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
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 21\textsuperscript{th} Century

- New epidemics related to infectious agents (Bacteria, Viruses)
- Chronic diseases
<table>
<thead>
<tr>
<th>Disease</th>
<th>Description</th>
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<tbody>
<tr>
<td>HIV/AIDS</td>
<td>40 million contaminated people. 3 million death</td>
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<tr>
<td>Malaria</td>
<td>300 à 500 million clinical cases 3 million death (90 % subsaharian, kids)</td>
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<tr>
<td>Tuberculosis</td>
<td>1 billion clinical cases 3 million death</td>
</tr>
<tr>
<td>Cancer</td>
<td>16 million death</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>14 to 20 million death</td>
</tr>
</tbody>
</table>
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 $\rightarrow$ RNA $\rightarrow$ DNA

RT*  

Cell  Virus  Cell

* Reverse Transcriptase
Reverse Transcriptase

- Endogeneous retroviruses
- Retroelements
- Search for exogeneous retroviruses (HTLV, HIV) in cancer, leukemia, AIDS
Enhancement of retrovirus production by anti-interferon serum.


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-Lymphotrophic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)


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

<table>
<thead>
<tr>
<th>Name</th>
<th>Gender</th>
<th>Description</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Bru</td>
<td>Male</td>
<td>Gay man, caucasian</td>
<td>Pre-AIDS</td>
</tr>
<tr>
<td>Loi</td>
<td>Male</td>
<td>Haemophiliac, caucasian</td>
<td>AIDS</td>
</tr>
<tr>
<td>Lai</td>
<td>Male</td>
<td>Gay man, caucasian</td>
<td>AIDS (Ks)</td>
</tr>
<tr>
<td>Eli</td>
<td>Female</td>
<td>Zaïre</td>
<td>AIDS</td>
</tr>
</tbody>
</table>
• **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*  
© 1984 by Cold Spring Harbor Laboratory

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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Francoise Barré-Sinoussi,*  
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Gerard-Adrien Saimot,† Willy Rozenbaum,‡  
Jean Claude Gluckman,‡ David Klatzmann,‡  
Etienne Vilmer,§ Claude Griscelli,§  
Claire Foyer-Gazengel,§ and Jean Baptiste Brunet†
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

140
26

HIV-1

110
34
25
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1987</td>
<td>First use of AZT as an antiretroviral drug</td>
</tr>
<tr>
<td>1991</td>
<td>Apoptosis as a mechanism of cell death in AIDS</td>
</tr>
<tr>
<td>1995</td>
<td>Decrease of HIV perinatal transmission with AZT</td>
</tr>
<tr>
<td>1995</td>
<td>Demonstration of high rate of HIV replication during the silent period of infection</td>
</tr>
<tr>
<td>1996</td>
<td>Identification of HIV main co-receptors</td>
</tr>
<tr>
<td>1996-97</td>
<td>Generalization of HAART in developed countries</td>
</tr>
</tbody>
</table>
HIV-1 Infection

- CD4+ cells
- HIV RNA

Infection vs. Time in Years
HIV-1 Infection

- CD4+ cells
- HIV RNA

Infection Time in Years
Thymus Involution versus Age

Birth
100% - 1010 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!
Reservoir Before HAART

Viral load

CD4+ T lymphocytes

After HAART

Reservoir

HAART interrupted

Reservoir
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

- 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

Reservoir $\rightarrow$ After HAART (3 - 6 months)
+ antioxidants
+ vaccinotherapy

Reservoir $\rightarrow$ HAART interrupted
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 (phase 3)
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