Towards an HIV Cure

Some progress, many questions

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Low-Level Viremia Persists Despite Effective ART

Log vRNA Copies/ml

Weeks Post Infection

Start Treatment
- Most (90%) HIV DNA is defective
- Of the apparently replication-competent virus, only a small subset is induced *in vitro*
- Size of relevant reservoir is not really known
There are three well-characterized non-mutually exclusive mechanisms for stability of the “reservoir”:

- **HIV replication** (lack of potency; T cell activation; tissue sanctuaries; failed host clearance)
- **Latency** (Memory CD4+ T cells, other)
- **T cell proliferation**
  - Antigen/TCR, cytokine
Functional Cure

• Long-term health in absence of therapy ("functional cure")
  – Cancer model (remission)
  – Occurs in ~1% of natural infections
• Will there be residual disease?
• Approach: Enhance HIV-specific immunity
Sterilizing Cure

- Complete eradication of all replication competent virus ("sterilizing cure")
  - Is this remotely possible?
  - Is this necessary?
  - How can this be proven?
- Approach: "Shock and Kill", gene therapy
How will HIV be eliminated or controlled in absence of ART?

- Prevent latency (early ART)
- Reverse latency ("shock")
- Clear virus-producing cells ("kill")
- Modify host environment
- Gene therapy/HST
Can we cure HIV with very early therapy?
Absence of Detectable HIV-1 Viremia after Treatment Cessation in an Infant

Deborah Persaud, M.D., Hannah Gay, M.D., Carrie Ziemniak, M.S., Ya Hui Chen, B.A., Michael Piatak, Jr., Ph.D., Tae-Wook Chun, Ph.D., Matthew Strain, M.D., Ph.D., Douglas Richman, M.D., and Katherine Luzuriaga, M.D.

- ART started at 31 hours and interrupted at ~18 months
- Classic viral decay consistent with infection of infant’s T cell population
- HIV seronegative; no consistently detectable HIV; no protective HLA alleles
Mississippi Child: HIV rebounded at month 27
ART at day 3 prevents seeding in blood, but not lymph node/gut

Virus rebound delayed but not prevented by early ART

Caveats: large bolus, short-term non-optimized ART

A delay in starting ART for a few days results in $> 1 \log_{10}$ increase in reservoir size (Okoye/Picker)
Is early ART doomed to fail?

Hatano: ART during “hyperacute” (end of eclipse period) in PrEP failures prevents detectable seeding of HIV in blood and tissues
• 14 subjects who started therapy early (but not Fiebig I/II), remained on therapy for years, and had no rebound after stopping therapy
• Lack CTL and protective HLA alleles
• Low reservoir of replication-competent virus
• HIV DNA declines in absence of ART (n=4)
• Very low T cell activation
Shock and Kill
Shock and Kill

- DNA
- HIV genome
- Memory CD4+ T cell
- Vorinostat
  - ‘Shock’
- HIV RNA
- HIV proteins
- Immune system
  - ‘Kill’
- HIV particles
- Dying infected cell
- Antiretroviral therapy
- Uninfected cell
Vorinostat (SAHA) increases RNA production during ART but does not cause virus production (Margolis/Lewin)
Romidepsin stimulates virus production

Plasma HIV-1 RNA

Days post first infusion

Romidepsin

* *
Despite clear efficacy as a “shock”, romidepsin does not affect the reservoir size.

*Søgaard and colleagues; AIDS 2014 (abstract TUAA0106LB)*
Can we enhanced killing of HIV-infected cells \textit{in vivo}?
CMV as SIV vaccine vector causes high levels of tissue-based effector CD8+ T cells that target novel epitopes.

These cells prevent/clear latency during early infection, resulting in cure (as shown by challenge studies).
Broadly neutralizing antibodies inhibit HIV replication in macaques, and can be optimized (if needed) to enhance clearance of virus-producing cells (ADCC)
Can we cure HIV infection with immune-based therapeutics?

- Immune activation
- T cell proliferation
- Negative regulators
- Enhanced clearance
Cell proliferation maintains the reservoir during ART

The HIV-1 reservoir in eight patients on long-term suppressive antiretroviral therapy is stable with few genetic changes over time.

- Up to 50% of infected cell population (blood) is clonal in nature
- Integration sites enriched for genes associated with cell growth/cancer
- Latency reversal/T cell activation may stimulate cell proliferation, thus maintaining if not increasing reservoir size
Comparative Analysis of Measures of Viral Reservoirs in HIV-1 Eradication Studies

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Frequency of HIV DNA-containing resting memory cells correlates with frequency of HLA-DR+ CD4+ T cells (rho=0.65, P=0.006)
Immunotherapy: Reduce T cell activation/proliferation (sirolimus, JAK/STAT inhibitors, anti-INFα)

Immunotherapy: Improve T cell function (anti-PD-1, anti-INFα)

Immunotherapy: Kill virus producing cells (vaccines, BNabs)
Will we need to eradicate all HIV?
Despite dramatic (1000 to 10,000 fold) reductions in “reservoir”, virus rebounded after several months.

Late rebounds will be hard to diagnose and could have profound effects on patient and his/her partners.

Modeling: latent reservoir will have to be depleted > $10^5 \log_{10}$ fold or a durable cure to be likely (Hill, PNAS 14)
Summary

• There will be no scalable and safe cure in the foreseeable future
• Treatment of hyperacute HIV may still be curative; early ART reduces reservoir and protects immune function (VISCONTI)
• Shock (HDAC inhibitors) work, but are not sufficiently potent
• A number of adjunctive anti-proliferation/anti-inflammation drugs are moving through pipeline
• In absence of host control, profound depletions in reservoir needed, and life long surveillance for late failures needed
• A biomarker for reservoir may be highest priority
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