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

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

New HIV Infections Among Women & Girls
- Black: 64%
- Latina: 15%
- White: 18%
- Other: 3%

U.S. Female Population
- White: 63%
- Latina: 16%
- Black: 13%
- Other: 8%

NOTES: Data are estimates among those ages 13 and older and do not include U.S. dependent areas.

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%)

Development of Neurocognitive Disorders in HIV/AIDS: http://dx.doi.org/10.2147/NBHIV.S7170
HIV-Associated Neurocognitive Disorders

- HAD
- Minor Neurocognitive Disorder
- Asymptomatic Neurocognitive Impairment
- HIV-associated Neurocognitive Disorder

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)

<table>
<thead>
<tr>
<th>Antiretroviral drug class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Zidovudine</td>
<td>Abacavir</td>
<td>Didanosine</td>
<td>Tenofovir</td>
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<tr>
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<td>Emtricitabine</td>
<td>Lamivudine</td>
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<td>Zalcitabine</td>
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<td>NNRTI</td>
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<td>Delavirdine</td>
<td>Etravirine</td>
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<td>Efavirenz</td>
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<td>PI</td>
<td>Indinavir/ritonavir</td>
<td>Darunavir/ritonavir</td>
<td>Atazanavir</td>
<td>Nelfinavir</td>
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<td></td>
<td>Fosamprenavir/ritonavir</td>
<td>Atazanavir/ritonavir</td>
<td>Ritonavir</td>
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<tr>
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<td>Indinavir</td>
<td>Lopinavir/ritonavir</td>
<td>Fosamprenavir</td>
<td>Saquinavir</td>
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<td></td>
<td></td>
<td>Saquinavir/ritonavir</td>
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<td></td>
<td></td>
<td></td>
<td>Tipranavir/ritonavir</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enfuvirtide</td>
</tr>
</tbody>
</table>

NRTI 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

- Biological
- Social
- Cultural
- Behavior
- Emotion
- Cognition
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:
URL: http://www.jstor.org/stable/20486241

IRB APPROVED
JUL 2 2 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
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 cytospins & *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

<table>
<thead>
<tr>
<th>Demographics-Study Visit Completed</th>
<th>Expected Male</th>
<th>Current Male</th>
<th>Expected Female</th>
<th>Current Female</th>
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<tbody>
<tr>
<td>Hispanic</td>
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<td>7</td>
<td>20</td>
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<tr>
<td>African American</td>
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<td>9</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Caucasian</td>
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<td>21</td>
<td>20</td>
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<table>
<thead>
<tr>
<th>Demographics (Age)</th>
<th>30-49</th>
<th>50-59</th>
<th>60-69</th>
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<tbody>
<tr>
<td>Age</td>
<td>17</td>
<td>25</td>
<td>4</td>
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## Demographics

<table>
<thead>
<tr>
<th>Marital Status</th>
<th>Frequency N=47</th>
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<tr>
<td>Divorced</td>
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<tr>
<td>Married/Not together</td>
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<tr>
<td>Married/Living with someone</td>
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<tr>
<td>Separated</td>
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<tr>
<td>Single</td>
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<td>Widowed</td>
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<table>
<thead>
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<th>Education Level</th>
<th>Frequency N=47</th>
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<tr>
<td>9-11 grades</td>
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<tr>
<td>Graduate School</td>
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<td>High School Graduate</td>
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<tr>
<td>Some College</td>
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<tr>
<td>Trade School -1 to 2 year</td>
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<tr>
<td>Trade School - 4 years</td>
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## Virological Parameters

<table>
<thead>
<tr>
<th>No of Years Since Diagnosed (years)</th>
<th>0-10 N=43</th>
<th>10-20 N=43</th>
<th>20-30 N=43</th>
<th>Average (years)</th>
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<tbody>
<tr>
<td>10</td>
<td>10</td>
<td>15</td>
<td>18</td>
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<table>
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<th>Viral Parameters</th>
<th>50-399 N=41</th>
<th>400-699 N=41</th>
<th>&gt;700 N=41</th>
<th>Average (cells/mm3)</th>
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<tbody>
<tr>
<td>CD4 count</td>
<td>11</td>
<td>19</td>
<td>11</td>
<td>590</td>
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Co-Morbidities

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<tr>
<td>CNS Co-Infections</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>CNS</td>
<td>22</td>
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<tr>
<td>Respiratory</td>
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<tr>
<td>Others</td>
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<tr>
<td>Cancer</td>
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## Plasma Biomarkers vs Neurocognitive tests

<table>
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<tr>
<th>Validation (NCI)</th>
<th>Psychomotor speed domain</th>
<th>Processing Speed</th>
<th>CD4 count</th>
<th>No of years since diagnosed</th>
<th>Verbal Memory</th>
<th>Reaction time</th>
<th>Complex Attention</th>
<th>Visual Memory</th>
<th>Cognitive Flexibility</th>
<th>Memory Domain</th>
<th>Executive Function</th>
<th>Neurocognitive Index (NCI)</th>
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<tbody>
<tr>
<td>+0.66</td>
<td>+0.57</td>
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<td></td>
<td></td>
<td>Positive</td>
<td>+0.93</td>
<td>+0.56</td>
<td>+0.87</td>
<td>+0.58</td>
<td>+0.87</td>
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### Biomarkers

<table>
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<tr>
<th>Biomarkers</th>
<th>Psychomotor speed domain</th>
<th>Processing Speed</th>
<th>CD4 count</th>
<th>No of years since diagnosed</th>
<th>Verbal Memory</th>
<th>Reaction time</th>
<th>Complex Attention</th>
<th>Visual Memory</th>
<th>Cognitive Flexibility</th>
<th>Memory Domain</th>
<th>Executive Function</th>
<th>Neurocognitive Index (NCI)</th>
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<tbody>
<tr>
<td>TIMP-1</td>
<td>(-0.35)</td>
<td>(-0.27)</td>
<td>(-0.14)</td>
<td>+0.38</td>
<td>(-0.39)</td>
<td>(-0.27)</td>
<td>(-0.28)</td>
<td>(-0.16)</td>
<td>(-0.25)</td>
<td>(-0.29)</td>
<td>(-0.25)</td>
<td>(-0.33)</td>
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<td>IL-13</td>
<td>+0.24</td>
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<td>Positive</td>
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<td>+0.56</td>
<td>+0.87</td>
<td>+0.58</td>
<td>+0.87</td>
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<td>TNF-α</td>
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<tr>
<td>GROα</td>
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<td>IL-6</td>
<td>+0.35</td>
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<td>+0.93</td>
<td>+0.56</td>
<td>+0.87</td>
<td>+0.58</td>
<td>+0.87</td>
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<tr>
<td>IP-10</td>
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<td>Positive</td>
<td>+0.93</td>
<td>+0.56</td>
<td>+0.87</td>
<td>+0.58</td>
<td>+0.87</td>
</tr>
</tbody>
</table>
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
Acknowledgements

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**Samaritan House**

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