Neurocognitive Function in HIV-Infected Persons with Cryptococcal Antigenemia

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Background:

HIV-infected persons with detectable cryptococcal antigen (CrAg) in blood have increased mortality compared with HIV-infected persons who are CrAg-negative.

This study examined neurocognitive function among persons with asymptomatic cryptococcal antigenemia in Uganda.

Methods:

- Three cohorts of HIV-infected persons enrolled in prospective clinical trials and cohort studies in Kampala, Uganda were included:

A. Persons who recently survived cryptococcal meningitis, N=90
B. Asymptomatic CrAg+ persons, N=87
C. HIV-infected controls without central nervous system infection(s), N=125

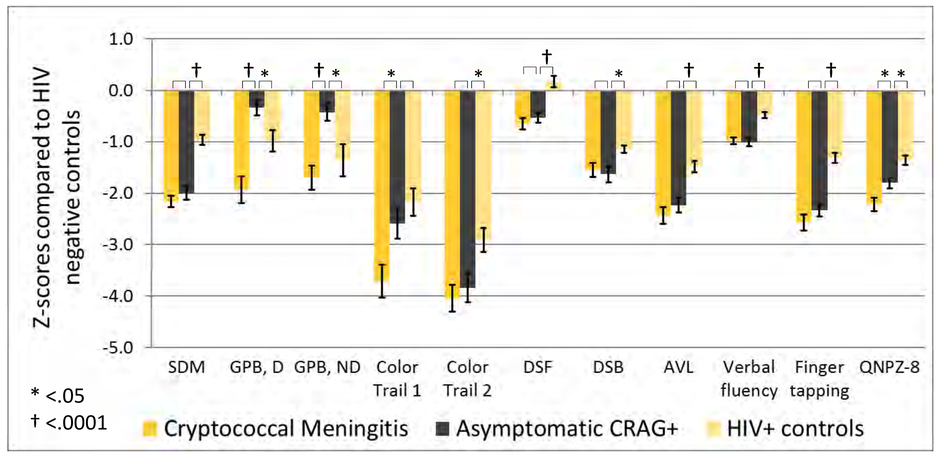
- All patients were ART-naïve at the time of neurocognitive testing.
- CrAg testing was performed using CrAg lateral flow assay (Immy, Norman, Oklahoma).
- Neurocognitive function was measured in eight neurocognitive domains at the time of ART initiation for all three cohorts.
- For asymptomatic CrAg+ participants, neurocognitive testing was repeated after four weeks of HIV therapy and pre-emptive fluconazole treatment.
- Z-scores for each neurocognitive test were calculated relative to an HIV-negative Ugandan population.
- A composite quantitative neurocognitive performance Z-score (QNPZ-8) created from eight tested domains.

Background and Clinical Characteristics of three Study Cohorts

	Cohort A Cryptococcal meningitis (N=90)		Cohort B Asymptomatic CrAg+ (N=87)		Cohort C HIV+ controls (N=125)		A vs. B	B vs. C
	median	(IQR)	median	(IQR)	median	(IQR)	*P* -value	*P* -value
Age (years)	36	(30 - 40)	31	(27 - 39)	37	(32 - 41)	0.02	<0.001
Sex (% Male)	60%		51%		32%		0.21	0.007
Education level (years)	8	(4 - 11)	7	(3-11)	8	(6 - 11)	0.15	0.05
CD4 count (cells/μL)	17	(7 - 79)	26	(9-59)	233	(183 - 297)	0.93	<0.001
Karnofsky score	60	(50-70)	70	(60-80)	90	(90 - 90)	<0.001	<0.001
International HIV dementia scale	7	(6 - 9)	9	(7-11)	10	(9 - 11)	0.001	0.003
CES depression scale	23	(16 - 30)	18	(10-26)	9	(5 - 17)	0.007	<0.001

P -values were calculated using student's T-test, Mann-Whitney U test, or chi-square test as appropriate.

Neurocognitive test Z-scores according CrAg status



SDM = Symbol digit modalities
Tests: Speed of information processing
GPB,D = Grooved pegboard, dominant hand
Tests: Fine motor skills
GPB,ND = Grooved pegboard, non-dominant hand
Tests: Fine motor skills
Color Trail 1
Tests: Speed of information processing, attention
Color Trail 2
Tests: Executive function
DSF = Digit span forward
Tests: Attention, working memory
DSB = Digit span backward
Tests: Attention, working memory
AVL = Auditory visual learning
Tests: Verbal learning
Verbal fluency
Tests: Language fluency
Finger tapping
Tests: Motor speed

QNPZ-8 = Quantitative neurological performance Z-score on 8 modalities.

Population characteristics and average neurocognitive test Z-scores for 73 persons with asymptomatic cryptococcal antigenemia

Population Characteristics	Pre-ART Visit Week 2 of fluconazole Average (±SD)	Week 4 of HIV therapy Week 6 of fluconazole Average (±SD)	Intra-Person Change (SD)	P-value
CD4 count (cells/mL), N=60	32 (±39)	80 (±74)	47 (±66)	<0.001
Karnofsky score	72 (±12)	75 (±11)	2.5 (±10)	0.04
International HIV dementia scale	8.7 (±2.3)	10 (±2.3)	1.4 (±2.6)	<0.001
CES depression scale	19 (±10)	16 (±10)	-3 (±12)	0.04
Neurocognitive Tests				
Symbol digit modalities	-1.9 (±1.2)	-1.5 (±1.5)	0.4 (±1.0)	0.002
Grooved pegboard dominant	-0.3 (±1.3)	0.1 (±1.1)	0.4 (±1.4)	0.02
Grooved pegboard non-dominant	-0.4 (±1.5)	0.02 (±1.3)	0.3 (±1.3)	0.03
Color Trails 1	-2.4 (±2.6)	-1.0 (±1.7)	1.4 (±2.3)	<0.001
Color Trails 2	-3.7 (±2.6)	-1.9 (±1.6)	1.7 (±2.1)	<0.001
Digit span forward	-0.5 (±0.9)	-0.3 (±0.9)	0.2 (±0.9)	0.15
Digit span backward	-1.4 (±1.4)	-1.1 (±1.3)	0.3 (±1.2)	0.03
Auditory verbal learning	-2.2 (±1.4)	-1.2 (±1.5)	1.0 (±1.2)	<0.001
Verbal fluency	-0.9 (±0.7)	-0.6 (±0.7)	0.3 (±0.7)	0.005
Finger tapping	-2.3 (±1.1)	-1.9 (±1.0)	0.4 (±1.1)	0.002
QNPZ-8	-1.7 (±1.0)	-1.0 (±0.8)	0.7 (±0.7)	<0.001

Numbers represent Z-scores referenced against age and education adjusted, HIV-negative Ugandan population norms.
Statistical testing by paired *t* -test.

Results:

- HIV+ controls had significantly higher CD4 counts than the other two cohorts.
- HIV+ controls also had significantly better Karnofsky performance status and lower levels of dementia and depression.
- Except for Color Trail 1 test, asymptomatic CrAg+ persons performed significantly worse than HIV-infected controls in every domain.
- On most neurocognitive tests, asymptomatic CrAg+ participants did not perform significantly worse than participants with recent cryptococcal meningitis.
- Asymptomatic CrAg+ participants showed improved neurocognitive function in all domains after four weeks of HIV treatment, except for Digit Span Forward.

Conclusions:

- Persons with very advanced AIDS (CD4<100) with asymptomatic cryptococcal antigenemia have substantial neurocognitive dysfunction with severe deficits in executive function, verbal memory, and speed of information processing compared to the typical HIV-infected person newly entering into HIV care.
- This work provides additional evidence of the benefits of CrAg screening in asymptomatic patients with advanced AIDS.
- As more countries roll out CrAg screening in populations with advanced HIV, some initial adherence support may be necessary due to the neurocognitive dysfunction present in CrAg+ persons.

This research was made possible through support from the Centers for Disease Control and Prevention (U01GH000517), Fogarty International Center and National Institute of Neurologic Diseases and Stroke (R21NS065713, R01NS086312, R25TW009345), and National Institute of Allergy and Infectious Diseases (U01AI089244, T32AI055433, K24AI096925).

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Abstract number: 761