THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Malawi-Liverpool-Wellcome Trust

Neurodevelopment of HIV-Infected Children in a Resource Poor African Setting

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Work funded by

BRAIN DISORDERS IN THE DEVELOPING WORLD: RESEARCH ACROSS THE LIFESPAN (R01)

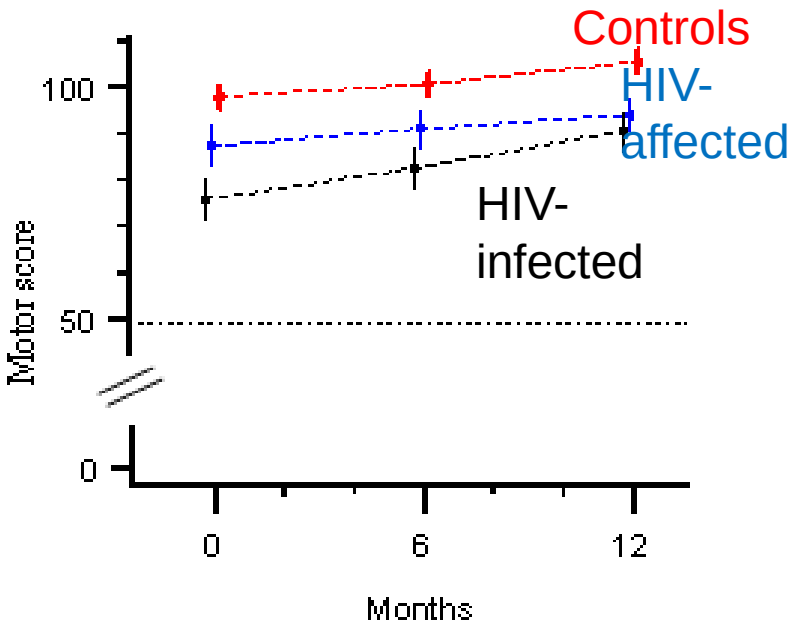
HIV infection and CNS in children

- Vertically-acquired HIV infection in children impairs the development of an immature CNS
- Prevalence in pre-HAART era in the USA: 30 to 50% (Epstein 1986, Sharer 1986)
- Access to HAART has dramatically decreased the incidence of active PHE to 1.6% (Chiraboga, 2005)
- Early ART associated with better locomotor and mental development scores (Laughton 2012)

Conclusions from Pilot Study

- Accelerated **motor** development during the 1st year of care and treatment program for HIV-infected

- No difference in rate of **cognitive** development between HIV-infected and control children after care and treatment



Van Rie et al. JAIDS 2009, 52:636-42

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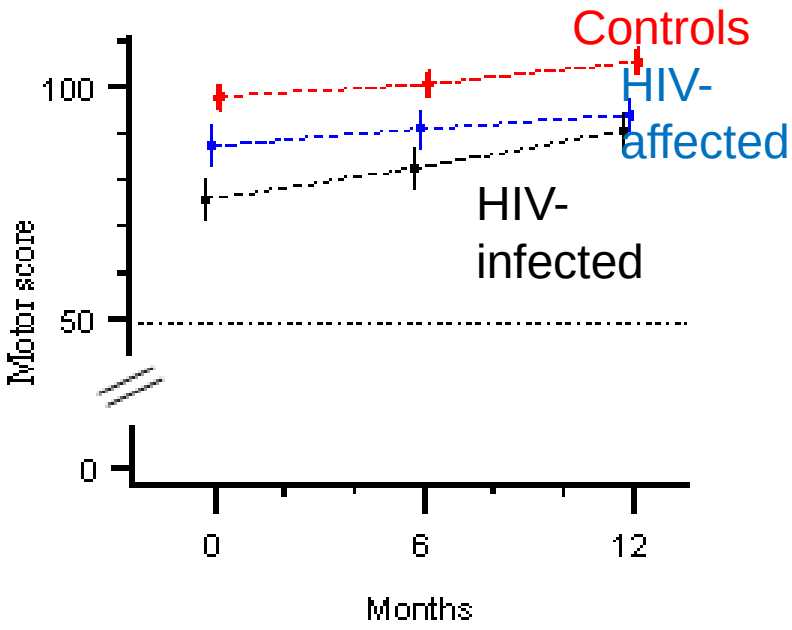

Conclusion – need to initiate HAART prior to presence of cognitive delay

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Study Design and Objectives

- Observational, community-based cohort study
  - Incidence of HIV-associated neurological manifestations in children participating in early HIV diagnosis program
  - Timing of HIV-associated neurological manifestations and predictive factors
  - Effect of ART

- Compartmentalization sub-study
  - Is HIV compartmentalized in the CNS of HIV-infected children?
  - Is compartmentalization associated with neurodevelopmental delay?
  - Effect of ART on compartmentalization

Cohort Study

Screening of 1288 HIV-exposed infants at 6 weeks using dried blood spots

Enrollment
10 weeks

96 HIV-infected infants	**290** HIV-exposed, negative infants	**170** HIV-unexposed (controls) infants

Follow-up
14 weeks
6 months
9 months
12 months
15 months
18 months
24 months
30 months

- Bayley Scales of Infant Development III
- Clinical Exam and Neurological Exam
- Sociodemographic Data Collection
- ART, CD4 and Viral Load monitoring (HIV+ children)

Progress and Results

- Final study visit occurred on March 31st, 2012
- Data cleaning and analysis are underway
- Creation of Malawi-based norms for the Bayley
    - *In progress*

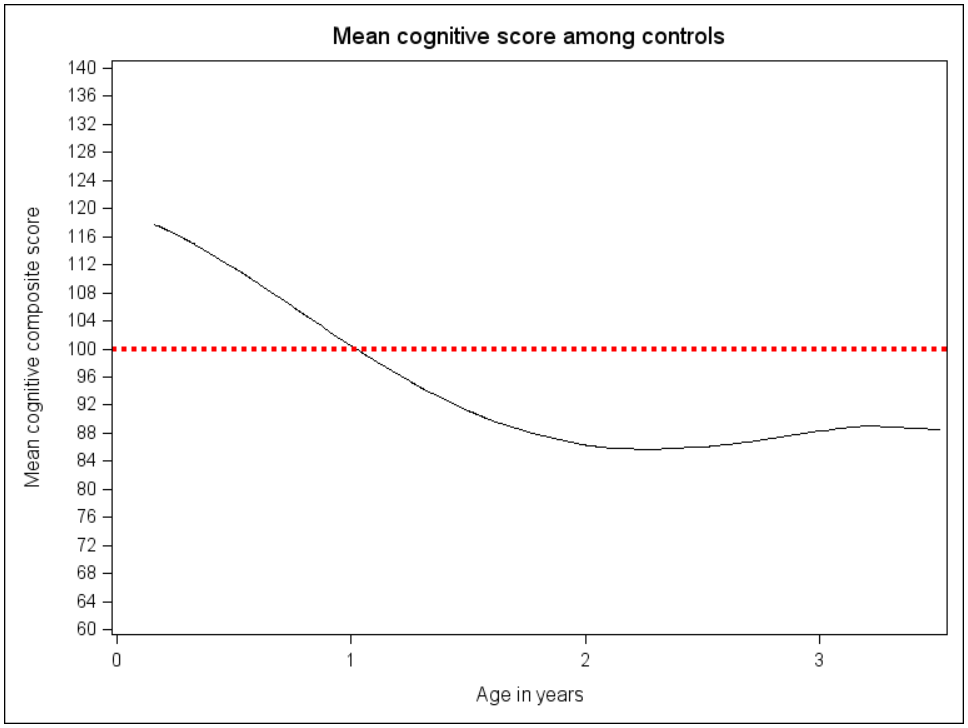
Bayley III Scoring

Raw: Range 0-72, as children age, they will score higher

Scaled: Range 1-19, mean=10 sd=3. Raw scores are transformed to scaled scores based on a linear transformation determined by the norms

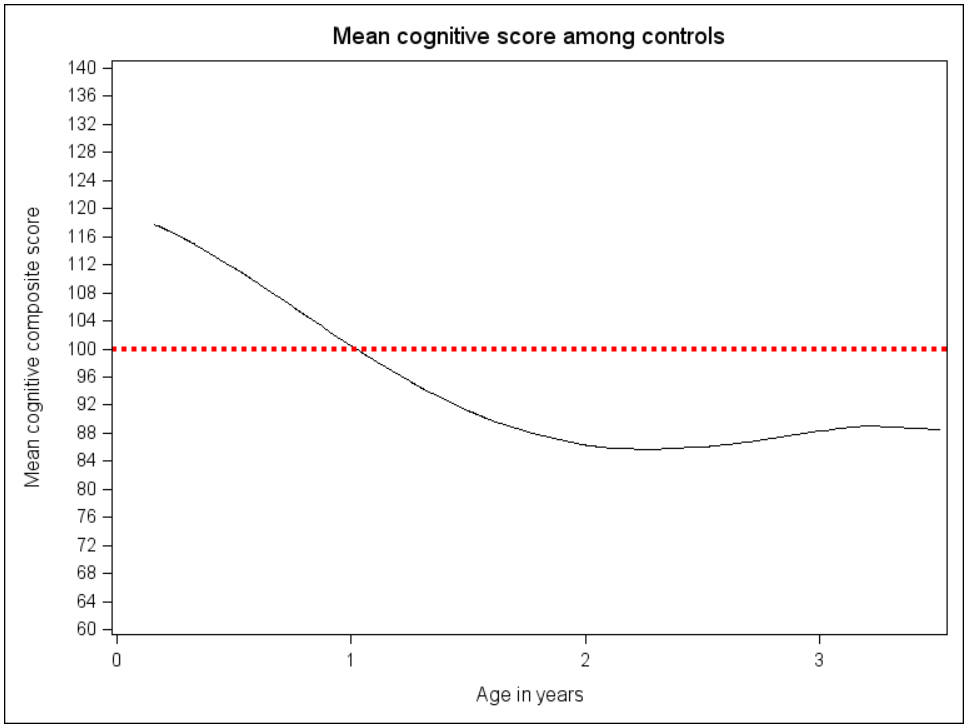
Composite: Scale 50-135, mean=100, sd=15. Scaled scores are transformed to composite scores through another linear transformation

The US norms do not apply

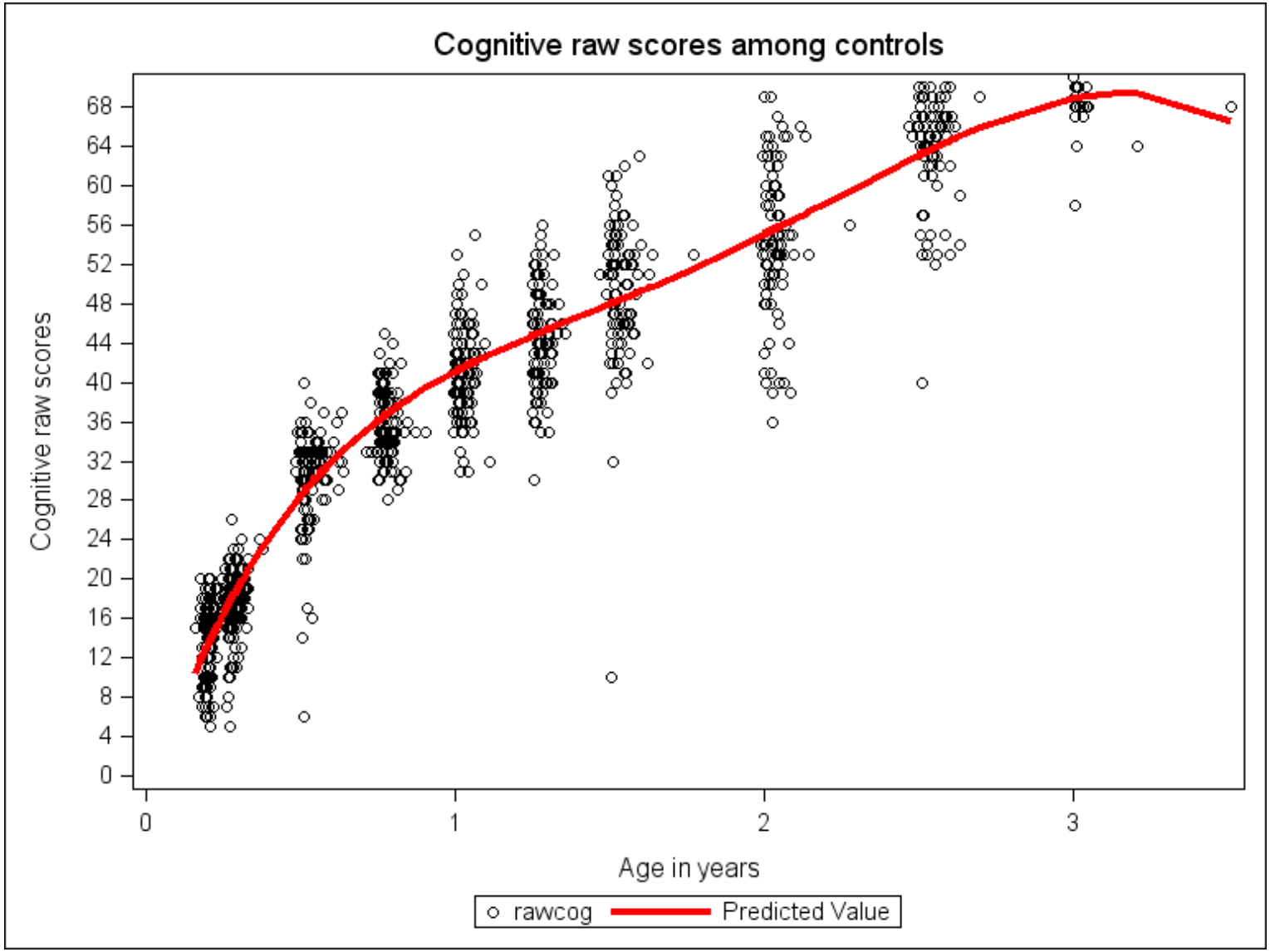


Example: Dog

The US norms do not apply



Creating norms from raw scores



Classifications based on derived norms

Upcoming Analysis

- Apply the Malawi-based norms to assess the association between HIV infection and treatment and neurodevelopmental delay

Compartmentalization Study Population

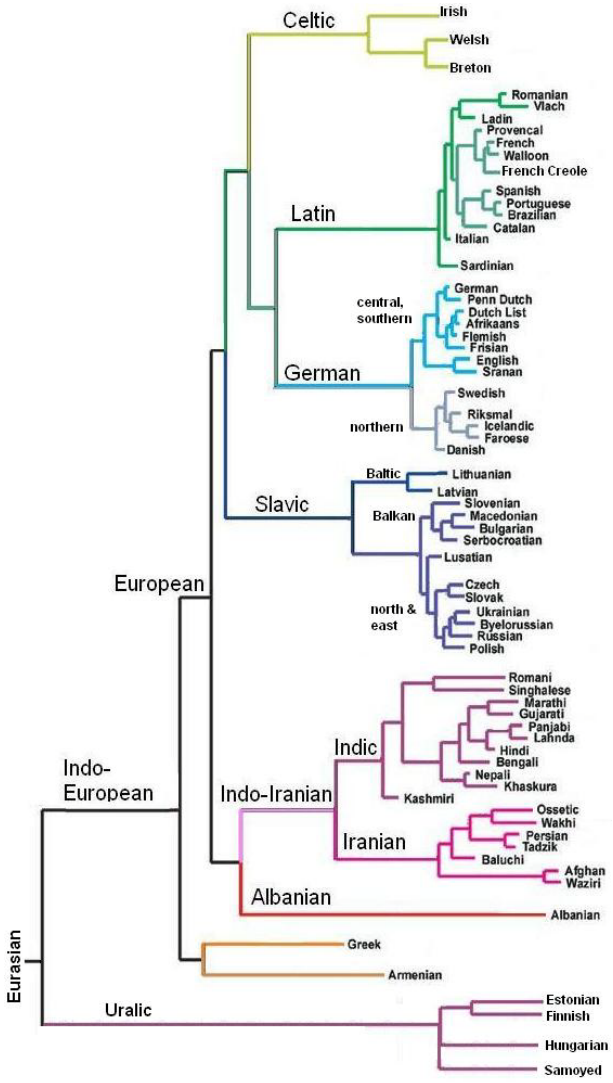
HIV-infected children presenting with severe neurodevelopmental delay

HIV-infected children presenting with 'normal' neurodevelopment

- ages 3-35 mos
- Subtype C

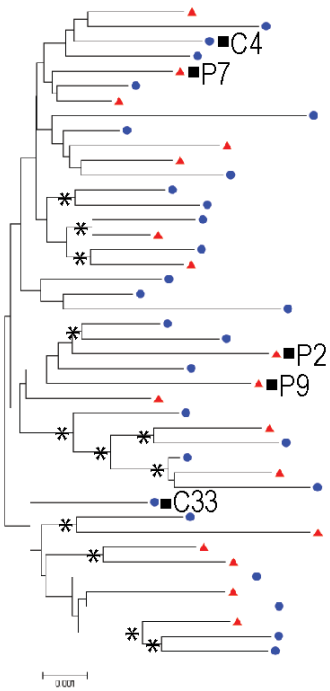
- Blood and CSF samples collected at baseline
- Total sample size: 43 Patients (blood/CSF pairs)
- Time of infection unknown → most likely at birth ± 6 months

Phylogenetic analysis of HIV-1 subtype C viral populations during pediatric infection



Phylogenetic analysis of HIV-1 subtype C viral populations during pediatric infection

A Sub. 4026



20 out of 43 subjects (46%) were equilibrated

CSF

Plasma

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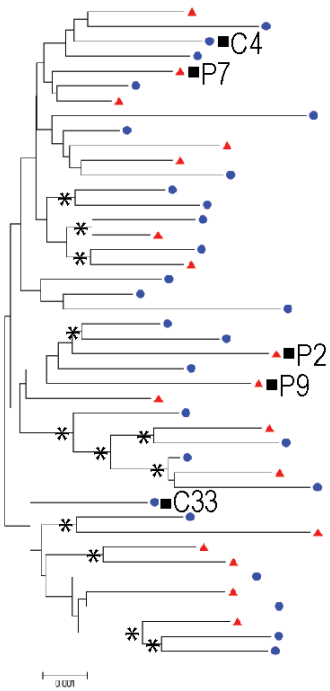

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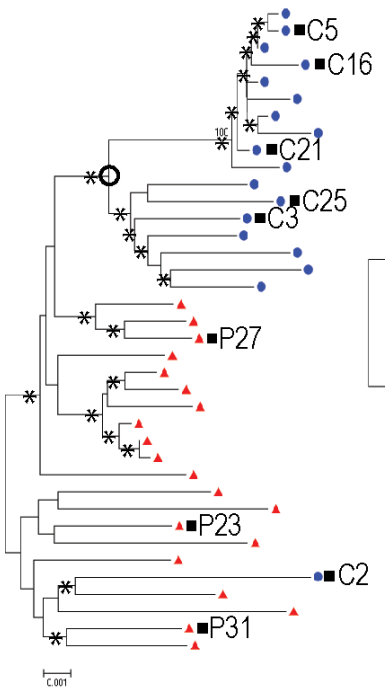
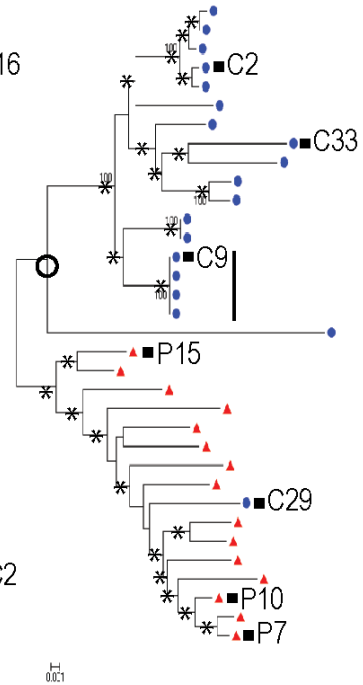
C Sub. 4049



Sub. 4004



12 out of 43 subjects (28%) were compartmentalized

CSF

Plasma

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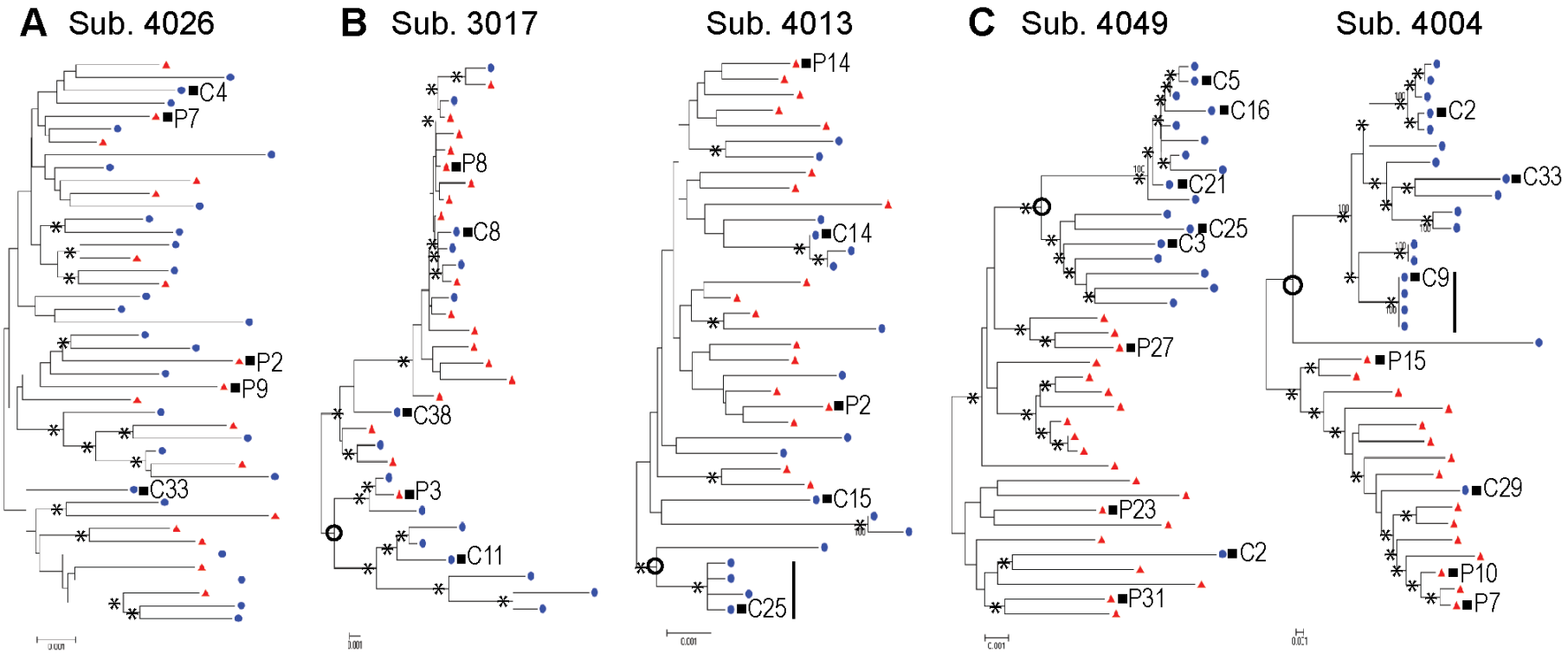


20 out of 43 subjects (46%) were equilibrated

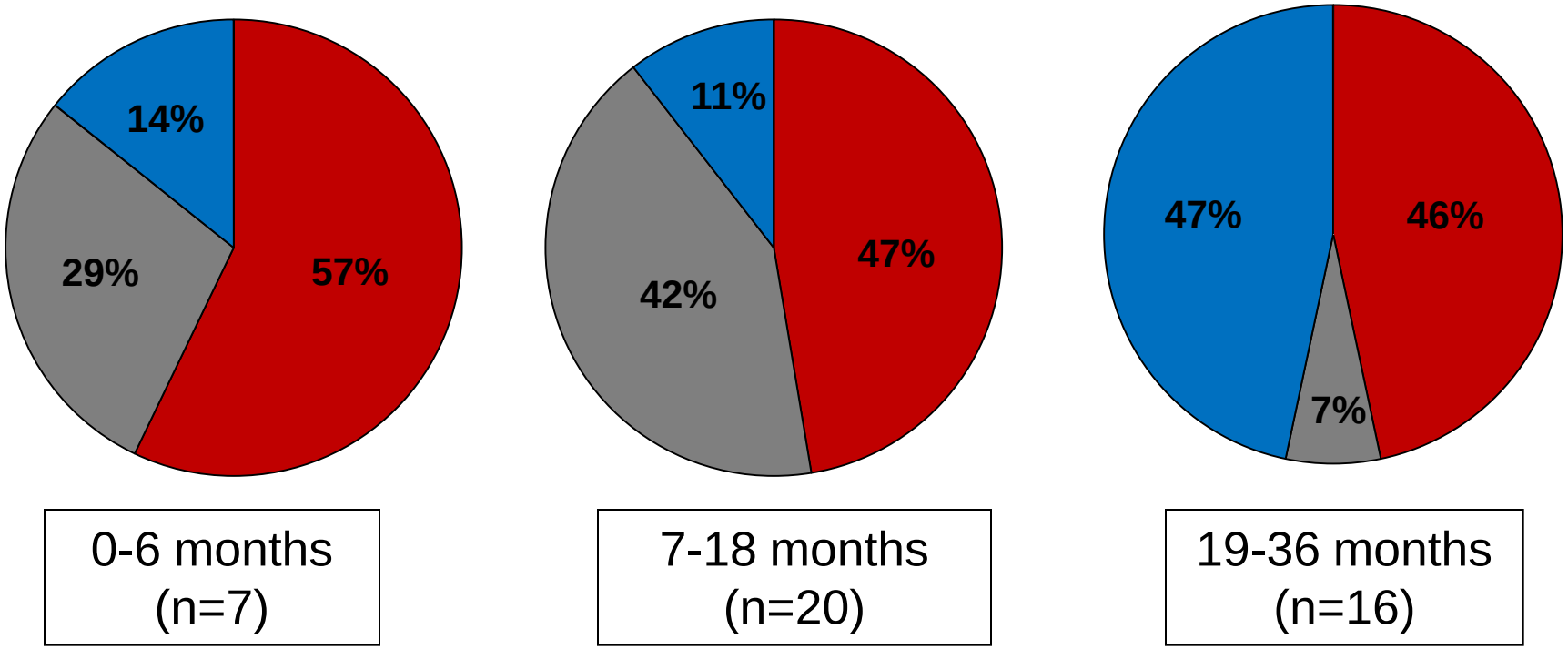
11 out of 43 subjects (26%) were intermediate

12 out of 43 subjects (28%) were compartmentalized

CSF

Plasma

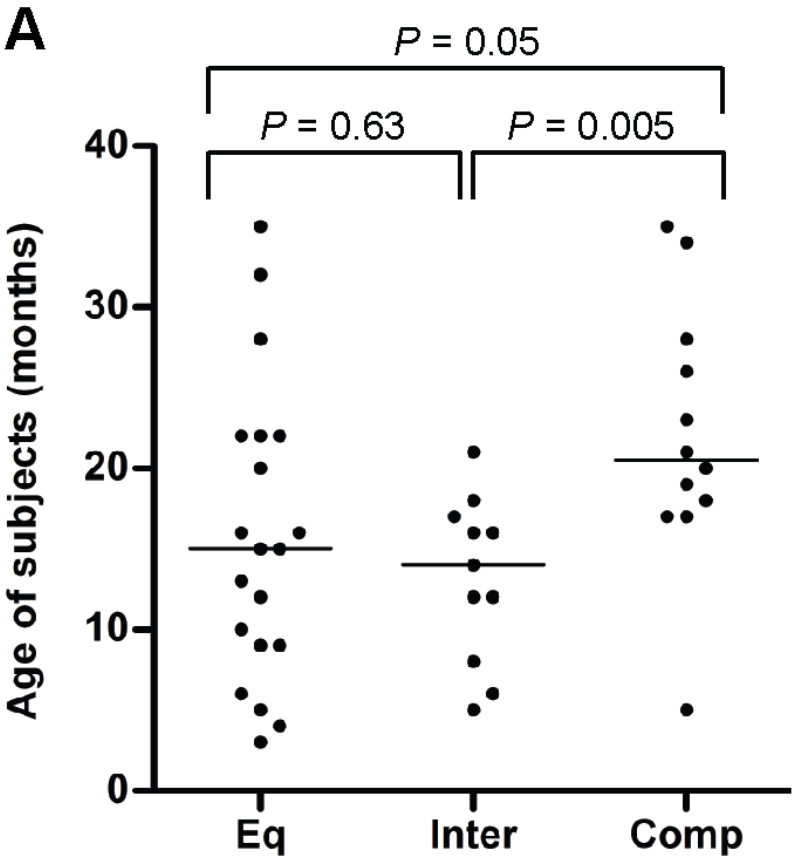
Compartmentalized viral replication in the CNS occurred in half of children by year three



Equilibrated
Intermediate
Compartmentalized

Associations with Compartmentalization

Older children were more likely to have compartmentalized CSF variants



Barriers Encountered

- Low participation in six week infant HIV testing
- Qualitative pilot study on barriers to testing and treatment found:
    - Only vague awareness of infant treatment availability
    - Confusion over cotrimoxazole
    - Hesitation to treat child without symptoms
    - Stigma
- High rate of false positive test results on DBS samples, inconsistent access to viral load
- Inconsistent access to HIV tests through PMTCT
- Slow data transfer and entry

Capacity Building in Malawi

- Staff training in child development, neurodevelopmental assessments, neurological examinations, & HIV infection and treatment in young children
- Short courses for staff in program management, GCP
- Study pediatrician pursuing PhD on neurological outcome among survivors of neonatal sepsis
- Early Infant Testing Program
- Laboratory training for CSF procedures

Acknowledgements

BLANTYRE

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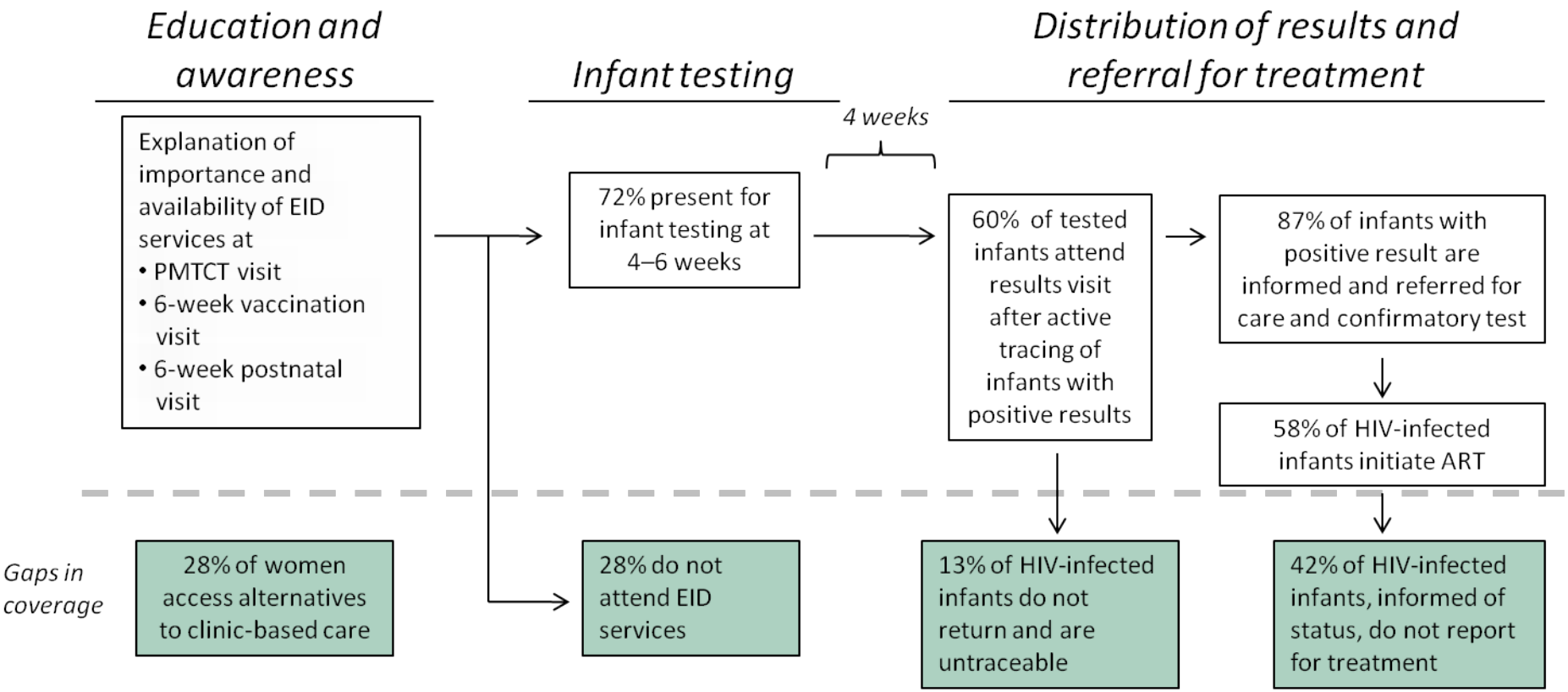
- Children and their parents

UNC

- Christa Sturdevent
- Liz Cromwell
- Ron Swanstrom
- Gretja Schnell
- Susan Fiscus's lab
- Marie Donahue

THE RIGHTS OF A PATIENT


Education and awareness
Infant testing
Distribution of results and referral for treatment
4 weeks
Explanation of importance and availability of EID services at
• PMTCT visit
• 6-week vaccination visit
• 6-week postnatal visit
72% present for infant testing at 4–6 weeks
60% of tested infants attend results visit after active tracing of infants with positive results
87% of infants with positive result are informed and referred for care and confirmatory test
58% of HIV-infected infants initiate ART
Gaps in coverage
28% of women access alternatives to clinic-based care
28% do not attend EID services
13% of HIV-infected infants do not return and are untraceable
42% of HIV-infected infants, informed of status, do not report for treatment

Viral tropism
MTCT of multiple variants

- In a subset of compartmentalized cases (n=2, 17%), the CNS virus evolved to become macrophage tropic
  - Able to infect cells with low CD4 expression

- Transmission of multiple variants was observed for 5 children
  - One variant was sequestered within the CNS in 4, consistent with early stochastic colonization of the CNS

Next steps – analyze associations with neurodevelopment and effects of ART