Why are we now talking about a cure?

- Emerging recognition that HAART does not fully restore health and/or that HAART is associated with long-term toxicity.
- Advances in understanding of latency.
- HIV prevention approaches have largely failed to prevent transmission.
- *Life-long adherence is often difficult.*
- *Resources may not be available to expand HAART beyond current levels.*
Long-Term Control of HIV by CCR5 Delta32/ Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganea, M.D., Arne Möß, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.
HIV cure: Definitions

• Complete eradication of all replication competent virus ("sterilizing cure")
  – Is this remotely possible?
  – How can this be proven?

• Long-term health in absence of therapy ("functional cure")
  – Cancer model (remission)
  – Definition: no readily detectable virus in absence of therapy for prolonged periods
Current antiretroviral drugs are unlikely to be curative
HIV persists even after 10 years of optimal therapy (potent HAART initiated during acute infection)

Chun et al, AIDS 2010
Mechanisms of HIV persistence (not mutually exclusive)

- Low-level (“cryptic”) viral replication, including cell-to-cell transfer of HIV
- Long-lived reservoir of resting CD4+ T cells that harbor transcriptionally silent, integrated (latent) HIV genomes
- Homeostatic proliferation of CD4+ T cells that harbor latent genomes
- Long-lived reservoir of non-T-cell populations harboring integrated HIV genomes (e.g., tissue macrophages)
- Lack of effective HIV-specific immunity
Are current regimens able to fully suppress HIV replication?
Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy


Short-Course Raltegravir Intensification Does Not Reduce Persistent Low-Level Viremia in Patients with HIV-1 Suppression during Receipt of Combination Antiretroviral Therapy


A Randomized, Controlled Trial of Raltegravir Intensification in Antiretroviral-treated, HIV-infected Patients with a Suboptimal CD4+ T Cell Response

Hiroyu Hatano, Timothy L. Hayes, Viktor Dahl, Elizabeth Sinclair, Tzong-Hae Lee, Rebecca Hoh, Harry Lampiris, Peter W. Hunt, Sarah Palmer, Joseph M. McCune, Jeffrey N. Martin, Michael P. Busch, Barbara L. Shacklett, and Steven G. Deeks
Addition of raltegravir to a stable regimen resulted in transient increase in pre-integration DNA ("2 LTR circles") in ~1/3 of patients, c/w ongoing rounds of HIV replication.

Transient increase in pre-integration DNA was associated with decline in "activation"
The frequency of infected cells (DNA, unspliced RNA) is higher in gut than in blood.

HIV DNA is 3 to 9 times higher in the gut.

Estimates of gut HIV reservoir:

83 to >95% of all infected cells in body

1 x 10^9 infected CD4+ T cells

Yukl et al, JID 2010
Therapeutic interventions and strategies for curing HIV infection
Why does HIV persist?

Collective data suggests that HIV persists due to presence of a long-lived latent reservoir (which may be maintained by chromatin silencing with or without homeostatic proliferation), ongoing “replenishment” of new targets (which is likely due to cell-to-cell transfer of virus and hence represents replication and lack of an effective HIV-specific immune responses. All can currently be addressed with interventions in a research setting.
Will combination therapy be needed to activate and then clear latently infected cells?

Reversal of host mechanisms (anti-PD1, chemokine antagonists, anti-inflammation, MCSF inhibition)
Negative Regulators of T Cell Activation

- PD-1 and its ligands negatively regulate immune responses

- PD-1/PD-L1 interaction inhibits activation, expansion and acquisition of effector functions of virus specific CD8+ T cells.

Will combination therapy be needed to activate and then clear latently infected cells?

Reversal of host mechanisms (anti-PD1, chemokine antagonists, anti-inflammation, MCSF inhibition)

\[ \text{\textup{\(\uparrow\)}} \text{ DNA transcription via chromatin modification (HDACi, HMTi, NF-\(k\)B activators)} \]
### Multiple HDAC inhibitors are in clinical development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Specificity</th>
<th>Licensing stage</th>
<th>Completed studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romidepsin (depsipeptide)</td>
<td>Class I specific</td>
<td>Licensed for CTCL (2009)</td>
<td>Phase I, II (x3)</td>
</tr>
<tr>
<td>Panobinostat (LBH589)</td>
<td>Pan HDAC</td>
<td>In clinical trials</td>
<td>Phase I (x2), II (x2)</td>
</tr>
<tr>
<td>Entinostat (MS-275)</td>
<td>HDAC1 and 3 specific</td>
<td>In clinical trials</td>
<td>Phase I</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Pan HDAC</td>
<td>Licensed</td>
<td>Limited activity in vivo*</td>
</tr>
<tr>
<td>MCT-1 and MCT-3</td>
<td>Class I specific</td>
<td>In vitro only</td>
<td>nil</td>
</tr>
</tbody>
</table>

CTCL = cutaneous T-cell lymphoma;
Will combination therapy be needed to activate and then clear latently infected cells?

Reversal of host mechanisms (anti-PD1, chemokine antagonists, anti-inflammation, MCSF inhibition)

↑ DNA transcription via chromatin modification (HDACi, HMTi, NF-kB activators)

Clearance of activated cells (therapeutic vaccine, immunotoxin)
In the absence of ongoing viral replication, strong HIV specific T cell response in the gut mucosa is associated with lower levels of viral persistence.

For CD8+ T cells (GALT):
- Correlation coefficient: \( \rho = -0.56 \)
- Significance level: \( p = 0.01 \)

For CD4+ T cells (GALT):
- Correlation coefficient: \( \rho = -0.37 \)
- Significance level: \( p = 0.12 \)
### Cure-Related Clinical Trials Recruiting Patients

<table>
<thead>
<tr>
<th>Principal Investigators</th>
<th>Sponsors</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christine Katlama and Eramune 01 team</td>
<td>ORVACS, Cytheris, Merck, Pfizer</td>
<td>IL-7 + HIV vaccine + intensification</td>
</tr>
<tr>
<td>Robert Murphy and Eramune 02 team</td>
<td>Northwestern University, ORVACS, NIAID, Pfizer, Merck</td>
<td>HIV vaccine + intensification</td>
</tr>
<tr>
<td>Steve Deeks, Adriana Andrade</td>
<td>UCSF, Johns Hopkins Univ.</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>David Margolis</td>
<td>University of North Carolina, NIH, Merck</td>
<td>SAHA</td>
</tr>
<tr>
<td>Sharon Lewin</td>
<td>Merck, Alfred Hospital in Melbourne, Australia</td>
<td>SAHA</td>
</tr>
<tr>
<td>Joseph Alvarnas, Richard Ambinder</td>
<td>NHLBI</td>
<td>Cytoablative therapy for lymphoma</td>
</tr>
<tr>
<td>John Mellors</td>
<td>University of Pittsburgh, NCI</td>
<td>Chemotherapy for lymphoma</td>
</tr>
<tr>
<td>Pablo Tebas, David Stein, Carl June</td>
<td>University of Pennsylvania, Sangamo</td>
<td>Autologous CD4s w/CCR5- gene</td>
</tr>
<tr>
<td>Amrita Krishnan</td>
<td>Beckman Res. Inst., City of Hope (Duarte, CA), NCI</td>
<td>Autologous stem cells w/CCR5- and anti-HIV genes</td>
</tr>
<tr>
<td>Frank Maldarelli</td>
<td>NIAID, NCI</td>
<td>Interferon α2B</td>
</tr>
</tbody>
</table>
The IAS effort on enabling a cure
Towards an HIV Cure Pipeline

MODELS
- Animals models
- Patient cohorts
- Blood
- Tissues and organs
- Cell models

Exploring the mechanisms of HIV persistence

Virological mechanisms of HIV persistence

Immunological mechanisms and compartments involved in HIV persistence

Pre-clinical & translational tools: quantification, characterization & monitoring HIV reservoirs

Clinical trials

Clinical research

Translational research: eradication & remission
Stakeholders
Advisory Board

Stakeholders Consultations

- Industry
- Research Funders
- Advocates
- Regulatory Agencies
- Researchers
- IOs

Launch @ AIDS 2012
- Symposium
- Publications

Follow-Up

Draft Strategy

Advocacy

International Scientific Working Group

International AIDS Society
Stronger Together
Conclusions

• Multiple mechanisms might account for how an inflammatory environment—which likely persists in all individuals—might contribute to persistence
  • All might be addressed with therapeutic interventions
• No single intervention is likely to be curative
  • Combination therapy
• Most early attempts are likely to be negative
  • Field will need to maintain long-term objectives
• Ethics of study potentially harmful drugs in study participants who are doing well may be a major barrier to progress