

NWCS 602: Inflammatory
Biomarkers of Neurodevelopmental
and Mental Health Outcomes in
Children with Perinatal HIV Infection

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Rationale

- Perinatally HIV-infected children (PHIV) have neurodevelopmental deficits compared with uninfected age matched controls (P1104s preliminary results)
- There is evidence in HIV-infected and uninfected hosts that mental health and other CNS functions are associated with inflammatory biomarkers
- HIV disease is characterized by an exacerbated inflammatory milieu
- Hypothesis: inflammatory and anti-inflammatory markers predict neurodevelopmental outcomes of PHIV

Primary objectives

1. Identify cross-sectional and longitudinal patterns of inflammatory biomarkers characteristic of the monocyte/glial and endothelial cascades in children enrolled in P1104s.
2. Identify inflammatory biomarkers, or groupings thereof, associated with neurodevelopmental, mental health, and behavioral outcomes in aviremic children enrolled in P1104s.

P1104s

- 246 children, ages 5 -11 y, with PHIV from P1060 (AZT+3TC+NVP or LPVr) + 185 HIV-exposed uninfected and 184 HIV-unexposed controls of the same ages
- 3 neuropsychological evaluations q 48 w
- 90% of PHIV have HIV plasma RNA < limit of detection (LOD) (33: <20; 170 < 40; 1 <100; and 39 < 200 RNA c/mL)
- Plasma collected q 12 weeks in P1060 versions 1 to 4 and q 48 weeks in version 5 (from Mar 2011; P1104s started in 2012)

Inclusion criteria

- PHIV enrolled in P1104s
- Aviremia for ≥ 1 year before entry in P1104s using the LOD of the test used by each site
 - A sensitivity analysis will be performed at the end of the study to determine if tests with an LOD = 100 to 200 c/mL introduced biases
 - A preliminary analysis showed differences in test scores by site, which makes it a priori undesirable to restrict participation to sites that used tests with LOD of 20 or 40
- ≥ 2 neuropsychological evaluations.
- Plasma samples available at the beginning of aviremia and within 6 months of each neuropsychological evaluation included in the analysis

Outcome measures

- Kaufman Assessment Battery for Children, 2nd Ed. (KABC-II)
 - Measures mental processing expressed as Mental Processing Index (MPI)
- Test of Variables of Attention (TOVA)
 - Measures attention and impulsivity expressed as D-prime
- Bruininks-Oseretsky Test of Motor Proficiency, 2nd Ed. (BOT-2)
 - Measures motor proficiency expressed as Total Standard score
- Behavior Rating Inventory of Executive Function (BRIEF)
 - Measures global executive functions expressed as Global Executive Composite (GEC)

Modifiers

- Multiple Indicator Cluster Survey, Version 4 (MICS4)
 - Measures the home environment as it applies to the child development
- Hopkins Symptoms Checklist
 - Measures the maternal emotional well-being
- *Initial ARV regimen (NVP vs. LPVr)*

Inflammatory and anti-inflammatory markers of the CNS, monocytes, endothelial cells

- Cytokines: $\text{IFN}\gamma$, $\text{IFN}\alpha$, $\text{IL1}\beta$, IL6 , IL10 , $\text{TGF}\beta$, $\text{TNF-}\alpha$
- Chemokines: CXCL10 , CCL4 , CX3CL4 , CCL2 ,
- Soluble ligands: CD54 , CD62 , CD106 , ICAM5 , sCD14 , sCD163 , sCTLA4
- Agents of endothelial cell dysfunction: VEGF , free fatty acids
- Other markers of systemic inflammation and regulation: Kynurenin/Tryptophan ratio, hsCRP , fibrinogen,
- Markers of CNS inflammation: neurofilament light chain protein, matrix metalloproteinase 9.

Analysis plan

- Aim 1 (monocyte/glial and endothelial cell inflammation markers): big data analyses to reduce the dimensions of the large set of variables
 - Factor analysis
 - Cluster analysis
- Aim 2 (correlating the neurodevelopmental outcome measures with the inflammation markers): regression analyses controlling for the false discovery rate (Benjamini-Hochberg procedure)
 - Cross-sectional
 - Longitudinal

Significance and innovation

- Identify a set of key inflammatory pathways associated with neurodevelopmental outcomes that can be targeted by an intervention
- Characterize the kinetics of key inflammatory pathways in PHIV who initiated effective cART early in life

Questions?

Comments?