



Twenty five years
of research on AIDS

Lessons and prospects
for cure and vaccine

By Luc Montagnier M.D.

The Prospects of Medicine Of the 21st Century:

More Prevention
Than Cure



Genetic Memory

Culture Memory

Genetic Memory

The code is the same
for all life forms
on earth

Culture Memory

- Recent # 10,000 years
- Transmission by writing, book, image, parents, school, social group,...
- Scientific Knowledge : exponential rising during the last 3 centuries.

Public Health Concern for the 21th Century

- New epidemics related to infectious agents (Bacteria, Viruses)
- Chronic diseases

HIV/AIDS

40 million contaminated people.
3 million death

Malaria

300 à 500 million clinical cases
3 million death
(90 % subsaharian, kids)

Tuberculosis

1 billion clinical cases
3 million death

Cancer

16 million death

Infectious diseases

14 to 20 million death

Factors for New Epidemics

- **Demographic growth in cities**
- **Culture Loss or gap for Hygiene, Water lack.**
- **World exchanges, travels**
- **Atmospheric and food pollution favorising oxidative stress and immune system depression**
- **Immunodepressed population aging**
- **Global warming leading to new ecological niche for infection vectors (insects).**

DNA → **RNA** → **DNA**

RT*

Cell

Virus

Cell

* Reverse Transcriptase

Reverse **T**ranscriptase

- **Endogeneous retroviruses**
- **Retroelements**
- **Search for exogeneous retroviruses (HTLV, HIV) in cancer, leukemia, AIDS**

Ann Microbiol (Paris). 1979 Oct;130B(3):349-62.

Enhancement of retrovirus production by anti-interferon serum.

Barré-Sinoussi F, Montagnier L, Lidereau R, Sisman J, Wood J, Chermann JC.

In order to investigate the role of endogenous interferon in retrovirus production by infected or induced cells, the effect of two sera raised against mouse interferon has been tested on various C-type murine viruses. Addition of a highly potent anti-interferon serum to 3T3/IC cells chronically infected by the Moloney strain of MLV results in a considerable increase of virus production, as tested by reverse transcriptase assay. This effect is neutralized by an excess of exogenous interferon. The greatest effect of anti-interferon sera was obtained in the derepression of endogenous retroviruses: in K. BALB/c cells treated by IUdR, anti-interferon serum increases up to 50-fold the expression of the endogenous virus. The extinction of virus production which secondarily occurs after its induction by IUdR is likely to be caused by cellular endogenous interferon. The biological parameters of the viral agent produced in the presence of anti-interferon serum are those of the xenotropic endogenous virus.

The circumstances of HIV isolation at the Pasteur Institute in 1983

AIDS study Group

(W. Rozenbaum, J. Leibovitch)

Institut Pasteur Production

(HBV Vaccine from plasmas)

Group of the Viral Oncology Unit

(L. Montagnier, F. Barré-Sinoussi,

J-C. Chermann)

**Biopsy of a lymph node from a gay men,
Lymphocytes put in culture (Protein A, IL2)**

L. Montagnier : Culture of lymphocytes from the biopsy



F. Barre-Sinoussi : RT + at 2,3 weeks



L. Montagnier : Passage to lymphocytes of a blood donor



F. Barre-Sinoussi : RT +

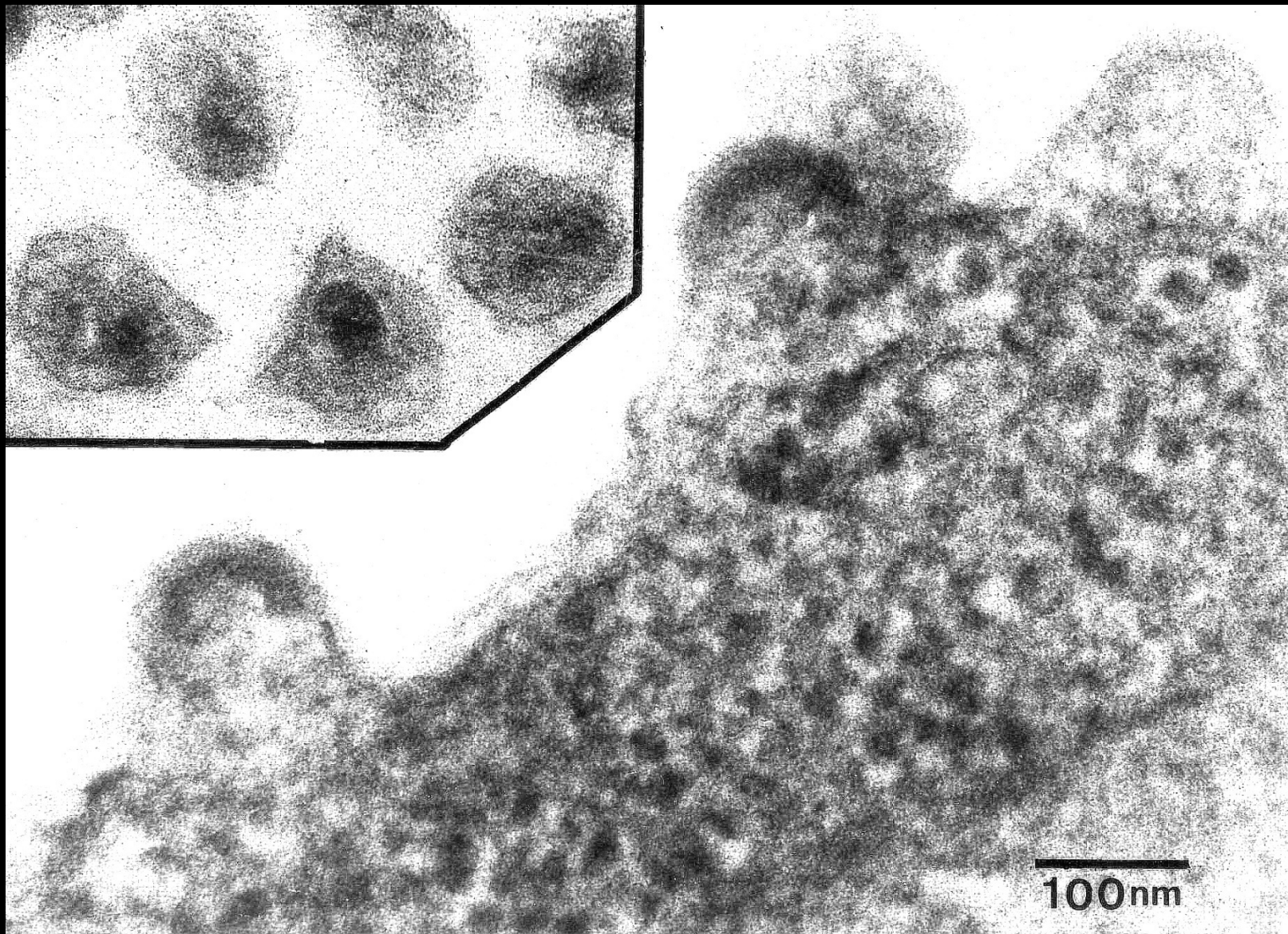


HTLV1 ? No !

Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)

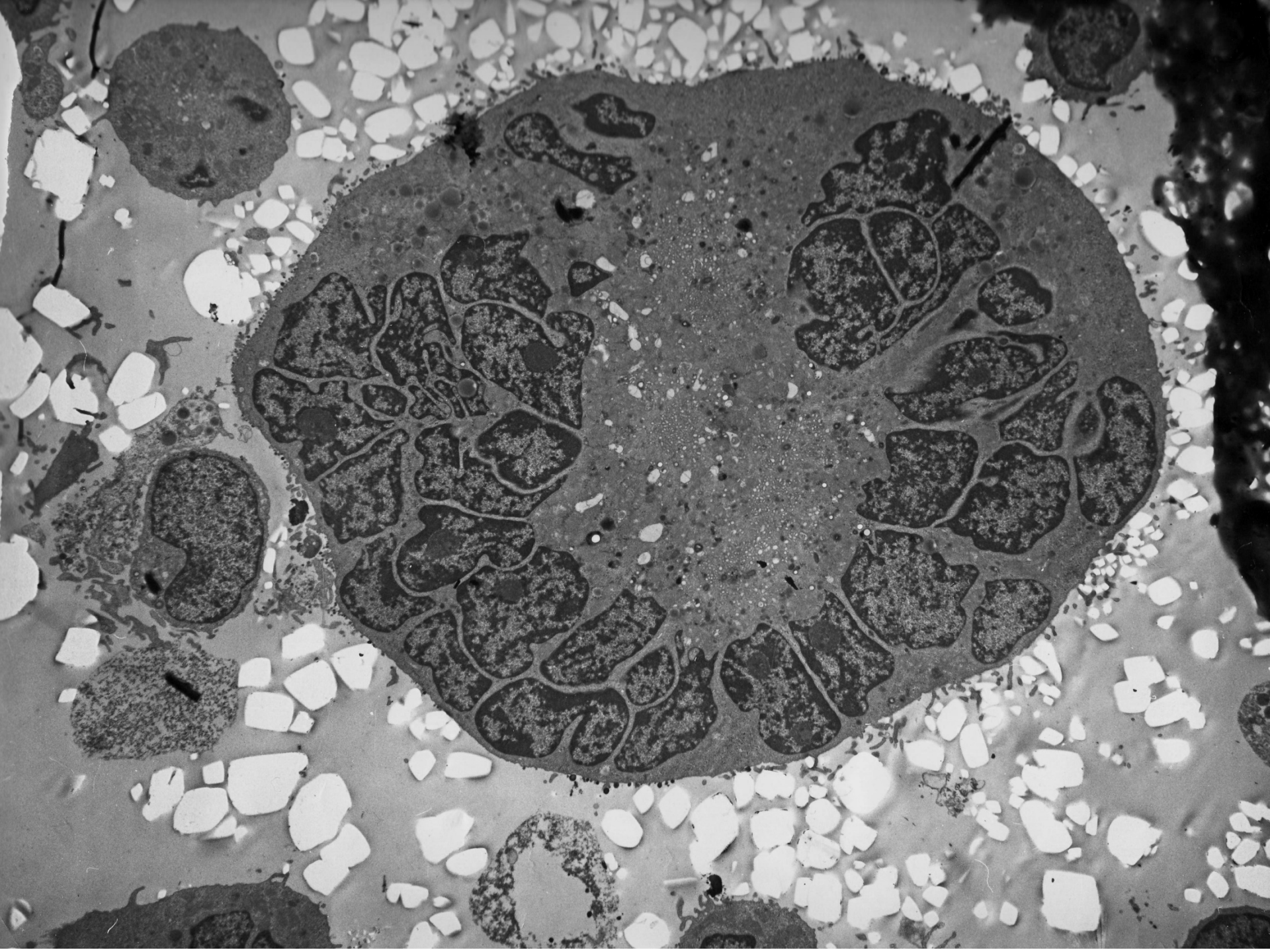
F. Barré-Sinoussi, J. C. Chermann, F. Rey, M. T. Nugeyre, S. Chamaret, J. Gruest, C. Dauguet, C. Axler-Blin, F. Vézinet-Brun, C. Rouzioux, W. Rozenbaum, and L. Montagnier

Abstract. A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumor virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.



First viral isolates of the viral oncology unit

Bru		Gay man, caucasian	Pre-AIDS
Loi		Haemophiliac, caucasian	AIDS
Lai		Gay man, caucasian	AIDS (Ks)
Eli		Zaire	AIDS



- *Sero-Epidemiology*

(F. Brun-Vesinet, Ch. Rouzioux, J.C. Chermann)

- *Tropism for CD4 T lymphocytes*

(J.C. Gluckman, D. Klatzmann, J. Gruest, L. Montagnier)

- *Identification of the first receptor as CD4*

(J.C. Gluckman, D. Klatzmann, J. Gruest, L. Montagnier)

- *Molecular cloning and sequencing*

(S. Wain-Hobson, M. Alizon, P. Sonigo, S. Cole, O. Danos, P. Tiollais)

Reprinted from *Human T-cell Leukemia/Lymphoma Viruses*
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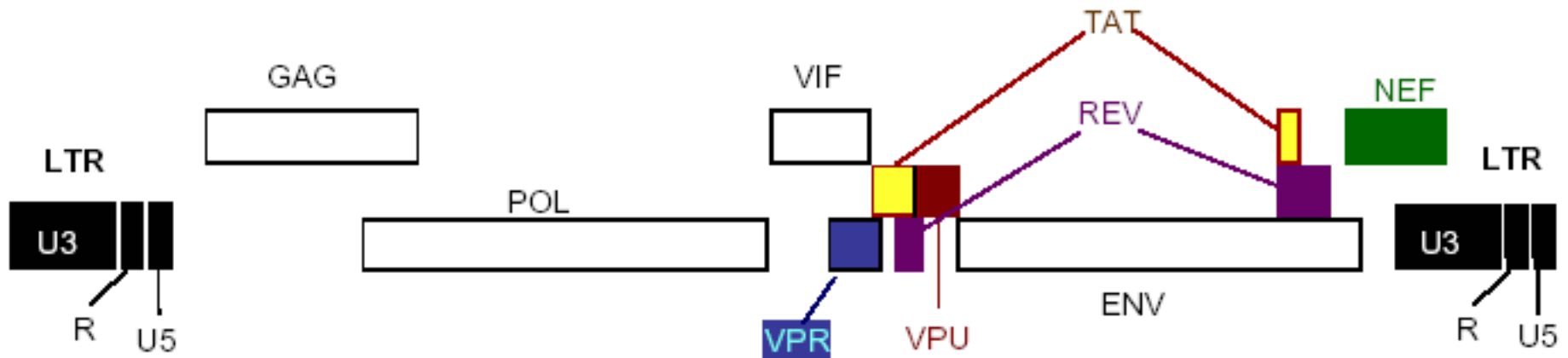
Presented at the meeting on
HTLV in Cold Spring Harbor,
September 15, 1983

A New Human T-Lymphotropic Retrovirus: Characterization and Possible Role in Lymphadenopathy and Acquired Immune Deficiency Syndromes

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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

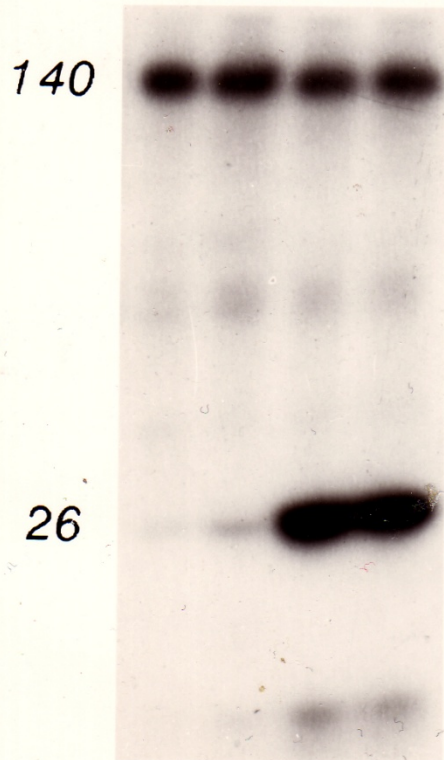
VIF: virion infectivity factor

VPU: enhancement of virion release and CD4 degradation by targeting to the proteasome

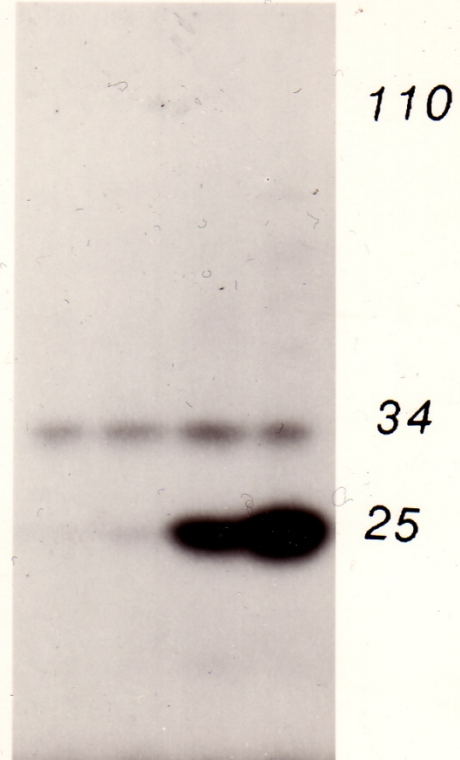
Some Milestones in the Research of AIDS

- 1981 Identification of the disease in the USA
- 1983 First isolation of HIV
- 1984 Confirmation of HIV as the causal agent of AIDS - Biological and molecular characterization
- 1985 First blood tests to eliminate transmission of HIV by blood transfusion
- 1986 Isolation of HIV-2

HIV-2



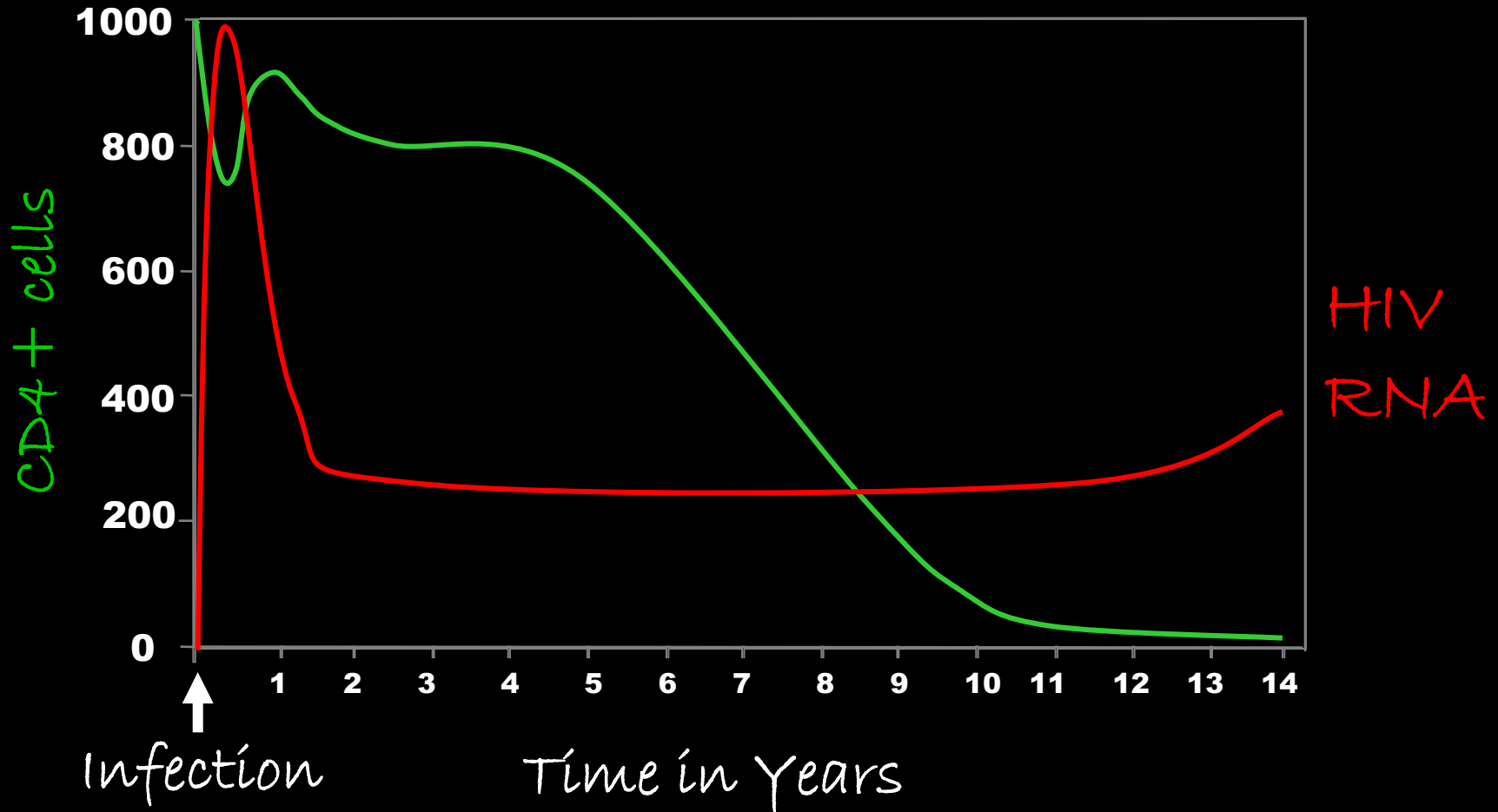
HIV-1



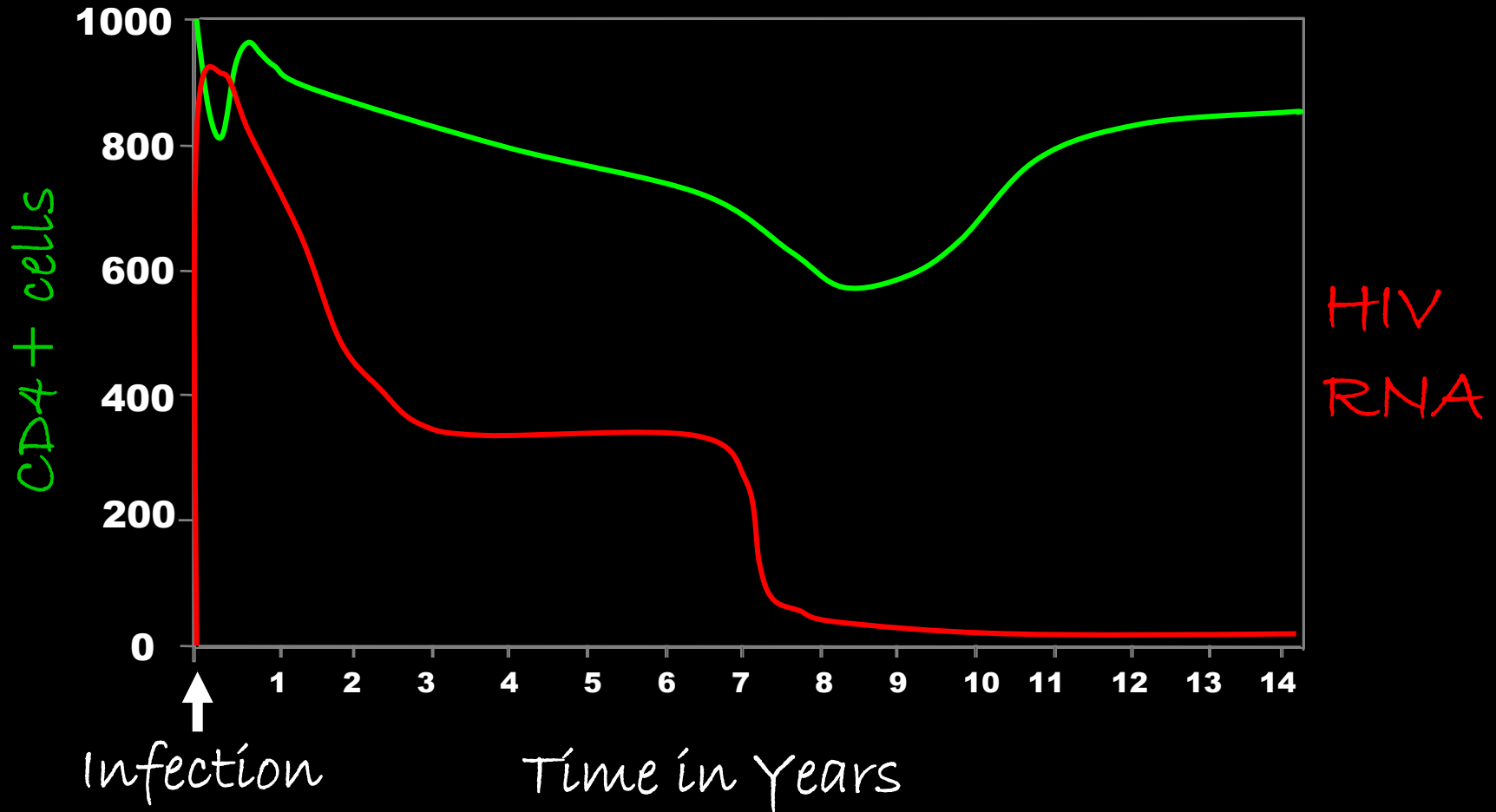
Some Milestones in the Research of AIDS 2

- 1987 First use of AZT as an antiretroviral drug
- 1991 Apoptosis as a mechanism of cell death in AIDS
- 1995 Decrease of HIV perinatal transmission with AZT
- 1995 Demonstration of high rate of HIV replication during the silent period of infection
- 1996 Identification of HIV main co-receptors
- 1996-97 Generalization of HAART in developed countries

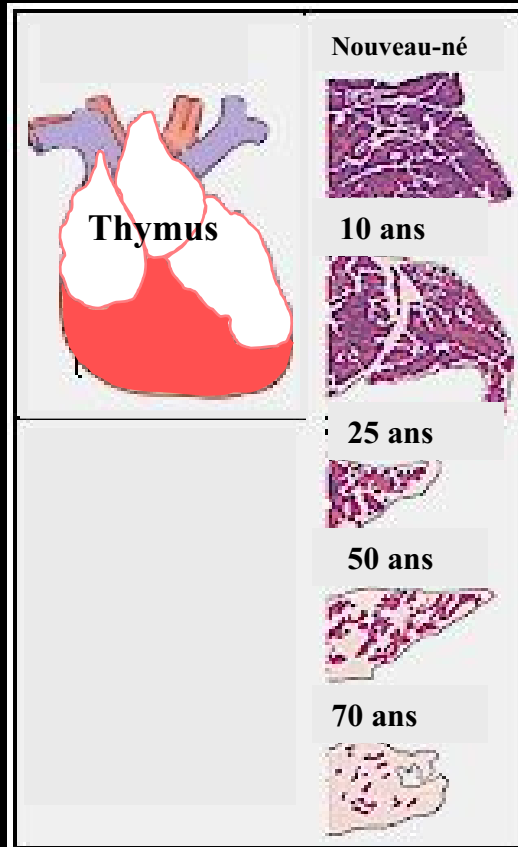
HIV-1 Infection



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

The 4 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

4 - Oxidative Stress

**Oxidative stress
Weakens the immune system**



**Activates transcription factors
(NF-kappa B)**



**Activates genes involved
in cell division, inflammatory cytokines,
lymphocytes activation**



**Immune dysfunction, apoptosis
(TH1 → TH2)**

Oxidative Stress in HIV infection and AIDS

- Oxidized glutathione increases
- Oxidized LDL increases
- Fast degradation of oxidized protein occurs in lymphocytes → Apoptosis
- Induction of DNA mutations and chromosome breakage

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
- Activation of T lymphocytes under low oxygen pressure

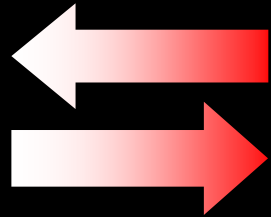
HIV/AIDS

twenty five years later

NO CURE!

Viral load

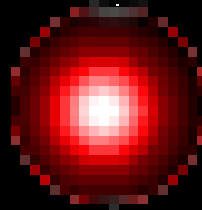
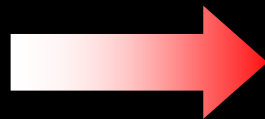
Reservoir



Before HAART

CD4+ T lymphocytes

Reservoir



After HAART

Reservoir



HAART
interrupted

What is the nature
of the reservoir?

HIV/AIDS

twenty five years later

NO VACCINE!

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

WHY?

HIV/AIDS

twenty five years later

NO cure, no vaccine,
but hopes for a
cure by a vaccine!

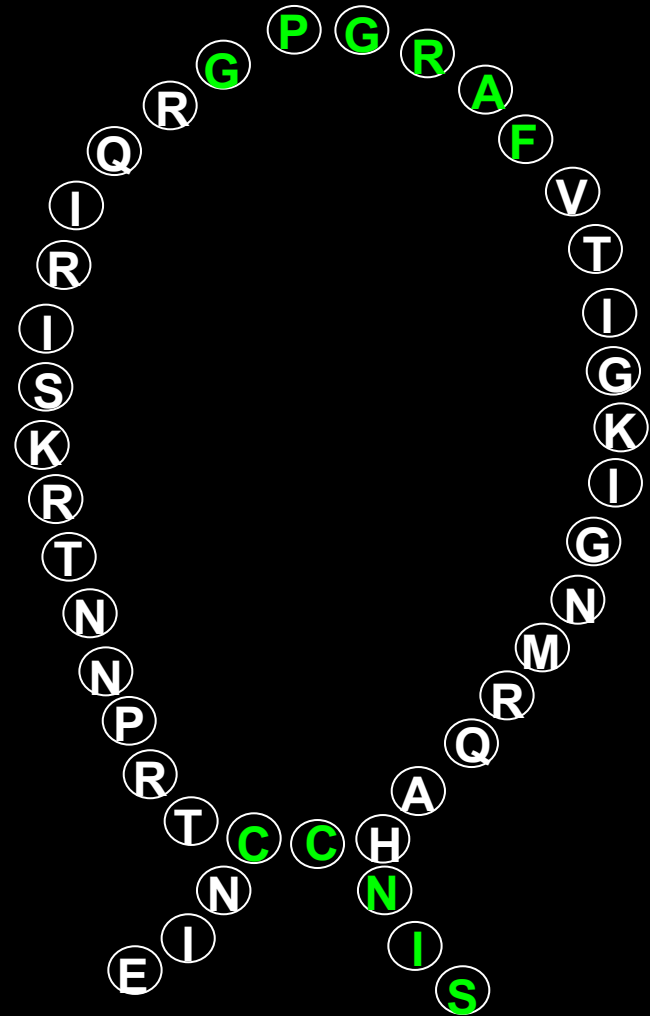
Objective

Self-control of HIV infection by the patient's own immune system:

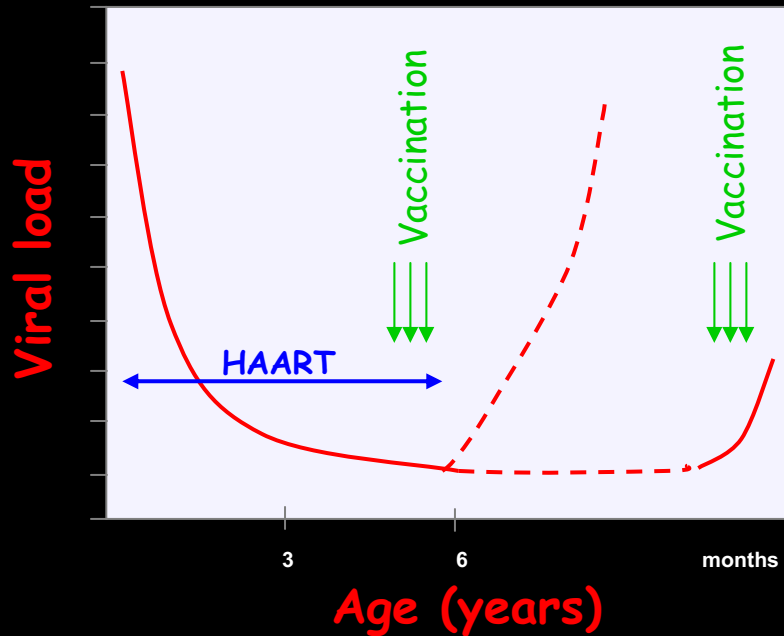
- No disease will occur
- The patient will have lower ability to transmit the virus

Immunodominant
and Hypervariable
Domain
in HIV-1 gp160

The V3 loop spans a.a. 303-338



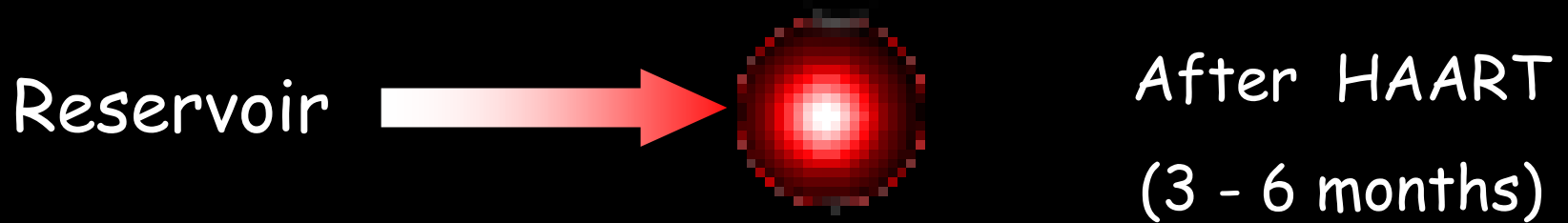
Vaccinotherapy



Therapeutic Vaccination

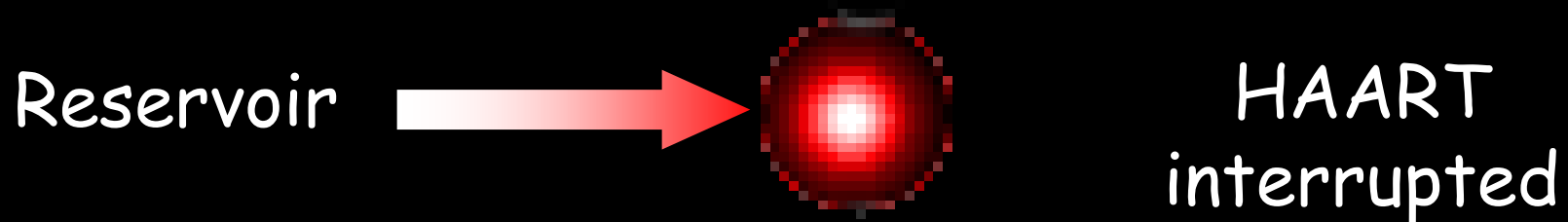
- Take advantage of the partial restoration of the immune system brought about by short term HAART to boost immunity against viral proteins and virus-infected cells
- End point: lack of rebound of plasma viral load following immunization and arrest of HAART.

Viral load



+ antioxidants

+ vaccinotherapy



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)

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