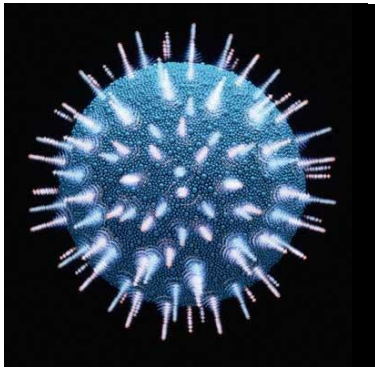
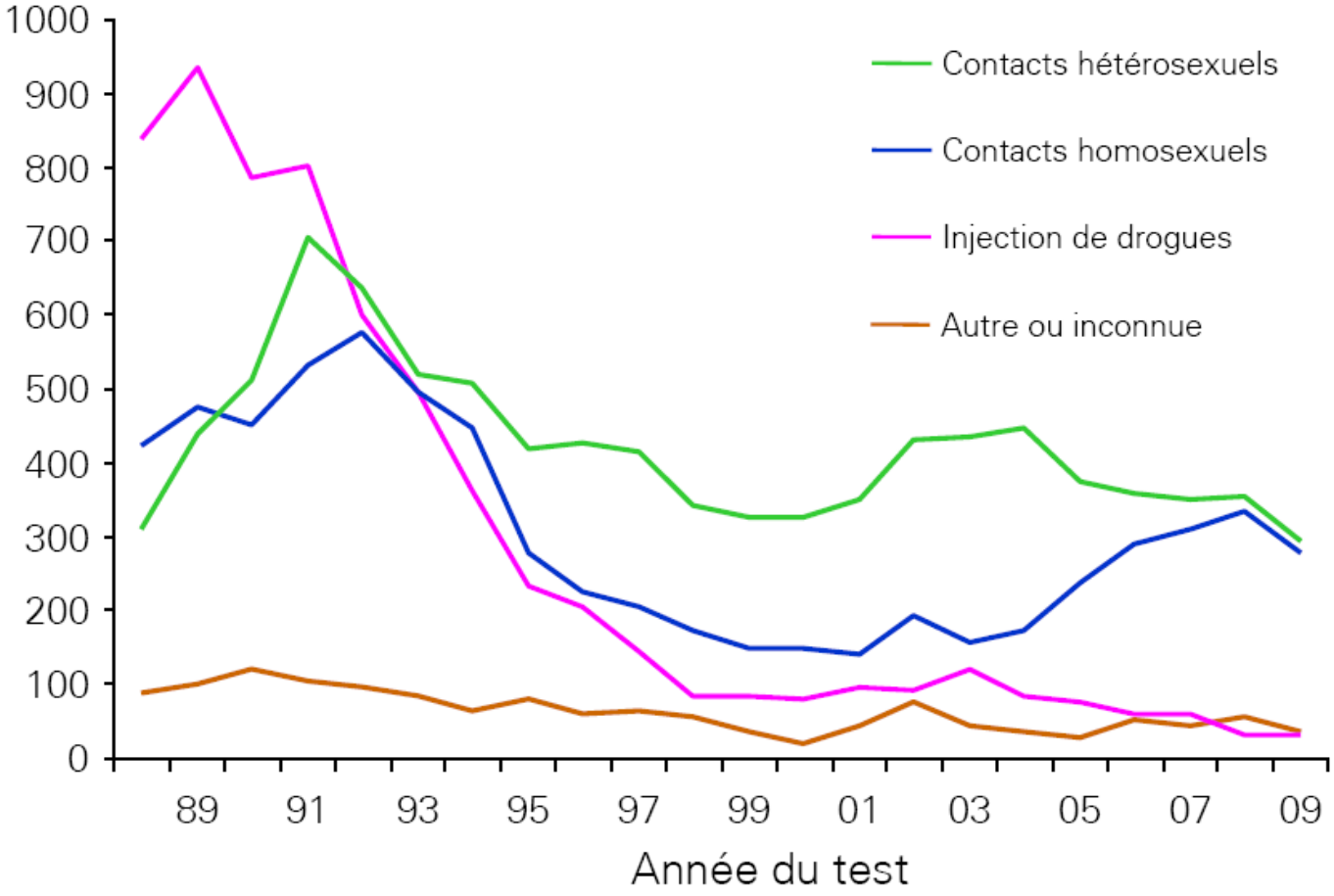


Hypertension Artérielle Pulmonaire associée à l'infection VIH

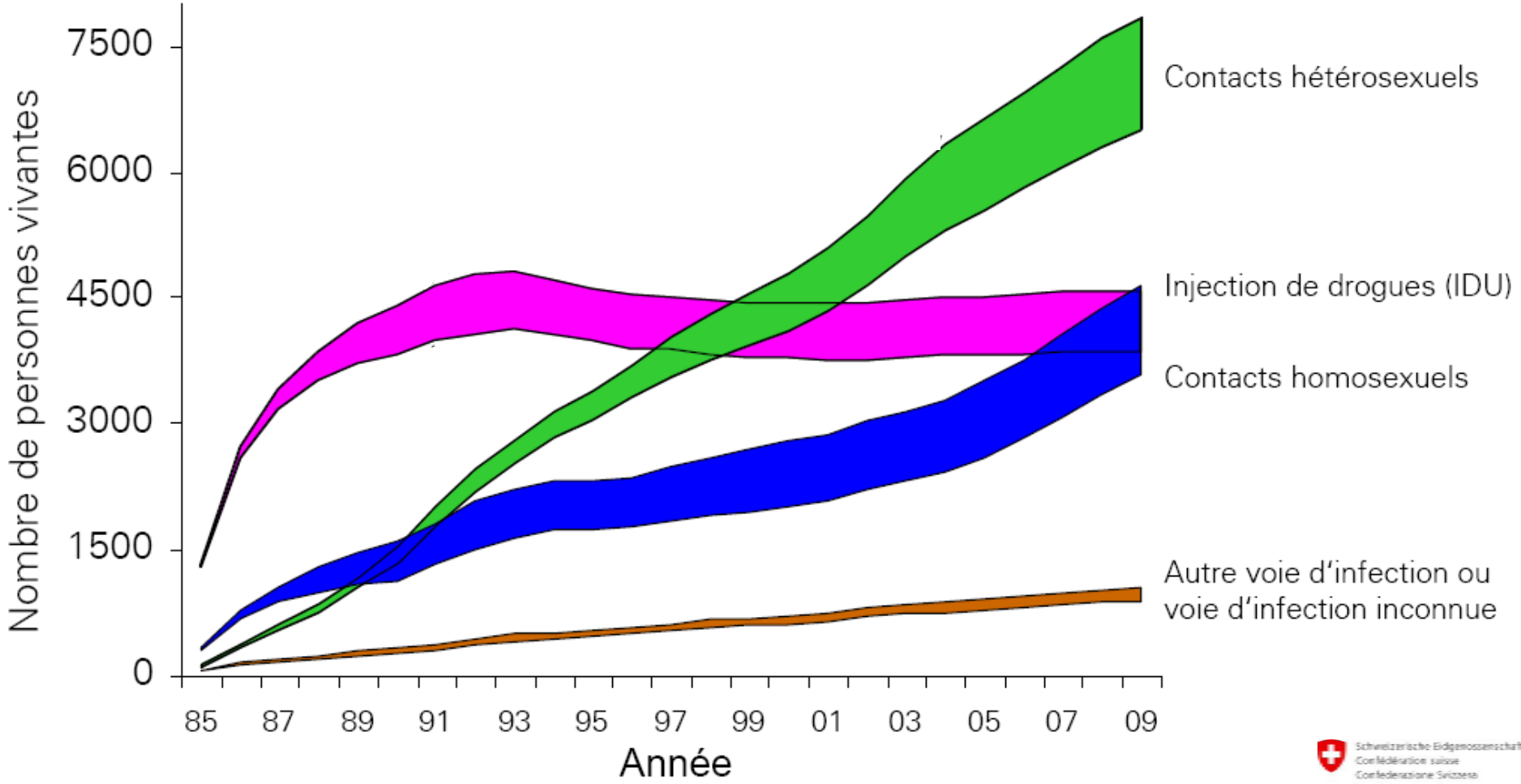
Hôpitaux Universitaires de Genève

Frédéric Lador
Service de Pneumologie

VIH: quelques éléments épidémiologiques



VIH: quelques éléments épidémiologiques



Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

HTAP-VIH: quelques éléments épidémiologiques

- Décrite avec les deux sérotypes du VIH
- Sex-ratio H : F ~ 1.2 : 1
- Diagnostic tardif au cours de l'infection VIH
- HTAP plus fréquente chez les toxicomanes IV (42-59 %)
- Pas de corrélation entre stade de infection VIH ou le degré d'immunodépression et la prévalence ou la sévérité de l'HTAP

Mehta NJ et al. Chest 2000
Niakara A et al. Bull Soc Pathol Exot 2002
Nunes H et al. AJRCCM 2003

Classification des hypertensions pulmonaires

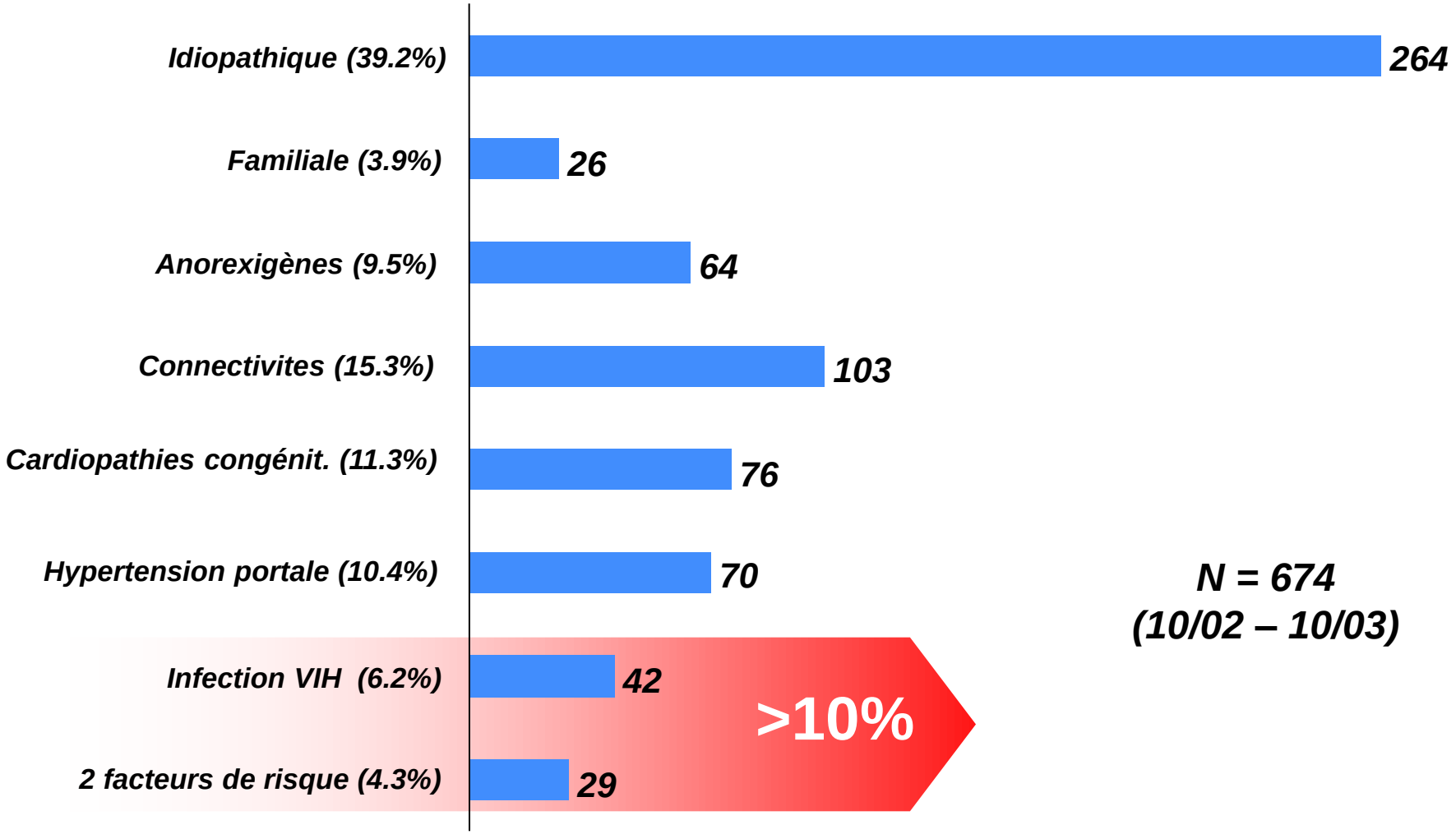
1 Hypertension artérielle pulmonaire (HTAP)

1.1 Idiopathique (HTAPi)
1.2 Héréditaire
- 1.2.1 Associée à une mutation BMPR2
- 1.2.2 Associée à une mutation ALK1, endogline
- 1.2.3 Inconnue.

1.3 Induite par des drogues ou des médicaments
1.4 Associée à:
- 1.4.1 Connectivite (sclérodermie, CREST, etc.)
- 1.4.2 Infection par le VIH
- 1.4.3 Hypertension portale
- 1.4.4 Cardiopathie congénitale
- 1.4.5 Schistosomiase
- 1.4.6 Anémie hémolytique chronique (Thalassémie, Drépanocytose)

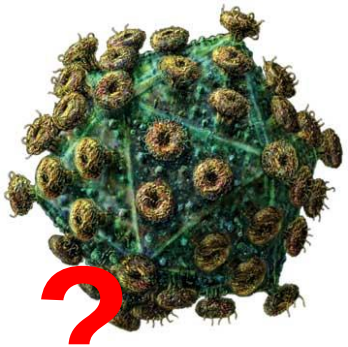
1.5 Hypertension pulmonaire persistante du nouveau-né

Type d'HTAP au diagnostic: registre national français



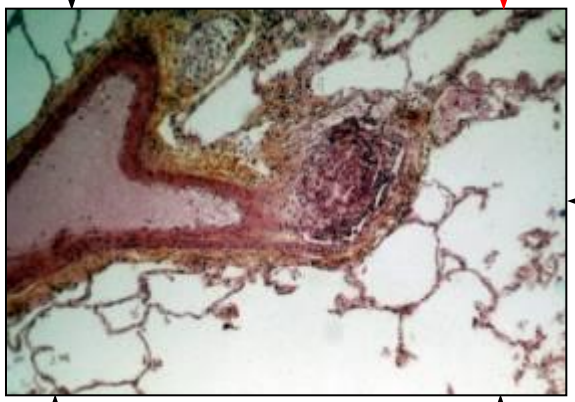
Humbert M, Sitbon O, Chaouat A, et al. AJRCCM 2006

Physiopathologie



Prédisposition génétique?

Toxiques (amphetamines, cocaine, corps étrangers)



Mediateurs (cytokines, facteurs de croissance, protéines virales)

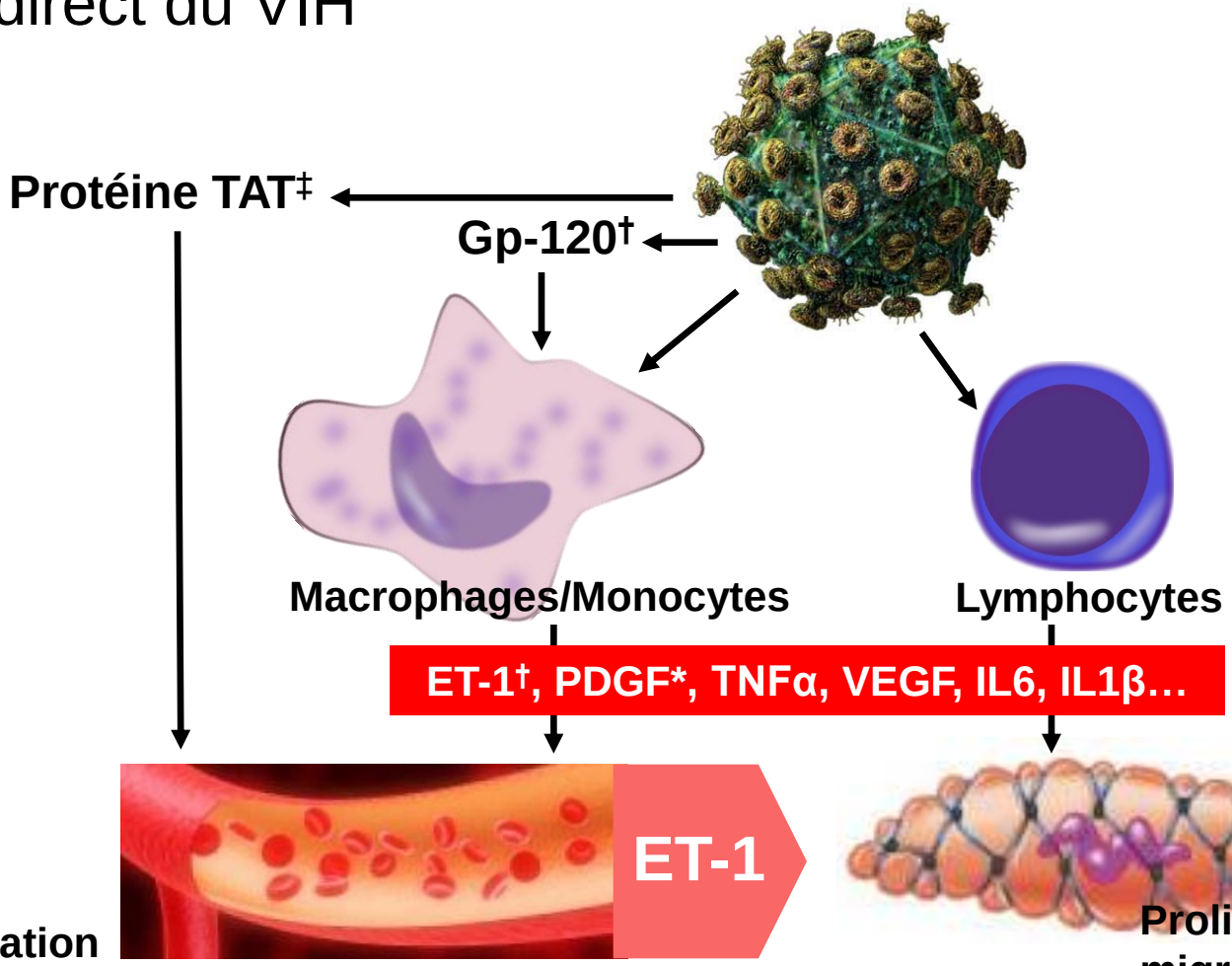
HTP

HHV8

Humbert M et al. ERJ 1998
Mehta NJ et al. Chest 2000

Montani D et al. AIDS 2005
Nunes H et al. AJRCCM 2003

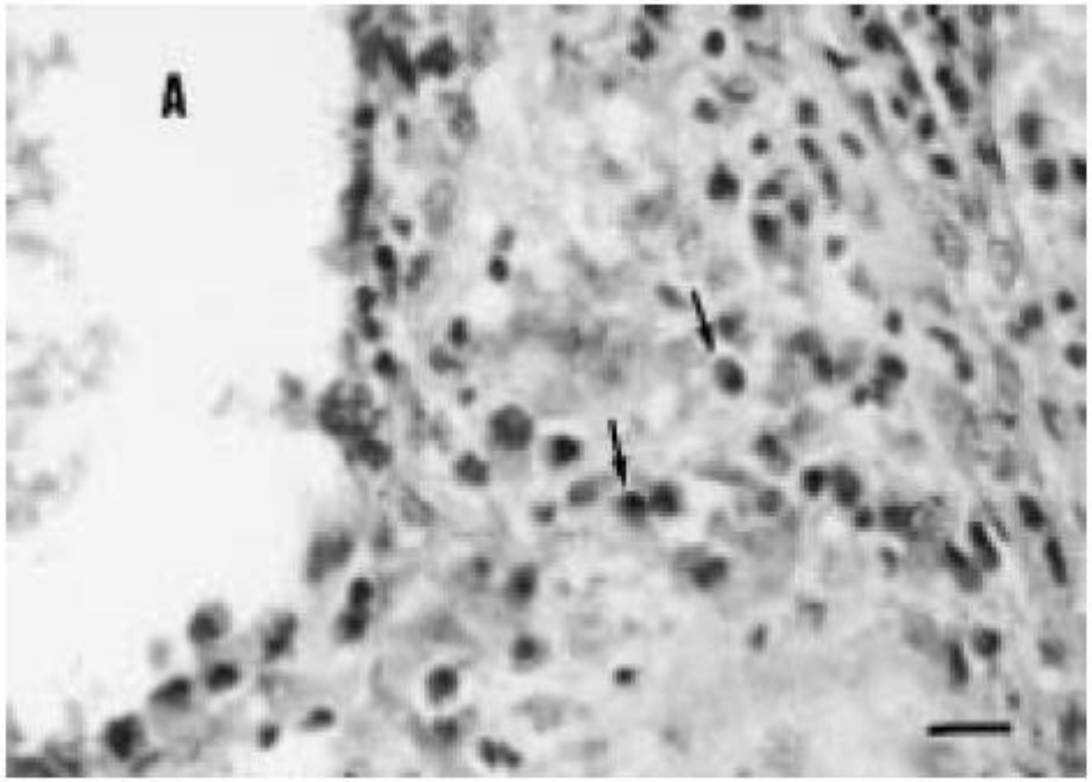
Le rôle indirect du VIH



‡ *Ensoli et al. Nature 1990*
‡ *Hofman et al. Blood 1993*

† *Ehrenreich et al. J Immunol 1993*
* *Humbert et al. Eur Respir J 1998*

Histopathologie



Humbert et al. ERJ 1998

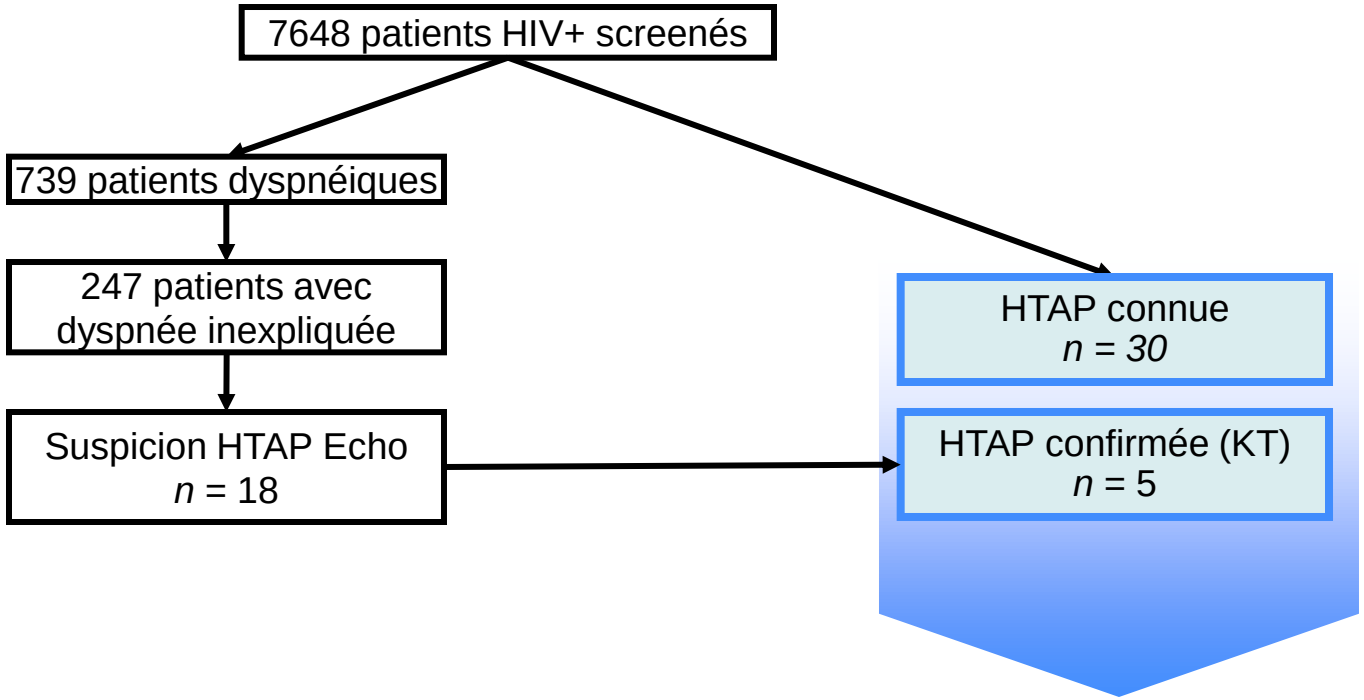
Prévalence de l'HTAP-VIH avant HAART

~ 0,5 % [IC-95% 0,10 – 0,90 %]

Réf/Année	*Pays*	*Etude*	*Patients VIH+*	*Patients HTAP-VIH*	*Prevalence*
1/1989	*USA*	*Retrospective*	*1,200*	*6*	*0.50 %*
2/1991	*Suisse*	*Prospective*	*1,200*	*6*	*0.50 %*
3/1997	*Suisse*	*Retrospective*	*3,349*	*19*	*0.57 %*

1. *Himelman RB, et al. Am J Cardiol 1989*
2. *Speich R, et al. Chest 1991*
3. *Opravil M, et al. AJRCCM 1997*

Prévalence de l'HTAP-VIH après HAART



Prévalence HTAP

30+5 / 7648 = **0,46 %**

[IC 95% : 0.32 – 0.64%]

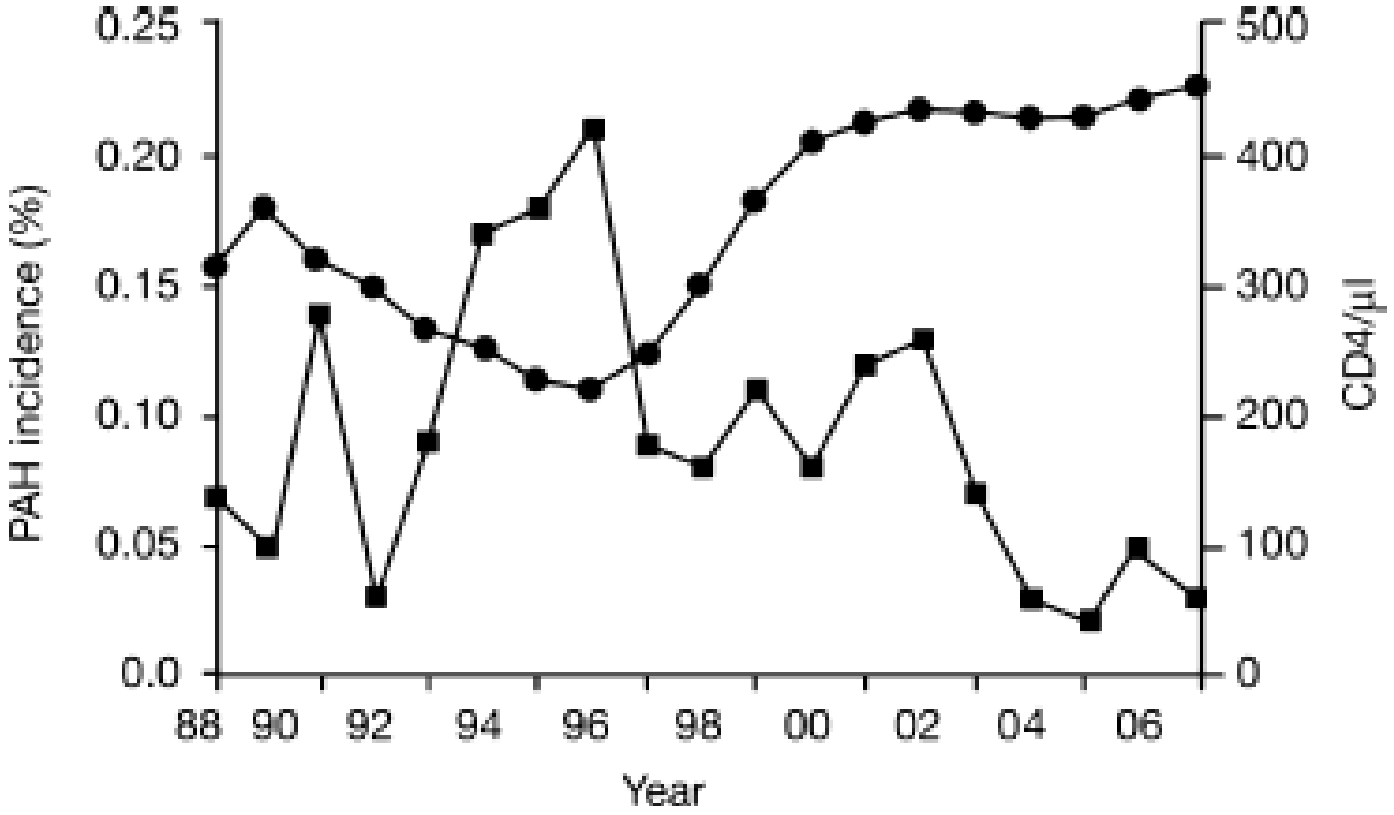
Sitbon O, et al. AJRCCM 2008.

Hémodynamiques

	HTAP connue n = 30	Nouveau Dx n = 5
mPAP (mmHg)	46 ± 13	30 ± 9
PCWP (mmHg)	7 ± 3	8 ± 4
PVR (Wood units)	9.6 ± 4.4	3.9 ± 2.7
Cardiac index (L/min/m^2)	3.0 ± 0.8	3.7 ± 0.8

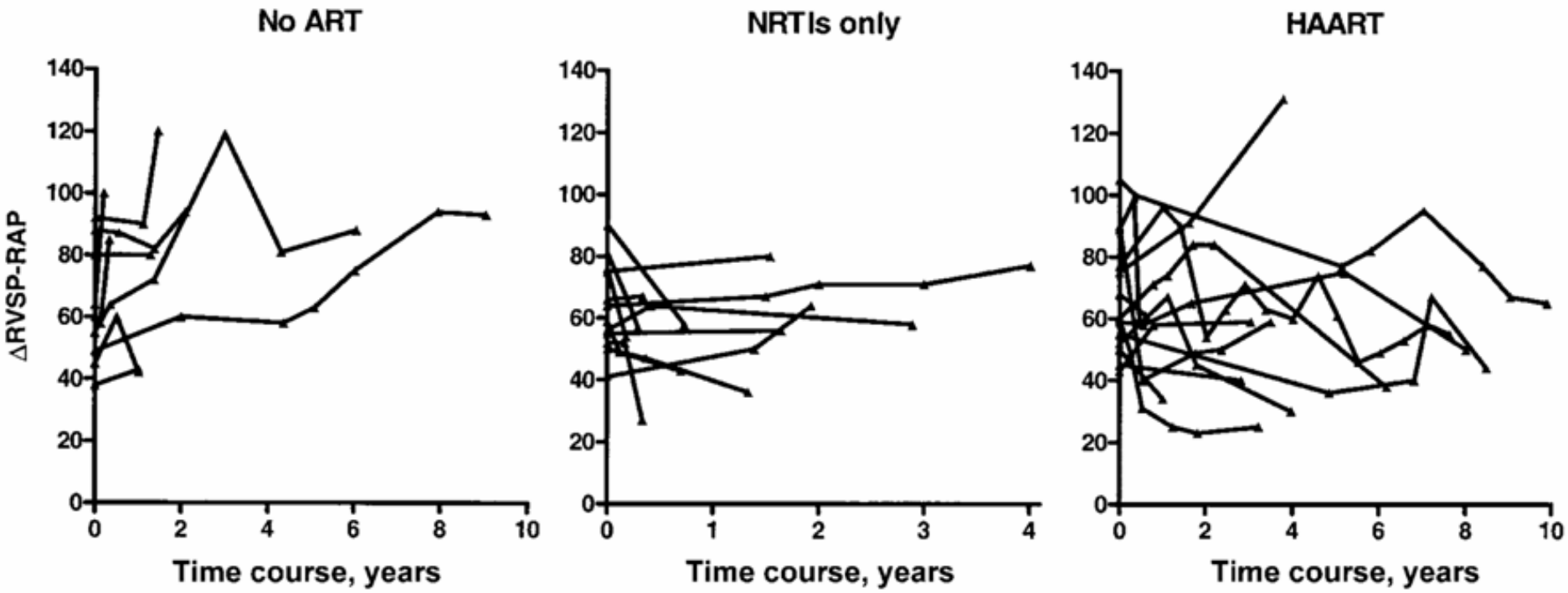
Sitbon O, et al. AJRCCM 2008.

Evolution de l'incidence de HTAP-VIH



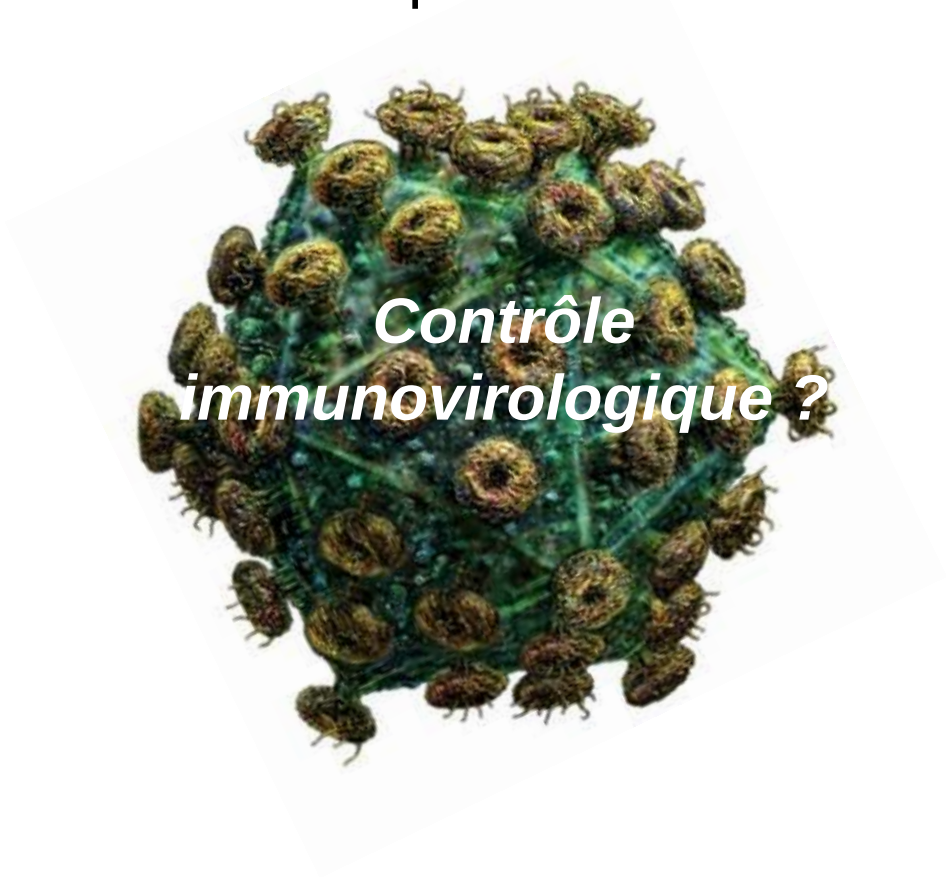
Opravil et al. AIDS 2008

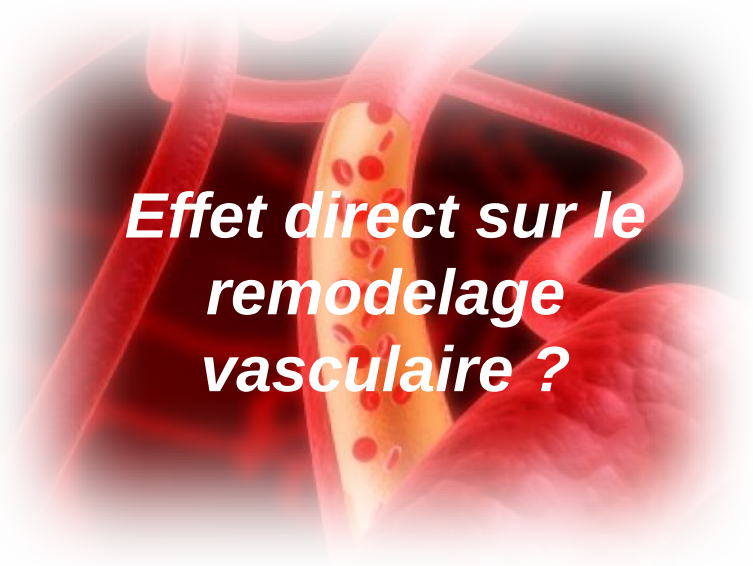
Efficacité des traitements antirétroviraux



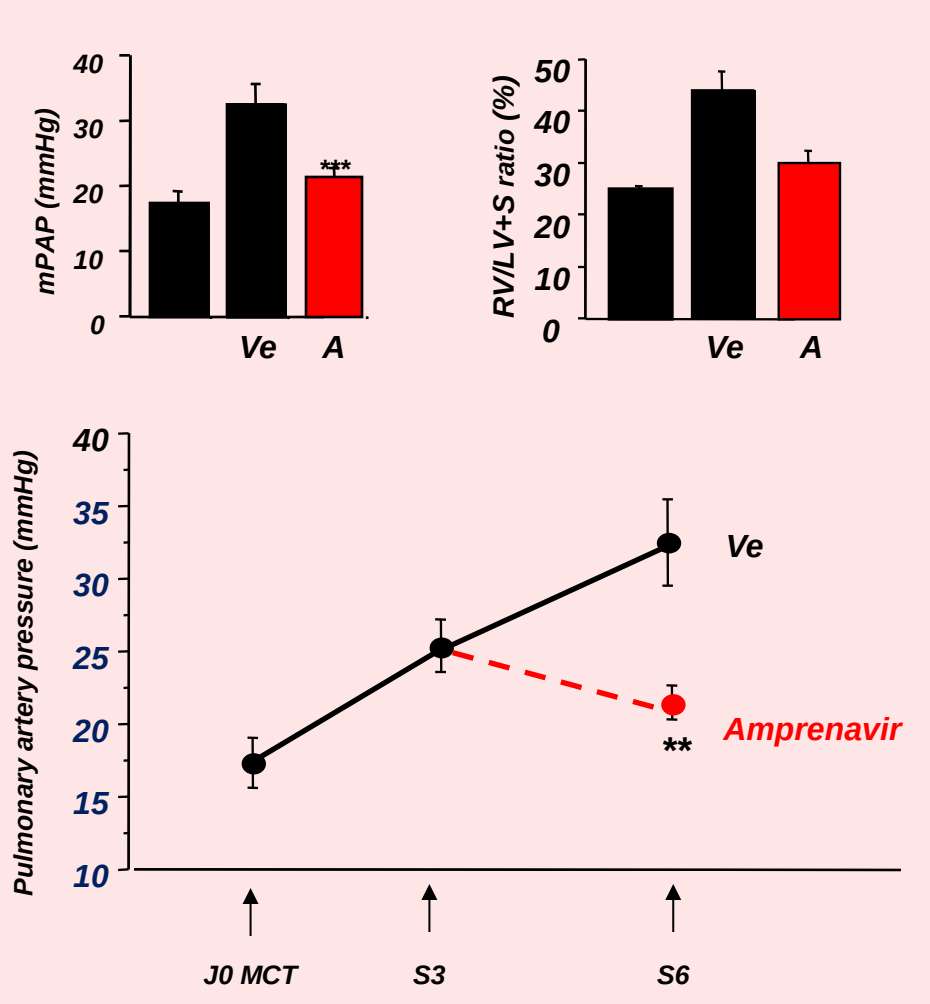
Zuber JP et al. Clinical Infectious Diseases 2004

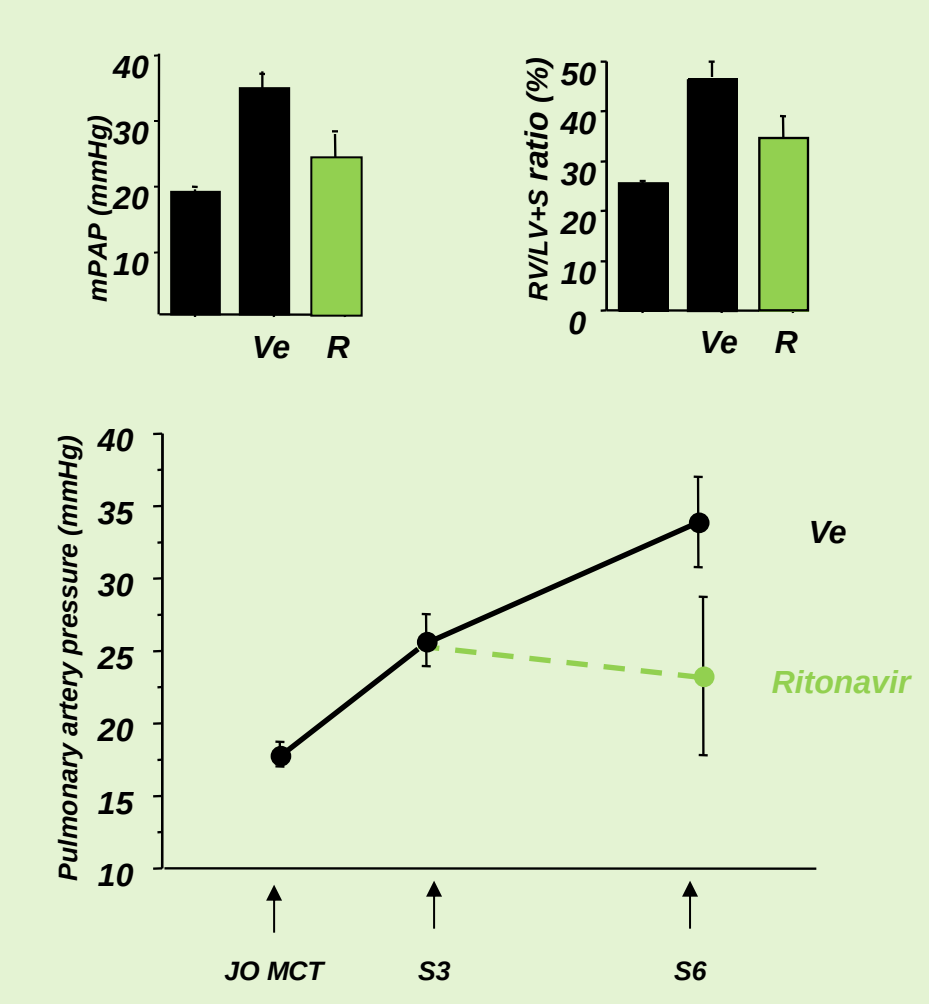
Effet des antiprotéases du VIH sur l'HTAP





Effet curatif de l'amprenavir et du ritonavir sur le développement de l'HTAP induite par MCT chez le rat.



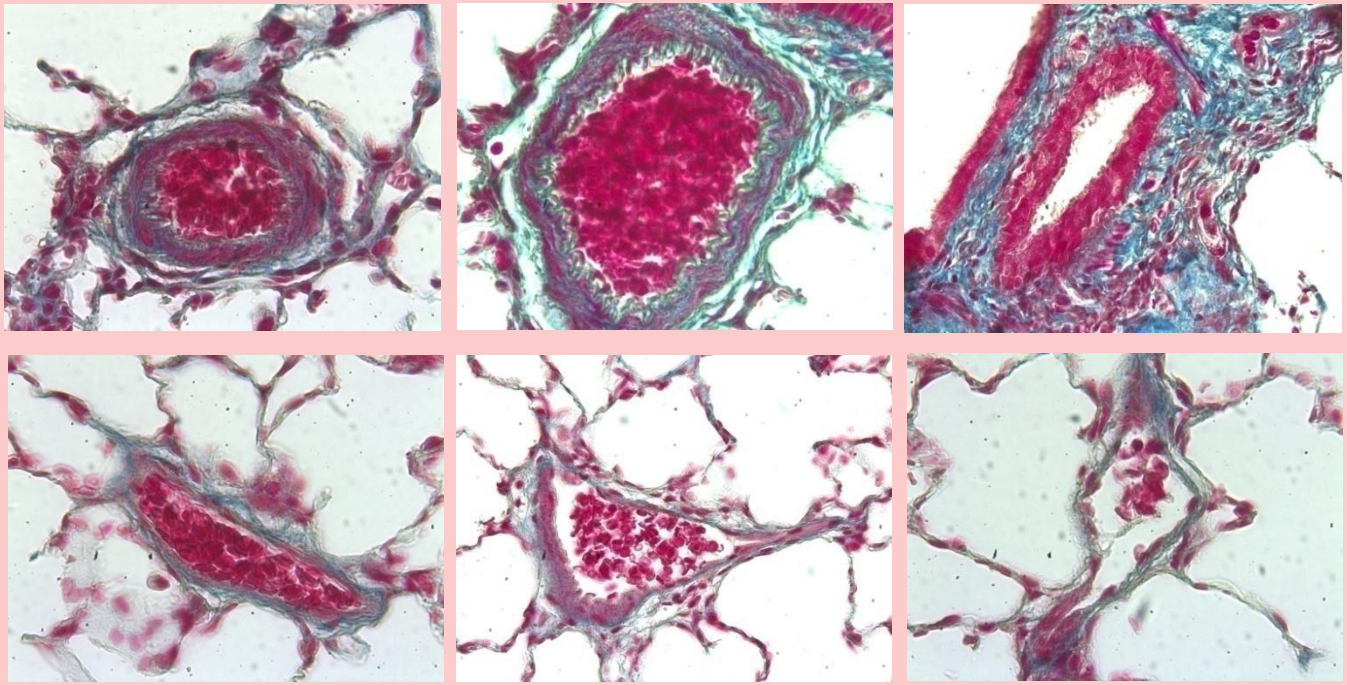


L. Savale, O. Sitbon, S. Adnot. INSERM U651. Faculté de Médecine de Créteil. ERS 2009

Effet sur le remodelage vasculaire

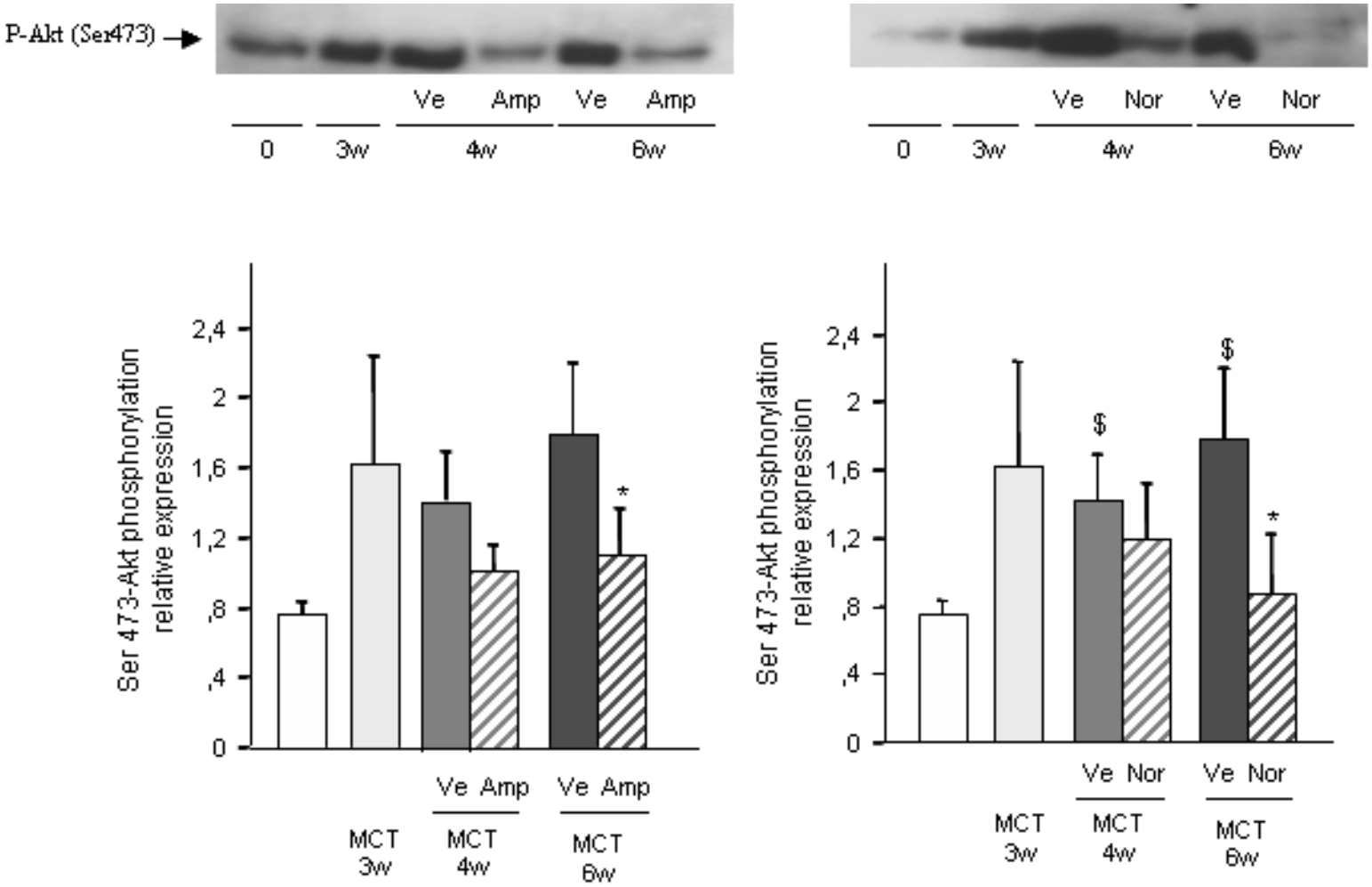
Ve

Amprenavir

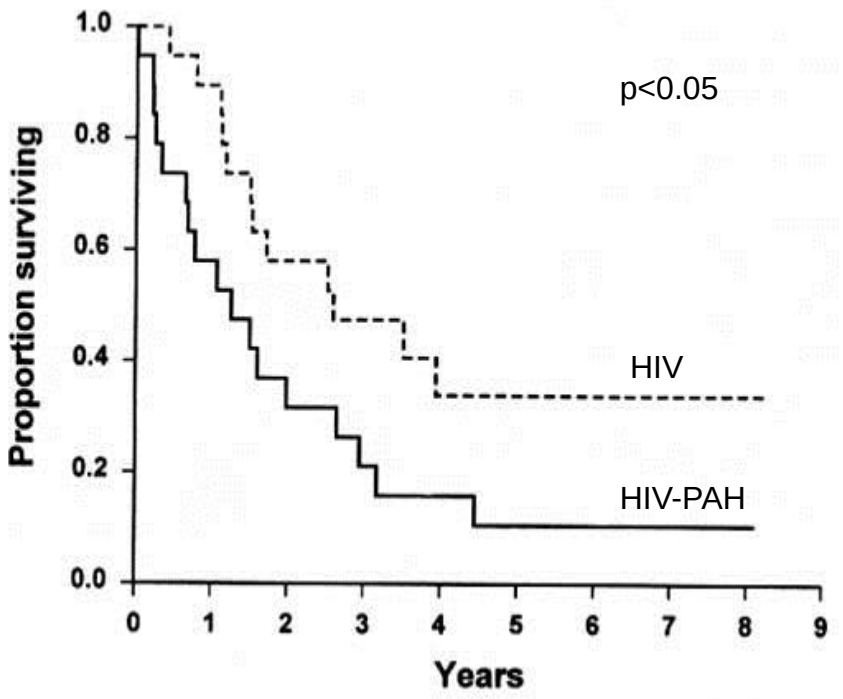


L. Savale, O. Sitbon, S. Adnot. INSERM U651. Faculté de Médecine de Créteil. ERS 2009

Inhibition de la phosphorylation de Akt



Pronostic



Série de 82 patients HTAP-VIH

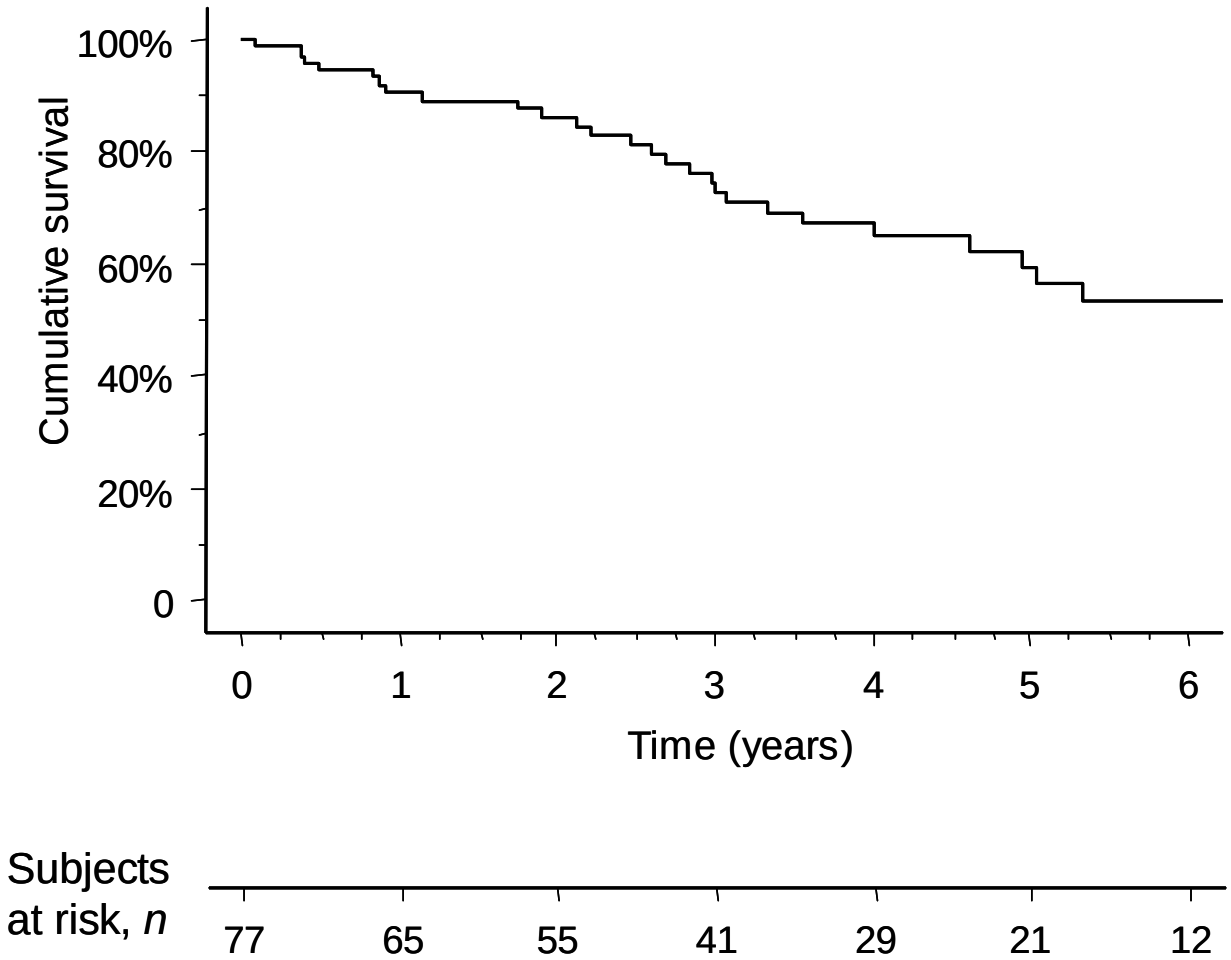
	All	Class I - II	Class III – IV
1 y	73 %	100 %	60 %
2 y	60 %	90 %	45 %
3 y	47 %	84 %	28 %

HTAP responsable du décès dans 72 % des cas

HTAP = FDR indépendant de mortalité au cours de l'infection par le VIH

Nunes H, et al. AJRCCM 2003
Opravil M, et al. AJRCCM 1997

Pronostic



Degano B, et al. AIDS 2010

Facteurs pronostiques

Prognostic Factors for Survival in Human Immunodeficiency Virus–associated Pulmonary Arterial Hypertension

Hilario Nunes, Marc Humbert, Olivier Sitbon, Jane H. Morse, Zemin Deng, James A. Knowles, Catherine Le Gall, Florence Parent, Gilles Garcia, Philippe Hervé, Robyn J. Barst, and Gérald Simonneau

UPRES 2705, Centre des Maladies Vasculaires Pulmonaires, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, Assistance Publique-Hôpitaux de Paris, Université Paris-Sud, Clamart, France; and the Departments of Medicine, Pediatrics, and Psychiatry, Columbia University College of Physicians and Surgeons, The New York State Psychiatric Institute, New York, New York

Série 82 patients de 1986 à 2000 (48 % HAART)

Nunes H, et al. AJRCCM 2003

Facteurs pronostiques

Variables	Hazard Ratio (*95% Confidence Interval*)	p Value
Age < 34	1.219 (0.619–2.399)	0.57
Sex, women/men	1.296 (0.654–2.568)	0.46
IV drug use, yes/no	0.678 (0.345–1.332)	0.26
CD4 count > 212 cells mm^{-3}	0.339 (0.154–0.743)	0.007
Viral load > 3.1 log	0.811 (0.202–3.268)	0.77
Six-minute walk test < 327 m	0.993 (0.341–2.896)	0.99
Baseline hemodynamic measures		
mRAP > 10 mm Hg	0.824 (0.418–1.623)	0.58
$\overline{Ppa}$ > 50 mm Hg	0.545 (0.272–1.089)	0.09
CI < 2.3 L $minute^{-1}$ m^{-2}	0.902 (0.453–1.798)	0.77
PVRI > 19 IU m^{-2}	0.517 (0.256–1.043)	0.07
Sv_{O_2} < 59%	1.192 (0.571–2.487)	0.64
Warfarine, yes/no	0.662 (0.305–1.435)	0.30
CART, yes/no	0.470 (0.223–0.989)	0.047
Epoprostenol infusion, yes/no	0.365 (0.158–0.844)	0.019

Nunes H, et al. AJRCCM 2003

Facteurs pronostiques

HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era

Bruno Degano[a], Mathilde Guillaume[b], Laurent Savale[a], David Montani[a], Xavier Jaïs[a], Azzedine Yaici[a], Jérôme Le Pavec[a], Marc Humbert[a], Gérald Simonneau[a] and Olivier Sitbon[a]

Série 77 patients 2000-2008 (81 % HAART au diagnostic HTAP, 100 % HAART au cours du suivi)

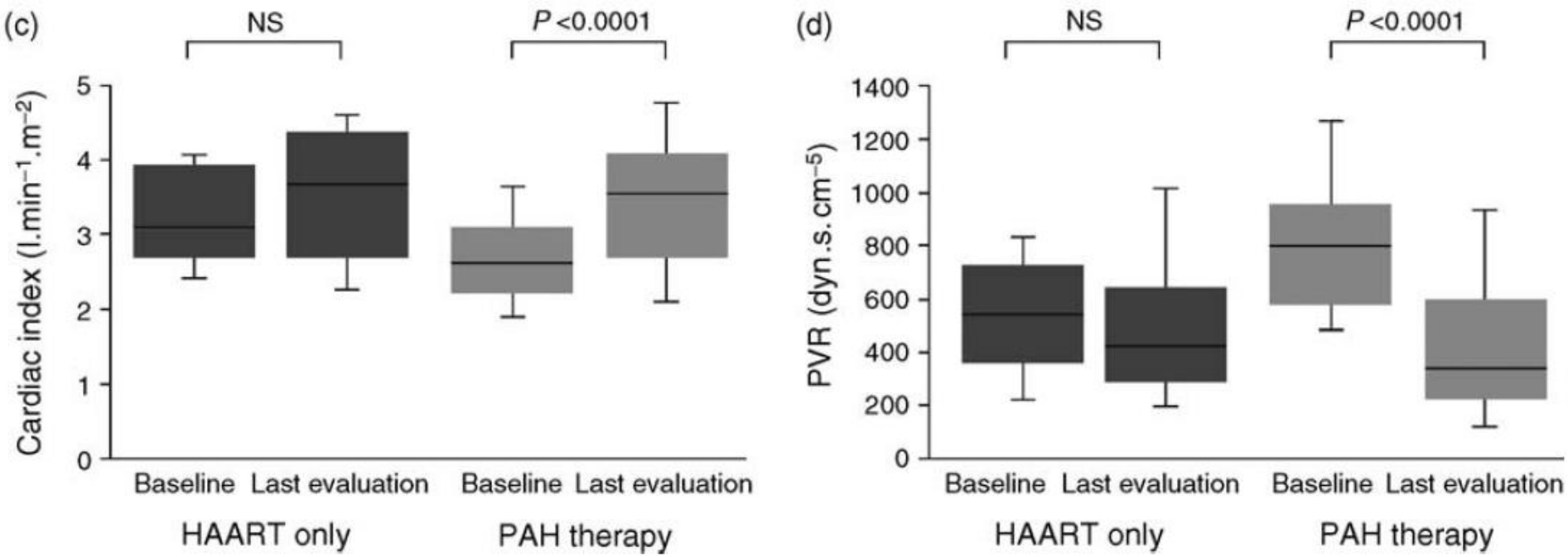
Degano B, et al. AIDS 2010

Facteurs pronostiques

Variable[a]	Hazard ratio (95% CI)[b]	*P*
Age > 41 years	1.02 (0.97–1.07)	0.45
Gender, women	1.07 (0.47–2.42)	0.88
History of right heart failure	2.77 (1.22–6.28)	0.01
Coinfection with HBV or HCV	1.28 (0.58–2.82)	0.53
HIV infection via intravenous drug use	1.20 (0.54–2.64)	0.66
NYHA FC IV	3.41 (1.16–10.06)	0.03
6MWD < 370 m	1.79 (0.79–4.05)	0.16
Detectable HIV viral load	2.44 (1.06–5.56)	0.04
$CD4^+$ lymphocyte count <200 cells/μl	3.13 (1.39–7.14)	0.006
No HAART regimen	1.41 (0.53–3.85)	0.49
mRAP > 6 mmHg	1.20 (0.54–2.68)	0.65
mPAP > 47 mmHg	1.49 (0.67–3.33)	0.33
Cardiac index < 2.8 l/min per m^2	2.65 (1.12–5.94)	0.02
PVR > 693 dyn s/cm^5	1.76 (0.73–4.26)	0.21

Degano B, et al. AIDS 2010

Effet de HAART sur HTAP-VIH

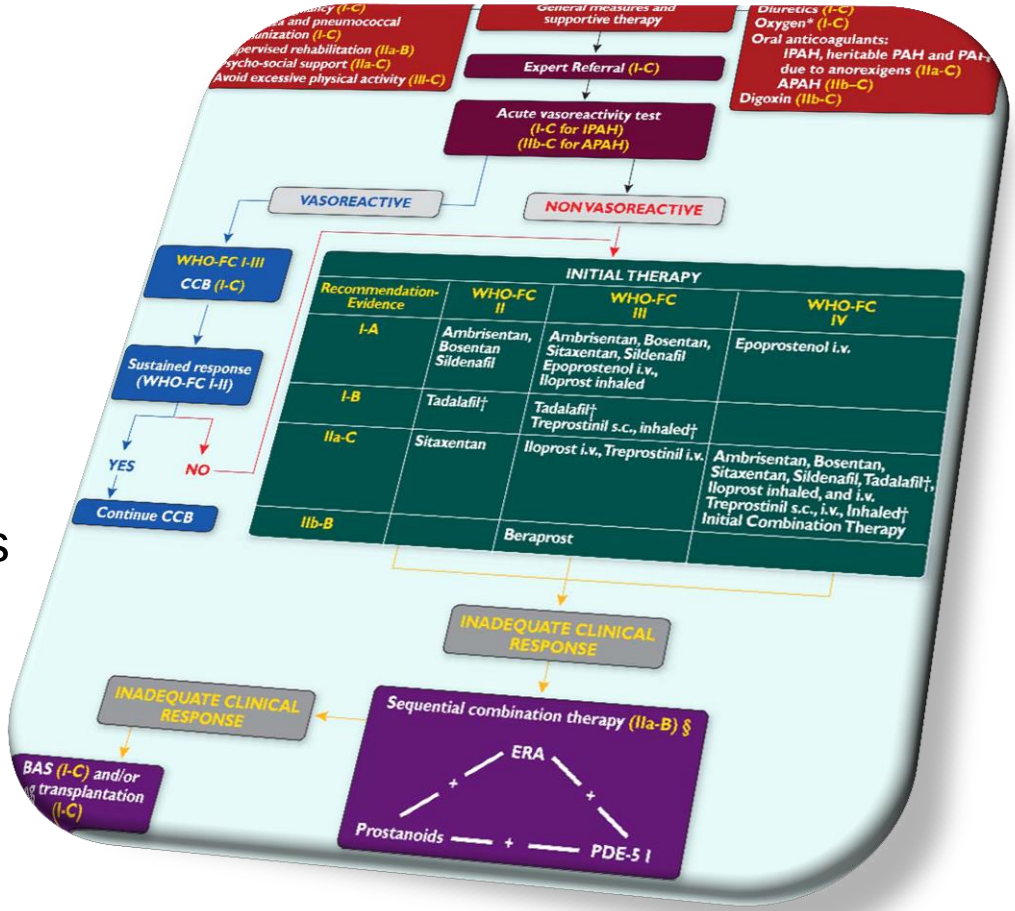


Degano B, et al. AIDS 2010

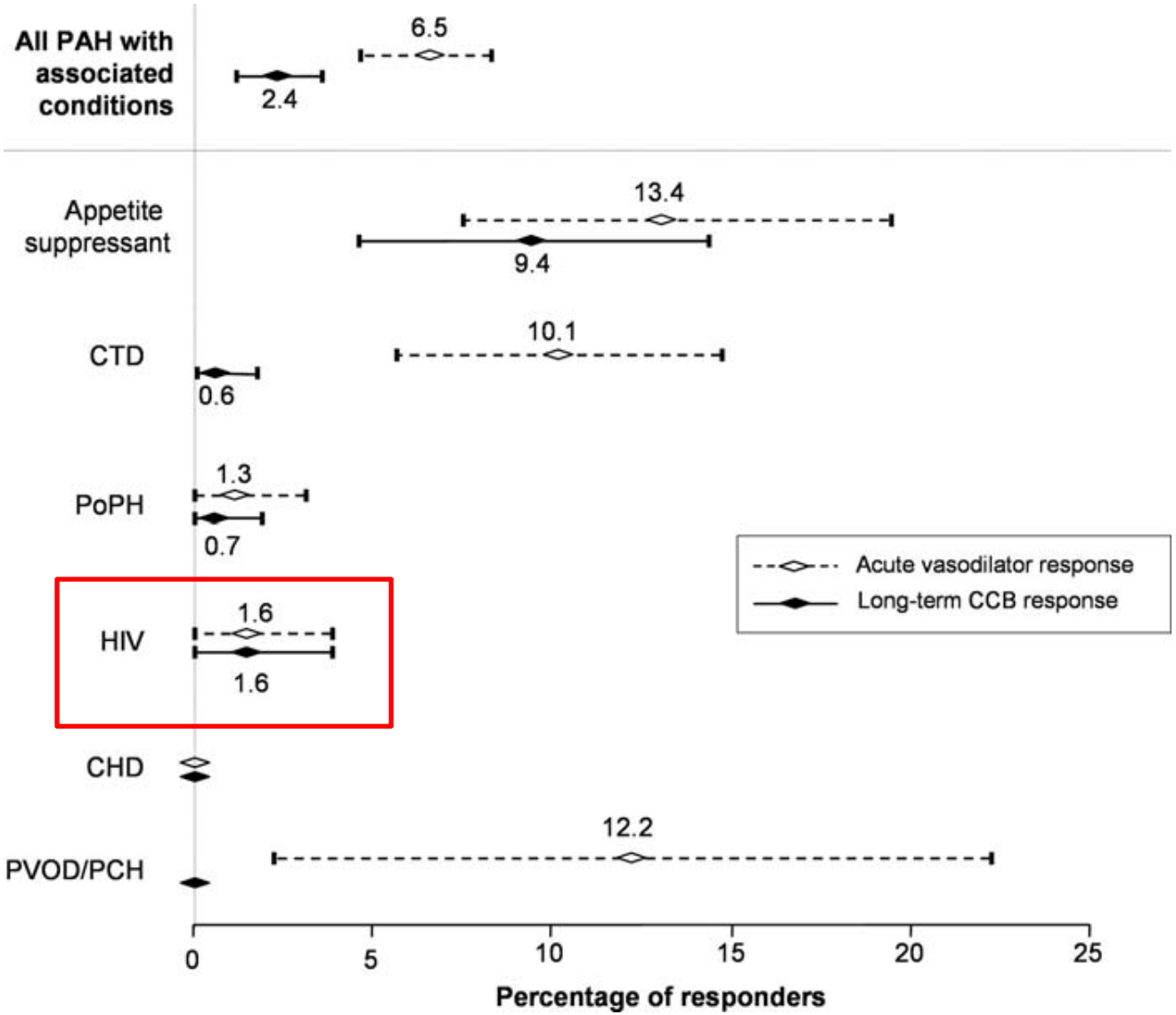
Thérapies conventionnelles

ESC/ERS Guidelines 2009

- Identique autres HTAP
- CAVE anticoagulation
- Interactions médicamenteuses



Réversibilité



Montani D et al. EHJ 2010

Epoprostenol

n = 12	Baseline	3 mois	long terme moy. 17 mois
6MWT (m)	213 ± 95	434 ± 86 *	456 ± 109 *
mPAP (mmHg)	55 ± 9	46 ± 10 *	45 ± 9 *
CI (L/min/m^2)	1.9 ± 0.4	2.5 ± 0.6 *	3.1 ± 1.0 *
PVR (Unités/m^2)	25 ± 6	16 ± 6 *	14 ± 6 *

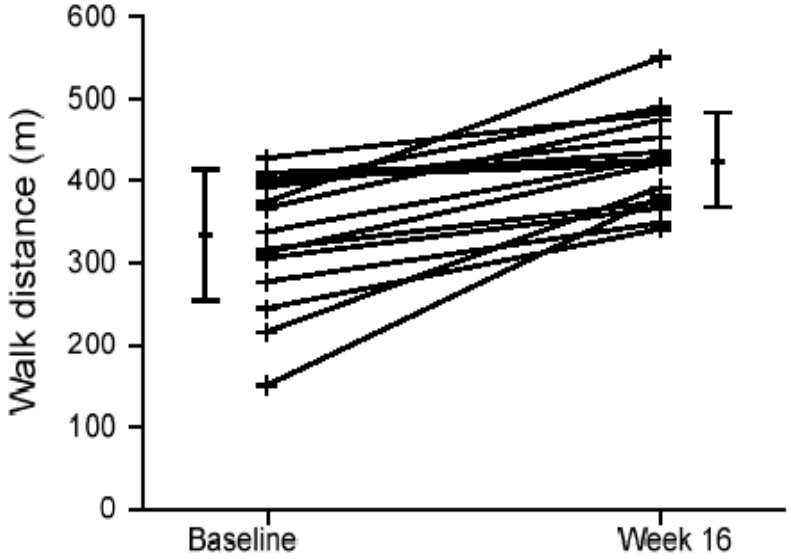
* $p < 0.05$ vs baseline

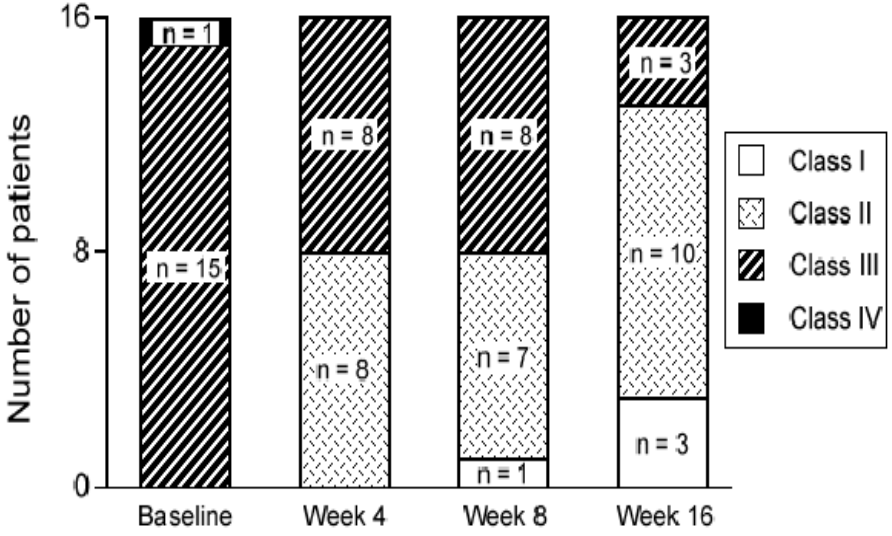
Dose of epoprostenol : 22 ± 9 ng/kg/min [10-40]

Nunes H, et al. AJRCCM 2003

Bosentan

- 16 patients, NYHA III-IV
- CDC stage : A (25%), B (25%), C (50%)
- HCV or HBV infection : n = 4
- HAART : 15 (94%)
- CD4 lymphocyte count (cells/mm3) : 333 (91–1’186)





Sitbon O, et al. AJRCCM 2004

Bosentan

	Baseline	Wk 16	Δ from baseline	p value
CI (L/min/m^2)	2.6 ± 0.7	3.4 ± 0.9	0.9 ± 0.7	< 0.001
PVR (dyn•sec/cm^5)	781 ± 250	442 ± 246	– 339 ± 209	< 0.001
mPAP (mmHg)	52 ± 13	41 ± 14	– 11 ± 12	0.002
PWP (mmHg)	7.2 ± 2.5	7.7 ± 2.6	0.5 ± 3.5	0.59
RAP (mmHg)	10.8 ± 7.5	7.6 ± 4.4	– 3.2 ± 7.5	0.11

Sitbon O, et al. AJRCCM 2004

Bosentan

N = 38	Baseline	4-month	29 ± 15 mo. [12-67]
NYHA FC I : II : III : IV (n)	0 : 2 : 34 : 2	6 : 25 : 7 : 0*	11 : 18 : 9 : 0*
6-min walk distance (m)	357 ± 80	424 ± 82*	449 ± 91*
mRAP (mmHg)	9 ± 5	6 ± 3*	6 ± 4*
mPAP (mmHg)	50 ± 10	40 ± 13*	37 ± 15* #
Cardiac index ($L.min^{-1}.m^2$)	2.8 ± 0.6	3.5 ± 0.7*	3.6 ± 0.9*
PVR ($dyn.s.cm^{-5}$)	769 ± 355	470 ± 285*	444 ± 356* #
SvO_2 (%)	59 ± 9	66 ± 7*	65 ± 8*

* $p<0.05$ vs baseline; # $p<0.05$ vs 4-month

Degano B, et al. ERJ 2009

Bosentan

n = 10	Baseline	32 ± 22 mo.
NYHA I : II : III : IV (n)	0 : 3 : 5 : 2	All in class I*
6MWD (m)	375 ± 102	532 ± 52*
mPAP (mmHg)	51 ± 10	19 ± 4*
CI ($L.min^{-1}.m^{-2}$)	3.3 ± 0.7	4.1 ± 0.8*
PVR ($dyn.s.cm^{-5}$)	713 ± 314	159 ± 76*
CD4+ (cells.mL)	304 ± 111	539 ± 180*

* $p<0.05$ vs baseline

Degano B, et al. ERJ 2009

Transplantation

International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update—A Consensus Report From the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation

Jonathan B. Orens, MD,[a] Marc Estenne, MD,[b] Selim Arcasoy, MD,[c] John V. Conte, MD,[a] Paul Corris, MD,[d] Jim J. Egan, MD,[e] Thomas Egan, MD,[f] Shaf Keshavjee, MD,[g] Christiane Knoop, MD,[b] Robert Kotloff, MD,[h] Fernando J. Martinez, MD,[i] Steven Nathan, MD,[j] Scott Palmer, MD,[k] Alec Patterson, MD,[l] Lianne Singer, MD,[g] Gregory Snell, MD,[m] Sean Studer, MD,[n] J. L. Vachiery, MD,[b] and Allan R. Glanville, MD[o]

Absolute contraindications.

Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus.

allocate the organs (e.g., time waited vs disease severity) and therefore cannot be based on broad guidelines. In general, this decision resides with the expertise and practice of individual transplant centers and will vary from country to country.

This document does not address specific selection criteria for recipients of living-donor lung transplants, for pediatric recipients (younger than 18 years), and for recipients of a second transplant. There are no data to support changes in the guidelines for pediatric transplantation (about 60 procedures per year)[3] from the guidelines that were proposed in 1998. Similarly, few new data have been published regarding the selection of appropriate candidates for retransplantation. In light of the severely limited pool of donor organs, efforts should be made to limit retransplantation to those individuals with the highest likelihood of successful outcome. In this regard, retransplantation should be considered largely for patients with advanced and progressive bronchiolitis obliterans syndrome (chronic rejection) who are ambulatory, ventilator-independent, and free of significant comorbidities that might compromise their general suitability as a transplant candidate.

PATIENT SELECTION

1. Indications

Lung transplantation is indicated for patients with chronic, end-stage lung disease who are failing maximal medical therapy, or for whom no effective medical therapy exists. Potential candidates should be well informed and demonstrate adequate health behavior and a willingness to adhere to guidelines from health care professionals.

The primary goal of lung transplantation is to provide a survival benefit. Several studies have demonstrated that lung transplantation confers such benefit, particularly in patients with advanced cystic fibrosis, idiopathic pulmonary fibrosis, and primary pulmonary hypertension.[4-7] Reports for emphysema patients are conflicted,[8] and 2 studies including patients with Eisenmenger's syndrome did not find a survival benefit.[4,5] Uncertainties regarding the methodology and the validity of several assumptions used in the analysis together with improved post-transplant survival rates over time affect conclusions drawn from these studies.

How to weigh expected survival benefit with gains in quality of life is a topic of considerable discussion in the transplant community. Lung transplantation for most patients is a palliative rather than curative treatment, and improvements in quality of life in addition to survival should be used to assess the effectiveness of the procedure,[9,10] a view shared by patients themselves.[11] Thus, the patient's quality of life should be taken into account when the need for a lung transplant is assessed, but owing to the shortage of donor organs, it is not currently possible to support transplantation solely for quality of life purposes.

2. General Contraindications

Lung transplantation remains a complex therapy with a significant risk of perioperative morbidity and mortality; therefore, it is important to consider the overall sum of contraindications and comorbidities. The following lists are not intended to include all possible clinical scenarios, but rather to highlight common areas of concern.

Absolute contraindications.

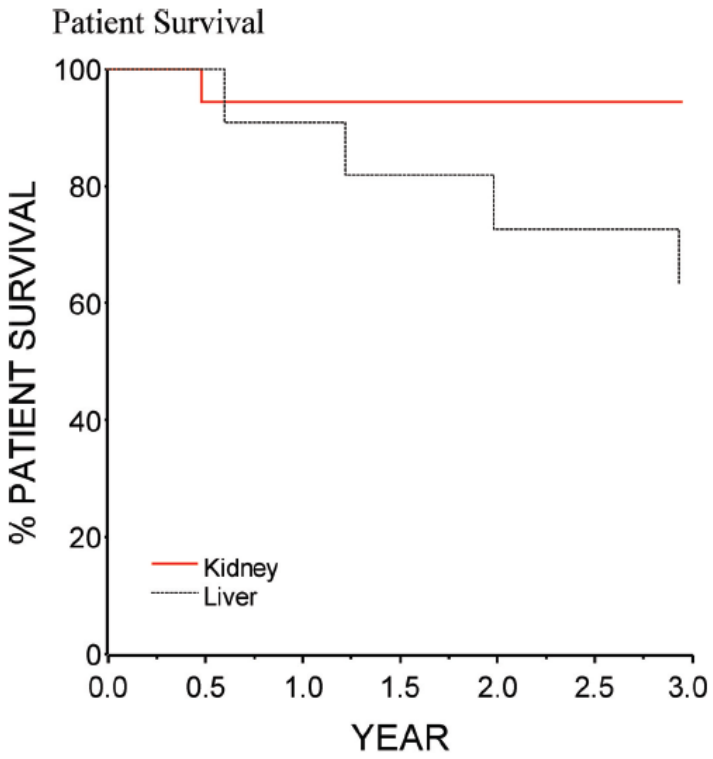
- Malignancy in the last 2 years, with the exception of cutaneous squamous and basal cell tumors. In general, a 5-year disease-free interval is prudent. The role of lung transplantation for localized bronchioalveolar cell carcinoma remains controversial.
- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney). Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in highly selected cases.
- Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus.
- Significant chest wall/spinal deformity.
- Documented nonadherence or inability to follow through with medical therapy or office follow-up, or both.
- Untreatable psychiatric or psychologic condition associated with the inability to cooperate or comply with medical therapy.
- Absence of a consistent or reliable social support system.
- Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months.

Relative contraindications.

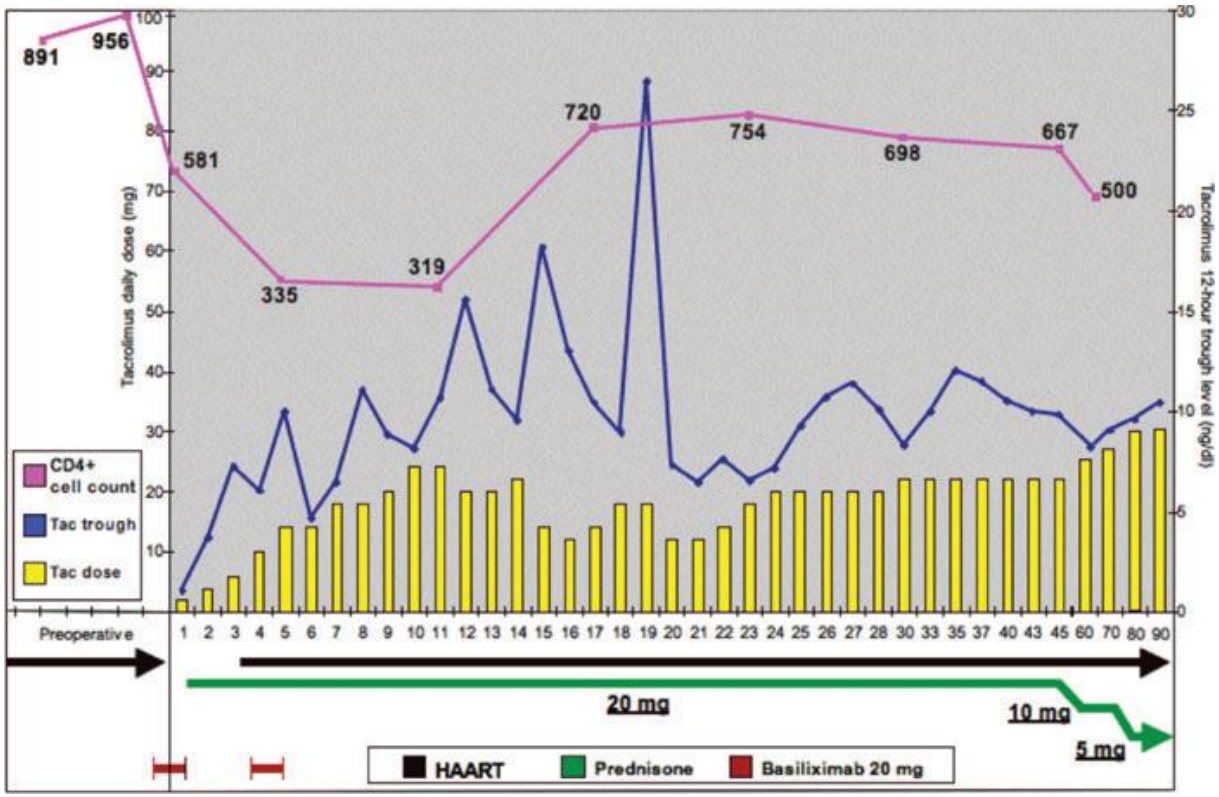
- Age older than 65 years. Older patients have less optimal survival,[2] likely due to comorbidities, and therefore, recipient age should be a factor in candidate selection. Although there cannot be endorsement of an upper age limit as an absolute contraindication (recognizing that advancing age alone in an otherwise acceptable candidate with few comorbidities does not necessarily compromise successful transplant outcomes), the presence of several relative contraindications can combine to increase the risks of transplantation above a safe threshold.

Orens JB et al. JHLT 2006

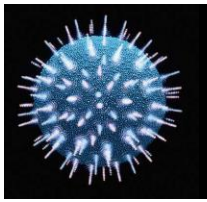
Transplantation



Roland ME et al. Am J Transplant 2008
Blumberg EA and Stock P, Am J Transplant 2009



Bertani A et al. Am J Transplant 2009



Conclusions

- HTAP est une complication rare mais grave de l'infection par le VIH
- Absence de corrélation entre le stade de l'infection VIH ou le degré d'immunodépression et la prévalence ou la sévérité de l'HTAP
- La multithérapie anti-rétrovirale est recommandée
- Traitements spécifiques de l'HTAP semblent particulièrement efficaces
- Les autres traitements spécifiques doivent encore être évalués (analogues stables de la prostacycline, inhibiteurs de PDE5, antagonistes sélectifs des récepteurs A de l'ET1)
- Transplantation pulmonaire?