High Prevalence of Neurocognitive Impairment, Symptomatic Peripheral Neuropathy and Depression in HIV Infected Outpatients within the Asia Pacific Region: Findings of the APNAC Study

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Introduction

•8.2 million HIV infected people are living in the Asia Pacific (AP) Region *(UNAIDS Report, 2005)*

•43% have advanced HIV disease *(Zhou et al, J Acquir Immune Defic Syndr 2005)*

•The prevalence of HIV-related neurological disease is 30% in untreated advanced HIV disease in Western, industrialised countries amounting to approximately 1 million in the AP Region if the epidemiology is the same

•However the prevalence of HIV-related neurocognitive (NC) impairment (NCI) in the AP Region has not been rigorously studied and reports suggest that both HIV dementia (HIVD) and symptomatic peripheral neuropathy (PN) are uncommon with opportunistic infections (OIs) being the leading cause of neurological disease (Table 1)

http://web.worldbank.org

Table 1. Prevalence of HIV-related Neurological Diseases in the Asia Pacific Region and in the Industrialised world pre-HAART

Disease	Prevalence or Incidence Asia Pacific Region	Industrialised world: pre-HAART
ADC	**4.6%-11.8%** (*Japan*: Nakagawa, Int Med 1997; *South Korea*: Oh, CID 1999)	**10% severe** (Portegies, AIDS 1993); **25%-30% mild** (McArthur, Neurol 1993)
HIV Cognitive Impairment	**Unknown**	**40%** (Cysique, Arch Neurol 2004; Saktor J Neurovirol 2002)
Symptomatic Peripheral Neuropathy	**2.6%-6.4%** (*Japan*: Nakagawa, Int Med 1997; *South Korea*: Oh, CID 1999)	**35%** (Schiffito, Neurol 2002)
Toxoplasmosis	**13%** (*India* :Lanjewar, AIDS 1998) **14.8 100-person years** (Subsai Eur J Neurol, 2004)	**10%** (Luft, CID, 1992)
Cryptococcal meningitis	**7%-12.6%** (*PNG*: personal communication G. Tau; *Cambodia*: Senya Int J STD AIDS 2003). **18.0 100-person years** (Subsai Eur J Neurol, 2004)	**7%** (Powderly, CID, 1993)
Lymphoma	**Uncommon**	**10%** (Rosenblum, Ann Neurol 1988)
PML	**1.2 100-person years** (Subsai Eur J Neurol, 2004)	**4%** (Berger, Ann Int Med 1987)

<ins>The Asia Pacific NeuroAIDS Consortium (APNAC)</ins>

•Established in 2002

•Comprises physicians, scientists and researchers from Fiji, Papua New Guinea, Indonesia, Hong Kong, Malaysia, Thailand, China, Cambodia, India and Australia with a shared interest in HIV-related neurological diseases.

•Currently undertaking The APNAC Study to determine the prevalence of NCI, symptomatic PN in outpatient clinics, and HIVD and CNS diseases in inpatients at 10 sites within 8 APNAC countries.

•Study Hypotheses

•NCI and symptomatic PN are prevalent but under-diagnosed in the region

•The epidemiology of CNS OIs is the same as in Western Countries

•Results from outpatient clinics at two sites in Thailand and single sites from Indonesia, China, and Malaysia are presented.

Methods

<ins>Subjects</ins>

•HIV positive outpatients were consecutively consented and screened for NCI and symptomatic PN

•Controls recruited from hospital staff (self-reported as being HIV seronegative)

<ins>Assessment Tools</ins>

•*Neuropsychiatric test battery*: grooved pegboard (GPB), finger tapper (FT), timed gait (TG) and category fluency (CF) (animals).

•The definitions employed for NCI were: *normal*: all tests >-1 SD; *minimal*: <-1SD on one test: *mild-moderate* <-1SD on two tests, <-2SD on one test, up to –4SD total; *severe*: greater than –4SD total.

•Test results were compared in two ways: (1) against published US norms for the FT and GPB tests (Heaton et al, P.A.R. 2004) and against local controls for TG and CF to allow for possible different cultural and ethnic performance on TG and CF, (2) against published US norms for all tests (Heaton et al, P.A.R. 2004; Robertson et al, J Clin Exp Neuropsychol, *in press*)

•*PN screening tool*: the AIDS Clinical Trial Group was used to screen for symptomatic PN

•The definition employed for symptomatic PN

•PN: symptoms + vibration at great toes <10 seconds + absent ankle reflexes

•Probable PN: symptoms + one of the remaining two criteria

•*Depression Screening Tool*: the Center for Epidemiologic Studies Depression Scale (CESD -20); validated published translations of the CESD-20 were used where possible otherwise the CESD-20 was translated and back-translated.

•A brief illicit drug and alcohol questionnaire was administered. Patients' demographic and medical data were obtained from their case records.

<ins>Assessors</ins>

•Researchers received standardized training at the Alfred Hospital/Burnet Institute for each of the abovementioned tools

•Researchers visited the APNAC sites for 2-3 week periods and provided standardized training at each site

•The tests were co-administered with in-country colleagues including the authors DI, SK and AA who are neurologists

<ins>Data Analysis</ins>

•Data obtained were sent to the Burnet Institute for analysis

•Statistical analysis included use of the Student t-test and tests for comparisons of proportions

Results

•504 HIV infected outpatients, 133 self-reported HIV negative outpatient controls and 117 HIV infected inpatients have been recruited to date.

•This analysis is restricted to 220 HIV infected outpatients and 75 HIV negative outpatient controls from clinic in Ubon Ratchathani (N.E Thailand), Bangkok, Jakarta, Beijing and Kuala Lumpa.

Table 2

•Plasma HIV viral load had been performed on 30% of patients and the median viral load was 488 copies/ml (range undetectable-700,000)

•The commonest ADIs were tuberculosis (24%), cerebral toxoplasmosis, *P.jerovicii* pneumonia (both 12%) and oesophageal candidiasis (11%)

Table 3

•No patients were reported to have a past history of HIVD, cerebral lymphoma or PML

•25/220 patients (11%) had a CNS AIDS illness within 6 months of the study assessment

•49 patients (22%) and 7 patients (3%) were receiving one, or two antiretrovirals only

•Of those patients receiving anti-tuberculous therapy all treatment regimens included isoniazid plus pyridoxine

Table 2. Baseline Characteristics of Study Patients and Controls

Site	Ubon Ratchathani	Bangkok	Beijing	Kuala Lumpa	Jakarta	All Patients	Controls
Number	23	53	50	31	63	**220**	**75**
Gender % Male	11 (48%)	37 (70%)	41 (82%)	20 (65%)	51 (81%)	**160 (73%)***	31 (41%)
Age, Median (range)	37 (34-46)	36 (18-76)	34 (22-51)	39 (25-75)	26 (20-41)	**33 (18-76)**	31 (20-61)
Education							
-Less than high school	5 (22%)	16 (30%)	6 (11%)	12 (39%)	7 (11%)	**46 (21%)**	10 (16%)
-High school	4 (17%)	30 (57%)	23 (43%)	12 (39%)	34 (54%)	**103 (47%)***	14 (19%)
-Some college	0 (0%)	3 (57%)	6 (11%)	3 (9.7%)	15 (24%)	**27 (12%)**	10 (16%)
-Degree	2 (9%)	3 (6%)	12 (23%)	4 (13%)	7 (11%)	**28 (13%)***	21 (33%)
-Post Grad	0 (0%)	0 (0%)	3 (6%)	0 (0%)	0 (0%)	**3 (1.3%)***	8 (13%)
-Unknown	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	**1 (0.5%)**	0 (0%)
Years since HIV diagnosis, median (range)							
	3 (0-19)	2 (0-14)	1 (0-11)	4 (0-17)	0 (0-7)	**1 (0-19)**	-
HIV acquisition Risk Factors							
Homosexual	1 (4%)	4 (8%)	31 (58%)	4 (13%)	2 (3.2%)	**42 (19%)**	-
Heterosexual	11 (48%)	43 (81%)	8 (15%)	19 (61%)	15 (24%)	**96 (44%)**	-
Injecting Drug Use	0 (0%)	7 (13%)	0 (0%)	1 (3.2%)	49 (78%)	**57 (26%)**	-
Blood Products	0 (0%)	0 (0%)	2 (4%)	2 (6.5%)	0 (0%)	**8 (3.6%)**	-
Other	0 (0%)	2 (4%)	0 (0%)	0 (0%)	4 (6.3%)	**2 (0.9%)**	-
Unknown	2 (9%)	0 (0%)	20 (40%)	7 (23%)	0 (0%)	**29 (13%)**	-
Hepatitis B surface antigen							
No. positive/ no. tested (% positive)	0 (0%)	2/27 (7%)	4/32 (8%)	3/26 (12%)	6/25 (24%)	**15/110 (14%)**	
Hepatitis C Antibody							
No. positive/ no. tested (% positive)	0 (0%)	4/30 (13%)	1/22 (5%)	3/26 (12%)	31/38 (82%)	**39/116 (33%)**	

**p<0.05 between controls and HIV infected outpatients*

Table 3. CD4 cell counts, Prior AIDS-defining Illnesses, Antiretroviral regimens and Intercurrent Medications

Site	Ubon Ratchathani	Bangkok	Beijing	Malaysia	Jakarta	All
Number	**23**	**53**	**50**	**31**	**63**	**220**
Most recent CD4 cell count, median, cells per uL, (range), (number tested), (median time since last test, months)	195 (40-580) (23) (4)	153 (0-886) (44) (4)	288 (12-2100) (48) (7.5)	325 (8-1356) (31) (7)	96.5 (1-465) (56) (6)	**177 (0-2100)** (202) (6)
Nadir CD4 cell count nadir, median, cells per uL, (range), (number tested)	86 (9-508) (23)	82.5 (0-886) (44)	111 (4-1405) (48)	121 (2-426) (31)	30.5 (1-353) (62)	**62.5 (0-1405)** (208)
AIDS-defining illnesses (% total patients)						
Past History ADI	14 (61%)	39 (73%)	17 (34%)	20 (65%)	44 (70%)	**134 (61%)**
Prior CNS AIDS-defining illnesses (% total patients)						
Cerebral toxoplasmosis	0 (0%)	2 (3.8%)	0 (0%)	6 (19%)	18 (29%)	**26 (12%)**
Cryptococcal meningitis	0 (0%)	0 (0%)	0 (0%)	3 (9.7%)	1 (2%)	**4 (2%)**
TB meningitis	0 (0%)	0 (0%)	1 (2%)	1 (3.2%)	0 (0%)	**2 (1%)**
Total number patients with prior CNS ADI						**32 (14%)**
Antiretroviral regimens (% total patients)						
Currently receiving 3 ARVs (HAART)	1 (4%)	39 (74%)	32 (60%)	25 (81%)	51 (81%)	**148 (67%)**
Regimen includes stavudine	1 (4%)	28 (53%)	23 (46%)	5 (16%)	22 (35%)	**79 (36%)**
Regimen includes didanosine	0 (0%)	1 (2%)	10 (20%)	2 (6%)	0 (0%)	**13 (6.0%)**
Intercurrent medication (% total patients)						
P. jerovicii prophylaxis	17 (74%)	28 (53%)	5 (10%)	18 (58%)	35 (56%)	**103 (47%)**
Anti-TB medications	0 (0%)	8 (15%)	1 (2%)	2 (6.5%)	20 (32%)	**31 (14%)**
Pain medication	1 (4%)	4 (7.5%)	0 (0%)	0 (0%)	6 (9.5%)	**11 (5%)**
Anti-depressants	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	**2 (1%)**
Anti-hypertensive agents	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	**2 (1%)**
Lipid-lowering agents	0 (0%)	0 (0%)	0 (0%)	2 (6.5%)	0 (0%)	**2 (1%)**

Table 4. Neuropsychological Test Results

Neuropsychological Tests	APNAC HIV+ Outpatient results N=220	Comparison groups: APNAC controls*	US normative data** (Heaton; Robertson)
Timed gait mean (SD) seconds	12.02 (3.57)	10.07 (1.33)	9.45 (1.1)
>-1SD - normal		48	19
-1 to -2SD		109	37
-2 to -3SD		38	50
-3 to -4SD		6	50
>-4SD		19	64
Verbal fluency mean (SD) animals	18.66 (6.38)	21.14 (5.27)	
>-1SD - normal		65	120
-1 to -2SD		81	57
-2 to -3SD		58	28
-3 to -4SD		16	7
>-4SD		0	4
Missing data			4
Pegboard mean (SD) seconds	73.78 (25.31)		
>-1SD - normal			127
-1 to -2SD			62
- 2 to -3SD			22
-3 to -4SD			3
>-4SD			2
Missing data			4
Finger tapping mean (SD) taps	35.57 (9.59)		
>-1SD - normal			60
-1 to -2SD			63
- 2 to -3SD			61
-3 to -4SD			20
>-4SD			12
Missing Data			4
Normal: All tests > -1SD		6 (2.7%)	4 (1.8%)
Minimal impairment: <-1SD on 1 test		21 (9.5%)	13 (5.9%)
Mild-moderate impairment: <-1SD on two tests, <-2SD on one test, up to –4SD total		52 (24%)	47 (21.2%)
Severe: >-4 SD total		141 (64%)	156 (71%)

*APNAC control data for Timed Gait and Verbal Fluency and US normative data for Grooved Pegboard and Finger Tapper.
**US normative data for all four Neuropsychological Tests.

Table 5. Factors associated with Severe Neurocognitive Impairment

	Severe CI >-4 SD on total (n=141)	Normal and Equivocal: > -1SD on all tests and <-1SD on 1 test (n=27)
Gender male	97 (69%)*	25 (93%)
Mean Age (SD)	35.7 (9)*	30 (9)
CNS ADI	25 (18%)	3 (11%)
Mean CD4 (SD) nadir **Mean CD4 (SD) recent**	108.3 (171)* 216.1 (249)	193 (178.6) 303.5 (247)
Pain medication	11 (7.8%)	0 (0%)
Depression	56 (40%)	6 (22%)
Drug use	42 (30%)	6 (22%)
Past Smoker	88 (62%)	18 (67%)
Current Smoker	43 (31%)*	15 (56%)

Significantly different *p<0.05* compared to normal and equivocal <-1 SD on all tests combined)

Table 6. Prevalence of Symptomatic Peripheral Neuropathy

Features (% total)	**Ubon**	**Bangkok**	**China**	**Malaysia**	**Jakarta**	**All sites**
	23	53	50	31	63	220
Pain	1 (4.3%)	4 (7.5%)	11 (22%)	4 (13%)	13 (21%)	**33 (15%)**
Pins and needles	1 (4.3%)	3 (5.7%)	9 (18%)	3 (9.7%)	13 (21%)	**29 (13%)**
Numbness	4 (17%)	15 (28%)	12 (24%)	3 (9.7%)	9 (14%)	**43 (20%)**
Vibration ? 10s one toe **Vibration ? 10s both toes**	5 (22%) 11 (48%)	15 (28%) 15 (28%)	2 (4%) 7 (14%)	6 (19%) 8 (26%)	4 (6.3%) 9 (14%)	**32 (15%)** **50 (23%)**
Tendon both absent **Tendon one absent**	10 (43%) 1 (4.3%)	10 (19%) 2 (3.8%)	18 (36%) 2 (4%)	7 (23%) 0 (0%)	5 (7.9%) 0 (0%)	**50 (23%)** **5 (2.3%)**
Peripheral neuropathy	4 (17%)	3 (5.7%)	5 (10%)	1 (3.2%)	1 (1.6%)	**14 (6.3%)**
Probable PN	15 (65%)	33 (62%)	18 (36%)	17 (55%)	31 (49%)	**114 (52%)**

Table 7. Factors associated with Symptomatic Peripheral Neuropathy

	PN (n=12)	Probable PN (n=114)	Normal (n=92)
Gender male	9 (75%)	86 (75%)	65 (71%)
Mean age (SD)	38.7 (7.7)*	36.3 (10.0)*	32 (7.4)
CNS ADI	2 (17%)	17 (15%)	12 (13%)
Mean CD4 (SD) nadir **Mean CD4 (SD) recent**	107.7 (131) 276.1 (235)	103.4 (149) 210.2 (203)	157.9 (200) 252.8 (282)
Pain medication	1 (8%)	9 (8%)*	1 (1%)
Depression	7 (58%)*	42 (37%)*	21 (23%)
Drug use	2 (17%)	33 (29%)	23 (25%)
Current d drug	5 (42%)	49 (43%)*	25 (27%)
Past d drug	2 (17%)	9 (8%)	11 (12%)
TB treatment	2 (17%)	35 (31%)	18 (20%)

*Significantly different *p<0.05* compared to normal (no symptoms of PN)

Conclusions

Summary of Results

•This is the first multi-site study across several countries within the AP Region to address the prevalence of HIV-related neurological diseases

•NCI, PN and depression are common (approx 2/3, ½ and 1/3, respectively) in HIV infected patients screened at large hospital sites in several countries of the Asia Pacific Region.

•These findings are in contradistinction to previous findings and should influence the future direction of clinical services, HIV management strategies and research in the Asia Pacific Region

•These data suggest that Clade C HIV-1 virus is not protective against HIV-related neurological diseases

•Older age, male gender and lower CD4 nadirs were associated with severe NCI

•Older age, depression and use of d-drugs were associated with the presence of PN

•Only a small proportion of patients were receiving pain relief or antidepressants suggesting that these conditions are largely under-diagnosed

Study Limitations

•Only a brief neuropsychological test battery was administered

•Control patients analysed to date differ significantly from the study population for gender and education and were also only self-reported as being HIV seronegative

•The use of US norms for the GPB and FT tests to compare against patient populations of the AP Region is not ideal and may have effected higher rates of NCI than actually exist

•The CESD-20 is a non-diagnostic screening tool for depression and has not been validated for all the patient populations in this study

•These prevalence rates have come from patients enrolled at single sites and cannot be extrapolated too broadly within or between countries of the AP Region.

Future Directions

•Study enrollment is continuing

•Improvement in the recruitment of controls

•Administration all four neuropsychological tests to the controls for the remainder of the study period

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