Update on Cure Research for HIV Infection

Robert F. Siliciano, MD, PhD
Professor of Medicine, Molecular Biology, and Genetics
The Johns Hopkins University
Baltimore, Maryland

Learning Objectives

After attending this presentation, learners will be able to:

• Describe the basic mechanisms that allow HIV to persist despite ART
• Describe the cause and time course of viral rebound following interruption of ART
• Describe current approaches for achieving a cure

HIV replication dynamics

- Plasma HIV RNA copies/ml
- Time (months)
- Set point
- ART
- Stop ART
- Limit of detection

HIV replication dynamics

- Plasma HIV RNA copies/ml
- Time (months)
- Set point
- ART
- Stop ART
- Limit of detection
HIV replication dynamics

Plasma HIV RNA (copies/ml)

Time (months)

Set point
Limit of detection
Residual viremia

\[ R_0 = 10 \]
\[ \frac{1}{2} t_{1/2} = 14 \text{d} \]

Wei et al. Nature 1995
Ho et al., Nature 1995
Perelson et al., Nature 1997
Finzi et al., Nature Med 1999
Dornadula et al., JAMA 1999
Dinoso et al., PNAS, 2009
Robb and Ananworanich, COHA, 2016

Physiology of resting and activated CD4+ T cells

Memory
Naive

Response of resting T cells to antigen

Memory
Naive
Recall response of memory T cells to antigen

Infection of activated and resting CD4+ T cells

Establishment and maintenance of a latent reservoir
**NFκB sites in the HIV LTR**

Cell DNA

- AP1
- NFAT1
- USF1
- Ets1
- LEF
- NFκB
- Sp1
- TBP
- LBP1

Tong Starksen SE, et al. PNAS. 1987
Bohnlein E, et al. PNAS. 1989

**A stable latent reservoir for HIV**

**Reactivation of latent HIV**

Naive

Memory

- HIV

- Ag

- NFκB sites

- TBP
Slow decay of latently infected CD4+ T cells

Time to eradication > 73.4 years

Finzi et al., Nature Med., 1999

HIV replication dynamics

Plasma HIV-1 RNA (log10 copies/ml)

Stop ART
ART
Set point
Time (months)

Limit of detection

HIV replication dynamics

Limit of detection

Stop ART
ART
Set point

Time to eradication > 73.4 years

Finzi et al., Nature Med., 1999

Slow decay of the reservoir

Time to eradication

\( t_{1/2} = 44 \) months

Crook et al., JID 2015

\( t_{1/2} = 43 \) months

Crook et al., JID 2015
Chronic Hepatitis C infection

- Continuous, high level viremia
- Rapid viral evolution
- Drug resistance with suboptimal treatment

Dose Response Curve

Inhibition of HCV replication by direct acting antiviral drugs

- HCV antivirals also have steep dose response curves that produce very high levels of inhibition
- HCV infection is readily curable
- HCV has no latent form
ART is completely suppressive but not curative due to latent reservoir

- Host immune system, including latently infected cells, largely eliminated by condition regimen (chemo + irradiation and by graft vs host disease).
- Donor cells protected from HIV infection due to absence of CCR5

---

“Boston Patient B”

---

The Mississippi baby

These delayed rebound cases prove that HIV can persist in a latent form for years and then begin to replicate

---

National Harbor, Maryland, December 9-11, 2018
HIV replication dynamics

Plasma HIV-1 RNA (copies/ml)

Time (months)

Set point

Limit of detection

$R_0 = 8 - 10$

$\tau_i = 1 \text{d}$

$\delta = 14 \text{d}$

ART

Stop ART

Viral rebound

- Rebound in ~14 d
- Exponential
- Multiple latently infected cells reactivate per day
- Long delays only when <1 cell reactivates per day

Time after interruption of ART (months)

Plasma HIV-1 RNA (copies/ml)

Davey et al, PNAS 1999
Approaches to cure

- Reservoir reduction results in a delay of rebound
- Sterilizing cure if reservoir is eliminated

Plasma HIV RNA (copies/ml)

Time after interruption of ART (months)

Approaches to cure

- Immunologic interventions may allow control of viral replication
- Permanent control of viremia = Functional cure

Plasma HIV RNA (copies/ml)

Time after interruption of ART (months)

The HIV envelope spike
Broadly neutralizing antibodies

- Neutralize diverse HIV isolates
- Arise slowly, generally after virus has already escaped
- Have been isolated and sequenced
- Can be administered passively as infusion or with AAV vectors
- Block infection and target infected cells for killing

Effects of antibodies

Slight delay with bNAb infusion
The shock and kill approach for eliminating latent HIV

LRA in clinical trials
• Histone deacetylase inhibitors – promote gene expression
• Toll-like receptor agonists – activate the innate immune response

Current status of LRA trials
• Numerous LRAs identified in model systems
• Few shown to work ex vivo with cells from patients
• Some evidence for slight transient increases in plasma HIV RNA after LRA treatment indicating some reactivation of latent HIV
• In clinical trials, no reduction in the reservoir yet demonstrated

Targeting the reservoir using antibodies

Study Design

Barouch et al, CROI 2018
Problems with the “kill” phase

- Infected cells may not die quickly after reversal of latency
- Cytolytic T lymphocyte (CTL) response is “exhausted”
- Unless treatment is started during acute infection, most of the viruses in the latent reservoir have CTL escape mutations
- Vaccines to enhance the cytolytic T cell response may be needed
**Conclusions**

- ART stops viral replication but does not eliminate latent HIV
- Reactivation of latently infected cells leads to viral rebound after ART interruption
- Current cure efforts are focused on eliminating the latent reservoir
- Broadly neutralizing antibodies have been isolated and developed as agents to block viral entry and target productively infected cells
- Reservoir reduction will likely the identification of effective latency reversing agents and effective kill strategies
- Long delays in viral rebound will require a 1000 fold reduction in the reservoir
Question-and-Answer
Update on Cure Research for HIV Infection  
Robert F. Siliciano, MD, PhD

SUGGESTED READINGS


