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International Neurocognitive Normative Study: Neurocognitive Comparison Data in Diverse Resource Limited Settings: AIDS Clinical Trials Group A5271

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Summary

ACTG A5271 collected neurocognitive normative comparison test data in 2400 at-risk HIV seronegative participants from Brazil, India, Malawi, Peru, South Africa, Thailand and Zimbabwe. The participants were enrolled in strata by site (10 levels), age (2 levels), education (2 levels), and gender (2 levels). These data provide necessary normative data infrastructure for future clinical research and care in these diverse resource limited settings.

Infrastructure for conducting neurological research in resource limited settings (RLS) is limited. The lack of neurological and neuropsychological (NP) assessment, and normative data needed for clinical interpretation impede research and clinical care. Here we report on ACTG 5271, which provided neurological training of clinical site personnel, and collected neurocognitive normative comparison data in diverse settings. At 10 sites in seven RLS countries, we provided training for NP assessments. We collected normative comparison data on HIV- participants from Brazil (n=240), India (n=480), Malawi (n=481), Peru (n=239), South Africa (480), Thailand (n=240) and Zimbabwe (n=240). Participants had a negative HIV test within 30 days before standardized NP exams were administered at baseline, and 770 at six-months. Participants were enrolled in 8 strata,

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gender (female and male), education (<10 years and ≥ 10 years), and age (<35 years and ≥35 years).

Of 2400 enrolled, 770 completed the six-month follow up. As expected, significant between-country differences were evident in all the neurocognitive test scores (p<.0001). There was variation between the age, gender and education strata on the neurocognitive tests. Age and education were important variables for all tests; older participants had poorer performance and those with higher education had better performance. Women had better performance on verbal learning/memory and speed of processing tests, while men performed better on motor tests. This study provides the necessary neurocognitive normative data needed to build infrastructure for future neurological and neurocognitive studies in diverse RLS. These normative data are a much-needed resource for both clinicians and researchers.

Keywords

Neurocognitive assessment; normative comparison data; resource-limited; cognitive impairment; neuropsychological functioning

Introduction

Resource-poor, developing parts of the world continue to have the greatest burden of the human immunodeficiency virus type 1 (HIV-1) epidemic(Robertson et al., 2010; UNAIDS, updated June 2014). The central and peripheral nervous system (CNS and PNS) are directly impacted by HIV-1, likely through underlying effects of viral and immune factors(Zayyad & Spudich, 2015).

The resulting direct effects of HIV within the CNS are called HIV-Associated Neurocognitive Disorders (HAND)(Antinori et al., 2007), which includes the more severe form of HIV-associated dementia (HAD), the less severe but more prevalent HIV-associated minor neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI).

A major limitation of conducting neurocognitive research in resource limited settings is the lack of infrastructure(Robertson et al., 2010; Robertson, Liner, & Heaton, 2009). The lack of infrastructure also impedes clinical neurological care. There are no neuropsychological instruments commonly available in many resource limited settings. In addition, there are no normative comparison data which are needed to provide the basis for clinical interpretation and diagnoses in almost all resource limited settings(Robertson et al., 2009). Very few studies have gathered normative neurocognitive comparison data in resource limited settings, and these have usually been small convenience samples. Perhaps the most comprehensive study was undertaken by the World Health Organization (WHO) in the early 1990's (Maj et al., 1994). The WHO study assessed HIV-associated cognitive impairment in 602 HIV-positive and 353 HIV-negative individuals in Bangkok, Thailand; Kinshasa, Zaire; Nairobi, Kenya; and São Paolo, Brazil, and was the first multinational study to accrue and use local normative data. Neurocognitive studies based in China (Heaton et al., 2008), India (Ghate et al., 2015; Gupta et al., 2007), and Brazil (de Almeida et al., 2013) among others, have

collected small HIV- neurocognitive data for individual studies using different tests and methods.

To address the lack of infrastructure and available normative data, ACTG 5271 study was designed and conducted to provide neurocognitive normative data for resource limited settings in 10 sites across seven countries.

Methods

Sites

ACTG 5271, the International Neurocognitive Normative Comparison Study enrolled from sites that participated in ACTG A5199(Robertson et al., 2011). The international ACTG sites that participated in A5271 were located in Rio de Janeiro, Brazil; Chennai, India; Pune, India; Blantyre, Malawi; Lilongwe, Malawi; Lima, Peru; Johannesburg, South Africa; Durban, South Africa; Chiang Mai, Thailand; and Harare, Zimbabwe. The volunteers were recruited at their local health clinic, voluntary counseling and testing (VCT) center, or other HIV testing site aligned with the primary ACTG site.

Procedures

Human subject reviews and approvals by local and country specific review boards were obtained at each site prior to study initiation, and written informed consent was obtained prior to study participation. Standardized training on the administration of the neurological and neuropsychological screening examinations was conducted. Site study personnel were trained in face-to-face meetings with the study neuropsychologist and neurologists on site. Study personnel were required to pass a certification examination after the training and prior to study initiation. In addition, written manuals and DVD video training materials were provided to the sites for interim training updates. Annual recertification tests were required of all study personnel. Rigorous data monitoring at data entry through computerized range checks, with follow-up data cleaning through multiple queries and replies was conducted throughout the duration of the study. Implausible values were queried, and confirmed or corrected at intervals. Statistical analyses were completed with SAS, multiple comparisons were not controlled for.

Participants

In order to recruit volunteers who mirror the economic, cultural, and risk factor epidemiology of the local HIV at-risk population, participants were recruited at their local health clinic, voluntary counseling and testing (VCT) center, or other HIV testing site aligned with the primary ACTG site.

Eligible participants were men and women 18 years or older who had documentation that they were HIV-1 seronegative within 30 days of study enrollment. Participants were excluded from participation in the study if they had any active severe psychiatric illness, active drug or alcohol abuse or dependence, serious illness and/or hospitalization within 14 days of study entry, or any other condition that in the opinion of the site investigator, would compromise the person's ability to participate in the study, adhere to study requirements, or

confound the analysis or interpretation of the results of the study. Participants were enrolled into each stratum until the stratum sample size limits were met. Participants were serially asked to participate in the follow-up visit on a voluntary basis, until the 6 month follow up strata was filled.

Neuropsychological and Neurological examinations

Standardized neurological and neuropsychological (NP) examinations (Hopkins Verbal learning test – Revised, Color Trails 1 and 2, Wechsler Adult Intelligence Scale Digit Symbol subtest, Grooved pegboard, Timed gait, Semantic Verbal fluency, Finger tapping and the International HIV Dementia Scale) were administered at baseline. A subset of participants consented to return for a 24-week follow-up assessment to estimate practice effect. The neuropsychological tests chosen were from ACTG 5199 The International Neurological Study (Robertson et al., 2011) based on prior experience in clinical trial and cohort studies in the ACTG, then augmented with additional tests to meet minimal HAND Frascati criteria while still maintaining a short battery with the least language- and culture-specific items. Details of the neurological examination have been reported(Robertson et al., 2011).

Results

Demographics

Participants were enrolled in the study beginning in February 2011, and the study was closed to all follow up visits in October 2013. The total enrollment was 2400 participants, 770 participating in the 6 month follow-up, and with final enrollment for each site as follows: Johannesburg (n=240) and Durban (n=240) in South Africa; Lima, Peru (n=239); Chiang Mai, Thailand (n=240); Pune (n=240) and Chennai (n=240) in India; Lilongwe (n=241) and Blantyre (n=240) in Malawi; Rio de Janeiro, Brazil (n=240); and Harare, Zimbabwe (n=240). The accrual target was 30 participants per 8 strata (gender (male/female) × age (< 35 and >=35 years) × education (<10 and >=10 years) at each site. The demographic means and standard deviations for the total sample and by country are presented in Table 1.

There were 1200 (50%) females and 1200 (50%) males enrolled. The median age was 35 years (Q1 = 26, Q3 =43), and the median educational level was 10 years (Q1= 8, Q3 = 12). For ethnicity/race, there were 725 (30%) Asians, 1,323 (55%) Blacks, 100 (4%) White, 1 (0%) American Indian, 250 (10%) Other, and 1 Unknown (0%). By country, there were 240 participants in Brazil, 480 in India, 481 in Malawi, 239 in Peru, 480 in South Africa, 240 in Thailand and 240 in Zimbabwe.

Neuropsychological Tests

The overall normative comparison neurocognitive test score means and standard deviations by stratification factors of gender, age, and education are presented in Table 2. As expected and stratified for, there was variation in neuropsychological performance across countries. For example, the overall (mean (SD)) for verbal fluency was 16.8 (5.3) and differed across sites (χ^2 (df 6) = 815.23, p<.0001); Johannesburg 13.55 (3.79), Durban 14.42 (3.59), Lima 21.14 (4.55), Chiang Mai 20.99 (5.39), Pune 16.38 (4.49), Chennai 17.95 (4.63), Lilongwe

15.41 (5.33), Blantyre 12.82 (2.95), Rio de Janeiro 19.81 (5.28), and Zimbabwe 15.46 (3.20)). For Timed gait, the overall scores were 12.4 (2.2) and differed across sites (χ^2 (df 6) = 420.89, p<.0001); Johannesburg 10.25 (1.42), Durban 12.45 (1.79), Lima 13.97 (3.06), Chiang Mai 11.36 (1.29), Pune 12.40 (1.69), Chennai 13.20 (1.66), Lilongwe 13.91 (1.78), Blantyre 11.77 (1.50), Rio de Janeiro 12.98 (2.81), and Zimbabwe 11.92 (1.83)).

The normative scores (means and standard deviations) for each NP test are presented for each site by gender, age, and education stratum in the supplemental tables.

Demographic differences

There was also variation between the age, gender and education strata. Age was an important variable and decreases in performance with increasing age were noted for HVLT-R learning (χ^2=83.01, p<.0001), HVLT-R delay (χ^2=124.86, p<.0001), Digit Symbol (χ^2=295.55, p<.0001), Grooved Pegboard dominant (χ^2=243.58, p<.0001) and nondominant (χ^2=232.25, p< .0001), Semantic verbal fluency (χ^2=9.61, p>.005), Timed Gait (χ^2=167.91, p<.0001), Fingertapping dominant (χ^2=23.08, p<.0001) and nondominant (χ^2=22.99, p<.0001), Color trails 1 (χ^2=184.82, p<.0001) and Color trails 2 (χ^2=232.33, p<.0001). Gender was an important variable and females had better performance on HVLT-R learning (χ^2=36.94, p<.0001), HVLT-R delayed recall (χ^2=23.08, p<.0001), and Digit Symbol (χ^2=34.47, p<.0001). Males performed better on fine motor (Fingertapping dominant (χ^2=177.09, p<.0001) and nondominant (χ^2=189.01, p<.0001)) and gross motor (Timed gait (χ^2=351.54, p<.0001) tests. No gender differences were found for semantic verbal fluency, Grooved pegboard dominant and nondominant, and Color trails 1 and 2. Education was an important variable for all the neurocognitive tests and increasing education was associated with better performance on HVLT-R learning (χ^2=303.37, p< .0001), HVLT delayed recall (χ^2=204.67, p<.0001), Digit Symbol (χ^2=589.67, p<.0001), Grooved pegboard dominant (χ^2=103.02, p<.0001) and nondominant (χ^2=79.72, p<.0001), Semantic verbal fluency (χ^2=140.66, p<.0001), Timed gait (χ^2=51.92, p<.0001), Fingertapping dominant (χ^2=40.73, p<.0001), and nondominant (χ^2=37.98, p<.0001), Color trails 1 (χ^2=215.68, p<.0001), and Color trails 2 (χ^2=326.05, p<.0001).

We also examined within country but between site test results to see if there were in fact substantial differences on the neurocognitive test results. Within Malawi (Lilongwe and Blantyre), South Africa (Durban and Johannesburg), and India (Chennai and Pune), there were differences on the neurocognitive tests which were not consistently in one site's favor. For example, in Malawi the Blantyre site would have better performance on some tests (verbal learning(χ^2=80.47, p<.0001, memory (χ^2=32.46, p<.0001), speed of processing (χ^2=328.60, p<.0001), and gross motor (χ^2=215.11,p<.0001)) while Lilongwe would perform better on others (fine motor (χ^2=18.15, p<.0001), executive functioning (χ^2=21.85, p<.0001), and verbal fluency (χ^2=41.40, p<.0001)). Similar results were found when comparing South African sites of Durban (better verbal memory (χ^2=14.08, p<.0005), speed of processing (χ^2=142.40, p<.001), and executive functioning (χ^2=7.54, p<.01)) and Johannesburg (better fine motor (χ^2=13.06, p<.0005) and gross motor skills (χ^2=258.72, p<.0001)); as well as the comparison of Indian sites of Chennai (better verbal memory (χ^2=48.65, p<.0001), verbal fluency (χ^2=14.97, p<.0001), fine motor (χ^2=106.35, p<.0001)

and executive functioning (χ^2=5.02,p<.05)) and Pune (better fine motor speed (χ^2=22.15, p<.0001), gross motor (χ^2= 36.36, p<.0001)).

Discussion

This study provides the first large-scale multisite normative comparison data in diverse international resource limited settings establishing a foundation to base future neurocognitive research and clinical studies upon. These data fill an existing limitation and need in both research and clinical neuropsychological areas(Robertson et al., 2009). Neuropsychological tests are used for assigning impairment ratings and for diagnoses (of HAND for example). Appropriate normative data are necessary to place these tests results into context and did not exist in these settings prior to the data provided in the current study.

There were substantial variations on the neurocognitive tests between countries, underscoring the need for country based normative data to be available to provide the appropriate context for valid interpretation. Other studies have found country differences, including one of the first neuropsychiatric studies in resource limited settings conducted by the WHO (Maj et al., 1994). Additional analyses found that there were differences within country between sites on the neurocognitive test results. While some of these differences are likely related to site demographic characteristics including education and age, it is likely that other issues such as cultural differences, rural vs. urban living and other factors could account for the variance seen. It is very clear that age, education and to a lesser extent gender, are important variables in the variance associated with neurocognitive test differences, and thus necessary to control for. The stratified sample collected here provides a foundation to build on for future studies.

The only known treatment for HAND is antiretroviral therapy (ART). We previously reported the first study on the impact of ART on neuropsychological functioning and neurological dysfunction in HIV-1 infected people in resource-limited settings(Robertson et al., 2011). We found that effective ART in resource limited settings improved neuropsychological and neurological functioning over time(Robertson et al., 2012).

With appropriate normative data made available here, screening for neurocognitive impairment, and diagnosing HAND would be possible in resource limited settings. Where available, initiation of ART in those who screen positive or are diagnosed with HAND will very likely improve their long-term neurocognitive outcomes, which in turn will reduce mortality, increase both productivity and quality of life.

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Table 1

Demographics

Characteristic		Total (N=2400)	Country						
			Brazil (N=240)	India (N=480)	Malawi (N=481)	Peru (N=239)	South Africa (N=480)	Thailand (N=240)	Zimbabwe (N=240)
Age	Mean	35	38	34	34	37	35	36	34
	SD	12	14	10	11	13	13	10	11
	Min, Max	18, 85	18, 71	18, 68	18, 71	18, 70	18, 85	18, 67	18, 75
Sex	M	1,200 (50%)	120 (50%)	240 (50%)	241 (50%)	119 (50%)	240 (50%)	120 (50%)	120 (50%)
	F	1,200 (50%)	120 (50%)	240 (50%)	240 (50%)	120 (50%)	240 (50%)	120 (50%)	120 (50%)
Race	Asian	725 (30%)	0 (0%)	480 (100%)	0 (0%)	0 (0%)	5 (1%)	240 (100%)	0 (0%)
	Black	1,323 (55%)	140 (58%)	0 (0%)	481 (100%)	1 (0%)	461 (96%)	0 (0%)	240 (100%)
	White	100 (4%)	94 (39%)	0 (0%)	0 (0%)	4 (2%)	2 (0%)	0 (0%)	0 (0%)
	American Indian	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Other	250 (10%)	4 (2%)	0 (0%)	0 (0%)	234 (98%)	12 (3%)	0 (0%)	0 (0%)
	Unknown	1 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Education	N	2,398	240	480	479	239	480	240	240
In Years	Mean	10	10	10	9	10	10	11	10
	SD	3	4	4	3	4	3	4	4
	Min, Max	1, 24	1, 24	2, 19	1, 19	1, 24	1, 17	2, 18	1, 21

Table 2

Overall Neurocognitive Tests by Age, Gender, and Education Strata

Tests		Total	Strata							
			Age< 35 yrs; Male; ED< 10 yrs	Age< 35 yrs; Male; ED>= 10 yrs	Age< 35 yrs; Female; ED< 10 yrs	Age< 35 yrs; Female; ED>= 10 yrs	Age>= 35 yrs; Male; ED< 10 yrs	Age>= 35 yrs; Male; ED>= 10 yrs	Age>= 35 yrs; Female; ED< 10 yrs	Age>= 35 yrs; Female; ED>= 10 yrs
		(N=2400)	(N=301)	(N=300)	(N=300)	(N=300)	(N=298)	(N=301)	(N=300)	(N=300)
HVLT Learning	Mean (SD)	7.8 (1.7)	7.6 (1.7)	8.4 (1.5)	7.7 (1.6)	8.6 (1.5)	6.7 (1.7)	7.7 (1.5)	7.2 (1.8)	8.2 (1.4)
HVLT Delayed recall	Mean (SD)	8.1 (2.4)	7.9 (2.5)	9.0 (2.2)	8.1 (2.2)	9.2 (2.2)	6.9 (2.4)	7.9 (2.3)	7.3 (2.4)	8.6 (2.2)
Digit symbol	Mean (SD)	54.6 (23.8)	52.9 (19.4)	66.3 (25.0)	52.3 (20.8)	73.2 (23.8)	37.8 (16.8)	53.4 (19.3)	40.6 (19.0)	59.8 (22.6)
GPD: Dominant	Mean (SD)	77.1 (24.9)	74.5 (23.7)	68.5 (13.7)	75.3 (22.9)	67.0 (12.9)	86.1 (25.5)	78.5 (20.6)	90.3 (38.4)	77.1 (23.2)
GPN: Nondominant	Mean (SD)	86.8 (28.6)	84.1 (27.7)	77.5 (16.6)	83.5 (22.9)	77.1 (16.6)	96.4 (30.4)	88.4 (24.4)	101.1 (43.9)	86.6 (28.0)
SVF: Total correct	Mean (SD)	16.8 (5.3)	16.4 (5.1)	18.1 (5.2)	16.0 (4.8)	18.2 (5.6)	15.6 (4.9)	17.3 (5.5)	15.7 (4.6)	17.1 (5.5)
IHDS: Total	Mean (SD)	10.9 (1.3)	11.0 (1.2)	11.4 (1.0)	10.9 (1.3)	11.3 (0.9)	10.5 (1.4)	10.9 (1.3)	10.5 (1.5)	11.0 (1.2)
Timed Gait	Mean (SD)	12.4 (2.2)	11.4 (1.9)	11.2 (1.8)	12.9 (2.3)	12.5 (2.0)	12.3 (2.1)	11.8 (1.8)	14.0 (2.5)	13.3 (2.1)
Finger Tap Dom	Mean (SD)	39.4 (9.7)	41.9 (8.7)	43.5 (9.9)	37.3 (8.7)	37.7 (8.4)	39.7 (9.8)	42.6 (10.2)	35.0 (8.7)	37.6 (9.9)
Finger Tap Non-Dom	Mean (SD)	37.3 (8.4)	39.6 (8.0)	40.7 (8.1)	35.4 (7.3)	35.9 (7.0)	37.6 (8.2)	40.3 (9.1)	33.4 (7.5)	35.8 (8.6)
Color trails 1	Mean (SD)	63.6 (32.0)	60.7 (29.7)	50.0 (22.7)	65.5 (31.4)	52.1 (26.4)	78.2 (34.5)	61.0 (31.6)	80.0 (37.6)	61.3 (26.7)
Color trails 2	Mean (SD)	128.4 (50.9)	126.1 (50.2)	103.1 (38.4)	132.0 (47.2)	105.4 (43.6)	152.4 (49.8)	124.3 (50.5)	157.7 (52.5)	126.5 (47.3)