

« Best Of » en Infectiologie Pathologies associées au VIH

**5^{ème} Edition
10 octobre 2008**

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Pathologies associées au VIH

- Infections opportunistes
- Affections malignes
- Survie

Toujours pas

- les effets secondaires des ARV
- les co-infections VHB, VHC
- tuberculose

Et... ni SMART, ni enquête mortalité 2005

(cf présentation 2007 : abstracts → publications)

Infections opportunistes

Cryptococcal Neuroradiological Lesions Correlate with Severity during Cryptococcal Meningoencephalitis in HIV-Positive Patients in the HAART Era

Caroline Charlier^{1,2}, Françoise Dromer¹, Christophe Lévêque³, Loïc Chartier⁴, Yves-Sébastien Cordoliani³, Arnaud Fontanet⁴, Odile Launay⁵, Olivier Lortholary^{1,2*} for the French Cryptococcosis Study Group

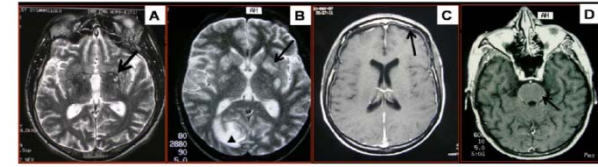


Figure 1. Examples of abnormal radiological findings. A. Magnetic Resonance axial T2-weighted image, displaying bilateral dilated Virchow-Robin spaces (arrow) in the basal ganglia. B. Magnetic Resonance axial T2-weighted image displaying a hyperintense right occipital mass (arrow) and bilateral dilated Virchow-Robin spaces (arrows). C. Magnetic Resonance axial T1-weighted image with contrast infusion displaying frontal subdural collection (arrow). D. Magnetic Resonance axial T1-weighted image with contrast infusion displaying basal meningeal enhancement (arrow). doi:10.1371/journal.pone.0001950.g001

- Etude rétrospective, multicentrique française;
 - 62 pts; analyse imagerie en aveugle (2 neuroradiologues)
- Anomalies imagerie cérébrale
 - TDM 53%, IRM 92%
 - associées à titres élevés ag ∇ signes neurologiques
 - sérique 78% vs 42%
 - LCR 81% vs 50%
 - non associées à la survenue d'échecs à S2 ET M3 ou à la survenue d'IRIS

Table 2. Initial computed tomography and magnetic resonance findings among the 17 patients with dual explorations during culture-proven cryptococcal meningoencephalitis.

Imaging findings, % (n)	Computed tomography	Magnetic resonance	p-value
Normal	47.1% (8)	5.9% (1)	0.085
Cryptococcosis-related lesions	23.5% (4)	76.4% (13)	0.005
VR dilatation	5.9% (1)	47.1% (8)	0.017
Pseudocysts	0	11.8% (2)	0.485
Intracerebral nodule(s) or mass(es)	17.6% (3)	17.6% (3)	1
Hydrocephalus	0% (0)	0% (0)	-
Radiological meningitis	0% (0)	5.9% (1)	1

doi:10.1371/journal.pone.0001950.t002

- Imagerie utile pour évaluation de la gravité initiale
- Indispensable même en l'absence de signes neurologiques, si titres élevés ag

Major Role for Amphotericin B–Flucytosine Combination in Severe Cryptococcosis

Françoise Dromer^{1*}, Claire Bernede-Bauduin^{2,3}, Didier Guillemot^{2,3,4}, Olivier Lortholary^{1,5} for the French Cryptococcosis Study Group

- Etude observationnelle Crypto A/D

Multicentrique française: 208 pts (160 infectés par VIH)

- Critère d'inclusion > culture + *Cryptococcus neoformans*.
- Contrôle de la stérilisation à S2 et M3
- Critère de jugement= Echec (décès, échec mycologique)

- Association AMB+5FC = Ttt d'induction le plus efficace en cas de méningo-encéphalite, de titres ag élevés et de signes neurologiques

- Taux d'échec = 26% vs. 56% (p 0.001).
- Facteurs associés à l'échec mycologique (analyse multivariée)
 - A S2
 - » Titre élevé ag (**OR 4.43** [1.21–16.23], p = 0.025)
 - » Imagerie cérébrale anormale (**OR= 3.89** [1.23–12.31], p= 0.021)
 - A M3
 - » Hémopathie (**OR = 4.02** [1.32–12.25], p = 0.015),
 - » Signes neurologiques à J0 [1.10–6.69], p = 0.030)
 - » 5FC < 14 jours (**OR = 3.30** [1.12–9.70], p = 0.030)

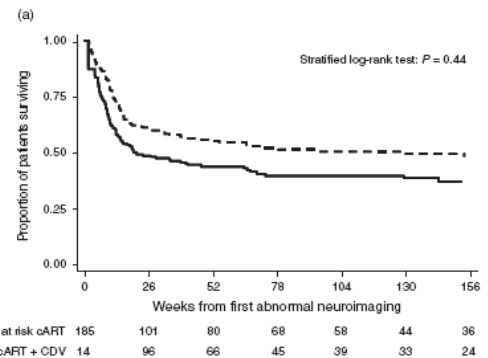
➤ **Traitement d'attaque par AMB+5FC ≥ 14 days chez tous les patients avec charge fongique élevée ∇ statut VIH et présence ou pas de méningo-encéphalite**

Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated PML: a multicohort analysis

De Luca A, et al, Aids, 2008, 22: 1759-67

- Méta-analyse de 6 études (Gesida 9/99, IRINA, ACTG 363, Bicêtre, Italie)
 - Critère de jugement : durée de survie (décès lié à LEMP)
- 300 patients avec LEMP
 - Dg > 1996 < 2004
 - traités par HAART ± cidofovir
- 64% LEMP confirmées (durée des symptômes avant Dg=20j)
- 47% Ttt ARV préalable
- 50% Ttt par cidofovir (m=5 cures)
- Décès: 36.6 pa (suivi: 463 pa)
- Taux de survie à 1 an: 56% (IC95% 50-61)
- Analyse multivariée

(stratification par cohorte, ajustement sur type de Dg et critères pronostiques)



➤ Cidofovir non associé à survie (HR pour décès: 93%)

- Id si critère de jugement = décès non lié à LEMP
- Id pour risque d'invalidité modérée à sévère à 12 mois

Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated PML: a multicohort analysis

De Luca A, et al, Aids, 2008, 22: 1759-67

Table 3. Crude and adjusted hazard ratios for the association of different variables with PML-related death.

	Univariate analysis hazard ratios (95% CI)	Multivariable analysis hazard ratios (95% CI)	
		Model 1	Model 2
Cidofovir treatment (yes vs no)	1.14 (0.82–1.57)	0.93 (0.65–1.32)	1.09 (0.77–1.54)
Baseline CD4 cell count (per ln cells/ μ l higher)	0.76 (0.67–0.85)*	0.75 (0.66–0.86)*	ND
CD4 cell count, time-updated (per ln cells/ μ l higher)	0.70 (0.62–0.80)*	ND	0.69 (0.60–0.78)*
Baseline HIV RNA \geq 500 vs < 500 cps/ml	1.43 (0.82–2.51)	1.27 (0.67–2.40)	1.23 (0.65–2.33)
Quantitative baseline JCV DNA (per log ₁₀ cps/ml higher) (n = 148)	1.26 (1.12–1.43)*	ND	ND
Baseline JCV DNA			
Negative	Reference	Reference	Reference
Positive	1.38 (0.86–2.21)	1.42 (0.85–2.39)	1.36 (0.81–2.28)
Not available	1.10 (0.63–1.94)	1.12 (0.62–2.04)	1.13 (0.62–2.06)
Karnofsky performance status, (per 10 points higher)	0.73 (0.65–0.81)*	0.74 (0.66–0.82)*	0.73 (0.65–0.82)*
Brainstem involvement, (yes vs no)	1.30 (0.90–1.87)	1.34 (0.92–1.97)	1.32 (0.90–1.94)
Confirmed vs presumptive PML diagnosis	0.78 (0.55–1.12)	0.76 (0.53–1.10)	0.83 (0.57–1.20)
Diagnosis during calendar year 1996 vs later calendar years	2.36 (1.05–5.33)**	2.08 (0.93–4.66)	2.17 (0.97–4.86)

The results of two separate multivariate Cox regression models are shown: in model 1, CD4 cell count was used as baseline value; in model 2, CD4 cell count was used as time-dependent variable. All analyses were stratified by cohort. CI, confidence interval; JCV, JC virus; ND, not done; PML, progressive multifocal leukoencephalopathy.

* $P < 0.001$.

** $P < 0.05$.

Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated PML: a multicohort analysis

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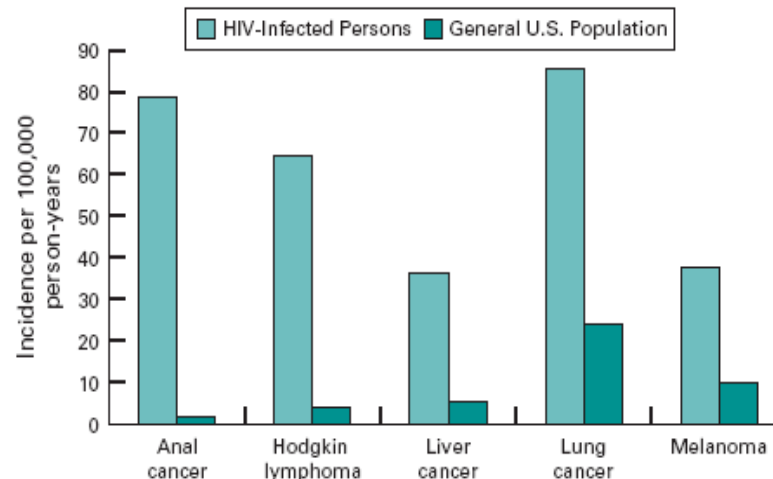
Affections malignes

Incidence of Types of Cancer among HIV-Infected Persons Compared with the General Population in the United States, 1992–2003

Pragna Patel, MD, MPH; Debra L. Hanson, MS; Patrick S. Sullivan, DVM, PhD; Richard M. Novak, MD; Anne C. Moorman, BSN, MPH; Tony C. Tong, MS; Scott D. Holmberg, MD, MPH; and John T. Brooks, MD, for the Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators*

- Etudes de cohorte observationnelles prospectives
 - Population infectée par VIH : 54 780 pts ; 157 819 personnes années, 1992-2003
 - 3350 cancers répertoriés : 80% classant sida, 20% non classant
- Cancers non liés au VIH plus fréquents dans population infectée par VIH que dans population générale

1. C anal
2. C oropharyngé
3. Leucémies
4. C colorectal
5. C rénal



6. Mélanome
7. C vaginal
8. Hodgkin
9. C foie
10. C poumons

Table 2. Trends in Standardized Incidence Rates of AIDS-Defining and Non-AIDS-Defining Types of Cancer among Persons with HIV*

Cancer	ASD and HOPSt (HIV-Infected Population)				SEER‡ (General Population)				
	Standardized Incidence Rate§ per 100 000 Person-Years			Linear Trend P Value	Standardized Incidence Rate§ per 100 000 Person-Years			Linear Trend P Value	
	1992–1995	1996–1999	2000–2003		1992–1995	1996–1999	2000–2003		
Kaposi sarcoma**	2628.5	848.8	356.3	<0.001	14.7	5.4	3.3	<0.001	
Non-Hodgkin lymphoma**	1011.8	494.1	212.2	<0.001	17.0	14.3	12.8	<0.001	
Cervical**	149.9	194.6	134.5	0.63	15.5	14.2	11.4	<0.001	
Anal	19.0	48.3	78.2	<0.001	1.0	1.2	1.3	0.02	anal
Hodgkin lymphoma	34.3	54.7	64.4	0.03	3.4	3.5	3.6	0.12	
Liver	19.9	35.9	35.4	0.35	3.3	4.1	4.7	0.01	hépatique
Lung	91.9	93.8	84.9	0.29	31.6	27.2	23.4	<0.001	
Melanoma	15.6	24.8	37.5	<0.05	9.0	9.8	9.9	0.12	
Oropharyngeal	29.0	31.0	36.9	0.22	14.4	13.0	11.7	0.01	
Colorectal	39.9	39.7	66.2	0.03	20.4	20.5	21.1	<0.01	colorectal
Breast	56.0	69.9	96.0	0.09	85.6	85.7	82.7	0.08	
Prostate	14.7	38.0	37.5	0.01	47.4	54.6	60.9	<0.001	prostatique

Facteurs de risque (RR)

- Homosexualité : Kaposi (3) – LNH (1.53) Co-infection VHB, VHC : foie (3.6)
- Nadir CD4 bas :
 - Kaposi (8)
 - LNH (6)
 - colorectal (6)
 - anal (6)
 - col (4)
 - poumons (2.4)

Cancer risk in people infected with HIV in the US

Engels EA et al, *Int J Cancer*, 2008, 123: 187-194

- SIR (ratio standardisé d'incidence) de cancer dans population infectée par VIH (n= 57 350) et population générale [Etude de registres VIH et cancers (3 états USA; 1991-2002)]

TABLE II - CANCER INCIDENCE AND STANDARDIZED INCIDENCE RATIOS AMONG HIV-INFECTED INDIVIDUALS IN THE FIVE-YEAR PERIOD AFTER HIV REGISTRATION

Cancer type	N	Incidence, per 100,000 person-years	SIR (95% CI)
All cancer types	871	468	2.1 (2.0-2.3)
AIDS-defining cancers			
Kaposi sarcoma	173	93	1,300 (1,100-1,500)
NHL	203	109	7.3 (6.4-8.4)
Burkitt NHL	12	7	15 (7.9-27)
DLBCL	93	50	9.6 (7.7-12)
Other histologic NHL subtypes	98	53	5.7 (4.6-7.0)
CNS NHL	28	15	250 (160-360)
Cervix	28	44	2.9 (1.9-4.2)
Non-AIDS-defining cancers			
Oral cavity/pharynx	26	14	1.7 (1.1-2.5)
Esophagus	6	3	1.1 (0.4-2.4)
Stomach	8	4	0.9 (0.4-1.9)
Small intestine	3	2	1.7 (0.4-5.0)
Colon and rectum	28	15	0.8 (0.5-1.1)
Anus	18	10	9.2 (5.5-15)
Liver	14	8	2.7 (1.5-4.6)
Pancreas	14	8	2.2 (1.2-3.6)
Larynx	15	8	2.6 (1.4-4.2)
Lung	109	59	2.6 (2.1-3.1)
Bones and joints	1	1	0.8 (0.0-4.4)
Soft tissue including heart	4	2	0.9 (0.2-2.2)
Melanoma	7	4	0.6 (0.2-1.2)
Breast	34	18	0.8 (0.5-1.1)
Uterus	1	2	0.2 (0.0-1.0)
Ovary	8	13	2.1 (0.9-4.1)
Vagina	2	3	7.8 (0.9-28)
Vulva	1	2	1.5 (0.0-8.5)
Prostate	21	17	0.3 (0.2-0.5)
Testis	6	5	0.7 (0.3-1.6)
Penis	3	2	5.4 (1.1-16)
Urinary bladder	4	2	0.6 (0.2-1.5)
Kidney and renal pelvis	12	6	1.0 (0.5-1.8)
Brain	2	1	0.3 (0.0-1.1)
Thyroid	4	2	0.4 (0.1-1.1)
Hodgkin lymphoma	36	19	5.6 (3.9-7.8)
Multiple myeloma	8	4	1.4 (0.6-2.7)
Lymphocytic leukemia	4	2	2.5 (0.7-6.4)
Myeloid and monocytic leukemia	3	2	0.5 (0.1-1.5)
Mesothelioma	0	0	0.0 (0.0-6.3)
Other/unknown site	42	23	2.2 (1.6-3.0)
Poorly specified histology at any site	23	12	1.9 (1.2-2.8)

– 871 évènements; CD4= 491

SIR

– Kaposi

1,3

– LNH

7,3

– C col

2,9

– Hodgkin

5.6

- RR 1996-2002 vs 91-95= 2,7

– C poumons

2,6

– C foie

2,7

- RR 1996-2002 vs 91-95= 1,1

- NADC 31,4% → 58%

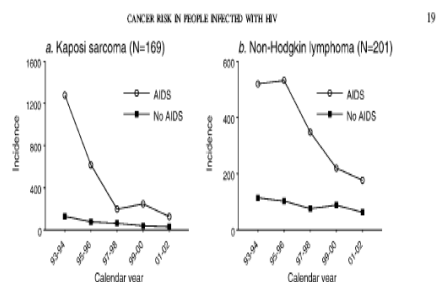
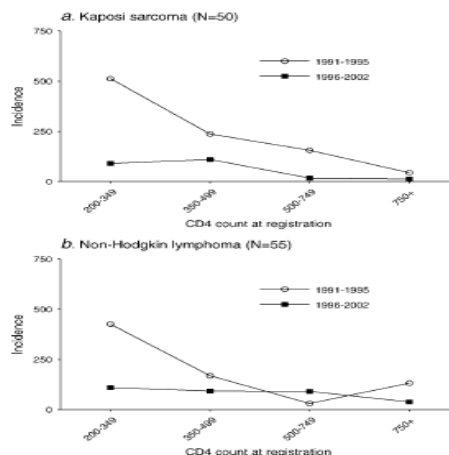


Figure 1 - Cancer incidence among HIV-infected individuals in the U.S. in relation to calendar year. Data are presented for the 4-60 month



Malignancies in HIV: pre- and post HAART

Nutankalva L et al, J Med Ass, 2008, 100(7) 817-820

- Etude de cohorte rétrospective, 1990-2003 : 203 pts
- revue des études récentes

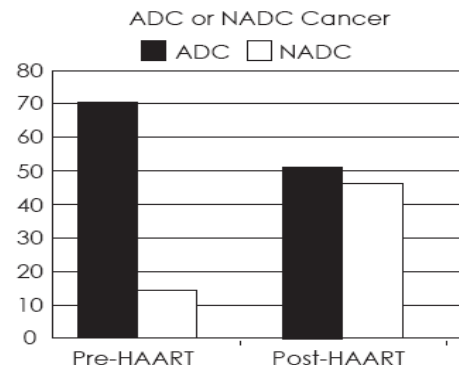
Table 2. Comparison of variables in the pre-HAART versus post-HAART period

	Pre-HAART	Post-HAART	P Value
N	93	110	
Age (mean)*	38	45	<0.0001
Age (median)*	37	43	<0.0001
Mean CD4 count (at cancer diagnosis)*	101 (n=69)	183 (n=90)	0.002
ADC*	74	55	<0.0001
Non-ADC*	18	50	<0.0001

* P value <0.05

ADC :
AIDS Defining
Cancers
(SK, LNH,
Cancer du col)

Figure 1. AIDS-defining cancer (ADC) versus non-ADC cancers



Pre-HAART (1995 & before) or
Post-HAART (after 1996)

HAART: Highly active antiretroviral therapy

Table 3. Most frequent cancer diagnoses during the study period

Cancer	Pre-HAART Period		Post-HAART Period		P Value
	Cases	Percentage	Cases	Percentage	
Kaposi's sarcoma*	53	57%	22	20%	<0.0001*
Non-Hodgkin's lymphoma*	16	17.2%	29	26%	0.117
Lung cancer*	6	6.5%	19	17.3%	0.019*
Cervical cancer**	5	5.4%	5	4.5%	0.785
Anal cancer**	2	2.2%	6	5.5%	0.228
Others	11	11.8%	29	26.4%	0.009*
Subtotal	93	100%	110	100	

* P values < 0.05; + Pearson's Chi-squared test; ++ Fisher's exact test

Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy

Piketty C et al, AIDS, 2008; 22: 1203-1211

- FHDH, 1992-2004, 86 322 patients

- 132 cas

- 94% hommes (75% homosexuels)
- 42.8 ans
- 78% préalablement traités par ARV (37 mois)
- Survie après Dg : 5 ans
- Taux de survie à 2 ans 45,5% → 80%

- Taux d'incidence/100 000 pa : 1992-96, 96- 98, 99-2004

11 18 40

- Risque plus élevé chez homosexuels masculins, et en 1999-2004 vs 92-96

➤ Importance du dépistage systématique

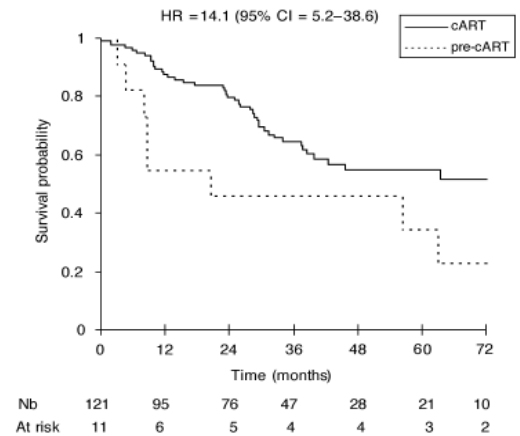


Fig. 2. Kaplan–Meier estimates of survival after anal cancer diagnosis in HIV-infected patients enrolled in the French Hospital Database, according to the cART periods. cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

AIDS-related malignancies : state of the art and therapeutic challenges

JP Spano, et al, Journal of Oncology, 2008, sept 15

- Groupe C
 - Kaposi
 - LNH
 - Cancer du col
- Non groupe C
 - Hodgkin
 - Cancer anal
 - Cancer pulmonaire
 - Autres

Table 2. Chemotherapy Combined With Rituximab for Patients With AIDS NHL

First Author	Schedule	Sample Size	CR (%)	2-Year OS (%)
Boué, 2006 ⁴⁶	R-CHOP	61	77	75
Kaplan, 2005 ⁴⁷	R-CHOP	99	58	55
Spina, 2005 ⁵⁰	R-CDE	74	70	64
Ribera, 2008 ⁵¹	R-CHOP	81	69	56

Abbreviations: NHL, non-Hodgkin's lymphoma; CR, complete response; OS, overall survival; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CDE, rituximab, cyclophosphamide, doxorubicin, and etoposide.

Table 4. Antineoplastic Agents Modulating or Metabolized by Cytochrome P450 Enzymes and Interaction With Antiviral Drugs

Anticancer Therapy	Primary Isoforms That Mediate Biotransformation	Interaction With NNRTI Drugs	Interaction With PI Drugs*
Alkylating agents			
Cyclophosphamide	3A4, 2B6, 2D6	↑	—
Ifosfamide	3A4	↑	↓
Lomustine	3A4	↑	↓
Anthracyclines			
Doxorubicin	3A4	—	↓
Mitoxantrone	3A4	—	↓
Camptothecins			
Irinotecan	3A4	↓	↑
Topotecan	3A4	↑	—
Epipophyllotoxins			
Etoposide	3A4	↓	↑
Taxanes			
Docetaxel	3A4	↓	↑ ↑
Paclitaxel	3A4, 2C8	↓	↑
Vinca alkaloids			
Vincristine	3A4	↓	↑

NOTE. Symbol definitions are as follows: ↑, interaction increases concentration of active metabolite; ↓, interaction decreases concentration of active metabolite; —, potential for interaction appears to be minimal.

Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.

*Effects may be more pronounced with ritonavir.

Survie

Survie des patients admis en USI

- Etude rétrospective San Francisco General Hospital, 2000-2004, *Powel K et al, Chest, 2008*,
 - 311 admissions (281 pts)

facteurs associés à

analyse univariée

- + albuminémie élevée

- + score APACHE II bas

- - PCP

analyse multivariée

- albuminémie (ORA: 2.08)

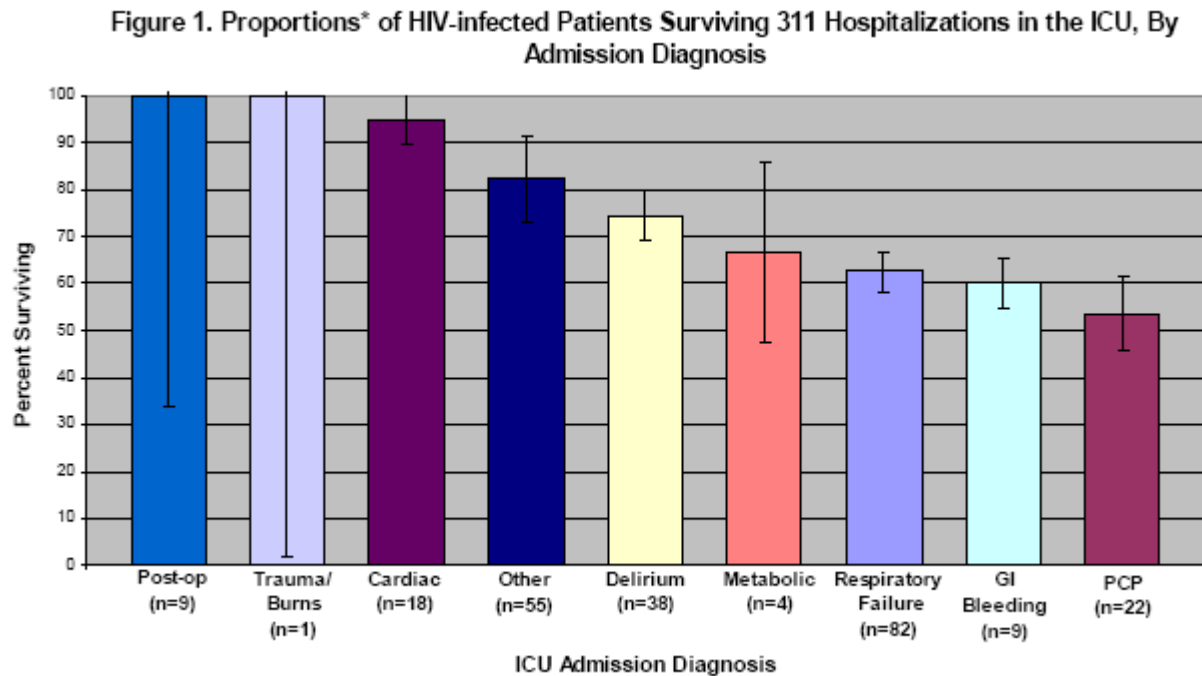
- absence de ventilation
mécanique (ORA 6.11)

Table 1. Admissions, ICU diagnoses, ART use, and survival among 311 ICU admissions of HIV-infected patients, according to study year*

	Year of Enrollment						P-value†
	Total	2000	2001	2002	2003	2004	
Admissions	311	50	52	75	66	68	
ICU Diagnosis (%)							0.02
Respiratory Failure	131 (42)	26 (52)	24 (46)	32 (43)	26 (39)	23 (34)	
PCP 28%							
Sepsis	62 (20)	11 (22)	9 (17)	14 (19)	11 (17)	17 (25)	
NI 40%, BGN 18%							
Neurologic	51 (16)	7 (14)	8 (15)	13 (17)	16 (24)	7 (10)	
Other	67 (22)	6 (12)	11 (21)	16 (21)	13 (20)	21 (31)	
Cause la + fréquente c/0 non Ttés							
AIDS-associated (%)	65 (21)	17 (34)	9 (17)	12 (16)	14 (21)	13 (19)	0.17
PCP diagnosis (%)	43 (14)	12 (24)	8 (15)	8 (11)	9 (14)	6 (9)	0.03
ART use (%)	101 (33)	18 (37)	16 (31)	26 (35)	16 (24)	25 (37)	0.11
Survival (%)	215 (69)	29 (58)	31 (60)	53 (71)	51 (77)	51 (75)	0.001

Survie des patients admis en USI

- Etude rétrospective San Francisco General Hospital, 2000-2004, *Powel K et al, Chest, 2008,*



Life expectancy of individuals on combination therapy in high-income countries: a collaborative analysis of 14 cohort studies

The ART CC, Lancet, 2008; 372: 293-299

- ART CC: 14 cohortes Europe, USA
- Patients >16 ans, Ttt ARV 1^{ère} ligne
- 3 périodes : 1996-99; 2000-02; 2003-05

– n	18 587	13 914	10 854
– Mortalité /100 pa	16.3	11.4	10.0
– Années potentielles de vie perdues/100pa	366		189
– Espérance de vie à 20 ans	36.1		49.4

= 2/3 de celle de la population générale

– Plus élevée chez les femmes

– Moins élevée chez

- UDVI

- Pts ayant CD4 initiaux < 100 (32,4 vs 50,4 si CD4 ≥ 200)