Early Antiretroviral Therapy

HIV Cure Research Training Curriculum
HIV and Cure Early ART
Presented by: Jintanat Ananworanich, MD, PhD
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Objectives

- Understand the current state of the HIV cure research field
- Summarize how early treatment could play a role in HIV cure research
- Explain the major cohorts involved in HIV cure research
What is an HIV Cure?
What is an HIV Cure?

Key elements of any cure:

- NO Transmission
- NO Disease Progression
- NO Medications
How Do We Define “Cure”?
How Do We Define “Cure”?  

- **Sterilizing/Eradication**
  - HIV is completely removed from every cell in the body
  - Person is HIV-free (virus free)
  - No need for medication

- **Functional/Remission**
  - HIV is NOT completely gone from the body
  - All requirements from previous slide met
  - No need for medication
  - *HIV has potential to resurface*
Why is HIV so Hard to Cure?
Why is HIV so Hard to Cure?

- HIV enters a cell and integrates into the cell’s DNA
- **Most** cells recognize infection - causing cell death
- **A few** infected cells become “long-lived” memory cells or “resting memory” cells
- The collection of long-lived memory cells is called the **Latent Reservoir**
Why is HIV so Hard to Cure?
Why is it so Hard to Cure HIV: Establishing the Latent Reservoir

Naïve CD4+ T cell → Activated CD4+ T cell → Latent Reservoir

HIV

Cell Death → Cell Survival

Adapted from D. Persaud
Why is it so Hard to Cure HIV: Establishing the Latent Reservoir

Latent Reservoir

Reactivated CD4+ T cell

Adapted from D. Persaud
What is the Definition of Early?

- There is NO consistent definition of early
- Researchers do not know when the latent reservoir forms
- Most researchers define “early ART” as 14-90 days post infection.
- Some protocols use the term early to describe treatment initiation within six months.
What is the Definition of Early?

Adapted from McMichael AJ, *Nature Reviews Immunology*, 2010

- **Eclipse Phase**
- **Reservoir Established**
- **Symptoms Begin**
- **Limit of detection of assay for Plasma viral RNA**

Virus concentration in extracellular fluid of plasma (copies per ml)

Days following HIV-1 Transmission

CUREiculum

Adapted from McMichael AJ, *Nature Reviews Immunology*, 2010
How is PEP Different From Early ART

- Post Exposure Prophylaxis is a regimen of drugs taken within 72 hours of HIV expected exposure.
- The closer PEP is taken to exposure increases efficacy.
- Early ART is ONLY given with a positive HIV test.
  - The earliest HIV tests are RNA and can be administered between 3-7 days post infection.

New antibody tests take 2-3 weeks to return results.
Why is Early ART Important?

- Preservation of Immune cells
  - Early ART = early protection of non-infected cells
  - This preserves the number of immune cells
- Smaller reservoirs
  - Early treatment = less seeding of the reservoir
What is an HIV Cure?

VISCONTI Cohort
Visconti Cohort

- French cohort of 14 men and women
- Treated within 10 weeks of infection
- On treatment for at least 3 years
- Able to control virus off treatment for an average of 7.5 years
- **NO** pre-existing markers for control
Innate Ability to Control HIV

**Elite Controllers**
- Individuals who can:
  - control their virus—sometimes to undetectable levels—without antiretroviral treatment
  - They generally have regular CD4 and CD8 counts.

**Long Term Non-Progressors**
- Individuals who may:
  - have low levels of virus but maintain normal T-cell counts with no disease progression
VISCONTI Cohort- An Unsolved Puzzle

- Researchers are not sure what caused the control of the virus
- Most people who begin treatment early do not demonstrate spontaneous control
- Spontaneous control does not translate to life-long control
- Virus is still known to be present in the body
What is an HIV Cure?

Mississippi Child
Mississippi Child

- HIV-positive at birth
- Started triple drug therapy 30 hours after birth
- Lost to follow-up and returned into care after 18 months off treatment
- Remained off treatment with no detectable virus for 27 months
- Rebounded and successfully restarted treatment at 28 months post-treatment
Mississippi Child

HIV detected in blood plasma

Begins ART

No HIV detected in blood plasma

Stops ART

Long term remission for 27 months

HIV detected in blood at 2 separate time points

Persaud et al 2013 NEJM; Luzuriaga et al 2015 NEJM
What Can We Learn From the Mississippi Child?

- Proof that sustained viral remission is possible
- Early treatment prevented a large viral reservoir from seeding
- Even a small amount of virally infected cells can reestablish the reservoir
Early ART in Infants

Timing Of ART Initiation

- **Very Early** (within 2 days)
- **Early** (3 days to 3 months)
- **Late** (>3 months)
- **No Treatment**

Latent Reservoir

- Minimal HIV Exposure
- Limited HIV Exposure
- Arrested HIV Exposure
- Extensive HIV Exposure

Remission Duration

- Duration

Viremia Re-Establishment

- Minimal Proviral Replication
- Limited Proviral Replication
- Arrested Proviral Replication
- Proviral Replication

RAINWATER-LOVETT ET AL 2015 CURR OPIN HIV AIDS
What is an HIV Cure?

Early Capture Cohorts
The FRESH Cohort

- Young women (18-25) diagnosed within 14 days post-infection
- Biweekly clinic visits that include an intensive educational component
- Treated as soon as infection becomes detectable
- Samples being used to determine how early immune system functions
The FRESH Cohort

South Africa
Early Capture HIV Cohort Study (RV217)

- MHRP began enrolling high risk individuals into the study in 2009
- Located in East Africa and Thailand
- As of 2016
  - 2000 participants enrolled
  - 115 early incidence cases captured
  - Some captured within days after infection
- Researchers are studying how the genes of the virus change after infection and early immune markers
What Can We Learn From Early Capture Cohorts?

● A better understanding of the immune system may contribute:
  ● To tests for latency
  ● To developing immune killing strategies
  ● To better ways to preserve or restore immune function
  ● To a preventive vaccine

● Individuals in these cohorts may be asked to participate in cure related trials in the future
Early Capture HIV Cohort Study (RV217)

Kenya
Uganda
Tanzania
Thailand
Challenges of Identifying Acute Infection

- Difficult to implement outside of a research center
  - Testing technologies
  - Testing frequency
  - Drug availability

- The urgency of starting treatment very early is not widely understood
Challenges of HIV Cure Trials

● Therapeutic Misconception
   ● Participants who are in early capture cohorts may believe a cure related trial will offer them direct benefit

● Participant Selection
   ● Participants are otherwise healthy and taking them off treatment could bring more risks than rewards
Conclusions

Early treatment can:

- Preserve the immune system function
- Reduce long term inflammation
- Limit the size of the reservoir
Acknowledgements
Questions

For additional information visit: www.avac.org/CUREiculum
Next Webinar

Join us on Wednesday June 29th at 10am ET for the Ethics of HIV Cure Research!