ASSOCIATIONS BETWEEN PLASMA BIOMARKERS AND CHANGES IN COGNITIVE FUNCTION OVER 2 YEARS

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N. Bakewell[1], C.A. Sabin[1], P.W.G. Mallon[2], M. Sachikonye[3], N.D. Doyle[4], **A. Winston[4]**, and K. Kunisaki[5]

[1]UCL, UK [2]University College Dublin, Ireland [3]UK Community Advisory Board, London [4]Imperial College London, UK [5]University of Minnesota, Minneapolis, MN USA

Correspondence:
Nicholas Bakewell, MSc
n.bakewell@ucl.ac.uk

POPPY
Pharmacokinetic and clinical observations in people over 50

Background

- Advances in, and improved access to, antiretroviral therapy (ART) have dramatically reduced morbidity and mortality among people living with HIV.
- However, many people living with HIV continue to exhibit chronic inflammation which may contribute to chronic conditions, including cognitive disorders[1-3].
- Whether chronic inflammation is associated with the development of cognitive disorders remains unclear.

Aim

- To examine the associations between plasma biomarkers of neuronal injury, systemic inflammation and innate immune activation and changes in cognitive function scores among people with HIV and demographically-similar people without HIV.

Methods

Participants

- The analysis included a subset of 350 participants from the POPPY (Pharmacokinetic and clinical Observations in PeoPle over fiftY) study in the UK and Ireland[4] who participated in the POPPY-Sleep sub-study. Detailed information was available on demographic, lifestyle and clinical factors at the baseline visit
- Of the participants, 255 were people with HIV (176 ≥50 years) and 95 were people without HIV≥50 years.

Assessment of Cognitive Function

- At baseline and 2-year follow-up, participants completed a cognitive test battery assessing psychomotor function, visual learning, visual attention, working memory, verbal learning and executive function.
- The primary outcome for analyses was the Global T-score of overall cognitive function obtained by averaging domain T-scores (higher T-score indicates better cognitive function)[5].

Plasma Protein Biomarkers

- For the present analysis, 10 protein biomarkers (tested in plasma samples) were considered:
  - **neuronal injury** (NFL, S100B),
  - **systemic inflammation** (IL-2, IL-2, TNF-α)
  - **innate immune activation** (sCD14, IL-10, MCP-1, CD163, MIP-1α).

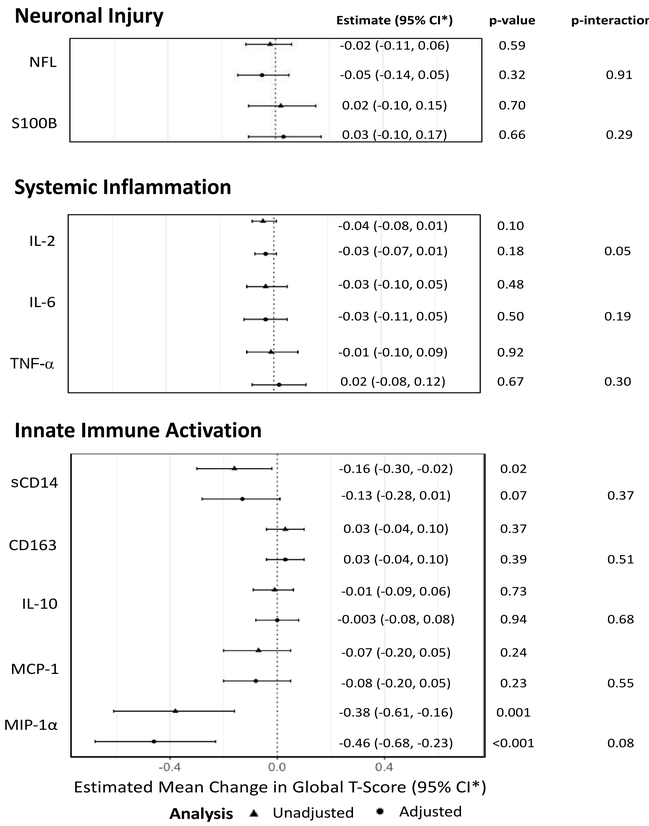
Statistical analysis

- Linear regression was used to explore associations between changes in Global T-scores and each (log-transformed) plasma protein biomarker, after scaling the biomarkers so that the regression coefficients represent a mean change in the Global T-score for every 10% change in the concentration of a biomarker.
- Analyses adjusted for HIV status, age, sex and education; and explored whether associations of biomarkers with the outcome differed by HIV status using likelihood ratio tests.

Table 1: Characteristics and biomarker levels at baseline POPPY visit, overall and stratified by HIV status

Characteristic	Overall (N=350)	People without HIV (N=95)	People with HIV (N=255)
Age (years)	54 (50, 60)	58 (54, 61)	53 (47, 59)
Male	297 (84.9%)	66 (69.5%)	231 (90.6%)
White	330 (94.3%)	91 (95.8%)	239 (93.7%)
Men having sex with men	271 (77.4%)	56 (58.9%)	215 (84.3%)
Biomarker concentration (pg/mL unless otherwise stated)			
Neuronal Injury			
NFL	57.2 (41.3, 77.8)	63.3 (45.4, 77.0)	55.4 (40.2, 77.9)
S100B	623.3 (515.3, 780.1)	666.3 (538.4, 790.3)	611.9 (507.7, 761.4)
Systemic Inflammation			
IL-2	1.0 (0.6, 1.8)	0.9 (0.5, 2.7)	1.0 (0.6, 1.6)
IL-6	2.1 (1.5, 3.1)	2.1 (1.6, 3.3)	2.1 (1.5, 3.1)
TNF-α	5.1 (4.2, 6.6)	5.3 (4.0, 7.7)	5.0 (4.2, 6.3)
Innate Immune Activation			
sCD14 (x10^3 pg/mL)	1620.6 (1335.0, 2036.2)	1516.9 (1239.4, 1825.0)	1741.6 (1399.6, 2112.2)
CD163 (x10^3 pg/mL)	640.5 (404.0, 976.2)	474.8 (342.1, 804.9)	677.1 (429.1, 1010.0)
IL-10	0.7 (0.5, 1.0)	0.8 (0.6, 1.2)	0.7 (0.5, 1.0)
MCP-1	152.7 (127.8, 194.0)	140.9 (119.6, 174.0)	157.2 (130.3, 202.7)
MIP-1α	526.2 (454.8, 598.0)	542.2 (454.7, 617.3)	524.8 (455.1, 593.3)

Figure 1: Estimates (with 95% confidence intervals [CI]) from unadjusted and adjusted linear regression analyses of the associations between changes in Global T-scores and log-transformed biomarkers



Results

- The 350 participants had a median age of 54 years, with most being male, white, and men having sex with men (Table 1). Among people with HIV, most (98%) were on ART, 236 (93%) had plasma HIV-RNA ≤50 copies/mL and median [IQR] blood CD4+ T-cell count was 629 [490, 794] cells/mm^3.
- Mean (95% CI) Global T-scores at baseline and follow-up are shown in Table 2. Overall, the mean (SD) change over a median [IQR] follow-up time of 26 [24, 29] months was 1.3 in those without HIV and 1.1 in those with HIV, with no evidence for a difference between the two groups (p=0.64).

Table 2: Mean (95% CI) Global T-scores at baseline and follow-up, with change between the two, stratified by HIV status

Mean (95% CI) Global T-score and change	People without HIV	People with HIV
N	95	255
At Baseline	49.3 (48.3, 50.3)	47.1 (46.4, 47.8)
At follow-up	50.7 (49.8, 51.6)	48.2 (47.5, 48.9)
Change	1.3 (0.5, 2.1)	1.1 (0.5, 1.7)

- In unadjusted analyses, only MIP-1α and sCD14 were associated with cognitive function, with higher concentrations of each being associated with a reduction in the Global T-score. No other biomarker demonstrated a significant association with the Global T-score (Figure 1).
- After adjustment for potential confounders, associations of each biomarker with cognitive function were similar with adjusted estimates [95% confidence interval] /10% increment:
  - MIP-1α -0.46 [-0.68, -0.23]
  - sCD14 -0.13 [-0.28, 0.01].
- There was some evidence that the association of MIP-1α with cognitive function was stronger in people living with HIV with estimates of -0.47 [-0.99, 0.05] and -0.09 [-0.55, 0.36] in people with and without HIV respectively (p-value for interaction=0.08)

Summary

Within an extensive panel of plasma protein biomarkers, we observed that higher levels of plasma MIP-1α and sCD14 were associated with a reduction in cognitive function over a 2-year period, suggesting innate immune activation and systemic inflammation may both be implicated in the pathogenesis of changes in cognitive function and these effects may differ in people living with HIV.

References

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