Recent Insights into HIV Pathogenesis and Treatment: Towards a Cure

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Overview

• Historical Perspective on the global burden of HIV infection
• Highlight gains in health outcomes due to advances in antiretroviral treatment through drug discovery and clinical trials
• Sobering reality on the extent to which HIV persists in viral reservoirs despite long-term effective suppression of virus replication that precludes CURE
• Recent optimism surrounding CURE through a single case of HIV cure: impact on scientific and pharmaceutical communities
• Update on current therapeutic approaches towards finding a CURE for HIV (19th Conference of Retroviruses and Opportunistic Infections; March 2012)
Historical Perspective (HIV/AIDS)

- AIDS epidemic surfaced nearly 31 years ago (June 1981)
- More than 60 million people infected
- 30 million have died
2012: 25 Antiretroviral Drugs from 6 Drug Classes Approved to treat HIV infection (Mechanisms of Action)
Combining Antiretroviral Drugs Leads to Durable Suppression of Virus Replication: Plasma Viremia Falls to below the Limit of Detection of Clinical Assays

Reviewed in: Goldberg DE, Silciano RF, Jacobs WR.; Cell 148, March 16, 2012
Average survival benefit with prophylaxis (PCP/MAC) was 3 months.
With HAART, average survival from AIDS diagnosis >14 years.
AIDS is now a highly treatable chronic condition.
Per-person survival gains exceed gains for patients treated for other chronic diseases (U.S.)
Survival Benefit of ART in HIV-Infected Children

• Pre-ART era: average survival 10.9 years

• Post-ART years: average survival is estimated at 27 years
**Challenge:** HIV Incurable with HAART: Persistence of a small pool of cells (resting memory CD4+ T cells) that carry HIV integrated within the host cell genome.
Establishment of HIV latency in Resting CD4+ T Cells

Siliciano’s Model; 1997
HIV is latent or transcriptionally silenced in resting memory CD4+ T cells and therefore cannot be seen by the immune system or targeted by antiretroviral drugs.
Immune Activation reverses transcriptional silencing of HIV in Resting CD4+ T Cells rendering cells susceptible to cell killing.

Richman et al. 2009 (Science)
Residual Plasma Viremia Persists in Most HAART-Treated Patients: One Source is Latently Infected CD4+ T Cells

Summary: State of HIV Persistence after 5 or more years of HAART

- Residual viremia persists at a level of 1-3 copies/ml of blood
- Total HIV DNA: 100-1000 copies for every million peripheral blood mononuclear cells
- Not all HIV genomes are infectious
  - (99-99.9%) are defective and not capable of replicating
- Infectious virus: 0.1 and 1 infectious units for every million PBMC
- Ratio of infectious virus: viral DNA (1:100-1:1000)
- Replication-competent reservoir: size is 100,000-one million cells
- Half-life is very long 44 months which translates into 72 years of HAART to achieve Cure
Additional HIV Reservoirs to consider in CURE Strategies

**Functional**
- Lymphoid
- Memory CD4 cell
- Regulatory CD4 cell
- CD34+
- Macrophage
- Microglial
- Langerhans
- Histiocytes
- Alveolar

**Anatomic**
- CNS
- GALT
- Genitourinary tract
Differences in HIV Burden in the Gut of HIV-Positive Patients on HAART

Yukl SA, JID 2010
Hypothesis. Red circles indicate infected cells, arrows indicate transmissions, hexagons or hexagons surrounded by circles indicate viruses, broken circles indicate degraded viruses, crosses indicate viruses blocked by drug and wavelets indicate successful infection. 

b, MT-4 cells were pre-incubated with TFV and infected with HIV coding for YFP. Infection multiplicity $m$ was 0.2 (blue squares) or 100 (red squares). Lines are a guide for the eye. Mean $\pm$ standard deviation (s.d.) of replicates ($n = 3$). Circles represent calculated values of $T_X$ at $m = 100$ according to equation (1) with $f(d)$ at each drug concentration determined empirically at $m = 0.2$. 

$\text{Transmission index}$

\begin{align*}
\text{TFV (µM)} & \\
0 & \longrightarrow 16
\end{align*}
A Case of CURE

• To date, there is one individual “cured” of HIV infection
  • Bone marrow transplantation (twice)
  • Stem cells from a donor homozygous for the delta 32 CCR5 gene
  • Homozygosity for delta 32 confers cellular resistance to HIV infection
    • CCR5 is required for R5-tropic viruses to enter CD4+ target cells
    • Dominant strains transmitted

Photos from Science 2012

Timothy Brown

Hutter et al. NEJM 2009
FIGURE 1. The clinical course and treatment of leukemia and HIV infection. Measurement of HIV-1 viremia by RNA-PCR (red line) and DNA PCR assays are displayed. HIV-1 RNA could not be detected in peripheral blood and bone marrow during the follow-up since HAART had been discontinued on day –1 up to date. The count of CD4+ T cells in the peripheral blood are displayed as the blue line.
What did it Take to Cure HIV in a Single individual

- Myeloablative chemotherapy x 2
- Total Body irradiation x 2
- Killing of HIV-infected and uninfected host cells
- Chemotherapy: ATG, cyclosporin, MMF and gemtizumal (anti-CD33)
- Allogeneic stem cells with CCR5 delta 32
- Graft vs. host disease (GVHD)
- Graft cells replaced hosts hematopoietic and immune systems
- Effort is high risk (25% mortality) and impractical to implement
Serves as proof-of-concept that HIV CURE is possible

Richman, et al, Science 2009;323
Finding a cure for HIV-infected individuals is one priority areas of the NIH

Millions of new dollars are being devoted to this charge

Optimism around this charge mirrors that of 1996 when David Ho was named Man-of-the Year for proclaiming that HAART will likely Cure HIV
What is “a CURE”

- Permanent remission of disease (and its consequences) in the absence of antiretroviral therapy
What Does it Mean to be Cured of HIV Infection?: Proposed Definitions

**Functional Cure/Remission**
- Cancer model, long health in absence of ART
- HIV RNA < 50 copies/ml without HAART
  - (post-CART controllers)
- No disease progression
- No CD4 loss or immunological defects
- Lack of HIV transmission

**Sterilizing Cure**
- Eliminate all HIV infected cells, HIV RNA <1 copy; sterilizing cure as in the Berlin patient

Lewin S, CROI 2012
Approaches to CURE

- Activating latent virus
- Gene therapy approaches that modify CD4+ T cells
- Boosting the immune system, so that it can control HIV replication on its own when ART is discontinued.
  - Therapeutic vaccines
  - Immunomodulators
Shock and Kill Approach (Re-awakening Latent HIV)

- Activate latent HIV to deplete reservoirs under protection of ART
- HDACi (SAHA or vorinstat)
- Chemical classes of inducers (disulfuram)
- Killing of cells may require induction of HIV specific CTLS
Re-awakening Latent HIV: Vorinostat (SAHA) Studies

- **Pilot study #1**: PI- Sharon Lewin, M.D. (Australia)
  - 10 HIV-infected patients on HAART have received a 14 day course of vorinostat
  - no major toxicities noted; CD4 counts and viral loads remained stable
- **Pilot Study #2**: PI: David Margolis, M.D. (UNC)
  - 6 HIV-infected patients on HAART have received a single dose of vorinostat
  - HIV RNA expression in cells and in plasma were measured 4-8 hours following the single dose
  - Levels of HIV RNA expression in resting CD4+ T cells were significantly increased in all 6 patients; plasma RNA stable
  - Suggest disruption of HIV latency is possible

CROI 2012
Re-awakening Latent HIV: Disulfuram

- Two weeks of daily disulfuram to patients on HAART
- 14 patients received study drug
- An unexplained significant increase (4.5-fold) in plasma viremia was observed within two hours of drug administration
- No change in latent reservoir size observed at 84 days following study regimen
Gene Therapy and Immune modulatory Approaches

- **Gene knockout strategies**
  - Zinc finger nucleases (modification of CCR5)
  - Stem Cell transplantation with CCR5 delta 32 positive cells for HIV infected persons requiring BMT for other reasons

- **Immune modulatory**
  - Target negative regulators of the immune response such as PD-1: anti-PD1
  - IFN, anti-IL-10, peg interferon
  - Therapeutic vaccination as an adjunct
Gene therapy approaches

General Approaches for Adoptive T Cell and Stem Cell Therapy

Harvest PBMCs bypheresis

Optional priming vaccine

Stem cell collection

T cell in vitro transduction and expansion

Optional lymphodepletion to enhance engraftment

T-cell transfer

HS cell transduction Host conditioning (chemotherapy = radiotherapy)

Stem-cell transfer Optional booster vaccines

Nat Biotech 2007 25:1449

Courtesy of Pablo Tebas; UPenn
Zinc finger nucleases/Decrease in HIV-RNA During HAART Interruption
Undetectable HIV-RNA in One subject - A CCR5 delta 32 heterozygote

Tebas P et al. CROI 2012
Studies on Immune modulators

- **Peg-IFN-α2A immunotherapy: modulation of host responses**
- A study of 20 individuals:
  - Viral suppression <400 copies/ml over 24 weeks of follow-up in 9/20 (44%) of Peg-IFN-α2-treated subjects when ART was stopped
  - Subjects who maintained viral control had a significant drop in integrated HIV DNA, suggesting the possibility that Peg-IFN-α2 treatment reduce viral reservoirs.
  - Proof-of-concept showing that immune modulation with Peg-IFN-α2A immunotherapy may lead to sustained control of HIV replication and a decrease in cell-associated integrated HIV-1 load.
  - Authors conclude: data suggest that a functional cure for HIV infection in which host responses are modified to control the virus is theoretically possible.

Azzoni L et al. CROI 2012, Poster 631
Summary

• Current HAART provides for durable suppression of HIV replication and greatly enhances life-expectancy
• Rebound viremia is inevitable if HAART is stopped
• A single case of CURE changed the field of HIV therapeutics where “CURE” is now once again a therapeutic goal
• Identifiable pathways towards this goal exist
• Pilot studies of disruption of HIV latency are encouraging
• Enhancing HIV-specific immune responses may also need to be a critical component of CURE strategies
References

- [www.retroconference.org](http://www.retroconference.org) (CROI 2012, relevant presentations on “HIV CURE” at CROI, including presentation by Dr. John Mellors for the Young investigator workshop)
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