On the road towards an HIV Cure?

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Department of Virology,
Institut Pasteur, Paris
30 years of HIV Science
A good example of translational research

Legend:
HIV biology & pathogenesis
Treatment
Prevention
Since 1996: A new era with Combined ART therapy…

**HIV infection**

Antiretroviral treatment (cART)

Stop HIV replication
Restore Immune function

Prevent AIDS
Improve quality of life
Prolong life expectancy
Prevent HIV transmission

> 25 antiretroviral molecules approved
Global number of people living with HIV & HIV-related deaths: Changes post-2005

2,1 M PLWH in 2013: 38% reduction since 2001

Source: UNAIDS Global Report 2014
Progress in access to antiretroviral therapy in low-and middle-income countries

35 million of PLWHIV
13 million have access to ARV treatments (+2,3 million in a year)

Adult access to antiretroviral therapy, UNAIDS GAP Report 2014

40+%: Botswana, Burundi, Burkina Faso, Cabo Verde, Eritrea, Ethiopia, Gabon, Kenya, Malawi, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe


<25%: Central African Republic, Chad, Democratic Republic of the Congo, Guinea, Guinea-Bissau, Liberia, Madagascar, Mauritius, Nigeria, Sao Tome and Principe, Sierra Leone, South Sudan

Since 1995: ARVs averted 7,6 million death globally

2013 WHO treatment guidelines: 28 millions HIV+ people now eligible for treatment initiation but 19 million are unaware of their HIV positive status
PREVENTION = a combination of tools scientifically validated

HIGHLY ACTIVE COMBINATION OF HIV PREVENTION TOOLS

- Condoms
- STI treatment
- Testing counseling
- Circumcision
- Addictions treatment
- Harm reduction
- Microbicides
- PrEP
- Vaccin
- HIV cure
- ARV treatment
- Education/behavior changes
Today a huge challenge is to test, treat and retain under treatment

• Testing coverage is low and inadequate linking between testing & care
• Late diagnostic & treatment initiation, low retention into care

19 millions PLWHIV are unaware of their serological status

Majority of PLWHIV is not treated

Piot and Quinn, NEJM 2013
Micek et al., JAIDS 2009
Gardner et al., CID 2011
Hall et al., JAMA IM 2013
Many other social, structural, behavioral, biomedical challenges

- Strengthen health systems to support prevention, care and treatment linked services
- International Investments
- Political willingness
- Leadership/governance
- National integrated policies
- Bridging programs, communities, implementers, researchers..
- Fighting stigma/discrimination
-......

There can’t be an end to AIDS without simultaneous progress in Human Rights
<table>
<thead>
<tr>
<th>HIV Vaccine discovery</th>
<th>Comorbidities on ART</th>
<th>HIV Cure discovery</th>
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<tbody>
<tr>
<td>Still no correlates of protection but significant progresses in HIV vaccine research open new perspectives: Thai trial, very potent broadly neutralizing Ab, protection in macaques...</td>
<td>HIV is now a chronic condition on life long HAART but non AIDS related comorbidities linked to persistent inflammation/chronic immune activation... new therapeutic strategies</td>
<td>Persistent HIV infection on HAART is the main hurdle science must tackle to achieve an HIV “Cure”</td>
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**MANY other CHALLENGES...**

- Novel creative ideas
- Multi-disciplinary collaborations
- Partnerships between private & public sectors
- International coordination
- Fundings
- /.....
Why do we need a Cure? PLWH Expectations.

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 10 millions on ART
  - 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 ART for all is unlikely to be sustainable…
Why do we need lifelong ART?

HIV infection persists on ART….

Barriers to HIV Cure

• Latently infected T-cells
• Residual viral replication related to inflammation/immune activation
• Anatomical reservoirs
• ARV penetration into tissues

HIV RNA

CD4 count

50

1

0 1

Years on HAART

off HAART

Undetectable?

Viral Rebound

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)
  - set points (predictive of progression)
- Generalized immune activation
- Intestinal CCR5⁺ CD4⁺ T memory cells

2-3 weeks
- Acute infection

3-10 weeks

> 6 months
- Chronic infection

Viral reservoirs & replication

Inflammation & immune activation
Why it’s time to accelerate HIV cure research now?

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

- Persistence and stability of reservoirs even after > 10 years of HAART
- CD4+ T cell latency is rare (1/10^5-10^6 resting CD4 T cells)

Resting central & transitional CD4+ memory T cells are the major reservoirs of HIV-1

- Latent infection also described in naive T cells, astrocytes, hematopoietic progenitor cells
- Anatomic reservoirs: GI & genital tract, lymphoid tissue, central nervous system

Need to improve our knowledge of latently infected cells...

Chomont et al, Nat Med, 2009

Why it’s time to accelerate HIV cure research now? Better knowledge on the persistence of latently infected cells.


Immune mechanisms that maintain cells in resting state also contribute to HIV persistence (upregulation of PD-1)
Sequestration of essential transcription factors like NFAT and NF-κB in the cytoplasm leads to silencing of viral gene expression.

Debbie S. Ruelas, Warner C. Greene
Cell Volume 155, Issue 3 2013 519 - 529
Better knowledge of drivers of chronic activation

HIV replication
HIV proteins (Nef, Tat, Vpx, ..)

HIV-associated fat
Metabolic syndrome

CMV
Excess pathogens

Gut Damage =>
Microbial translocation

Inflammation
↑ Monocyte activation
↑ T cell activation
Dyslipidemia
Hypercoagulation

Co-morbidities
Aging

Loss of regulatory cells

Altered balance of CD4+ T cell subset

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

<table>
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<tr>
<th>Eradication</th>
<th>Remission</th>
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<td><strong>Sterilizing Cure</strong></td>
<td><strong>Functional Cure</strong></td>
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<tr>
<td>Elimination of all latently infected cells</td>
<td>Long-term health without cART &amp; without risk of transmission</td>
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- Berlin patient
- Proofs of concept
Why do we are optimistic about at least a Functional Cure (life-long 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), 2 Boston Patients. Some data show no efficacy on viremia & DNA level after BMT in 10 patients (Cillo AR et al, JAIDS 2013) and relapse of HIV viremia after ART cessation in the Boston patients.

HIV Controllers: <0.3% of HIV+ people, treatment naïve naturally control infection (undetectable VL; low level of reservoirs): very efficient suppressive CD8 response; restricted infection of their CD4 cells and macrophages; genetic factors.

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): 14 HIV+ patients treated about 10 weeks PI for 3 years, ≈9 years of control off treatment.
Global Scientific Strategy

Towards an HIV cure: a global scientific strategy

The International AIDS Society scientific working group on HIV Cure.

Global Scientific Strategy

Seven Priority Research Areas:

1. Molecular, cellular and viral mechanisms that maintain 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. Assays to study and measure persistent infection: comparison and validation
6. Therapeutic agents or immunological strategies to safely eliminate latent infection in individuals on ART
7. Strategies to enhance the capacity of the host response to control active viral replication
Where are we?
Can we cure HIV with latency “reactivation” drugs?

- NF-kB activators (*Prostratim, PMA, TNFα*)
- HDAC inhibitors (*VPA, Vorinostat in phase 3*)
- Jak/Stat pathway (*IL7*)
- Akt/HEXIM-1 modulators (*Hexamethylbisacetamide HMBA*)

Methylation inhibitors (*5-aza-2’-deoxycytidine or 5-aza-dC*)


Other more potent HDACi studied in clinical trials (*Romidepsin, Panobinostat in Danemark*) BUT Probably not enough.....
Can we cure HIV infection with immune-based therapeutics?

- Frequency of HIV DNA-containing resting memory cells correlates with frequency of activated CD4+ T cells (S.Eriksson/J.Siliciano et al. PlosPathogens)

- Sirolimus (rapamycin)—which reduces CCR5 expression, T cell activation and T cell proliferation—is associated with a low reservoir size post-renal transplant (DARE, S.Deeks et al.)

Does immune activation contribute to persistence, or does persistence contribute to activation?

Should we identify specific markers (e.g., PD-1)?

Should T cell proliferation be inhibited as a adjunct to other curative studies?
Can we enhanced killing of HIV-infected cells by vaccine therapy *in vivo*?

**Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine**

Scott G. Hansen¹, Julia C. Ford¹, Matthew S. Lewis¹, Abigail B. Ventura¹, Colette M. Hughes¹, Lia Coyne-Johnson¹, Nathan Whizin¹, Kelli Oswald², Rebecca Shoemaker², Tonya Swanson¹, Alfred W. Legasse¹, Maria J. Chiuchiolo³, Christopher L. Parks³, Michael K. Axthelm¹, Jay A. Nelson¹, Michael A. Jarvis¹, Michael Piatak Jr², Jeffrey D. Lifson² & Louis J. Picker¹

- **CMV as SIV vaccine vector induces high levels of effector CD8+ T cells in lymphoid/mucosa tissues**

- **SIV-specific CD8+ T cells prevent/clear latency during early infection, resulting in cure as shown by challenge studies in monkeys.**
Therapeutic vaccination may be a necessary component of a cure strategy?


- Dendritic cell vaccine using patient-derived virus and CD40L reduces viral load set-point, with at least one becoming a controller (Argos study by JP. Routy et al.)

Should we use non T cell approaches (bNAbs, ADCC)?

Encouraging data with bNAbs in animal models...
Can we cure HIV infection with allogenic stem cell transplants?

- Allogeneic stem cell transplant during ART may be curative, even with HIV-susceptible donor cells (n=2 in Boston, n=1 in Bethesda)

  Ablation with ART, IBT and/or GVHD could be curative? (Henrich and colleagues, JID)

- Infusion of CCR5-modified T cells results in sustained decline in HIV DNA over one year in individuals exhibiting sustained CD4+ T cell increases (Sangamo study by Dale Ando et al.)

Gene modification of T cells for a cure, is it feasible?

Can stem cells be harvested, gene modified and transplanted in a safe, effective, affordable and scalable manner?
Barriers but new opportunities for clinical research toward an HIV cure...

Others ongoing or planned studies in the North...

1. Direct acting anti-latency drugs
2. Anti-inflammatory drugs
3. Therapeutic vaccination
4. Cell therapy

BUT

What about HIV cure research in resource-limited-settings?

1. Early therapy to prevent spread?
2. Early therapy to preserve host responses?
Future HIV Cure Strategies? 
A combined approach...

**Gene therapy**
- To make cells resistant to HIV;
- To excise latent HIV...

**Therapeutic vaccination**
- to enhance host-control

**Immune-based therapies**
- to reverse pro-latency and/or inflammatory signals

**Treatment optimization & intensification**
- To eliminate all replication

**Targeting HIV latency**
- to activate/repress latent HIV

**Others ongoing or planed studies**
1. Very early therapy to prevent spread and preserve host responses
2. Direct acting-latency drugs
3. Immune based therapy, including anti-inflammatory drugs
4. Therapeutic vaccination
5. Gene therapy
Quantifying the HIV reservoir and tools for cure studies.

What do we want the tools to do?

- To understand the **biology** of HIV persistence on cART
- To serve as a **biomarker** to predict “functional cure”
- To evaluate the impact of an **intervention** on the reservoirs

*And, in the future…*

- To use the tools for multisite international feasible, affordable and scalable interventional **clinical studies**…

**Personalized cure therapy?**
Towards an HIV Cure: an Integrated Strategy...

Funding

Int. scientific collaborations

Community engagement

Data exchange platforms between pilot studies

Cooperation public + privates sectors

Interaction between Basic + Clinical Science

New concepts, new generation

Cross-talk with other scientific disciplines

J. Martinez-Picado, AIDS 2012
## A Global and a Multidisciplinary Initiative

### Stakeholders Advisory Board
- **Implementation & follow up of the strategy; Funding Coordination Focus; Coordination of all components**

<table>
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<tr>
<th>Group</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Ethics Working Group</strong></td>
<td>Lo B, Grady C et al. Ethical considerations in HIV cure research. COHA 2013</td>
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<tr>
<td><strong>Cost-Effectiveness Working Group</strong></td>
<td>Role of Mathematical Modeling and Cost-Effectiveness Analysis (<em>article in preparation</em>)</td>
</tr>
<tr>
<td><strong>Psychosocial studies group</strong></td>
<td>Several on-going research projects in US &amp; France</td>
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<tr>
<td><strong>Industry collaboration Group</strong></td>
<td>Forum to discuss crosscutting industry and academic issues in HIV cure research and foster public-private partnership</td>
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<tr>
<td><strong>Exchanges between HIV &amp; non HIV scientists</strong></td>
<td>Think Tank meeting (May 2013)</td>
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<tr>
<td><strong>Interactions between basic &amp; clinical science</strong></td>
<td>International scientific symposium</td>
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<tr>
<td><strong>Information exchanges</strong></td>
<td>Annual resource tracking policy paper analyzing global investment in HIV cure research, acting as support for call for increased funding; Regional community training workshops (India and Australia in 2014)</td>
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“Towards an HIV Cure” symposium

18 & 19 July 2015,
More info at www.iasociety.org
HIV Cure Advisory Board of Stakeholders

- Implementation & follow up of the strategy;
- Funding Coordination Focus;
- International Multidisciplinary of all components
We have been and we will be stronger altogether like in the early years!!

Keeping in mind!