



Health Disparities & Novel Biomarkers for HIV-1 Associated Neurocognitive Disorders

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Introduction

- Investigate links between HIV-1 Associated Neurocognitive Disorders (HAND) in a Bio-Psyco-Socio-Cultural model
- We will evaluate biomarker(s) as predictors of HIV-1 associated Neurocognitive Disorder in context to health disparities



Insight

Synergize basic science with issues related to health disparities



HIV Epidemiology

- 35.3 (32.2–38.8) million people living with diagnosed HIV worldwide (2012)
- 1.1 million people in the United States living with HIV infection



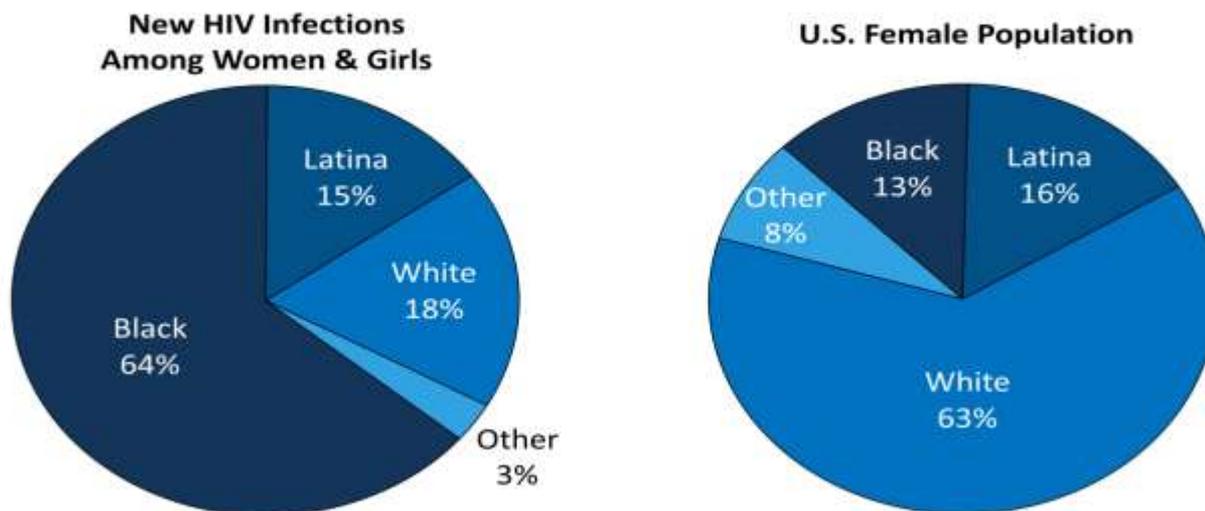
[World AIDS day report and fact sheet \(2013, November - WHO, UNAIDS & UNICEF\)](#),
HIV in United States at a glance (2013, December-CDC) & NCHHSTP Atlas (2014-CDC)

Disparities in HIV/AIDS

- African Americans represent 12% of the US population but they account for 44% of newly diagnosed HIV infections
- Hispanics/Latinos represent 16% of the US population but they account for 21% of newly diagnosed HIV infections
- The prevalence of HIV is 44% in African Americans and 19% in Hispanic/ Latinos in the US

Feminization of HIV

New HIV Infections Among Women & Girls and U.S. Female Population, by Race/Ethnicity, 2010



NOTES: Data are estimates among those ages 13 and older and do not include U.S. dependent areas.
SOURCES: CDC, HIV Surveillance Supplemental Report, Vol. 17, No. 4; December 2012. U.S. Census Bureau, 2010 Population Estimates.



HIV in United States Surveillance Report (2012, -CDC)

US Census Bureau 2010 population estimates

Women and HIV/AIDS (2014, Kaiser Foundation Family Report-)

HIV in Texas

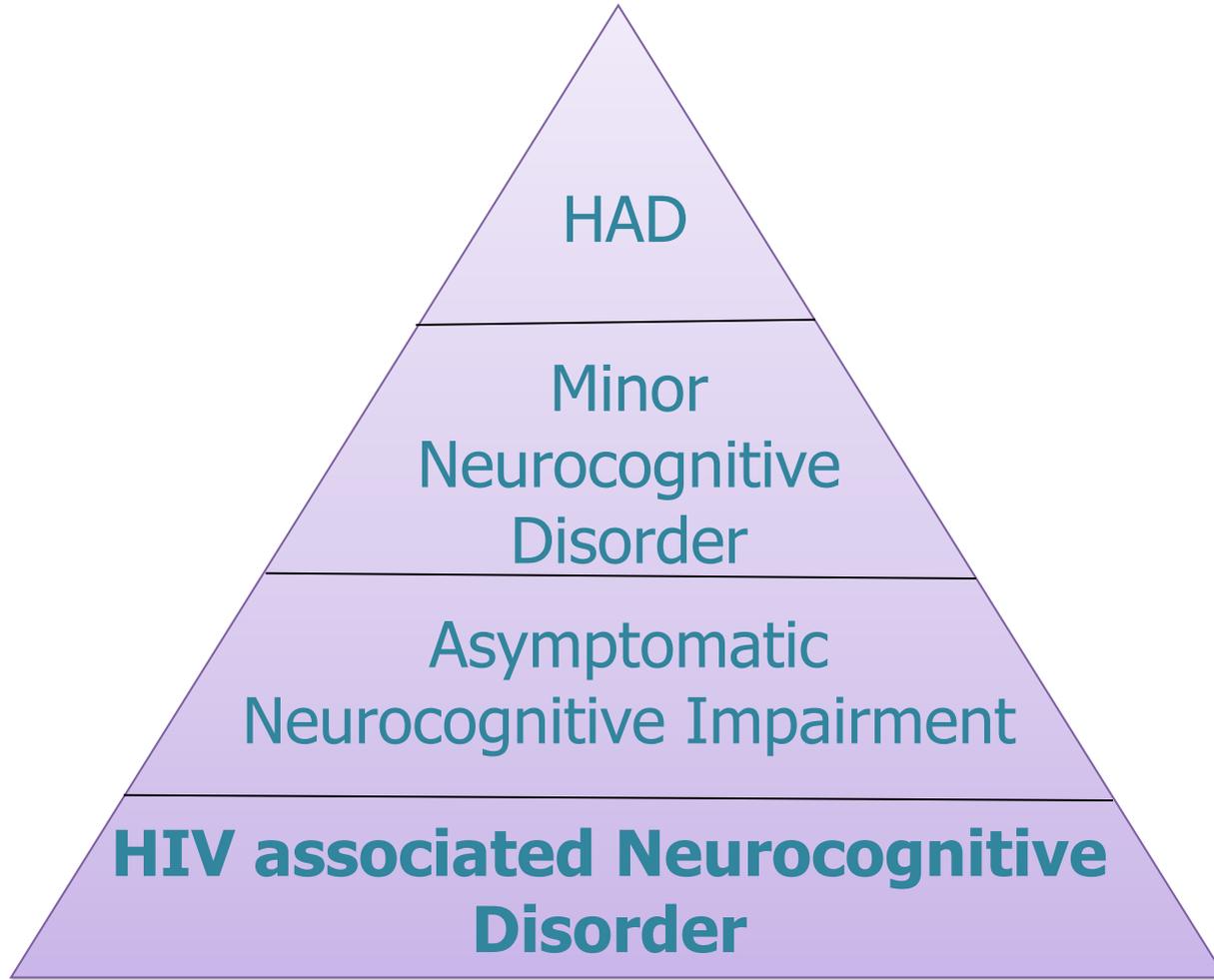


- Texas is third in the Nation for number of diagnosed HIV cases (approximately 64,498 living with HIV)
- The rates of newly diagnosed HIV cases are 52.1% African Americans and 15.5% Hispanics
- Majority of the persons living with HIV in Texas are racial/ethnic minorities with 37.5% African Americans, 29.4% Hispanics and 29.4% Caucasians

HIV-1 and Aging in USA

- 17% of all new reported HIV diagnoses > 50; 25% > 60s
- 31% of HIV-1 patients living with HIV > 50, by 2015 – 50%
- After ART-
 - HIV-1-Associated Dementia incidence decreased, but not prevalence – AIDS defining (2-8%)
 - HIV-1-Associated Neurocognitive Disorders: milder forms of cognitive, behavior and motor dysfunctions increasing (30-60%)

HIV-Associated Neurocognitive Disorders



Antiretroviral therapy

Table 1 Revised CNS penetration-effectiveness (CPE) ranking (reprinted with permission from IAS–USA. Letendre et al. [18]. Updates available at: <http://www.iasusa.org>)

| Antiretroviral drug class ^a | 4 | 3 | 2 | 1 |
|--|---------------------|-------------------------|----------------------|----------------------|
| NRTI | Zidovudine | Abacavir | Didanosine | Tenofovir |
| | | Emtricitabine | Lamivudine | Zalcitabine |
| NNRTI | Nevirapine | Delavirdine | Stavudine | |
| | | Efavirenz | Etravirine | |
| PI | Indinavir/ritonavir | Darunavir/ritonavir | Atazanavir | Nelfinavir |
| | | Fosamprenavir/ritonavir | Atazanavir/ritonavir | Ritonavir |
| | | Indinavir | Fosamprenavir | Saquinavir |
| | | Lopinavir/ritonavir | | Saquinavir/ritonavir |
| Entry/fusion inhibitors | | Maraviroc | | Tipranavir/ritonavir |
| Integrase strand transfer inhibitors | | Raltegravir | | Enfuvirtide |

NNRTI non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside reverse transcriptase inhibitor, *PI* protease inhibitor

^a Larger numbers reflect estimates of better penetration or effectiveness in the CNS

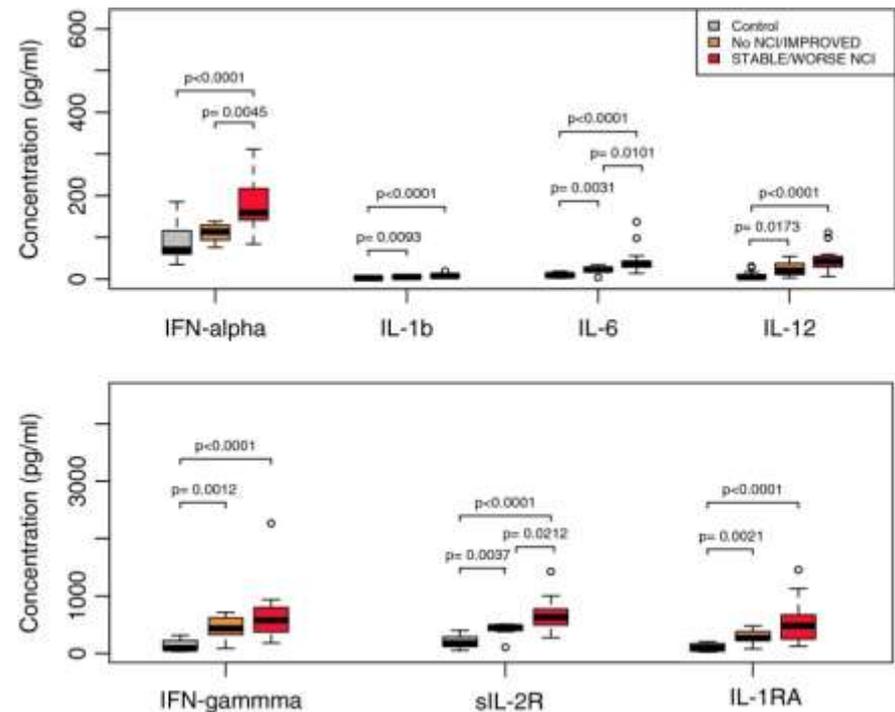
Biomarkers indicating Progression Towards HAND

- Inflammatory biomarkers in a small cohort have been studied in plasma/serum looking for association with HAND

- CXCL9, CXCL10, sIL-2r, IFN- α 2b, IL-6**

- Limitation of Study:**

- Study limits in size (40)*
- Co-morbidity association*

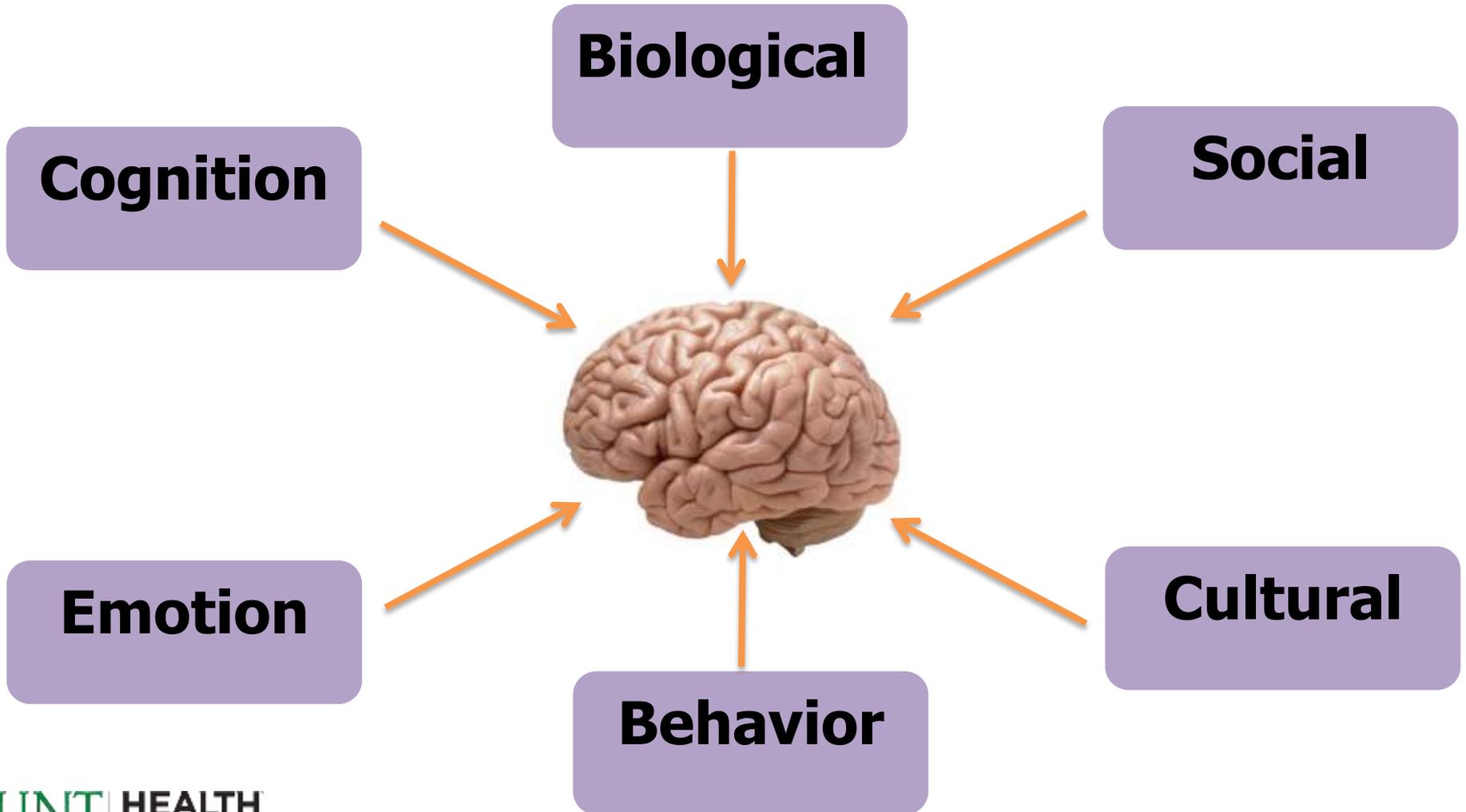


Bridge the GAP

- Study HIV Neurocognitive Biomarkers in context of sex, gender & race in a larger cohort
- To analyze peripheral and plasma profile(s) of patient cohort and correlate with socio-demographic survey, neurocognitive assessment and known surrogate biomarkers



Bio-Psycho-Sociocultural Model



Hypothesis

sCD40L & other biomarkers of inflammation
correlate with the level of neurological impairment

&

that these factors may vary in individuals living with
HIV/AIDS dependent on
their racial/ethnic background and gender

Why sCD40L?

- Soluble CD40L (sCD40L)- Novel surrogate marker for disease progression
- Co-stimulatory molecule expressed by activated T cells, B cells, myeloid cells and platelets during inflammation
- Elevated circulating sCD40L levels associated with a variety of diseases that involve immune activation such as atherosclerosis, acute coronary syndromes, type 1 diabetes & HIV-1/AIDS
- Higher level of sCD40L plasma of HIV-infected patients with cognitive impairments as compared to non-impaired controls
- Other preliminary biomarkers will be studied as well

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC120000/>
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3906985/>

Methods

- Consent
- Alcohol and Drug Testing
- Demographics Survey
- Coping Stress Test
- Computerized Neurocognitive Assessment
- Blood Draw and Process Whole Blood
- Medical History Review and Summary

Consent

- Subject consent for study and HIPAA Release of Protected Health Information
- Subject can withdraw from the study at any time without any loss or benefit that they are otherwise entitled



Alcohol & Drug testing

- Testing for drugs of abuse prior to neurocognitive assessment
- These substances alter their ability to perform the neurocognitive tests
- Exclusion of False positives (ex: Efavirenz/Atripla = THC+)



Demographics Survey

A questionnaire about:

- Gender, Age, Racial/Ethnic identification
- Education, Income, Occupation
- Marital status, Number of children, Household composition, Housing type, Number of persons residing in the household
- Place of birth, English Comprehension & Religious preference/importance
- Self reporting of PHI & Family History

Coping/Stress test

1. At this moment, do you think or feel that you are stressed out and/or unable to cope?

Yes Definitely

Yes Probably

Yes A Little

Not much

Not At All

2. In the past month have you experienced a significant life event such as (checkmark as many as applies)

- The death or loss of a loved one (e.g. divorce, missing in action, run-away)
- Money, school, or work problems (e.g. inability to pay bills or buy necessities, foreclosure, bankruptcy; self or other's job loss)
- Upsetting conflicts or confrontations with others (e.g. family, friends, neighbors, co-workers, boss, strangers)
- Bodily injury or assaults (e.g. accidents, muggings, robberies, or similar events)
- Residential move
- None of the above, but I did encounter this _____

The above questions are (in part) based on the following reference:

Alyson J. Littman, Emily White, Jessie A. Satia, Deborah J. Bowen and Alan R. Kristal, (2006). Reliability and Validity of 2 Single-Item Measures of Psychosocial Stress. *Epidemiology*, 17(4): 398-403

URL: <http://www.jstor.org/stable/20486241>

IRB APPROVED

JUL 22 2013

University of North Texas
Health Science Center

Computerized Neurocognitive Assessment

Simple tasks that will test:

- Verbal Memory
- Visual Memory
- Finger Tapping
- Symbol Digit Coding
- Stroop Test
- Shifting Attention Test
- Continuous Performance Test



| CNS Vital Signs Report | Test Date: May 02 2013 18:13:16 |
|---------------------------------------|-----------------------------------|
| Subject Reference/ID: IRB2010063100V1 | Administrator: administrator |
| Age: 52 | Language: English (United States) |
| Total Test Time: 33:40 (min:secs) | Version 3,2,0,62 |

| Patient Profile: | Percentile Range | | | | > 74 | 25 - 74 | 9 - 24 | 2 - 8 | < 2 |
|----------------------------|----------------------|----------------|------------|------|-------|----------|-------------|---------|----------|
| | Standard Score Range | | | | > 109 | 90 - 109 | 80 - 89 | 70 - 79 | < 70 |
| Domain Scores | Subject Score | Standard Score | Percentile | VI** | Above | Average | Low Average | Low | Very Low |
| Neurocognition Index (NCI) | NA | 75 | 5 | Yes | | | | x | |
| Composite Memory | 86 | 77 | 6 | Yes | | | | x | |
| Verbal Memory | 44 | 74 | 4 | Yes | | | | x | |
| Visual Memory | 42 | 90 | 25 | Yes | x | | | | |
| Psychomotor Speed | 149 | 88 | 21 | Yes | | | x | | |
| Reaction Time* | 783 | 82 | 12 | Yes | | | x | | |
| Complex Attention* | 17 | 67 | 1 | Yes | | | | | x |
| Cognitive Flexibility | 16 | 62 | 1 | Yes | | | | | x |
| Processing Speed | 38 | 80 | 9 | Yes | | | x | | |
| Executive Function | 16 | 61 | 1 | Yes | | | | | x |

Domain Dashboard: Above average domain scores indicate a standard score (SS) greater than 109 or a Percentile Rank (PR) greater than 74, indicating a high functioning test subject. Average is a SS 90-109 or PR 25-74, indicating normal function. Low Average is a SS 80-89 or PR 9-24 indicating a slight deficit or impairment. Below Average is a SS 70-79 or PR 2-8, indicating a moderate level of deficit or impairment. Very Low is a SS less than 70 or a PR less than 2, indicating a deficit and impairment. Reaction times are in milliseconds. An * denotes that "lower is better", otherwise higher scores are better. Subject Scores are raw scores calculations generated from data values of the individual subtests.

VI** - Validity Indicator: Denotes a guideline for representing the possibility of an invalid test or domain score. "No" means a clinician should evaluate whether or not the test subject understood the test, put forth their best effort, or has a clinical condition requiring further evaluation.

| Verbal Memory Test (VBM) | Score | Standard | Percentile | |
|----------------------------|-------|----------|------------|---|
| Correct Hits - Immediate | 9 | 78 | 7 | Verbal Memory test: Subjects have to remember 15 words and recognize them in a field of 15 distractors. The test is repeated at the end of the battery. The VBM test measures how well a subject can recognize, remember, and retrieve words e.g. exploit or attend liberal representations or attribute. "Correct Hits" refers to the number of target words recognized. Low scores indicate verbal memory impairment. |
| Correct Passes - Immediate | 15 | 110 | 75 | |
| Correct Hits - Delay | 5 | 65 | 1 | |
| Correct Passes - Delay | 15 | 110 | 75 | |
| Visual Memory Test (VIM) | Score | Standard | Percentile | |
| Correct Hits - Immediate | 8 | 70 | 2 | Visual Memory test: Subjects have to remember 15 geometric figures, and recognize them in a field of 15 distractors. The test is repeated at the end of the battery. The VIM test measures how well a subject can recognize, remember, and retrieve geometric figures e.g. exploit or attend symbolic or spatial representations. "Correct Hits" refers to the number of target figures recognized. Low scores indicate visual memory impairment. |
| Correct Passes - Immediate | 12 | 105 | 63 | |
| Correct Hits - Delay | 11 | 100 | 50 | |
| Correct Passes - Delay | 11 | 101 | 53 | |
| Finger Tapping Test (FTT) | Score | Standard | Percentile | |
| Right Taps Average | 56 | 98 | 45 | The FTT is a test of motor speed and fine motor control ability. There are three rounds of tapping with each hand. The FTT test measures the speed and the number of finger-taps with each hand. Low scores indicate motor slowness. Speed of manual motor activity varies with handedness. Most people are faster with their preferred hand but not always. |
| Left Taps Average | 54 | 97 | 42 | |
| Symbol Digit Coding (SDC) | Score | Standard | Percentile | |
| Correct Responses | 39 | 81 | 10 | The SDC test measures speed of processing and draws upon several cognitive processes simultaneously, such as visual scanning, visual perception, visual memory, and motor functions. Errors may be due to impulsive responding, misperception, or confusion. |
| Errors* | 1 | 99 | 47 | |

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| Stroop Test (ST) | Score | Standard | Percentile | |
|-----------------------------------|-------|----------|------------|---|
| Simple Reaction Time* | 533 | 64 | 1 | The ST measures simple and complex reaction time, inhibition / distribution, mental flexibility or directed attention. The ST helps assess how well a subject is able to adapt to rapidly changing and increasingly complex set of directions. Prolonged reaction times indicate cognitive slowing / impairment. Errors may be due to impulsive responding, misperception, or confusion. |
| Complex Reaction Time Correct* | 709 | 84 | 14 | |
| Stroop Reaction Time Correct* | 857 | 84 | 14 | |
| Stroop Commission Errors* | 0 | 110 | 75 | |
| Shifting Attention Test (SAT) | Score | Standard | Percentile | |
| Correct Responses | 32 | 65 | 1 | The SAT measures executive function or how well a subject recognizes set shifting (mental flexibility) and abstraction (rules, categories) and manages multiple tasks simultaneously. Subjects have to adjust their responses to randomly changing rules. The best scores are high correct responses, few errors and a short reaction time. Normal subjects may be slow but accurate, or fast but not so accurate. Attention deficit may be apparent. |
| Errors* | 16 | 63 | 1 | |
| Correct Reaction Time* | 1388 | 74 | 4 | |
| Continuous Performance Test (CPT) | Score | Standard | Percentile | |
| Correct Responses | 39 | 64 | 1 | The CPT measures sustained attention or vigilance and choice reaction time. Most normal subjects obtain near-perfect scores on this test. A long response time may suggest cognitive slowing and/or impairment. More than 2 errors (total) may be clinically significant. More than 4 errors (total) indicate attentional dysfunction. |
| Omission Errors* | 1 | 64 | 1 | |
| Commission Errors* | 0 | 107 | 68 | |
| Choice Reaction Time Correct* | 473 | 87 | 19 | |

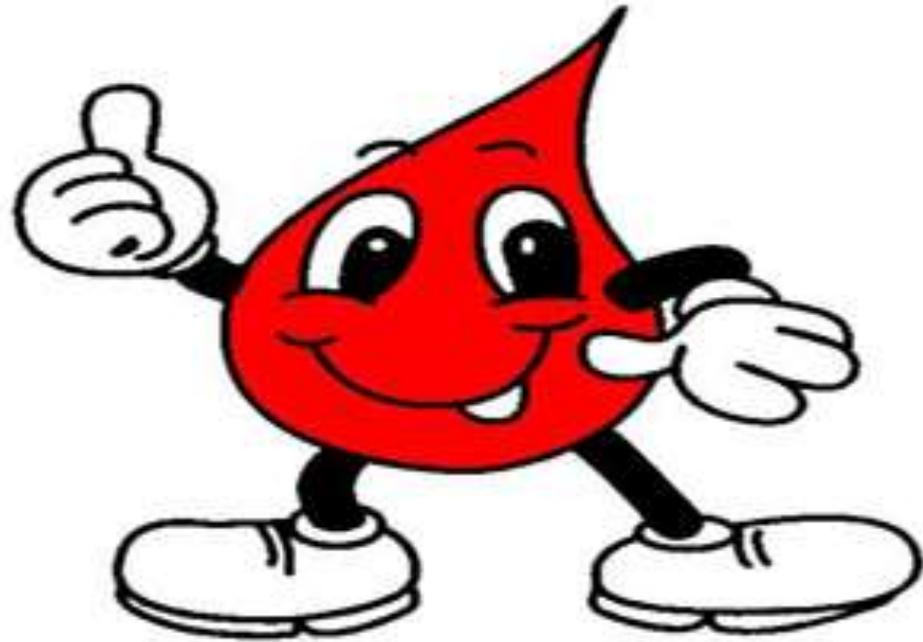
Test results for research only

Validity Index

- If No – subject repeats the test once
- Indicates subject
 - May not have understood the instructions
 - Didn't try hard enough according to the software
 - May not be capable of performing the tested assessment

Blood Draw and Process Whole Blood Samples

- Within 30 minutes of blood draw we process the blood:
- Plasma & PBMCs for cytopins & *in vitro* culture
- Cellular RNA, protein, chromosomal & extra-chromosomal DNA, and culture supernatants



Medical History Review & Summary

- Relevant PHI reviewed for research purposes
 - Date of HIV-1 diagnosis/seroconversion & timeline of progression
 - Viral loads & T-cell counts
 - Current and past Drug/Anti-retroviral therapies
 - History of risk factors
 - Other central nervous system diseases that may influence our findings

Patient Cohort

| Demographics-Study Visit Completed | Expected Male | Current Male | Expected Female | Current Female |
|------------------------------------|---------------|--------------|-----------------|----------------|
| Hispanic | 20 | 7 | 20 | 3 |
| African American | 20 | 9 | 20 | 4 |
| Caucasian | 20 | 21 | 20 | 3 |

| Demographics (Age) | 30-49 | 50-59 | 60-69 |
|--------------------|-------|-------|-------|
| Age | 17 | 25 | 4 |

Demographics

| Demographics Marital Status | Frequency N=47 | Demographics Education Level | Frequency N=47 |
|--------------------------------|-------------------|---------------------------------|-------------------|
| Divorced | 4 | 9-11 grades | 4 |
| Married/Not together | 1 | Graduate School | 1 |
| Married/Living with someone | 17 | High School Graduate | 17 |
| Separated | 1 | Some College | 1 |
| Single | 23 | Trade School -1 to 2 year | 23 |
| Widowed | 1 | Trade School - 4 years | 1 |

Virological Parameters

| Viral Parameters | 0-10 N=43 | 10-20 N=43 | 20-30 N=43 | Average (years) |
|-------------------------------------|------------------------|-------------------------|-------------------------|--------------------------------|
| No of Years Since Diagnosed (years) | 10 | 15 | 18 | 16 |
| Viral Parameters | 50-399 N=41 | 400-699 N=41 | >700 N=41 | Average (cells/mm3) |
| CD4 count (cells/mm3) | 11 | 19 | 11 | 590 |

Co-Morbidities

| Co-Morbidities | Frequency N=47 |
|-------------------|----------------|
| CNS Co-Infections | 24 |
| Cardiovascular | 32 |
| CNS | 22 |
| Respiratory | 29 |
| Others | 16 |
| Cancer | 4 |

Plasma Biomarkers vs Neurocognitive tests

| | Psychomotor speed domain | Processing Speed | CD4 count | No of years since diagnosed | Verbal Memory | Reaction time | Complex Attention | Visual Memory | Cognitive Flexibility | Memory Domain | Executive Function | Neurocognitive Index (NCI) |
|------------------|--------------------------|------------------|-----------|-----------------------------|---------------|---------------|-------------------|---------------|-----------------------|---------------|--------------------|----------------------------|
| Validation (NCI) | +0.66 | +0.57 | | | +0.47 | Positive | +0.93 | +0.56 | +0.87 | +0.58 | +0.87 | 1 |
| Biomarkers | | | | | | | | | | | | |
| TIMP-1 | (-0.35) | (-0.27) | (-0.14) | +0.38 | (-0.39) | (-0.27) | (-0.28) | (-0.16) | (-0.25) | (-0.29) | (-0.25) | (-0.33) |
| IL-13 | +0.24 | | | +0.28 | (-0.22) | | | (-0.20) | +0.27 | (-0.22) | | |
| IL-2 | (-0.35) | (-0.49) | | | | | (-0.21) | | (-0.21) | | (-0.25) | |
| TNF- α | | | (-0.35) | +0.28 | (-0.52) | +0.30 | | | | (-0.30) | | |
| GRO α | (-0.22) | (-0.26) | +0.24 | +0.23 | | | | | | | | |
| IL-6 | | +0.35 | | +0.30 | | +0.24 | | | | | | |
| IL-12p70 | +0.37 | +0.28 | | | | | | | | | | +0.24 |
| Eotaxin | (-0.20) | | +0.23 | | | (-0.20) | | | | | | |
| IP-10 | | | (-0.23) | +0.28 | | | (-0.20) | | | | | |

Summary

- An IRB protocol was established for recruitment of patients
- Standardized procedures and protocols were established to conduct study visit
- ≈114 number of patients were referred and 47 continued with the study
- Approval of additional sites for subject recruitment are currently in progress
- Within the current subject population, trends were obtained for few of the immune biomarkers that may reach statistical significance upon analyzing the entire cohort
- With additional subject recruitment we will address health disparities in HAND incidence and hope to deliver an intervention biomarker test indicative of HAND between different racial/ethnic backgrounds with HIV infection

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Thank You!

