HIV Cure Trial Design Considerations for Pediatric Populations

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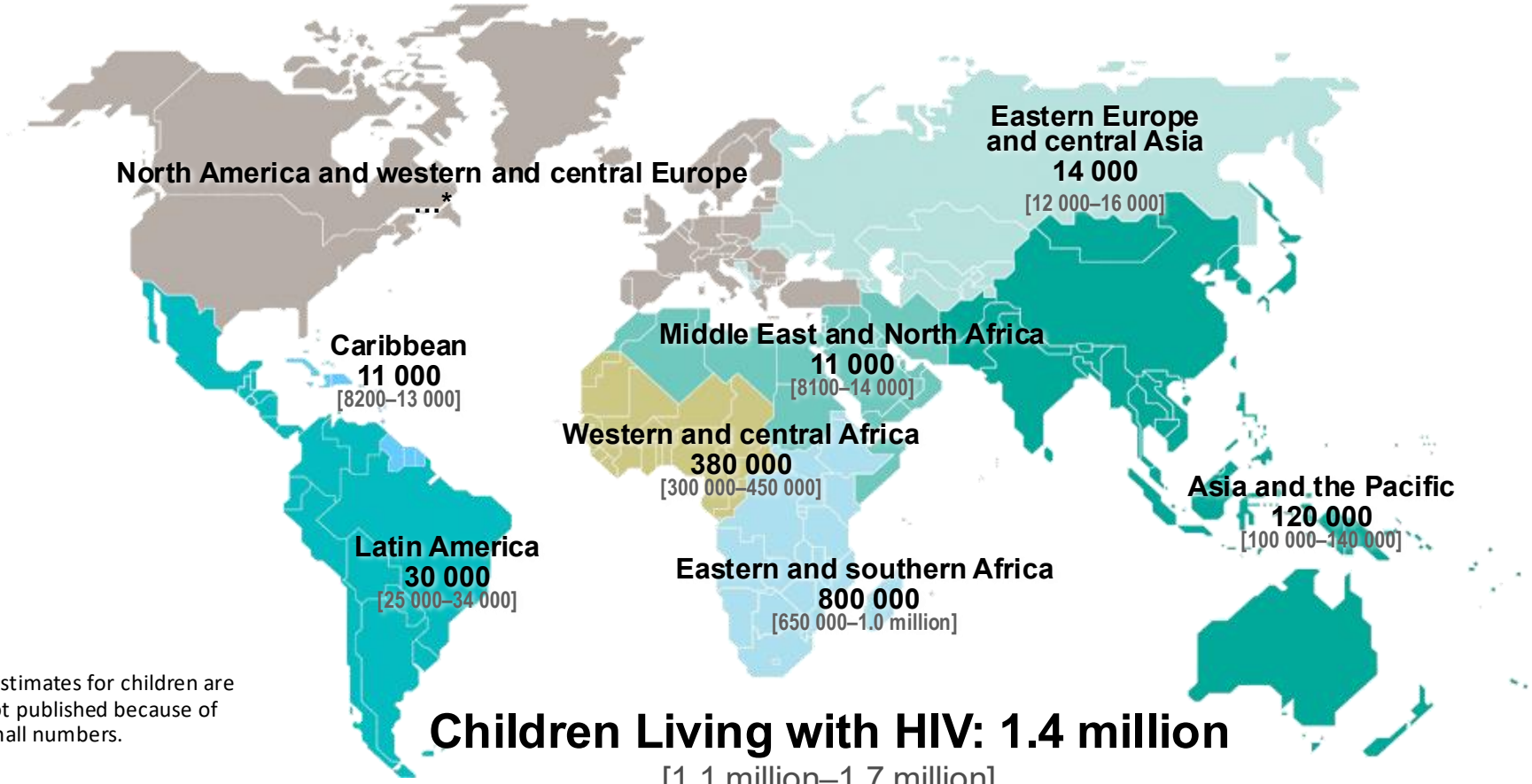
Children (<15 years) estimated to be living with HIV 2023



*Estimates for children are not published because of small numbers.

Children Living with HIV: 1.4 million

[1.1 million–1.7 million]

Annual New Pediatric Infections: 120 000

[83 000–170 000]

Annual Pediatric AIDS-Related Deaths: 76 000

[53 000–110 000]

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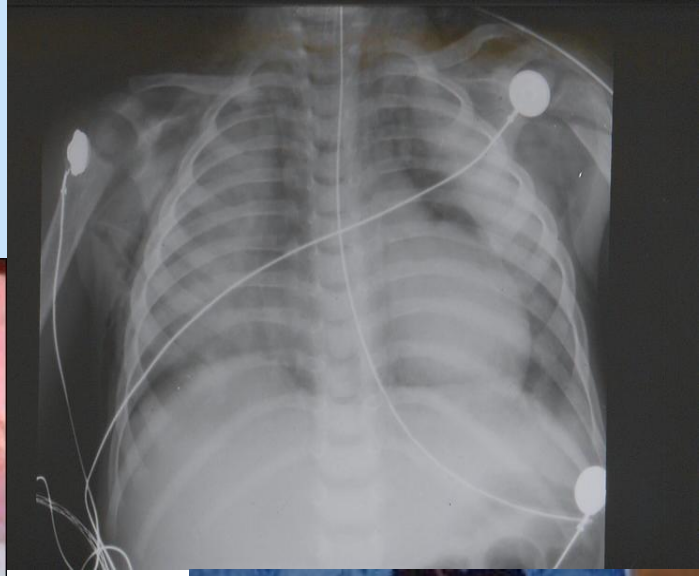
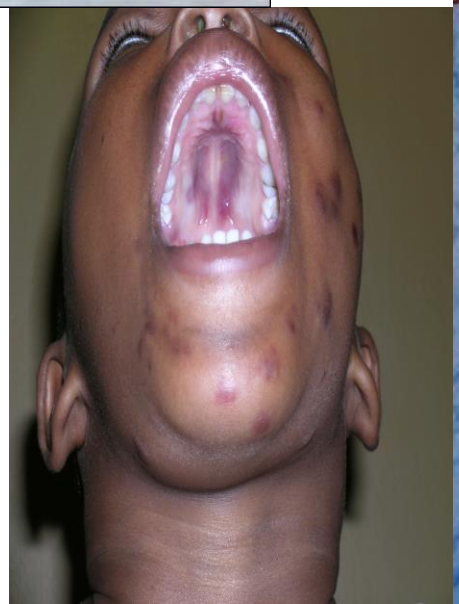
Clinical Progression of HIV in Children

- ~90% of pediatric infections occur via vertical transmission
- Generally, children progress more rapidly than adults
- Highest incidence of AIDS in 1st year of life
- Untreated, up to 51% mortality in children with HIV by 18 months of age
- In infants with HIV, early initiation provides 76% relative reduction in mortality





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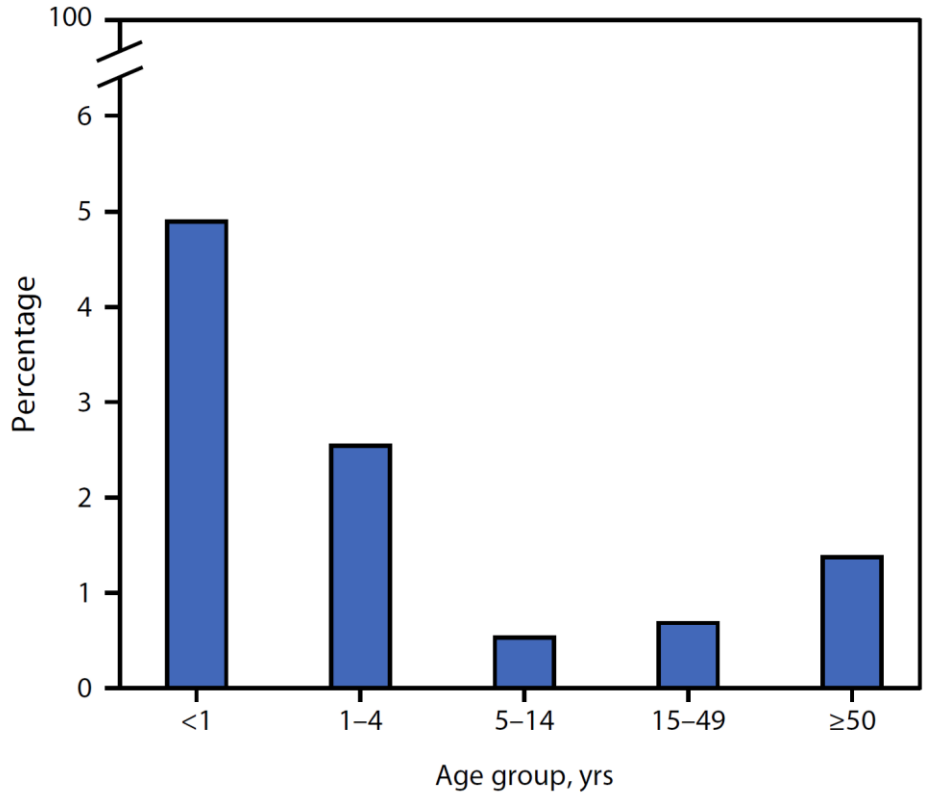
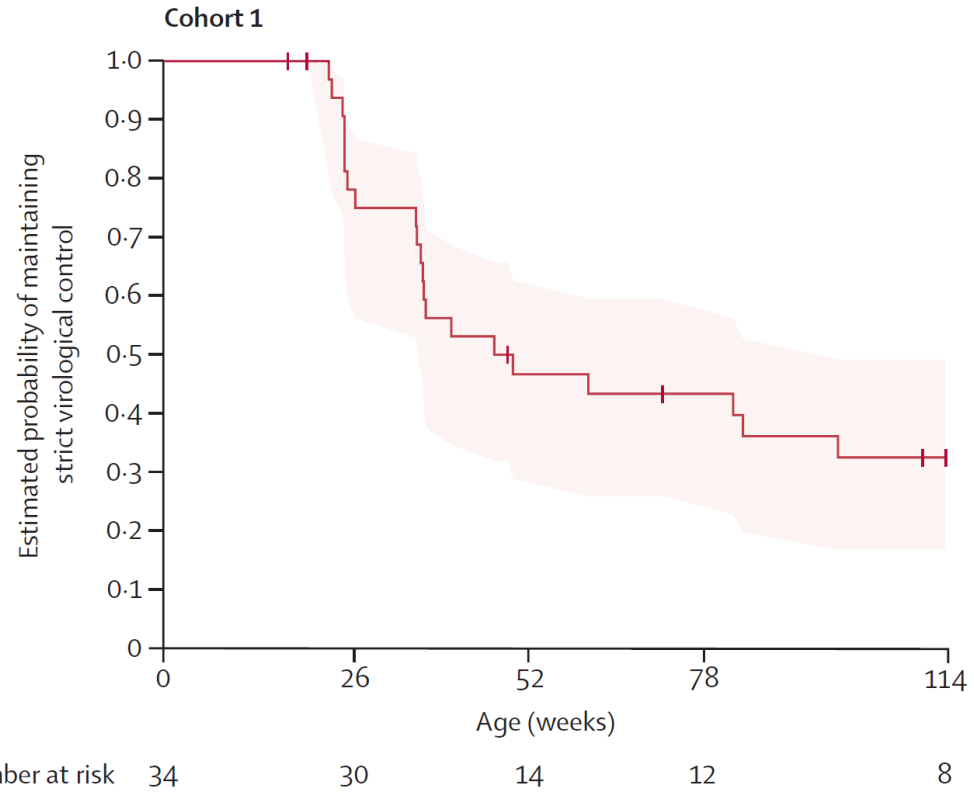
AIDS 2001, 15:771-779
N Engl J Med 2008;359:2233-44
Photos courtesy of Mark Kline, MD, BIPAI

Outcomes in Young Children Poor Despite ART

Annual percentage of reported deaths among persons living with HIV and receiving ART in 28 PEPFAR countries and regions, 2021–2022



Probability of maintaining strict virological control after very early ART initiation in IMPAACT P1115



Children have greatest potential for direct benefit from an HIV cure

Agathis et al., MMWR 2023
Persaud et al., Lancet HIV 2023

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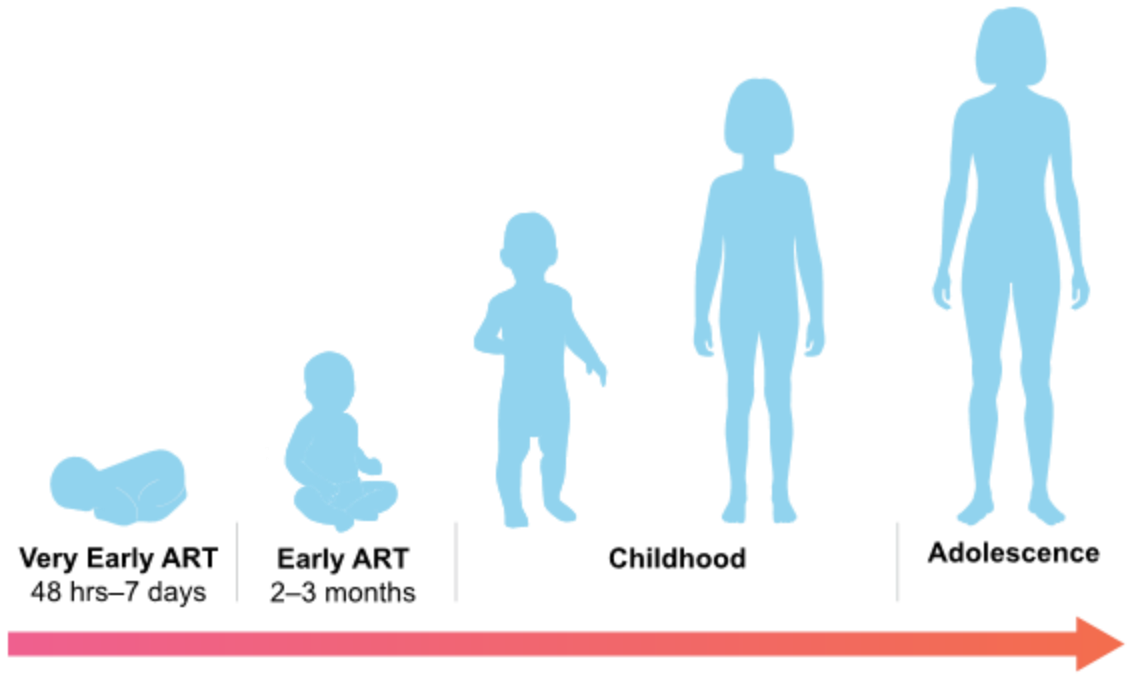
Populations of Interest for Pediatric HIV Cure

Unique Immunological Considerations for Pediatric HIV Cure Research

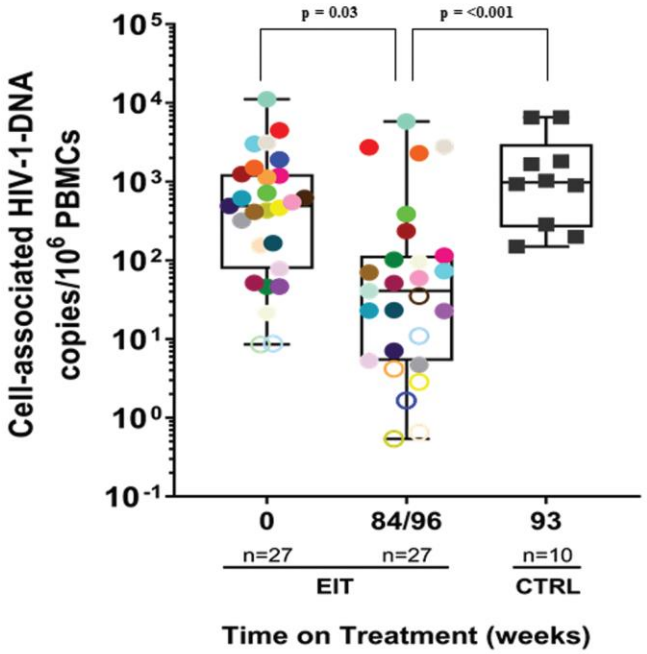
- **Unique** immune environment in which HIV-1 reservoirs are established: **low activation levels**
  - High proportion of naïve CD4+ target cells (>90%)
  - Low expression of CCR5
  - T cell repertoire is less biased and less likely to respond to HIV infection
  - More effective Ab, Tfh, and CTL responses
- Timing of exposure known—providing a **window of opportunity to intervene very early** in the course of infection



Goulder PJ et al. 2016, Deeks SG et al. 2021 and Berendam et al. 2022

Unique Virological Considerations for Pediatric HIV Cure Research

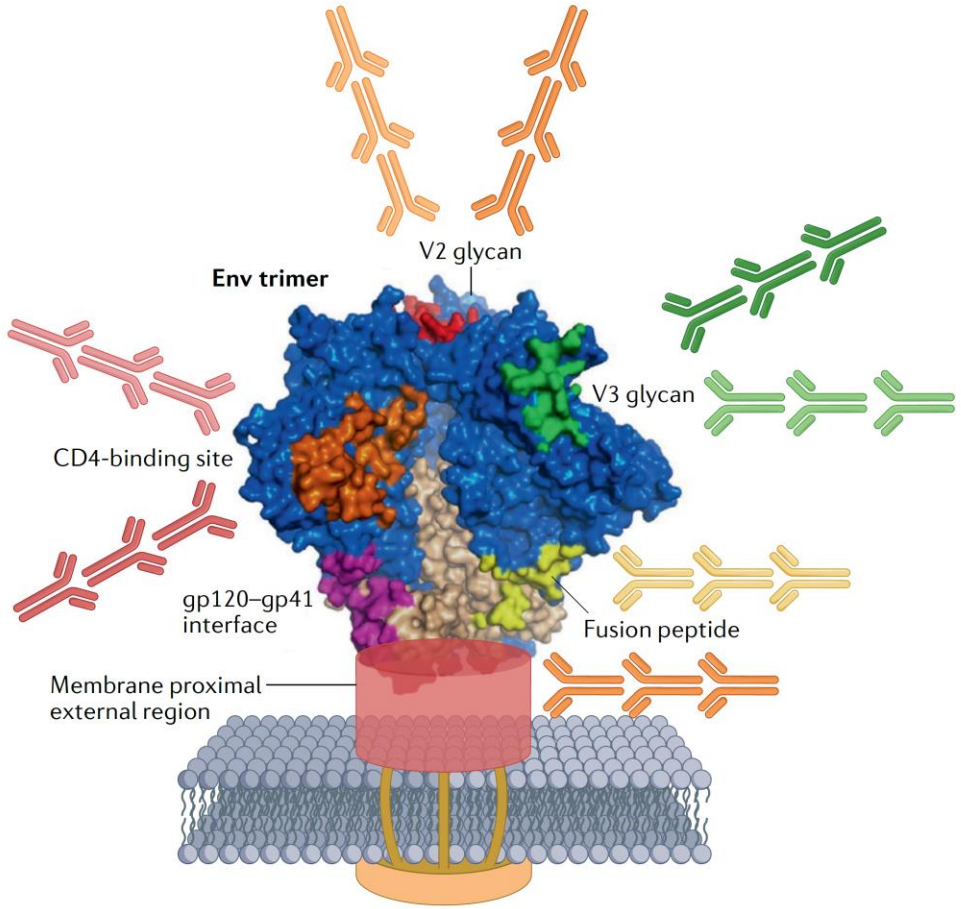
- Different **distribution of cell types** containing HIV reservoir compared to adults
- Reduced fitness of placentally transmitted T/F virus
- **Early treatment:**
  - Smaller, more homogeneous reservoirs
  - Faster reservoir **decay**
  - Minimal **CNS reservoir**
- **Examples** of sustained remission **in children**:
  - Mississippi Baby (*NEJM, 2013*); French perinatal cohort child *(Lancet HIV, 2016);* South African child *(Nat. Commun., 2019)*
  - Very early ART in neonates with *in utero* HIV-1 significantly reduced viral reservoirs and enabled >48-week ART-free remission in 4 participants. IMPAACT P1115 (*Persaud et al, CROI 2024 and Lancet HIV 2024)*



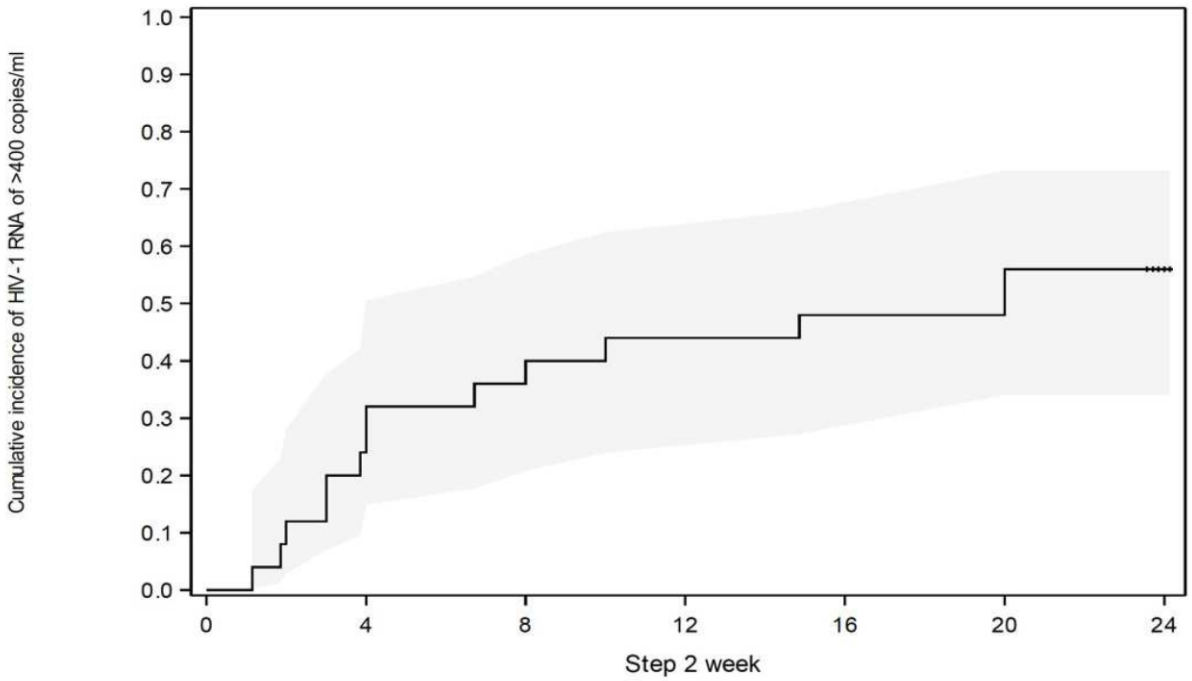
Ajibola G, et al. *Clin Infect Dis* 2021

Promising Pediatric HIV Cure Interventions

Broadly Neutralizing Antibodies (bNAbs) in Children



VRC01LS + 10-1074 maintained VL <400 c/mL in 44% of early ART-treated children at 24 weeks



	Cumulative number with HIV-1 RNA of >400 copies/ml						
Number failed	0	8	10	11	12	14	14
	Number at risk						
Number at risk	25	19	16	14	13	13	8

Haynes, B.F. et al. *Nat Rev Immunol*. 2023 Mar;23(3):142-158.
Shapiro, R.L., et al. *Sci Transl Med.* 2023 Jul 5;15(703):eadh0004.

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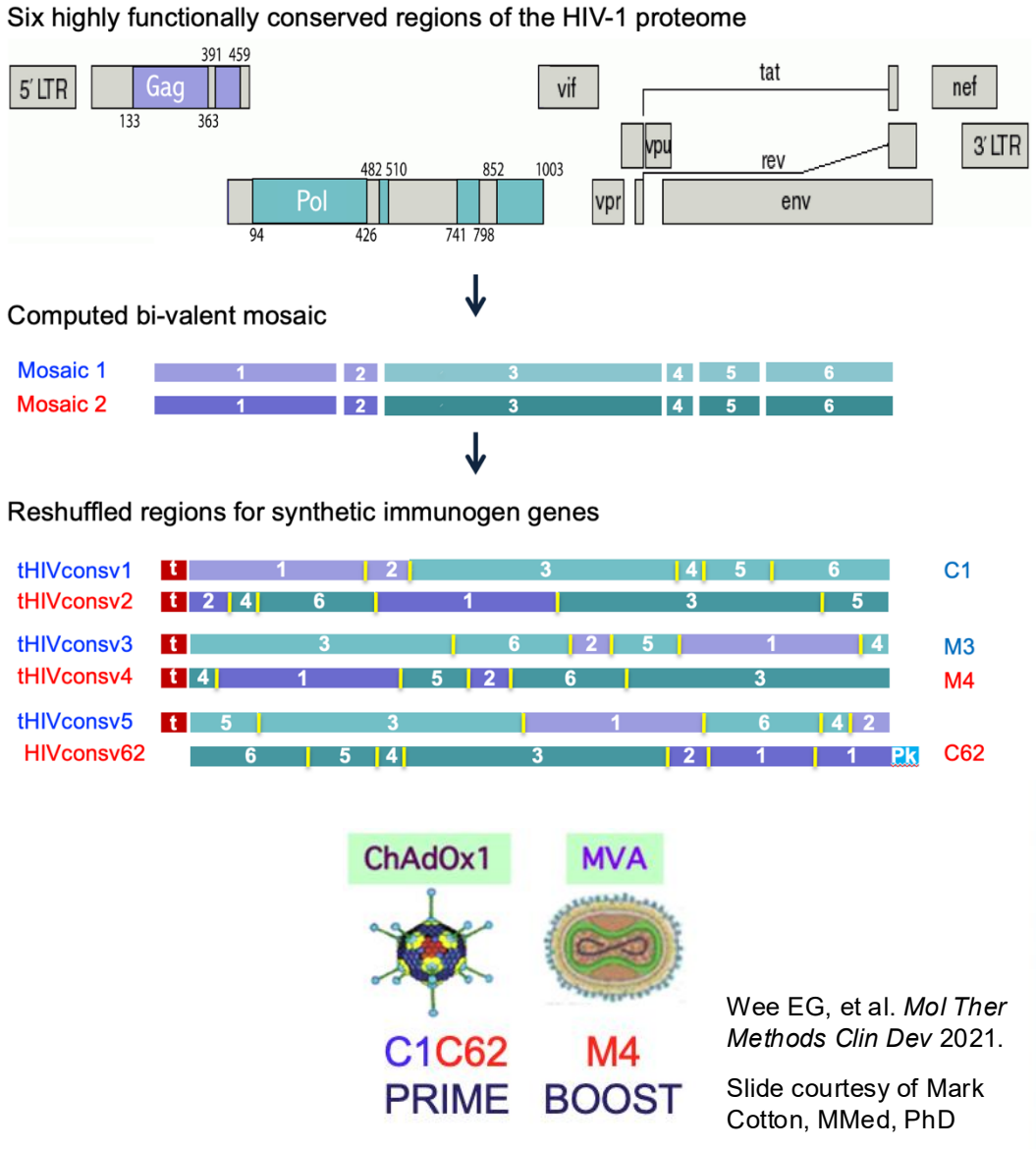
T-Cell Vaccines: The HIVconsvX Vaccines

- Six conserved HIV regions
  - common to group M (global) HIV-1 variants
- Each region is computed as a bivalent mosaic
  - two mutually complementary HIV-1 protein sequences
  - mosaics are always used together (as prime or boost)
  - maximize perfect match of the vaccine to group M variants
  - reaches 80% of vaccine T-cell epitopes matching group M
- Six regions are uniquely ordered to minimize induction of responses to potential junctional (irrelevant) epitopes
- Prime - replication-deficient ChAdOx1
  - low pre-existing immunity
- Boost - replication-deficient MVA (Mpox vaccine)
  - Mpox vaccine – added benefit



Wee EG, et al. *Mol Ther Methods Clin Dev* 2021.

Slide courtesy of Mark Cotton, MMed, PhD

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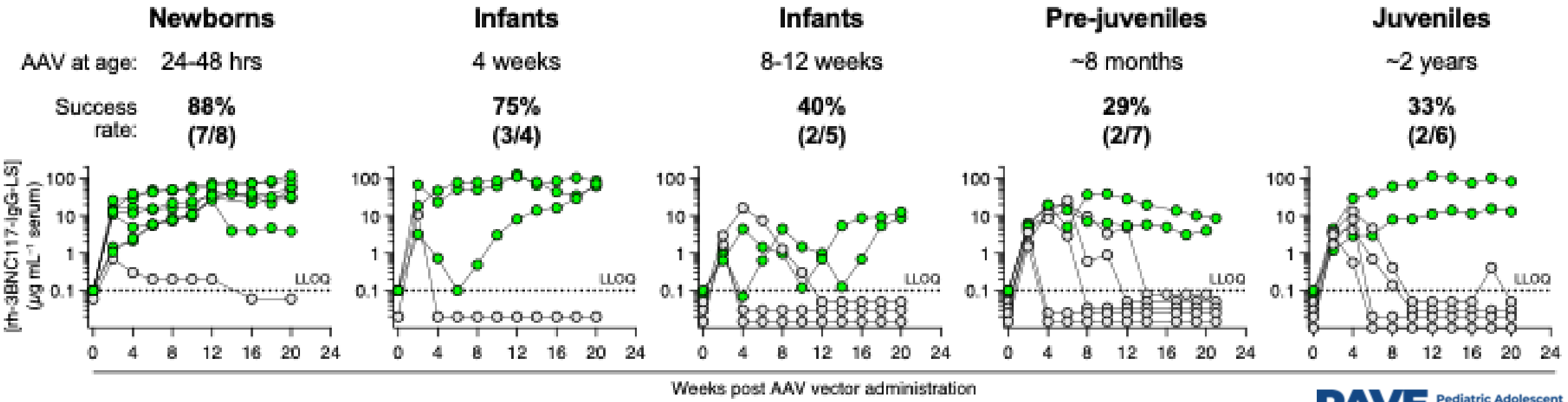
Gene Therapy with AAV/bNAb Vectors: Neonatal Tolerance Enhances the Effectiveness

Given the tolerance-prone immune system in early life, the first weeks after birth may provide a natural window of opportunity for improving the efficacy of AAV-vectored delivery of bNAbs



Ardeshir et al., *Nature* 2025.

Adapted slide, courtesy of Mauricio Martins, PhD

PAVE Pediatric Adolescent Virus Elimination
A Martin Delaney Collaboratory

Challenge #1: Regulatory and Ethics

FDA Guidance on Pediatric Extrapolation

Pediatric Extrapolation Concept

Disease, Drug Pharmacology, and Response to treatment

Different ← → Same

- Sources and types of data (PK/dosing, efficacy, & safety): clinical trial data; nonclinical data; real world data; other sources (see Table 1)
- Assessment of gaps in knowledge and degree of uncertainty (see section 3.6)
- Support for degree of similarity will also depend on the quality and quantity of the data, and the confidence in the data

Potential Study Designs are dependent on gaps in knowledge and degree of uncertainty

Pediatric Extrapolation Plan

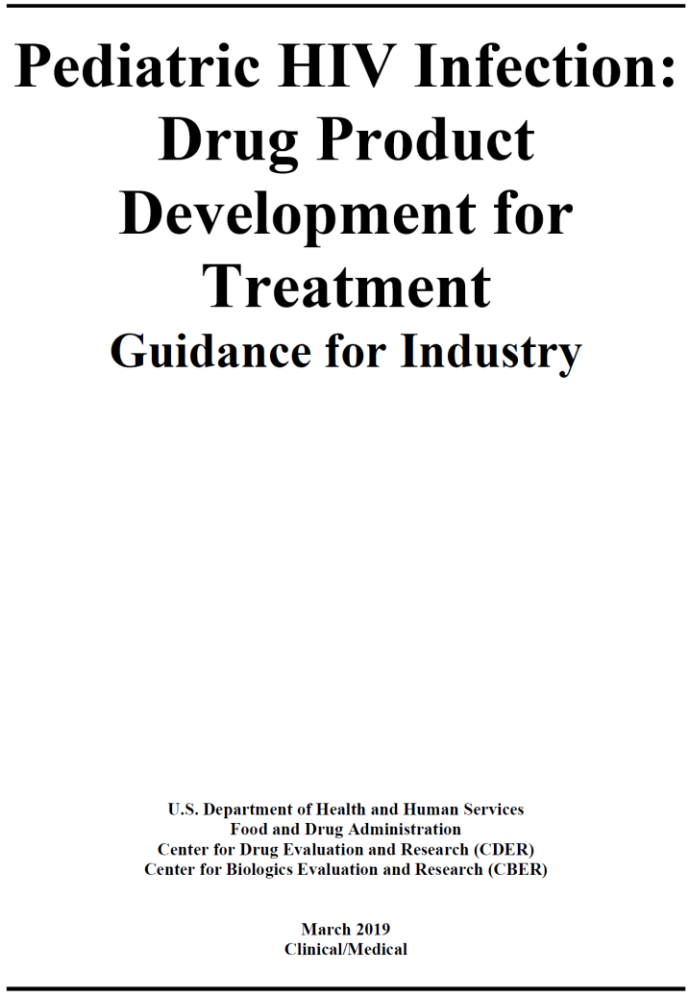
More data required ← → Less data required

Potential study designs could include (see section 4.2):

- RCTs; bridging biomarkers or other response markers; Bayesian strategies; alternative frequentist success criteria (e.g., p>0.05 or widened NI margin); single-arm PK/PD/safety studies; exposure matching; enrollment in adult trials

Food and Drug Administration. E11A Pediatric Extrapolation. 2024. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e11a-pediatric-extrapolation. Accessed July 17, 2025.

FDA Guidance on Drug Product Development for Treatment of Pediatric HIV



- Allows extrapolation of antiretroviral efficacy from adults to children
  - Pediatric studies need data on safety, PK
- No requirements for age de-escalation, excluding neonates
- Applies to HIV treatment, not cure interventions

Food and Drug Administration. Pediatric HIV Infection: Drug Development for Treatment. 2019. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-hiv-infection-drug-development-treatment. Accessed July 17, 2025.

Key Regulatory Challenges

- **Requirement for the exact same products and regimens to be studied in adults first, for safety and sometimes with demonstrated efficacy data**
  - Adult cure strategies may not use the exact regimen appropriate for children, e.g. hesitancy to study latency reversal agents in pediatrics due to toxicity concerns
  - In adults, AAV/bNAb-based gene therapy may need to be specifically modified to overcome immunological barriers in adults. Such modifications would not be necessary, or even desirable, in neonates
  - Efficacy data for HIV cure in adult humans often not available and may not extrapolate to pediatrics

- **Requirements for age de-escalation**
  - Slows scientific progress
  - Interventions may be most beneficial in the youngest, e.g. AAV/bNAb immune tolerance and lack of seropositivity against AAV
  - If less efficacy observed in older populations, intervention may be downselected before reaching the youngest populations, who may benefit

- **Misperception of benefit:risk in young children**
  - Poor outcomes in youngest children even in the ART era
  - Safety precedence for certain components, e.g. AAV9 vectors for spinal muscular atrophy, bNAbs

Potential Solutions

- Reframe benefit:risk in infants and young children according to their poor outcomes even in the ART era (normal use), rather than only product-related efficacy and risks in clinical trial settings (ideal use)
- Optimize preclinical development pathway for pediatric products
- Engage regulators early during product development
- Coordinate adult and pediatric protocols in parallel
- Expedite or facilitate alternative pathways with respect to age de-escalation

Challenge #2: Comparator Groups

Comparator Group Considerations

Comparator Groups

- Single-arm
- Intervention versus Placebo
- Intervention versus Active Control
- Intervention versus Historical or Modeled Controls

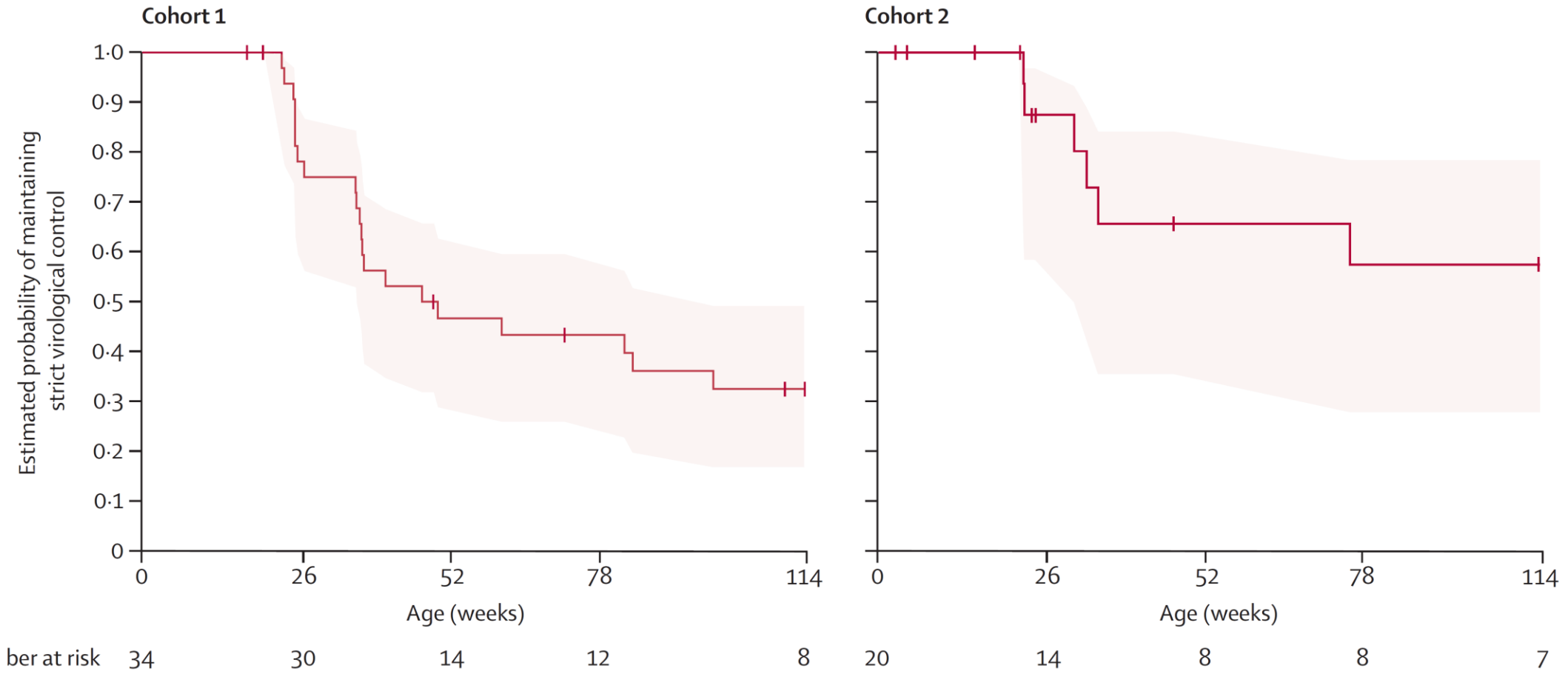
Modifications

- Single intervention versus combination
- Crossover

Comparator Group Challenges

- Use of placebo
  - Ethical concerns regarding placebo, especially if ATI, e.g. loss of viral control
  - Potential participants may not be willing to enroll into a protocol that gives placebo and then an analytical treatment interruption
- Populations have unique biomarker signatures without sufficient numbers of appropriate comparators
- Comparator interventions may not be appropriate
- If combination, do all components have demonstrated safety and efficacy individually?
- May not be appropriate historical controls

What is the appropriate comparator for very early ART in neonates diagnosed with HIV?



Small number of eligible participants:

Only 17/54 (31%) had sustained viral suppression

Only 6 also had biomarker profile qualifying for ATI

Persaud et al.
Lancet HIV 2023

Potential Solutions

- Consider use of placebo on case-by-case basis according to the study
  - SANTHE Consensus Pediatric ATI Group strongly supported placebo when indicated
  - If main endpoint is AAV-mediated bNAb expression, then such may be accomplished without an ATI
- Comparator groups should be tailored according to the research question
  - Single-arm studies may be the most appropriate in certain situations
- Crossover designs offer a potential option that alleviates many comparator challenges

Challenge #3: Outcomes and Endpoint Measurements

Outcomes and Endpoint Measurement

- Analytical Treatment Interruption (ATI)

- Viral Load
  - Time to viral rebound
  - Viral set point

- Reservoir and Immune Assays
  - Total DNA, QVOA, IPDA

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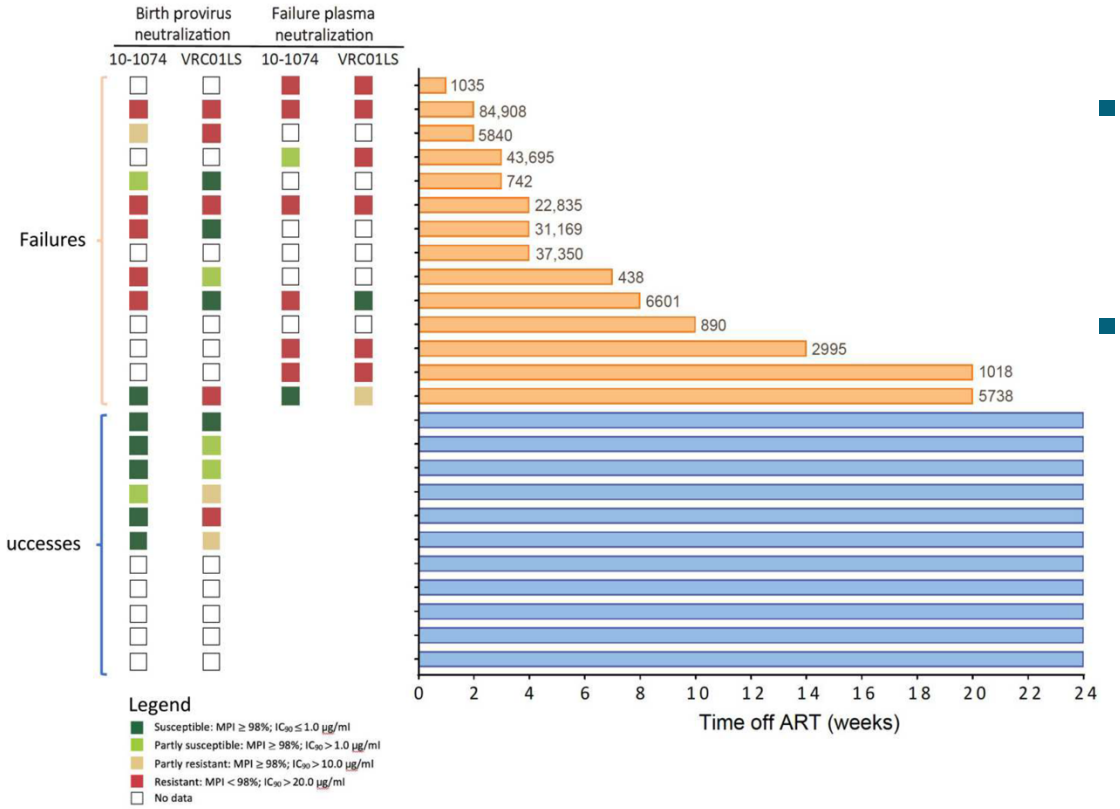
Biomarker Profiles

Tatelo



IMPAACT P1115

- Only 17/54 (31%) had sustained viral suppression
- Only 6 had biomarker profile qualifying for ATI
  - No confirmed plasma HIV RNA ≥200 copies/mL at Week 24 and not detected at Week ≥48
  - 2 consecutive negative HIV antibody tests
  - 2 consecutive negative HIV DNA tests
  - CD4% ≥25 and CD4 cell count normal for age

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Shapiro, R.L., et al. *Sci Transl Med.* 2023
Persaud et al. Lancet HIV 2023

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Analytical Treatment Interruption Considerations

- Risk of moving a virally suppressed child to being unsuppressed
  - IMPAACT P1115: 2 cases of acute retroviral syndrome
  - However, in IMPAACT P1115 and Tatelo, all rebounding participants resuppressed on ART
  - Similar CD4 outcomes in children with and without viral rebound
- Biomarkers may predict pediatric ATI success
- In pediatric structured treatment interruption trials and in unplanned treatment interruptions in practice, children largely do well when restarted on ART
- ATI likely best clinical outcome measure at present

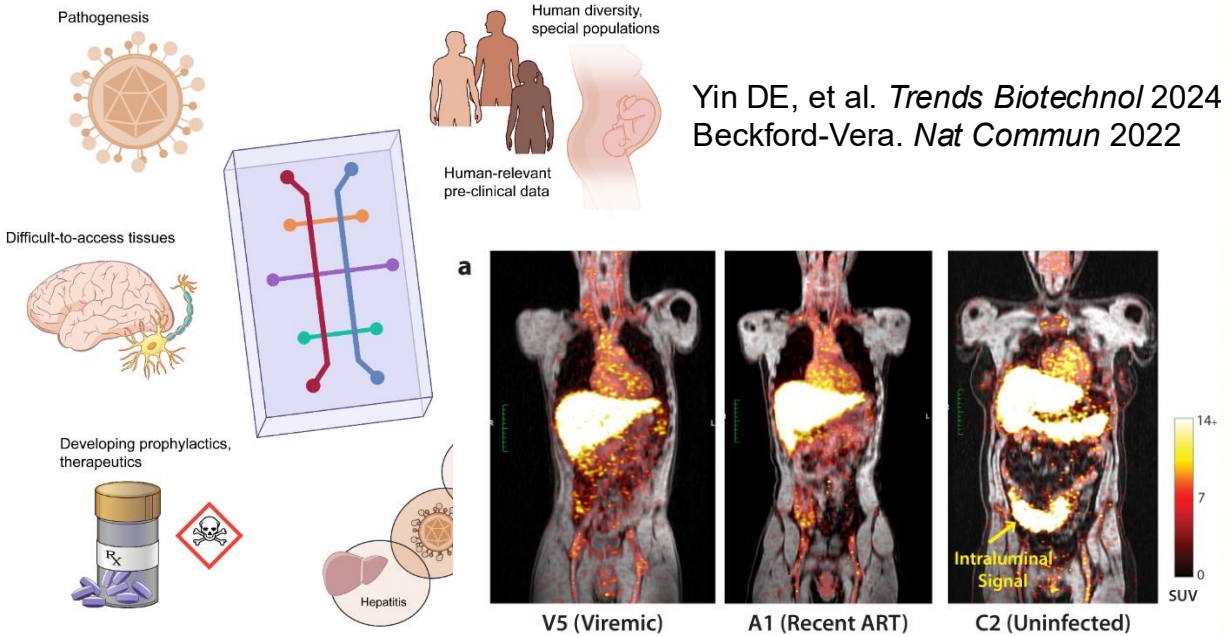
Reservoir and Immune Assays

Challenges

- Blood sampling limitations
  - Pediatric low blood volumes
  - Large number of PBMCs required for reservoir and immunological assays
- Tissue sampling
  - Important sanctuary reservoirs
  - Greater hesitancy and practical limitations on sampling in children
- Frequent assay failures, e.g. bNAb neutralization resistance

Potential Solutions

- Assay optimization
- Sample sparing strategies
- Reservoir biomarkers
- Alternative methods



Yin DE, et al. *Trends Biotechnol* 2024
Beckford-Vera. *Nat Commun* 2022

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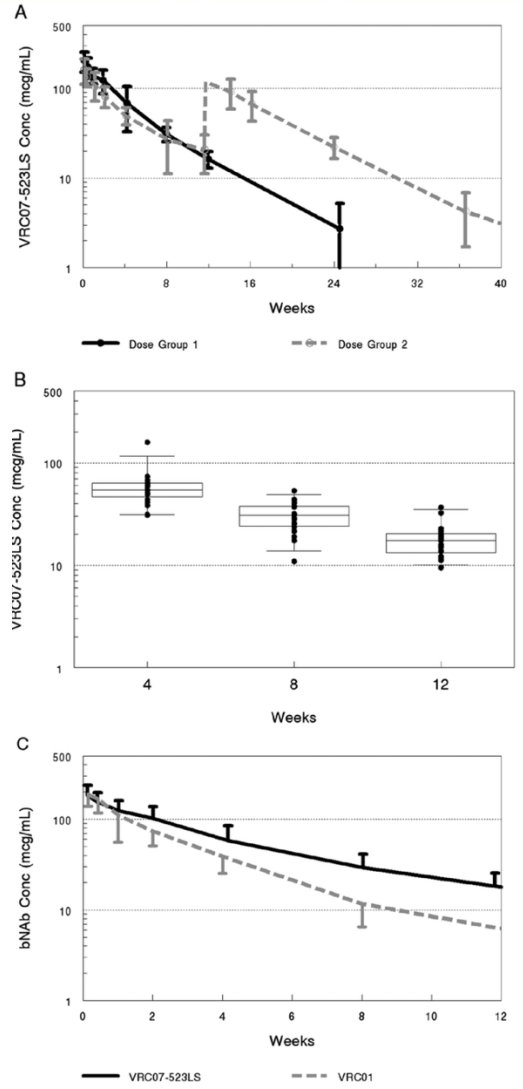
Clinical Trial Design and Conduct

Early Phase Studies

- Pharmacokinetics and Safety
- In infants, difficulty in achieving good, consistent drug exposures with standard antiretrovirals
- Drug exposures affect resistance potential and early formation of reservoir
- Current long-acting antiretrovirals will be difficult to administer in this population, all requiring loading
- Rapid absorption of bNAbs administered subcutaneously



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Cunningham CK, et al. *J Pediatr Infect Dis Soc.* 2025

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Proof-of-Concept Trials Under a Master Protocol

- Start with small, carefully designed proof-of-concept clinical trials
- Master protocol template could facilitate rapid evaluation of new interventions
- If promising outcomes, move on to a larger trial design
- As an acceptable regulatory pathway is determined, the master template would facilitate propagation of acceptable trial designs

Pediatric HIV Clinical Trials Infrastructure

- Sites and investigators that are familiar with pediatric HIV cure trial issues or willing to develop the expertise
- Good relationships with pediatric participants and their families
- Pediatric HIV cure clinical trials network infrastructure is critical

Conclusions

- Young children living with HIV continue having poor outcomes even in the ART era and have the greatest potential for direct benefit from a cure
- Infants have viral and immunological characteristics that may better facilitate an HIV cure
- A number of HIV cure interventions are particularly promising in children
- Regulatory challenges include requirements demonstrating safety and possibly efficacy of the exact same regimen in adults first, age de-escalation, and misperceived pediatric benefit:risk
- Comparator groups should be chosen according to the research question of the specific study, but crossover designs hold promise
- Key outcome considerations include analytical treatment interruption and limitations on sampling of blood and tissues for assays
- Pediatric HIV cure trials may be advanced through proof-of-concept trials under a master protocol but require strong clinical trials infrastructure

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