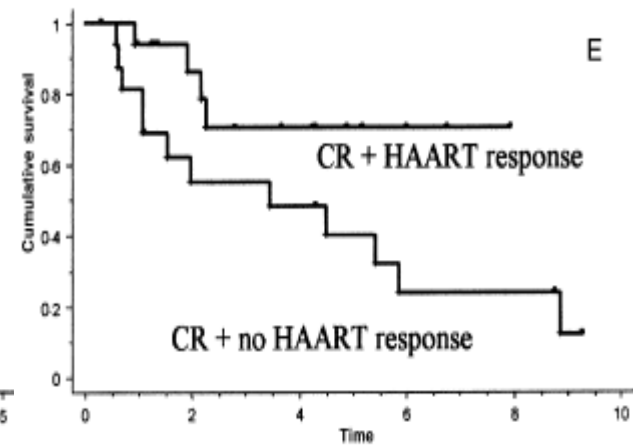
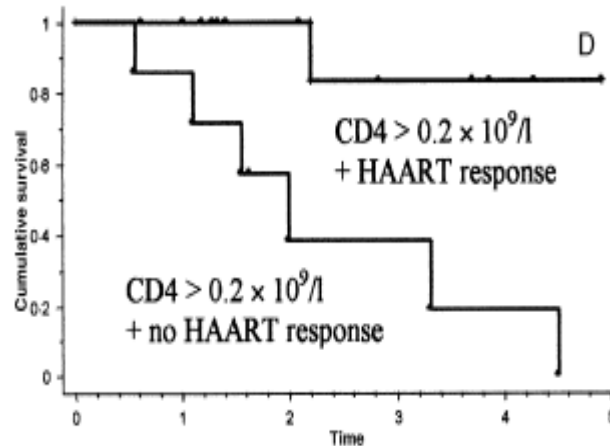
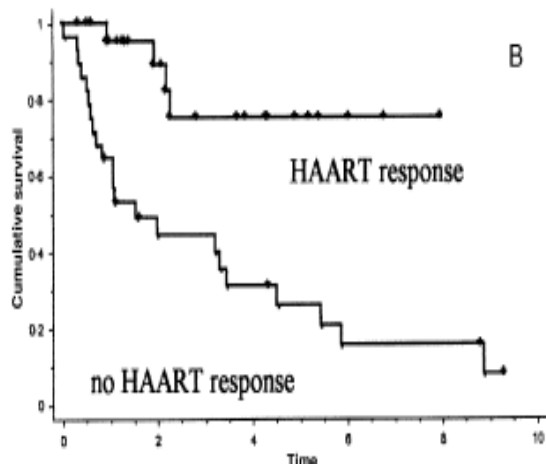
# Facteurs pronostiques (1)

**TABLE 2. THE FINAL COX REGRESSION MODEL.\***

FACTOR	LOG HAZARD RATIO	P VALUE	RELATIVE RISK
Serum albumin, <4 g/dl	0.40±0.10	<0.001	1.49
Hemoglobin, <10.5 g/dl	0.30±0.11	0.006	1.35
Male sex	0.30±0.09	0.001	1.35
Stage IV disease	0.23±0.09	0.011	1.26
Age, ≥45 yr	0.33±0.10	0.001	1.39
White-cell count, ≥15,000/mm <sup>3</sup>	0.34±0.11	0.001	1.41
Lymphocyte count, <600/mm <sup>3</sup> or <8% of white-cell count	0.31±0.10	0.002	1.38

# Facteurs pronostiques (3)

	RH (95% CI)	P-value*
<i>Multivariate analysis†</i>		
Response to HAART‡	0.19 (0.06–0.60)	0.0045
Age ≤45 years	0.23 (0.09–0.60)	0.003
Complete remission	0.30 (0.13–0.72)	0.007



# Attitudes thérapeutiques (1)

## *Quelles polychimiothérapies?*

- ABVD: doxorubicine, bléomycine, vinblastine, dacarbazine
- Stanford V : doxorubicine, méclorétamine, étoposide, vincristine, bléomycine et prednisone (*Spina, 2002*)
- BEACOPP: cyclophosphamide, doxorubicine, étoposide, procarbazine, prednisone, bléomycine et vincristine (*Hartmann, 2003*)
- VEBEP: épirubicine, cyclophosphamide, vinorelbine, bléomycine et prednisone (*Spina, 2005*)

# Attitudes thérapeutiques (2)

## *Quelles polychimiothérapies?*

**Table 4. Studies in patients with HIV-associated Hodgkin's lymphoma treated with chemotherapy and HAART.**

<i>Regimen (reference)</i>	<i>Stanford V<sup>9</sup></i>	<i>BEACOPP<sup>10</sup></i>	<i>VEBEP<sup>11</sup></i>	<i>ABVD (Present study)</i>
Number of patients	56	12	28	62
Median age, yr. (range)	38 (28-64)	33 (22-49)	39 (NS)	37 (24-61)
Stages III-IV(%)	71	92	71	100
B symptoms (%)	74	83	NS	89
Median CD4 lymphocyte counts/ $\mu$ L (range)	238 (32-1,008)	205 (110-1,020)	257 (44-589)	129 (5-1,209)
Median HIV RNA/mL (range)	3,400 (60-455,000)	16,846 (0-1,086,398)	9,402 (89-500,000)	14,000 (0-39,000)

# Attitudes thérapeutiques (3)

## *Quelles polychimiothérapies?*

<i>Regimen (reference)</i>	<i>Standford V<sup>9</sup></i>	<i>BEACOPP<sup>10</sup></i>	<i>VEBEP<sup>11</sup></i>	<i>ABVD (Present study)</i>
Known HIV infection(%)	20	25	32	47
HAART at diagnosis	yes	yes	yes (25% patients)	yes
G-CSF	yes	yes	NS	20% patients
Complete response (%)	81	100	75	87
Survival probability, %(years)	51 (3)	NA	86 (2)	76 (5)

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# Attitudes thérapeutiques (4)

## *Place du G-CSF?*

- Absence d'essai randomisé
- Recommandation de bonne pratique clinique
- Diminue la durée de neutropénie
- Diminue le risque infectieux qui est majoré en cas d'infection VIH
- Absence d'interactions prouvées avec la trithérapie antirétrovirale

# Attitudes thérapeutiques (5)

## *Prophylaxies?*

- Compte tenu du fort risque infectieux pendant la chimiothérapie:
  - Prophylaxie Pneumocystose par Bactrim ® ou aérosols de Pentacarinat® recommandé
  - Prophylaxie HSV par Zelitrex® discuté
- Prophylaxie des patients VIH en fonction du taux de CD4

# Attitudes thérapeutiques (5)

## *Trithérapie: Quand? Laquelle?*

- Pas de consensus à ce jour → avant, pendant ou après mais il faut impérativement débiter la trithérapie antirétrovirale
- Nombreuses interactions médicamenteuses
  - Choix de la trithérapie doit se faire en fonction des voies d'élimination des produits de chimiothérapies: ex: CYP450

# Attitudes thérapeutiques (6)

## *Trithérapie: Quand? Laquelle?*

Table 1  
Elimination of drugs used in cART.

Drug	Elimination	Effect on CYP450 system
<b><u>Nucleoside and nucleotide reverse transcriptase inhibitors</u></b>		
Zidovudine (ZDV)	Hepatic metabolism with renal excretion	None
Didanosine (ddI)	Renal excretion 50%	None
Stavudine (d4T)	Renal excretion 50%	None
Lamivudine (3TC)	Renal excretion 70%	None
Abacavir (ABC)	Hepatic	Minimal
Emtricitabine (FTC)	Renal excretion 86%	None
Tenofovir (TDF)	Renal excretion 70–80%	None
<b><u>Non-nucleoside reverse transcriptase inhibitors</u></b>		
Nevirapine (NVP)	Hepatic	CYP3A4 inducer
Efavirenz (EFV)	Hepatic	CYP3A4 inducer
<b><u>Protease inhibitors</u></b>		
Saquinavir (SQV)	Hepatic	CYP3A4 inhibitor
Ritonavir (RTV)	Hepatic	CYP3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 inducer
Indinavir (IDV)	Hepatic	CYP3A4 inhibitor
Fosamprenavir (f-APV)	Hepatic	CYP3A4 inhibitor
Lopinavir/ritonavir (LPV/r)	Hepatic	CYP3A4 and CYP2D6 inhibitor; CYP3A4 and CYP1A2 inducer
Atazanavir (ATZ)	Hepatic	CYP3A4 inhibitor, CYP1A2, CYP2C9 inhibitor
Darunavir (DRV)	Hepatic	CYP3A4 inhibitor
Tipranavir (TPV)	Hepatic	CYP3A4 inducer
<b><u>Integrase inhibitors</u></b>		
Raltegravir (RTV)	Hepatic	None
<b><u>Fusion inhibitors</u></b>		
Enfuvirtide (ENF)	Hepatic	None

Abbreviation: CYP450, cytochrome P-450.

# Attitudes thérapeutiques (7)

## *Trithérapie: Quand? Laquelle?*

Table 2

Antineoplastic agents modulating or metabolised by cytochrome P450 enzymes and interaction with antiviral drugs.

Anticancer therapy	Primary isoforms that mediate bio-transformation	Interaction with NNRTI drugs (CYP inducers)	Interaction with PI drugs (CYP inhibitors)
<b>Alkylating agents</b>			
Cyclophosphamide	3A4, 2B6, 2D6	↑	-
Ifosfamide	3A4	↑	↓
Lomustine	3A4	↑	↓
<b>Anthracyclines</b>			
Doxorubicin	3A4	-	↓
Mitoxantrone	3A4	-	↓
<b>Epipophyllotoxins</b>			
Etoposide	3A4	↓	↑
<b>Vinca alkaloids</b>			
Vincristine	3A4	↓	↑

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# Perspectives

- Place du Rituximab
  - Essai de phase 3
- Place de l'autogreffe en rechute
  - Essai de phase 2 en cours:
    - LMNH et maladie de Hodgkin en rechute ou réfractaire associés à VIH (*ClinicalTrials.gov Identifier: NCT00345865*)
    - Une étude déjà publiée prouvant la faisabilité de cette procédure mais critiquable (Gabarre, 2004)
- Place du TEP-TDM
  - Essai de phase 2 en cours:
    - Évaluation de la réponse par TEP TDM et corrélation avec survie (*ClinicalTrials.gov Identifier: NCT00822120*)

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