Group #2: Approaches to Pediatric Studies I: Extrapolation of Efficacy

Lead Discussants: Ann Chahroudi

Prabha Viswanathan

Regulatory Elements that define extrapolation of efficacy from adults to children

- Disease pathogenesis and outcome is similar in adults and children
  - Immunity may vary among treatment subgroups
- Similar Intervention responses relative to toxicity and efficacy

Extrapolation of Efficacy among Similar Populations

- Adolescents infected through adult behavior
  - Adolescents <18 yo could benefit and should be included
- Children and adolescents infected by MTCT
  - Immunity and viral reservoir differ from adults
  - Factor impact of timing ARV initiation
- Efficacy trials should be done across the life span
  - Parallel study design for perinatal infection

Study design considerations for extrapolation of efficacy

- Age specific pK for dosing and frequency
- Define outcome measures beyond ATI
  - Tissue reservoirs (CNS), immune and inflammatory biomarkers
    - HIV antibody reversion
- Define functional cure outcomes that are not predicated on viral elimination

Extrapolation of Safety Outcomes

- Considerations of risk/benefit for perceived toxicity of interventions
- Factor age specific toxicities
  - Toxicity studies needed for infants < 2y
  - Development of Resistance to therapy
  - Impact of intervention on immune development
  - Organ specific toxicity (CNS)
- Study design should include long term outcomes

Vedolizumab

- **Compelling results showing viral load reduction in NHP**
- **Small phase I/II study in HIV-infected adults showing safety and efficacy potential**
- **Based on phase I/II results phase 3 trial to include participants across the life span**
  - **Parallel study for perinatally infected children**
  - **Age-specific toxicity monitoring in <2 y cohort**
  - **Long term outcome monitoring**

Vedolizumab

Populations in which adult outcomes cannot be extrapolated
Neonates/Infants

- **Unique features**
  - **Immune development**
  - **Viral dynamics**
  - **Toxicity profiles**
- **Unique opportunities for outcomes that differ from similar interventions in adults**
  - **Novel (infant specific) interventions**

Neonates and Infants

- **Require more scrutiny of risk/benefit**
  - **Does the interventions improve over SOC?**
- **Need to establish proof of principle**
  - **Importance of NHP models**
- **Unique factors likely to impact outcomes**
  - **Timing and modes of transmission**
  - **Age specific pk**
  - **Treatments to interrupt MTCT**

Filling the Gaps

- **Role of Non-human Primates**
  - **Provides proof of principle for unique populations**
  - **Models human immune development**
  - **Enables examination of targets not accessible in humans**
  - **Explore age specific toxicity**
  - **Recognize viral and immune limitations of NHP**
- **Further Development of human *ex vivo* studies**
  - **Systems biology**
  - **Cellular immunology and virology**
  - **Novel measures of viral replications and reservoir size**

QUESTIONS AND DISCUSSION