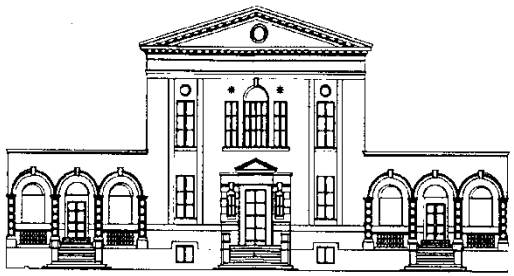
Pulmonary Hypertension secondary to HIV

Nicola Petrosillo MD

National Institute for Infectious Diseases
"Lazzaro Spallanzani" – Rome, Italy



Mortality in the Highly Active Antiretroviral Therapy Era

Changing Causes of Death and Disease in the HIV Outpatient Study

Frank J. Palella, Jr., MD, Rose K. Baker, MA,† Anne C. Moorman, BSN, MPH,‡ Joan S. Chmiel, PhD,* Kathleen C. Wood, BSN,† John T. Brooks, MD,‡ Scott D. Holmberg, MD, MPH,‡ and HIV Outpatient Study Investigators*

J Acquir Immune Defic Syndr • Volume 43, Number 1, September 2006

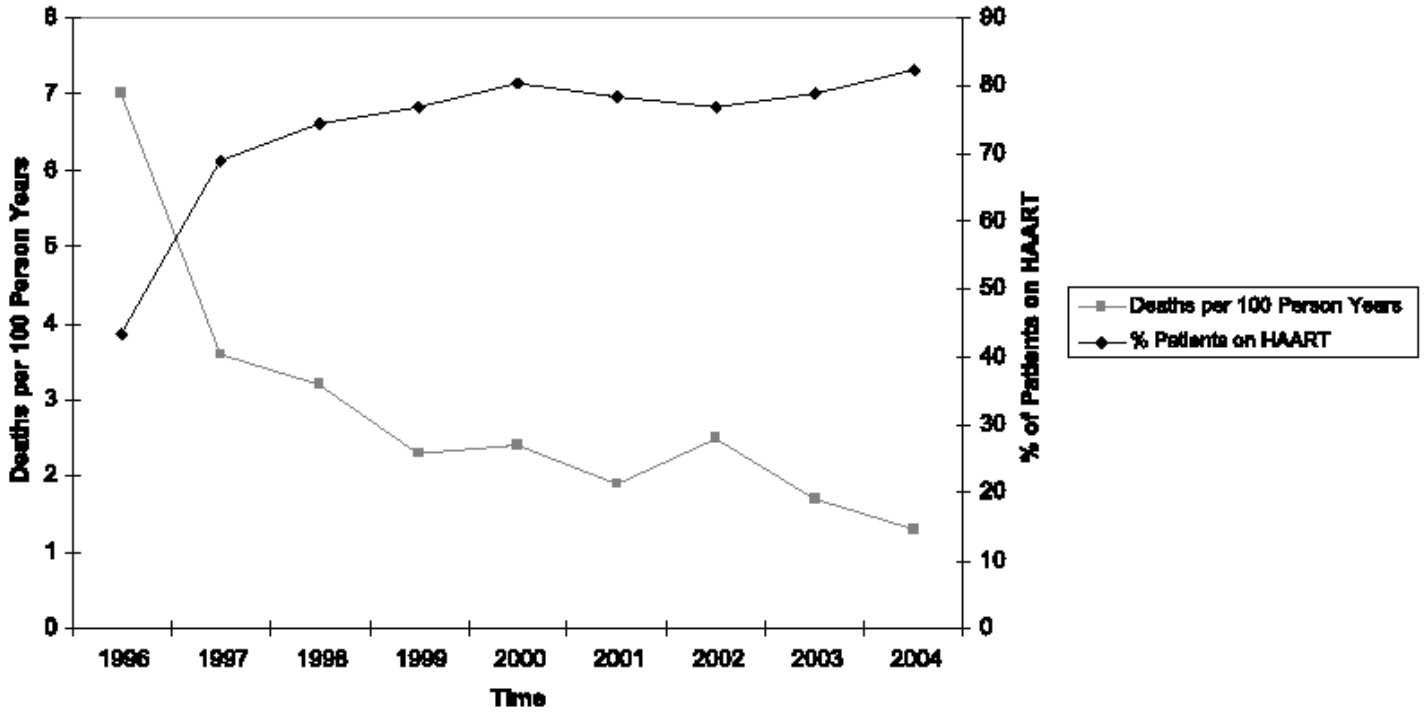


FIGURE 1. Mortality and HAART use over time.

Challenges for the Future

Although antiviral treatment regimens have dramatically reduced the mortality rates there remain many obstacles to successful management of an HIV patient:

- Lack of adherence
- Drug absorption
- Drug metabolism
- Drug toxicity
- Narrow therapeutic ranges
- Resistance

The emergence of chronic diseases

Table 2. Cardiac diseases in HIV-infected patients

Pericardial diseases

- Pericardial effusion
- Pericarditis (viral, bacterial, mycotic)
- Neoplasm (Kaposi's sarcoma, lymphoma)

Myocardial diseases

- HIV-associated dilated cardiomyopathy
- Myocarditis (acute or chronic)
- Neoplasm (Kaposi's sarcoma, lymphoma)
- Drug side-effects (especially by antiretroviral therapy)

Endocardial diseases

- Infective endocarditis (bacterial, mycotic)
- Nonbacterial thrombotic endocarditis

Vascular diseases

- Arteriosclerosis
- Vasculitis, perivasculitis
- Pulmonary artery hypertension

A clinical case

- **46 y-o female; HIV+ 2000**

- **Ex IVDU, on methadone**

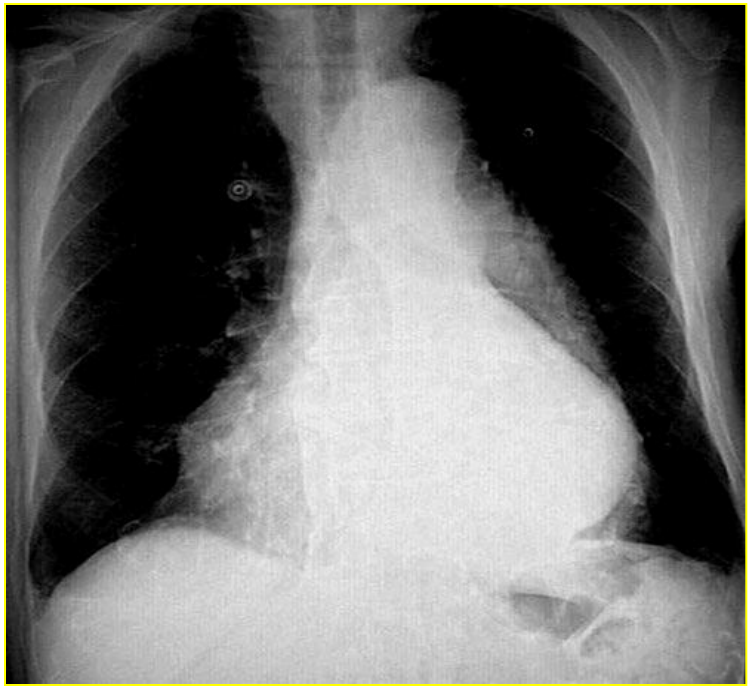
- **Within past 4 months:**

- shortness of breath
- asthenia, fatigue
- pedal edema

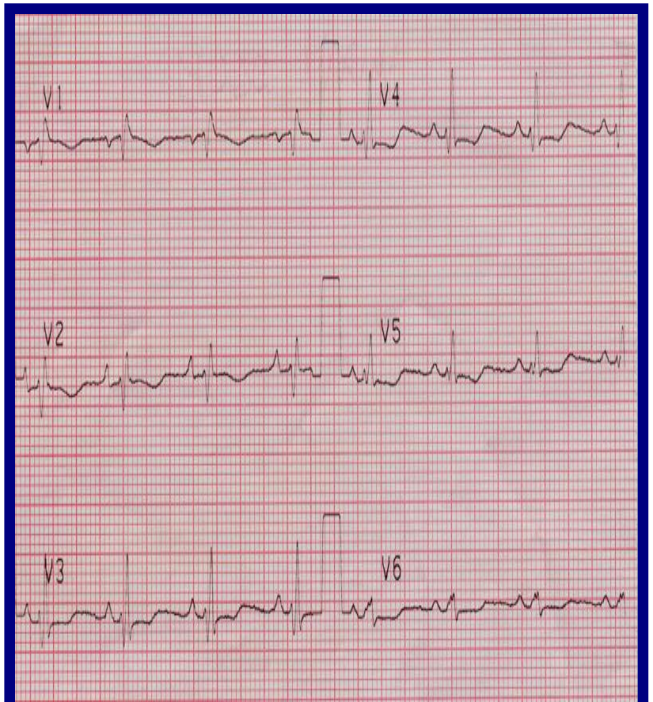
- **Physical signs:**

- increased pulmonic component of P2
- peripheral edema
- hepatomegaly

- Chest X rays

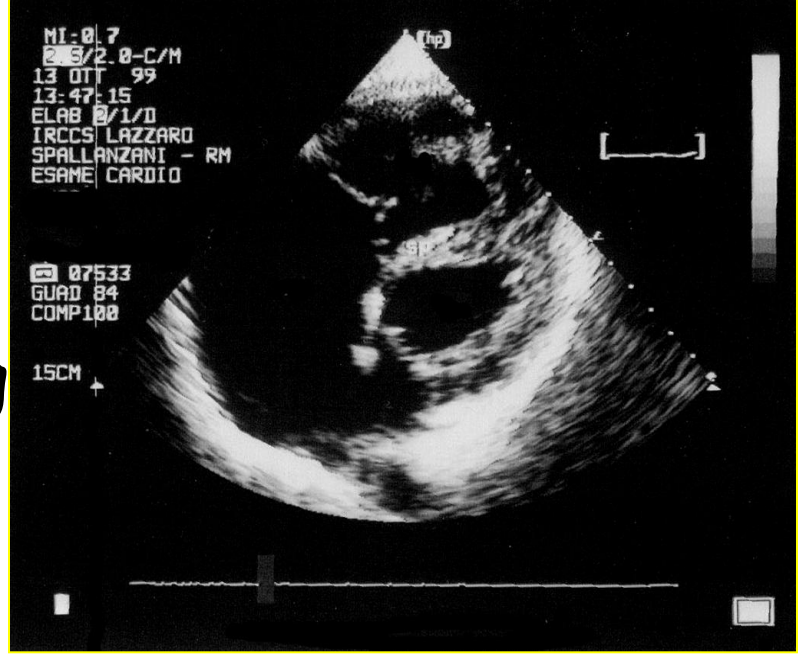


- ECG



- Echocardio

PASP: 50 mmHg



- R **HIV-related pulmonary hypertension NYHA 3** SP 50

•HIVRNA 4000 cp/ml CD4+ 690/mmc
•HCVAb+ cryoglobulinemia IgGk and cryocrite 4%
•HCVRNA 285,000 cp/ml NO TARV

Clinical Classification of Pulmonary Hypertension (Dana Point)

1 Pulmonary arterial hypertension (PAH)
- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease
- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 = activin receptor-like kinase 1 gene; APAH = associated pulmonary arterial hypertension; BMPR2 = bone morphogenetic protein receptor, type 2; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

Simonneau G et al. J Am Coll Cardiol 2009; 54: S43-45

HIV associated pulmonary arterial hypertension

Prevalence in HIV population

0.5%	(6/1200)	Speich, Chest 1991
0.4%	(47/11894)	Zuber, CID 2004
0.5%	(66/13400)	Opravil, AIDS 2008
0.5%	(35/7648)	Sitbon, Am J Respir Crit Care Med 2008
0.4%	(19/5000)	Cicalini, AIDS 2008

- **Higher prevalence than in general population (0.5% versus 0.02%)**

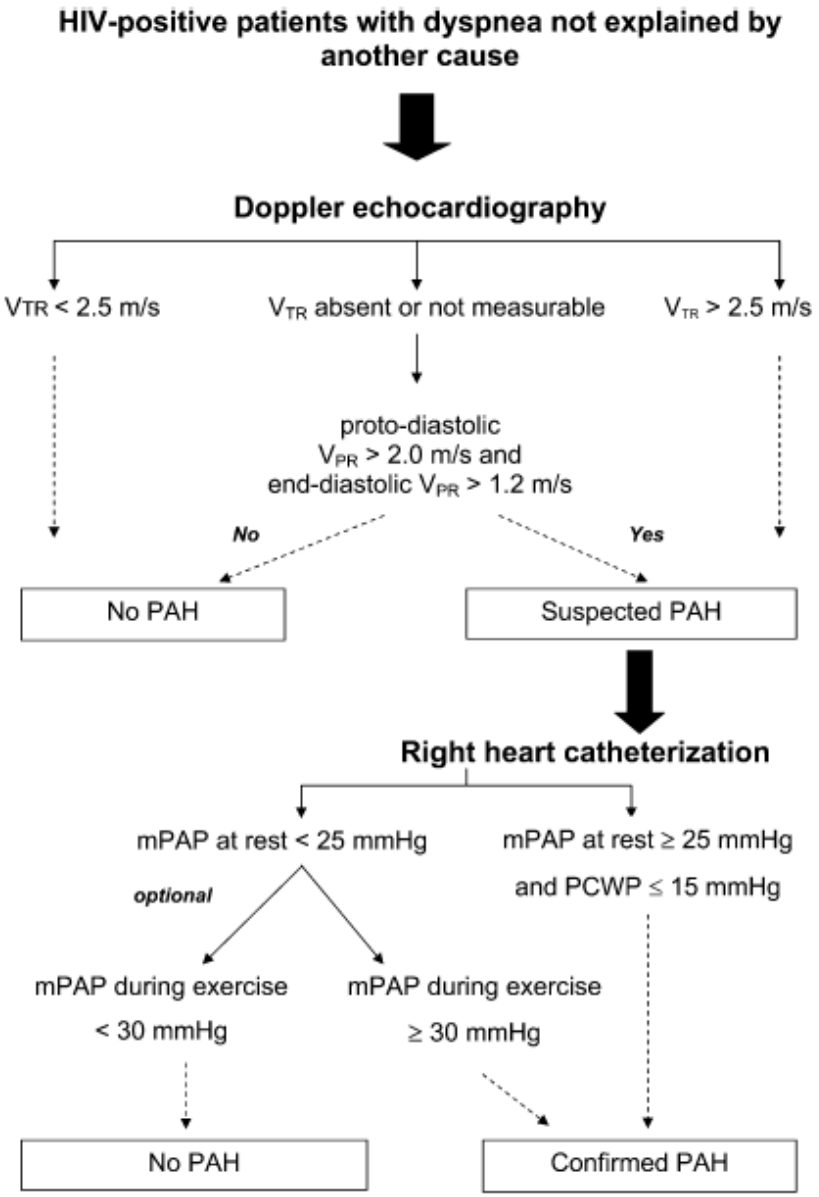
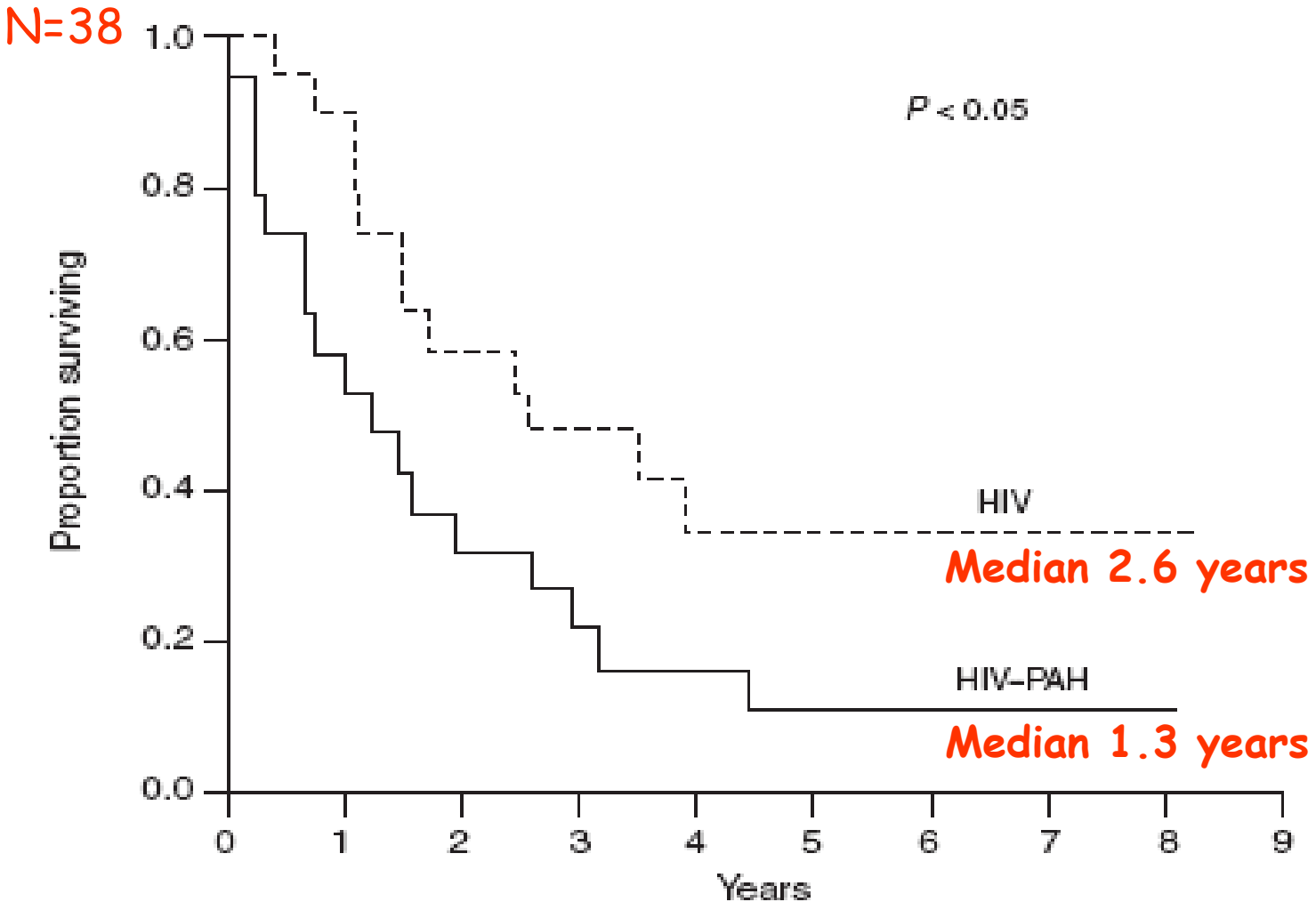


Figure 1. Diagnostic algorithm based on clinical symptoms of dyspnea, transthoracic Doppler echocardiography, and right heart catheterization. mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; V_{PR} = peak velocity of pulmonary regurgitation; V_{TR} = peak velocity of tricuspid regurgitation.

Sitbon O et al. Am J Respir Crit Care Med 2008; 177: 10813

Survival of HIV+ pts with and without PH



Opravil, Am J Respir Crit Care Med 1997

Role of HAART-Swiss Cohort

Retrospective study- 47 pts with HIV-PAH (1988-2001)

- Reduction of incidence from 0.24% in 1993 to 0.02% in 2001 (HAART)

Characteristic	Treatment group: No ART during follow-up (n = 9)	Only NRTIs during follow-up (n = 12)	HAART during follow-up (n = 14)
ΔRVSP-RAP, mm Hg			
First	60 (47–84)	62 (54–76)	60 (51–83)
Final	93 (64–98)	58 (49–66)	50 (36–61)
Change	+25 (+6 to +35)	−3 (−24 to +4)	−21 (−30 to −6)[d]
Increase by >10 mm Hg	6 (67)	2 (17)	2 (14)[e]
Decrease by >10 mm Hg	0 (0)	5 (42)	10 (71)[f]

p<.005

- Reduction of hazard rate for mortality

HR for pts on HAART 0.075; 95% CI,0.02-0.28;p<0.001

Zuber, Clin Infect Dis 2004

Role of HAART-Swiss Cohort

HAART does not prevent the occurrence of PAH

- 66 pts (1988-2006)

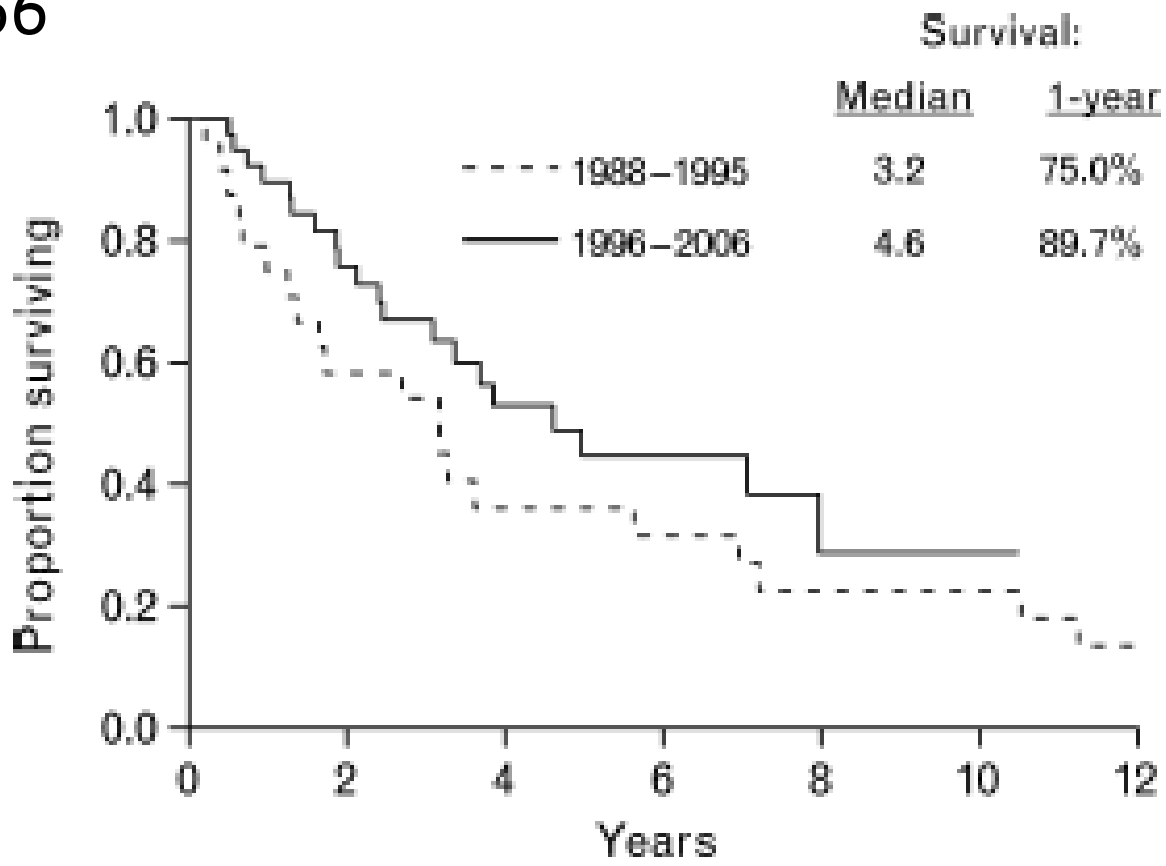
-19 pts with a new PAH diagnosis after 2001

-2/3 of pts on HAART since at least 3 months at the diagnosis of HIV-PAH

Opravil, AIDS 2008

Role of HAART-Swiss Cohort

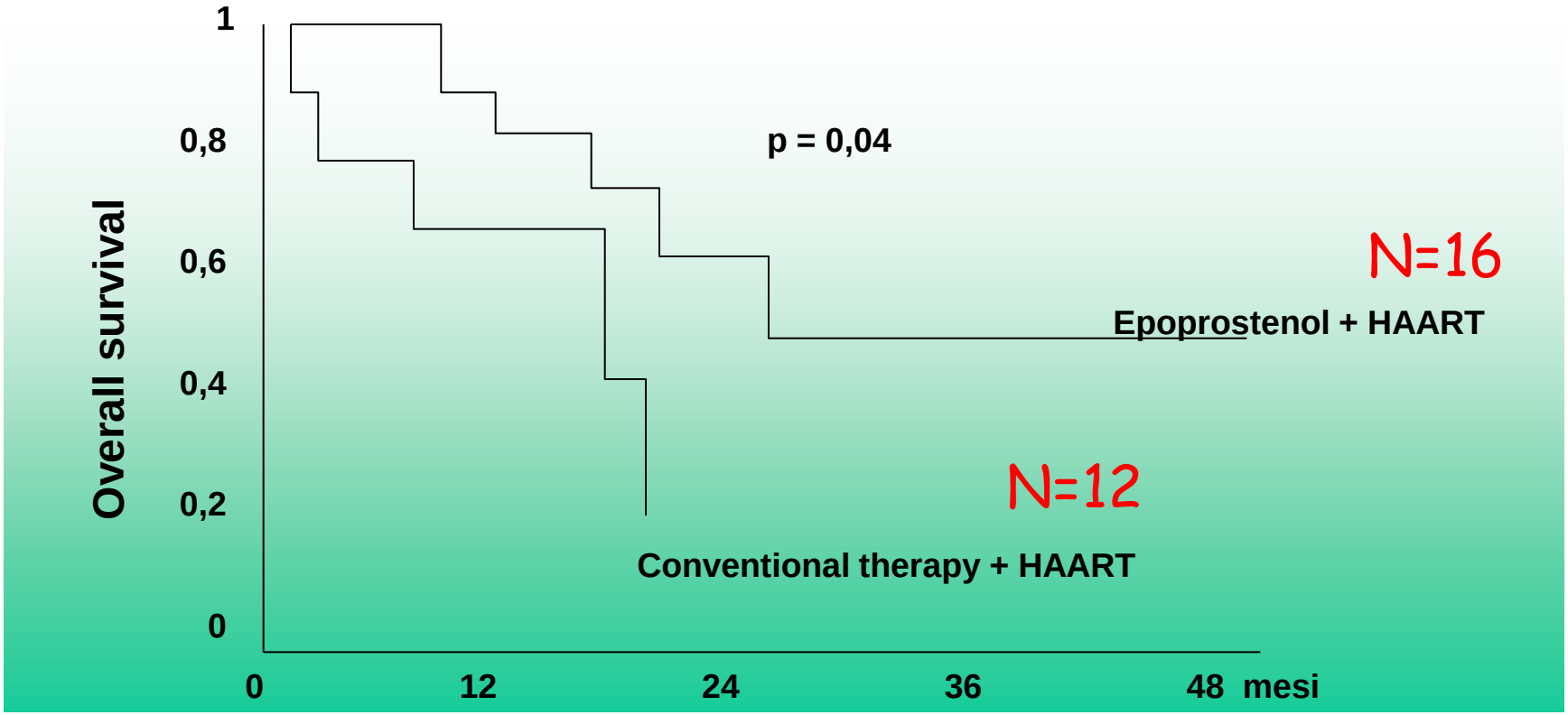
N=66



Opravil, AIDS 2008

Prognostic factors in HIV-PAH- French Registry

Pts in NYHA class III-IV



Nunes H, Am J Respir Crit Care Med, 2003

Table 2: Pathogenesis of HIV-related pulmonary hypertension

Pathogenetic mechanism	Comments
Direct role of HIV	Poorly understood HIV not detected in endothelium of pulmonary arteries HIV Nef protein recently evidenced in the alveolar mononuclear cells and in the lungs endothelial cells of two HRPH patients
Indirect role of HIV	Increased ET-1 levels in HIV patients Increased levels of IL-1β, IL-6, TNFα, PDGF
α1 adrenergic hypothesis	Several factors can induce a chronic stimulation of α_1-adrenoreceptors: chronic hypoxia (by activation of HIF-1), increased levels of norepinephrine, appetite suppressant agents or cocaine use, and pulmonary overload.
Toxic substances	Heroin, talc, cocaine, appetite suppressant agents
Liver diseases	Enhanced synthesis and reduced metabolism of ET-1. Over expression of proliferative and angiogenetic mediators such as VEGF and HIF. Imbalance between the vasodilator/antiproliferative and vasoconstrictor/growth mediators. Use of β-blockers.
Autoimmune diseases	Unclear role in the development of HRPH Anticardiolipin IgM and anti-SS-B more frequent in HRPH
Genetics	Increased frequency of HLA DR52, DR6, and the linked alleles HLA-DRB1 1301/2, DRB3 0301, DQB1 0603/4 in patients with HRPH. Unclear role of BMPR2 gene mutation in HRPH

HRPH: HIV-related pulmonary hypertension; ET-1: endothelin-1; IL: interleukin; TNF: tumor necrosis factor; PDGF: platelet-derived growth factor; HIF-1: hypoxia inducible factor 1; VEGF: vascular endothelial growth factor; BMPR2: bone morphogenetic protein receptor type 2

Petrosillo N Cicalini S. PVRI Review 2009; 1: 173-9

Pathogenesis

Direct role of HIV

- HIV never isolated in endothelial cells of affected pulmonary vessels
- Protein *Nef* in mononucleolar alveolar cells and in endothelial cells of lung

Indirect role of HIV

Increased levels of ET-1, IL-1 beta, IL-6, TNF alpha and PDGF

alpha 1 adrenergic hypotesis

- Chronic stimulation (chronic hypossia, high circulating levels of norepinephrine, cocaine, appetite suppressant agents) of $alpha_1$adrenergic receptors => excessive proliferation of smooth muscle cells and fibroblasts, pulmonary vascular hypertrophy and excessive vasoconstriction of pulmonary vascular medium-sized arteries

Pathogenesis

Coinfection with hepatitis viruses

-Enhanced synthesis and reduced metabolism of ET-1 (in cirrhosis)

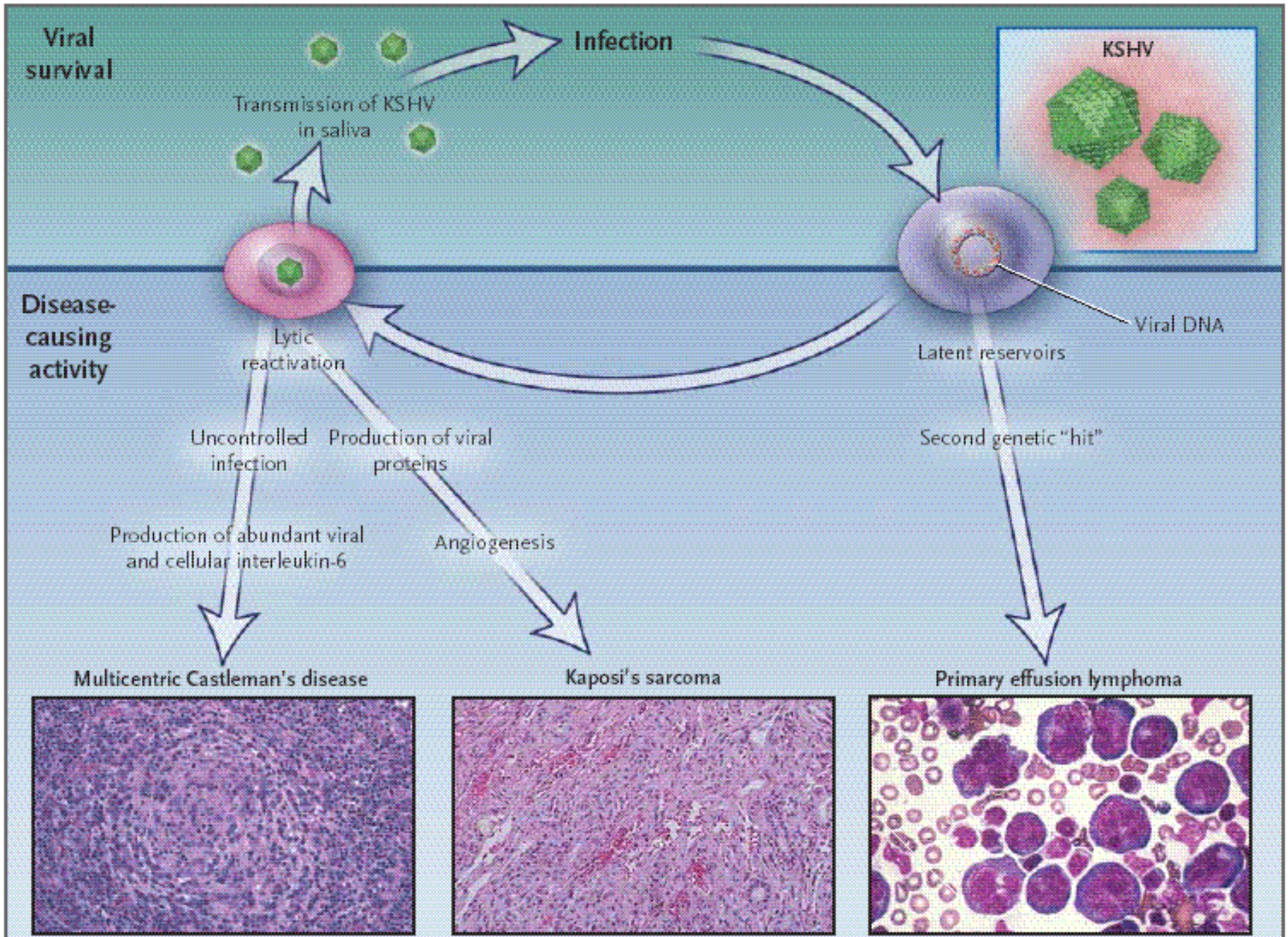
- PAPS higher in HIV+ pts with PH and cirrhosis vs HIV+ pts with PH without cirrhosis

Genetic factors

HLA DR52 e DR6 ?

HHV8

-HHV-8 antigens and genoma in pts with HP (no HIV)
-HHV8 represents a common infection in HIV + pts


Viral survival
Infection
Transmission of KSHV in saliva
KSHV
Disease-causing activity
Lytic reactivation
Viral DNA
Latent reservoirs
Uncontrolled infection
Production of viral proteins
Second genetic "hit"
Production of abundant viral and cellular interleukin-6
Angiogenesis
Multicentric Castleman's disease
Kaposi's sarcoma
Primary effusion lymphoma

Human Herpesvirus 8 and Pulmonary Hypertension

Table. Human herpesvirus 8 (HHV-8) seroprevalence among candidate patients for lung transplantation

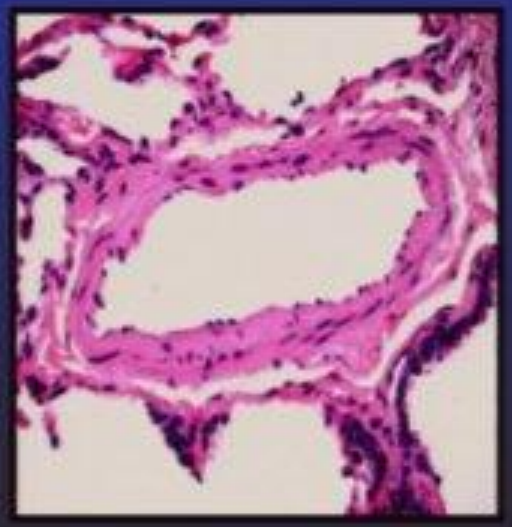
Diagnosis	Patients	Female sex (%)	Median age (range)	HHV-8 seroprevalence (%)
Patients with pulmonary hypertension				
Idiopathic pulmonary arterial hypertension	16	14 (87.5)	46 (28–74)	1 (6.3)
Secondary pulmonary hypertension	17	11 (64.7)	44 (22–65)	0 (0)
Patients without pulmonary hypertension				
Cystic fibrosis	29	9 (31.0)	23 (14–28)	5 (17.2)
Interstitial lung disease	13	3 (23.1)	47 (43–74)	3 (23.1)

Emanuele Nicastri,* Carmine Dario Vizza,†
Fabrizio Carletti,* Stefania Cicalini,*
Roberto Badagliacca,† Roberto Poscia,†
Giuseppe Ippolito,* Francesco Fedele,†
and Nicola Petrosillo*

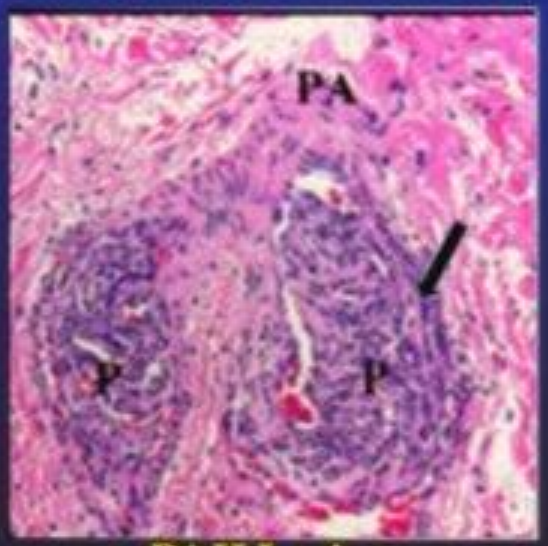
Emerg Infect Dis 2005;11:1480-2

Lung Vascular Lesions in PAH

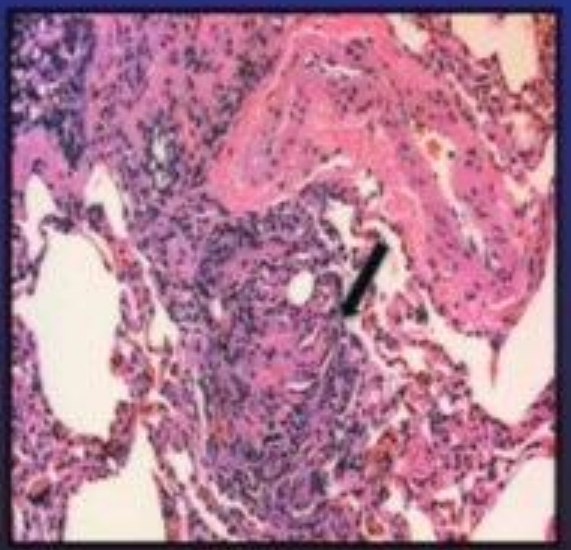
- Histological analysis has shown:
  - Vascular remodeling
  - Lumenal obliteration
  - Inflammatory cells



Normal



PAH Lesion



HRPAH Lesion

Cool, et al;

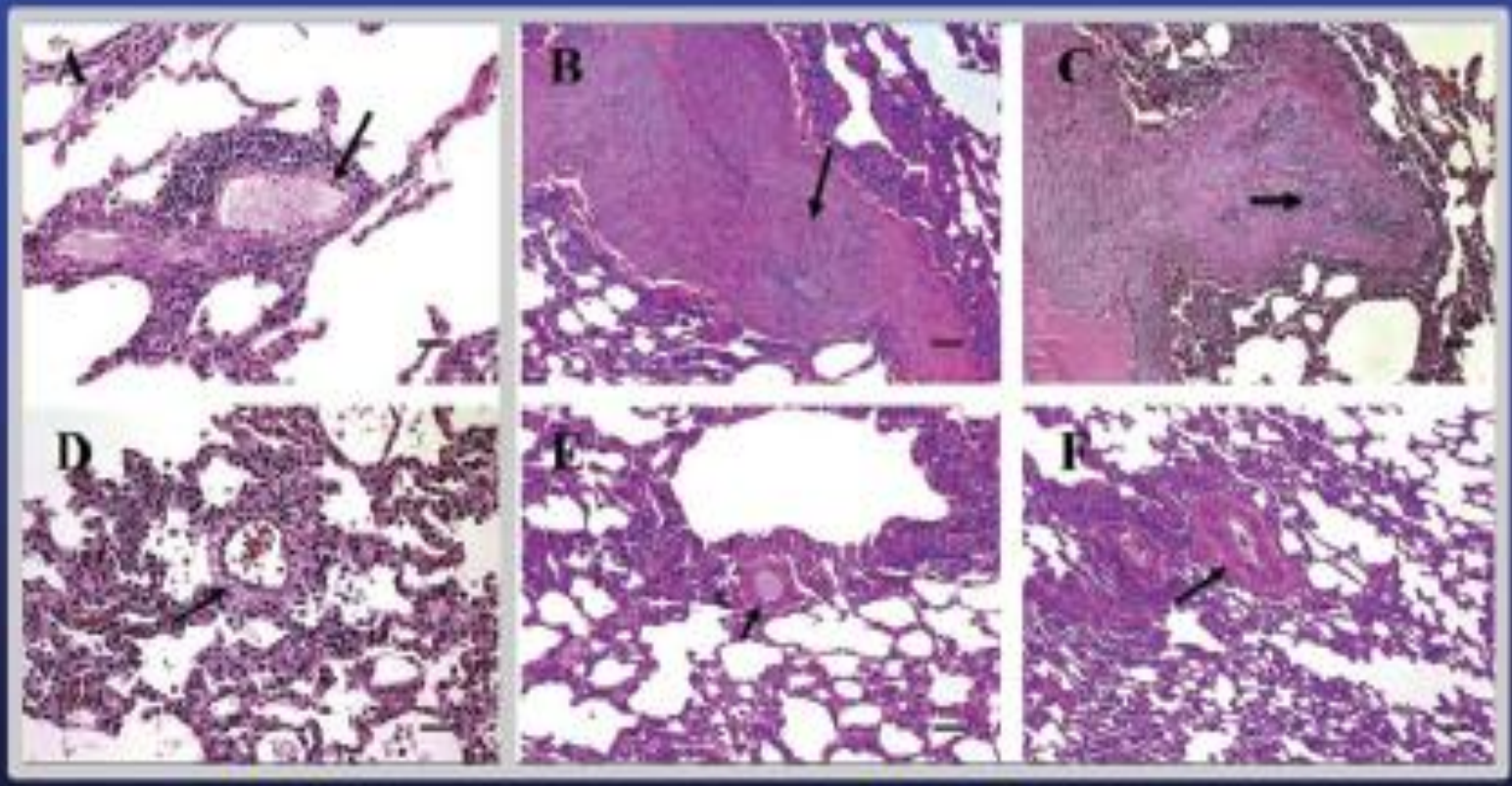
What is the connection between HIV and pulmonary hypertension?

SIV_{mac} as a model for HIV infection

SIV infection of macaques closely recapitulates HIV infection

Since the SIV-macaque model closely recapitulates HIV infection and immunodeficiency, we wondered if we could find evidence for the pulmonary pathologies observed in HRPAH?

HIV Nef is required for lung vascular remodeling associated with PAH



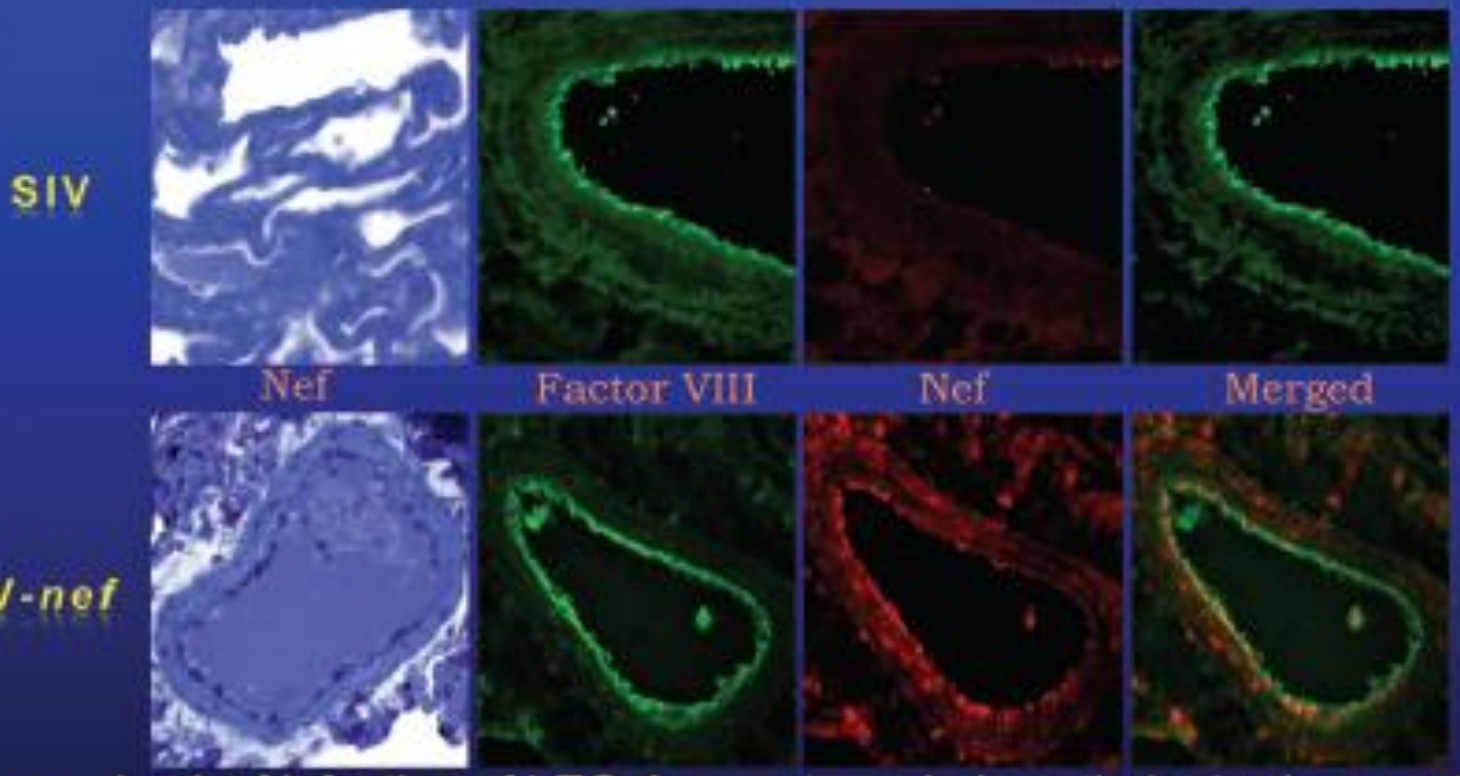
SIV

SHIV-*nef*

Marecki, et al, 2006; American Journal of Respiratory and Critical Care Medicine

Nef is present in lung vascular endothelial cells

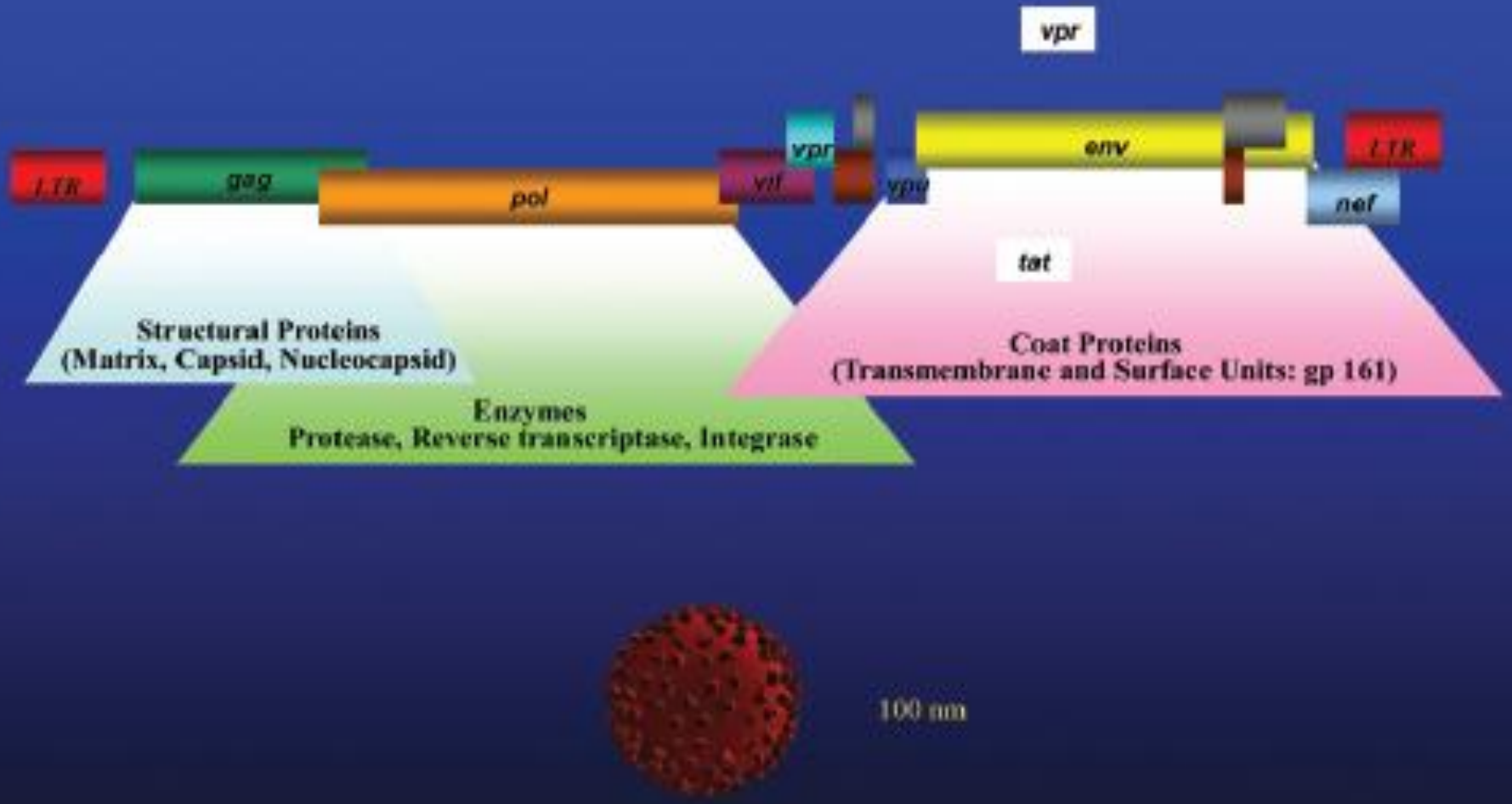
- HLMEC lack receptors required for HIV infection



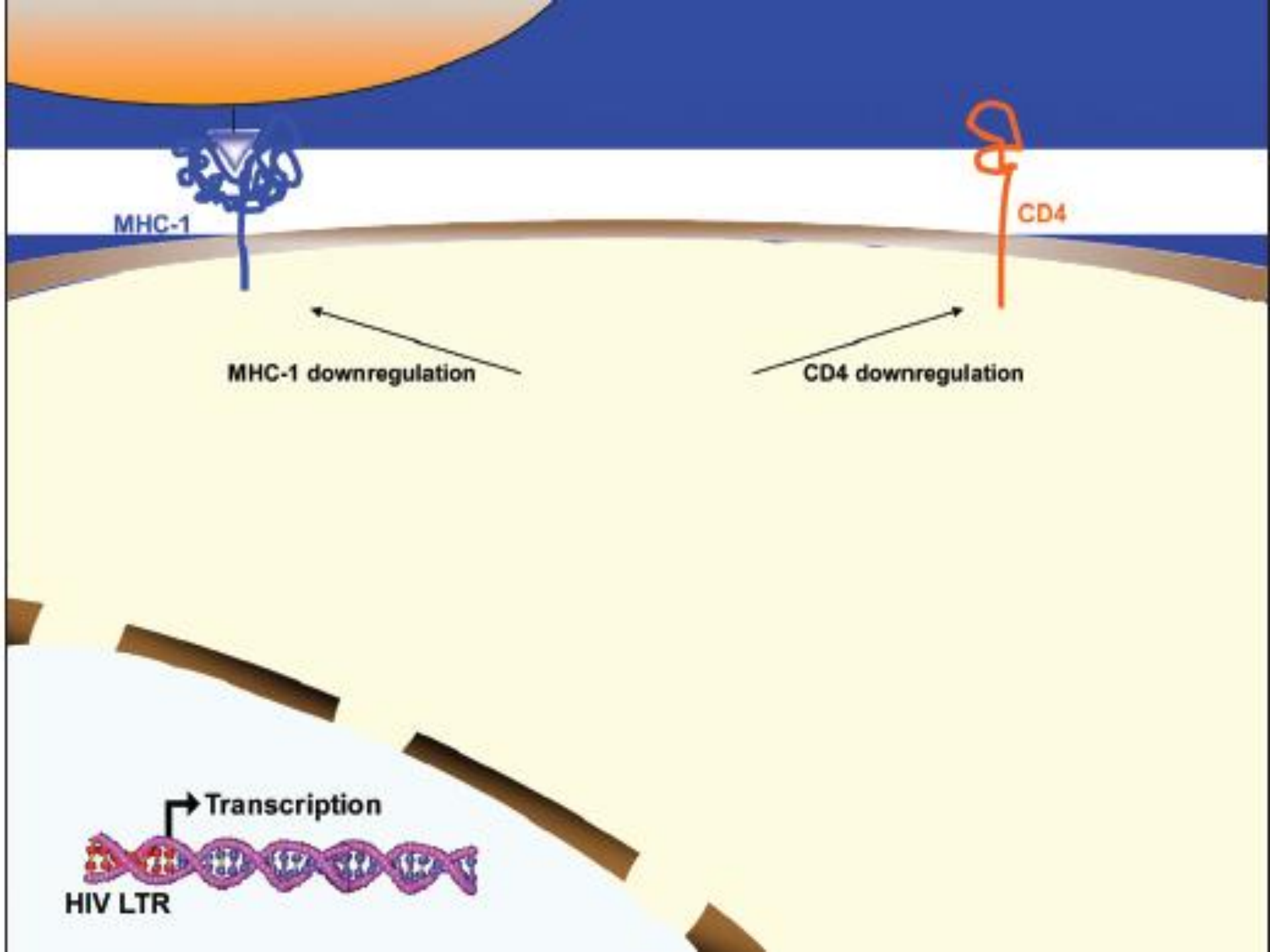
- Lack of infection of LEC does not preclude pathologic changes that result from presence of viral proteins and/or inflammatory cytokines and growth factors.

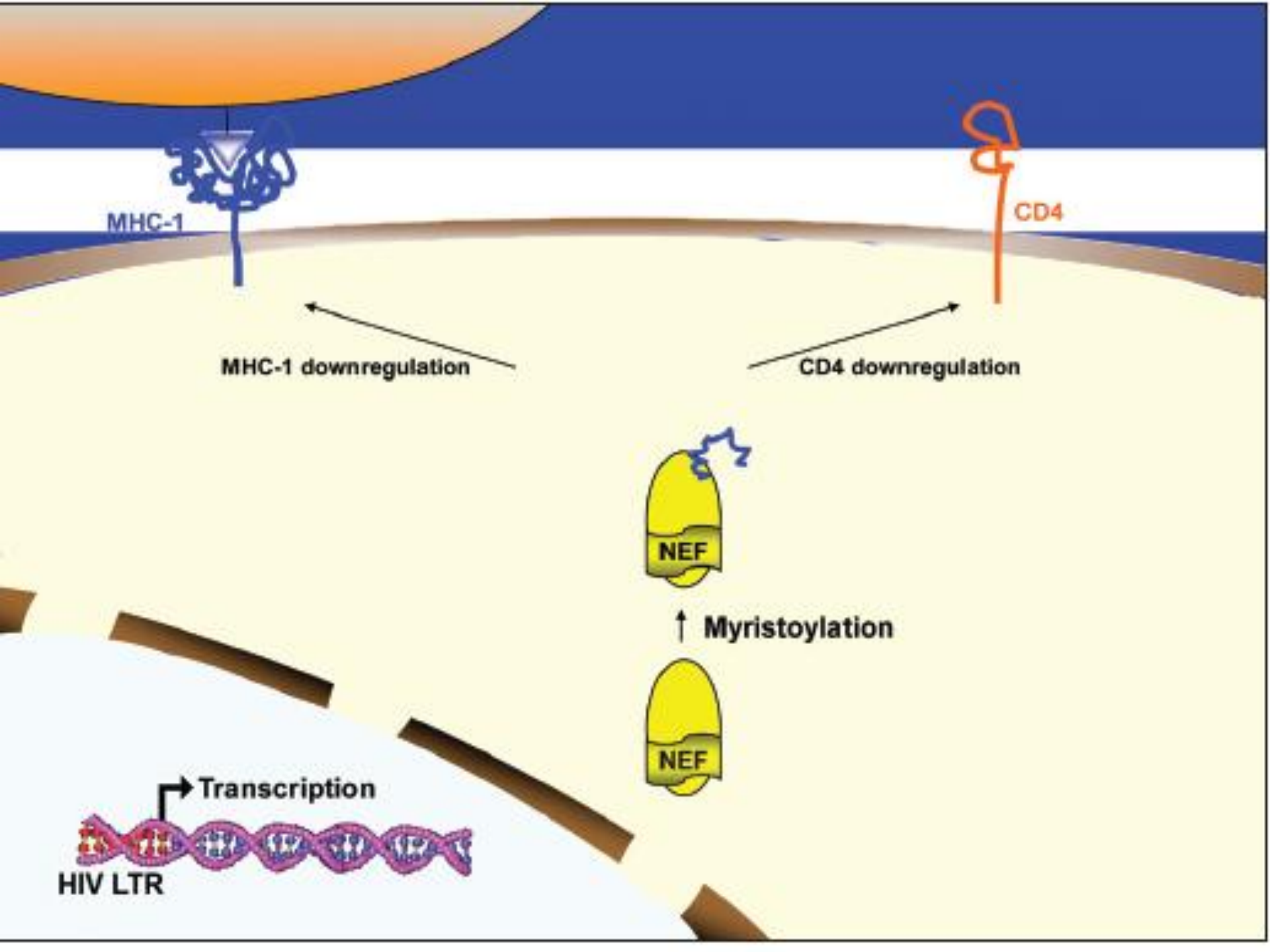
Marecki, et al, 2006; American Journal of Respiratory and Critical Care Medicine

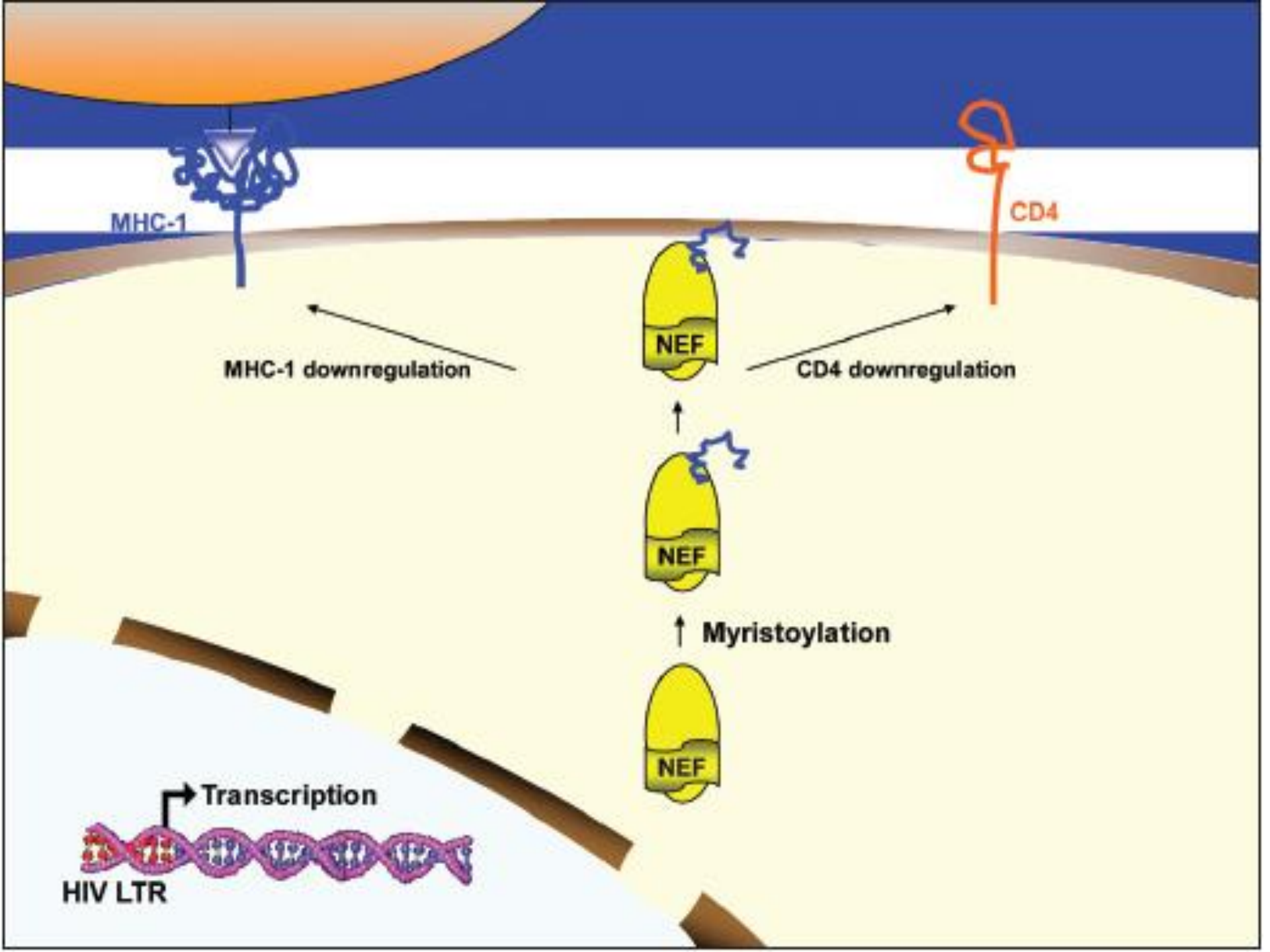
HIV-1 nef gene

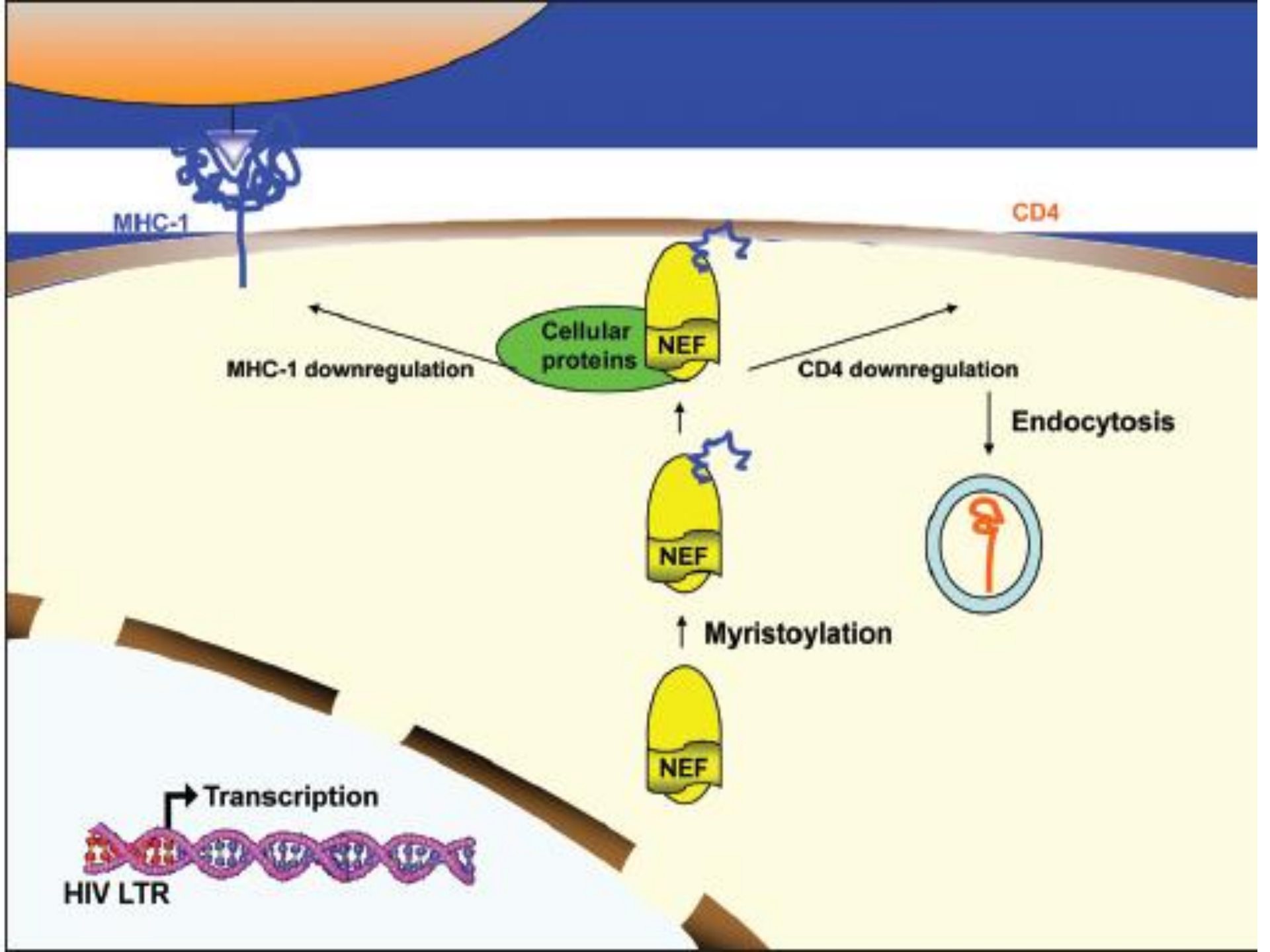


Adapted from "Human Immmunodeficiency Virus (HIV): A Global Pandemic", URL: http://www.stanford.edu/group/virus/retro/2005gongishmail/HIV.html


MHC-1
CD4
MHC-1 downregulation
CD4 downregulation
Transcription
HIV LTR


MHC-1
CD4
MHC-1 downregulation
CD4 downregulation
NEF
Myristoylation
NEF
Transcription
HIV LTR


MHC-1
CD4
NEF
MHC-1 downregulation
CD4 downregulation
NEF
NEF
Myristoylation
Transcription
HIV LTR


MHC-1
CD4
Cellular proteins
NEF
MHC-1 downregulation
CD4 downregulation
Endocytosis
NEF
Myristoylation
NEF
Transcription
HIV LTR

HIV Nef (*negative factor)*

- **is an accessory protein expressed early during viral infection, together with Tat.**
- **The Nef protein is a molecular adaptor and is a key player in HIV pathogenesis.**
- **For example, Nef complexes with several host cell proteins (including members of the p21-activated kinase family), and recruits host adaptor proteins to commander trafficking of intracellular vesicles participating in secretory and endocytic pathways.**

Fackler OT et al. Mol Cell Biol 2000; 20:2619-2627.
Roeth JF et al. Microbiol Mol Biol Rev 2006; 70:548-563.

HIV Nef (*negative factor)*

- **Nef downregulates essential molecules such CD4 receptor by targeting it to the endocytic degradation pathway in clathrin-coated vesicles and MHC-1 by sequestering it in the trans-Golgi and hence, preventing the recycling of this receptor from the Golgi to the membrane.**

Miller MD et al. J Exp Med 1994; 179:101-113

- **Also, Nef is a migratory stimulus for monocytes and induce the release of inflammatory molecules.**

Lehmann MH et al. Exp Cell Res 2006; 312:3659-3668.
Olivetta E et al. J Immunol 2003; 170:1716-1727.
Capoccia BJ et al. J Leukoc Biol 2008; 84:760-768

Potential clinical role of Nef

- **The potential of Nef as a vascular insult is underscored by its capacity to enter lymphocytes via the human chemokine receptor CXCR4 and exert apoptotic effects** (James CO et al. J Virology 2004; 78:3099-3109).

- **Endothelial cells express this receptor and therefore, it is conceivable that Nef may be present in endothelial cells in the absence of infection.**

- **Nef localizes to vascular and perivascular cells** (Marecki J et al. Chest 2005; 128(6 Suppl):621S-622S; Marecki JC et al. Am J Respir Crit Care Med 2006; 174:437-445) **and induces apoptosis in brain endothelial cells when expressed intracellularly or exogenously.**

- **Nef also impairs vasomotor functions in pulmonary artery cells, decreases the expression of endothelial nitric oxide synthase and increases oxidative stress** (Duffy P et al. J Surg Res 2009. 53).

Nef is mutated in the lung of a patient with HRPAH.

- **Nef sequences in the blood of patients with pulmonary hypertension show signature patterns that are specific to this disease phenotype, compared to their normotensive counterparts** (Almodovar S et al. Am J Respir Crit Care Med 2009; 77:A440.55).

- **Peripheral blood samples are the main biological specimens analyzed in clinical research because lung tissues from these patients are extremely difficult to obtain.**

- **Nevertheless HIV-1 *nef* sequences from archived lung tissue from an HRPAH patient from the Italian *Latium* Registry of HRPAH** (Petrosillo N et al. AIDS 2006; 20:2128-2129) **were amplified and cloned.**

Almodovar S et al. Chest 2010; 137(6 Suppl):6S-12S.

Nef is mutated in the lung of a patient with HRPAH.

The patient was diagnosed with HIV infection in 2000 and with HRPAH in 2006, the same year the patient died.

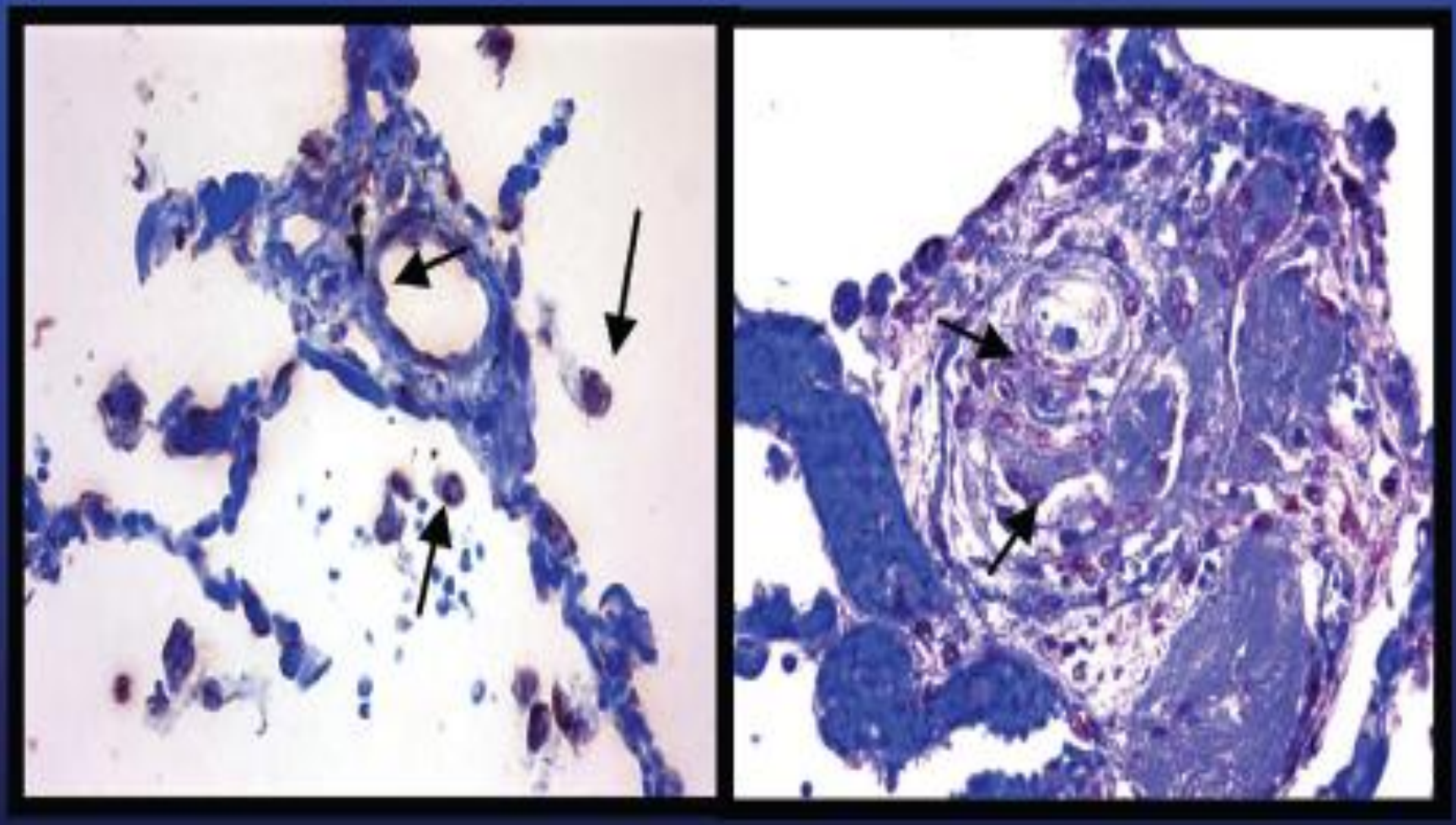
The lungs were collected during autopsy and subsequently analyzed.

Sequence analyses of the HIV *nef* showed the presence of 4/5 Nef mutations reported in SHIV*nef*-infected macaques (Mandell CP et al. Virology 1999; 265:235-251) with plexiform lesions.

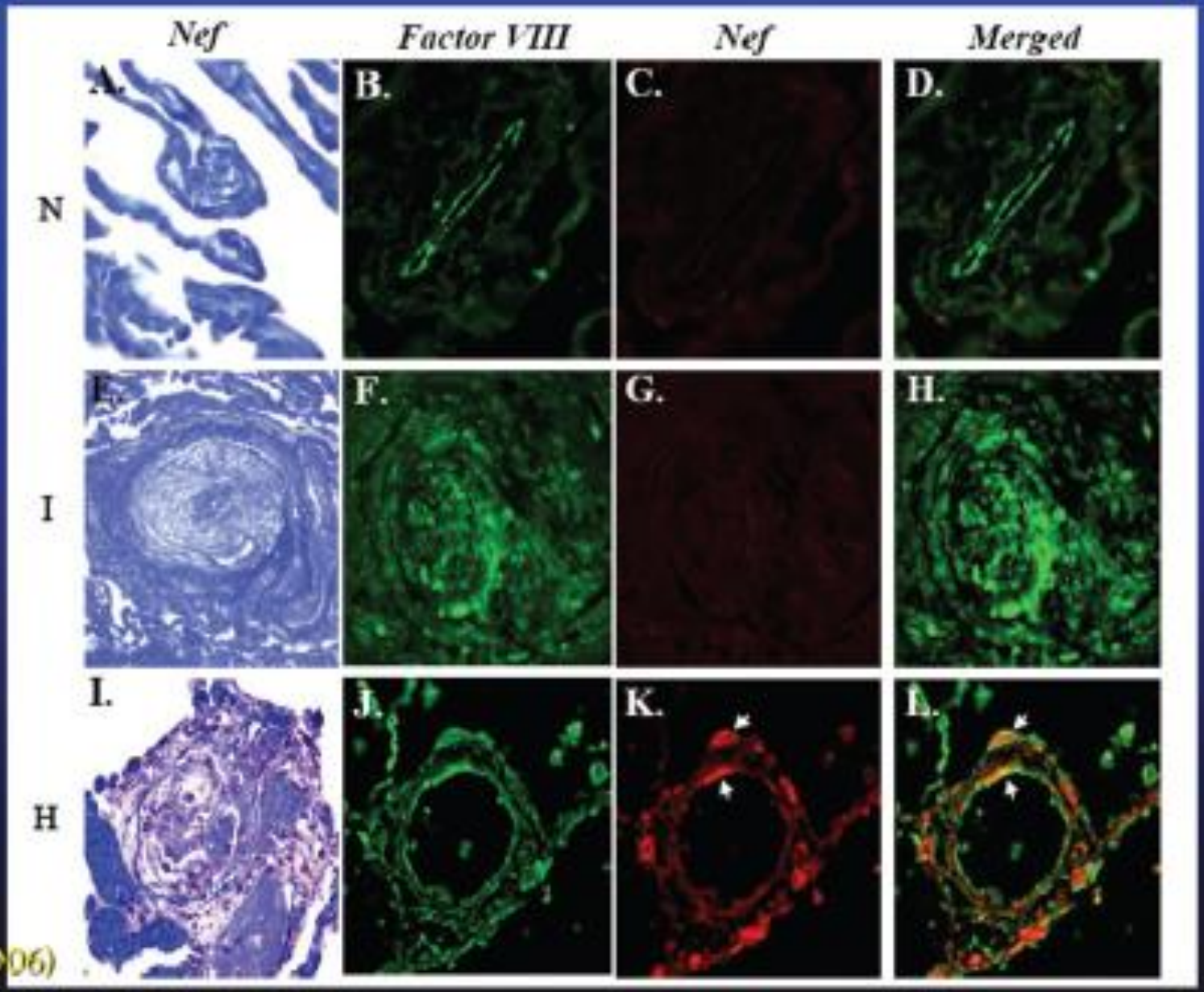
Furthermore, this Nef sequence had six Nef functional domains mutated, all of them found only in the lung tissues collected in 2006, and interestingly, none of the mutations was found in PBMC collected at the time of HIV diagnosis.

Almodovar S et al. Chest 2010; 137(6 Suppl):6S-12S.

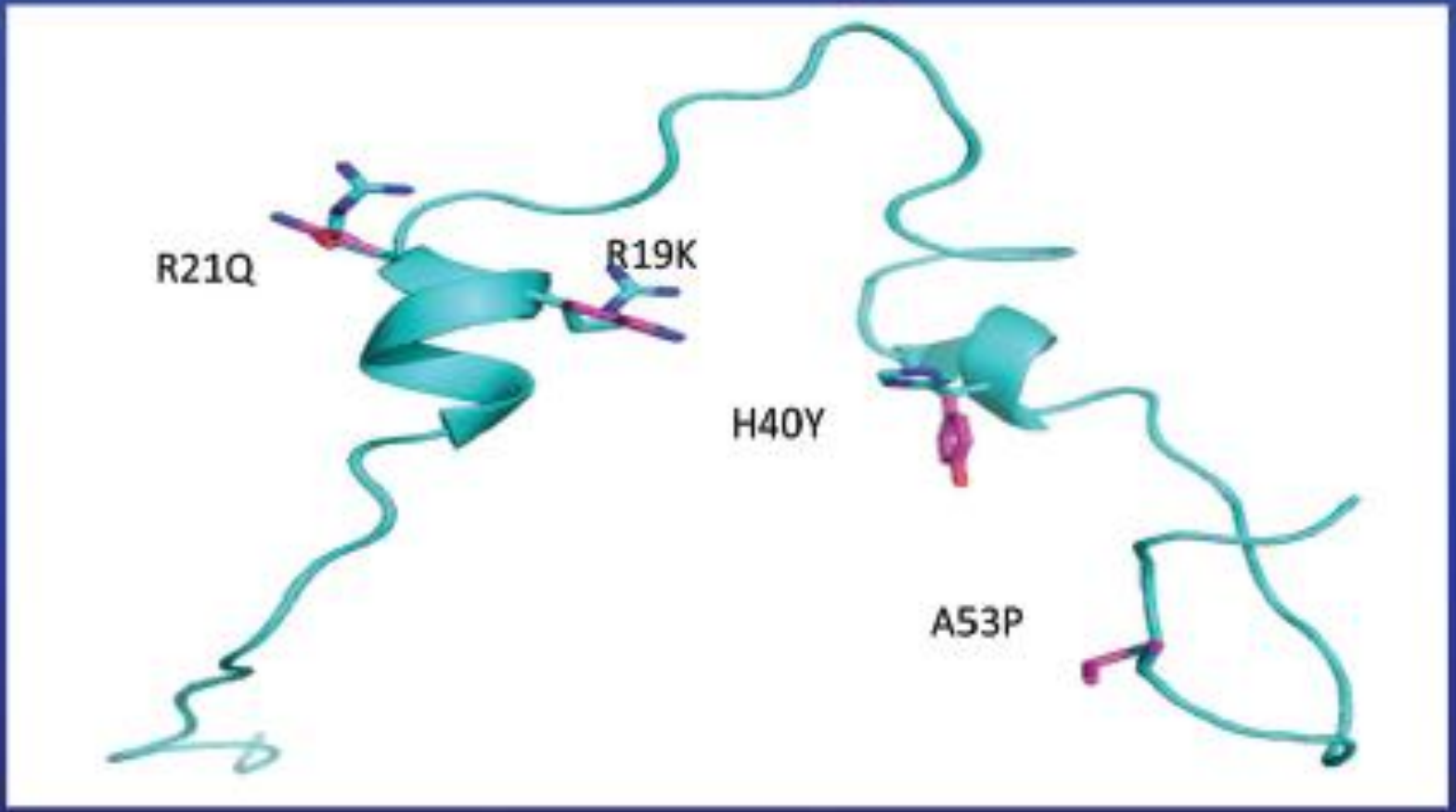
Nef staining in 2 lungs from HRPH



Co-localization of HIV-1 Nef and the vasculature in human PH

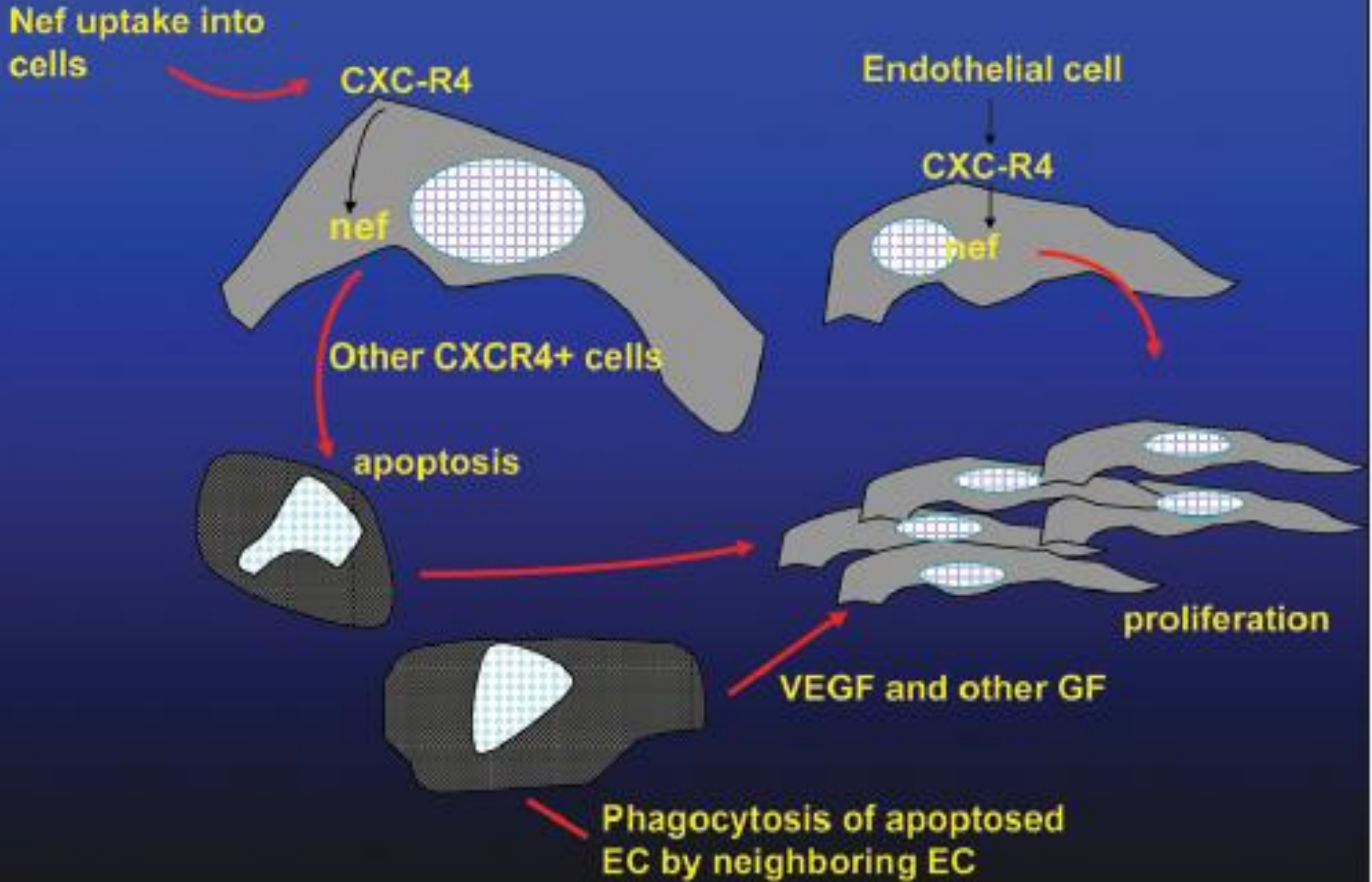


(Marecki, et al, 2006)



Model of the N-terminus of the Consensus B Sequence (cyan) based on model 1 of the 1qa5 NMR structure as determined by PHYRE (Protein structure prediction on the web: a case study using the Phyre server. Kelley LA and Sternberg MJE. Nature Protocols 4, 363-371 (2009)). Point mutants R19K, R21Q, H40Y, and A53P are indicated in magenta. The A53P mutant shows a a proline with a broken ring, which is bonded to the COO of an aspartate side chain, to maintain the backbone. The prediction is that the proline would actually introduce a major bend in the loop region. In almost every case, the A53P mutation occurs with the H40Y mutation.

Proposed Direct Effects of Nef on the Endothelium



Pulmonary Hypertension Associated With HIV Infection : Pulmonary Vascular Disease: The Global Perspective

Sharilyn Almodovar, Stefania Cicalini, Nicola Petrosillo and Sonia C. Flores

There are clear phylogenetic differences between the quasispecies of the lung vs the periphery

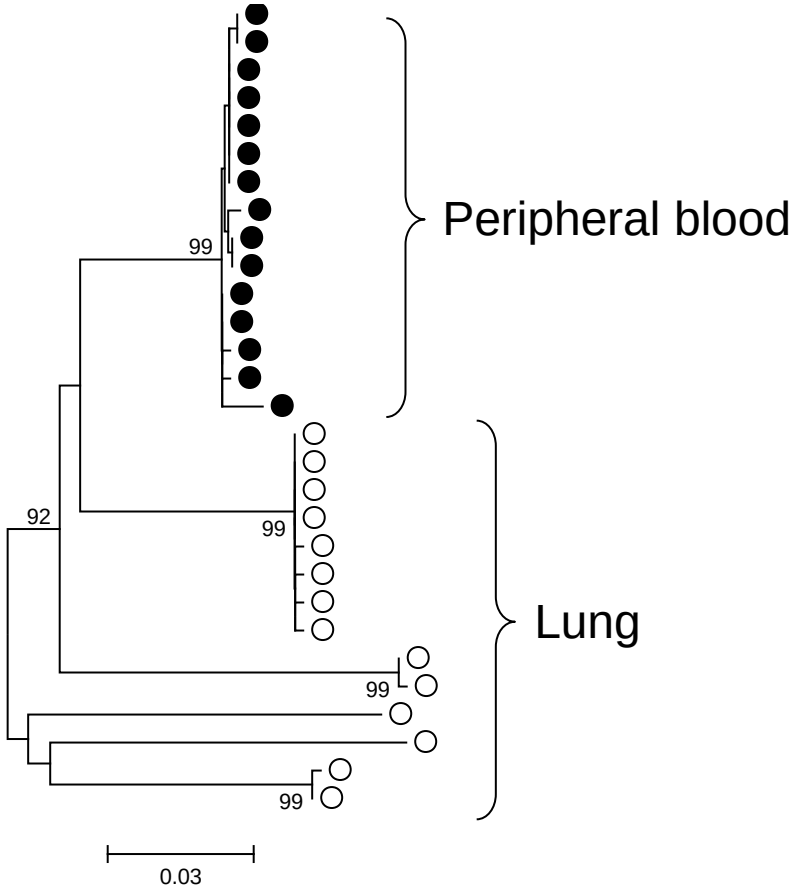


Figure 2. Phylogenetic reconstruction of HIV-1 *nef* sequences from a patient diagnosed with HRPAH. Archived PBMC and lung tissue was obtained from a patient diagnosed with HRPAH by echocardiography, and enrolled in the *Latium* Registry of HRPAH in Rome. HIV *nef* was PCR-amplified, cloned and sequenced; sequences were aligned using BioEdit and the phylogenetic tree was created using MEGA4. The analysis was statistically supported by 1000 boostrapre-samplings and only values >70% are shown. Tissue-specific clustering of the *nef* quasispecies suggest differential evolution at the level of blood (closed circles) and lung (open circles).

Chest 2010; 137(6 Suppl):6S-12S.

Nef is mutated in the lung of a patient with HRPAH.

- **These findings suggest either that the viral quasispecies in the lung arose later in the course of infection, or that these variants are replicating more efficiently in the lung than in the periphery.**

- **These aspects warrant further research efforts in order to validate (and possibly implement) the use of Nef sequences as potential screening tools to identify subjects at risk of HRPAH, especially in the low-resource settings**

Almodovar S et al. Chest 2010; 137(6 Suppl):6S-12S.

Myocardial and microvascular inflammation/ infection in patients with HIV-associated pulmonary artery hypertension

Andrea Frustaci[a,b], Nicola Petrosillo[c], Dario Vizza[a], Marco Francone[d], Roberto Badagliacca[a], Romina Verardo[b], Francesco Fedele[a], Giuseppe Ippolito[c] and Cristina Chimenti[a,b]

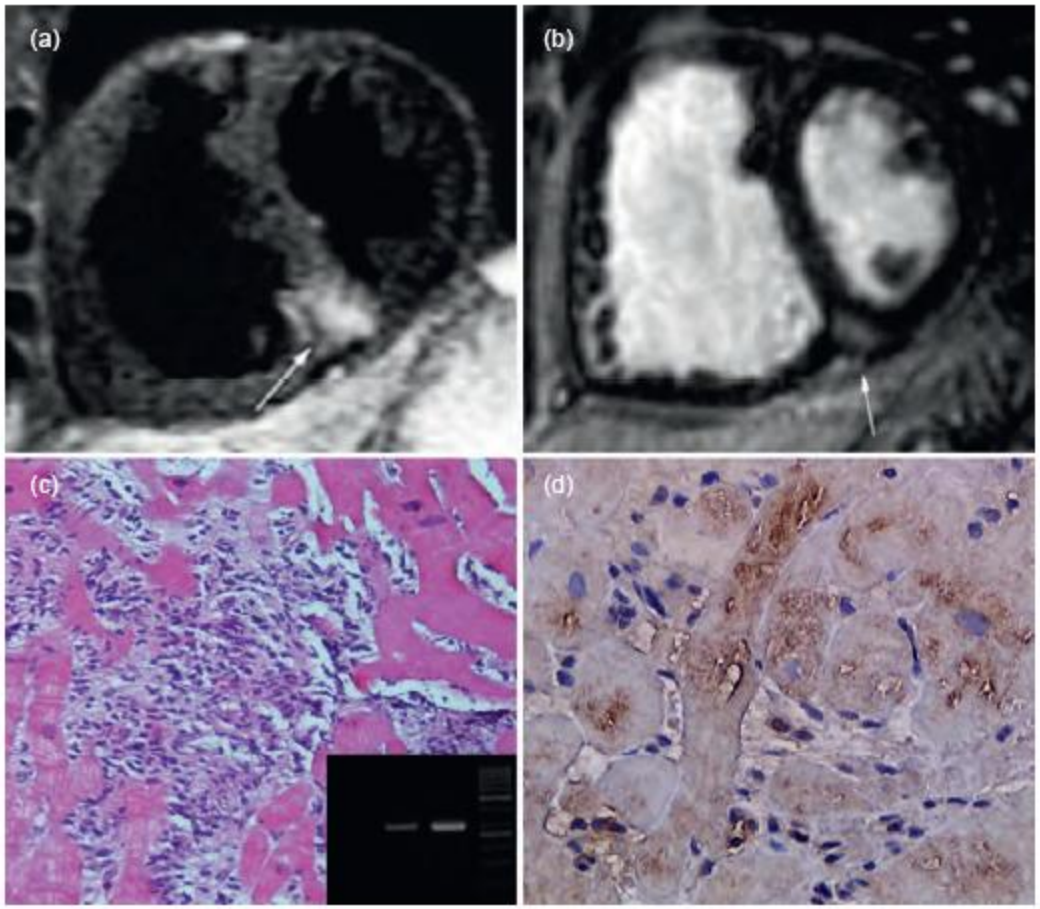


Fig. 1. Myocarditis due to AV infection in an HIV patient with PAH. Cardiac magnetic resonance T2w short tau inversion

Myocardial and microvascular inflammation/ infection in patients with HIV-associated pulmonary artery hypertension

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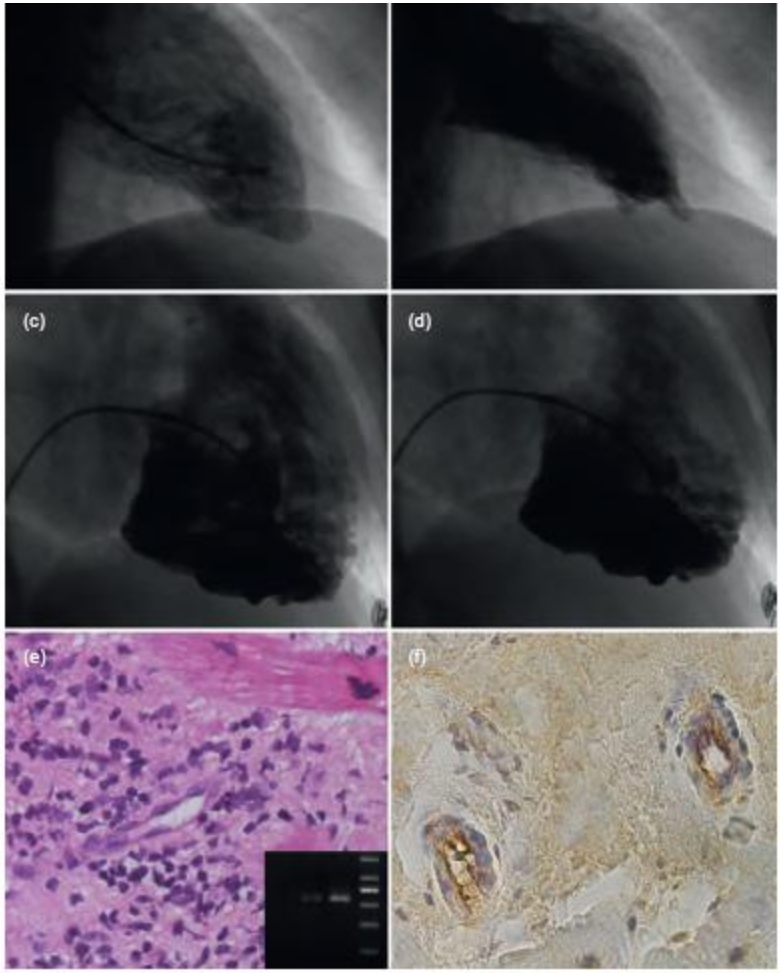

Fig. 2. Myocarditis and vasculitis due to HCV infection in an HIV patient with PAH. Left ventricular (panel a = diastole, panel

AIDS 2014, **28**:2541–2549

Myocardial and microvascular inflammation/ infection in patients with HIV-associated pulmonary artery hypertension

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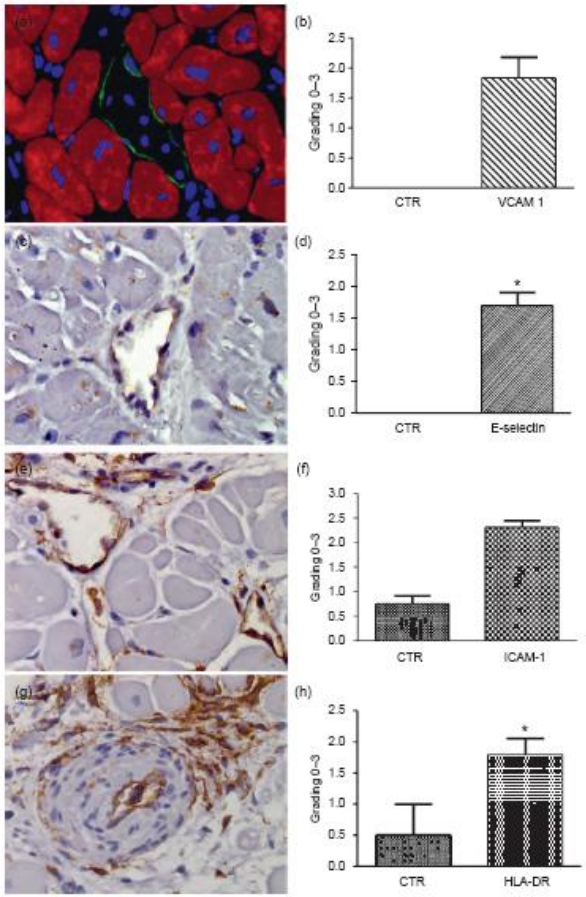
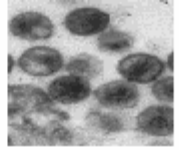
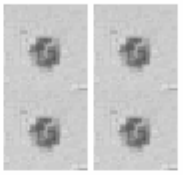
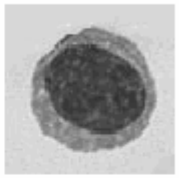


Fig. 3. Immunohistochemical evidence of an increased expression of adhesion molecules in intramural vessels of pulmonary artery hypertension patients (panel a, c, e, g) compared with controls (graphs in panels b, d, f, h). Panel a shows VCAM-1 (immunofluorescence, magnification 400×, green fluorescence = VCAM-1, red fluorescence = alpha-sarcomeric actin, blue fluorescence = nuclei); panel c shows E-selectin (immunoperoxidase, magnification 400×); panel e shows ICAM-1 (immunoperoxidase, magnification 400×); panel g shows HLA-DR (immunoperoxidase, magnification 400×).



HIV





Macrophage Platelets Lymphocyte

ET-1- PDGF- IL6- $IL1_{beta}$- TNF_{alfa}

Endothelial cell

Endothelial cell

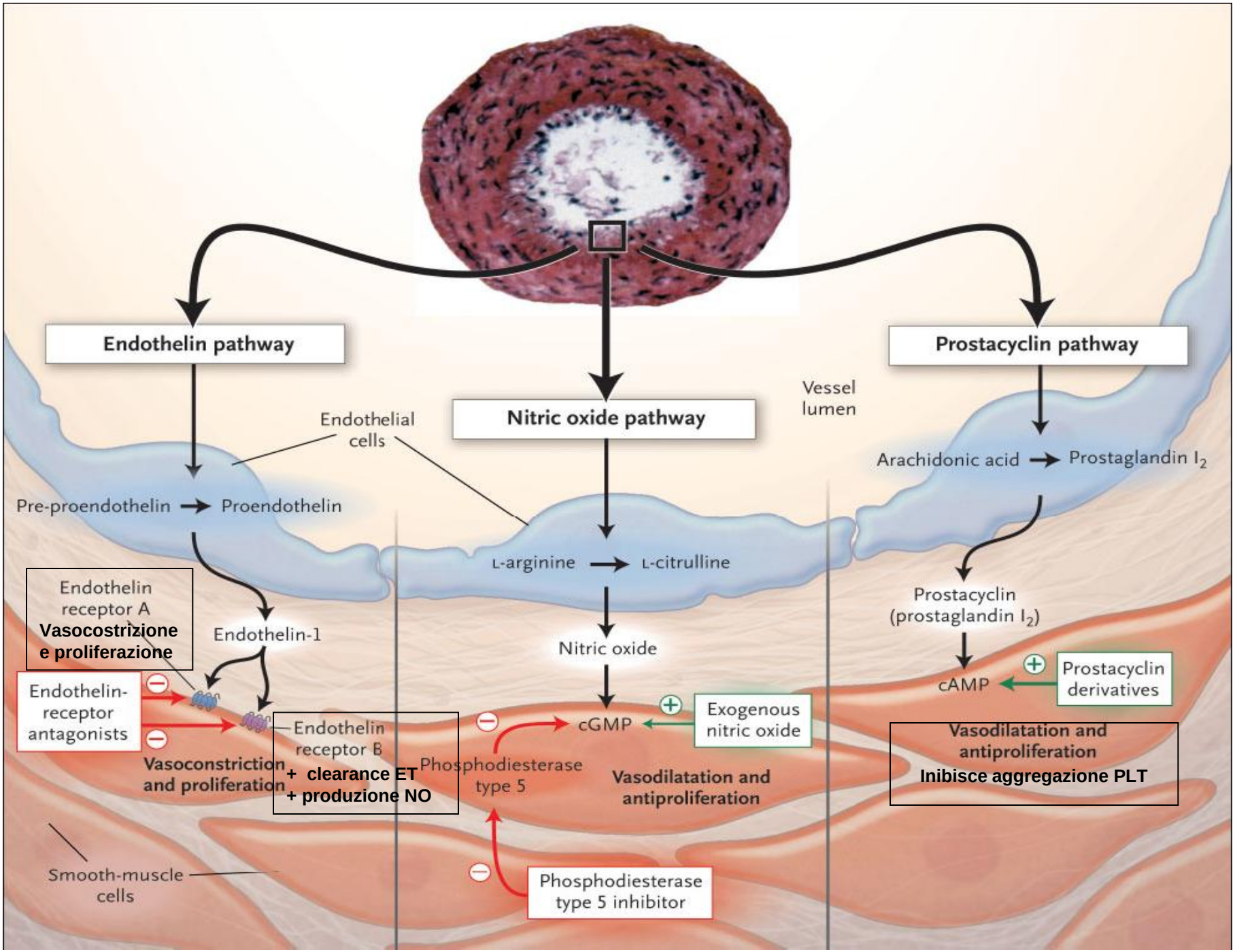
Smooth-muscle cells

ET-1 production
from endothelial cells

·*Reduction of NO synthesis*

·*Proliferation*
·*Vasoconstriction*

·*Proliferation*
·*Migration of smooth muscle cells*


Endothelin pathway
Nitric oxide pathway
Prostacyclin pathway
Vessel lumen
Endothelial cells
Pre-proendothelin
Proendothelin
Endothelin-1
Endothelin receptor A
Vasocostrizione e proliferazione
Endothelin-receptor antagonists
Endothelin receptor B
+ clearance ET
+ produzione NO
Vasoconstriction and proliferation
L-arginine
L-citrulline
Nitric oxide
cGMP
Exogenous nitric oxide
Phosphodiesterase type 5
Vasodilatation and antiproliferation
Phosphodiesterase type 5 inhibitor
Arachidonic acid
Prostaglandin I2
Prostacyclin (prostaglandin I2)
cAMP
Prostacyclin derivatives
Vasodilatation and antiproliferation
Inibisce aggregazione PLT
Smooth-muscle cells

TREATMENT OF HIV-PAH
Epoprostenol IV

Table 1. Exercise capacity and hemodynamics in patients with HIV-associated pulmonary arterial hypertension treated with epoprostenol ($n = 12$).

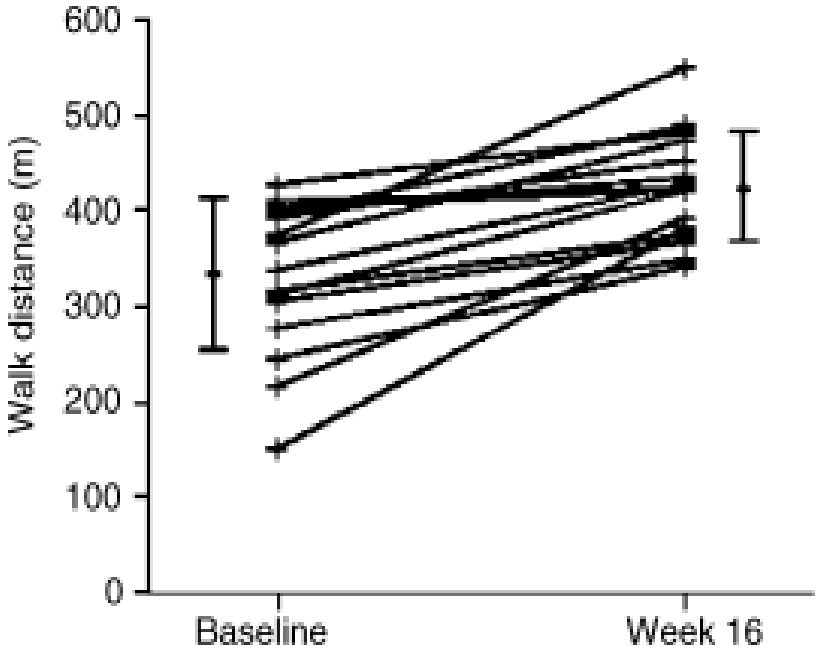
	Baseline	3 months	Follow-up[a]
6-Minute walk distance (m)	213 ± 95	434 ± 86*	456 ± 109*
Mean PAP (mmHg)	55 ± 9	46 ± 10*	45 ± 9*
Cardiac index (l/min/m^2)	1.9 ± 0.4	2.5 ± 0.6*	3.1 ± 1.0*
PVR index (IU/m^2)	25 ± 6	16 ± 6*	14 ± 6*

PAP, Pulmonary arterial pressure; PVR, pulmonary vascular resistance.
*$P < 0.05$ versus baseline.
[a]Mean 17 months.

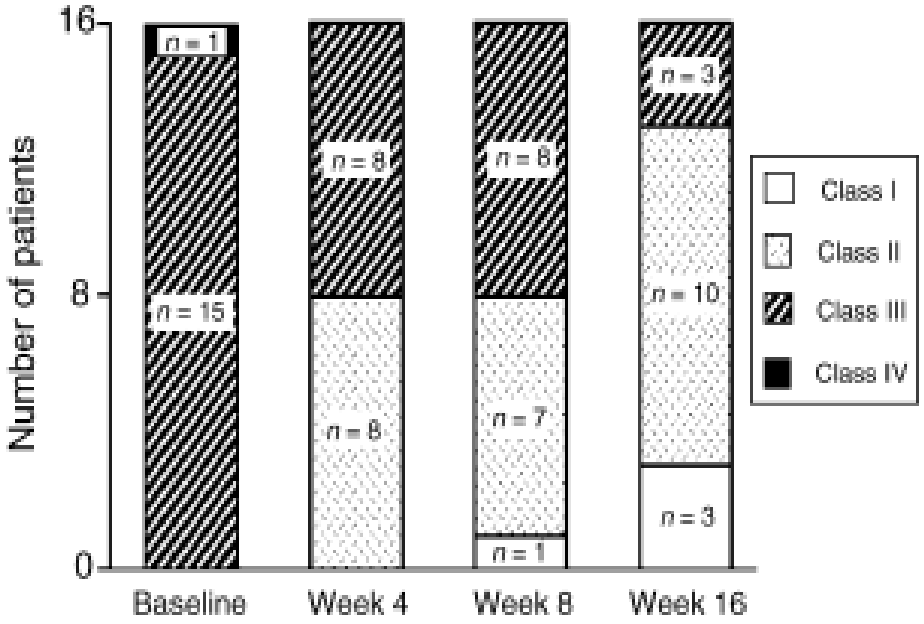
Nunes, Am J Respir Crit Care Med, 2003

Bosentan in HIV-PAH

6MWT



NYHA



N=16
p<0.001

	Baseline	Week 16	Δ
6MWD (m)	333 ± 79	424 ± 57	+ 91 ± 60

Sitbon, Am J Respir Crit Care Med 2004

Bosentan in HIV-PAH

TABLE 3. CARDIOPULMONARY HEMODYNAMIC PARAMETERS AT BASELINE AND WEEK 16

Parameters	Baseline	Week 16	Change (95% CI)	p Value*
Right atrial pressure, mm Hg	10.8 ± 7.5	7.6 ± 4.4	−3.2 ± 7.5 (−7.2:0.8)	0.11
Mean pulmonary artery pressure, mm Hg	52 ± 13	41 ± 14	−11 ± 12 (−17:−5)	0.002
Pulmonary capillary wedge pressure, mm Hg†	7.2 ± 2.5	7.7 ± 2.6	0.5 ± 3.5 (−1.5:2.5)	0.59
Cardiac index, L/min/m²	2.6 ± 0.7	3.4 ± 0.9	0.9 ± 0.7 (0.5:1.3)	< 0.001
Pulmonary vascular resistance, dyn · s/cm⁵†	781 ± 250	442 ± 246	−339 ± 209 (−454:−223)	< 0.001

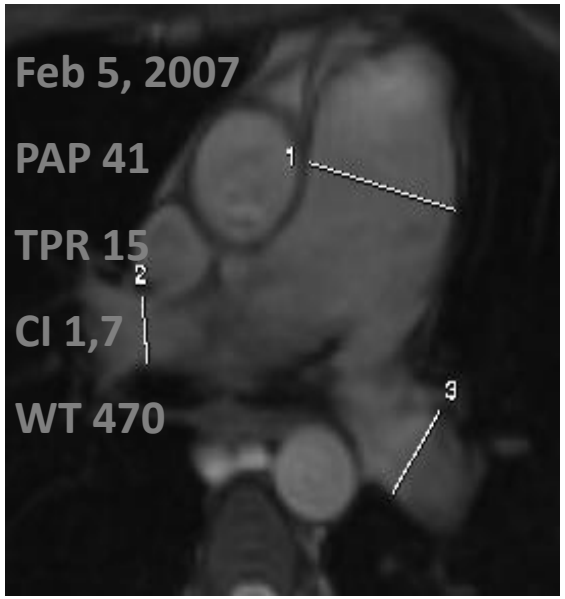
Sitbon, Am J Respir Crit Care Med 2004

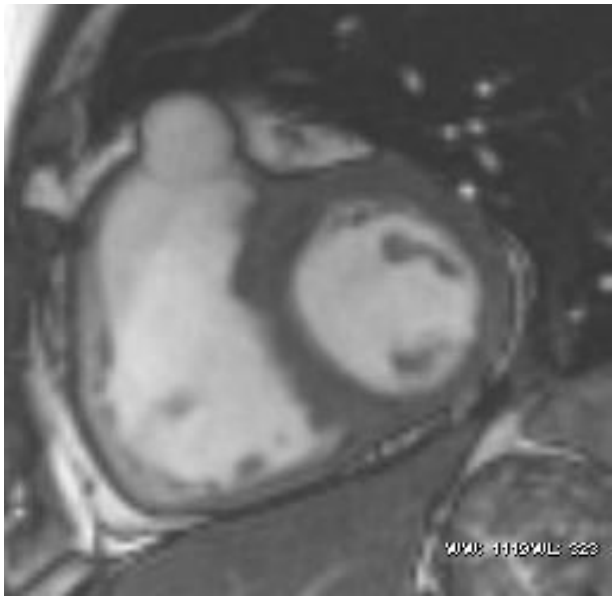
Sildenafil and HIV-PAH

- No controlled studies on its efficacy.
- Data on efficacy derive from case series

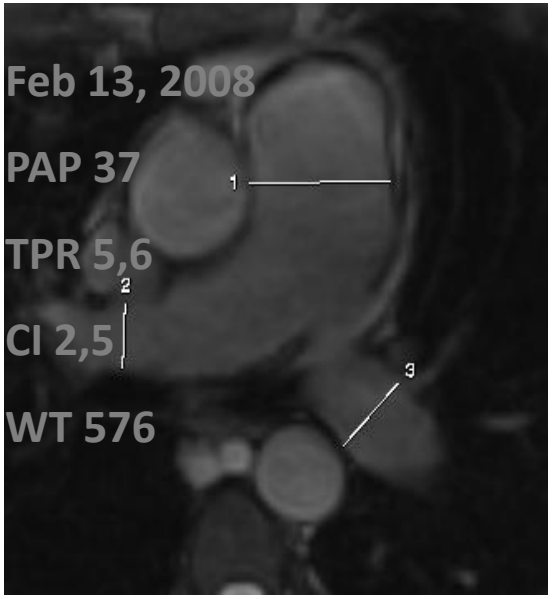
Schumacher, AIDS 2001
Alp, AIDS 2003

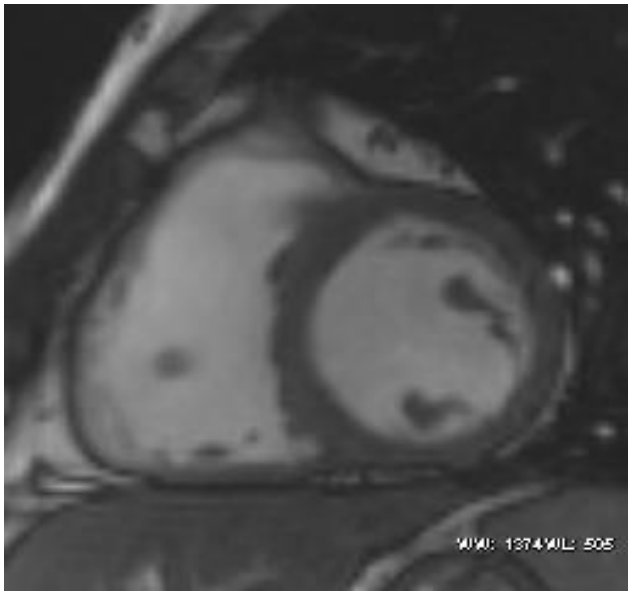
Cardiac NMR at the beginning of sildenafil therapy and 1 year later





- P.A. 40 mm, right P.A. 22, left P.A. 14 mm
- Right Ventricle
- Major axis 90 mm
- Minor axis 43 mm
- ED volume 88 ml
- ES volume 62 ml
- EF: 30 % (n.v. 40-60%)





- P.A. 35 mm, right P.A. 20, left P.A. 15 mm
- Right Ventricle
- Major axis 78 mm
- Minor axis 43 mm
- ED volume 87 ml
- ES volume 46 ml
- EF: 46 % (n.v. 40-60%)

Interactions sildenafil-HAART

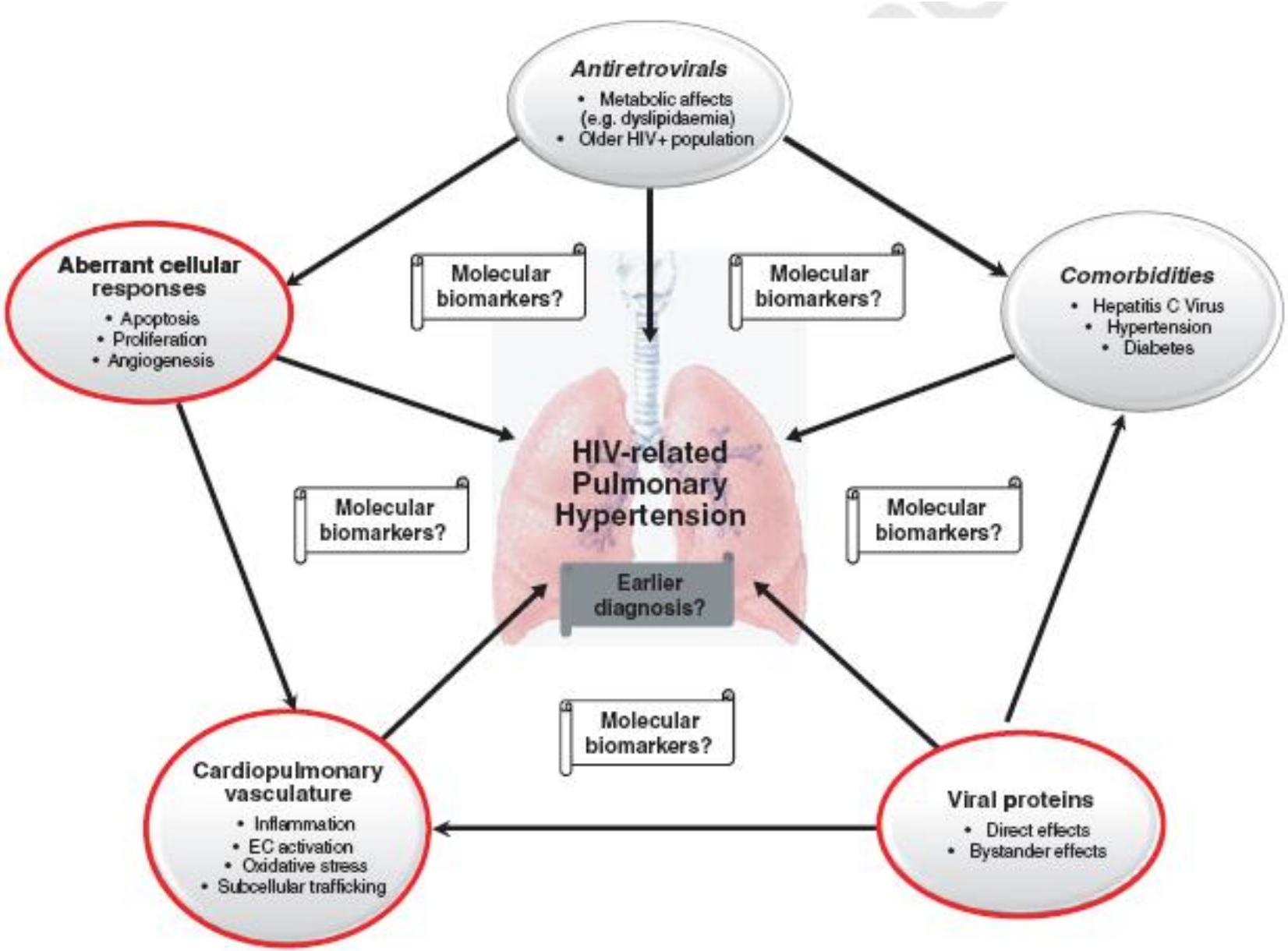
- Protease inhibitors (PI) interfere with cyt P 450

Indinavir, saquinavir, darunavir & ritonavir modify FK of sildenafil

RTV => ↑ AUC of sildenafil (11 times; 95%IC 9.0-12.0)
↑ Cmax of sildenafil (3.9 times; 95%IC 3.2-4.9)

Combination of sildenafil & ritonavir should be given with caution

Muirhead, Br J Clin Pharmacol 2000



Cicalini S et al. Clin Microbiol Infect 2010

CONCLUSIONS

The current interest in this severe and life threatening manifestation is based on the following facts:

- **the frequency of pulmonary arterial hypertension is higher (>600 times) than in the general population.**

- **This estimate means that only in North America and Western Europe, where almost 3.8 million people are living with HIV, there are about 8 – 10 000 cases of HIV infected patients with likely severe and life-threatening pulmonary arterial hypertension.**

- **PAH occurs independent of the CD4+ cell count, it is not dependent on presence or absence of antiretroviral treatment, and may develop before a patient meets criteria for the initiation of antiretroviral treatment.**

- **Recent advances in the pathobiology of PAH suggest a role of nef gene mutatiopns, viral coinfections, such as herpes viruses, viral hepatitis viruses, etc. This could partly explain the higher frequency of pulmonary arterial hypertension in HIV infected individuals,**

- **New and potent drugs against pulmonary arterial hypertension are available, and additional drugs are under development. Some of these drugs can interact with antiretroviral drugs.**

- **Finally, there are some controversies in the role of antiretroviral treatment regarding the clinical course of PAH.**