HIV

HIV cure research
Summary of talk

• The immune system
• HIV
• HIV treatment
• HIV cure?
The role of the immune system

• Danger signal and recognise and remove abnormal cells
• Check for cancer cells identify sick cells
• Remove invaders
• Kill the bad cells
• Ignore “self”
Cells of the immune system

**Humoral Immunity**
- Extracellular microbe (e.g., bacteria)
- B lymphocytes
- Secreted antibody
- Neutralization
- Lysis (complement)
- Phagocytosis (PMN, macrophage)
- Destruction of phagocytosed microbes

**Cellular Immunity**
- Intracellular microbe (e.g., viruses)
- Antigen-presenting cell
- T cell
- Processed and presented antigen
- T cell receptor
- Cytokines
- Cytokine receptors
- Proliferation and activation of effector cells (macrophages, cytotoxic T cells)
- Killing of infected cell
HIV virus
HIV attaches to any cell with certain receptors on its surface and inserts virus genetic material into the cells own DNA.
What happens to the person living with HIV?

- Virus infects usually through mucosal surfaces - genital or gut
- Passes to local lymphoid tissue
- Spreads all round the body
- Kills CD4 - cells and rests in “sleeping” cells of the immune system to form a latent pool of invisible and inaccessible cells
Treatment works!!

Haitian Patient before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public-private partnerships.
Actual and projected numbers of people receiving antiretroviral therapy in low- and middle-income countries by WHO region and in high-income countries across WHO regions, 2003–2015

*Country income classification by the World Bank at the time of the 2011 Political Declaration on HIV and AIDS.

Source: Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)
The success of ART

Expected survival of a 20-year-old person living with HIV in a high income country

<table>
<thead>
<tr>
<th>Era before ART</th>
<th>Era of ART</th>
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<tbody>
<tr>
<td>HIV+ 1995–1996</td>
<td>+8 years</td>
</tr>
<tr>
<td>HIV+ 2000–2002</td>
<td>+36 years</td>
</tr>
<tr>
<td>HIV+ 2003–2006</td>
<td>+45 years</td>
</tr>
<tr>
<td>HIV+ 2006–2007</td>
<td>+51 years</td>
</tr>
<tr>
<td>HIV+ 2010</td>
<td>+55 years</td>
</tr>
<tr>
<td>HIV-negative</td>
<td>+60 years</td>
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Why do we need a cure?
HIV persists during ART

ART does not eradicate HIV
Why can’t ART cure HIV?
Barriers to an HIV cure

HIV persistence in tissues

Latently infected cells are rare and undistinguishable from uninfected cells

Latently infected cells are diverse

Eradication strategy should reach tissues

Eradication strategy should be specific

Eradication strategy should target all infected cells
Where does HIV hide?

Two types of cure

- “Sterilizing” cure

- “Functional” cure
What is the difference between the two types of Cure?

**Functional cure**
- Absence of ongoing viral replication in the absence of antiretroviral therapy
- Detectable viral DNA but no/little evidence of viral transcription or replication
- No risk of onward transmission
- No ongoing immunological damage

**Sterilising Cure**
- No detectable virus DNA AND RNA
- No detectable viral reservoir
- No detectable viral transcription
- Timothy Brown
1 man in the world has been Cured

- Was it the stem cell transplant alone?
  - 2 recent reports of “no detectable virus” following allogeneic transplantation with continuous ART (IAS 2013)
- Was it the CCR5Δ32 transplant?
- Was it GVHD?
- Was it EVERYTHING
Cure strategies

To reduce the size of the reservoir

- Render uninfected cells resistant to HIV
- Deplete infected cells
- Flush out the latent reservoir

and facilitate clearance of infected cells
and enhance immune control
Approach 1: Treat EARLY
Impact of early ART on HIV persistence (RV254)

Very early ART (<2-3 weeks after infection) dramatically reduces the frequency of cells carrying integrated genomes

Approach 2: Render uninfected cells resistant to HIV

SB-728 vector (CCR5 disruption Zn Finger)

Approach 3: Flush out the latent reservoir (Shock and kill)

“Latency reversing agent”

Cytopathic effect

Immune response
Drugs that have been shown to disrupt latency in vitro

Combinations of anti-latency drugs induce robust levels of HIV production in latently infected cells

Approach 4: (plus 3?) Help the immune system

Immune checkpoints and HIV persistence

- Immune checkpoints (PD-1, LAG-3, TIGIT, CTLA-4) negatively regulate (switch off) T cell responses and contribute to immune exhaustion.

- These molecules can be blocked by antibodies to restore HIV-specific immunity.

Immune checkpoints are expressed at the surface of infected cells and inhibit viral reactivation from latency.

R. Fromentin et al. in preparation.
Protocol Overview
A two-arm (proof of concept) randomised phase II trial
Step 1: ART is used to make sure HIV is undetectable

Step 2: Two vaccines (V) train the immune system to recognise cells that will be activated

Step 3: Vorinostat is used to wake the sleeping cells

Step 4: The immune system, boosted by the vaccine, attacks and kills the newly activated cells
Summary

• New ideas to cure HIV
• Block viral replication with ART
• Add in drugs that activate virus from the latently infected pool
• Wake up the immune system to kill these virus expressing cells
• Will people get re-infected though?
• Are the drugs toxic
• How much will this cost?
Thanks
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