Journal of NeuroVirology, 14: 465–473, 2008

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280802235932

informa
healthcare

Review

NeuroAIDS in the Asia Pacific Region

Edwina J Wright,[1–3] Michael Nunn,[4] Jeymohan Joseph,[5] Kevin Robertson,[6] Luxshimi Lal,[2,3] and Bruce J Brew[7,8]

[1]Department of Infectious Diseases, The Alfred Hospital, Melbourne, Australia; [2]Department of Neurovirology, Burnet Institute, Melbourne, Australia; [3]Department of Medicine, Monash University, Clayton, Australia; [4]Grants Development, Salk Institute, San Diego, California, USA; [5]National Institute of Mental Health (NIMH), National Institutes of Health, Bethesda, Maryland, USA; [6]Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; [7]Department of Neurology, St Vincent's Hospital, Sydney, Australia; and [8]Department of Medicine, University of New South Wales, Sydney, Australia

Over 8.3 million people living in the Asia Pacific region are human immunodeficiency virus (HIV) positive and up to 40% of these individuals have had prior acquired immunodeficiency syndrome (AIDS) illnesses. Recently endeavors have been made to better characterize the burden of HIV-related neurological disease within the Asia Pacific region and, with this in mind, the NeuroAIDS in Asia and the Pacific Rim workshop was held in Sydney, Australia, as an affiliated event of the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. The workshop was supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH) of the United States National Institutes of Health and the Australian Government overseas AID program, AusAID. HIV neurologists, infectious disease physicians, pediatricians, psychiatrists, immunologists, virologists,and researchers from 12 countries of the Asia Pacific region (including Australia), the United States, and the United Kingdom attended the meeting. A broad range of topics were addressed, including common HIV neurological disorders, the lack of diagnostic, management, and research infrastructure, central nervous system (CNS) immune restoration disease, pediatric neuroAIDS, and current clinical and laboratory research projects being undertaken within the Asia Pacific region. *Journal of NeuroVirology* (2008) **14,** 465–473.

Keywords: Asia Pacific; Clade; neuroAIDS; HAD; HIV; host genotype

In July 2007 The NeuroAIDS in Asia and the Pacific Rim workshop was held in Sydney, Australia, as an affiliated event of the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention (Figure 1). The meeting's chief aim was to bring together leading practitioners and researchers from both the Asia Pacific (AP) region and other international settings to (1) address neuroAIDS within the AP region with respect to epidemiology, clinical, diagnostic, and management issues, and current regional research initiatives; (2) provide the regional audience with updates on HIV-related neurological disorders; and (3) provide information on funding programs and opportunities available for current as well as prospective researchers from within the region. The workshop was supported by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH) of the United States National Institutes of Health and the Australian Government overseas AID program, AusAID.

The meeting was attended by human immunodeficiency virus (HIV) neurologists, infectious disease physicians, pediatricians, psychiatrists, immunologists, and virologists, including members of the Asia Pacific NeuroAIDS Consortium (APNAC). Countries represented included China, Hong Kong, India, Malaysia, Taiwan, Indonesia, Japan, Papua New Guinea (PNG), Cambodia, Thailand, Vietnam, the United Kingdom, the United States, and Australia.

Address correpondence to Dr. Edwina Wright, MBBS, Department of Infectious Diseases, The Alfred Hospital, Commericial Road Melbourne, Melbourne, 3004 Australia. E-mail: e.wright@alfred.org.au
Received 28 April 2008; accepted 21 May 2008.

Figure 1 Group photo of participants attending the NeuroAIDS in Asia and the Pacific Rim Meeting. July 19-20, 2007, Sydney, Australia. *Photo courtesy of Dr Robert Owe-Young.*

The workshop program and presentations are available online at http://synapse.neurology.unc.edu/sydney/archive.htm.

HIV-1 epidemiology and clade subtypes in the Asia Pacific region

Dr. Matthew Law from the National Centre of HIV Epidemiology and Clinical Research presented data from the TREAT Asia HIV Observational Database (TAHOD) group. TAHOD comprises sites from over a dozen countries in the AP region and collects data on HIV-positive outpatients attending those sites (Zhou *et al*, 2005). He reviewed the regional HIV-1 seroprevalence, which varies from 0.01% in Japan and the Philippines to 1.8% in PNG. Dr. Law noted that the HIV-1 epidemic in Asian countries typically begins in injecting drug users, spreading to sex workers, their clients, and thence to clients' partners wherein vertical transmission evolves as an acquisition factor. *Pneumocystis jerovecii pneumonia* and tuberculosis (TB) are the leading acquired immunodeficiency syndrome (AIDS)-defining illnesses at TAHOD sites, with cryptococcal disease and cerebral toxoplasmosis occurring in 3% to 4% of patients.

A number of HIV-1 clade types are prevalent across the AP region and include clades CRF01_AE, B, C, and recombinant B/C strains in China (Oelrichs, 2004). Recently clade C has been shown to be the predominant clade type in PNG (Ryan *et al*, 2007).

Epidemiology and clinical presentations and management issues of HIV-related neurological disease in the Asia Pacific region

The Asia Pacific region—an overview

Dr. Wright from the Alfred Hospital and Burnet Institute Melbourne, Australia, reported on the APNAC study. APNAC conducted a study of HIV-positive outpatients and inpatients at 10 sentinel sites within Fiji, PNG, Indonesia, Malaysia, Hong Kong, Thailand, Cambodia, and China. Six hundred fifty-eight HIV-positive outpatients were enrolled into the study and, of these 12% had moderate-severe HIV-related neurocognitive impairment (NCI), 20% had symptomatic sensory peripheral neuropathy (SN), and 36% of patients were depressed (Wright *et al*, 2008) Less than one quarter of patients with symptomatic neuropathy were receiving pain relief and only a small proportion of patients with depression were receiving antidepressant agents, suggesting that these conditions are underdiagnosed in the region (Wright *et al*, 2008). One hundred sixty HIV-positive inpatients were enrolled during the study period, of whom 43% were diagnosed with a neurological disorder. The most common neurological inpatient diagnoses were opportunistic infections (OIs), including cryptococcal meningitis and cerebral toxoplasmosis (each occurring in 31% of patients) (Wright *et al*, 2007). The APNAC study demonstrates that HIV-associated neurocognitive disorders (HAND) and depression are prevalent in HIV patients across the Asia Pacific region.

Indonesia
Dr. Darma Imran from the University of Indonesia, Jakarta, Indonesia, reported that at his hospital in Jakarta—the Dr. Cipto Mangunkusomo Hospital—56% of inpatients were diagnosed with a neurological illness during the period 2003 to 2006, with an attendant mortality rate of 44%. Dr. Darma is involved in a neuroAIDS network of neurologists across Indonesia and plans to train non-neurologist clinicians in neurological skills to augment available treating personnel across Indonesia.

Papua New Guinea
Dr. Goa Tau of Port Moresby General Hospital, Port Moresby, PNG, reported on the findings of the APNAC study as they pertained to his site, Port Moresby General Hospital. Eighteen percent of patients had NCI, 26% had symptomatic SN, 33% were depressed, and 15% of inpatients had a neurological diagnosis. Dr. Tau reported on the sobering challenges that PNG faces regarding the diagnosis and management of neuroAIDS illnesses, including inadequate laboratory, diagnostic and therapeutic resources, as well as personnel. Public patients in PNG currently lack access to neuroimaging, and, further, toxoplasma serology and tuberculosis diagnostics are unavailable.

Hong Kong
Dr. Patrick Li from the Department of Medicine, Queen Elizabeth Hospital, Hong Kong, reported that, contradistinct to PNG, the Queen Elizabeth Hospital has excellent diagnostic and management infrastructure, including neuroimaging and neurosurgical support. Dr. Li reported that between 2004 and 2007, of 95 patients with AIDS attending his service, 24% had AIDS-defining neurological disease and their mortality rate was 47%.

Japan
Dr. Shinichi Oka from the AIDS Clinical Centre, International Medical Centre of Japan reported on neuroAIDS in Japan. Although the range of neuroAIDS conditions seen in Japan mirror those seen in Western countries, they are very uncommon wherein during the period 1997 to 2005 less than 1% of 1680 patients were diagnosed with a central nervous system (CNS) opportunistic disease. Mortality rates are over 30% for conditions that include HIV-associated dementia (HAD), cryptococcal meningitis, and progressive multifocal leukoencephalopathy (PML).

China
Dr. Robert Heaton and Dr. Lucette Cysique from the HIV Neurobehavioral Research Center (HNRC) and University of San California, San Diego (UCSD), USA, presented data on the prevalence of HIV-related neurocognitive impairment in a population from Anhui province, central China. This work was done in collaboration with China's Center for Disease Control and Peking University. Two hundred and two HIV-positive and 198 HIV-negative patients were recruited and underwent detailed neuropsychological testing. The chief study finding was that 37% of patients with prior AIDS were neurocognitively impaired and this finding was significant when compared to non-AIDS patients and controls.

Dr. Cysique reported on their finding that HIV-negative females from the same Anhui cohort have significantly poorer neuropsychological test performance compared to HIV-negative males. Contributive factors may include that HIV-negative women have significantly less education and less social interaction and use of academic skills than their male counterparts. In addition, it was noted that HIV-negative and HIV-positive women are significantly more likely to be hepatitis C antibody positive than HIV-negative or HIV-positive men, respectively. This finding is something of a conundrum because although blood product donation is the leading HIV acquisition risk factor for the Anhui cohort, women donate blood significantly less often than men. Examining the impact of hepatitis C further, Dr. Cysique reported that when HIV-negative/hepatitis C–negative women and men are compared head-to-head, there is no significant difference between their neuropsychological test scores, suggesting that hepatitis C is a contributive factor in the women's neurocognitive performance. Indeed HIV-positive/hepatitis C–positive women performed significantly worse than their HIV-negative/hepatitis C–negative female counterparts. These findings suggest that normative data will need to be collected from hepatitis C–positive and –negative controls. Recently the group demonstrated that the neuropsychological effects of HIV appear to be similar between patients in China and the United States (Cysique *et al*, 2007).

Thailand
Dr. Victor Valcour from the University of Hawaii, the UCSF, and the South East Asia Research Collaboration with Hawaii (SEARCH) group has previously demonstrated that HAD occurs in patients infected with HIV-1 clade CRF01_AE (Valcour *et al*, 2007). Dr. Valcour reported on the SEARCH 001 study which compared the neuropsychological test profiles of HIV-1 clade CRF01_AE–infected, antiretroviral-naive patients with ($n = 30$) and without ($n = 30$) HAD. HAD patients were more impaired in the area of verbal learning and memory and visuospatial skills that non-HAD patients. After 12 months of highly active antiretroviral therapy (HAART), neurocognitive recovery of HAD patients plateaued compared to non-HAD patients. Further, at baseline and at 12 months post HAART, HAD patients had significantly higher levels of proviral HIV DNA in circulating peripheral blood mononuclear cells (PBMCs). Additional details on the broad range of

other current neuroAIDS research by the SEARCH group are outlined below.

India

Dr. P. Satishchandra of Department of Neurology, National Institute of Mental Health & Neuro Sciences (NIMHANS), Bangalore, India, gave a comprehensive overview of the HIV-related neurological disorders encountered at NIMHANS. CNS OIs were the leading cause of neuroAIDS illnesses in 1239 patients reviewed between 1989 and 2006. The most common diagnoses were tuberculous meningitis and cryptococcal meningitis, each occurring in 32% of patients, followed by cerebral toxoplasmosis. Dr. Satishchandra reported that HAD occurred in only 1.5% of patients in this cohort and that CNS lymphoma, PML, and vacuolar myelopathy are similarly infrequent (Shankar *et al*, 2003, 2005).

Dr. Thomas Marcotte of the HIV Neurobehavioural Research Center (HNRC) reported on the first 32 patients from a study that the HNRC and the National AIDS Research Institute in Pune, India, are undertaking. This is a randomized antiretroviral treatment (ART) trial of HIV-positive patients randomized to defer ART until <200 CD4+ cells/μl or commence ART with >200 cells/μl upon study entry. Patients will undergo regular neuropsychological evaluations during the study and 15/32 (47%) patients enrolled to date were neurocognitively impaired.

Pediatric neuroAIDS

The burden of neurological disease in pediatric populations of HIV-infected infants and children is high, yet little is known about neurological manifestations in children living in developing countries (Van Rie *et al*, 2007). The neuropathogenesis of pediatric CNS infection remains to be elucidated but there is evidence that HIV infects neural progenitor cells (Schwartz *et al*, 2007; Schwartz and Major, 2006) and this may be an etiological determinant.

Dr. Charcrin Nabangchang from the Division of Neurology, Department of Pediatrics, Phramongkutklao Hospital, Bangkok, Thailand, gave an overview of pediatric neuroAIDS, noting that 50% of untreated children with vertically acquired HIV-1 infection will develop an AIDS illness by age 5 years. Neurological disorders are AIDS-defining illnesses in 10% to 20% of children and, overall, up to 40% of children with AIDS will develop a neurological disorder. These disorders include HIV encephalopathy, microcephaly, and opportunistic CNS infections. Dr. Nabangchang presented a retrospective review of data from 103 HIV-positive children with AIDS illnesses who had attended Phramongkutklao College of Medicine Pediatric AIDS Clinic. The mean age of the children was 4 years and mean follow-up time was 4 years. Children with febrile convulsions or brief, nonrecurrent neurological symptoms were excluded from the evaluation. Overall, 12 children (12%) were identified as having neurological disease. Their diagnoses included developmental delay, HIV encephalopathy, tuberculous and cryptococcal meningitis, vacuolar myelopathy, and peripheral sensory neuropathy in a child treated with combination stavudine and didanosine.

Host genetics

The endorsement of performing human leukocyte antigen (HLA)-B57 testing in patients prior to commencing abacavir-based ART has pushed us past the cusp of using host genetic testing as a tool for optimization of patient care. In the following presentations, the authors' data tacitly herald testing strategies and paradigms that may become routine in the clinical care of HIV-positive patients.

Dr. Sunil Ahuja from the University of Texas Health Science Center San Antonio, Texas, gave a plenary talk on host genetics and neuroAIDS. Dr. Ahuja discussed his group's work on the influence of different monocyte chemoattractant protein (MCP)-1 host genotypes upon the pathogenesis of HAD wherein HIV-positive individuals in possession of an MCP-1GA/GA haplotype pair are at a 4.7-fold increased risk of accelerated HIV disease progression and the development of HAD (Gonzalez *et al*, 2002) Further work from this group has focused upon CCR5 genotypes and copy numbers of the *CCL3L1* gene wherein CCL3L1 is CCR5's most potent ligand. When individuals with predefined deleterious *CCR5* genotypes also possess low CCL3L1 copy numbers, they incur an increased risk for HAD and other CNS neuroAIDS conditions (Gonzalez *et al*, 2005) as well as increased risk for rapid HIV disease progression. Recent work from this group has shown that CCL3L1-CCR5 genotypes are also key determinants of the robustness of individuals' cell-mediated immunity (Dolan *et al*, 2007). Dr. Ahuja raised the important question of whether host genetic testing of patients' CCL3L1-CCR5 genotypes should be routinely introduced to provide information on individuals' proximal risk for HIV disease progression and need for ART.

Dr. Oka from Japan (see above) noted results of his group's recent study into the efficacy of dose-reducing efavirenz in those individuals with polymorphisms in the *CYP2B6* gene (Gatanaga *et al*, 2007). Individuals with a single polymorphism in the *CYPB26* gene at position 516 (G→T) have higher plasma concentrations of efavirenz and higher rates of CNS side effects (Haas *et al*, 2004). Gatanga *et al* identified this polymorphism in 18% of 456 HIV-positive Japanese patients receiving, or due to start,

efavirenz (Gatanaga *et al*, 2007). Dose reduction of efavirenz in those receiving and a lower starting dose for those initiating efavirenz was successful in controlling HIV replication and attenuating CNS side effects (Gatanaga *et al*, 2007), the latter strategy not being currently routine in clinical practice.

Dr. Kate Cherry from the Burnet Institute, Alfred Hospital, and Monash University, Melbourne, Australia, discussed the role of host genetics and risk of nucleoside analog–associated sensory neuropathy (NRTI-SN) that is seen with prescription of stavudine and didanosine (Cherry *et al*, 2006). This is of key relevance to populations of the Asia Pacific region wherein use of the stavudine-containing fixed drug combination with nevirapine and lamivudine is commonplace. The putative pathogenesis of NRTI-SN is that of mitochondrial toxicity (Cherry *et al*, 2003); however, HIV has a *de novo* association with SN through increased cytokine production. Hence Dr. Cherry's group focused upon polymorphisms in genes associated with cytokine production to determine any role that inflammatory cytokines might play in NRTI-SN. They found that the tumor necrosis factor (TNF) allelic variant (TNFA-1031*2) was overrepresented in patients with NRTI-SN. Conversely patients who did not develop NRTI-SN despite long-term stavudine or didanosine therapy were found to be likelier to possess the interleukin variant (IL12-B(3'UTR)*2 (Cherry *et al*, 2008). The authors found that a model that includes patient height and cytokine genotype could significantly predict patients' risk for NRTI-SN (Cherry *et al*, 2008).

Clade C HIV-1 and HIV-associated neurocognitive disorders (HAND)

HIV-1 clade C is the predominant subtype found throughout India. HIV-1 clade C Tat has less monocyte chemotactic activity than wild-type Tat (Ranga *et al*, 2004) and it is believed that this may partially explain the infrequency of HAND in India. Dr. Satishchandra reported on recent work that looked at the prevalence of HAND in 119 well-functioning, asymptomatic patients infected with HIV-1 clade C. The mean CD4+ cell count of the group was 396 cells/μl (SD 212). The findings were interesting wherein both the nature of the deficits, frontostriatal, and their prevalence, 60%, were similar to that observed in European/Western populations (Gupta *et al*, 2007). The majority of patients had very mild deficits, moderate-severe deficits were seen in only 3% of patients, and no patient was diagnosed with HAD. Of note was that the severity of the cognitive deficits was similar across all CD4 cell count ranges, suggesting that, although deficits are prevalent, that clade C–infected populations may incur milder deficits than clade B–infected populations (Gupta *et al*, 2007).

Dr. Pankaj Seth from the National Brain Research Centre Manesar, India, provided further insights into the neuropathogenesis of the attenuated neurocognitive deficits in clade C–infected populations. He reported on his work looking at the neurotoxic properties of Tat derived from different HIV-1 clade types. Using human fetal cell–-derived neurons and astrocytes through a number of approaches he demonstrated that C-Tat is less neurotoxic than B-Tat (Mishra *et al*, 2007), a finding that plausibly supports the clinical reports to date.

HIV neurology and other infectious diseases and disorders within the Asia Pacific region

Dr. Bruce Brew of St Vincent's Hospital and the University of New South Wales, Sydney, Australia, addressed how HIV infection may potentiate or alter the presentation of other infections and illnesses common to the populations of the Asia Pacific region. Measles, Japanese B, Nipah, West Nile, and polio viruses occur throughout the Asia and Pacific regions and may cause encephalitis or acute flaccid paralysis. Other endemic infections including malaria also have CNS manifestations.

HIV-1 infection more than doubles the risk of mortality in children infected with the measles virus (Moss *et al*, 2008) and diagnosis of CNS complications may be difficult as the measles rash may be absent in HIV-infected children. Uncommon CNS manifestations of measles have been reported in HIV-infected children, including pathologically proven measles myelopathy, subacute sclerosing pancencephalitis (reviewed by Moss *et al*, 1999), and the onset of epilepsia partialis continua following measles infection in HIV-infected Romanian children (Duiculescu *et al*, 2005).

Japanese B virus and HIV-1 coinfection goes virtually unreported (Neogi *et al*, 1998). The published literature on HIV-1 and malaria coinfection was recently reviewed (Walker *et al*, 2006): HIV-1–positive patients with malaria are likelier to have more severe malaria and a higher rate of coma than their HIV-1–seronegative counterparts, as evinced in a recent study (Grimwade *et al*, 2004). Up to one quarter of children may have neurocognitive deficits following *Plasmodium falciparum* malaria and whether these effects are compounded by HIV-1 coinfection in children remains unknown and requires urgent study (Gwer *et al*, 2007; Newton, 2005). There are no reports of the CNS manifestations of Nipah virus and HIV-1 coinfection. West Nile virus has been described in a small number of case reports as causing encephalitis and acute flaccid paralysis in HIV-infected patients (Jamison *et al*, 2007; Torno *et al*, 2007). In the Asia Pacific region, wild polio virus infections remain prevalent in India where 866 cases were reported in 2007

(http://www.polioeradication.org/casecount.asp), but the natural history of HIV-1 and polio virus coinfection is largely unknown. Vaccine-associated paralytic poliomyelitis in an HIV-infected child has been reported (Chitsike and van Furth, 1999), and although there is evidence that HIV-infected adults do not have prolonged shedding of oral polio virus vaccine strains (Gouandjika-Vasilache *et al*, 2005; Hennessey *et al*, 2005), HIV-infected immunodeficient children have been shown to shed both oral polio vaccine strains and strains that had reverted towards neurovirulent wild-type polio virus (Pavlov *et al*, 2006a,b).

Dr. Brew noted that hypertension, obesity, diabetes, and cigarette smoking are prevalent throughout some countries of the Asia Pacific region. Combination antiretroviral therapy is associated with raised lipids (Friis-Moller *et al*, 2003a), increased risk for myocardial infarction (Friis-Moller *et al*, 2003b, 2007), and an increased risk for diabetes mellitus (De Wit *et al*, 2008). Hence ART-treated populations of the Asia Pacific region may be at increased risk for cerebrovascular disease in the future.

Current neuroAIDS studies and research initiatives within the Asia Pacific region

SEARCH
Dr. Cecilia Shikuma from the University of Hawaii (UH), Honolulu, USA, outlined the research initiatives being undertaken by the SEARCH group http://www.searchthailand.org/. SEARCH is a collaboration between the John Burns School of Medicine, UH, Honolulu, the Thai Red Cross AIDS Research Center, and the Armed Forces Research Institute of Medical Sciences Institute, Bangkok, Thailand. SEARCH has a number of key neuroAIDS studies underway, including (1) a study of 300 Thai controls that will provide Thai normative data for the NIMH/WHO Neuropsychological Battery; (2) a head-to-head study of three ART regimens to determine their relative mitochondrial toxicities, including sensory neuropathy; (3) a study to determine the long-term neurocognitive status of subjects fully HIV suppressed on NNRTI-based ART; (4) a study to examine whether the loss of HIV-1–specific T-cell responses influences risk of HAD; and (5) the PREDICT neurodevelopmental substudy, which is being funded by NIMH/NICHD. In PREDICT, the Pediatric Randomized to Early versus Deferred ART Initiation in Cambodia and Thailand study, children ages 1 to 12 years with mild or moderate HIV symptoms and CD4 percentage 15% to 24% are randomized to immediate versus deferred (CD4 percentage $<15\%$) ART. The 3-year substudy is designed to evaluate the neurodevelopmental outcomes of children enrolled in PREDICT.

INSIGHT
Dr. James Neaton from the School of Public Health, University of Minnesota, Minneapolis, gave an overview of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) network. INSIGHT is an NIAID clinical trials network (http://insight.ccbr.umn.edu/index.php) that performs HIV clinical trials across 36 studies, including, within the region, Thailand and Australia. INSIGHT is due to commence the Strategic Timing of Antiretroviral Treatment (START) Study in 2008. START is a randomized clinical trial designed to answer the question of whether it is better to start ART with high CD4+ cell counts (>500 cells/μl) versus deferral of ART to <350 cells/μl. A neurology substudy of START is being planned to determine whether there are neurocognitive benefits associated with early ART.

China CDC/UCLA ICHORTA
Dr. Roger Detels from the Department of Epidemiology, University of California Los Angeles (UCLA) gave an overview of the Chinese CDC /UCLA International Clinical, Operational and Health Services Research and Training Award (ICHORTA) program, with which he is closely involved. This program has been developed in China to train clinical research scientists in the area of AIDS and tuberculosis and is an initiative of the Chinese Union School of Public Health, Yale, and UCLA.

The International Neurological Study NIMH ACTG 5199
Dr. Kevin Robertson from the University of North Carolina, Chapel Hill, North Carolina, gave an overview of the NIMH ACTG 5199 study. This is a prospective, observational international study linked to ACTG 5175 wherein ART-naive HIV-positive patients with <300 CD4+ cells/μl are randomized to three different ART regimens. Patients' neuropsychological performance will be followed during the study. Asia Pacific sites include India and Thailand.

TAHOD
See above description of TREAT Asia's TAHOD initiative (http://www.amfar.org/cgi-bin/iowa/asia/).

TREAT Asia Pediatric Network
TREAT Asia has launched an important initiative that will collect data on pediatric HIV infection across a number of sites within the Asia Pacific region and it is anticipated that important information will emerge on the profile and burden of pediatric neurological disease from this network (http://www.amfar.org/cgi-bin/iowa/asia/).

APPHAC
The Asia Pacific Pediatric HIV/AIDS Consortium (APPHAC) was launched in 2007. It comprises

pediatricians, physicians, nurses, pharmacists, surgeons, and epidemiologists with a shared interest in Pediatric HIV medicine from 11 countries across the Asia Pacific region. Pediatric neuroAIDS will be a key area of focus for the Clinical Research Arm of APPHAC.

APNAC
The Asia Pacific NeuroAIDS Consortium was formed in 2002 and comprises physicians, neurologists, infectious diseases specialists, neuropsychologists, and neuroscientists with a shared interest in neuroAIDS. Its members represent 11 countries from the Asia Pacific region. APNAC has undertaken research into neuroAIDS within the Asia Pacific region and devised local diagnostic and treatment algorithms for neuroAIDS.

Panel Discussions

Dr. Patrick Li chaired a panel discussion that addressed building clinical research capacity across the Asia Pacific region and Drs. Jeymohan Joseph and Eugene Major chaired a panel discussion on Research Priorities within the region with a number of panelists (see meeting agenda at http://synapse.neurology.unc.edu/sydney/archive.htm).

A summary of the points made is provided herein:

- The prevalence, morbidity, and mortality of CNS OIs are high in the Asia Pacific region. Patients in the region frequently present very late with CNS Ois, which may account for the high mortality rate.
- Notably CNS OIs retain relatively high mortality rates in developed countries and yet—it was noted—there is minimal current research being undertaken into CNS OIs at a global level.
- The incidence of CNS immune restoration disease is unknown but may be contributing to the burden of CNS OI disease and presentations.
- Improvement in and increased infrastructure, including trained personnel and diagnostic and treatment modalities, are vital for enhanced patient care and enhanced capacity for clinical research in the region.
- An increase in lumbar punctures, brain biopsies, and autopsies with ancillary microbiological and histopathological diagnostics are needed to enhance diagnostic and epidemiological acuity. Of note, postmortems are infrequently performed in the region. This appears to be a combination of cultural and religious factors as well as the lack of neuropathological services.
- Training of personnel was identified as key to improving the region's clinical research capacity.
- The need for normative neuropsychological data across many of the regional countries is an urgent and vital need.
- Further research is needed to address the possible role played by different HIV-1 clade subtypes in the pathogenesis of HAD and (potentially) other CNS Ois.
- The engagement and training of neurologists across the region will be vital to the success of all clinical and research endeavors within the Asia Pacific region.
- Pediatric neuroAIDS was identified as a key area that remains under-studied and under-resourced across the region and requires urgent focus and attention. This focus should come from adult HIV neuroAIDS specialists in the immediate future until full engagement of pediatric and general practice physicians is possible.

In summary, the conference provided a unique forum wherein neuroAIDS in the Asia Pacific region was addressed with respect to epidemiology, clinical disease manifestations, current diagnostic and treatment practices, capacity-building needs with respect to personnel and clinical and laboratory research infrastructure, and current and future research priorities.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Cherry CL, McArthur JC, Hoy JF, Wesselingh SL (2003). Nucleoside analogues and neuropathy in the era of HAART. *J Clin Virol* **26:** 195–207.

Cherry CL, Rosenow A, Affandi JS, McArthur JC, Wesselingh SL, Price P (2008). Cytokine genotype suggests a role for inflammation in nucleoside analog-associated sensory neuropathy (NRTI-SN) and PREDICTS AN INDividual's NRTI-SN risk. *AIDS Res Hum Retroviruses* **24:** 117–123.

Cherry CL, Skolasky RL, Lal L, Creighton J, Hauer P, Raman SP, Moore R, Carter K, Thomas D, Ebenezer GJ, Wesselingh SL, McArthur JC (2006). Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* **66:** 867–873.

Chitsike I, van Furth R (1999). Paralytic poliomyelitis associated with live oral poliomyelitis vaccine in child with HIV infection in Zimbabwe: case report. *BMJ* **318:** 841–843.

Cysique LA, Jin H, Franklin DR Jr, Morgan EE, Shi C, Yu X, Wu Z, Taylor MJ, Marcotte TD, Letendre S, Ake C, Grant I, Heaton RK (2007). Neurobehavioral effects of HIV-1 infection in China and the United States: a pilot study. *J Int Neuropsychol Soc* **13:** 781–790.

De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte AD, Fontas E, Law MG, Friis-Moller N, Lundgren JD (2008). Incidence and risk

factors for new onset diabetes mellitus in HIV infected patients: the D:A:D study. *Diabetes Care* **31:** 1267–1268.

Dolan MJ, Kulkarni H, Camargo JF, He W, Smith A, Anaya JM, Miura T, Hecht FM, Mamtani M, Pereyra F, Marconi V, Mangano A, Sen L, Bologna R, Clark RA, Anderson SA, Delmar J, O'Connell RJ, Lloyd A, Martin J, Ahuja SS, Agan BK, Walker BD, Deeks SG, Ahuja SK (2007). CCL3L1 and CCR5 influence cell-mediated immunity and affect HIV-AIDS pathogenesis via viral entry-independent mechanisms. *Nat Immunol* **8:** 1324–1336.

Duiculescu D, Major EO, Vinters HV, Ungureanu E, Barcau M, Ene L, Zamfirescu A, Ciprut T, Ionescu P, Calistru P, Achim CL (2005). An unusual cluster of epilepsia partialis continua in a pediatric AIDS cohort. In: *HIV Infection and the Central Nervous System: Developed and Resource limited Settings Conference*, Frascati (Rome), Italy. June 11–13.

Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiebaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD (2007). Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* **356:** 1723–1735.

Friis-Moller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, Thiebaut R, Morfeldt L, De Wit S, Pradier C, Calvo G, Law MG, Kirk O, Phillips AN, Lundgren JD (2003a). Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* **349:** 1993–2003.

Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD (2003b). Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS* **17:** 1179–1193.

Gatanaga H, Hayashida T, Tsuchiya K, Yoshino M, Kuwahara T, Tsukada H, Fujimoto K, Sato I, Ueda M, Horiba M, Hamaguchi M, Yamamoto M, Takata N, Kimura A, Koike T, Gejyo F, Matsushita S, Shirasaka T, Kimura S, Oka S (2007). Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis* **45:** 1230–1237.

Gonzalez E, Kulkarni H, Bolivar H, Mangano A, Sanchez R, Catano G, Nibbs RJ, Freedman BI, Quinones MP, Bamshad MJ, Murthy KK, Rovin BH, Bradley W, Clark RA, Anderson SA, O'Connell R J, Agan BK, Ahuja SS, Bologna R, Sen L, Dolan MJ, Ahuja SK (2005). The influence of CCL3L1 gene-containing segmental duplications on HIV-1/AIDS susceptibility. *Science* **307:** 1434–1440.

Gonzalez E, Rovin BH, Sen L, Cooke G, Dhanda R, Mummidi S, Kulkarni H, Bamshad MJ, Telles V, Anderson SA, Walter EA, Stephan KT, Deucher M, Mangano A, Bologna R, Ahuja SS, Dolan MJ, Ahuja SK (2002). HIV-1 infection and AIDS dementia are influenced by a mutant MCP-1 allele linked to increased monocyte infiltration of tissues and MCP-1 levels. *Proc Natl Acad Sci U S A* **99:** 13795–13800.

Gouandjika-Vasilache I, Akoua-Koffi C, Begaud E, Dosseh A (2005). No evidence of prolonged enterovirus excretion in HIV-seropositive patients. *Trop Med Int Health* **10:** 743–747.

Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF (2004). HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS* **18:** 547–554.

Gupta JD, Satishchandra P, Gopukumar K, Wilkie F, Waldrop-Valverde D, Ellis R, Ownby R, Subbakrishna DK, Desai A, Kamat A, Ravi V, Rao BS, Satish KS, Kumar M (2007). Neuropsychological deficits in human immunodeficiency virus type 1 clade C-seropositive adults from South India. *J NeuroVirol* **13:** 195–202.

Gwer S, Newton CR, Berkley JA (2007). Over-diagnosis and co-morbidity of severe malaria in African children: a guide for clinicians. *Am J Trop Med Hyg* **77:** 6–13.

Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, Clifford DB, Hulgan T, Marzolini C, Acosta EP (2004). Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* **18:** 2391–2400.

Hennessey KA, Lago H, Diomande F, Akoua-Koffi C, Caceres VM, Pallansch MA, Kew OM, Nolan M, Zuber PL (2005). Poliovirus vaccine shedding among persons with HIV in Abidjan, Cote d'Ivoire. *J Infect Dis* **192:** 2124–2128.

Jamison SC, Michaels SR, Ratard R, Sweet JM, Deboisblanc BP (2007). A 41-year-old HIV-positive man with acute onset of quadriplegia after West Nile virus infection. *South Med J* **100:** 1051–1053.

Mishra M, Vetrivel S, Siddappa NB, Ranga U, Seth P (2007). Clade-specific differences in neurotoxicity of human immunodeficiency virus-1 B and C Tat of human neurons: significance of dicysteine C30C31 motif. *Ann Neurol* **63:** 366–376.

Moss WJ, Fisher C, Scott S, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts FT (2008). HIV type 1 infection is a risk factor for mortality in hospitalized Zambian children with measles. *Clin Infect Dis* **46:** 523–527.

Neogi DK, Bhattacharya N, Chakrabarti T, Mukherjee KK (1998). Detection of HIV seropositivity during an outbreak of Japanese encephalitis in Manipur. *J Commun Dis* **30:** 113–116.

Newton CR (2005). Interaction between Plasmodium falciparum and human immunodeficiency virus type 1 on the central nervous system of African children. *J NeuroVirol* **11 Suppl 3:** 45–51.

Oelrichs R (2004). The subtypes of human immunodeficiency virus in Australia and Asia. *Sex Health* **1:** 1–11.

Pavlov DN, Van Zyl WB, Kruger M, Blignaut L, Grabow WO, Ehlers MM (2006a). Poliovirus vaccine strains detected in stool specimens of immunodeficient children in South Africa. *Diagn Microbiol Infect Dis* **54:** 23–30.

Pavlov DN, Van Zyl WB, Van Heerden J, Kruger M, Blignaut L, Grabow WO, Ehlers MM (2006b). Prevalence of vaccine-derived polioviruses in stools of immunodeficient children in South Africa. *J Appl Microbiol* **101:** 1367–1379.

Ranga U, Shankarappa R, Siddappa NB, Ramakrishna L, Nagendran R, Mahalingam M, Mahadevan A, Jayasuryan N, Satishchandra P, Shankar SK, Prasad VR (2004). Tat protein of human immunodeficiency virus type 1 subtype C strains is a defective chemokine. *J Virol* **78:** 2586–2590.

Ryan CE, Gare J, Crowe SM, Wilson K, Reeder JC, Oelrichs RB (2007). The heterosexual HIV type 1 epidemic in Papua New Guinea is dominated by subtype C. *AIDS Res Hum Retroviruses* **23:** 941–944.

Schwartz L, Civitello L, Dunn-Pirio A, Ryschkewitsch S, Berry E, Cavert W, Kinzel N, Lawrence DM, Hazra R,

Major EO (2007). Evidence of human immunodeficiency virus type 1 infection of nestin-positive neural progenitors in archival pediatric brain tissue. *J NeuroVirol* **13:** 274–283.

Schwartz L, Major EO (2006). Neural progenitors and HIV-1-associated central nervous system disease in adults and children. *Curr HIV Res* **4:** 319–327.

Shankar SK, Mahadevan A, Satishchandra P, Kumar RU, Yasha TC, Santosh V, Chandramuki A, Ravi V, Nath A (2005). Neuropathology of HIV/AIDS with an overview of the Indian scene. *Indian J Med Res* **121:** 468–488.

Shankar SK, Satishchandra P, Mahadevan A, Yasha TC, Nagaraja D, Taly AB, Prabhakar S, Nath A (2003). Low prevalence of progressive multifocal leukoencephalopathy in India and Africa: is there a biological explanation? *J NeuroVirol* **9 Suppl 1:** 59–67.

Torno M, Vollmer M, Beck CK (2007). West Nile virus infection presenting as acute flaccid paralysis in an HIV-infected patient: a case report and review of the literature. *Neurology* **68:** E5–E7.

Valcour VG, Sithinamsuwan P, Nidhinandana S, Thitivichianlert S, Ratto-Kim S, Apateerapong W, Shiramizu BT, Desouza MS, Chitpatima ST, Watt G, Chuenchitra T, Robertson KR, Paul RH, McArthur JC, Kim JH, Shikuma CM (2007). Neuropsychological abnormalities in patients with dementia in CRF 01_AE HIV-1 infection. *Neurology* **68:** 525–527.

Van Rie A, Harrington PR, Dow A, Robertson K (2007). Neurologic and neurodevelopmental manifestations of pediatric HIV/AIDS: a global perspective. *Eur J Paediatr Neurol* **11:** 1–9.

Walker M, Kublin JG, Zunt JR (2006). Parasitic central nervous system infections in immunocompromised hosts: malaria, microsporidiosis, leishmaniasis, and African trypanosomiasis. *Clin Infect Dis* **42:** 115–125.

Wright E, Brew B, Arayawichanont A, Robertson K, Samintharapanya K, Kongsaengdao S, Lim M, Vonthanak S, Lal L, Sarim C, Huffam S, Li P, Imran D, Lewis J, Lun WH, Kamarulzaman A, Tau G, Ali ST, Kishore K, Bain MP, Dwyer R, McCormack G, Hellard M, Cherry C, McArthur J, Wesselingh S (2008). Neurologic disorders are prevalent in HIV-positive outpatients in the Asia-Pacific region. *Neurology* **71:** 50–56.

Wright E.J, Brew BJ, Arayawichanont A, Samintharapanya K, Kongsaengdao S, Lal L, Lewis J, Imran D, Robertson K, Saphonn V, Sarim C, Huffam SE, Li P, Lim M, Lun WH, Kamarulzaman A, Tau G, Ty Ali S, Kishore K, Bain M, Dwyer R, McCormack G, Hellard ME, Cherry CL, McArthur JC, Wesselingh SL (2007). High burden of neurological disease in HIV positive inpatients within the Asia Pacific (AP) region: the APNAC Study. Abstract MOPEB078. In: *4th International AIDS Society Conference,* July 22–25. Sydney, Australia.

Zhou J, Kumarasamy N, Ditangco R, Kamarulzaman A, Lee CK, Li PC, Paton NI, Phanuphak P, Pujari S, Vibhagool A, Wong WW, Zhang F, Chuah J, Frost KR, Cooper DA, Law MG (2005). The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr* **38:** 174–179.

This paper was first published online on iFirst on 26 November 2008.