Pediatric HIV Cure Research

HIV Cure Research Training Curriculum

Pediatric HIV Cure Research

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CUREiculum

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

Objectives

- Understand the current state of HIV cure research in pediatric populations
- Summarize the challenges of working with pediatric populations
- Explain the major cases of virologic remission

How Do We

Define “Cure”?

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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

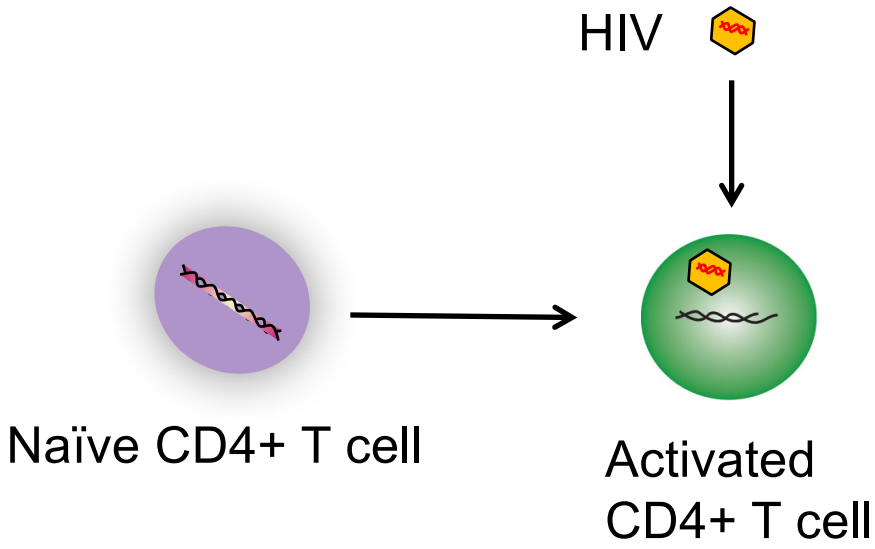
HIV so Hard to Cure?

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



Adapted from D. Persaud

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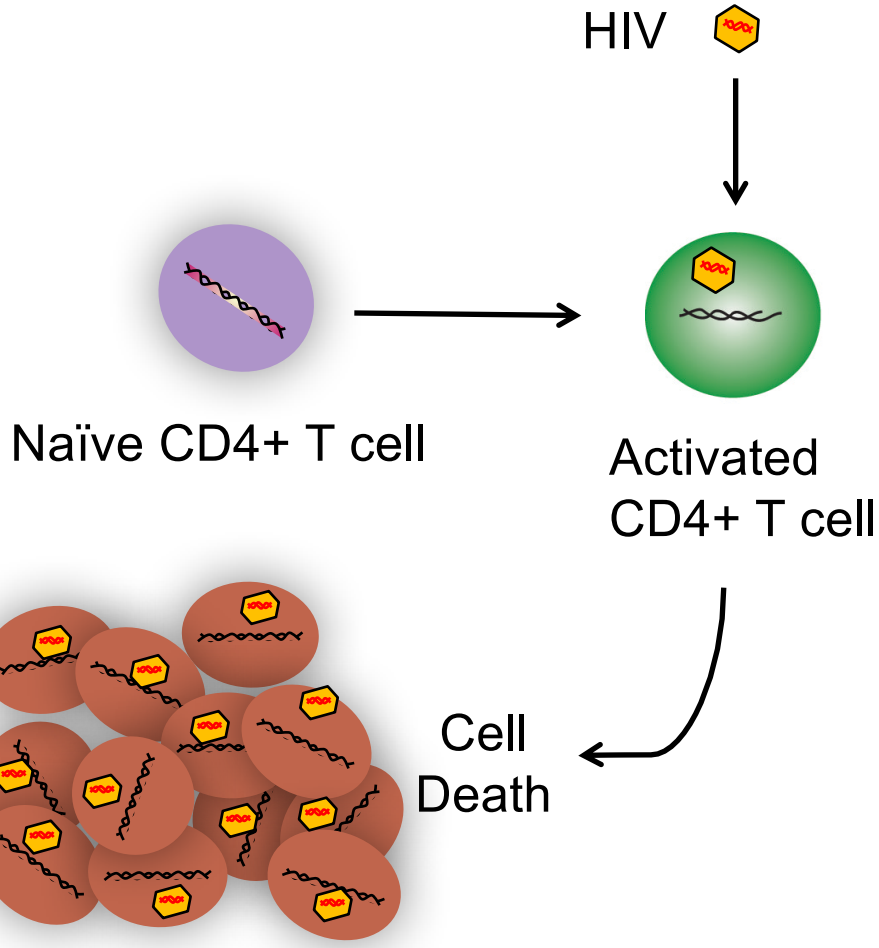

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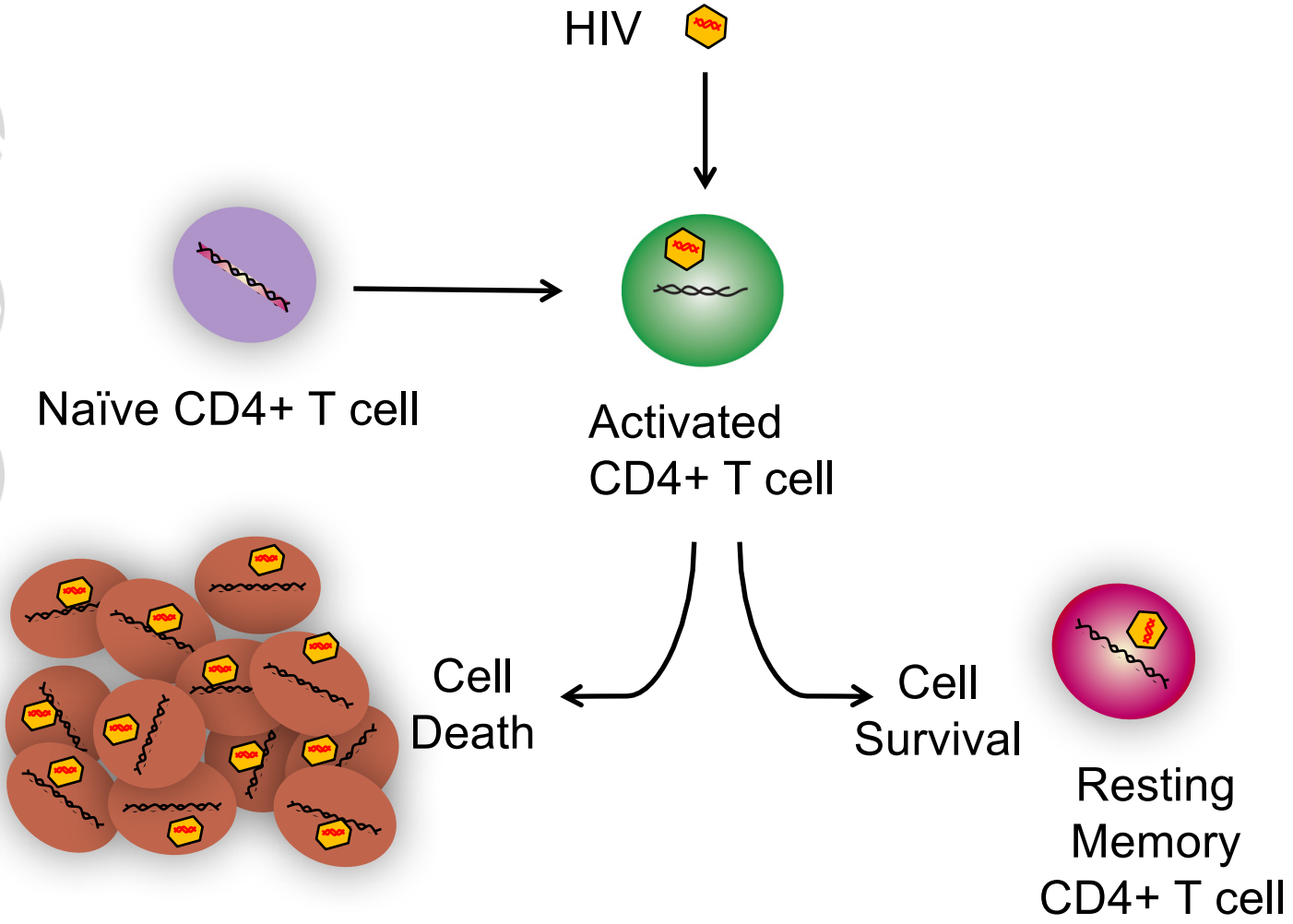

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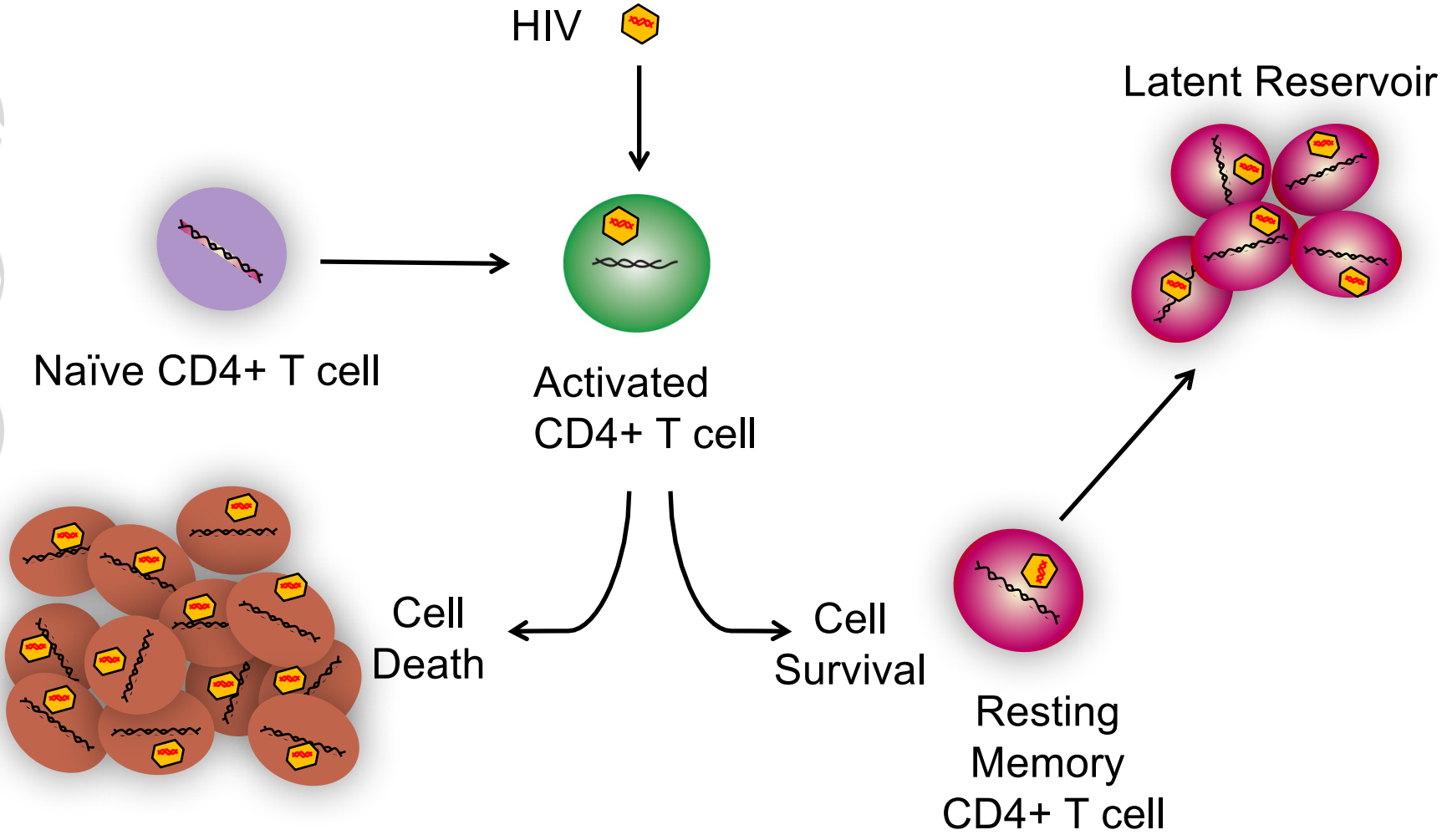

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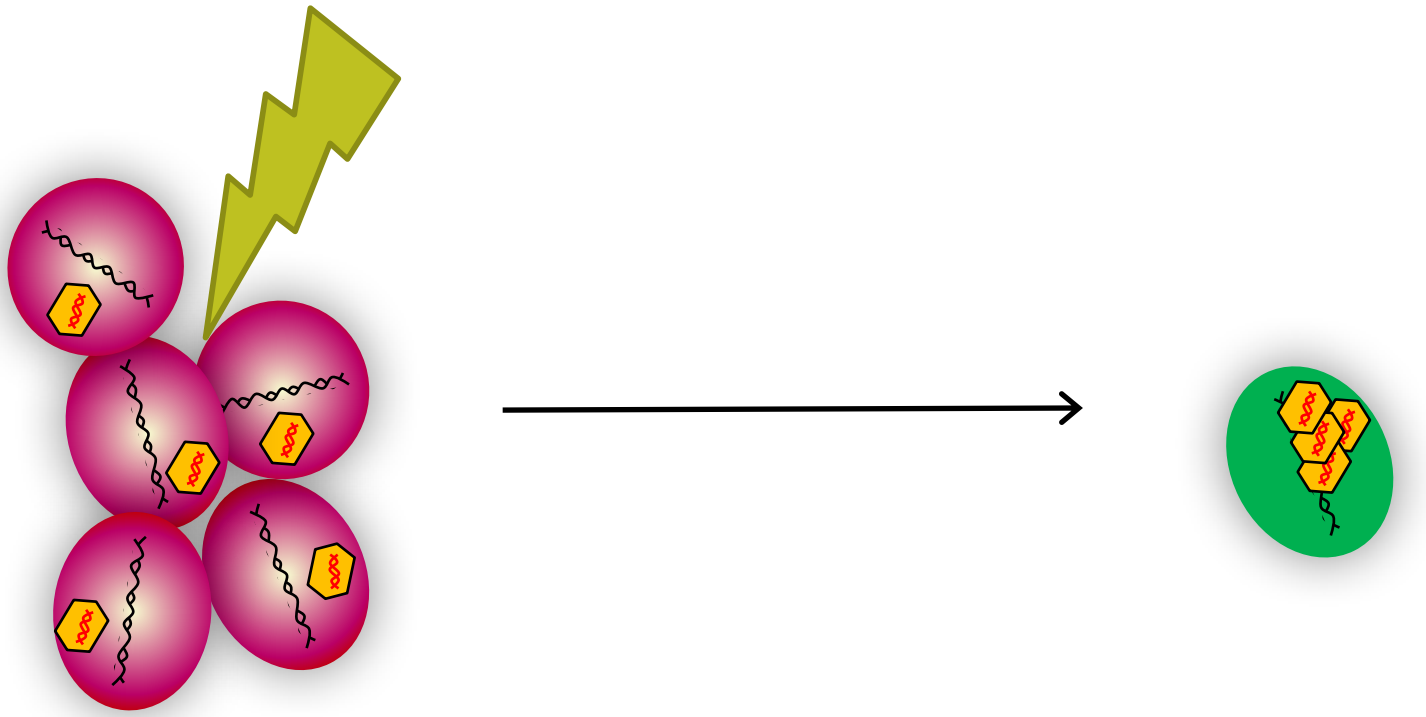

Latent Reservoir

Reactivated
CD4+ T cell

Adapted from D. Persaud

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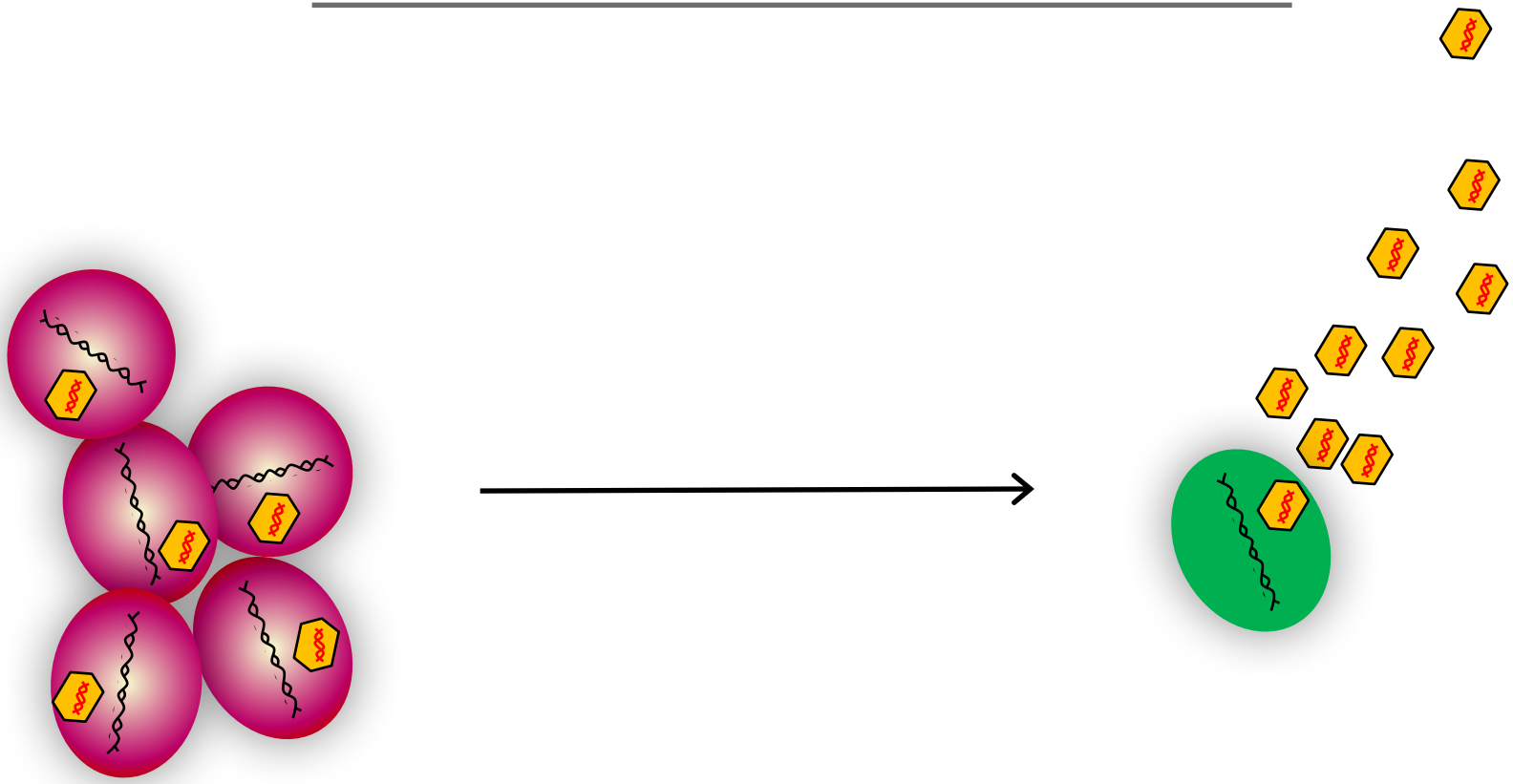

Latent Reservoir

Reactivated CD4+ T cell

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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**

Difference Between Adults and Children?

Infants have unique immune systems that:

- Discourage the inflammatory response
- Have fewer long lived memory cells
- Increased immune activation after birth can increase risk of infection

Adults have immune systems:

- Increased long lived memory cells from long term exposure to pathogens
- Increased number of differentiated cells

Perinatal HIV Infection

- HIV infection that is transmitted from mother to child
- Three routes of perinatal HIV transmission
  - **In utero:** during the pregnancy
  - **Intrapartum:** during delivery
  - **Postpartum**: during breastfeeding

Perinatal HIV Infection and Latency

Unique aspect of in utero or **intrapartum** HIV

- Time of exposure is known
- Allows for timely intervention

What are risk factors for mother-to-child transmission?

What Are Risk Factors for Mother-to-Child Transmission?

- Knowledge of HIV status
- Acquiring HIV infection during pregnancy
- Low CD4 count
- High viral load
- Maternal ART and infant prophylaxis
- Access to care
- Stigma

Prevention of Mother-to-Child Transmission (PMTCT)

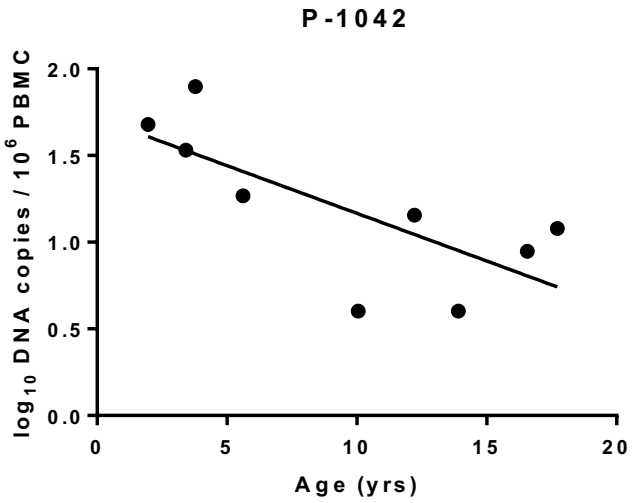
- Mother-to-child transmission of HIV is preventable
- Antiretroviral Therapy (ART) for mother during pregnancy + ART for baby after birth prevent HIV transmission from the mother to the baby
- ART during breastfeeding prevents transmission through the breast milk
- Formula feeding, when safe and affordable, prevents further exposure of the baby to HIV
- Risk of perinatal transmission during pregnancy and delivery:
  - When mother does not receive ART: 15-37% of infants acquire HIV
  - When mother receives ART that suppresses HIV viral load: 1-4%

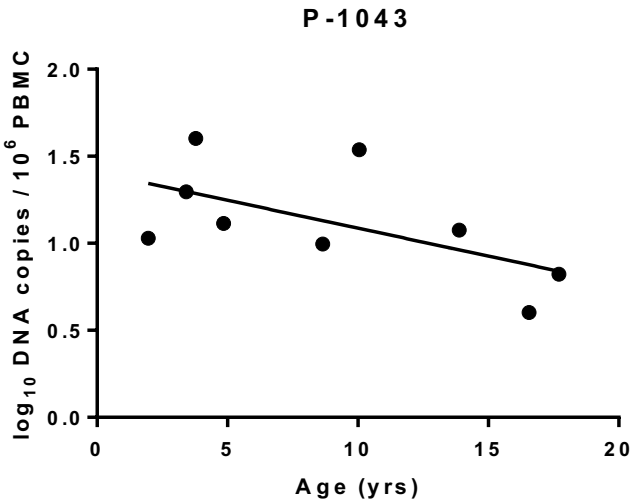
Rollins et al 2012 Sex Transm Infect

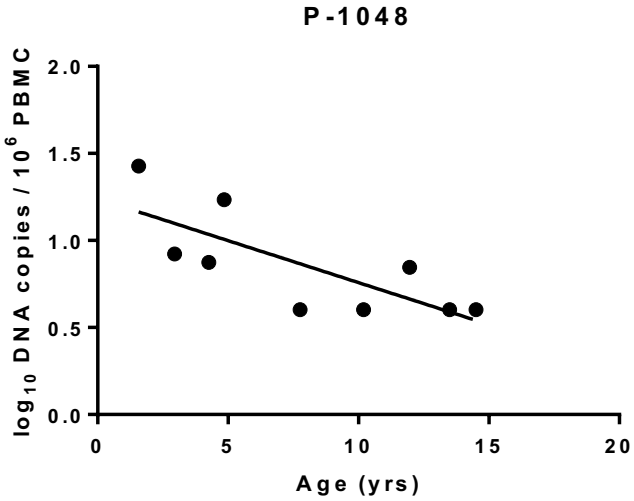
Early ART is Life-Saving

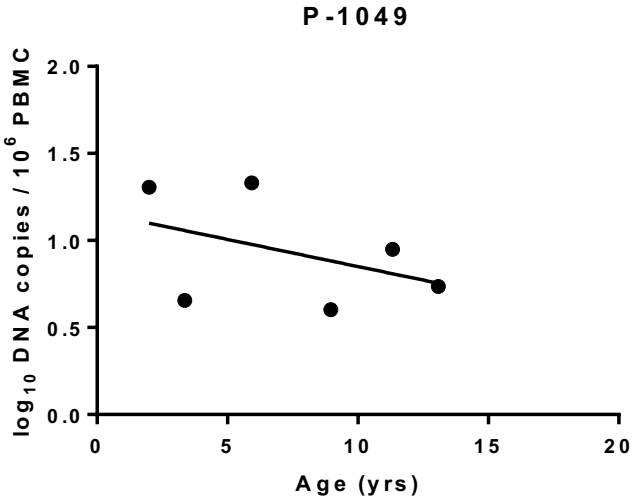
- Decreases morbidity and mortality
- Reduces the size of the latent HIV reservoir
- First step to long-term remission
- May permit ‘functional cure’ when combined with immune-based therapies
  - *Control of HIV in the absence of ART*

Longer ART Duration, Smaller Reservoir









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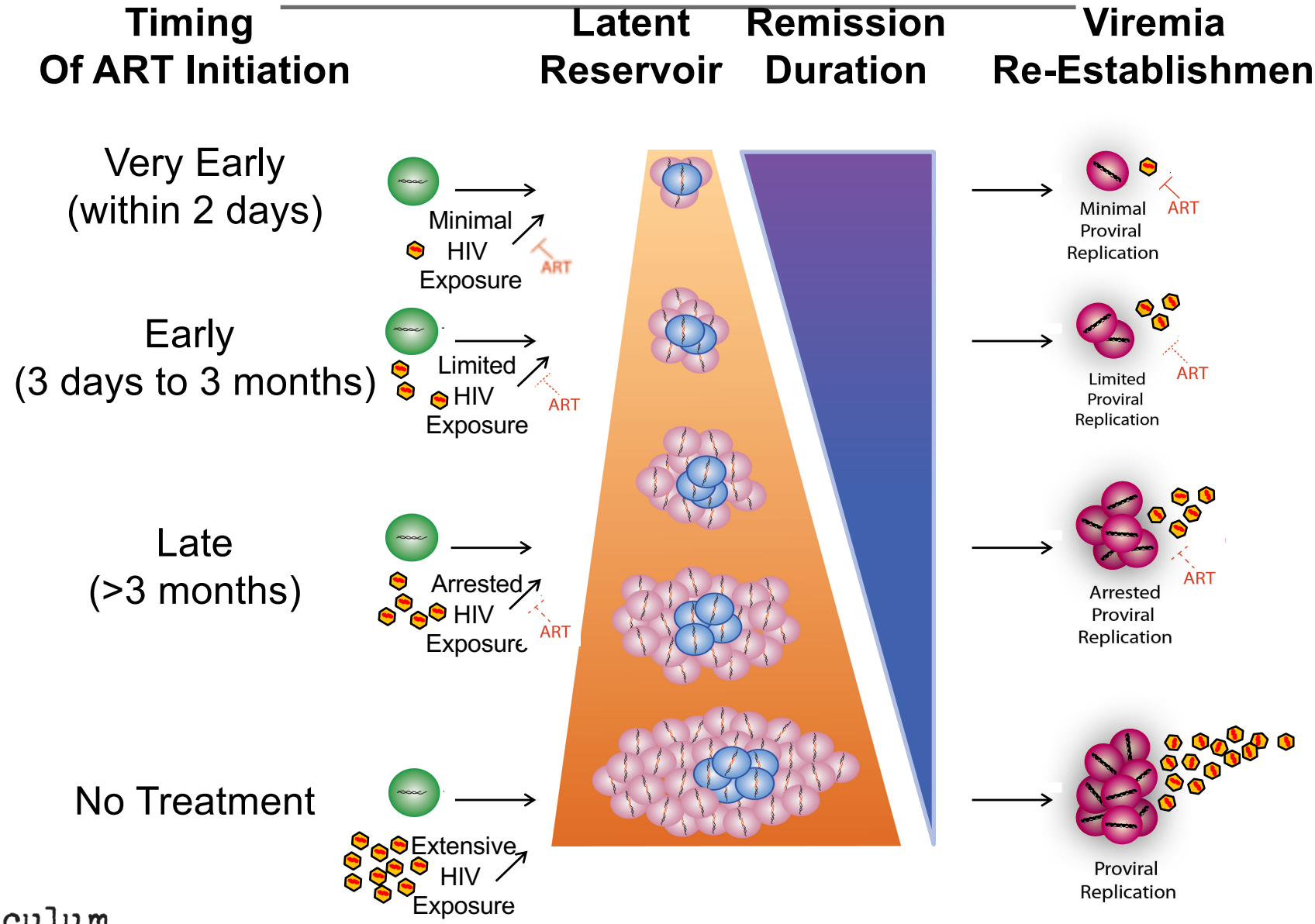
Luzuriaga et al 2014 J Infect Dis

Early ART in Infants



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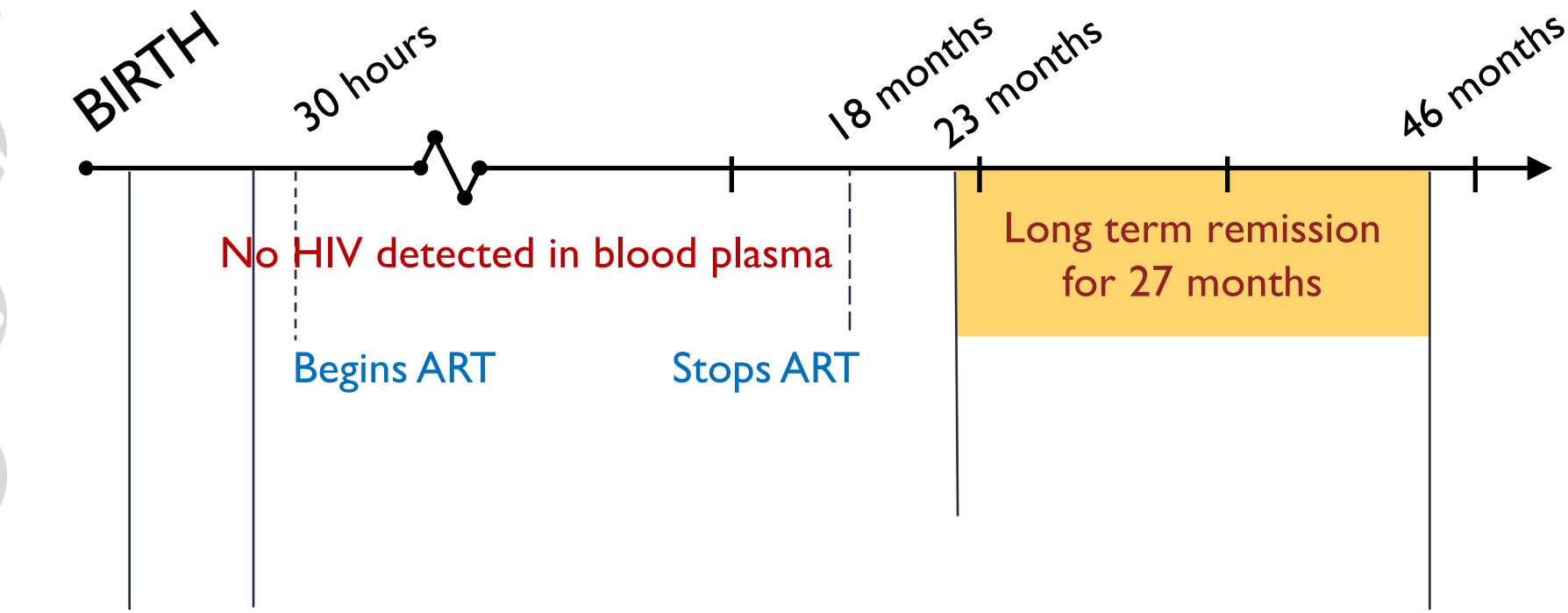
Rainwater-Lovett et al 2015 Curr Opin HIV AIDS

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



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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 forming
- Even a small amount of reservoir cells can reestablish infection

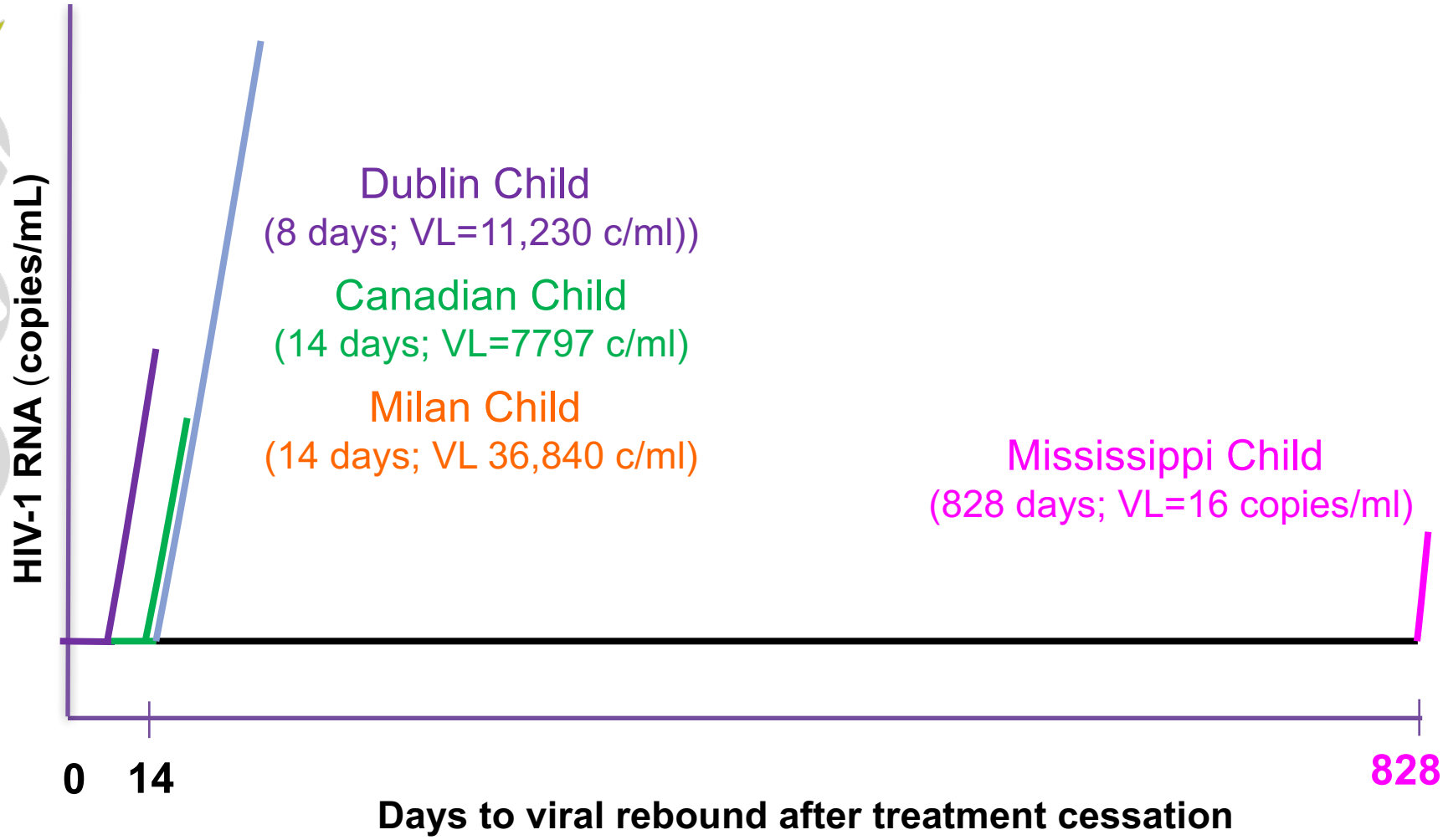
Other Cases of Pediatric Viral Suppression

Long Beach Child

- Started ART within 4 hours of birth
- Undetectable HIV and immune responses to HIV in blood for >9 months, **BUT**
- **Child remains on ART**
- This case highlights that very early therapy can limit the reservoir in early infancy
- Unclear if child is capable of long-term remission
- Given other cases of rebound viremia, ethical concerns with ART cessation?

Persaud, Deveikis et al CROI 2014

Cases of Short Virologic Remission



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Butler et al 2014 Pediatr Infect Dis J; Bitnun et al 2014 CID; Giacomet et al 2014 Lancet; Luzuriaga et al 2015 NEJM

What Makes the Mississippi Child Different?

Case	Initial VL (c/mL)	ART Initiation	ART Duration	Remission Duration	Rebound VL
Mississippi Child	19,812	30 hours	18 months	27 months	16
Dublin Child	653	<24 hours	4 years	8 days	11,230
Canadian Child	808	<24 hours	3 years	14 days	7,797
Milan Child	152,560	4 days	3 years	14 days	36,840

Butler et al 2014 Pediatr Infect Dis J; Bitnun et al 2014 CID; Giacomet et al 2014 Lancet; Luzuriaga et al 2015 NEJM

What Makes the Mississippi Child Different?

- Stages of in-utero infection
- Viral load of mother
- HIV Exposure duration and viral load
- Genetic differences in immune response
- ART adherence Co-infections
- Latent reservoir size
- Viral strain
- ART regimen and dose

Post-Treatment Control

The VISCONTI Child

- ART initiated at 3 months
- Two separate episodes of ART non-adherence in the second year that resulted in viral rebound
- ART discontinued a third time with sustained viral suppression
- Small viral blips at 11 years old and 13 years old
- Remains a **post-treatment controller**

Innate Ability to Control HIV in Adults

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

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

Ethics of Empiric ART

Ethical consideration of ‘functional cure’ regimen for 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. 2014 Lancet Infect Dis

What Are Other Ethical Considerations?

What Are Other Ethical Considerations?

- Consent during labor and delivery
- Pressure to discontinue ART
- Drug fatigue in adolescence
- Frequency of viral rebound assessment
- Ability to emotionally support parents

Many Remaining Questions

- How early is early enough for ART initiation?
- What biomarkers should be used to indicate ART cessation? HIV remission?
- What duration of remission is appropriate to refer to one as “cured”?

Challenges

- Implementation of early ART
  - Early infant HIV diagnosis, particularly in low-income settings
  - Need for point-of-care diagnostic tests
- Low blood volumes
- Treatment cessation
- Reservoirs other than blood
  - Sampling challenges in bodily sites

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
- Potential to further lengthen HIV remission and/or encourage post-treatment control

Conclusions for Older Children and Youth

- Need immunotherapeutic interventions that are safe and plausible for HIV-infected adults
- Some will have the advantage of low reservoir size from long-term virologic control
- Most will benefit from the capacity of the immune response to reconstitute due to thymic reserve

Acknowledgements


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National Institute of Child Health
& Human Development

AVAC
Global Advocacy for HIV Prevention


CENTER FOR
AIDS
RESEARCH
JOHNS HOPKINS UNIVERSITY


IMPAACT

amfAR
25 yrs
MAKING AIDS HISTORY


ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION


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CHARITABLE FOUNDATION

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Tomorrow at 11am ET

for Operationalizing Ethics!

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