Effects Of Long-term ART On The HIV Reservoir

2023 Pre-CROI Community HIV Cure Research Workshop

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Overview

• **Key question(s) of the research**
  - How does HIV persist in people on suppressive antiretroviral therapy (ART) and how does ART change the composition of the HIV reservoir over time?

• **Key findings and take-home messages**
  - HIV can establish a chronic infection of T-cells (reservoir) with some viruses being more active than others
  - On ART, active HIV-infected cells are cleared faster than inactive cells
  - The HIV reservoir becomes less active over time on ART

• **How does this work relate to an HIV cure?**
  - A less active reservoir affects how well cure strategies may work depending on their approach
  - Differences in the composition of the HIV reservoir may require tailoring of cure interventions
The Central Dogma of Biology

- Deoxyribonucleic acid (DNA) is the genetic code to produce everything our cells – and bodies – need.
- Ribonucleic acid (RNA) is the message transcribed from DNA
- RNA is translated into proteins necessary for cellular functions
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What makes HIV such a Retro-virus?

- HIV’s genome is made of RNA and is **reverse transcribed** into DNA
- The new HIV DNA genome is **integrated** into the host cell’s DNA
- As HIV goes from RNA → DNA → RNA → protein, it goes **against the central dogma** of biology, hence “retro”virus
- All currently licensed ART, except for lenacapavir (capsid inhibitor), act pre-integration
- Once a cell has an integrated viral genome (provirus), it will remain infected until it dies
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The Human Genome

- The human genome is 3,117,275,501 base pairs (bp) long
- The King James Bible is 3,116,480 letters long
- The HIV genome is 9,800 bp long
- ~10% of the human genome are endogenised retroviruses (ERVs)

Fig 1. Rosa and Shaw, 2013 [10.3390/biology2041378]
The Human Genome

- Only 1% of the human genome are **genes** encoding for proteins
- Because of its considerable length, DNA is a highly organized structure **supercoiling** around itself to form chromosomes
- In order to read genes, DNA needs to be in a relaxed and open state
- Actively transcribed genes are located in the nuclear periphery
- HIV tends to integrate into actively transcribed genes, but not always
- The site of HIV integration can impact the viral activity of infected cells

Fig. 1. Rosa and Shaw, 2013 [10.3390/biology2041378](https://doi.org/10.3390/biology2041378)
HIV Latency – Not All Proviruses Are Made Equally

**Latent infection**
- DNA positive
- RNA negative
- HIV protein negative

**Productive infection**
- DNA positive
- RNA positive
- HIV protein positive

Courtesy of Sharon Lewin
Productive Infection is Required for Clearance of Infected Cells

**Latent infection**
- DNA positive
- RNA negative
- HIV protein negative
- Cell Survival

**Productive infection**
- DNA positive
- RNA positive
- HIV protein positive
- Cell Death
The HIV Reservoir Becomes Increasingly Latent Over Time on ART

- On ART, proviruses that are more active are cleared rapidly
- The HIV reservoir persists on ART by clonal expansion
- Viruses that can remain latent during cell division avoid clearance by the immune system
- This means that the HIV reservoir becomes increasingly clonal and latent over time on ART
Summary

• ART is highly effective at preventing cells becoming infected with HIV, but it is **ineffective against cells already infected with HIV**

• HIV uses unique biology to **integrate** its genome into the host cell’s DNA, thus the virus persists for as long as an infected cell survives

• HIV integration is somewhat random, but there are preferences for **actively transcribed genes**

• For infected cells to be cleared, viral expression is necessary

• HIV can establish a **latent** state of infection where it remains inactive in a cell and is hidden

• Proviruses that are more latent are able to be hidden and survive longer in people with HIV

• The HIV reservoir becomes **more latent over time** on ART

• Though the HIV reservoir decreases on ART, this is counteracted by division of infected cells by **clonal expansion**

• The HIV reservoir becomes **more clonal over time** on ART
Major Outstanding Research Questions

• What determines if a cell will be latent or productively infected?
• What determines if a cell will switch from being latent to productive?
• What makes one cell undergo clonal expansion and not another?
• Can HIV itself make infected cells divide and survive better?
• Should a cure make HIV less latent (less hidden, more easily cleared) or more latent (more hidden, but less likelihood of virus being made)?
• Is long ART enough to enrich for a deeply latent HIV reservoir that doesn’t rebound when ART is stopped?