Poster #489

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Blood Cell Indices and Neurocognitive Impairment in the HAART Era: A CHARTER Study

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CHARTER
CNS HIV Anti-Retroviral Therapy Effects Research
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Objective

To examine the relationship between red blood cell indices , which are sensitive to changes in iron status and inflammation, and the risk of HIV-associated neuro-cognitive disorders (HAND) in the highly active antiretroviral therapy (HAART) era.

Background & Significance

- HIV-associated neurocognitive disorder (HAND) remains a major threat to quality of life in the HAART era, occurring even when virus is undetectable.
- Anemia correlates with increased morbidity/mortality in HIV/AIDS but its impact on HAND in the HAART era has not been adequately studied.
- Red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and hemoglobin (Hgb) are routine laboratory indices of iron status and inflammatory/metabolic disease activity.
- Due to their inability to produce new organelles, red cells are likely to be sensitive to mitochondrial dysfunction, which is implicated in HAND.

Methods

- CHARTER is a U.S.-based observational study of neuro-HIV outcomes, which enrolled ambulatory, HIV-infected adults from 2003 to 2007.
- Subjects underwent standardized neuromedical/neuropsychiatric and laboratory assessments, including complete blood counts and red cell indices.
- A subset (N~600) was followed with serial assessments every 6 months.
- Neurocognitive outcome ascertainment: 1) Global Deficit Score (GDS) impairment, defined as normal (<0.5) or impaired (≥0.5); 2) continuous GDS; and 3) HAND, defined by Frascati criteria (absence of confounding conditions, at least 2 impaired domains, and presence or absence of functional impairment by self report and/or performance-based criteria).
- Sex-specific definition of anemia: Hgb<11g/dL in women or <14 g/dL in men
- Baseline characteristics were compared using parametric or non-parametric statistics, based on variable distributions.
- Adjusted β-coefficients or odds ratios and their 95% Confidence Intervals were estimated by multiple linear or logistic regression analyses, respectively (associations of red cell indices with HAND or GDS at baseline).
- Association of low Hgb (anemia) with GDS impairment over time using repeated measures: Cox proportional hazards regression analysis
- Covariates included in regression models: age, sex, ethnicity, zidovudine (ZDV) use, HAART, nadir CD4⁺ T-cell count, plasma HIV RNA, premorbid IQ (WRAT-III Reading) score at entry, and comorbidity (incidental *vs.* contributing).

Results – Baseline Characteristics & Comparisons

Table 1. Characteristics of the CHARTER Cohort at baseline by neurocognitive status

Baseline Characteristic	GDS<0.5 (Normal) N=804	GDS≥0.5 (Impaired) N=457	No HAND N=665	ANI or MND N=558	HAD N=37
Age (years)	43±9	43±8	43±9	43±9	44±6
Female sex, N (%)	171 (21)	119 (26)	150 (23)	131 (23)	8 (22)
Race/ethnicity					
Black	416 (52)	174 (38)	351 (53)	230 (41)	8 (22)
White	318 (40)	200 (44)	261 (39)	235 (42)	6 (16)
Hispanic	53 (7)	70 (15)	35 (5)	82 (15)	22 (59)
WRAT-III (IQ) score	97 (87, 105)	90 (79, 102)	98 (87, 105)	92 (81, 103)	87 (77, 98)
Comorbidity, N (%)					
Incidental	565 (70)	242 (53)	474 (71)	320 (57)	12 (32)
Contributing	239 (30)	215 (47)	191 (29)	238 (43)	25 (68)
HIV RNA, plasma (log_{10} copies/mL)	2.5 (1.7, 4.1)	2.1 (1.7, 3.8)	2.5 (1.7, 4.1)	2.2 (1.7, 3.9)	1.9 (1.7, 3.7)
Nadir CD4+ T-cells, cells/mm³	190 (56, 329)	162 (41, 277)	196 (59, 332)	150 (34, 265)	123 (50, 190)
On HAART, N (%)	534 (66)	352 (77)	442 (66)	410 (73)	33 (89)
ZDV use, N (% yes)	122 (18)	95 (24)	130 (19)	100 (21)	7 (21)
Anemia, N (%)*	232 (29)	138 (30)	186 (28)	171 (31)	13 (35)
RBC, million/mm³	4.5 (4.1, 4.9)	4.4 (4.0, 4.8)	4.5 (4.1, 4.9)	4.4 (4.0, 4.8)	4.6 (4.0, 4.9)
MCV, femtoliter	92 (87, 97)	94 (88, 100)	92 (87, 97)	93 (89, 99)	95 (90, 100)
MCH, pg/cell	31 (29, 33)	32 (30, 34)	31 (29, 33)	32 (30, 34)	32 (30, 35)

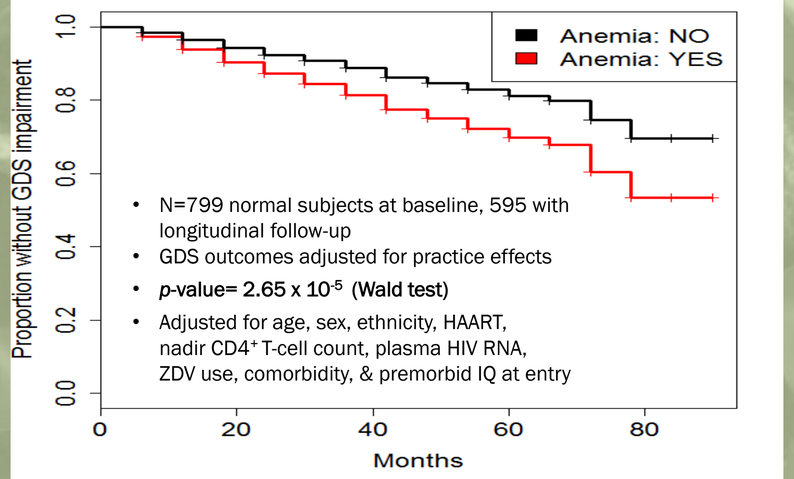
Data presented: mean±standard deviation for normally distributed variables or median (interquartile range), if skewed. Abbreviations: *GDS*, Global Deficit Score; *HAND*, HIV-Associated Neurocognitive Disorder; *ANI*, Asymptomatic Neurocognitive Impairment; *MND*, Mild Neurocognitive Disorder; *HAD*, HIV-Associated Dementia; *WRAT*, wide-range achievement test; *HAART*, highly active antiretroviral therapy; *ZDV*, zidovudine; *RBC*, red blood count; *MCV*, mean corpuscular volume; *MCH*, mean corpuscular hemoglobin; *pg*, picograms.

*Anemia was defined as hemoglobin<11 g/dL in women and <14 g/dL in men.

p-value<0.05, normal *vs.* impaired

Multivariable Time-Dependent Analysis

Figure 1. Cox proportional hazards regression of GDS impairment on anemia status



Multivariable Analyses...

Table 2A. Multiple Linear Regression – Global Deficit Score (GDS, continuous) on MCV

Variable	β-coefficient	95% Confidence Interval	*p*-value
MCV	0.006	0.002, 0.009	<0.01
Age	0.0003	-0.003, 0.004	0.88
Sex (female referent)	-0.045	-0.116, 0.027	0.22
On HAART	0.095	-0.006, 0.196	0.06
Nadir CD4⁺ T-cells (per cell/mm³)	-5.7 x 10-5	-0.0002, 0.0001	0.56
ZDV use	-0.054	-0.139, 0.032	0.22
Plasma HIV RNA (per log_{10}copies/mL)	0.008	-0.022, 0.037	0.61
WRAT (premorbid IQ) score	-0.004	-0.006, -0.002	<0.01
Ethnicity (Hispanic referent)	-0.235	-0.337,-0.134	<0.01
Comorbidity ("incidental" *vs.* "contributing" referent)	-0.167	-0.228, -0.105	<0.01

Model p-value=1.2×10^{-15}

Table 2B. Multiple Linear Regression Models – GDS (continuous) on RBC or MCH

Variable	β-coefficient	95% Confidence Interval	*p*-value	Model *p*-value
RBC	-0.052	-0.109, 0.005	0.07	3.1×10^{-14}
MCH	0.014	0.005, 0.024	<0.01	1.6×10^{-15}

Data shown are adjusted β-coefficients in separate regression models of GDS, each adjusted for the same covariates as in Table 2A (N=1038). Other significant covariates in all models included: premorbid IQ (WRAT) score, ethnicity, and comorbidity.

Table 3. Multivariable Logistic Regression – Categories of HAND on blood cell indices*

Variable	GDS impairment (GDS≥0.5)	*p*-value	MND OR (95% CI)	*p*-value	HAD OR (95% CI)	*p*-value
RBC	0.84 (0.68-1.0)	0.13	0.59 (0.38-0.90)	<0.01	1.02 (0.49-2.06)	0.96
MCV	1.02 (1.00-1.03)	<0.05	1.03 (1.00-1.06)	<0.05	1.06 (1.00-1.11)	<0.05
MCH	1.04 (1.01-1.08)	<0.01	1.11 (1.03-1.19)	<0.01	1.13 (1.00-1.30)	0.06

Referents: GDS<0.5, or for MND and HAD, normal cognition (binary). *Adjusted for age, sex, HAART, nadir CD4+ T-cells, HIV RNA (plasma), WRAT, Hispanic ethnicity, comorbidity, and ZDV use. *OR*, Odds Ratio; *CI*, confidence interval; *MND*, Mild Neurocognitive Disorder; *HAD*, HIV-Associated Dementia

Summary & Conclusions

- **Low hemoglobin (anemia) remains an independent predictor of HAND susceptibility (GDS impairment) in the HAART era**, possibly due to persistent inflammation with impaired iron transport, mitochondrial function and/or oxygen delivery.
- **MCV and MCH, sensitive markers of metabolic status and iron metabolism, are also positively associated with GDS impairment and symptomatic HAND.** These associations may be due to HAART-related mitochondrial dysfunction, which is implicated in HAND & has been shown to correlate with increased MCV.

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CHARTER NEUROAIDS DATA RESOURCE

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