Neurocognitive Functioning in HIV+ and HIV-
Resource Limited Settings

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Overview

- Background
  - Why resource limited settings?
  - Why Women?
  - Why HIV Associated Neurocognitive Disorders (HAND)?
- The International Neurological Study: ACTG 5199
  - Design
  - Results
- The International Neurocognitive Normative Study: ACTG 5271
  - Design
  - Results – preliminary
- Combining and Applying 5271 to 5199 - preliminary
- Context
Why Resource Limited Settings?

- The Virus is different
Origins

- HIV predecessor ~1625
- Zoonotic transmission
- Chimpanzee to human
  - SIVcpzPTT-> HIV-1 group M
  - HIV-1 group M 1920-1930’s
Why Resource Limited Settings?

- The Burden is greater
Adults and children estimated to be living with HIV | 2013

Total: 35.0 million [33.2 million – 37.2 million]
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### Estimated adult and child deaths from AIDS | 2013

<table>
<thead>
<tr>
<th>Region</th>
<th>Estimated Deaths</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>1.1 million</td>
<td>[1.0 million – 1.3 million]</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>53 000</td>
<td>[43 000 – 69 000]</td>
</tr>
<tr>
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<tr>
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<td>[23 000 – 34 000]</td>
</tr>
<tr>
<td>Caribbean</td>
<td>11 000</td>
<td>[8300 – 14 000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>47 000</td>
<td>[39 000 – 75 000]</td>
</tr>
<tr>
<td>Total</td>
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Estimated adult and child deaths from AIDS | 2013

- Sub-Saharan Africa: 1.1 million [1.0 million – 1.3 million]
  - Middle East & North Africa: 15 000 [10 000 – 21 000]
  - North America and Western and Central Europe: 27 000 [23 000 – 34 000]
  - Latin America: 47 000 [39 000 – 75 000]
  - Caribbean: 11 000 [8300 – 14 000]

- Eastern Europe & Central Asia: 53 000 [43 000 – 69 000]

- Asia and the Pacific: 250 000 [210 000– 290 000]

- Total: 1.5 million [1.4 million – 1.7 million]
Estimated number of adults and children newly infected with HIV | 2013

- **Middle East & North Africa**: 25,000 [14,000 – 41,000]
- **Sub-Saharan Africa**: 1.5 million [1.3 million – 1.6 million]
- **Eastern Europe & Central Asia**: 110,000 [86,000 – 130,000]
- **Latin America**: 94,000 [71,000 – 170,000]
- **Caribbean**: 12,000 [9,400 – 14,000]
- **Asia and the Pacific**: 350,000 [250,000 – 510,000]
- **North America and Western and Central Europe**: 88,000 [44,000 – 160,000]
- **Caribbean**: 12,000 [9,400 – 14,000]

**Total**: 2.1 million [1.9 million – 2.4 million]
Estimated number of adults and children newly infected with HIV | 2013

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Estimated number of adults and children newly infected with HIV | 2013

Total: 2.1 million [1.9 million – 2.4 million]
About 6 000 new HIV infections a day in 2013

- About 68% are in Sub Saharan Africa
- About 700 are in children under 15 years of age
- About 5 200 are in adults aged 15 years and older, of whom:
  - almost 47% are among women
  - about 33% are among young people (15-24)
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Overview

- Background
  - Why resource limited settings?
    - Burden is greater
    - Virus is different
  - Why Women?
Every minute, a young woman is newly infected with HIV.

As a result of their lower economic, socio-cultural status in many countries, women and girls are disadvantaged when it comes to negotiating safe sex, accessing HIV prevention information and services.

11-45%
Between 11% and 45% of adolescent girls report that their first sexual experience was forced.¹

Women living with HIV are more likely to experience violations of their sexual and reproductive rights, for example forced sterilisations.²

2x
Globally, young women aged 15-24 are most vulnerable to HIV with infection rates twice as high as in young men, and accounting for 22% of all new HIV infections.³

Two-thirds of the world’s 796 million literate adults are women.⁴

Only one female condom is available for every three women in Sub-Saharan Africa.⁵

In many countries customary practices on property and inheritance rights further increase women’s vulnerability to AIDS and reduce their ability to cope with the disease and its impact.

More than one third of women aged 15-24 years in the developing world marry before they are 18 years old.⁶

More than 30% of young women have comprehensive and correct knowledge on HIV.⁷

Globally, less than 30% of pregnant women are provided with antiretroviral therapy (ART) for HIV.⁸

32/94
Women living with HIV are regularly involved in formal processes to plan and review the national HIV response to HIV in 32 out of 94 countries.⁹

References:
1. UNAIDS World AIDS Day report 2011
2. Gender dynamics, UNAIDS, 2015
3. AIDS in women and girls: still agency need for action, 2012
4. Gender dynamics, UNAIDS, 2015
8. UNAIDS Fact Sheet: Comprehensive Condom Programming - July 2010
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HIV is the leading cause of death of women of reproductive age.
Globally, young women aged 15-24, are most vulnerable to HIV with infection rates twice as high as in young men, and accounting for 22% of all new HIV infections.
Overview

- **Background**
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    - Burden is greater
    - Virus is different
  - Why Women?
  - Why assess for HAND?
Why assess for HAND?

- Highly prevalent even with treatment
  - ALLRT
    - 39% mild impairment
    - 21% developed impairment after baseline
  - CHARTER
    - 40% neurocognitive impairment (incidental confounds)

- Impact on
  - Mortality
  - Productivity
  - Quality of life
Overview

- **Background**
  - Virus is different and burden is greater in RLS
  - Women heavily impacted in RLS
  - HAND is prevalent
International Neurological Study
AIDS Clinical Trials Group 5199

- First international neurological clinical trial in HIV for ACTG/NIMH
- Cross NIH collaboration NIMH-NIAID
- Multinational collaboration
Methods

• Sample size 860
  • (80 subjects * 11 sites = 880)

• Population and eligibility
  • Co enrolled in ACTG 5175
  • CD4+ < 300
  • Treatment naive

• Study regimen or intervention
  • Observational – parent 5175
    ■ 2 NRTI + NNRTI (3TC/ZDV/EFV)
    ■ 2 NRTI + PI (FTC/ddI-EC/ATV)
    ■ 2 NRTI + NNRTI (FTC/TDF/EFV)

  • WHO recommended first line for RLS
Evaluations

- Neurological Exam
  - Developed by team for the study
  - Reviewed by Sites, Field Tested, Revised
  - Site visits/training, Video training, Web training

- Neuropsychological Exam
  - Brief
    - Language – 11 sites, many languages at some sites
    - Literacy/numeracy issues
  - Timed Gait
  - Fingertapping
  - Grooved Pegboard
  - Verbal Fluency
  - Changes from baseline to follow-up
Sites

- Rio de Janeiro, Brazil
- Porto Alegre, Brazil
- Chennai, India
- Pune, India
- Blantyre, Malawi
- Lilongwe, Malawi
- Lima, Peru
- Chiang Mai, Thailand
- Harare, Zimbabwe
- Durban, South Africa
- Johannesburg, South Africa
Neurocognitive/Neurological

- Overall baseline
  - Between Country significant variation expected
    - Sites, populations, cultures, HIV subtypes,
  - Baseline between tx arms very similar

- Longitudinal follow up
  - Treatment Arms equal
    - Improved overall abnormality
    - Improved CNS dysfunction
    - Improved peripheral neuropathy
    - Neurocognition improved in all arms
Median (Q1, Q3) Changes in Grooved Pegboard Non-Dom from Baseline by Treatment
Neurocognitive - gender

- Overall baseline
  - Few gender differences
  - Baseline between arms similar

- Longitudinal follow up
  - Few gender differences
    - Timed Gait, Fingertapping
  - Treatment Arms equal
    - Neurocognition significantly improved in all arms

- But what about impairment?
- No context to put normal in
The International Neurocognitive Normative Study: ACTG 5271

- Lack of infrastructure
- No normative data
- Unable to assess
  - Normal versus impaired
The International Neurocognitive Normative Study: ACTG 5271

- 2400 HIV- subjects stratified by
  - Gender, Age, Education, Country
    - VCT sites
    - Neuropsychological tests expanded
    - Neurological exam
    - 6 month follow up
Baseline Gender differences

- 5271 normative data
  - 1200 women
  - 1200 men
  - 240 at each of 10 sites
- Strata
  - Education x 2 (10 years)
  - Age x 2 (35 years)
  - Gender x 2
    - Timed Gait, Fingertapping small differences
Grooved Pegboard Dominant raw by gender

- Mean
- Min-Max

sex

- f
- m
Grooved Pegboard Nondominant raw by gender

Grooved pegboard nondominant raw

sex

Mean

Min-Max
Semantic Verbal Fluency by gender

<table>
<thead>
<tr>
<th>sex</th>
<th>f</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min</td>
<td>max</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>30</td>
</tr>
</tbody>
</table>

Semantic Verbal Fluency
Timed Gait raw by gender

<table>
<thead>
<tr>
<th>Sex</th>
<th>f</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Min-Max</td>
<td>14</td>
<td>9</td>
</tr>
</tbody>
</table>
Fingertapping Dominant raw by gender

<table>
<thead>
<tr>
<th>sex</th>
<th>f</th>
<th>m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Min-Max</td>
<td>25</td>
<td>50</td>
</tr>
</tbody>
</table>

Fingertapping dominant raw
Fingertapping nondominant raw by gender

<table>
<thead>
<tr>
<th>Sex</th>
<th>Mean</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>m</td>
<td></td>
<td></td>
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</table>
Baseline 5199 z scores

- Create norms for z scoring
  - 5271 HIV- raw test scores
  - Gender, Age, Education, Country
  - Applied to 5199 HIV+ S’s scores
    - Gender
Grooved Pegboard Nondominant z by gender
Semantic Verbal Fluency z score by gender

Mean
Min-Max

-3  -2  -1  0  1  2

Semantic Verbal Fluency

m  f

sex

Mean
Min-Max

02/22/2015  K Robertson, 5th International Workshop on HIV and Women
Timed Gait z score by gender

<table>
<thead>
<tr>
<th>Sex</th>
<th>Mean</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>f</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

The graph shows the Timed Gait z score for males (m) and females (f) with mean and min-max values indicated.
Fingertapping Dominant z score by gender

<table>
<thead>
<tr>
<th>sex</th>
<th>m</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Min-Max</td>
<td>-0.7 to -0.3</td>
<td>-0.7 to -0.3</td>
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</table>
Fingertapping nondominant z score by gender

<table>
<thead>
<tr>
<th>sex</th>
<th>m</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min-Max</td>
<td>-3</td>
<td>-2</td>
</tr>
<tr>
<td>Mean</td>
<td>-1</td>
<td>0</td>
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Prevalence of Neurocognitive Impairment
Baseline ART Naive

- Normal, 54%
- Mild, 25%
- Moderate, 17%
- Severe, 3%
Neurocognitive Impairment over time
Baseline Naive and follow up on ART

Week

Percent

Normal
Mild
Moderate
Severe

normal%
imd%
moderate%
severe%
Neurocognitive Impairment

**Baseline Prevalence**
- 54% normal
- 25% Mild
- 17% Moderate
- 3% Severe

**Improved with ART**
- 46% baseline
- 38% week 24
- 39% week 48
- 33% week 72
- 29% Week 96
- 27% Week 120
- 31% Week 144
- 28% Week 168
- 22% Week 192

No gender differences in Impairment
Neurocognitive

- Preliminary findings
- Neurocognitive Impairment
  - No gender differences
- ART treatment and neurocognition
  - No gender differences
- Individual test gender differences eg
  - Timed gait, Fingertapping
Gender

- The Gender difference hypothesis
  - Tannen 1991, stereotypes
  - Women are from Venus
    - Tender, cooperative, submissive, emotional, talkative, verbal
  - Men are from Mars
    - Tough, competitive, dominant, stoic, quiet, mathematical
Gender

- Often cited meta-analyses supporting
  - Math
  - Aggression
  - Self-esteem
  - Personality

- Relatively small differences found
Gender

- The Gender similarities hypothesis
  - Hyde 2005
  - Are females and males really that different?
    - Salient characteristic in social perception
      - Age, race
    - Anatomical/Biological differences
    - Assume psychological differences
    - Illusion that cultural stereotypes are correct
Gender

- **Metasynthesis**
  - Meta-analysis of meta-analyses
  - Second order meta-analysis
  - (Zell, Krizan, Teeter, 2015)
  - 106 meta-analyses, 386 effects
    - 12,238,667 participants in
    - Over 20,000 studies
  - Overall magnitude small
    - Cohens d = .21
Cohen's $d$: 0.2

Interpretation:

- Cohen's $U_1$: 57.93%
- % Overlap: 92.03%
- Probability of Superiority: 55.62%
- Number Needed to Treat¹: 16.5
Neurocognitive Impairment

- Prevalent in RLS
- No differences in gender
  - Some differences on tests
- Both women and men impacted
Future

- Build Infrastructure
- Early treatment
- Novel CNS treatment