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Neurocognitive Impairment in Diverse Resource Limited Settings: The International Neurological Study ACTG A5199 and The International Neurocognitive Normative Study ACTG A5271

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ABSTRACT

Background.
While neurocognitive impairment in HIV remains prevalent despite potent antiretroviral therapy (ART), there is a lack of infrastructure for conducting neurological research in resource limited settings (RLS), including normative data needed for clinical interpretation. A5271 provided training of clinical site personnel and collected normative comparison data. Here we provide estimates of neurocognitive impairment in seven RLS countries for HIV+ ART-naive participants from ACTG 5199.
Methods.
We provided training for site personnel and collected normative comparison data on 2400 high risk HIV negatives from 10 VCT sites aligned with ACTG PEARLS (5175) in seven countries: Brazil (n=240), India (n=480), Malawi (n=481), Peru (n=239), South Africa (480), Thailand (n=240) and Zimbabwe (n=240) which was then utilized to create mild, moderate and severe mpairment ratings. Associations were estimated from linear and logistic regression models using generalized estimating equations.
Results.
Of the 860 HIV+ enrolled in A5199, 54% had no neurocognitive impairment at baseline (Table 1). Mild neurocognitive impairment was found in 25%, moderate in 17% and severe in 3%. With the initiation of ART, the odds of neurocognitive impairment reduced 12% (95% CI: 9%, 14%) for every 24 weeks (p<.0001). At week 24, 62% were normal and at week 168, 72% were normal. At week 168, moderate reduced to 6% and severe to 0.5%. Mild impairment dropped slightly, and then remained at about 18% out to week 168. Analyses indicated that drop out did not account for improvement. There were no differences between treatment arms. There were differences between countries in overall neurocognitive performance as expected (p<.0001).
Conclusions.
There was substantial prevalence of neurocognitive impairment at baseline in HIV+ ART naive participants in diverse RLS. With ART, there were significant overall reductions in neurocognitive impairment over time, especially in those with moderate and severe impairments. The observed changes with ART may reflect both improvement and learning effect. ART in RLS led to reductions in neurocognitive impairment, and would likely lead to improved productivity and quality of life. A5271 provides infrastructure in diverse RLS, a much needed resource for clinicians and researchers conducting neurological and neuropsychological assessments.

INTRODUCTION

While neurocognitive impairment in HIV remains prevalent despite potent antiretroviral therapy (ART), there is a lack of infrastructure for conducting neurological research in resource limited settings (RLS), including normative data needed for clinical interpretation. ACTG 5271:the International Neurocognitive Normative Study provided training of clinical site personnel and collected normative comparison data in 2400 HIV- participants.

We previously reported the first multinational neurological clinical trial of ART in RLS, ACTG 5199, the International Neurological Study. Here we report the application of the normative data from ACTG 5271 as applied to ACTG A5199 to provide estimates of neurocognitive impairment in RLS.

METHODS

Subjects

5199 HIV+ ART
- Antiretroviral naïve
- CD4+ < 300 cells/mm^3
- 860 subjects enrolled
- ART (5175) Treatment Regimens**:**
  - Arm 1A - EFV/3TC/ZDV, n=289
  - Arm 1B - FTC/ATV/ddIEC, n=293
  - Arm 1C - EFV/FTC/TDF, n=278

5271 HIV- Normative
- HIV- within 30 days
- Presenting to VCT
- 2400 subjects enrolled
- Stratified by
  - Site, age (<35,35+), education (<10, 10+), gender

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

Demographics 5199
- Gender
  - Male 404 (46%)
  - Female 456 (53%)
- Age Mdn 34 yrs

Education Mdn 10 yrs

Demographics 5271
- Gender
  - Male 1200 (50%)
  - Female 1200 (50%)
- Age Mdn 35 yrs
- Education Mdn 10 yrs

Neuropsychological Exam

5199
- Timed Gait
- Grooved Pegboard
- Finger Tapping
- Semantic Verbal Fluency

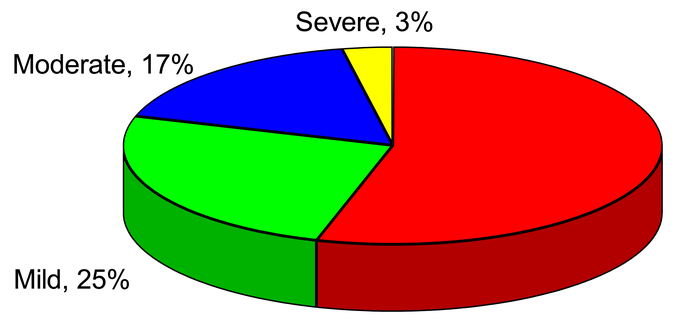
5271 additions
- Hopkins verbal learning
- Color Trails 1 and 2
- Digit Symbol

Impairment Ratings

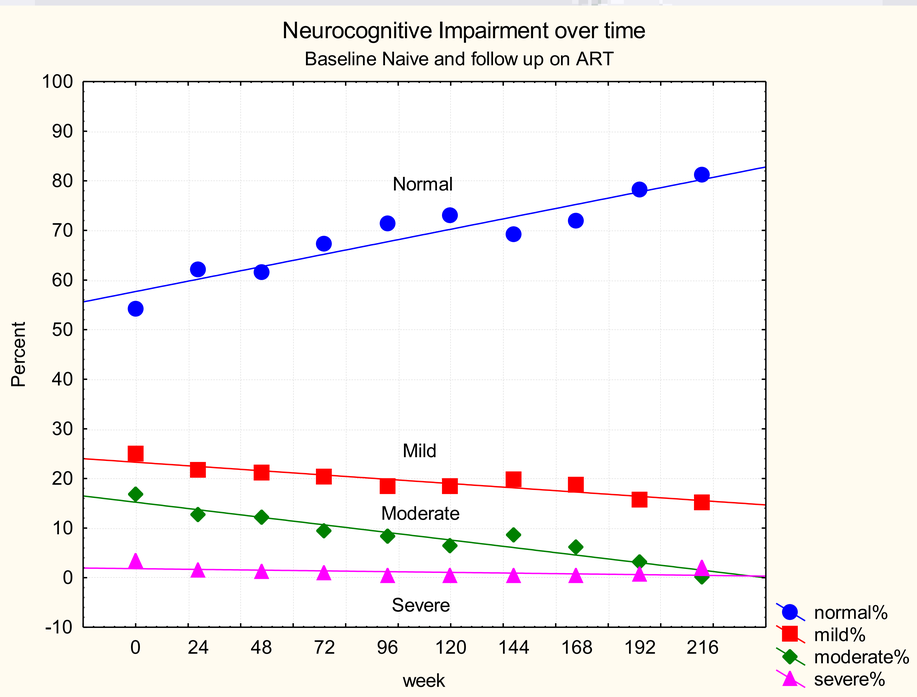
Mild: -1 SD below the mean on 2 tests, or 2 SDs on 1 test
Moderate: 1 SD on 3 to 4 tests, or 2 SDs on 2 tests
Severe: 1 SD on 5 tests or more, or 2 SDs on 3 tests or more

EFV- Efavirenz, 3TC-Lamivudine, ZDV- Zidovudine, FTC- Emtricitabine, ATV-Atazanavir, ddIEC- Didanosine, TDF-Tenofovir

Prevalence of Neurocognitive Impairment
Baseline ART Naive



Baseline



RESULTS

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

- **ART**
  - Reduced odds of NCI by 12% for every 24 weeks (p<.0001) on ART
- **Sustained improvement**
  - At week 168 of ART
  - Normal improved from 54% to 72%
- **No treatment differences**

With the initiation of ART, the odds of neurocognitive impairment reduced 12% (95% CI: 9%, 14%) for every 24 weeks (p<.0001) on ART. At week 24, 62% were normal and at week 168, 72% were normal. At week 168, moderate reduced to 6% and severe to 0.5%. Mild impairment dropped slightly, and then remained at about 18% out to week 168. Analyses indicated that drop out did not account for improvement. There were no differences between treatment arms. There were differences between countries in overall neurocognitive performance as expected (p<.0001).

CONCLUSIONS

- **First multinational RLS study of NCI**

This is the first multinational study addressing the prevalence of neurocognitive impairment in RLS. We found a substantial prevalence of neurocognitive impairment at baseline in HIV+ ART naïve participants in diverse RLS, consistent with US estimates.

- **NCI Prevalent**

With ART initiation, there were significant overall reductions in neurocognitive impairment over time, especially in those with moderate and severe impairments. The observed changes after ART initiation may reflect both improvement and learning effect.

- **ART improved NCI**

ART in RLS led to reductions in neurocognitive impairment, and would likely lead to improved productivity and quality of life.

- **Normative Data Resource**

A5271 provides a much needed resource for clinicians and researchers conducting neurological and neuropsychological assessments in diverse RLS.