Future challenges in HIV/AIDS prevention and therapy

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“...One can think of the middle of the twentieth century as the end of one of the most important social revolutions in history, the virtual elimination of the infectious disease as a significant factor of social life.”

Burnet, 1962.

Interest, curiosity, motivation for other major and lethal human pathologies

Retrovirus, cancers et leukemia...
First alarming signals of an emerging epidemic

➢ June-July 1981: First cases of pneumocystosis associated with immunedepression in homosexual patients in the US.

➢ July 1982: First cases of AIDS detected in haemophilic patients
➢ October 1982: First cases of AIDS in women, heterosexual infection
➢ December 1982: First cases of infected children

Mobilization of researchers by epidemiologists and clinicians....
The 80’s and the years after: a collective adventure

Evolution of technologies and research on retroviruses

- Identification of TCGF or IL2 (1979)
- FeLV and immunodeficiency in cat
- Gallo et Yoshida (1981) - First human retrovirus (HTLV-Human T Cell Leukemia Virus)

Clinicians mobilized the retrovirologists of the Institut Pasteur

F. Brun-Vezinet
W. Rozenbaum
C. Rouzioux

A decisive meeting

NO DOGMA
May 20th 1983: first report of LAV in Science

Science 1983 May 20;220(4599):868-71

**Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).**


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.

- Propagation of LAV on PBMCs and on cord blood lymphocytes
- RT activity deatedected according to HTLV-1 RT conditions

**BUT**

- 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 - To face the emergency: reactivity, mobilization

1. 1983-1984: Convince scientific community and authorities that LAV was the etiological agent of AIDS
   - Link between the virus and the AIDS disease (viral isolate, sero-epidemiological investigation)
   - Characterization of LAV and other viral isolates.

   ➢ Stop any other research programs in our lab
   ➢ Mobilize other clinicians and researchers...

2. 1983-1985: Develop serological tests for diagnosis

   Mobilization of private sector: a strong and efficient partnership with Sanofi Diagnostics Pasteur
1983

Identification of HIV-1 (LAV, HTLVIII, ARV) and viral antigens

Tropism and cytopathogenicity of HIV-1

Characterisation HIV-1 replication cycle and of RT

Characterisation HIV-1 genetic material and identification of its diversity

Diagnostic Tests

Prevention of transmission by blood

Prevention of mother to child infection and of sexual transmission

CD4 cell monitoring

Development of first ARV

AZT as therapy

HAART

AZT as prevention (MTCT)

Monitoring tests for Viral load and ARV resistance

HIV research: from bed-side to bench to bed-side

An example of translational research
Main milestones in 27 years of research on HIV

M. Müller-Trutwin & F. Barré-Sinoussi

Number of people living with HIV (million)

HIV biology and pathogenesis

SIV

Identification VIH-2

HIV-1 Diversity

HIV-1 Sequence

CD4 Receptor

HIV-1 Identification

Co-receptors

Recombinants VIH-1

HIV-1 O

HIV-1 subtypes

HIV Reservoirs

HIV-1 N

HIV Restriction factors

Immune activation

Microbial Translocation

CD4 Depletion in gut

Origin of HIV

HIV controllers

HIV-1 P

HIV testing

AZT Therapy

ARV Resistance

HAART

HIV-1 O

Microbial Translocation

1st phase I trial

AIDS

African epidemic

VaxGen Trial

Circumcision (risk reduction)

STEP Trial

« Thai » trial

Therapy and prevention research

Prophylactic and therapeutic vaccine research

AIDS

1st phase I trial

VaxGen Trial

Circumcision (risk reduction)

STEP Trial

« Thai » trial

Therapy and prevention research

Prophylactic and therapeutic vaccine research

1980 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09

Number of people living with HIV (million)

35

25

15

5

M. Müller-Trutwin & F. Barré-Sinoussi

Main milestones in 27 years of research on HIV
Today HIV is a chronic infection

More than 85% decrease in treated patients mortality

Mortality rate per 1000

Hogg et al. unpublished; 2009


6 therapeutic classes:

✓ nucleoside inhibitors of reverse transcriptase
✓ non nucleoside inhibitors of reverse transcriptase
✓ Protease inhibitors
✓ Fusion inhibitors
✓ Integrase inhibitor
✓ CCR5 inhibitor

A Panel of about 30 drugs for HAART
Responsibility and mobilization toward a global scale epidemic
« Science has no frontiers because knowledge belongs to humanity and it is the flame that enlightens the world. »

« La science ne connaît pas de frontière parce que la connaissance appartient à l’humanité et que c’est la flamme qui illumine le monde. »

Louis Pasteur
(1822-1895)
Translating Research into large scale public health actions

Main steps and issues

- **Validation of research evidences** => *Credibility*
  - Surveillance and epidemiological studies
  - Establishment of well characterized cohorts
  - Clinical and operational research (*physiopathology, therapeutic trials, strategy evaluation…*)
  - Socio-economic research
  - Pilot studies
  - Scaling up, Implementation & sustainability…

- Need of a strong interface and partnerships (*policymakers, scientists, health & service providers, patients, civil society, community groups & activists, private and public sectors…*)

- **Awareness, diffusion & advocacy** (*information, communication, education and training*)
  - National Programs, Guidelines and decisions
  - Coordination of activities
  - Evaluation & Updating (*effectiveness and gap identification*)
    - Integrated and Permanent research activities ……
Global health systems improvements

National programs with international collaborations...

- Quality operational research in resource-limited countries
- Reinforcement of local infrastructures
  - Capacity building
  - Training of health workers
  - Organisation of health systems
- Interventions
  - Preventions
  - Access to treatment and care
  - Monitoring

3 compulsory synergetic components.....

- Thailand: 1.4% in 2008
- Kampala, Uganda: 5.4% in 2008
- KwaZulu Natal, South Africa: 39.1% in 2008
Translating research into clinical practices: successes and failures

Example of HIV/AIDS issues in Cambodia

- Mobilization and response of national authorities;
- Supports from international organizations;
- Operational research on site;
- Evidence: >90% of effectiveness of MSF ARV program after 2 years.
- Today about 35,000 patients on HAART.
Recent progress in translating science into Public health in Southern Africa: Antiretroviral therapy coverage and all-cause mortality, 2003–2006
For every 2 new persons starting HAART: 5 new infections
Relationship between scientists, health workers, activists and politicians for the benefit of global health...

- Scientific evidences
- Activism
- Government Leaders and Health authorities

Decisions for Public Health Benefit.
Priorities:

1) Co-infections
2) Complications on long term HAART
3) HIV reservoirs (mechanisms of establishment and persistence, depletion of reservoirs)
4) Early events during acute phase of infection (early signals of immune activation, cross-talk between cells of innate and adaptive immunity, mechanisms of protection, host genetics)
5) Interaction between viral factors and cellular partners
6) /......

New therapeutic and vaccine strategies

Urgent need for further research....
AIDS associated morbidity in resource limited settings: need to get drugs to people who need them!

Non AIDS associated morbidity in high Complications (resistance, metabolic disorders, including cardiovascular injury, premature aging, cancer…): impact of HAART toxicity, HIV induced persistent inflammation and lifestyle?

Eradication of HIV or at least functional cure…: Not yet there but a renewed effort begun to at least reduce the size of HIV reservoirs…

Need for more mobilisation and research

New molecules
New targets
Solutions to cure the infection?
Potential strategies targeting HIV reservoirs:

- **Unlocking latency mechanisms**
- **Use of immuno-modulating agent**
- **Enhancement of anti-HIV immunity**
- **Early intense HAART**
- **Intensifying antiretroviral treatment**
- **Antiretroviral drugs with improved penetration and potency**
ARV in pre- or post-exposition prophylaxis? *Test and Treat Concept...*

Failure of microbicides => *New specific microbicides?*

Circumcision associated to other prevention means?

Vaccine: Failure of the classical approaches *(until the Thai RV144 vaccine trial....)*
Toward the eradication of HIV/AIDS? Test and treat concept...

ARV stop viral replication...

Undetectable viral load in blood and genital secretions..

Significant Reduction of HIV transmission...

Modelisation:
R Granich, C Gilks, C Dye, K De Cock, B Williams.
Lancet, 2008
Reducing the incidence of HIV-1: A Priority!
A Global Response combining Treatment and Prevention...

Leadership and scaling up of treatment/prevention efforts

- Behavioral change
- Biomedical strategies
- Highly active HIV prevention
- Social justice and human rights
- Treatment/Antiretroviral/STI/Antiviral

Community involvement

HIV Vaccine history

**August 1987**
1st phase I trial

**1987-2007**
> 110 trials (10 Phase II/III) with 67 products (27 500 volunteers)

*Candidate vaccine are usually safe and showed some degree of immunogenicity*

**2003**
Data of the 1st phase III efficacy trial VaxGen

*Lack of efficacy of rgp120 definitively proven*

**Sept. 2007**
STEP/Phambili phase IIb trial (HIV-1B gag, pol, nef / rAd5)

*Discontinued for lack of efficacy*

**Oct. 2009**
RV144 “Thai”: ALVAC (gag/pol/env) + AidsVax (B/ErGp120)

*Modest Efficacy 31%*

Ongoing phase II trials (DNA+MVA, DNA+NYVAC, lipopeptides…)
Is an AIDS vaccine possible?

Yes, according to the « Thai » RV144 efficacy trial

More than 16,000 volunteers enrolled
125 infections: 51 in vaccinees/74 controls
31% of protection => For the 1st time a vaccine shows a modest efficacy in humans

More research are needed:

✓ Why does this vaccine reduce the risk of HIV infection?
✓ What are the mechanisms of protection?
✓ Must we revise/redefine vaccine efficacy endpoints?
✓ Is the strategy using a “prime” (induction) with an immunogen then “boost” (stimulation) with another immunogen, the right one?
✓ How can we improve the vaccine efficacy?
✓ ........

New vaccine strategy…

To learn from vaccinees …
To learn from models of protection

Against HIV infection

Exposed but uninfected individuals

Protected Vaccinees

Against AIDS

HIV controllers

Control of HIV replication

African monkeys natural hosts of SIV

Control of abnormal immune activation
Vaccine Failure

⇒ Why?: Many, many obstacles!
  ✓ Transmission by cell to cell infection
  ✓ Very rapid attack and alteration of key players of the immune response in effector sites.
  ✓ Latency and thus, no detection of the infection by our defense
  ✓ HIV diversity and Immune response viral escape

⇒ Which solutions? New innovative concepts based on a better knowledge of early events resulting (or not) in signals required to induce protective immunity, in particular at effector sites.
What should a vaccine aim at?
Re-thinking future strategies for an optimal HIV-1 vaccine...

Viral RNA/ml plasma CD4+ /CD8+ DR+CD38+

Immunological setpoint

Viral setpoint (6 months p.i.)

Intense generalized T cell activation

Viremia

Blood CD4+

Acute Infection (6-12 weeks)

Chronic Infection (≈ 10 years)

AIDS

Intestinal CCR5+ CD4+ T memory cells (destruction of GALT, Microbial translocation)

infection, dissemination and HIV reservoirs

Chronic immune activation
HIV/AIDS, a key challenge in global health equity and development.

UNAIDS, WHO 2009

Total: 33, 4 million

- 2nd position of HIV/AIDS on the list of death caused by infectious diseases.
- Sensitive topic (sex & addiction, stigma, politics, religion, media..)
- Needs for governance & policymakers to understand HIV/AIDS science & socio-economic implications to respond.
- Long term disease requiring very quick policy responses
- Unprecedented international responses with success and failures

≈ 7400 new infections and 5500 deaths every day

More than 95% in resource-limited countries

60% of HIV+ persons ignore their serological status

- North America 1.4 million
- Central and Western Europe 850 000
- North Africa and Middle-East 310 000
- Sub-Saharan Africa 22.4 million
- Latin America 2.0 million
- Caribbean 240 000
- Eastern Europe and Central Asia 1.5 million
- Eastern Asia 850 000
- South and South-East Asia 3.8 million
- Oceania 59 000
- Eastern Asia 850 000
- South and South-East Asia 3.8 million
- Oceania 59 000
Combat HIV/AIDS, One of the Millenium development Goals

Millenium Development Goal #6
(set at millenium summit 2000 to be reached in 2015)

“Halt and begin to reverse the spread of HIV/AIDS”

But

“Ensure that the response to HIV/AIDS is further integrated within, and benefits, health systems as a whole”

A unique opportunity to change the course of history in global health equity
Resources available for HIV/AIDS: What’s next?

In 2010 an estimated $25.1 billion will be needed, to reach objectives.

International leaders must keep their promises.

Notes:
[1] 1986-2000 figures are for international funds only
[2] Domestic funds are included from 2001 onwards
The fight against HIV/AIDS from the beginning up to now: a unique impulse of solidarity

People from different walk of life, raised their voices

Equal access to treatment, care and prevention

Social and legal justice for all

End of stigma and discrimination based on serological status, gender or sexual orientation

POLITICAL COMMITMENT
"Today, we know that security means far more than the absence of conflict. (...) We know that lasting peace requires a broader vision encompassing areas such as education and health, democracy and human rights, protection against environmental degradation, and the proliferation of deadly weapons. We know that we cannot build peace without alleviating poverty, and that we cannot build freedom on foundations of injustice. These pillars of what we now understand as the people-centred concept of human security are inter-related and mutually reinforcing". *(Former UN Secretary-General Kofi Annan)*

In a globalized world, health must be considered as a non-negotiable right for every human being and equity in access to it, as an international responsibility.