Learning Objectives

After attending this presentation, learners will be able to:

- Define the mechanisms behind HIV persistence
- Describe challenges in achieving HIV eradication and remission
- List ongoing efforts and strategies for inducing HIV remission

Overview

- Status of the HIV epidemic
- Mechanisms behind HIV persistence
- Success stories
  - The Berlin and London patients
  - Post-treatment controllers
- Strategies for inducing HIV remission
Decline in HIV incidence and mortality over time

People dying from AIDS-related causes globally

Update on the Epidemic
- 37 million people living with HIV
- 22 million people on ART
- 1.8 million new infections yearly
- 1 million AIDS-related deaths yearly

Why Do We Need a Cure?
Challenges in ART Initiation and Adherence

Issues Surrounding Long-Term ART

Complications of Long-Term ART Despite ART
Overview

• Status of the HIV epidemic
• Mechanisms behind HIV persistence
• Success stories
  ▫ The Berlin and London patients
  ▫ Post-treatment controllers
• Strategies for inducing HIV remission

HIV Persists Despite Long-Term ART

HIV Life Cycle Leads to Persistence
Overview

- Status of the HIV epidemic
- Mechanisms behind HIV persistence
- Success stories
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  - Strategies for inducing HIV remission

Is HIV Cure Possible?

HIV Requires a Co-Receptor for Cell Entry
CCR5 Deletion Prevents HIV Entry

Allogeneic Stem Cell Transplantation (ASCT)

HIV Remission after CCR5-Δ32 Donor HSCT

The New England Journal of Medicine
Long-term Control of HIV by CCR5 DeficitΔ32 Donor HSCT Stem-Cell Transplantation
Differences between Berlin and London patients

<table>
<thead>
<tr>
<th>Berlin patient</th>
<th>London patient</th>
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<tbody>
<tr>
<td>Heterozygous for Δ32</td>
<td>Homozygous for wild type CCR5</td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>Two HSCT</td>
<td>Single HSCT</td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>No irradiation</td>
</tr>
<tr>
<td>Full intensity conditioning</td>
<td>Reduced intensity conditioning</td>
</tr>
<tr>
<td>T cell depletion with ATG</td>
<td>T cell depletion with aCD52</td>
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HIV Suppression Requires Life-long ART

Fun Poll #1
In the average patient, how quickly does HIV return to detectable levels in the blood after ART is discontinued?
1. <48 hours
2. 2-4 days
3. 2-4 weeks
4. 2-4 months
5. >4 months

HIV Rebound after Treatment Interruption (TI)

- Assess the timing of HIV rebound in a pooled analysis of 6 AIDS Clinical Trials Group (ACTG) TI studies
- Inclusion criteria
  - On combination ART
  - HIV-1 RNA <50 copies/mL at time of ATI
  - No immunologic intervention (e.g., therapeutic vaccination)
- Viral rebound threshold definitions
  - Confirmed HIV-1 RNA ≥200 copies/mL or a single HIV-1 RNA ≥1,000 copies/mL
Most Patients will Rebound Between 2-4 Weeks

Definitions of an HIV Cure

The Timing of HIV Rebound is Not Uniform
HIV Post-Treatment Controllers (PTCs)

Overview

- Status of the HIV epidemic
- Mechanisms behind HIV persistence
- Success stories
  - The Berlin and London patients
  - Post-treatment controllers
- Strategies for inducing HIV remission

How Do We Transform Our Patients into PTCs?

- Bone marrow transplant (with CCR5 wild-type donors)
- Early HIV treatment
- Shock and kill
- Gene therapy
The “Boston BMT Patients”

Fun Poll #2

Stem-cell transplant with donor cells containing wild-type CCR5 had what effect after ART interruption?

1. Led to a sterilizing HIV cure
2. Significant delay in HIV rebound, but eventual HIV rebound
3. Rapid HIV rebound

HSCT Alone Resulted in Delayed HIV Rebound

Patient A

Patient B
How Do We Transform Our Patients into PTCs?

- Bone marrow transplant (with CCR5 wild-type donors)
- Early HIV treatment
- Shock and kill
- Gene therapy

Early ART Dramatically Decreases HIV Reservoir

Ananworanich, EBioMed 2016

The Control of HIV after Antiretroviral Medication Pause (CHAMP) Study

Namazi, J Infect Dis 2018
Example of a PTC

Higher PTC Frequency with Early ART Initiation

How Do We Transform Our Patients into PTCs?

- Bone marrow transplant (with CCR5 wild-type donors)
- Early HIV treatment
- Shock and kill
- Gene therapy
Shock and Kill Overview

- Latency reversing agent = TLR7 agonist (GS-9620)
- Reservoir clearing agent = broadly-neutralizing Ab (PGT-121)
- 44 rhesus monkeys randomized to 4 groups:
  - sham (placebo), GS-9620 alone, PGT-121 alone, or both
- ART interruption 16 weeks after end of intervention
How Do We Transform Our Patients into PTCs?

- Bone marrow transplant (with CCR5 wild-type donors)
- Early HIV treatment
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- Gene therapy

Zinc-Finger Nucleases (ZFN)

- Zinc-finger nucleases induce breaks in the gene of interest (e.g., CCR5)
- DNA repair is error-prone and frequently result in disruption and inactivation of the gene

The NEW ENGLAND JOURNAL OF MEDICINE

Gene Editing of CCR5 in Autologous CD4+ T Cells of Persons Infected with HIV
Chinese scientist’s claim of gene-edited babies creates uproar

Cure Strategy Score Card

- Stem cell transplant
  - CCR5-Δ32 donor cells
  - CCR5 wild type donor cells
- Early HIV treatment
- Shock and kill
- Gene therapy

“I know in my heart and soul that I will not be the only one cured of AIDS. Hope is alive in me.”
Question-and-Answer