**Therapeutic approaches for a sustainable remission and cure for HIV**

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Therapeutic approaches for a sustainable remission and cure

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Why do we need a cure in an era of effective ART?

• Human costs
  – Stigma/discrimination
  – Long-term health: Obesity, co-morbidities, polypharmacy

• Public health costs
  – ART is lifelong and expensive: Total spent on HIV/AIDS: ~ $50 billion/year
  – Social disruptions affect access (COVID)
  – Despite massive global investments, many (~50%) not
What will a cure need to do?

**Optimal (aspirational) target product profile**

From a **public health** perspective, the **ideal** curative intervention will be readily scalable, safe, effective in everyone – including those not on ART – and protect against re-infection.
What will a cure need to do?

Optimal (aspirational) target product profile

A cure is not needed for those who are doing well on ART and can access these drugs indefinitely but for everyone else, including those who are untreated.
Why does HIV persist indefinitely?
The Problem: Latent Reservoir

- HIV persists as fully integrated genome in largely tissue-based memory T cell population
- Only ~1% of genomes are fully intact and only a subset of these proviruses are “rebound-competent”, making reservoir hard to measure
T cell proliferation is the main cause of persistence

Specific HIV integration sites are linked to clonal expansion and persistence of infected cells

F. Maldarelli,²,* X. Wu,²,* L. Su,² F. R. Simonetti,²,* W. Shao,² S. Hill,¹ J. Spindler,¹ A. L. Ferris,¹ J. W. Mellors,* M. F. Kearney,* J. M. Coffin,* S. H. Hughes;¹

Proliferation of cells with HIV integrated into cancer genes contributes to persistent infection

Thor A. Wagner,²,* Sherry McLanahan,²,* Kavita Garg,² Charles Y. K. Cheung,² Brendan B. Larsen,² Sheila Styrchak,³ Hannah C. Huang,¹ Paul T. Edlefsen,²,* James I. Mullins,²,* Lisa M. Frenkel²,*

HIV-1 Integration Landscape during Latent and Active Infection

Lillian B. Cohn,¹ Israel T. Silva,¹,² Thago Y. Oliveira,¹ Rafael A. Rosales,³ Erica H. Parrish,³ Gerald H. Lai,³ Beatrice H. Hahn,¹ Julie L. Czartoski,² M. Juliana McElrath,¹ Clara Lehmann,³ FLORIAN KLEIN,¹ Marina Caskey,¹ Bruce D. Walker,²,* Janet D. Siliciano,¹,³ Robert F. Siliciano,¹,³ Mila Jankovic,¹ and Michel C. Nussenzweig¹,³

Longitudinal Genetic Characterization Reveals That Cell Proliferation Maintains a Persistent HIV Type 1 DNA Pool During Effective HIV Therapy

Susanne von Stockenstrum,¹,² Lina Odevar,¹ Eunok Lee,¹,² Elizabeth Sinclair,¹ Peter Bacchetti,¹ Maudl Killian,¹ Lorrie Epling,¹ Wei Shao,¹ Rebecca Ho,¹ Terrence Hsia,¹ Nous R. Faria,¹ Philippe Lenney,¹ Juan Albert,¹ Peter Hunt,¹ Lisa Leck,¹ Christopher Pitcher¹ Lauren Poole,¹ Hiyoe Hatae,¹ Ma Sonneveld,¹ Daniel Dosek,¹ Eli Beeren,² Steven G. Deeks,¹ Frederick M. Hecht,¹,³ and Sarah Palmer¹,³
Proliferation: latently infected cells clonally expand

- Clonally expanded cells make up most of the reservoir
- Expanded cells can produce virus resulting in low level viremia and/or viral rebound
- Drivers for proliferation
  - Antigen specific expansion
  - Homeostatic proliferation
  - Site of integration


Slide: Nicolas Chomont
How will it be defined and measured?
Goal of therapy: Cure (eradication)

- Complete removal of all replication-competent HIV
- No residual stigma (key outcome in surveys)
- May have been achieved with Berlin Patient but impossible to prove
  - People may never really know if they are cured
- Will likely require gene modifications therapies
Goal of therapy: Remission (control)

- Durable control of a residual population
  - Elite/exceptional control
  - Post-treatment controllers
  - Long-term ART (depot formulations)
- Antibody positive, persistent inflammation, possible risk of rebound
- Readily achieved in monkey models with various combination approaches (immunotherapy)
Initiation of ART as PrEP (“Fiebig 0”) resulted in multi-log reduction in reservoir, but at least one virus had established latency.
• Carefully performed treatment interruptions often the only interpretable way to answer the question
  • No validated biomarker of the systemic rebound-competent reservoir
  • No validated immunologic correlates of post-ART control
• Can it be done safely?
  • Exclude those with low nadir, history of cancer/CAD
  • High baseline CD4+ T cell count
  • Age limits
  • Partner engagement (PrEP)
  • Conservative restart criteria: Symptoms, CD4+ T cell decline, sustained viremia
How will HIV be cured?
HIV cure strategies
Most approaches involve combination of reservoir reduction and immune enhancement ("reduce and control"), with growing interest in gene therapy and eventually "one shot" cures.
Early ART
Very early ART is not curative

Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection

Very early ART (including “Fiebig 0”) is not curative

ART in Fiebig I for >96 weeks

Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection

Donn J. Colby1, Lydie Trautmann2, Suteeraporn Pinyakorn3, Louise Leyte4, Amélie Pagliuzza5, Eugène Kroon6, Morgane Rolland2, Hiroshi Takata7, Supranee Buranapraditkun8, Jintana Intaan2, Nitya Chomchoy, Roshill Mu5, Elais K. Hadida5, Sodsai Tovanabutra2, Sasiwimol Uboyan5, Diane L. Bolton3, Brandie A. Fullmer2, Robert J. Gorelick5, Lawrence Fox1, Trevor A. Crowell3, Rapee Trichavaroj2, Robert O’Connell2, Nicolas Chomont2, Jerome H. Kim7, Nelson L. Michael3, Merlin L. Robb2, Nittaya Phanuphak, Jintanat Ananworanich1,2,15 and The RV411 study group

HIV-1 persistence following extremely early initiation of antiretroviral therapy (ART) during acute HIV-1 infection: An observational study

Timothy J. Henrich1,2,3, Hiroyu Hatano2,3, Oliver Bacon2,3, Louise E. Hogan1, Rachel Rudishauer2,3, Alison Hill2,3, Mary F. Kearney2,3, Elizabeth M. Anderson4, Susan P. Buchbinder1,2, Stephanie E. Cohen2,3, Mohamed Abdel-Mohsen5,6, Christopher W. Pohlmeier2, Remi Fromentin2, Rebecca Hoh2, Albert Y. Li5, Joseph M. McCune2, Jonathan Spindler2, Kelly Metcall-Patel2, Kristen S. Hobbs2, Cassandra Tharr1, Erica A. Gibson2,4, Daniel R. Kurtzkes5,6, Robert F. Siliciano1,2,3, Richard W. Price5,6, Douglas D. Richman1,2,3, Nicolas Chomont2, Janet D. Siliciano5,6, John W. Mellors8,9, Steven A. Yuk1,2,9, Joel N. Blankson2, Teri Liegler2, Steven G. Deeks2
Some (~10%) of people who start therapy early (but not too early) and remain on therapy for years exhibit at least partial control after ART is interrupted.

- May occur in chronic infection (rare)
- No biomarker available
- Mechanism unknown
  - Elite controllers: Adaptive immunity (CD8+ T cells)
  - PTCs: Innate immunity (NK cells)
Most PTCs started ART early, but not too early.

Some host response likely needs to be primed (but not overwhelmed) during acute infection to set the stage for post-treatment control.
Latency reversal (shock and kill)
Shock and kill

- Multiple latency reversing agents (LRAs) tested: effect in humans is modest at best and inconsistent, and has rarely associated with reservoir reduction
- Basic discovery aimed at identifying novel pathways or combinations
SMAC-mimetics routinely induce latency reversal in animal models

- No change in reservoir or delay in rebound
  - Why do productive, virus-producing cells persist?
- Toxicity may prevent rapid clinical development
Latency silencing (block and lock)
Natural cures and exceptional control
Intact proviral genomes accumulate in “gene deserts”, which is associated with deep and possibly irreversible latency.
**Natural Cure**

HIV diagnosed in 1992, no ART, undetectable virus 24 years (39 viral loads; one blip), no intact HIV DNA, low and declining HIV antibody levels; lowest level of HIV ever recorded

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<th>Test</th>
<th>Cell number</th>
<th>Cell type</th>
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<tbody>
<tr>
<td>Sequencing</td>
<td>&gt;1.5b</td>
<td>PBMC</td>
</tr>
<tr>
<td>Intact DNA (PCR)</td>
<td>14m</td>
<td>Resting CD4</td>
</tr>
<tr>
<td>Viral outgrowth</td>
<td>340m</td>
<td>Resting CD4</td>
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![Graph showing Intact HIV-1 DNA /10^6 PBMCs](image)
Exceptional Controllers and “Block and Lock”

- Rare clinical phenotype
- Mechanism unknown
- Are we treating too many elite controllers?
- Can we recapitulate this phenotype therapeutically?
  - Lock-and-block strategies: mTOR inhibitors
  - Long-term ART
Gene therapy
“It’s great that I finally have someone added to my family. It’s been too long”
Timothy Brown, Science March 2019

**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 Ganepola, M.D., Arne Müßig, 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-1 remission following CCR5Δ32/Δ32 haematopoietic stem-cell transplantation**

Ravindra K. Gupta1,2,3,4,5,6, Sultan Abdul-Jawad1, Laura E. McCoy1, HoI Ping Mok4, Dimitra Peppa5,6, Maria Salgado7, Javier Martinez-Picado7,8,9, Monique Nijhuis8,9, Annemarie M. J. Wensing8,9, Helen Lee8, Paul Grant12, Eleni Nastouli12, Jonathan Lambert13, Matthew Pace6, Fanny Salasc6, Christopher Morlat1, Andrew J. Innes14,15, Luke Muir1, Laura Waters1, John Frater6,18, Andrew M. L. Lever1,17, Simon G. Edwards3, Ian H. Gabriel14,15,18,19 & Eduardo Olavarria14,15,19
Gene Therapy: Targets and Strategies

- **Protect:** engineer uninfected cells to be resistant to HIV
  - Proof-of-concept: Berlin, London and Dusseldorf cases
- **Kill:** enhance anti-HIV immune responses (CAR-T cells)
  - Proof-of-concept in people pending
- **Control:** Induce life-long production of antiviral antibodies
  - POC established in monkeys (Miami monkey)
  - POC in people pending (VRC07, CROI LB)
- **Purge:** Selectively disrupt and deactivate provirus
  - POC established in mice

*Paula Cannon*
One-shot cure approaches

Gene delivery of long-acting antiviral (bANb) or direct in vivo gene editing (HIV, CCR5) might eventually lead to durable cure for treated and even untreated people

Aspirational, but theoretically possible
Gene editing for an HIV Cure

Can cells be made into antibody factories that persist indefinitely?

- Miami Monkey: Cured by a vector (AAV) that introduced bNAb genes into tissues
- VRC 603: 8 people received AAV (three doses); 2/3 at high dose had sustained production of VRC-07

Casazza et al., CROI 2020 (LB 41)
Immunotherapy: Vaccines, broadly neutralizing antibodies, adjuvants, cytokines, and immune checkpoint blockers
“Elite” control is most consistently associated with HIV-specific CD8+ T cell responses, although other pathways are likely involved.

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<tr>
<th>Protective Class I Alleles</th>
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<td>B<em>57, B</em>27, B<em>13, B</em>58</td>
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<tr>
<th>CD8+ T Cell Proliferation</th>
<th>Gag-specific degranulation, cytokines (polyfunctional CD8+ T cells)</th>
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<tr>
<th>Inhibitory activity (ex vivo autologous CD4+ T cells)</th>
<th>Perforin and granzyme killing</th>
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<tr>
<th>Low PD-1, CTLA-4, TIGIT</th>
<th>Low CD38</th>
<th>Vulnerable epitopes</th>
<th>TCR diversity</th>
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<th>Polyfunctional CD4+ T cells</th>
<th>Public TCR</th>
<th>Low T reg function</th>
<th>Low IDO</th>
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Combination Immunotherapy: Proof-of-concept in monkeys

**Immune clearance of highly pathogenic SIV infection**

**Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys**

**Early antibody therapy can induce long-lasting immunity to SHIV**

**Antibody and TLR7 agonist delay viral rebound in SHIV-infected monkeys**
Erica N. Bordachar, Jinnyan Liu, Joseph P. Nikolai, Anthony C. Cadena, Wei-Han Yu, Stephanie Fischinger, Thomas Broge, Peter Ahlbrand, Soo B. Merkel, Alibek Chandra, David Jetton, Lauren Peters, Katherine McMahan, Edward J. Mosley, Elena Belkin, Joseph Hesselgesser, Wenjuan Li, Mark G. Lewis, Galit Alter, Roman Gekko, & Dan H. Barouch
Reduce and Control

Combining Multiple Modalities To Achieve a Sustained Viral Remission in the Absence of ART

Courtesy of Warner Greene
Combinatorial therapy with a therapeutic conserved element DNA/MVA vaccine strategy, a TLR9 agonist and broadly neutralizing antibodies: A pilot study aimed at inducing an HIV remission (IND 18488)
A short history of HIV cure research: from cure to remission to cure again

1997
HIV latency identified

2009
The Berlin patient

2014-now
Case reports of remission

2010
Post treatment control (remission)

2019
The London patient

VISCONTI
SPARTAC
CHAMP

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Conclusions

• Progress continues to be made, primarily in animal models
• Multiple approaches are being tested
  – All are likely to initially be less effective than optimally delivered ART
  – Iterative process expected with multiple “shots on goal” and ultimate optimization for addressing the needs of the global pandemic
• Massive synergies exist with HIV prevention (vaccines, bNAbs) and non-HIV immunotherapies (cancer, transplant, autoimmunity)
Thank You for Your Attendance!

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