# 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)

| | | Pre-HAART Period: 1992-1995 | | | | HAART Period: 1996-1999 | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cancer Site | ICD IX | 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 |



*Herida, 2003*

# Epidémiologie (4)

Table 2. Risk of cancer among people with AIDS in the United States, 1980–2002.[a]

| | No. cases (%) | | | SIR (95%CI) | | |
|---|---|---|---|---|---|---|
| Cancer type | 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[b] | 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* (6.4–10.1) | 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) |

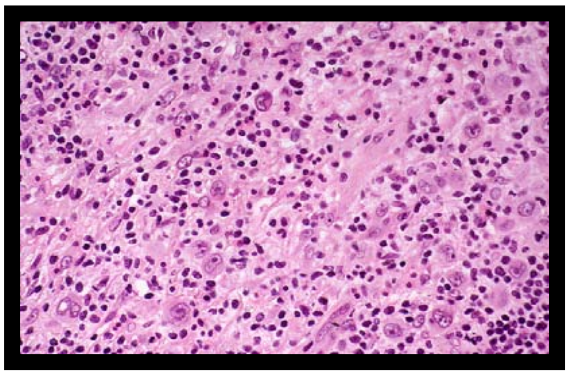


*Engels, 2006*

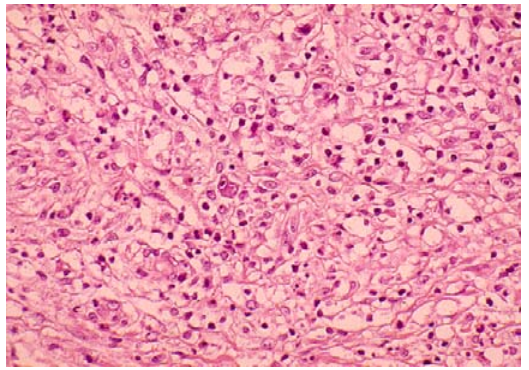
# Physiopathologie (1)

## *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*

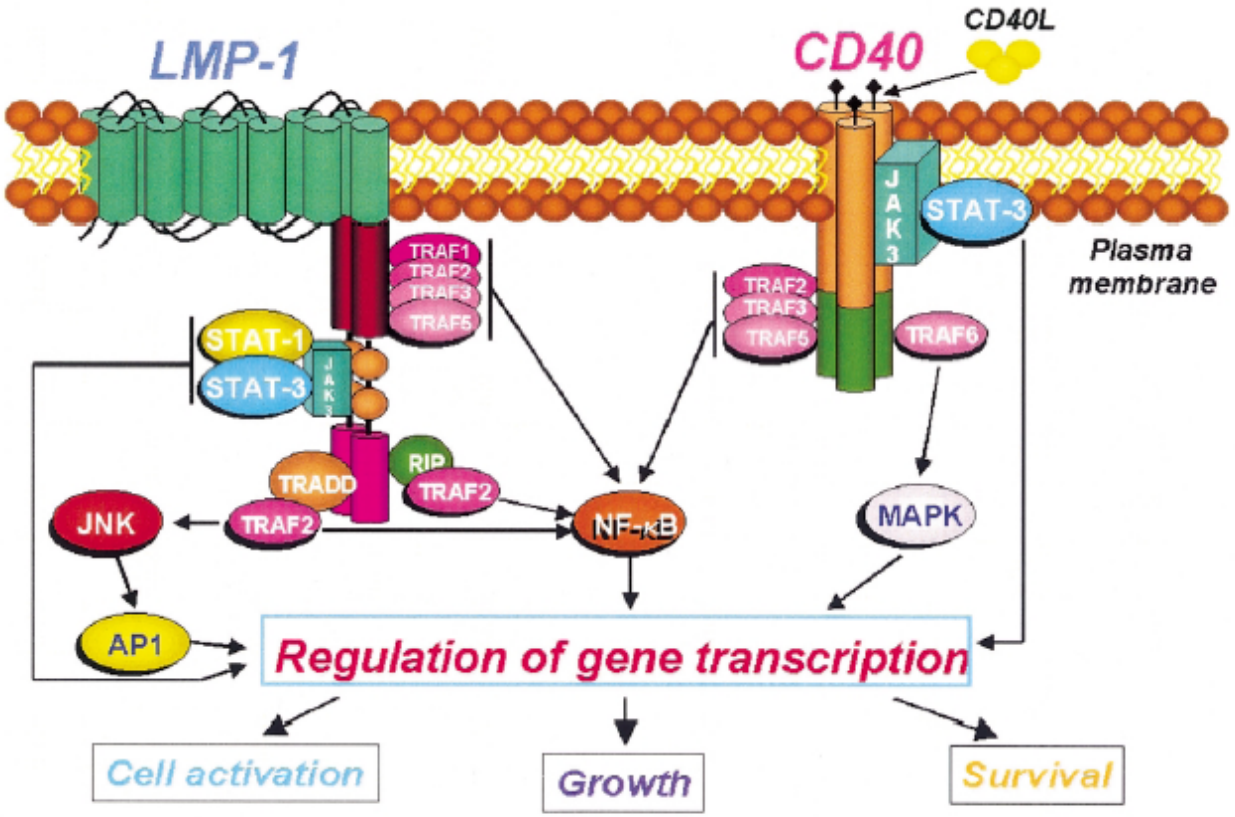



Fig. 1. Schematic representation of the known signalling pathways activated by the EBV-encoded LMP-1 in comparison with those activated by CD40 triggering.

*Dolcetti, 2001*

# 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**

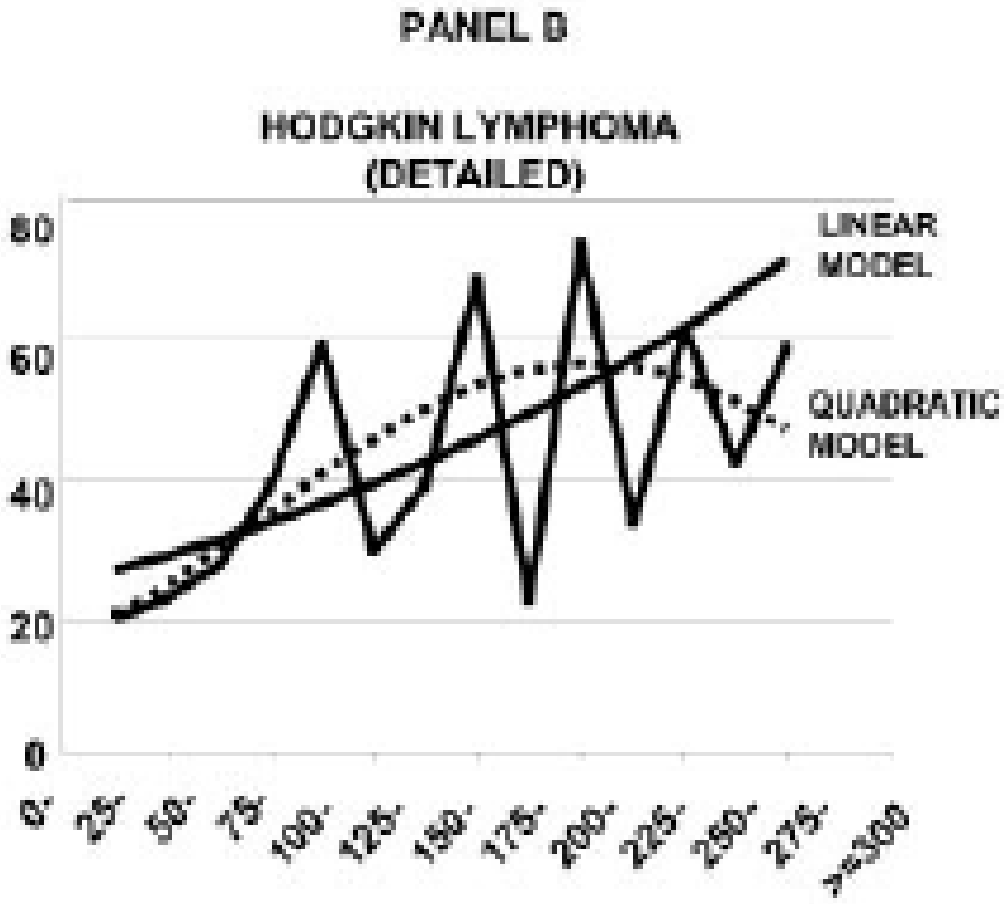
| Category | No. of cases | Person-years at risk | Incidence per $10^5$ py's | Adjusted RR (95% CI) | Adjusted *P* | Expected cases* | SIR (95% CI)* |
|---|---|---|---|---|---|---|---|
| All | 173 | 477 368 | 36.2 | — | | 18.2 | 9.4 (8.0-10.9) |
| CD4 cells/μL | | | | | .002† | | |
| 0-49 | 17 | 81 977 | 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

*Biggar, 2006*

# Physiopathologie (5)

## *Rôle de l'immunodépression ?*




Pic d'incidence
Autour de 225-249
CD4/mm$^3$

Hypothèse:
Intervention de
L'environnement
Cellulaire?

*Biggar, 2006*

# Facteurs pronostiques (1)

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

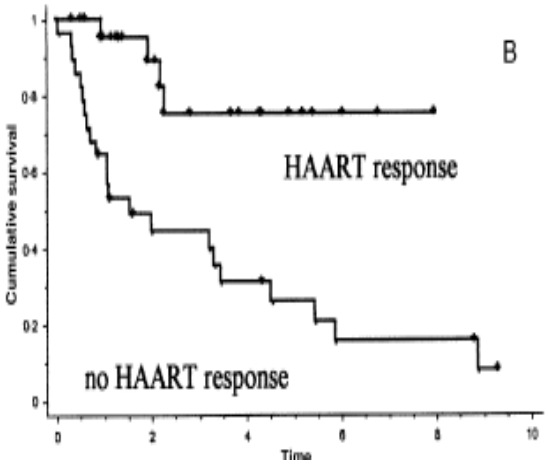
| FACTOR | LOG HAZARD RATIO | P VALUE | RELATIVE RISK |
|---|---|---|---|
| Serum albumin, <4 g/dl | 0.40±0.10 | <0.001 | 1.49 |
| Hemoglobin, <10.5 g/dl | 0.30±0.11 | 0.006 | 1.35 |
| Male sex | 0.30±0.09 | 0.001 | 1.35 |
| Stage IV disease | 0.23±0.09 | 0.011 | 1.26 |
| Age, ≥45 yr | 0.33±0.10 | 0.001 | 1.39 |
| White-cell count, ≥15,000/mm³ | 0.34±0.11 | 0.001 | 1.41 |
| Lymphocyte count, <600/mm³ or <8% of white-cell count | 0.31±0.10 | 0.002 | 1.38 |

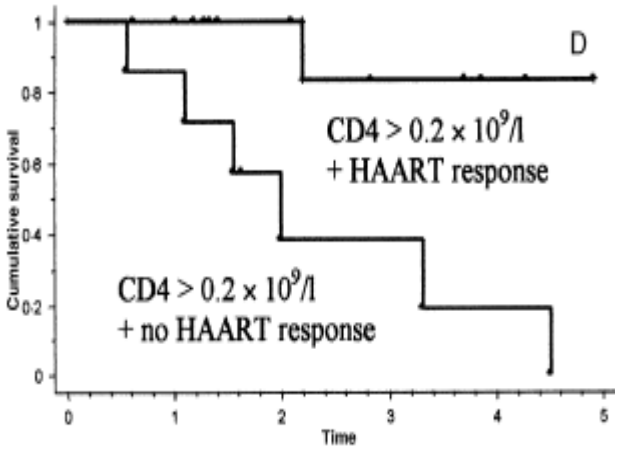


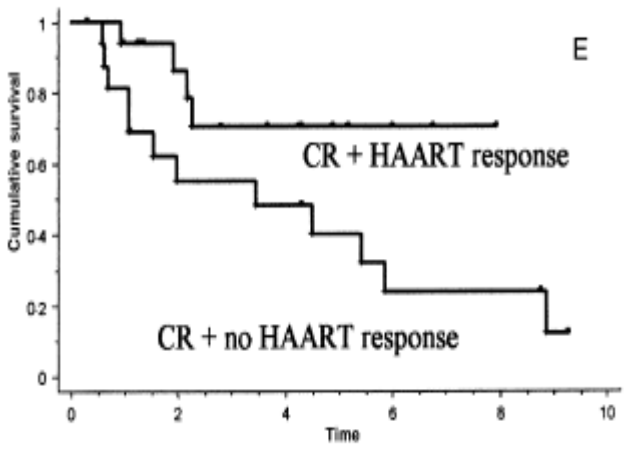
*Hasenclever, 1998*

# Facteurs pronostiques (3)

| | RH (95% CI) | *P*-value* |
|---|---|---|
| *Multivariate analysis†* | | |
| 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 |




*Hoffman, 2004*

# Attitudes thérapeutiques (1)
## *Quelles polychimiothérapies?*

- ABVD: doxorubicine, bléomycine, vinblastine, dacarbazine
- Standford 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.**

| *Regimen (reference)* | *Standford V*[9] | *BEACOPP*[10] | *VEBEP*[11] | *ABVD (Present study)* |
|---|---|---|---|---|
| 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/μL (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) |

*Xicoy, 2007*

# Attitudes thérapeutiques (3)

## *Quelles polychimiothérapies?*

| *Regimen (reference)* | *Standford V*[9] | *BEACOPP*[10] | *VEBEP*[11] | *ABVD (Present study)* |
|---|---|---|---|---|
| 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) |

*Xicoy, 2007*

# 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 débuter 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 |
|---|---|---|
| **Nucleoside and nucleotide reverse transcriptase inhibitors** | | |
| 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 |
| **Non-nucleoside reverse transcriptase inhibitors** | | |
| Nevirapine (NVP) | Hepatic | CYP3A4 inducer |
| Efavirenz (EFV) | Hepatic | CYP3A4 inducer |
| **Protease inhibitors** | | |
| 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 |
| **Integrase inhibitors** | | |
| Raltegravir (RTV) | Hepatic | None |
| **Fusion inhibitors** | | |
| Enfuvirtide (ENF) | Hepatic | None |

*Abbreviation*: CYP450, cytochrome P-450.

*Mounier, 2008*

# 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) |
|---|---|---|---|
| Alkylating agents | | | |
| Cyclophosphamide | 3A4, 2B6, 2D6 | ↑ | – |
| Ifosfamide | 3A4 | ↑ | ↓ |
| Lomustine | 3A4 | ↑ | ↓ |
| Anthracyclines | | | |
| Doxorubicin | 3A4 | - | ↓ |
| Mitoxantrone | 3A4 | - | ↓ |
| Epipophyllotoxins | | | |
| Etoposide | 3A4 | ↓ | ↑ |
| Vinca alkaloids | | | |
| Vincristine | 3A4 | ↓ | ↑ |

*Mounier, 2008*

# 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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