HIV/AIDS, 30 years later: which challenges remain?

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30 years ago: 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....
Evolution of technologies and of research on retroviruses

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

Clinicians mobilized the retrovirologists at the Institut Pasteur

A decisive meeting

When, Where, How to look for which virus? No Dogma....
May 20th 1983: first report of LAV in Science

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 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 - 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, researchers, patients...

2. 1983-1985: Develop serological tests for diagnosis

Mobilization of private sector: a strong and efficient partnership with Sanofi Diagnostics Pasteur
HIV research: from bed-side to bench to bed-side
An example of translational science...

1983

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

Tropism and cytopathogenicity of HIV-1

Characterization HIV-1 replication cycle and of RT

Characterisation HIV-1 genome and identification of its diversity

1985 First diagnostic tests on the market

Prevention of transmission by blood
Prevention of mother to child infection and of sexual transmission

CD4 cell monitoring

Late 80s, Development of first ARV

1987-88 AZT as therapy
1994 AZT as prevention (MTCT)

1996: HAART

Late 90s, First monitoring tests for Viral load and drug resistance
Fusion inhibitors
Reverse transcriptase inhibitors
Integrase inhibitors
Protease inhibitors

HIV targets for antiretroviral therapy

23 antiretroviral molecules approved by US FDA today available in North but few combination are available for resource limited countries and prices for recommended 1st line regimen are still high
The Power of HAART: treatment is prevention

>85% reduction of mortality in treated patients but in addition to saving lives, treatment can also prevent new infections

A  Linked HIV Transmission

- HPTN 052 Trial
  - 27 infections in delayed arm
  - 1 infection in early arm

MS Cohen et al, NEJM 2011

No. at Risk
- Delayed: 882, 655, 297, 80, 26, 22

HIV prevalence

- Treat 30%
- Treat 100%

Montaner et al, Lancet 2006

Early efficient ART led to 96% reduction of sexual transmission of HIV-1 in serodiscordant couples. “Test and treat early” strategies could lead to dramatic decrease of HIV incidence.
Effectiveness of antiretroviral molecule in preventing HIV transmission

- Decrease in prevalence in populations where ART is highly used \((\text{Fang 2004, Montaner 2010, Das 2010, Bezemer 2010})\)
- Mathematical models on TASP efficacy \((\text{Granich 2009, Case 2010})\)
- Microbicides using ART \((39 - 54\%, \text{CAPRISA 2010})\)
- PreP in MSM: 44\% reduction of HIV incidence \((\text{iPrEx study; NEJM 2010})\)
- Virtual elimination of MTCT in high income countries using ARV
Scientific evidences

Multi-disciplinary research

Activism
HIV Communities Participation

Political Leaders and health authorities

Interventions
Organization
Care and treatment access

Training, strengthening capacities and structures

Decisions for the benefit of all communities everywhere...
Successful Response to HIV/AIDS in Cambodia

• High level of commitment of decision makers, of health care workers and of community based support team
• Good partnership between governmental institutions and stakeholders through transparency and accountability
• Implementation of the Continuum of Care (CoC) Program by the NCHAD in 2003 and scaling up country wide in 2005:
  • Local Integrated Program Based Approach, integrating HIV services into health care delivery services
  • Standardize Framework, Training, Protocol, LSM, M&E for Public and NGO services
• Implementation of Home and Community Based Care Support (HCBS) in 2009 involving primary health care network teams and HIV self support groups (20 provinces covered in 2010)
Response to HIV/AIDS in Cambodia: Toward Zero New HIV Infection By 2020

- Total population of Cambodia in 2010 is approximately 14 million
- HIV prevalence among general population (> 15 yo):
  1.7% in 1998 => 0.8% in 2010 => 0.6% in 2015?
- HIV prev. among CSW was 42% in 2000 => 14% in 2010
- HIV Prevalence among IDU: 24%
- HIV Prevalence among MSM was 2.2% (2010, Bros Khmer Study)
- ART coverage in 2010 is 92 % (UN MDG Award 2010)
- TB screening in PLWH: 73% in 2010 and HIV testing in TB: 83% as of June 2011
- ANC attendance: 38% in 2000 => 89 % in 2010
- HIV testing and received test result in PW: 16.4% in 2007 => 57% in 2010
- HIV PW received ARV Prophylaxis or ART:
  11.1 % in 2007 => 49% in 2010
Early signs showing that ARV are effective in preventing new infections

Since 2009, Botswana has maintained more than 90% eligible people on antiretroviral treatment.

Data from modelling suggest that the number of new HIV infections is 30 to 50% lower than it would have been in the absence of universal access to treatment.

Need for sustained international efforts...
Progress in access to ARV in resource limited countries

At the United Nations High Level Meeting on AIDS in New York in June 2011, governments committed to reaching 15 million people with HIV treatment by 2015 (~9 million more than today)

One critical challenge is the long-term sustainability....

3 patients starting treatment : 5 new infections (2.7 millions/year)

Million of people on ARV in resource limited settings (UNAIDS 2011)

>80%

Botswana
Cambodia
Chile
Comoros
Croatia
Cuba
Namibia
Nicaragua
Guyana
Rwanda
Slovakia
Global has cancelled its 11th funding round due to lack of resources!!!

Economical crisis...

Urgent needs for new funding strategies/mechanisms!
Despite unprecedented international efforts, HIV/AIDS remains a key challenge in global health equity and development.

- HIV/AIDS remains at the 2nd position on the list of death caused by infectious diseases with 5500 deaths and ≈ 7400 new infections every day
- More than 95% in resource-limited countries
- About 60% of HIV+ persons ignore their serological status (15 to 50% in Europe...)
- Still a sensitive topic (sex & addiction, stigma, politics, religion, media..)
30 years after the identification of AIDS…

AIDS mortality and HIV incidence still high globally *(2,6 new infections & 1,9 million deaths in 2009)*

<table>
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<th>Need to implement Evidence based interventions</th>
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<td>- Early testing and Access to HAART <em>(including 2nd and 3rd line treatment)</em>,</td>
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<td>- PMTCT <em>(only 53% of pregnant women receive HAART)</em>,</td>
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<td>- Monitoring patients on HAART <em>(access to viral loads, drug resistance tests…)</em></td>
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**CHRONIC HIV INFECTION under ARV treatment but, still…**

- **Coinfections**: Tuberculosis (21%), meningitis Cryptococosis (20%), HCV, HBV, CMV…

- **Immune reconstitution syndrome on HAART**

- **Complications associated to long term HAART**, including metabolic disorders, cardiovascular diseases (8%), cancers (15,4%), liver diseases (7%)… *(The antiretroviral therapy cohort collaboration, CID, 2010)*, neurological disorders, aging diseases *(osteoporosis, Alzheimer…)*

- **Viral persistence, HIV reservoirs**

- **Inflammation, activation, insufficient immune restoration on HAART**

**New therapeutic and vaccine strategies => Further Science**
HIV pathogenesis...

Viral RNA/ml plasma

CD4+ /CD8+DR+CD38+

Intense generalized T cell activation

Viremia

Blood CD4+

Intestinal CCR5+ CD4+ T memory cells (loss of gut integrity and Microbial translocation)

Acute Infection (6-12 weeks)

Chronic Infection (∼10 years)

AIDS

Viral reservoirs, persistence and replication

Inflammation, Chronic immune activation
HIV transmission and pathogenesis:
A complex interplay between the virus and its host

Host Determinants
- Mediators of Host Innate and Adaptive Immunity
- Host Cell factors involved in virus life cycle
- Intrinsic cellular defense (restriction factors APOBEC, TRIM5α, Tetherin/BST2, SAMHD1, p21, others…)

Viral Determinants
- Tropism & replicative capacity in host cells (CD4 \( T \) lymphocytes, macrophages, DCs)
- Immunosuppressive capacity
- Abnormal activation signaling pathways

Impact of host and viral genetic diversity on pathogenesis….
Looking for the key of early and persistent control: learning from models of natural protection against AIDS

HIV-1/SIVControllers/HIV-2

- Efficient suppressive CD8 responses
- Low viremia
- Low generalised T cell activation
- No or Slow progression to AIDS

Viremic LTNP

- Restriction factors (p21, others?)
- Low viremia
- Low generalised T cell activation

NATURAL HOSTS

- HLA Ag stimuli
- Moderate viremia
- No generalised T cell activation
- Resistance to AIDS

Liovat AS et al, CHIR, 2009
Innate Immunity ad HIV infection outcome?

M. Altfeld, L. Fadda, D. Frleta, N. Bhardwaj, March 2011,

Activated cDCs produce pro-inflammatory cytokines that stimulate NK cells

pDCs produce type I IFNs and promote NK cell proliferation and cytotoxicity

IL-12, IL-15, IL-18

NK cell

During HIV infection, NK cells are less responsive to type I IFNs

Actived cDCs

NK cell

NK cells promote adaptive immunity by killing immature DCs

Immature DC

During HIV infection, NK cells have a decreased ability to kill immature DCs

Activated NK cells produce IFNγ and promote T_H1-type immunity

NK–cDC crosstalk is attenuated during HIV infection

IFNγ
Dendritic cells at the cross road between innate and adaptive immune response

**TLR-7**

**IFN-α/β**

**NK**

**Recrutement**

**Activation**

**Cytotoxicity**

**NKT**

**Recrutement**

**Activation**

**Monocyte**

↑ microbicide activity

Différenciation DC GM-CSF/IFN-α ?

**mDC**

**pDC**

**IFN-α/β**

**Recrutement**

**Activation**

**CD4**

**CD8**

**CD80**

**CD86**

**CD40**

**CD4**

**CXCR4**

**CCR5**

**CCR7**

**TLR-7**

**IDO**

**Trp**

**Kyn**

**Apoptosis**

**Suppression of replication**

**Infection**

**Activation**

**Death?**

**HEV**

**Vaslin B, IMETI, CEA**
30 years after the discovery of AIDS, no HIV vaccine yet...

- Animal model limitations
- Genetic Variability of HIV and evasion of the host immune response
- Cell to cell transmission of the virus
- HIV infects and very rapidly alters the functions of key players of both innate and adaptative immune responses
- Pathways to elicit protective responses through vaccination? Immune mechanisms of protection against acquisition of HIV infection and disease progression

.../BUT...

- One vaccine prime-boost strategy showed for the first time a modest efficacy (31% of protection in the Thai-RV144 vaccine efficacy trial)
- Very few individuals are naturally protected against HIV-1 infection (e.g. exposed non-infected subjects)
- Some experimental vaccines confer protection to monkeys infected with SIV
- Recent identification of new very potent (80-90%) and broadly reactive neutralizing antibodies targeting V2/V3 or CD4bs env
What about preventing immune activation?

Control of viral acquisition

Measles
Hepatitis
Polio...

Control of pathogenesis

Diphteria
Tétanos
Cholera

Vaccines

HIV-1?

First Viral Factor(s) implicated in early pathogenic signals resulting in abnormal activation?

Ascher MS et Sheppard HW, Clin Exp Immunol 1988
Giorgi JV et al, J Infect Dis 1999
What about an “HIV cure”, at least a life-long remission?

*Definition:* Permanent suppression of viral replication without eradicating the virus from the body => Long-term remission + Prevention

- A decrease in viral load is clearly associated with clinical benefit
- Proof of concept from the Berlin patient (*bone marrow transplant of CCR5Δ32 stem cells*)
- A very small percentage (<0.3%) of HIV-1-infected subjects are naturally controlling HIV infection (non detectable VL; low level of reservoirs): “*HIV Controllers or Elite controllers*”: very efficient suppressive CD8 response; restricted infection of their CD4 cells and macrophages; genetic factors;

- Natural protection against AIDS of African NHP infected by SIV related to an attenuated immune activation (*no microbial translocation and no gut destruction; restricted infection of memory CD4 T cells; distinct innate immune response to SIV, in particular at the level of pDC and type I IFN*)

It is time to accelerate research towards a life-long HIV remission…
Potential strategies to reduce HIV reservoirs

- Maraviroc
  - Anti-inflammatory drugs
  - Statins
  - OH-Chlorochin

- Massive CD4 T-cell depletion
- Bacterial translocation

- Systemic Inflammation

- Pre-Probiotics

- Antiviral drugs

- Viral Co-Infections

- Anti-co-stimulatory molecules
  - anti PD1 / anti PDL1
  - anti-CTLA4
  - anti-CD137

- ARV Intervention
  - Intensification
  - Nevirapine

- Cellular Immunity
  - Immune Intervention
  - Anti-HIV vaccine
  - IL7

- Gene therapy

Immune Activation

Residual Replication

HIV Reservoirs Latency

From C. Katlama
Towards an HIV cure: an integrated translational strategy

Patient cohorts, animal models, blood and tissues, cell models

New strategies & clinical studies

Eradication and/or remission? Prevention...

Current knowledge on persistence in HIV patients on HAART

Exploring the basic mechanisms of HIV persistence

New tools to quantify, monitor and/or predict HIV persistence
Evidence based Prevention
Implementation of combined tools

Highly active HIV prevention tools

- EDUCATION
- VACCINE
- HIV CURE
- MICROBICIDES
- PrEP
- HARM REDUCTION
- TREATMENT AS PREVENTION
- CONDOMS
- STI TREATMENT
- TESTING COUNSELING
- CIRCUMCISION
- DRUG ALCOHOL TREATMENT
New Challenges: HIV and emerging non communicable diseases...

- Cancer, lymphomas
- Ageing diseases
- Cardiovascular diseases

Immune defects, inflammatory and autoimmune malignancies

HIV Infection
Chronic on HAART
Non AIDS related mortality

Learning from each other beyond HIV/AIDS.....
New discoveries in HIV/AIDS can impact Global Health!

New challenges, new concepts, new technologies…
A new generation of players…
But keeping in mind…
All together like in the early years!!!
Thank you !!!

All the scientific community and the health professionals worldwide,

All the patients and their representatives

My team...

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