Breakout Group #3

Prioritization of Select Intervention/Strategies

What are risk/benefit considerations to help prioritize interventions?

- Regulatory concept of “Prospective of Benefit”
- Likely efficacy weighs heavily in consideration of acceptable risks
- Clarity on difference between concept of “Prospective of Benefit” vs. “efficacy”

- Start with the children most likely to benefit
- Not aim for generalizability but to maximize chances of success

What are risk/benefit considerations to help prioritize interventions?

- Bench mark for safety (lifetime ART) has distinct salience in children (may tip balance towards accepting greater risks)
  - ART may not address all neurodevelopmental problems
  - High rates of failure
  - Long-term toxicities
  - High likelihood of non-adherence in adolescence
- Age-dependent balance of risks e.g. additional potential risks and benefits of interventions earlier (neurodevelopment and immune function)
- Sequential process (start in adults move to children) has been slow, has left the most vulnerable with poor ART choices need a more responsive approach that is child-focused

What are risk/benefit considerations to help prioritize interventions?

- Perinatal context may be exposing uninfected children to interventions
- Lack of consensus about biomarkers to predict who will respond best to interventions
- Lack of consensus about biomarkers to indicate efficacy
- Some products e.g. vaccines strong history of research in safety in children without requiring adult data
- Start with new insights from basic science and juvenile NHP models specific for pediatric populations

Classes of interventions for which age groups

	Neonates	Children	Perinatal Inf Adolescents	Horizontal Inf Adolescents
BNAbs	Doing it already Start intrauterine	Young	No	Yes
Therapeutic vaccines	No	6m-2 years maybe >2 years	It depends	Early-treated a useful model
LRA/Cell/CAR	No	No	No	No
Vedolizumab	Yes	Yes	Yes	Yes

Combinations – Remission interventions + ART

- Interventions use **during** early ART (neonates, newly-infected adolescents)
- Interventions use once ART is already in place
  - Early–treated (how early hours, days, weeks, months?)
  - How long on ART? How long suppressed?
  - Best biomarkers
  - Accessible populations

Study design considerations

- Selection criteria – healthier participants
- Greater monitoring frequency but focused on biologically-relevant parameters
- Consideration of statistical issues in interpretation of data (e.g. too frequent looks vs safety for serious events)
- Smart and responsive study designs e.g. sequentialize enrollment
- Appropriate control groups depending on design
- Neurodevelopment monitoring very difficult in anyone under 2 years

Treatment interruptions

- >2 years
- Eligibility biomarkers remain unknown: “Never” rebound group “best”? but the previous rebound may have less to lose?
- What is a biologically meaningful endpoint?
- Studies in adults moving towards tolerating periods of viremia with goal of shifting the viral set point down not necessarily to undetectable

Further study design/safety considerations

- Importance of long-term follow-up > years