HIV: a discovery opening the road to novel scientific achievements and global health improvement

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Early 1980s: the world faces the alarming signals of a new epidemic

June 1981

- First clinical and epidemiological observations of *Pneumocystis carinii* pneumonia and Kaposi’s sarcoma in homosexual men in the US (*MMWR Weekly*)

1982

- The term AIDS (acquired immunodeficiency syndrome) is coined.
- First known cases of AIDS in patients having received blood transfusions
- First known cases of AIDS in women, infected by heterosexual transmission

December 1982

- Mobilization of retrovirologists at the Institut Pasteur
Early 1983: Isolation of LAV

Fig. 1. Analysis of virus from patient 1 on sucrose gradients. Cord blood T lymphocytes infected with virus from patient 1 were labeled for 18 hours with $[^3]H$-uridine (28 Ci/mmole, Amersham; 20 µCi/ml). Cell-free supernatant was ultracentrifuged for 1 hour at 50,000 rev/min. The pellet was resuspended in 200 µl of NTE buffer (10 mM tris, pH 7.4, 100 mM NaCl, and 1 mM EDTA) and centrifuged over a 3-ml linear sucrose gradient (10 to 60 percent) at 55,000 rev/min for 90 minutes in an IEC type SB 498 rotor. Fractions (200 µl) were collected, and 30 µl samples of each fraction were assayed for DNA polymerase activity with 5 mM Mg$^{2+}$ and poly(A)$\cdot$oligo-(dT)$_{12-18}$ as template primer; a 20-µl portion of each fraction was precipitated with 10 percent trichloroacetic acid and then filtered on a 0.45-µm Millipore filter. The $[^3]H$-labeled acid precipitable material was measured in a Packard β counter.
• Propagation of LAV on PBMCs and on cord blood lymphocytes
• RT activity detected according to HTLV-1 RT conditions
• Identification of p25: no cross reactivity with HTLV1p24 (IFA& RIA)
• No cross reactivity with HTLV-1 p19
• Presence of LAV Ab in a second patient
May 1983
Urgent need for reactivity and mobilization

1. Further characterization of the virus

2. Convince the scientific community and authorities that LAV was the etiological agent of AIDS by establishing a clear link between the virus and the disease (1983-1984).

- Stop any other research programs in our lab
- Mobilization of a network of efficient collaborations

Mobilization of a private company: a strong and efficient partnership with Sanofi Diagnostics Pasteur

1. Develop serological tests for diagnosis (1983-1985)
HIV research: from bed-side to bench to bed-side

1983

Identification of HIV-1 antigens

Tropism and cytopathogenicity of HIV-1

Characterisation of RT

Cloning and sequencing of HIV

Diagnostic Tests

Prevention of transmission by blood
Prevention of sexual transmission

CD4 cell monitoring

Development of first ARV

AZT as therapy
AZT as prevention (MTCT)

Viral load and ARV resistance

HAART
Diversity and origin of HIV

HIV-1
- group N
- group O

HIV-2

HIV-1

HIV-2
HIV pathogenesis:
what do we know and how can we learn more?
Natural History of HIV infection

- Immunological setpoint (before seroconversion)
- Viral setpoint (6 months p.i.)
- Primary infection
- Chronic infection
- AIDS
- Blood CD4+ viremia
- Intestinal CCR5+ CD4+ T memory cells
- Viral Reservoirs
- Chronic Immune Activation
Interplay of host and viral determinants in HIV pathogenesis

Viral factors
(tat, nef, vif, vpr, vpu, gag, pol, env, rev..)

- Tropism & Replicative capacity
- Genetic Variations in critical genes
- Immunogenicity
- Immunosuppressive factors
-....

Host Determinants

- Host Immune Responses
  - Adaptive Immunity (CD8 and/or CD4 responses; Mucosal immunity)
  - Innate Immunity (NK; Suppressive factors; Non Cytotoxic CD8 responses; CCR5 antibody...)

- Host genetics and polymorphisms
  - HIV coreceptors and ligands
  - HLA (B27, B57 alleles...)
  - Host restriction factors (APOBEC, TRIM...)

HIV Pathogenesis
Models to understand protection against HIV/AIDS

1. Resistance to Infection
   Exposed Un-infected (EU)

2. Control of HIV infection
   HIV Controllers

3. Control of HIV pathogenesis
   Non-pathogenic SIV model
1. Resistance to Infection

EU: HIV-negative by serology and PCR despite repeated exposure to HIV-1

- Sexually exposed (CSW, partners of HIV-1\textsuperscript{+} patients)
- Systematically exposed (IDU)

✔ EU: Increased NK cell activity in Vietnamese IDU
2. HIV Controllers: Lessons from the lucky few

HIC: Infected individuals spontaneously controlling HIV-1 infection
HIV infected for more than 10 years
Undetectable plasma viral RNA
Naïve of antiretroviral treatment

3. Control of Pathogenesis: the simian model

<table>
<thead>
<tr>
<th>Markers</th>
<th>SIVagm</th>
<th>SIVmac</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Viral Load</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Chronic Phase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T cell activation</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>IFN-α</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Interferon Stimulated Genes</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
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Gene Profiling of CD4+ T Cells in Non-Pathogenic vs Pathogenic SIV infection

Type I interferon pathway is differentially modulated in African Green Monkey and Rhesus Macaque
### Pathogenic SIVmac vs non-pathogenic SIVagm - Early Acute Phase

<table>
<thead>
<tr>
<th>Marker</th>
<th>SIVagm (Non-pathogenic)</th>
<th>SIVmac (Pathogenic)</th>
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<tbody>
<tr>
<td><strong>T cell activation</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Intestinal Mucosa</strong></td>
<td>CCR5+CD4+ depletion ++++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Microbial translocation</td>
<td>-</td>
</tr>
<tr>
<td><strong>Cytokines</strong></td>
<td>TNF-α, IL-6, IL-12, -</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>TGF-β1</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Smad7</td>
<td>-</td>
</tr>
<tr>
<td><strong>Recruitment of PDC to LN</strong></td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

CD85j NK cells suppress HIV replication

In Vitro model of NK cell co-culture with HIV-1 infected or uninfected DC

P24 production is restored by blocking receptor/ligand interaction with a CD85jr but not by HLA class I mAbs
Possible mechanisms of HIV control
HIV/AIDS in 2008: the current situation
**HIV/AIDS: the state of the epidemic at the end of 2007**

<table>
<thead>
<tr>
<th>Region</th>
<th>Number</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Western &amp; Central Europe</td>
<td>760 000</td>
<td>600 000 – 1.1 million</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>1.6 million</td>
<td>1.2 – 2.1 million</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>380 000</td>
<td>270 000 – 500 000</td>
</tr>
<tr>
<td>South &amp; South-East Asia</td>
<td>4.0 million</td>
<td>3.3 – 5.1 million</td>
</tr>
<tr>
<td>East Asia</td>
<td>800 000</td>
<td>620 000 – 960 000</td>
</tr>
<tr>
<td>Latin America</td>
<td>230 000</td>
<td>210 000 – 270 000</td>
</tr>
<tr>
<td>Caribbean</td>
<td>22.5 million</td>
<td>20.9 – 24.3 million</td>
</tr>
<tr>
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<td>Eastern Europe &amp; Central Asia</td>
<td>1.6 million</td>
<td>1.2 – 2.1 million</td>
</tr>
<tr>
<td>North America</td>
<td>1.3 million</td>
<td>0.8 – 1.9 million</td>
</tr>
<tr>
<td>Caribbean</td>
<td>73 000</td>
<td>53 000 – 120 000</td>
</tr>
</tbody>
</table>

- **33 million people** [30.3 – 36.1 million] were living with HIV.
- **2.7 million** [2.2 – 3.2 million] new cases of HIV infection
- **2 million** [1.8 – 2.3 million] AIDS-related deaths last year.
Therapy: Progress in ARV access

Number of people receiving antiretroviral drugs in low- and middle income countries, 2002–2007

For every new person starting treatment, 2 -3 new HIV infections

Only 30% of people needing treatment receive it

Source: Data provided by UNAIDS & WHO, 2008.
Decline in adult mortality with introduction of ART: Botswana

The graph shows a decline in registered deaths (Thousands) and the number of persons on ARV (Thousands) from 1991 to 2005. The data indicates a significant decrease in deaths aged 25-54 coinciding with the introduction of ART. The Global Fund, investing in our future, is highlighted as an organization supporting such initiatives.
Therapeutic Progress and Challenges

ARV Treatment
- The survival benefits of ARV treatment are immense, **BUT...**
- Life-long commitment ---> economical limits
- Complications (drug resistance, metabolic disorders...)

Search for a CURE for HIV infection
Prevention Progress and Challenges

• **Prevention of infection: successes....**
  – Prevention of sexual transmission
  – Mother-to-Child transmission
  – Circumcision as part of a comprehensive prevention approach

.... and work in progress....
- Pre and Post-Exposure prophylaxis
- Early diagnosis and treatment
- Specific Microbicides
- Vaccine
Therapy and Vaccines: scientific challenges

- Genetic Variability of HIV
  - Viral evasion of the immune system
- Early establishment of viral reservoirs
- Cell-cell transmission
- Correlates of protection still undefined
- HIV infects, dysregulates and/or depletes key players of immune system
  - Rapid induction of dysfunctions of immune responses
- Animal model limitations
HIV/AIDS research: 25 years on...

Priorities for future research:
1. Early events during acute phase of infection (immune activation, innate and adaptive immune responses, cross-talk between immune cells, mechanisms and correlates of protection, role of host genetics)
2. HIV reservoirs (mechanisms of establishment and persistence, depletion of reservoirs)
3. Interaction between viral factors and cellular partners
4. Co-infections

Urgent need: CARE, THERAPY and PREVENTION

New therapeutic & vaccine strategies

New targets
- siRNA?
- Limitation of microbial translocation?
- Therapeutic vaccine?
Vaccine Research: Hope and Progress

• Shift from conventional to novel HIV vaccine strategies in the post-STEP era
• Better understanding of the early events of HIV infection
• Better understanding of the basic immunology in HIV infection (e.g. cross-talk between innate and adaptive immunity)
• International Agenda to promote collaboration and cooperation
Benefits beyond HIV/AIDS...
HIV: a tool for new scientific knowledge

• Better understanding of virus/host interactions
  – Pathways of intracellular innate immunity
  – Identification of novel cellular factors (*high-throughput screening for essential proteins for viral replication*)

• Better understanding of immune responses
  – Identification of new receptors, ligands and signalling pathways
  – Standardised T cell functional test

• Vaccine research
  – Novel concepts and strategies for other diseases

• Lentivirus gene therapy vectors
Global health systems improvement

National Programs with International Collaborations

Reinforcement of local infrastructure
Capacity building
Training of health workers
Organisation of Health Systems

Quality operational research in resource-limited countries

Interventions
- Prevention
- Access to treatment and care
- Monitoring
Reinforcement of the Health System in Cambodia

**VCCT sites from 1995 to Q2-2008**

**OI/ART sites and active patients on ART from 2001 to Q2-2008**

Source: NCHADS, MoH, Cambodia

*Figure 9: Trend in number of OI/ART sites and active patients on ART from 2001 to Q2-2008*
Towards a world without AIDS and with better global health...

International partnerships and multidisciplinary approaches

Opposing the fight against HIV to other primary health issues is a total misunderstanding and a major mistake. HIV care, prevention and treatment programs are rather strengthening the global health system. It is time to stop ideological oppositions!