When Will It All Be Over?  
HIV Cure Efforts

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Learning Objectives

After attending this presentation, participants will be able to:

- Describe differences between functional and sterilizing cure efforts.
- Recognize HIV cure strategies currently in clinical research.
- Describe ethical issues around HIV cure research.
Thing 1: HIV Reservoir Persists during ART

Antiretroviral drugs are capable of suppressing HIV to undetectable levels. However, HIV rebounds after stopping therapy.

HIV infection is characterized by high levels of circulating viruses in the blood.

Thing 2

The HIV Reservoir is Stable during ART

Slower-than-exponential decay of HIV-1 DNA during the first 4 years of ART.


Types of Cure

- Sterilizing vs. Functional cure
  - Sterilizing: HIV is cleared everywhere.
  - Functional: the host’s immune system is able to control HIV infection without help from ART.
The Berlin Patient

The Mississippi Baby

Rebound 3 years later 16k VL
Interruption of Long-term ART Started During Primary Infection May Lead to Viremia Control

- PTCs may not be rare
  - 15% of VISCONTI cohort
  - PTCs also identified in ACTG ATI studies of patients treated during acute and chronic infection.
- What proportion of patients are PTCs?
- What is special about PTCs?
Current Efforts

- Eliminating latency (kick and kill)
  - Kicking: HDACi, TLR-7 agonists
  - Killing: Antibodies, Immunotoxins, DARTs

- Enhance HIV-specific immune response
  - Therapeutic vaccines
  - Immune checkpoint blockade
    - PD-1, CTLA-4

- Making cells resistant to HIV
  - Gene therapy: adding protective stuff, subtracting needed stuff (e.g. CCR5), cutting out provirus

Untreated HIV Infection = Rampant Pollination

ART Stops Rampant Pollination

ART Stops HIV Replication
The Latent Problem

- Latent reservoir's in a million CD4+ T cells

Use a Kick to Find Latently Infected Cells

- Use a Kick to find latently infected cells
  - HIV-specific immune response or immunotoxin or antibody kills cells producing virus
  - ART will keep new cells from being infected

Kick and Kill

- ART will keep new cells from being infected
HDAC-i induces HIV-1 transcription

Romidepsin induced HIV-1 transcription

Kick
No Kill

Antibodies
Triple PGT121, 3BNC117 and b12 monoclonal antibody cocktail.


Dual-Affinity Re-targeting Molecules Bind HIV Envelope and Recruit Cytotoxic T Cells


Improving Host Immune Response
RhCMV/SIV Vector-Mediated Protection

- Live RhCMV vectors that contain SIV genes (SIV Gag, Rev/Tat/Nef, Env and Pol) establish persistent, SIV-specific effector memory T-cell (TEM) responses in rhesus macaques and control SIV infection.

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Immune Checkpoint Blockade

- IC regulate T cell activation, proliferation and cytokine production
- Associated with chronic T-cell dysfunction during HIV infection (PD-1, CTLA-4, TIM-3, CD160)
PD-1 Axis: Immune Checkpoint

- PD-1: a negative regulator of activated T cells is upregulated on exhausted virus-specific CD8 T cells.
- Blockade of this pathway using antibodies against the PD-1 and PD-1 ligand 1 restores CD8 T-cell function and reduces viral load.

APC
Exhausted HIV-specific T-cell
Latently infected T-cell

Energized HIV-specific T-cell
Increased HIV expression
Increased CTL activity
Decreased HIV reservoir

Cutting Out Latent HIV

Types
- Zinc fingers
- CRISPR CAS
- TALENS

Issues
- Off-target effects
- Cellular delivery
- Resistance
Making Cells Resistant to HIV

- Zinc Finger Nucleases
- Integrate gene replacement
- Take out CCR5 gene

Adoptive Immunotherapy

- CCR5-Modified CD4 T Cells During Treatment Interruption Did Not Decrease, Unlike Unmodified CD4 T Cells

Which of these is likely an example of a functional HIV cure?

- The Berlin Patient
- The Mississippi Baby
- The Boston Patients
- The Visconti Cohort
Which of these is an example of a functional HIV cure strategy?

- 33% 1. Therapeutic Vaccine
- 22% 2. HDAC inhibitor therapy
- 16% 3. PD-1 blockade
- 31% 4. CRISPR HIV DNA modification

Which of these is an example of a “kick and kill” HIV cure strategy?

- 0% 1. Therapeutic Vaccine
- 89% 2. HDAC inhibitor therapy
- 3% 3. CRISPR HIV DNA modification
- 5% 4. CCR5 gene deletions

How long will we have to wait?

- 87% 4. CCR5 gene deletions
- 7% 2. HDAC inhibitor therapy
- 6% 3. CRISPR HIV DNA modification
- 8% 1. Therapeutic Vaccine
Thank you for your attention.