Primer on Cure

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What Does Cure Mean?

- **Merriam-Webster says:**
  - A complete or permanent solution or remedy
  - To bring about recovery from
  - To permanently restore to health, soundness

- **For well known viral infections what is cure?**
  - Influenza
  - Hepatitis C
  - HIV
Influenza

- Uncomplicated flu
- After exposure, short incubation (1-2 days)
- Fever (3-4 days)
- Weakness and/or fatigue (up to 2-3 weeks)
- Clear virus within 10-14 days
- As influenza evolves, susceptibility to infection recurs
Hepatitis C Virus

- Approximately 15-25% of people infected with HCV clear their infection within the first 6 months of infection.
- Early in infection most people are asymptomatic.
- Progression to liver disease takes time and is accelerated by cofactors such as excessive alcohol consumption.
- Curable in greater than 90% of people with HCV with current medications.
- If cured by drug treatment, reinfection is possible.
What Makes HIV Unique

- A central tenet in immunology is activate and respond, create memory and rest, poised to respond should the pathogen return.
- By becoming part of the CD4 cell DNA, HIV thrives by exploiting the process that works against other pathogens.
The Importance of Accurate Measurement
Blood Test for AIDS Proves Reliable and Practical

A team of National Cancer Institute (NCI) and collaborating scientists has demonstrated that a simple blood test for the virus called HTLV-III, the probable cause of AIDS, is a reliable, specific, and sensitive tool for screening large numbers of blood samples for antibodies to HTLV-III.
Immediate Importance of Blood Test for HIV

- Protect blood supply
- Diagnosis, especially early in disease
- Demonstration of extent of asymptomatic disease
- Epidemiological and natural history studies
High Levels of HIV-1 in Plasma During all Stages of Infection Determined by Competitive PCR

M Piatak Jr., JD Lifson, et al.
Rapid Turnover of Plasma Virions and CD4 Lymphocytes in HIV-1 Infection

DD Ho, M Markowitz, et al.

Viral Dynamics in Human Immunodeficiency Virus Type 1 Infection

X Wei, GM Shaw, et al.
A quantitative approach for measuring the reservoir of latent HIV-1 proviruses

Most proviruses are defective in most viral genes

- Cells with defective and intact proviruses may be affected differently by shock and kill interventions
Intact Proviral DNA Assay

Optimized DNA extraction → Droplet formation → ddPCR assay for intact proviruses → Assay analytics → Intact proviruses per 10^6 cells

Q1: Hypermutated and/or 3' deletion
Q2: Intact
Q3: no provirus
Q4: 5' deletion

Decay of Intact and Defective Proviruses

Bruner et al, submitted
Pathways to Sustained ART-Free HIV Remission

Eradicate the replication-competent HIV reservoir – classic “cure”

Control viral rebound without eradication of HIV in the absence of ART – “sustained virologic remission”
Pathways to Sustained ART-Free HIV Remission

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What Can We Still Learn From TRB?

- Eradicate the replication competent HIV reservoir required replacement, twice of Timothy’s immune system
- Once to clear HIV, the second to clear his leukemia
- This sledgehammer strategy is applicable when faced with a lethal cancer
Latency-reversing agents to deplete HIV reservoirs

Modified antibodies and/or effector cells directed at reservoir

Potential Strategies to Eradicate HIV from an HIV-Infected Individual

Stem cell transplantation

Gene editing
Multiple Targets for Anti-HIV Gene Therapy

A) Latently infected T cells can reactivate and produce virus that reseeds the reservoir. B) Cell and gene therapy strategies that block viral production, kill infected cells, or protect cells from infection.
Pathways to Sustained ART-Free HIV Remission

Eradicate the replication-competent HIV reservoir – classic “cure”

Control viral rebound without eradication of HIV in the absence of ART – “sustained virologic remission”
Optimal Criteria for Maintaining ART-Free Remission of HIV Infections Without Direct Eradication of Virus

- Low risk to patient
- Scalable
- Potentially leads to induction of durable immune-mediated control of virus
ART-Free Remission of HIV Infection

- ART-free remission, but requiring intermittent or continual non-ART intervention

- ART-free remission resulting from induction of durable immune-mediated control of virus without further intervention
“...sustained virologic control...”

“One patient (patient 18) in this study appeared capable of maintaining significant control of viral replication after discontinuation of drug therapy.”

Davey et al., 1999, PNAS
- ART-free remission, but requiring intermittent or continual non-ART intervention

- ART-free remission resulting from induction of durable immune-mediated control of virus without further intervention
ART-Free Approaches Towards Durable Control of HIV Infection Requiring Intermittent or Continual Non-ART Intervention

- Therapeutic vaccination

- Passive transfer of broadly neutralizing anti-HIV monoclonal antibodies (bNAbs)
Activities of a Therapeutic Vaccine

- Dysfunctional innate responses
- Exhausted CD8 T cells
- Infection of Th in B cell follicles
- Improved priming by professional APCs
- Increased breadth and functionality of CD8 T cells
- Enhanced targeting of virus-infected Th cells

- Co-inhibitory receptors
- Perforin
- Granzyme
- IL-2
- IFN-γ
- PD-1

- Targeting SIV specific responses to the mucosa
- Generation of NAbS and mAbS with effector function

- ART interruption
- Reduction in set-point VL to achieve a functional cure
- Delay in viral rebound

- Plasma Viral Load
- HIV/SIV DNA
- Limit of detection for plasma viremia
- ART

Mylvaganam, G. Current Opinion in Immunology, 35, 1-8
LETTER

doi:10.1038/nature20583

Ad26/MVA Therapeutic Vaccination with TLR7 Stimulation in SIV-Infected Rhesus Monkeys

Erica N. Borducchi, Crystal Cabral, Kathryn E. Stephenson, Jinyan Liu, Peter Abbink, David Ng’ang’a, Joseph P. Nkolola, Amanda L. Brinkman, Lauren Peter, Benjamin C. Lee, Jessica Jimenez, David Jetton, Jade Mondesir, Shanell Mojta, Abishek Chandrashekar, Katherine Molloy, Galit Alter, Jeff M. Gerold, Alison L. Hill, Mark G. Lewis, Maria G. Pau, Hanneke Schuitemaker, Joseph Hesselgesser, Romas Geleziunas, Jerome H. Kim, Merlin L. Robb, Nelson L. Michael and Dan H. Barouch
Summary of a Functional Cure Study with rh-eCD4-Ig

![Graph showing viral RNA copies per mL over weeks post-cART cessation for controls and AAV-eCD4-Ig groups.](image)

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In Conclusion

- We are approaching the end of the beginning
- Do we have a new assay, will it be dynamic enough?
- Hints of success are appearing
- We will build upon our successes and learn from our failures
- Together we can succeed