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Development of normative neuropsychological performance in Thailand for the assessment of HIV-associated neurocognitive disorders

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Abstract

International studies of HIV-associated neurocognitive disorder (HAND) are needed to determine the viral and host factors associated with cognitive impairment particularly as more than 80% of HIV+ subjects reside in resource-limited settings. Recent diagnostic nomenclature of HAND requires comparison of cognitive performance specifically to local normative data. To evaluate this need for local norms, we compared normative data obtained locally in Thailand to Western norms. The current study examined cognitive performance in 477 seronegative Thai participants (male=211, female=266) who completed a battery of tests sensitive to cognitive changes in HIV. The cohort was divided into three age brackets (20–34; 35–49; 50–65) and four educational levels (no education or primary education, less than secondary certificate, high school/associates degree, Bachelor's degree or greater). The Thai cohort was compared (using ANCOVA) on a number of measures to a seronegative US cohort (n=236; male=198 female=38) to examine cultural differences in performance. Normative data are provided with age and education stratification. The Thai and US groups performed significantly differently on all neuropsychological measures with the exception of verbal fluency. The Thai group performed better on measures of verbal learning ($p<0.001$) and memory ($p<0.001$), and measures of psychomotor speed ($p<0.001$). Education was a more powerful predictor of performance in the Thai cohort compared to the US group. These results highlight the continued need for the development of normative data within local populations. The use of Western norms as a comparison group could lead to inaccurate identification of HAND in culturally distinct groups.

Cognitive dysfunction associated with human immunodeficiency virus (HIV) remains a global health concern. Despite advances in the availability of antiretroviral therapy worldwide, the frequency of cognitive impairment among individuals infected with HIV remains high. Recent studies in North America and in international settings suggest that as many as 50% of individuals infected with HIV experience some form of cognitive impairment (Heaton et al., 2010; Robertson, 2007). While access to treatment has reduced the frequency of the most severe form of cognitive impairment, persistent complications associated with mild to moderate impairment represent important limitations for patients.

International studies of HIV associated neurocognitive disorder (HAND) have become increasingly concerned with determining the viral and host factors associated with cognitive impairment. This interest is promoted by debate regarding potential differences in the neurovirulence of various HIV clades distributed globally (Ranga et al, 2004; Satishchandra, 2000). Members of our team have been particularly interested in HAND among Thai patients, who are predominately infected with clade A/E recombinant HIV. An early study assessing HIV-associated cognitive impairment in Thailand reported that the prevalence of cognitive impairment in Thailand was 18.4% (Maj et al, 1994) among symptomatic HIV+ individuals (CDC stage IV). Recently, members of the research team assessed the frequency of cognitive impairment among combination antiretroviral (cART) treated Thai patients (Pumpradit et al., 2010) using 230 HIV- controls, all of whom are included in the current study, for comparison. Unlike the Maj study, the Pumpradit study included well-controlled HIV+ individuals without symptomatic HIV disease. Still, 37% of the study population had some form of HAND when compared to local HIV- controls. Additional studies reveal elevated HIV DNA in monocytes among Thai patients diagnosed with HIV dementia (HAD) compared to patients without HAD (Shiramizu et al, 2007) and these elevated levels remain after treatment among individuals exhibiting impairment (Valcour et al, 2010). Furthermore, there have been studies reporting an increased expression of monocyte markers among both demented and non-demented patients relative to healthy controls (Ratto-Kim et al. 2008), the latter representing a different pattern than what is evident in clade B HIV among North American patients.

The assessment of cognitive status obtained through neuropsychological test batteries has become necessary to understand the deficits associated with HIV in international settings, yet relatively little information is available regarding normative comparisons. Given that most neuropsychological measures used to assess HAND have been developed in English speaking countries, there is a need to examine normative performance on cognitive tests among local cultural groups. Such normative data are critical, as cognitive rating systems such as the Global Deficit Score (Heaton et al., 1994) and the recent diagnostic nomenclature of HAND described by Antinori et al. (2007) require comparison of cognitive performance to local norms. Cultural and demographic influences within various international regions likely influence performances on cognitive measures to a degree that invalidates the application of western norms for use with clinical rating scales such as the GDS and the most current diagnostic system. Currently there are no published normative data for the Thai population available. The purpose of this study is to examine normative performance on a battery specifically designed to assess HIV-associated cognitive function in an international setting, and report normative scores for this cohort with age and education adjustments. We applied this international battery to a normative population in Thailand, one of the five original sites used to validate the cross-cultural application of these cognitive tests (Maj et al, 1994b). Additionally, we examined performances between the seronegative Thai individuals to a comparison group comprised of a culturally diverse group of seronegative individuals recruited for comparison to HIV cohorts in the US.

Participants

Thai cohort

Participants from Thailand were recruited for the study via posters, flyers and word of mouth with a target of 25 individuals per age-education strata. Four hundred and seventy-seven individuals between the ages of 20–65 were included. Data from 230 of these individuals has been used in other studies of HAND in Thailand (Valcour, 2004). The study was conducted at two locations in Bangkok: SEARCH-Thailand, a research office affiliated with The Thai Red Cross AIDS Research Centre and the Division of Neurology at Phramongkutklao Hospital. Each participant provided informed consent. A trained physician

assessed neurological function and recorded a history of medical illnesses. To minimize potential confounds, individuals were excluded from the study if they reported any factor deemed by the clinician to potentially impact cognition including: head injury with loss of consciousness >1 hour, current or past illicit drug use or positive drug screen, severe illness within 30 days of study, current or recent fevers or meningeal signs, history of previous neurologic disease including stroke, multiple sclerosis, or autoimmune disease, active major depressive disorder (controlled or minor depressive symptoms not excluded), known learning disability including dyslexia, confusion or other signs and symptoms of metabolic encephalopathy or delirium, or focal neurologic deficit on examination.

Hawaii cohort

A sample of culturally diverse seronegative individuals enrolled in the Hawaii Aging with HIV Cohort (Valcour et al, 2004) was included to provide a comparison to an independent control group utilized in HIV studies of neuropsychological function. Two hundred thirty-six individuals (ages 20– 65) who met the inclusion/exclusion criteria provided informed consent as per the guidelines of the University of Hawaii Institutional Review Board. In general, the same criteria for exclusion criteria were used in both the Thai and Hawaii cohorts; however, the exclusion for history of drug use was slightly different in the Hawaii group. Individuals with self-reported drug use within the 30 days prior to enrollment or a positive urine toxicology screen were excluded; drug use more than 30 days prior to enrollment was not exclusionary.

Procedure

Demographic information was collected along with an assessment of neurological function, an HIV screen, and a history of medical illness. After screening, Thai participants underwent neuropsychological assessment using the WHO/NIMH/UCLA international battery (Maj et al., 1993, Maj et al. 1994a,b) and completed the Thai Depression inventory (Lotrakul and Sukanich, 1999). The WHO/NIMH/UCLA International Battery consists of 10 measures (see Table 1) assessing motor speed and fine motor control, verbal learning and memory, attention, cognitive flexibility, visual memory, and verbal fluency. The battery was chosen by experts in order to meet the following criteria: sensitive to HIV-affected domains of cognitive function, sensitive to milder forms of cognitive dysfunction, ability to administer on a large scale, and lacking cultural biases. The battery was developed specifically for administration in the cross-cultural setting and validated in five regions, including Bangkok (Maj et al., 1994b). For the purpose of the present study the battery was modified to ensure cultural relevancy of the words comprising the verbal memory test. One measure, the WHO/NIMH/UCLA Picture memory and Interference test was not included in this study. Instead, the Brief Visual Memory Test-Revised (Benedict, 1997) was added to the battery to provide an additional measure of learning and memory. A trained nurse or technician at each location administered all measures with quality assurance completed every six months or with turnover of staff.

Participants were grouped into 15-year age bands (20–34; 35–49; 50–65). The 15-year age band was selected as previous studies have utilized a similar stratification approach allowing for comparison to the extant literature (Hseih and Tori, 2000; Norman, Evans, Miller, Heaton, 2000; Ruff and Parker, 1993). In addition, this distribution provided greater than 25 individuals per cell, providing increased confidence that the mean scores on the measures within age and education brackets accurately reflects population means. Education was subdivided into four groups: no education or primary certificate (typically 6 years or less), less than secondary certificate, high school or associate's degree, and bachelor's degree or beyond.

Statistical Analysis

Prior to analyses, distributions of all neuropsychological variables were examined to ensure normality of distributions. Several variables did not fit a normal distribution and these were subsequently log-transformed and utilized in all subsequent analyses (Trails A, Color Trails 1 and 2, Grooved Pegboard dominant and non-dominant hands). Residual plots were checked to ensure a linear relationship between the variables.

Correlations were analyzed to determine relationships between age group, highest education completed on all of the neuropsychological measures. T-tests were used to compare the effects of gender on each of the measures. Stepwise linear regressions were implemented to determine the contribution of age and years of education on each of the neuropsychological variables. This analysis was performed to determine if stratification for age and education or gender would be necessary for any or all of the variables. ANOVAs were completed for each of the measures to determine differences between age groups and education levels, and whether or not there was an age by education interaction. Finally, one-way ANCOVAs were conducted to compare the scores between the Thai and Hawaii cohorts on select neuropsychological measures that were obtained in both groups co-varying for age, education and gender. Regression analyses were performed to determine the predictive value of age and education level on each of the measures completed by the Hawaii cohort for comparison with the Thai cohort.

Results

As demonstrated in Tables 2 and 3, there were significant differences between the cohorts in terms of education level, and gender due to recruitment practices that matched local epidemiology of HIV. The Hawaii cohort was predominantly male, with only 38 total female participants out of 236 given that this cohort aimed to enroll socio-economically matched individuals, often related to the subjects. The Thailand cohort had more female than male participants in most of the education strata given broad community enrollment to better match the epidemic in Thailand. In the latter, the only exception was in the secondary education level where the percentage male to female was proportionate.

Normative analyses (among Thai Cohort only)

Correlational analyses revealed that both age and education levels were significantly associated with all neuropsychological measures. Gender was most significantly associated with Finger Tapping Speed, but had only a nominal correlation with the other neuropsychological measures. The stepwise linear regressions indicate that education was the strongest predictor of performance on the Block Design task (R^2= 0.17 $p<0.001$), verbal fluency tasks (first names R^2=0.17 $p<0.001$ and animals R^2= 0.13 $p<0.001$), WAIS-III Digit Symbol (R^2= 0.31 $p<0.001$), Verbal learning (WHO/UCLA AVLT R^2= 0.09 $p<0.001$), and the BVMT-R delayed recall (R^2= 0.136 $p<0.001$). Age was the best predictor of performance for Finger tapping (dominant R^2= 0.10 $p<0.001$ and non-dominant R^2= 0.10 $p<0.001$), verbal learning delay (AVLT delay R^2 = 0.10 $p<0.001$), the BVMT-R learning (total trials 1–3 R^2= 0.15 $p<0.001$), Color Trails 1 (R^2= 0.20 $p<0.001$) and Color Trails 2 (R^2= 0.22 $p<0.001$), Grooved Pegboard (dominant R^2= 0.19 $p<0.001$ and non-dominant R^2= 0.15 $p<0.001$), Timed Gait (R^2= 0.16 $p<0.001$), and Trails A (R^2= 0.22 $p<0.001$). The predictive value of both age and education were significant on all measures and were included in the subsequent ANOVAs. The t-tests comparing male to female performance for each of the neuropsychological measures did not indicate any significant differences between the genders on any of the measures; gender was not included as an additional stratification for further analysis.

For each of the ANOVAs, differences on each measure for age group and education level were considered, as well as a possible interaction between age group and education level. Significant age group by education level interactions were observed where older age and low education resulted in the lowest scores for block design, BVMTR learning and delay, Grooved Pegboard (non-dominant hand), and Trails A. Table 5 provides mean and standard deviation values for each of the measures stratified by age group and education level.

Cross-cultural comparison analyses

The comparison between the Thai and Hawaii cohorts revealed that both groups performed significantly different on all of the neuropsychological measures with the exception of verbal fluency. ANCOVA was used for comparisons of the groups using only individuals with a high school education or greater for both groups. The analysis controlled for age, education, and gender revealing the Thai group (n=254) had significantly higher scores than the Hawaii cohort (n=232) on verbal learning ($p<0.001$), verbal memory ($p<0.001$), Digit Symbol ($p<0.001$), and Grooved Pegboard dominant and non-dominant hands ($p<0.001$ and $p= 0.002$ respectively). In contrast, the Hawaii cohort had higher scores (e.g. less time to complete measures) on Timed gait ($p<0.001$) and Trails A ($p<0.001$) (See table 4 for detail).

Discussion

The present study provides a large-scale evaluation of neuropsychological function among seronegative individuals in Thailand, with comparisons to a demographically similar cohort of seronegative individuals in Hawaii. Normative data on this international battery have not been previously available. Previous studies of HAND in Thailand by members of the research team have been conducted using a smaller number of healthy, local controls (n=230; Pumpradit et al., 2010; Valcour et al., 2004) with different age stratifications. Since those studies were published the number of healthy controls available for comparison has doubled, and the current stratification changes provide more stable normative data.

Comparison with the Hawaii cohort highlights the importance of using culturally specific normative data when assessing HIV neurocognitive disorders to ensure appropriate classification of HAND. This is necessary even among tests that are not altered when translated into foreign languages. Measures of psychomotor speed and motor tasks such as finger tapping, grooved pegboard tests, and timed gait may be influenced by underlying cultural importance of speed emphasizing that cultural factors influence performance. There was a stronger effect of education on performance for most measures in the Thai group compared to the Hawaii cohort. This was the case even when subjects with very limited education were removed from the analysis. Education has been shown to be a better predictor of performance in other cultural groups, when compared to US cohorts (Ponton, 1996; Manly et al., 1998). There were virtually no individuals in the Hawaii group who did not complete a high school education. Although education was predictive of performance on almost all measures in the Thai cohort, education was not a good predictor of performance in the Hawaii cohort. This could be due to a ceiling effect of education on the measures in the Hawaiian group, as most of the cohort had at least a high school education, whereas there were a number of Thai indivduals who had less than a high school education.

The difference in educational impact between the two cohorts underscores the importance of culturally specific norms that reflect the population of interest with regard to socioeconomic status, access to educational resources, and other environmental factors. Neuropsychological tests commonly administered to assess HAND in North America utilize norms that often correct for differences in age, sex, and in some cases, education. Results from the present study indicate that similar cognitive tests require correction for age and education but not necessarily sex, in order to accurately identify neurocognitive impairments in Thailand.

Studies are needed to determine whether similar culturally specific corrections are needed in other international settings where HAND is actively investigated.

The classification of HAND requires assessment of functional status as well as neurocognitive performance. At present, methods to determine functional status rely on rating scales and self-report measures that emphasize western-oriented activities such as driving, financial management, and employment. In international settings, particularly rural regions, these categories of function can be particularly challenging to assess and modifications are likely required in order to better match the functional activities of the population under consideration. The assessment of culturally relative measures of function is beyond the scope of this paper, but remains an important area of research to accurately diagnose HAND internationally.

Limitations of this study include the differences in educational structure between Thailand and Hawaii. In order to minimize the differences we considered both the number of years of formal education and certificate earned to group individuals. The measures available for comparison between the groups were limited; however, the observed group differences further emphasize the need for the development of normative data in local populations to accurately characterize HAND in an international setting. Also, individuals from the Thai cohort did not report past histories of drug use whereas the Hawaii cohort had a number of individuals with a history of previous drug use. Although there were no individuals from the Hawaii group who had current drug use, or self-reported drug use in the past 30 days it is uncertain whether or not past drug use may have altered current performance on any of the measures.

Overall the present results provide additional information to assist with the diagnosis and classification of HAND in Thailand. The results also provide novel information regarding the impact of demographic factors on cognitive status in a unique cultural population relative to a US comparison group. Additional studies are needed that provide similar input regarding functional status in international settings. Collectively this work facilitates efforts to understand the impact of HIV on the nervous system, which remains a global concern in both developed and less developed regions of the world.

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Table 1

List of measures used for normative data.

Neuropsychological measures	Brief Description of outcome variable
Finger tapping	Average of five 10-second trials for both dominant and non-dominant hands
WHO/AVLT- total learning	Total scores across five learning trials, words adjusted for cultural relevancy in Thai population
WHO/AVLT recall	Recall after delay and interference trial
BVMT-R learning - total	Total scores across three learning trials; not originally part of WHO/NIMH/UCLA battery, added for additional memory measure.
BVMT-R delay	Number of items recalled after delay
Timed gait	Average across three trials in seconds
Verbal fluency	Number of first names generated in one minute
EIWA block design	Points scored for accurate trials completed. Less time to complete results in higher score
EIWA Digit Symbol	Number completed correctly in 90 seconds
Verbal fluency (animals)	Number of animals named in one minute
Color Trails 1	Time in seconds to complete
Color Trails 2	Time in seconds to complete
Grooved Pegboard	Time in seconds for dominant and non-dominant hands
Trails A	Time in seconds to complete

Table 2

Number of participants from Thai cohort in each age and education bracket.

Education	Thai Cohort							
	20–34 yo (n=171)		35–49 yo (n=166)		50–65 yo (n=140)		Total (n=477)	
	Male	Female	Male	Female	Male	Female	Male	Female
0–6 years (primary cert)	18	16	18	26	18	31	54 (43%)	73 (57%)
7–12 years (did not complete HS	16	15	18	19	15	13	49 (51%)	47 (49%)
HS diploma/some college	29	25	20	30	11	23	60(43%)	78 (57%)
Completed BA/BS	21	31	16	19	11	18	48 (41%)	68 (59%)
Total84	84	87	72	94	55	85	211 (44%)	266 (56%)

Table 3

Number of Participants from Hawaii cohort in each age and education bracket.

Education	Hawaii Cohort							
	20–35 yo (n=53)		35–49 yo (n=80)		50–65 yo (n=103)		Total (n=236)	
Male	Female	Male	Female	Male	Female	Male	Female	
<12 years	1				3		4 (100%)	0 (0%)
HS/some college	32	10	48	6	54	4	134 (87%)	20 (13%)
Completed BA/BS	5	5	17	9	38	4	60 (77%)	18 (23%)
Total	38	15	65	15	95	8	198 (84%)	38 (16%)

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Table 4

Means and standard deviations for Thai cohort neuropsychological measures

Education Level	Age Group		Finger tapping avg dominant hand	Finger tapping avg non-dominant hand	Color Trails 1	Color Trails 2	Grooved Pegboard Dominant (sec.)	Grooved Pegboard, non-dominant (sec.)	Trials A time (sec.)	EIWA Digit Symbol
primary Certificate	**20–34**	Mean	52.48	48.74	40.16	85.97	58.61	65.63	28.90	56.44
	n=34	SD	7.86	6.74	10.83	29.17	6.82	12.28	9.72	12.28
	35–49	Mean	48.43	44.37	52.93	114.55	68.61	73.77	33.21	44.18
	n=44	SD	8.66	6.31	17.64	37.78	13.96	13.56	9.73	14.76
	50–65	Mean	46.35	43.14	64.85	142.59	78.92	88.23	46.71	32.14
	n=49	SD	7.28	6.01	20.30	47.40	19.50	16.49	13.71	8.51
secondary certificate	**20–34**	Mean	52.06	47.12	43.90	78.26	61.77	67.09	27.55	62.13
	n=31	SD	5.15	5.34	16.99	27.79	10.32	12.60	8.32	14.29
	35–49	Mean	48.21	44.97	50.45	97.42	70.82	74.14	34.02	50.81
	n=37	SD	8.57	7.29	16.74	26.59	18.95	13.50	9.94	13.31
	50–65	Mean	45.74	42.34	59.20	114.09	75.20	78.57	37.08	44.23
	n=28	SD	9.13	7.57	42.19	38.23	15.15	14.67	10.97	12.48
HS/some college	**20–34**	Mean	53.60	49.33	36.60	70.11	57.95	67.15	24.80	65.38
	n=54	SD	6.59	4.83	10.98	22.18	6.54	11.85	6.94	11.93
	35–49	Mean	50.62	46.18	44.12	83.76	65.17	73.92	29.61	56.10
	n=50	SD	7.10	6.55	13.95	27.80	12.85	13.40	8.66	12.07
	50–65	Mean	47.48	43.34	46.81	95.77	64.79	73.04	30.91	51.27
	n=34	SD	6.21	5.75	14.80	31.86	8.16	13.44	9.06	12.96
BS/BA and beyond	**20–34**	Mean	53.92	48.14	33.45	65.50	58.36	65.89	22.69	71.44
	n=52	SD	6.78	5.74	10.91	22.43	6.69	12.43	6.86	10.78
	35–49	Mean	50.38	45.73	45.15	87.53	65.16	70.31	28.82	61.43
	n=35	SD	8.18	6.13	14.18	29.25	12.40	13.12	8.48	10.21
	50–65	Mean	49.90	44.58	47.99	97.13	74.39	77.32	33.72	54.39
	n=29	SD	7.43	6.13	15.33	32.52	26.85	14.27	9.94	12.47

Education Level	Age Group		AVLT- total learning	AVLT recall	BVMT-R learning - total	BVMT-R delay	Timed gait average (sec.)	Verbal fluency (first names)	EIWA block design	Verbal fluency (animals)
Primary certificate	**20–34**	Mean	54.74	12.44	23.94	9.35	11.61	18.44	35.06	21.12
	n=34	SD	7.06	2.29	7.40	2.72	1.46	5.26	6.54	4.14
	35–49	Mean	50.18	11.14	15.34	6.52	11.76	17.77	29.09	20.43
	n=44	SD	6.66	1.72	8.01	3.27	1.36	6.10	7.24	5.28
	50–65	Mean	49.39	10.45	14.92	6.49	13.32	15.67	25.24	19.33
	n=49	SD	8.55	2.53	6.15	2.67	2.17	5.33	6.24	5.11
secondary certificate	**20–34**	Mean	53.90	12.06	25.84	10.35	11.58	18.87	36.94	22.65
	n=31	SD	6.64	2.13	6.05	2.33	1.02	6.43	6.86	4.75
	35–49	Mean	52.76	11.73	21.62	8.32	12.10	20.24	32.51	22.00
	n=37	SD	7.30	2.45	7.99	2.98	1.21	5.43	6.45	4.46
	50–65	Mean	51.14	10.43	17.43	7.46	12.71	18.54	28.96	21.29
	n=28	SD	6.41	2.22	6.57	2.63	1.61	4.61	7.48	4.62
HS/some College	**20–34**	Mean	55.30	12.24	26.20	10.00	10.87	22.35	36.91	23.96
	n=54	SD	5.62	1.81	5.81	1.84	1.52	4.23	6.77	6.11
	35–49	Mean	53.86	11.48	21.70	8.56	11.99	21.92	33.30	22.44
	n=50	SD	6.05	2.26	5.88	2.46	1.55	6.84	7.37	5.29
	50–65	Mean	54.74	11.35	22.62	9.32	12.51	20.97	34.88	24.06
	n=34	SD	6.16	2.27	7.41	2.68	1.39	4.53	6.56	5.52
BS/BA and beyond	**20–34**	Mean	59.77	13.60	28.10	10.77	10.71	24.37	40.65	27.48
	n=52	SD	5.79	1.55	5.37	1.59	1.43	4.99	5.88	5.23
	35–49	Mean	54.51	11.51	22.89	9.51	11.61	24.03	35.51	23.97
	n=35	SD	7.30	2.44	6.54	2.45	1.87	5.23	5.98	5.91
	50–65	Mean	54.52	11.55	23.17	9.72	12.36	21.83	35.59	24.59
	n=29	SD	7.72	2.41	6.50	2.31	1.54	5.89	6.14	4.78

Table 5

Shows the significant mean differences between the Thai and Hawaii cohorts with at least a high school education. Significant differences were controlled for age, education and gender.

	Thai (n=254)	Hawaii (n=232)	p
Digit Symbol	63.82 (12.55)	54.54 (13.06)	<0.001
AVLT total learning	55.67 (6.61)	47.84 (10.58)	<0.001
AVLT delayed recall	12.07 (2.23)	9.15 (3.38)	<0.001
Verbal fluency	24.47 (5.72)	23.30 (5.27)	<0.001
Trails A	28.91 (9.60)	26.92 (8.74)	<0.001
Timed Gait	11.54 (1.68)	9.99 (1.38)	<0.001
Grooved Pegs Dominant	63.24 (13.63)	73.64 (26.57)	<0.001
Grooved Pegs Nom-Dominant	71.58 (14.49)	80.82 (32.70)	0.002