The HIV CURE training curriculum is a collaborative project aimed at making HIV cure research science accessible to the community and the HIV research field.
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Perinatal HIV Infection

Defined as HIV infection that is transmitted from mother to child

3 routes of perinatal HIV transmission

1. *In utero*: Infection is transmitted during the pregnancy
2. *Intrapartum*: Infection is transmitted during delivery
3. *Postpartum*: Infection is transmitted during breastfeeding
Prevention of Mother-to-Child Transmission (PMTCT)

Mother to child transmission of HIV is a preventable disease.

Antiretroviral Therapy (ART) during pregnancy + antiretroviral drugs after birth to the baby prevent HIV transmission from the mother to the baby.

ART during breastfeeding prevents transmission through the breast milk.
Formula feeding, when safe and affordable, prevents further exposure of the baby to HIV.

Risk of transmission during pregnancy and delivery to infant when an HIV-infected mother is:

- Not receiving ART: 15-37% of infants acquire HIV
- Receiving effective ART that suppresses HIV viral load in the blood: 1-4%
What are the risk factors for Mother-to-child Transmission?
HIV is not curable: Prompt formation of latent reservoir in long-lived cells

- Reservoir expands with delay in treatment
- Virus not expressed
- Cells survive for life
Latent Reservoir Reactivation

Repeat exposure to antigen and cytokines

Re-activated CD4+ T cell

Latent Reservoir
Longer ART duration, smaller reservoir

Luzuriaga et al 2014 J Infect Dis
Approaches to HIV Cure

Drugs that reactivate HIV-infected resting cells

*Latency reversing agents*

Genetic modification of CD4+ T cells to prevent HIV entry and replication

*Zinc-finger nucleases: delete part of CCR5 co-receptor*

Boosting the immune system to kill residual virus expressing cells

*Therapeutic vaccines; Broadly neutralizing antibodies*

Early ART initiation to limit the size of the reservoir
Perinatal HIV Infection and Latency

Unique aspect of in utero or intrapartum HIV:
Time of exposure is known
→ Allows for timely intervention

http://birthwithoutfearblog.com/2012/01/31/the-beauty-of-pregnant-women/
Early ART is Life saving

Decreases morbidity and mortality
Reduces the size of the latent HIV reservoir
First step to long-term remission
May permit ‘functional cure’ when combined with immune-based therapies

Control of HIV in the absence of ART
Begin ART earlier, smaller latent reservoir

**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**

- Minimal
- Limited
- Arrested
- Extensive

**Viremia Re-Establishment**

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

Rainwater-Lovett et al 2014 Curr Opin HIV AIDS
Well-Known Case of HIV Remission

Mississippi Child

How does cure and long term remission occur?

Persaud D et al. NEJM 2013
Mississippi Child: Timeline of Events

- **BIRTH**
- 30 hours: Begins ART
- 18 months: Stops ART
- 23 months: Long term remission for 27 months
- 46 months: No HIV detected in blood plasma
- HIV detected in blood at 2 separate time points
- HIV detected in blood plasma

Persaud D et al. NEJM 2013; Persaud et al. IAS 2014
Adult HIV remission cases

Boston Patients
Two adults who experienced remission for 12 and 32 weeks

Diagnosed with acute myeloid leukemia

Treatment included bone marrow transplant and strong drugs to suppress their immune systems

Henrich T et al 2014 Ann Intern Med
Mississippi Child: The Science

The inability to detect HIV in blood plasma while the child was not receiving ART is called **long-term remission**

Detection of HIV after long-term remission in the absence of any immune response to HIV shows that the child had a dormant reservoir

The close match to the mother’s virus support HIV latency prevented cure
Mississippi Child: What we learnt

Starting ART very early in the time course of HIV infection likely led to few HIV-infected cells that could become dormant

The small number of dormant cells took more than 2 years to re-kindled HIV infection

This permitted long-term HIV remission but not cure
The Disappointment: Virologic Rebound within 14 Days off CART in Three Children Treated in the First Week of Life

- Dublin Child (8 days; VL=11,230 c/ml)
- Canadian Child (14 days; VL=7797 c/ml)
- Milan Child (14 days; VL 36,840 c/ml)
- Mississippi Child (828 days; VL=16 copies/ml)

What could explain differences between Mississippi child’s prolonged duration of remission and other children’s faster rebounds?

- **Mississippi Child**: (828 days; VL=16 copies/ml)
- **Dublin Child**: (8 days; VL=11,230 c/ml)
- **Canadian Child**: (14 days; VL=7797 c/ml)
- **Milan Child**: (14 days; VL 36,840 c/ml)
Perinatal Remission Stories

All started ART within hours of birth

None had detectable HIV in blood by standard clinical or ultrasensitive assays

None had immune responses to HIV

Those who stopped ART experienced viral rebound
Long Beach Child

Started ART within 4 hours of birth

Undetectable HIV or immune responses to HIV in blood for 9 months, **BUT**

Child remains on ART

Unclear if child is capable of long-term remission

This case highlights that very early therapy can limit the reservoir early in infancy

Persaud, Deveikis et al 2014 CROI
Perinatal HIV Remission Case and Biological Plausibility

Justifies clinical trial to test whether very early ART can lead to long-term remission

Funded by the U.S. National Institutes of Health

Organized by the International Maternal and Perinatal Adolescent AIDS Clinical Trials (IMPAACT) Network
IMPAACT P1115 Trial

Study Objective:
To study HIV remission (48 or more weeks off ART) among HIV-infected neonates who begin ART within 48 hours of birth

Design:
Small, proof-of-concept exploratory study in US, sub-Saharan Africa, and Thailand
Ethics of Empiric ART

Ethical consideration of ‘functional cure’ regimen on neonates:

Very early treatment with aggressive drug regimen can have toxic side effects

Therapy discontinuation to assess remission can lead to:

- Drug resistance
- Increased HIV reservoir size

Shah et al. Lancet Infect Dis 2014
What could be other ethical implication of Very Early ART initiation in neonates?
Challenges

Implementation of early ART
   Early infant HIV diagnosis, particularly in low-income settings
   Need for point-of-care diagnostic tests

Low blood volumes restrict ability to research perinatal HIV remission (compared to adults)

Reservoirs in other bodily sites (e.g., central nervous system, gastrointestinal tract)
Conclusions for Infants

Very early ART to achieve HIV remission in perinatal infection:

- Biologically plausible as shown by the Mississippi Child
- Potential for widespread global implementation given existing structure for delivery of PMTCT
- Combined with immune-based therapies, such as monoclonal antibodies, has potential to further lengthen HIV remission and the need for lifelong ART
Conclusions for Older Children and Youth

Need immune therapeutical interventions that are found to be safe and plausible for HIV-infected adults.

Some will have the advantage of low reservoir size from longstanding virologic control.

Most will benefit from the capacity of the immune response to reconstitute due to thymic reserve.

“We must accept finite disappointment, but never lose infinite hope.” - Martin Luther King, Jr.
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