Past, Present and Future of HIV Research.

Françoise BARRÉ-SINOUSSEI
More than 30 years ago: Alarming signals of an emerging epidemic

MS Gottlieb, HM Schanker, PT Fan, A Saxon, JD Weisman.

June 5, 1981 / Vol. 30/ No. 21

Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homosexual Men – New York City and California

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Mobilization of virologists by epidemiologists and clinicians
2 years later in May 1983: First report on HIV…
1. **1983-1984: to convince scientific community and authorities that the virus 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.

2. **1983-1985: Develop serological tests for diagnosis**

- Stop any other research programs in our lab
- Mobilize others (Clinicians, nurses, virologists, immunologists, biochemists, molecular biologists...)
- Patients...

Mobilize the private sector....
Los Angeles, USA, 1981

Paris, France 1983

Bangui, Central African republic, 1987

Hanoi, Vietnam 1988

UN agencies, governments, international organizations & foundations, national programs, research institutions, communities....
More than 30 years of HIV Science
A good example of translational research

A new era since cART in 1996...
A unique engagement of patient representatives for the universal access to treatment

Evolution of 1st line treatment price (MSF)

Generic competition and activists pressure = drastic reduction of ARV prices in ressource-limited countries but still too few combination available + 2nd/3rd line treatments prices too high!

Today: The revolution of Hepatitis C treatment!

New fight to achieve universal access at an affordable price to save lifes…
2,1 M PLWH in 2013: 38% reduction since 2001

4,2 millions death avoided thanks to ARVs!

"Test & Treat early"… Treatment is prevention!

Source: UNAIDS Global Report 2014
Tenofovir is a First-Generation PrEP Agent: We Must Move Forward Smartly

**PrEP Efficacy Estimates from 0-75%...**

What is the best strategic use of tenofovir-based PrEP?

Landmark health research is a process of continued development

We need a choice of strategies to meet different needs

Adherence remains important with less user-dependent strategies (i.e., vaginal rings & injectable PrEP...)

Pill  Gel  Vaginal film  Vaginal ring  Injectable
PREVENTION

Combination of tools scientifically validated…

- EDUCATION/ BEHAVIOR CHANGES
- CONDOMS
- STI TREATMENT
- TESTING COUNSELING
- CIRCUMCISION
- ADDICTIONS TREATMENT
- HARM REDUCTION
- Early cART
- PrEP & PEP
- MICROBICIDES

HIV Vaccine? Don’t worry we will not loose our jobs yet…
Many challenges (social, structural, behavior, biomedical...) to efficiently implement tools to ...

Prevent new infections
(education, condoms, circumcision, risk reduction...)

Test, treat and retain
- 30-50% of HIV+ people ignore their status.....
- Cascade of continuum of care
  (only 25 to 60% of viral suppression...)

- Strengthen health systems (linking diagnosis, prevention, care and treatment services)
- Leadership/governance
- National integrated policies
- Bridging programs (communities, implementers, health workers, researchers...)

- Political willingness
- International Investments
- Fighting against repressive legislation/stigma/discrimination/......
Key scientific challenges and Priorities in HIV/AIDS today

<table>
<thead>
<tr>
<th>HIV Vaccine discovery</th>
<th>Comorbidities on ART</th>
<th>HIV Cure discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still no correlates of protection but significant progresses in HIV vaccine research with new perspectives since the Thai trial in 2009..</td>
<td>HIV infection, a chronic condition on life long cART but non AIDS related comorbidities</td>
<td>Persistent HIV infection on HAART is the main hurdle science must tackle to achieve an HIV “Cure”</td>
</tr>
</tbody>
</table>

New therapeutic strategies?

- Novel creative ideas
- Multi-disciplinary collaborations
- International coordination
- Partnerships between private & public sectors
- Fundings
- /.....
Significant progresses in HIV vaccine research since 2009 opening new perspectives...

- Identification of new very potent broadly neutralizing antibodies in HIV+ patients ("elite neutralizers"), structurally and functionally characterized.
- Identification of new sites of vulnerability of HIV env (MPER, CD4bs, V1/V2 and V3, glycan side chain on outer domain)
- Non neutralizing but protective antibodies (ADCC, Fc-mediated, others...)?


- Structure-based immunogen design & novel delivery systems
- Gene transfer and genetic engineering of T cells...
Experimental vaccines induce protection in SIV infected macaques

Protection obtained by passive immunization in diverse models

Some hopes in HIV vaccine science....

Therapeutic efficacy of potent neutralizing HIV-1-specific monoclonal antibodies in SHIV-infected rhesus monkeys


Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques


Combine vaccine candidates to elicit conventional and non-conventional protective responses.

Combine vaccine therapy to other strategies in HIV cure research...
2011 workshop on HIV persistence in St Marteen, Fred Verdult asked Steve Deeks why is it important to cure HIV. The answer of Deeks: «life expectancy, long term side effects, financial reasons ».

Fred Verdult (Volle Maan) conducted a survey on 458 PLWHIV in May 2012 presented at HIV Cure symposium in Washington in July: 72% thought it is was very important for them to be cured. When asked what are the most disadvantages of HIV many replied about medical issues but also not having to be anxious about the future anymore, not having to deal with stigma anymore, not being afraid of infect others anymore
Why do we need novel therapeutic strategies?

• **35 millions PLWH: only 13 millions on cART**
  - Only very few countries with >80% coverage
  - New WHO recommendations = 28 millions eligible

• **Lifelong cART:**
  - Substantial stigma and discrimination
  - Fears
  - Difficult adherence
  - Toxicity
  - Life expectancy reduced
  - Still a significant morbidity
  - Long term cost

• **Treating is preventing HIV infection…**

Lifelong cART for all is unlikely to be sustainable…
Why do we need lifelong ART?
HIV infection persists on ART....

HIV RNA

CD4 count

0 1

Years on HAART

off HAART

Undetectable?

Viral Rebound

HIV DNA

50

1

Palmer et al., Proc Natl Acad Sci U S A. 2008;105:3879-84
Maldarelli et al., Plos Pathogens 2007; 3:484
Why it’s time to accelerate HIV cure research now?
A better knowledge on HIV pathogenesis...

Viral load
- HIV-specific CD8 T cells
- CD4 count (blood)
- Generalized immune activation
- Intestinal CCR5⁺ CD4⁺ T memory cells

- Set points (predictive of progression)

2-3 weeks
3-10 weeks
> 6 months

Acute infection
Chronic infection

Viral reservoirs & replication
Inflammation & immune activation
Inflammation & immune activation

Why it’s time to accelerate HIV cure research now?
A better knowledge on HIV pathogenesis...

Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys


- Viral load
- HIV-specific CD8 T cells
- CD4 count (blood)

Generalized immune activation set points
HIV-specific CD8 T cells (predictive of progression)

Viral reservoirs & replication
Inflammation & immune activation

Acute infection
2-3 weeks
3-10 weeks
> 6 months
Chronic infection
Why it’s time to accelerate HIV cure research now?

A better knowledge on HIV reservoirs in many cell subsets and tissues


✓ Major reservoirs are resting central & transitional CD4+ memory T cells (Persistent and stable on cART (>10 years); rare latently infected cells: around 1/10^6 resting CD4 T cells)

✓ Other reservoir cells: naive T cells, astrocytes, hematopoietic progenitor cells

✓ Anatomic reservoirs: GI & genital tract, lymphoid tissue, CNS...

Viral replication

T cell survival

Homeostatic Proliferation

Need to better determine latently infected cells...
Better knowledge of drivers of chronic activation

- HIV replication
- HIV proteins (Nef, Tat, Vpx, ..)
- Loss of regulatory cells
- Altered balance of CD4+ T cell subset
- Inflammation
  - Monocyte activation
  - T cell activation
- Dyslipidemia
- Hypercoagulation
- Co-morbidities
  - Aging

- CMV
  - Excess pathogens
  - Gut Damage => Microbial translocation

- Steven Deeks, IAS 2013
### Which kind of HIV Cure are we looking for? 

<table>
<thead>
<tr>
<th>Eradication</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sterilizing Cure</strong></td>
<td><strong>Functional Cure</strong></td>
</tr>
<tr>
<td>Elimination of all latently infected cells</td>
<td>Long-term health without cART &amp; without risk of transmission</td>
</tr>
<tr>
<td><strong>Berlin patient</strong></td>
<td><strong>Proof of concept</strong></td>
</tr>
</tbody>
</table>
Why do we are optimistic about at least sustainable remission?

**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

**Bone Marrow Transplantations**: Proof of concept from the Berlin patient (*BMT with CCR5Δ32 stem cells*). No **efficacy** on viremia & DNA level after BMT in 10 patients (*Cillo AR et al, JAIDS 2013*); **Relapse of HIV viremia after ART cessation in the 2 Boston patients**

**HIV Controllers**: <0.3% of HIV+ people, treatment naïve naturally control infection (undetectable VL; **low level of reservoirs**; **moderate T cell activation**): Genetic background and very efficient suppressive CD8 response; restricted infection of their CD4 cells and macrophages.

**Cases of “Functional” cure after very early treatment**: “Mississippi baby” treated 30h after birth for 18 months, 27 months of control off treatment before relapse of viremia;

**ANRS EP 47 VISCONTI** (*Saez-Cirion et al, PloS Pathogens 2013*): 20 HIV+ patients treated about 10 weeks PI for 3 years, ≈9 years of control off treatment
**Towards an HIV Cure: a global scientific strategy**

The International AIDS Society Scientific Working Group on HIV Cure

Although the current threat that HIV poses to public health and individual well-being is greater than ever before, many of the interventions available to control the spread of HIV have been successful. However, the challenges in controlling the spread of HIV are not as significant as those posed by the global HIV epidemic. The scientific community has made significant progress in the development of new strategies to control the spread of HIV. However, the global HIV epidemic has reached a critical point, and urgent action is needed to halt the spread of the virus. The International AIDS Society Scientific Working Group on HIV Cure has developed a global scientific strategy to control the spread of HIV. This strategy aims to ensure that the scientific community continues to make progress in the fight against HIV and that the epidemic is eventually brought under control.

**Towards an HIV Cure**

Scientific research has led to remarkable discoveries since HIV was first identified thirty years ago. Today, individuals living with HIV can expect to live a relatively normal lifespan provided they are both diagnosed and treated early enough and they comply to life-long antiretroviral drug regimens. However, combination therapy — even when taken for decades — is not curative, as HIV persists despite even the best treatment.

*The International AIDS Society scientific working group on HIV Cure. Towards an HIV cure: a global scientific strategy.*

Global Scientific Strategy

Seven Priorities

1. Molecular, cellular and viral mechanisms of HIV persistence

2. Tissue and cellular sources of persistent SIV/HIV in animal models and in long-term ART-treated individuals

3. Origins of immune activation and dysfunction in the presence of ART and their consequences for HIV/SIV persistence

4. Host and immune mechanisms that control HIV/SIV infection but allow viral persistence

5. Biomarkers and Assays to predict and quantify persistent infection

1. Therapeutic agents or immune-based strategies to safely eliminate latent infection in individuals on ART

2. Strategies to enhance the capacity of the host response to control active viral replication
Future HIV Cure Strategies?
A combined approach...

Gene therapy
To make cells resistant to HIV and/or to excise latent HIV...
To make genetic engineering of T cells

Early Treatment optimization & intensification
To limit reservoirs and control viral replication

Latency Acting Drugs (LAD)
to activate/definitively repress latent HIV

Therapeutic vaccination
To enhance host innate and adaptive B and T cells immune responses

Immune-based therapies
to reverse inflammatory and activation signaling pathways

Cure? Remission?
Implement a Multidisciplinary, Integrated and Coordinated Strategy: IAS Advisory Board…

Decision Makers Funding agencies

Int. scientific collaborations

Cooperation public + privates sectors

Cross-talk with non HIV scientists

Platforms of Information & Data exchanges

New concepts, New technologies New generation

Interaction between Basic + Clinical Science

Social and Economical Science

Community engagement

Towards an HIV cure people focused science driven
**Infectious diseases**
- AIDS, Tuberculosis, malaria, hepatitis
- Diarrhoeal diseases in infants
- Respiratory infections
- Emerging/re-emerging infectious diseases (influenza, encephalitis, antimicrobial resistance, Ebola...)

**Non communicable diseases**

Now the most important cause of death globally:

1) Cardiovascular diseases: 17.3 millions death/year;
2) Cancers: 7.6 millions
3) Diabetes: 1.3 million

**Maternal & child health**

**Alcohol, Tobacco**

**Climatic change**

**Lack of health professionals**

**Urbanization**

---

**GLOBAL HEALTH 2035**

*To invest in health is to build a sustainable future for all...*
Ebola, a call for action

Ebola: time to act
Government and research organizations must mobilize to end the West African outbreak.

Ebola: learn from the past
Drawing on his experiences in previous outbreaks, David L. Heymann calls for rapid diagnosis, patient isolation, community engagement and clinical trials.
We have been and we will be stronger altogether like in the early years!!

Keeping in mind!
Ministry of Health
on site

ANRS
France

Local coordinator

French coordinator

Local hospitals, Health Structures, Laboratories, NGOs

Hospitals, Research Institutions in France and elsewhere

Pluri-disciplinary research programs

International partnerships

Strengthening health facilities
Training & Technology Transfer
20 years of an evolutive partnership...

**Vietnam**
- 1988: 1st Course in Hanoi
- 1994: 1st contact with National Authorities
- 1995: 1st Official ANRS-MoH cooperation
- 2000: ANRS-MoH Sites
- Pilot Study on ART
- HIV infection in IDUs
- PMTCT: pilot study, then clinical trials...
- HIV molecular epidemiology
- Early testing, Generic VL tests, Resistance to ARVs
- Immune and genetic makers of HIV infection
- Diagnosis and Treatment of pneumopathies
- HIV-TB Co-infections in adults and infants

**Cambodia**
- Socio-cultural factors impacting access to prevention, care and treatment in adults and infants