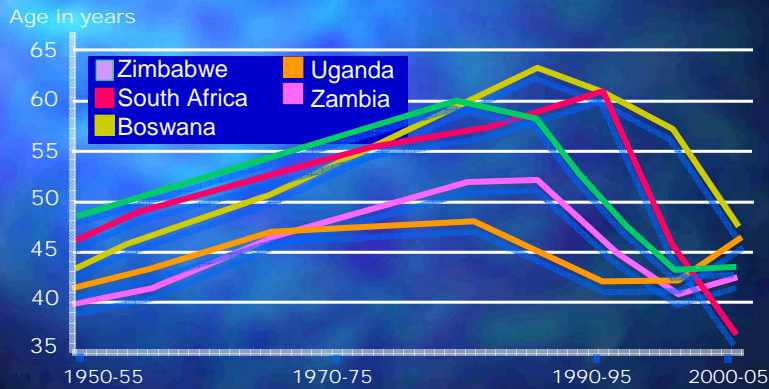
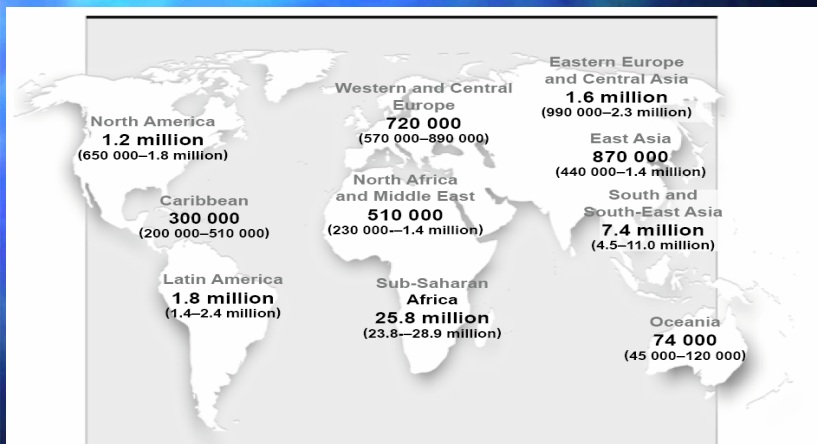


## Aids in Africa, life-expectancy



Source : united nations population division  
CNN report: Nov. 28, 2001

## ADULTS AND CHILDREN ESTIMATED TO BE LIVING WITH HIV IN 2005



**Total: 40.3 (36.7–45.3) million**

Cette présentation a été effectuée le 24 octobre 2006, au cours du Symposium "L'utilisation des analyses de laboratoire en santé publique" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse <http://www.inspq.qc.ca/jasp>.

## Problems in HIV/AIDS: 2006

- Origin of HIVs
- Origin of the AIDS epidemic
- How HIV destroys the immune system ?
- Why there is no cure
- Why there is no vaccine
- What to do !
  - For HIV infected people
  - To prevent HIV infection

## Origin of HIVs

- HIV2 : SIVmn
- HIV1 : SIVcpz for some strains ?  
The case of HIV1 O

**Simian immunodeficiency virus  
replicates to high levels in sooty  
mangabeys without inducing disease.**

CUILLE M.A., BERTHIER J.L., BOMSEL-  
DEMONTOV M.C., CHADUC Y., MONTAGNIER L.,  
HOVANESSION A.G. and CHAKRABARTI L.  
J. of Virol, 72, n°5, 3872-3886 (1998).

## **Origin of the AIDS epidemic**

- **Sociocultural factors**
- **Biological factors**
- **Environmental factors**

## The 3 Mechanisms for HIV Variability

- 1 - Errors of Reverse Transcription
- 2 - Genetic Recombination
- 3 - Incomplete Neutralization by Vif of the activity of the APOBEC3G cellular gene (A to G mutations)



**Distribution of HIV subtypes**  
Major subtypes in capitals

## Massive nosocomial infection in a children Hospital In Benghazi (Libya)

More than 420 children found  
infected in 1997-1998 with the  
same strain of HIV1  
( A/G recombinant subtype)  
(by sequence analysis of PCR gag,  
Pol, and Env fragments)

## The A/G HIV1 strain of Benghazi

More than 100 children investigated (lymphocytes  
or plasma) by PCR

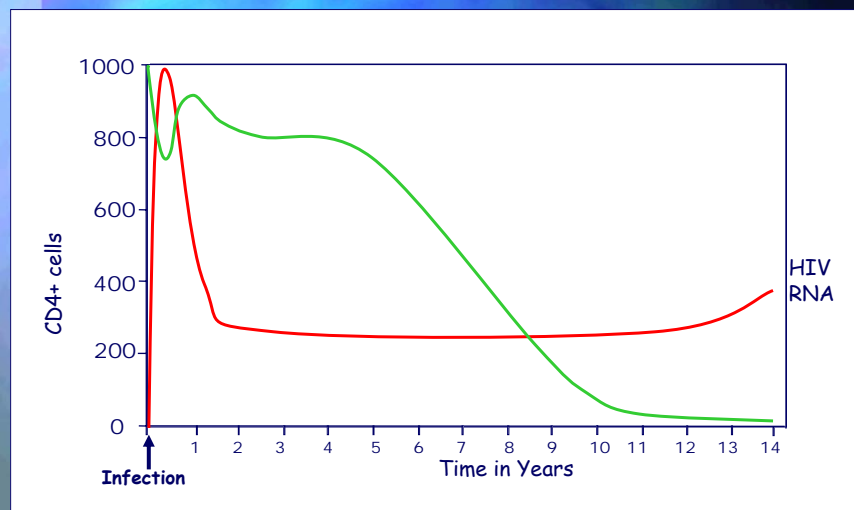
**Gag gene** (4 different areas) overall sequence  
variability: 0,87 % with 8,5% of the  
gag sequence involved in mutations.  
Compared to adult population of Ivory  
Coast, where 90% of the strains are  
A/G: 4,6% sequence variability with  
29% of the sequence showing  
mutations.

**Env gene (V3-V5)** Variability 1,5 3.5%

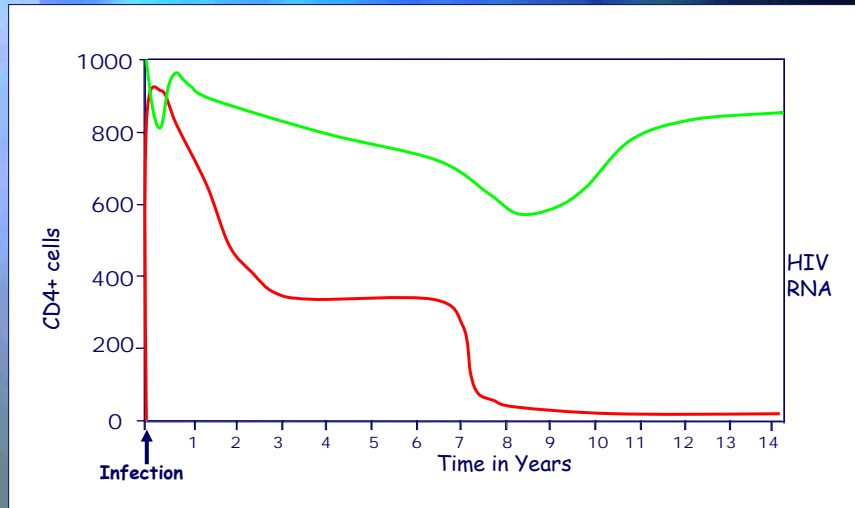
## How HIV destroys the immune system ?

- Direct Killing
- Undirect killing:
  - apoptosis
  - oxidative stress
- Co-factors

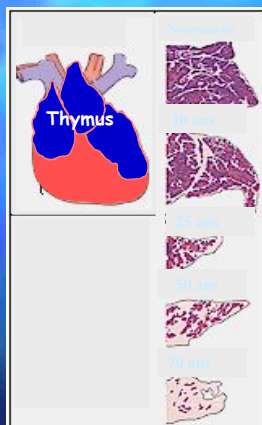
## HIV-1 Infection



# HIV-1 Infection



# Thymus Involution versus Age



Birth  
100% -  $10^{10}$  lymphocytes per day

70 year old  
**Or 25 year old AIDS patient**  
0.001% -  $10^5$  lymphocytes per day

Luc, Montagnier

World Foundation AIDS Research & Prevention

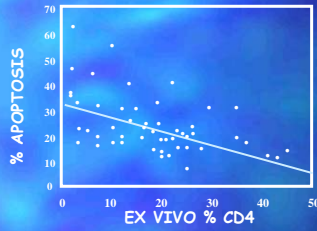
**Human immunodeficiency  
virus infection and AIDS in  
a person with negative  
serology.**

L. MONTAGNIER, C. BRENNER, S.  
CHAMARET, D. GUETARD, A. BLANCHARD,  
J. DE SAINT-MARTIN, J.D. POVEDA, G.  
PIALOUX & M.L. GOUGEON.  
J. of Infect. Dis., 175, 955-959 (1997).

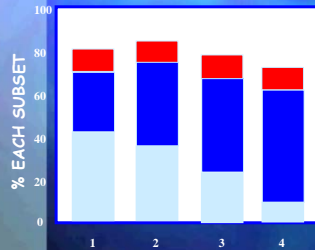
**Many uninfected lymphocytes die of apoptosis  
during HIV infection and AIDS**



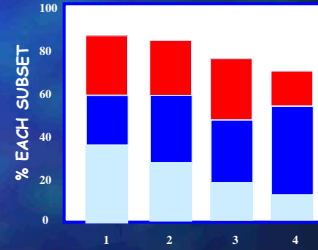
### CORRELATION BETWEEN APOPTOSIS AND EX-VIVO CD4 PERCENTAGE



EX VIVO PHENOTYPE OF THE SUBSETS



PHENOTYPE OF APOPTOTIC POPULATION

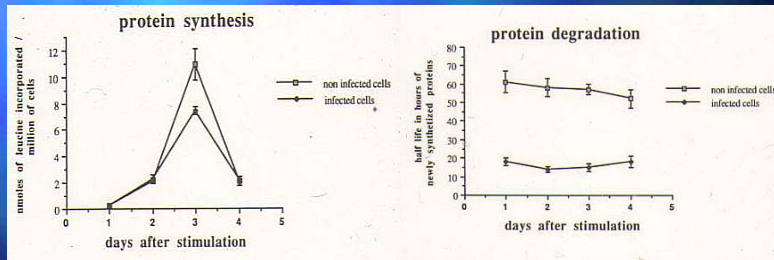


■ CD19  
■ CD8  
■ CD4  
 1: Controls  
 HIV-infected patients  
 2: CD4 > 29%  
 3: 14% < CD4 < 28%  
 4: CD4 < 13%

THE PROPORTION OF EACH SUBSET IN THE APOPTOTIC POPULATION IS CORRELATED WITH THE PROPORTION OF THE SAME SUBSETS IN THE FRESHLY ISOLATED POPULATION

M. L. Gougeon, Ph. D.

### Protein Metabolism during HIV infection



Giuseppe Piedimonte et al.

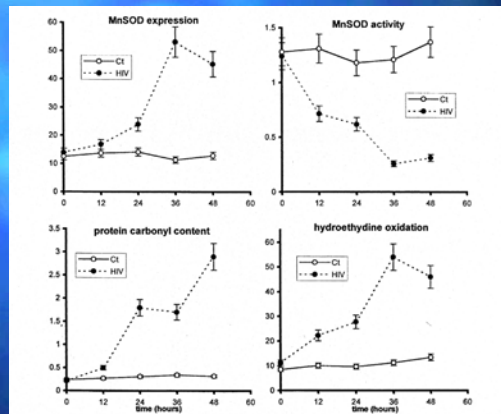
# Oxidative Stress

Unbalance between Reactive Oxygen Species and antioxidant compounds of the organism.

## Oxidative Stress in HIV infection and AIDS

- Oxidized glutathione increases
- Oxidized LDL increases
- Fast degradation of oxidized protein occurs in lymphocytes → Apoptosis

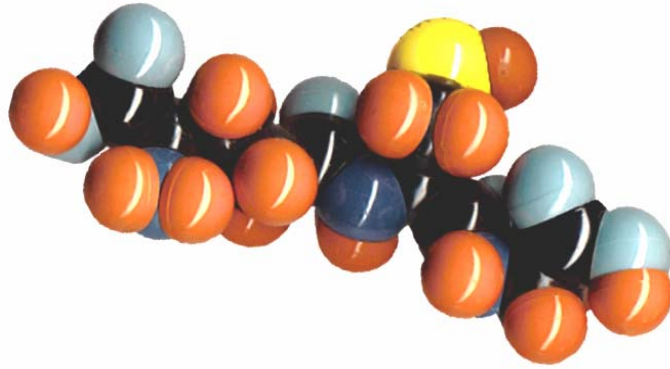
## Modification of Redox balance in patients' lymphocytes versus controls



Oxidative Protein Damage and Degradation in Lymphocytes from Patients infected with Human Immunodeficiency Virus,  
G.Piedimonte et al., J.of Infectious Diseases 1997, 176:655-64

|                             |             | Unités | Valeurs de référence |
|-----------------------------|-------------|--------|----------------------|
| Vitamines C                 | non décelée | µg/ml  | 6,21 à 15,18         |
| B Carotene                  | 9,90        | µg/dl  | 10 à 85              |
| Gluthation Réduit (GSH)     | 1195,00     | µM     | 753 à 958            |
| Gluthation Oxydé (GSSH)     | 65,08       | µM     | 1,17 à 5,32          |
| Rapport GSH/GSSH            | 16,37       | —      | 156 à 705            |
| Sélénium                    | 53,00       | µg/l   | 99 à 130             |
| Cuivre                      | 1,02        | mg/l   | 0,70 à 1,40          |
| Zinc                        | 0,56        | mg/l   | 0,70 à 1,20          |
| Rapport Cu/Zn               | 1,82        | —      | 1 à 1,17             |
| LDL oxydées                 | 192,73      | U/l    | 26 à 117             |
| Anticorps contre LDL oxydés | 71,50       | U/l    | 200 à 600            |
| ADN oxydé (8OH-dG)          | 37,02       | µg/ml  | 0 à 16               |

## Glutathione



ThyoGen Pharmaceuticals, Inc.

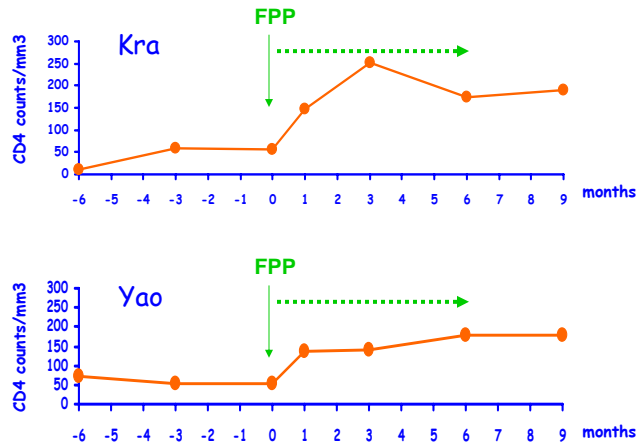


## Fermented Papaya Preparation

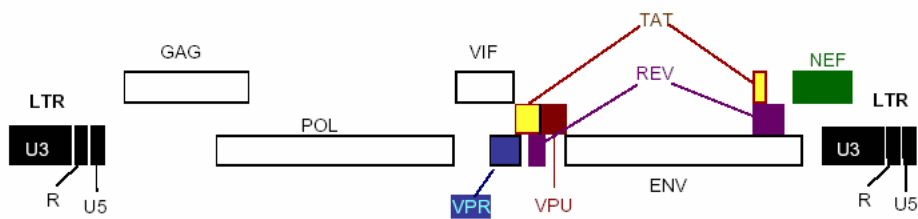
Product from non GMO Papaya fruit  
Thru a long biofermentation process  
(8 to 10 months)



## Evolution of CD4+ cell count (2 patients) according to FPP (Fermented Papaya Preparation) treatment



## HIV-1



### Regulatory proteins:

TAT: Trans-activator of HIV promoter  
 REV: Nuclear export of late, unspliced RNA to the cytoplasm

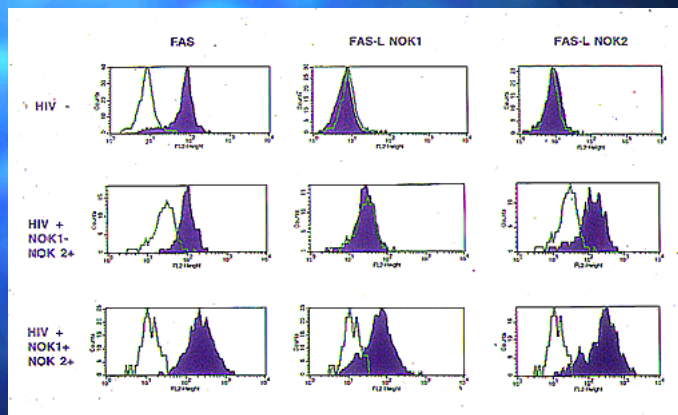
### Accessory proteins:

VPR: Induces G2 cell cycle arrest and nuclear import of the preintegration complex  
 NEF: Down-regulation of cell surface CD4 and MHC1. Enhances virion infectivity  
 VIF: virion infectivity factor  
 VPU: enhancement of virion release and CD4 degradation by targeting to the proteasome

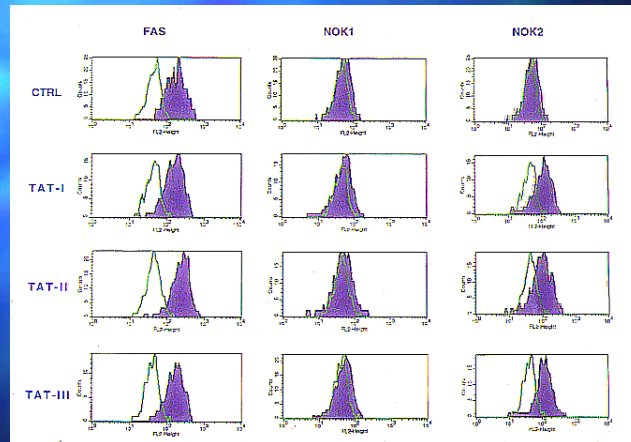
## Paracrine effects of TAT

- Decreased Expression of Mn-dependent SOD
- Induction of apoptosis in T-lymphocytes (in synergy with GP-120)
- Induction of FAS-L on monocytes

## Fas & Fas-L expression on Monocytes

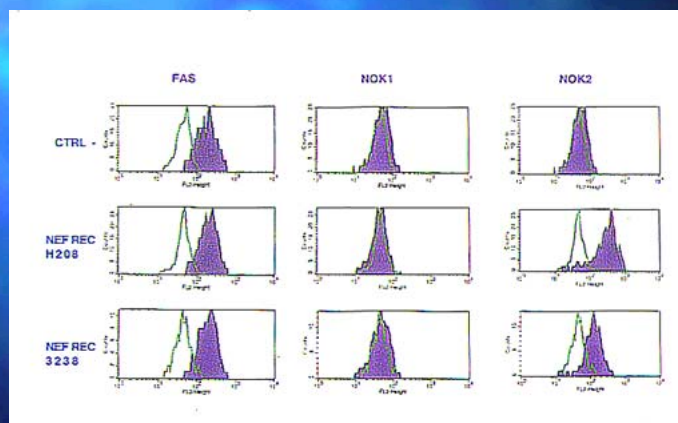


## Effect of Tat on Fas & Fas-L expression on Monocytes



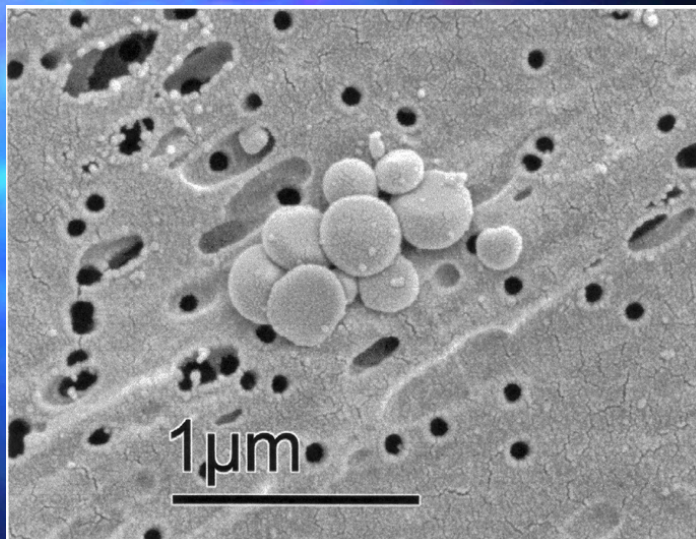
Luc Montagnier / René Olivier

## Effect of Nef on Fas & Fas-L expression on Monocytes

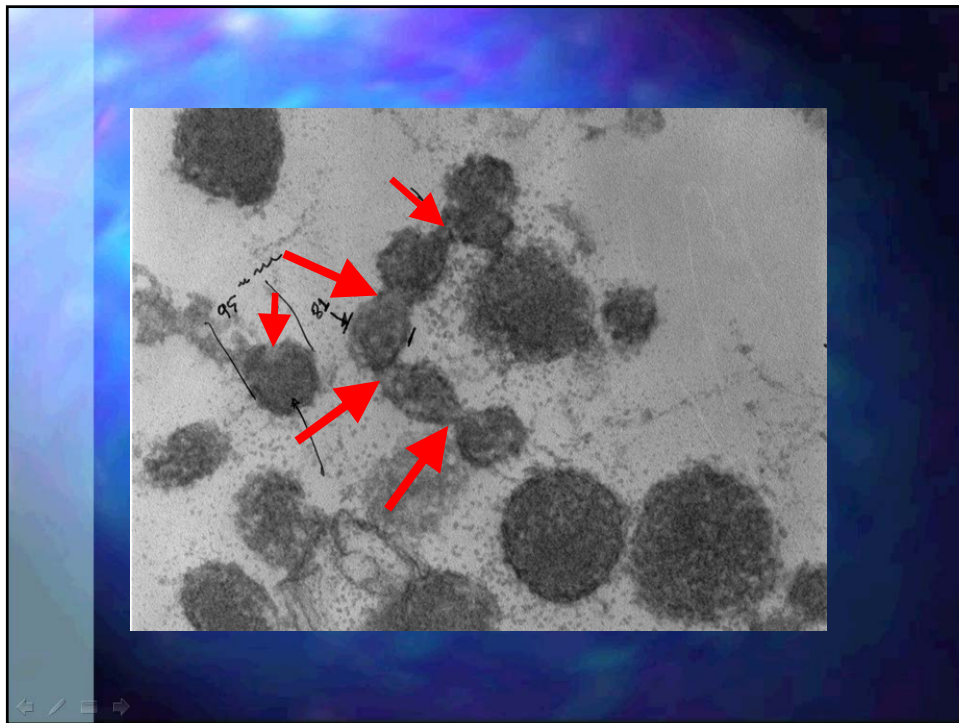
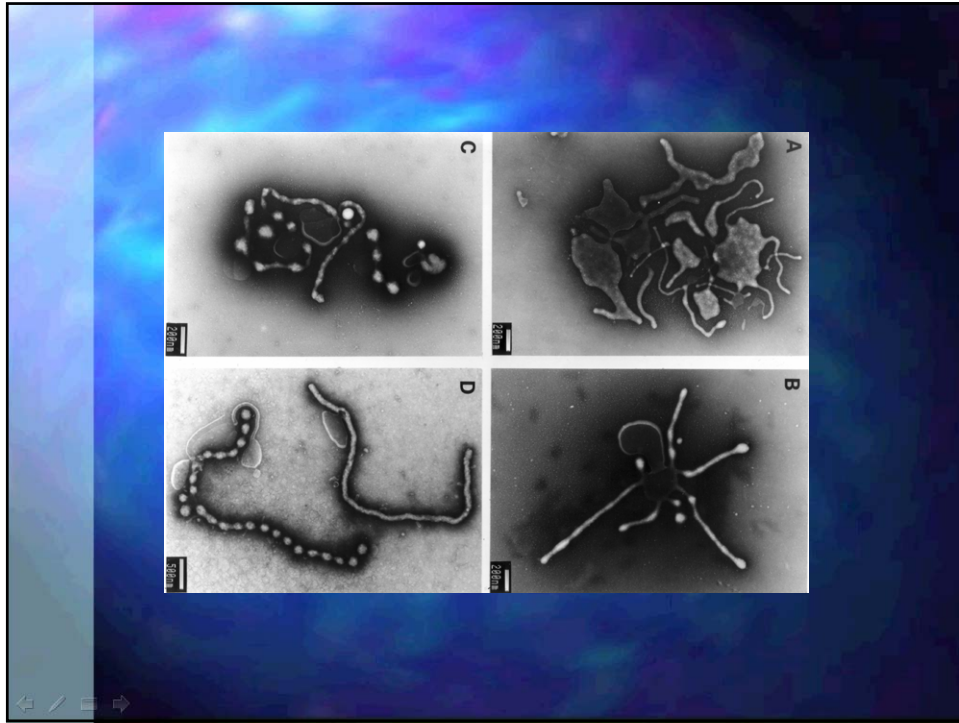


# Latent form and nanoforms of Bacteria

Role in AIDS and Chronic Diseases ?







**A longitudinal study of seroreactivity  
against *Mycoplasma penetrans* in HIV-  
infected homosexual men : association  
with disease progression.**

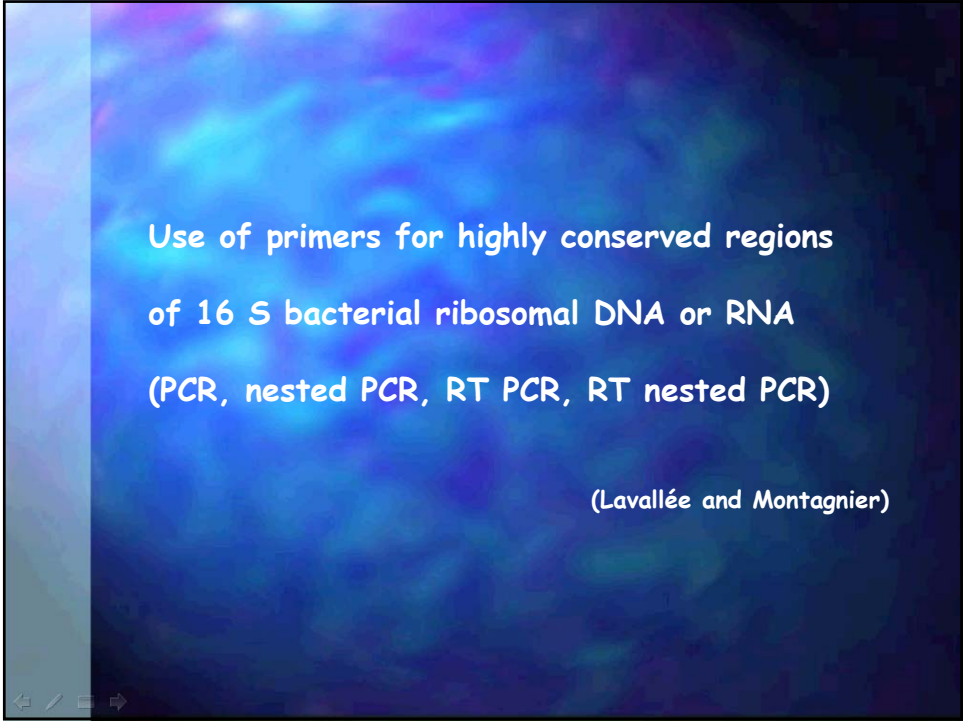
GRAU O., TUPPIN P., SLIZEWICZ B., LAUNAY V.,  
GOUJARD C., BAHRAOUI E., DELFRAISSY J.F. and  
MONTAGNIER L.  
AIDS Res. and Hum. Retr., 14, N°8, 661-667 (1998).



**High prévalence of antibodies to  
*Mycoplasma penetrans* in human  
immunodeficiencyvirus-  
seronegative and seropositive  
populations in Brazzaville,  
Congo.**

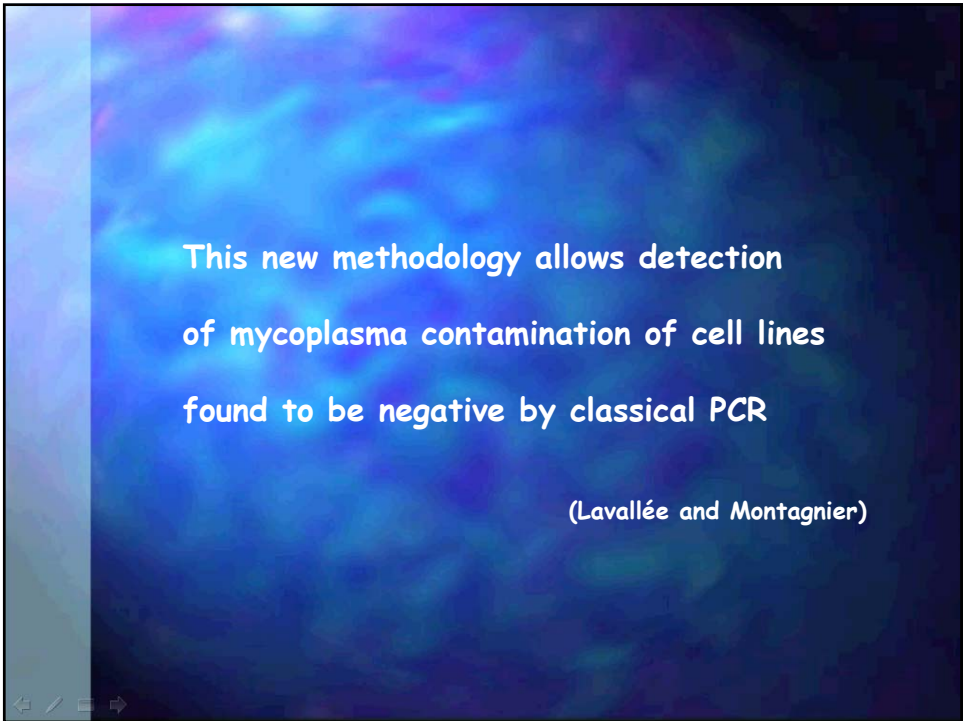
P.Tuppin, O. Delamare, V. Launay, M.Guguen,  
M.C. Samba, L. Pambou, L. Montagnier & O. Grau.  
Clin.&Diagn. Lab.Immunol. 4, N°6, 787-788  
(1997).





Use of primers for highly conserved regions  
of 16 S bacterial ribosomal DNA or RNA  
(PCR, nested PCR, RT PCR, RT nested PCR)

(Lavallée and Montagnier)

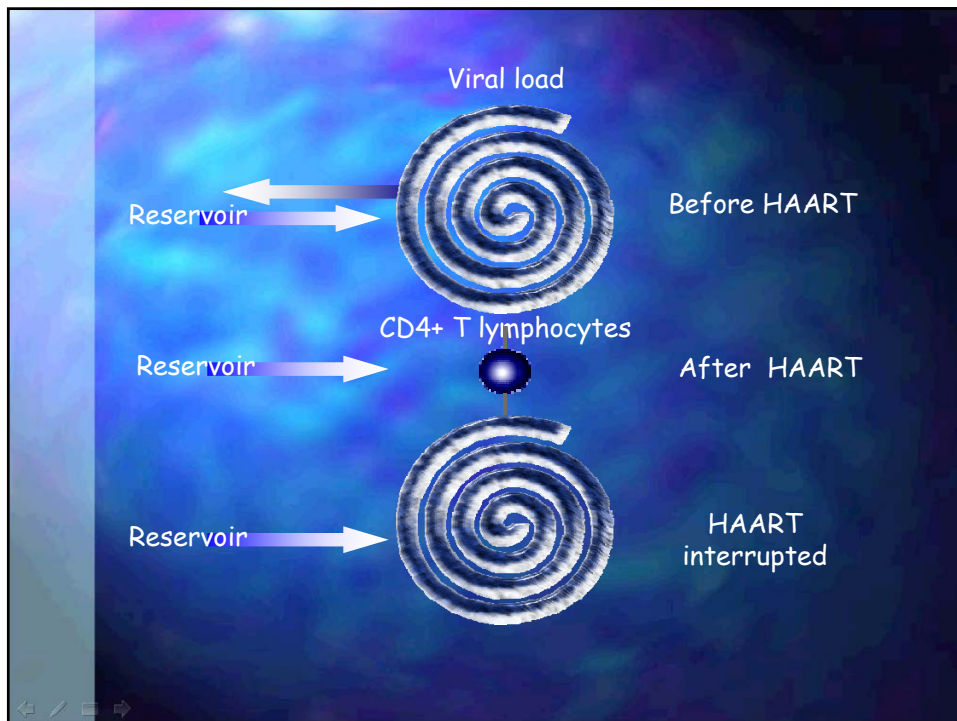


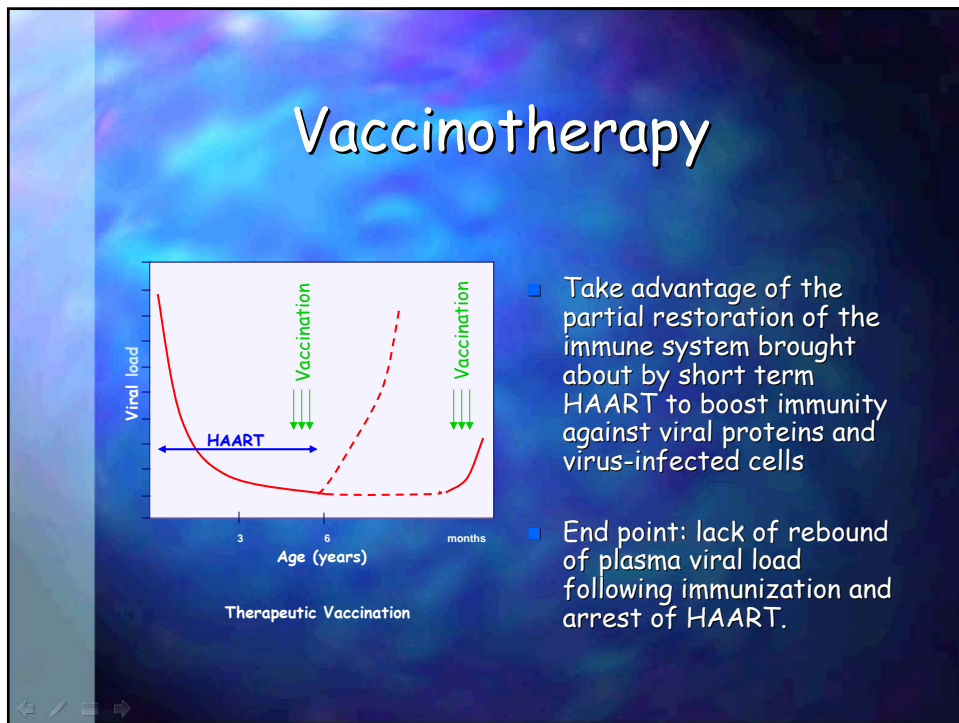
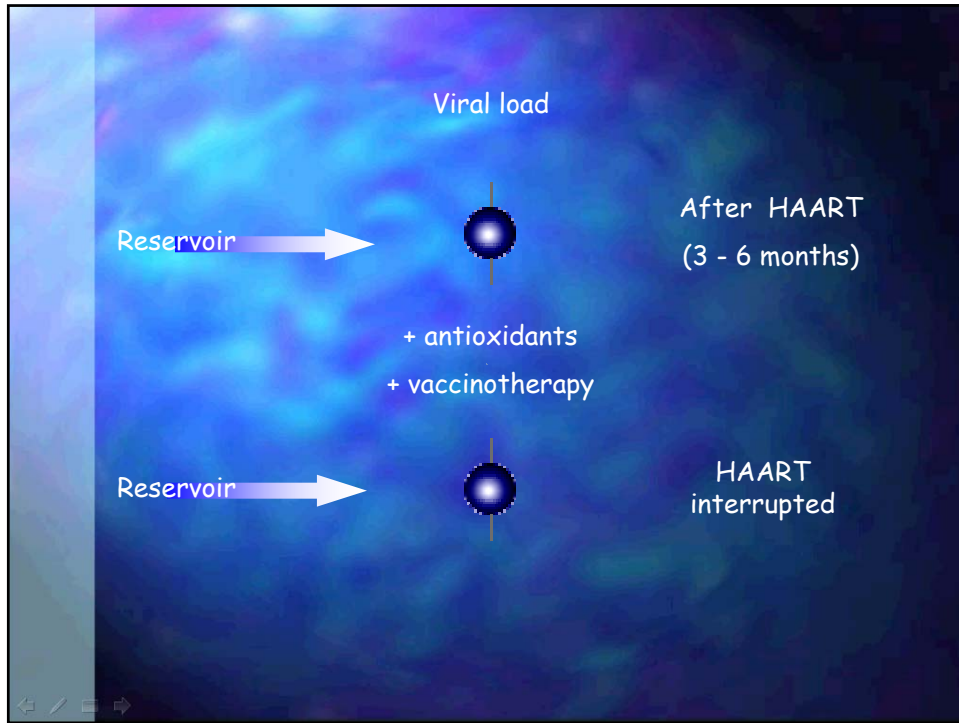
This new methodology allows detection  
of mycoplasma contamination of cell lines  
found to be negative by classical PCR

(Lavallée and Montagnier)

# Why there is no cure

- Origins of the "reservoir"
- The gap between Primary Infection and HAART period
- The residual disease



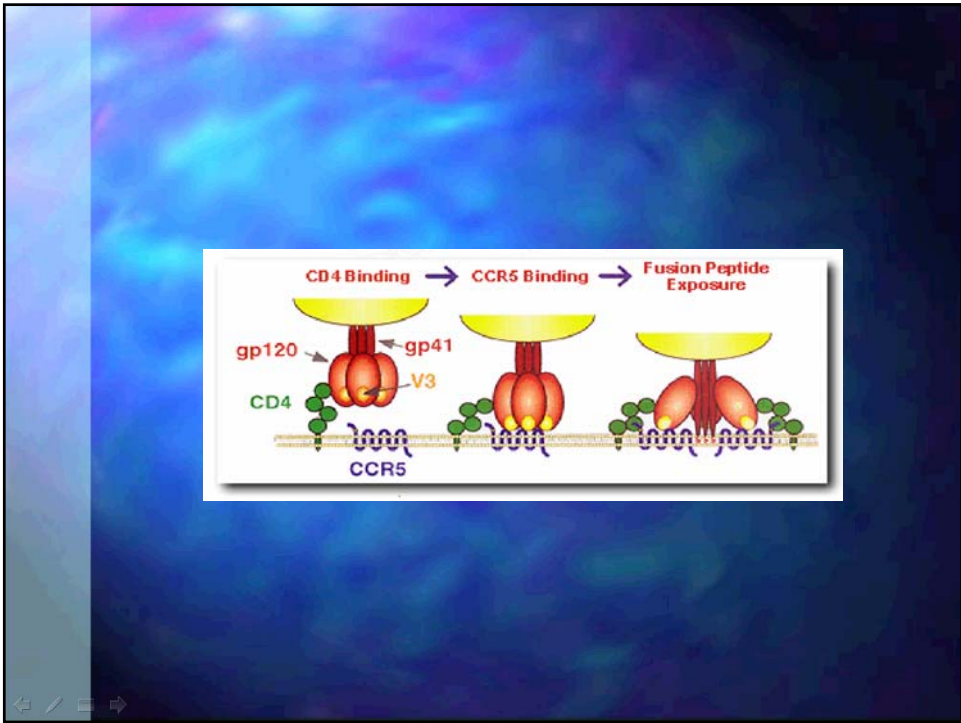
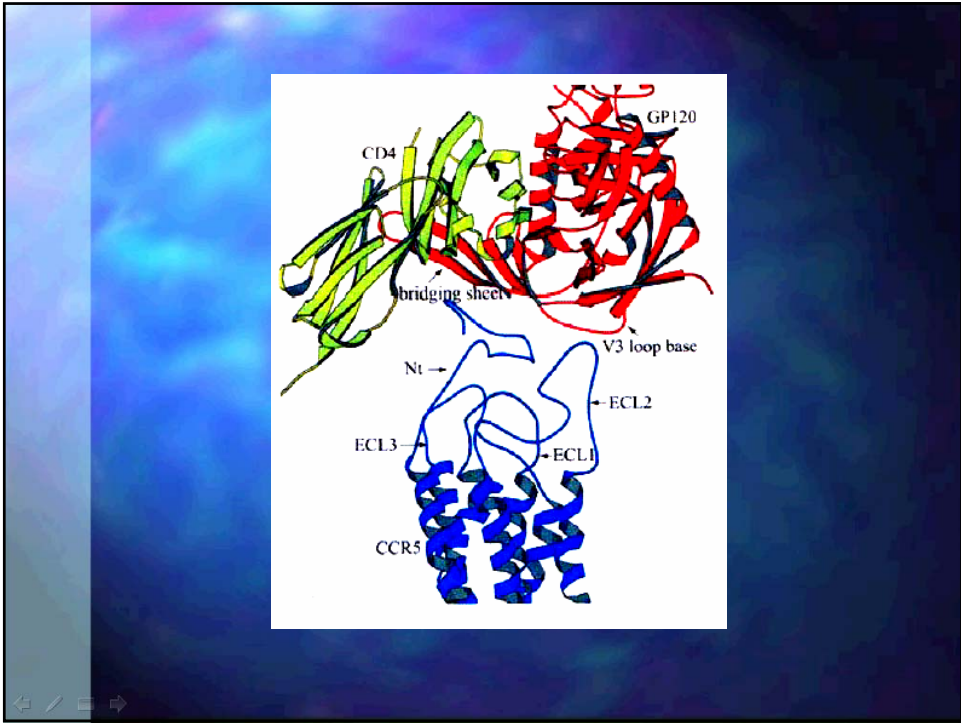


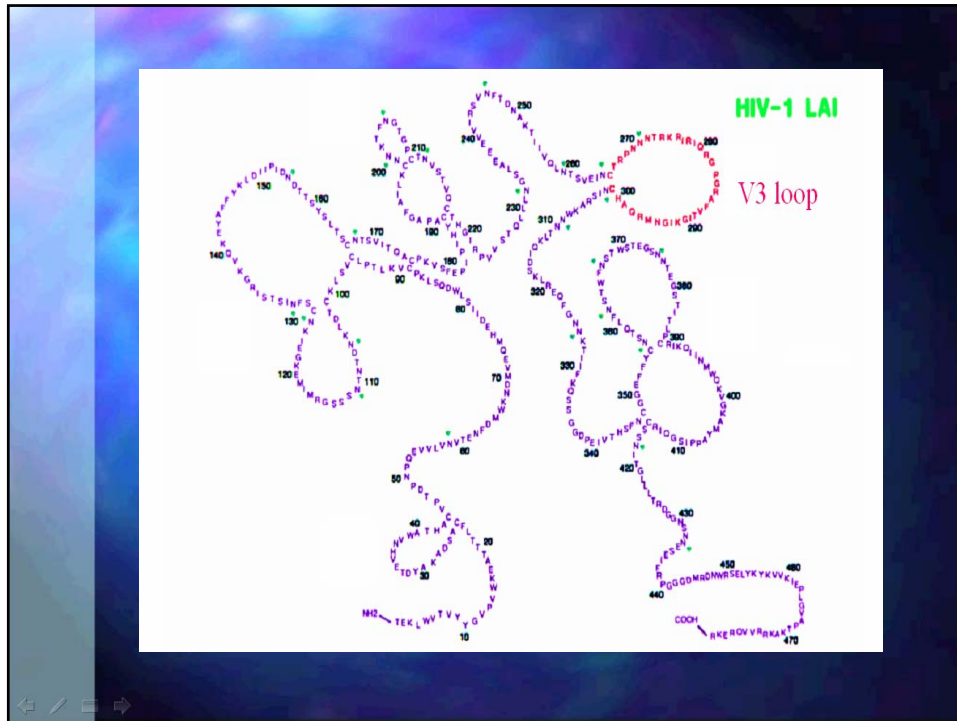
## Why there is no vaccine

- Many "dead ends" already explored
- DNA or subunit vaccines ?
- Ethical issues

Failure of vaccines  
Using the native surface  
glycoprotein of HIV...

WHY ?





## A new vaccine strategy:

1. - Show efficacy as therapeutic complement
  2. - Adapt to prevention of mucosal transmission
  3. - Test the best formulation as preventive vaccine (phase3)
- Subunit vaccines are the safest (peptides or recombinant proteins).



# What to do !

- For HIV infected people
- To prevent HIV infection
- For infants : high risk of transmission after birth



**WORLD FOUNDATION  
FOR AIDS  
RESEARCH & PREVENTION**



Centre d 'Abidjan  
(CIRBA)  
Abidjan Center



Centre Intégré de Recherche Clinique Chantal Biya

