

Assessment of neuroAIDS in Africa

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Introduction

In June of 2004, the Center for AIDS Mental Health Research, National Institute of Mental Health sponsored a conference on the Assessment of NeuroAIDS in Africa, which was held in Blantyre, Malawi. The conference presentations summarized here highlight the need for research on NeuroAIDS in Africa and methods for assessing HIV-related neurological diseases (Robertson, 2004).

Overview

Globally, 40 million individuals are HIV-infected with 5 million new infections occurring each year; rates are increasing. Three million individuals died from HIV/AIDS in 2003 (World Health Organization, 2003). The global burden of the HIV epidemic is staggering, but in the short term, it is largely unfelt in the developed world. Ninety-five percent of new infections occur in the developing world (World Health Organization, 2003). Almost 1 million people have been infected with HIV in North America (prevalence 0.6%). However, there are 25–28.2 million infected in sub-Saharan Africa alone; (prevalence 8.0%); 350,000–590,000 infected people in the Caribbean; 1.3–1.9 million in Latin America; and 4.6–8.2 million in South and Southeast Asia.

From the early stages of the HIV epidemic in the United States, it has been recognized that cen-

tral and peripheral nervous systems (CNS and PNS) are affected by HIV. The exact mechanism of neurotoxicity is not established, as there is no compelling evidence of productive infection of neurons. There is considerable evidence to suggest that local changes in immune and inflammatory activity in the CNS and PNS are responsible for this neurotoxicity. Initial reports indicated that as many as 40% of infected patients developed a dementing disease. This dementing illness appeared to be due to HIV infection of the CNS, and not to one of many CNS-opportunistic infections. This primary HIV neurological disease has been given the name HIV-Associated Dementia (HAD) (American Academy of Neurology, 1991) or AIDS Dementia Complex (ADC) (Navia *et al*, 1989a, 1989b; McArthur, 1992; Robertson and Hall, 1992). Many more patients have evidence of less severe nervous system dysfunction, which has been termed HIV-associated minor cognitive/motor disorder (MCMD) (American Academy of Neurology, 1991). In the pre-HAART era, in the United States, as many as 80% who died from AIDS had autopsy evidence of CNS injury attributable to HIV regardless of whether there had been manifestations of ADC during life (Elder and Sever, 1998). In 1992, McArthur reported a 15% incidence of ADC after the diagnosis of AIDS in the Multicenter AIDS Cohort Study (MACS), a closely followed cohort of infected men (McArthur, 1992).

Another common neurological problem in HIV infection is peripheral neuropathy, one that is associated with the HIV infection itself and one that is a toxic neuropathy associated with “d-drug” antiretroviral regimen, including ddC (zalcitabine), ddI (didanosine), and d4T (stavudine) (Brew, 2003). Distal symmetric sensory polyneuropathy occurs in approximately 30% of HIV-1-infected persons with CD4+ cell counts below 200, and is more severe in those with higher plasma viral loads (Simpson *et al*, 2002). Toxic nucleoside neuropathy has an estimated incidence of 15% to 40%

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in those on antiretroviral regimen, and can be debilitating.

In addition to the primary or direct effects of HIV on the nervous system, there are many (OIs) that can occur in the CNS due to HIV-induced immunosuppression. These CNS OIs can be protozoal (*Toxoplasma gondii*, *Trypanosoma cruzi*, *Acanthamoeba*, *Pneumocystis carinii*), viral (Cytomegalovirus, herpes simplex types 1&2, varicella zoster, JC virus (PML), Epstein-Barr virus (primary CNS lymphoma), bacterial (*Mycobacterium tuberculosis hominis*, *Treponema pallidum*, *Mycobacterium avium* complex, *Listeria*, *Salmonella*, *Pneumococcus*, *Nocardia*, and fungal (*Cryptococcus neoformans*, *Candida*, *Aspergillus*, *Coccidioides*, and *Histoplasma*) (Marra, 1999). In the developed world, the most common CNS OI's prior to HAART were toxoplasmosis and cryptococcal meningitis (Simpson and Tagliati, 1994). Neuropathological studies in the period prior to HAART (1987-1992) showed that the most frequent CNS infections were cytomegalovirus (36%), CNS lymphoma (11%), and toxoplasmosis (8%) (Nueunberg *et al*, 2002). Some of the HIV related Neurological OI's important in Sub-Saharan Africa will be covered next.

HIV in Africa

Dr. Jens Mielke presented an overview of the epidemiology of HIV in Africa, reminding us that the brunt of the HIV epidemic is in sub-Saharan Africa, where 70% of those infected worldwide live and the infection is primarily in heterosexuals (Hakim and Mielke, 2004). The epidemic started in the early 1980s in east Africa and the epicenter has gradually moved to southern Africa. The prevalence in most southern African countries is very high (Swaziland—38.6%; Botswana—35%; South Africa—20%; Zimbabwe—24.6%—33%; Malawi—15%; Zambia—15.6%—19%; Namibia—22%). While this region has less than 2% of the world's population, southern Africa is home to approximately 30% of people living with HIV/AIDS worldwide. West Africa—including Nigeria (5.8%), Senegal (1.43%), Cote D'Ivoire (10.76%), and Cameroon (11%)—has lower prevalence rates than southern Sub-Saharan Africa, and includes the relatively milder HIV-2 infection. The initial infection in Sub-Saharan Africa was spread through long-distance truck drivers along trade routes from the East to southern Africa, commercial sex workers, blood transfusion recipients, hemophiliacs, and migrant workers. Gradually, the epidemic has become widespread in the general population. Women are disproportionately infected with a higher prevalence than men, and a younger age at seroconversion. The epidemic cuts across all socioeconomic strata and affects those in both urban and rural settings.

The staggering numbers have a substantial impact on families, countries, regions, and the continent. The segments of the population who should be in their prime and the most productive are sick or have died of HIV. Women, who generally have their sexual debut at a younger age than men (e.g., at 11-13 yrs), are disproportionately affected and are seropositive at a younger age than men. Weaker negotiation positions, negative cultural practices, transactional sex and prostitution, and lower educational opportunities all contribute to higher prevalence rates in women. Children infected with HIV have poor health and social services. Many are orphans, and children are heading families and raising siblings. Education becomes a luxury and most are school dropouts. Within families, there is cultural disruption, with a heavy burden on grandparents and children. With the death of parents, children are often dispersed, and may lose all contact with each other. There is a falling life expectancy across sub-Saharan Africa, with average life expectancy falling from 55-60 years in the early 1980s to less than 40 years in many countries presently. Absenteeism in the work force due to attending the sick, and funerals, is prevalent. The productive workforce is substantially reduced and is often ill, leading to a falling per capita income.

Across countries, there is a reversal of the gains that followed independence. Resources are being redirected from developmental projects or combating poverty to fight HIV/AIDS. The continuous need for assistance has resulted in donor fatigue. Corruption, with misuse of donor funds for non-HIV-related purposes such as food donations to promote political agendas has also contributed to wariness on the part of potential donors.

In summary, sub-Saharan Africa remains by far the region worst-affected by the HIV/AIDS epidemic. In 2003, an estimated 26.6 million people in this region were living with HIV, with 3.2 million new infections in the past year. AIDS killed approximately 2.3 million people in 2003. African women are at least 1.2 times more likely to be infected with HIV than men, and among young people aged 15-24, women are 2.5 times as likely to be HIV-infected as their male counterparts.

Social and cultural implications

Dr. Kuku Appiah, from Johannesburg, South Africa presented on social and cultural issues related to conducting HIV-treatment research in resource poor countries (Appiah, 2004). She illustrated a diverse array of problematic issues faced in bringing quality healthcare and clinical research to those infected with HIV in resource-limited countries, including: the effects of poverty, disease, gender issues, cultural differences, social stigma, infrastructure deficiencies, and political issues. Clinical research can be impacted and follow-up care problematic due to

the lack of identifiable physical addresses, telecommunication failures, limited access to refrigeration and choice of drugs, as well as the stigma and violence that can ensue once a participant's seropositive status has been inferred due to frequent home visits or possession of HIV medications. Further limiting both the health of the participants and the quality of the research, many participants share their medications with family members, underplay the side effects to remain in the trial, and will not have access to medication once the trials end. There is a large pool of subjects in resource limited settings, which are generally IV-drug-free and have good levels of adherence to trial medications. Involving local investigators early in the protocol development process provides substantial benefit to clinical researchers and many potential pitfalls can be avoided. In addition, local investigators being invested in the protocol process will also help derive the most benefit from the research process, and stay within social or cultural norms in study design and conduct. Local investigators can help avoid political issues in the process, and to understand the national health priorities in these resource-limited settings.

HIV-related neurological disease

Dr. Hall presented an overview of neurological diseases in HIV in the developed world. Prior to HAART 40% developed neurologic disease and 30% of these had multiple lesions (Hall, 2004). More than 90% at autopsy have changes in the CNS. HIV can have an impact on the nervous system in many ways, including disease believed to be primarily due to HIV itself, secondary viral infection, nonviral infection, neoplasms, cerebrovascular disease, and nervous system complications related to treatment. Neurologic conditions believed due to HIV infection without additional opportunistic infection include acute encephalopathy, HIV-associated dementia (AIDS Dementia Complex), myelopathy, peripheral neuropathy, and myopathy. Acute encephalopathy may occur at the time of infection with a presentation similar to mononucleosis. The vast majority clear rapidly, although there are rare reports of coma and death. AIDS Dementia Complex or HIV Associated Dementia is unique to HIV infection, has a late onset, and was rarely seen before substantial immunocompromise. The incidence was 7% per year prior to HAART and is about 1% per year in the HAART era, with an increasing prevalence due to longer survival with better treatment. Features include early concentration and memory difficulty, losing track of conversation, progressing to difficulty with written material, and apathy, with marked response slowing. There is generally associated motor dysfunction with slowing, gait ataxia progressing to bladder/bowel incontinence, hyperflexia, increased jaw jerk and snout, and abnormal saccades.

AIDS myelopathy with spastic paraparesis, or even quadriparesis and sphincter disturbance, occurs late in the course. While it is sometimes an isolated condition, there is usually concomitant encephalopathy and neuropathy. Pathologically there are vacuolar changes in the spinal cord, similar to but more extensive than those seen in Vitamin B-12 deficiency. In the earlier phases of infection, acute and chronic inflammatory neuropathies may occur with clinical patterns similar to Guillian-Barre syndrome and chronic inflammatory demyelinating neuropathy. Bell's palsy and other isolated cranial nerve palsies may also be associated with earlier stages. All are believed to be related to immune perturbation, and respond to the therapies used in non-HIV patients. The commonest form of neuropathy, distal symmetric polyneuropathy, affects approximately 30% of patients and occurs in the late stages of disease. It is primarily a painful sensory neuropathy, although it may progress to severe motor and sensory deficits. It is clinically indistinguishable from the dose-related painful neuropathy resulting from treatment with ddi, ddC, or d4T.

An immune mediated myopathy similar to polymyositis or more rarely dermatomyositis may also occur, and myopathy may also result from AZT-induced mitochondrial toxicity. Rarely, neuropathy may occur as a result of infection with varicella zoster, CMV, Hepatitis C, and more rarely Cryptococcus and syphilis.

Of the secondary viral infections, cytomegalovirus infection may result in encephalopathy, myelopathy and a characteristic radiculoneuropathy, but this rarely occurs in patients receiving adequate HAART. Progressive multifocal leukoencephalopathy as a result of JC virus infection remains a serious problem, with no identified effective therapy, although optimal antiretroviral treatment may be of some benefit. Herpes simplex and varicella zoster may result in multiple radiculopathies, encephalopathy, and myelopathy. Epstein-Barr virus infection is strongly associated with central nervous system lymphoma.

The major nonviral secondary infections in the HAART era include toxoplasmosis and cryptococcosis, although the former is rare in patients taking adequate prophylaxis. It is also important to consider syphilis, nocardia, histoplasmosis, and other less common pathogens. Mycobacterium avium complex rarely affects the central nervous system, and tuberculosis, a dreadful scourge in Africa, is seen less commonly with AIDS in the United States.

Central nervous system neoplasms seen with AIDS are most commonly primary CNS lymphoma or systemic lymphoma with CNS spread. Kaposi's sarcoma, a common systemic tumor with HIV infection, rarely involves the nervous system, but an increased incidence of glioma has been suggested. HIV-infection is associated with an increased incidence of

cerebrovascular disease, and was even before the advent of antiretrovirals that caused metabolic changes associated with high stroke risk. This may again be due to immune perturbation.

AIDS dementia complex

Dr. Price (2004) presented a review of AIDS Dementia Complex (ADC) and minor cognitive motor disorder (MCMD) and briefly discussed some of the salient issues of syndromic definition, patient diagnosis and research subject evaluation, pathogenesis, and treatment. The CNS is exposed early and continuously to HIV. ADC is a clinical syndrome that has been classified with the subcortical dementia based upon major cognitive, motor, and behavioral symptoms and signs. It characteristically develops late in the course of systemic HIV infection and immunosuppression, though this is variable. Its major pathological substrate is HIV encephalitis with infection of perivascular macrophages and, at times, of parenchymal macrophages and microglial, though inconsistencies in clinical-pathological-virological correlations have been noted since the beginning of the epidemic. Among the fundamental conundrums of HIV pathogenesis are 2 questions: (1) How is it that the central nervous system (CNS) is exposed very early and likely continuously in the course of systemic HIV infection in virtually all those infected, yet HIV encephalitis and ADC only develops in some and usually late in the course of infection? (2) How is the brain injured in ADC if infection is confined largely or exclusively to nonneural cells (of the monocyte-macrophage-microglial lineage) and does not directly infect the functional elements of the brain, that is, the neurons, oligodendrocytes and astrocytes that underlie its structural and physiological integrity? Contemporary theories of pathogenesis focus on the role of virus- and cell-coded signals and toxins that cause indirect injury and death of these cells.

Fortunately, at least in the developed world, combination antiretroviral therapy has been shown to prevent ADC and substantially reverse its symptoms and signs if treated. While there has been considerable concern that the reduced exposure of the brain to antiretroviral drugs related to restricted diffusion from the blood due to the blood-brain barrier would lead to continued CNS infection and progressive ADC in the face of systemic viral suppression, this appears to be unusual. While studies using cerebrospinal fluid (CSF) responses as an index or model of antiviral treatment effect have shown that viral decay may be slower than that in plasma, generally viral suppression in the CNS has been favorable.

As in other areas of HIV disease and treatment, the high morbidity of ADC and its potential for response to available treatments increase the importance of better defining the clinical presentation and epi-

demology of ADC in sub-Saharan Africa and other resource-poor parts of the world that now bear the brunt of the epidemic, and more particularly of implementing proven treatment strategies in these regions to reduce the presumed neurologic burden of this condition.

Dr. Price outlined strategies for evaluating ADC, its natural history, and responses to treatment in these settings resource-poor settings, though accumulated experience will importantly dictate how these methods need to be modified to deal with local medical, language, and cultural variety in these circumstances.

HIV-related peripheral neuropathy

Dr. Mielke (2004), from Harare, Zimbabwe, presented on peripheral nerve disease in HIV-infected subjects. Of primary emphasis were the classification, pathology and neurophysiology, clinical characteristics, investigations, management, and prognosis of distal symmetrical polyneuropathy (DSP). DSP was first described 1983 (Snider *et al*, Simpson). Clinical and electrophysiological signs occur in one-third or more of all AIDS victims, with some pathological change in almost all AIDS autopsies. Dr. Mielke compared reports of the incidence of distal symmetrical polyneuropathy in infected persons in the United States (53%, Simpson *et al*, 2004) to that in a recent Ugandan study (37%, Nakasujja *et al* 2004). He also described the findings of from Burkina Faso of 50% prevalence in early infection to 80% in those with CD4+ counts under 200 (Millago *et al*, 2002), and his own findings of a 35% prevalence in symptomatic and AIDS patients in Harare. Clinically most patients present with a history of burning feet and paresthesias, and examination showing reduced or absent deep tendon reflexes at the ankles jerks, and impaired vibration sensation. Dr. Mielke's talk also included a review of the toxic neuropathy induced by antiretroviral treatment with "d" drugs including D4T, ddI, ddC, of inflammatory demyelinating polyneuropathies in HIV disease, including Guillian-Barre syndrome and chronic inflammatory demyelinating polyneuropathy, and of mononeuropathy multiplex and progressive polyradiculopathy.

HIV treatment in Africa

Dr. Ian Sanne (2004) from the Clinical HIV Research Unit at the University of the Witwatersrand, presented on antiretroviral treatment in South Africa. The national prevalence of HIV is currently estimated at 12% in South Africa, with the highest in those ages 15-40 years old and one-third of 1 million orphans. Of all deaths in the country, an overwhelming 40% are AIDS related. In a study of adherence in 480 participants, several factors were found to have

no influence on adherence during the 96-week observation: participants' gender, distance from clinic, and age (except a very small subgroup of teenagers who did have a problem with adherence). Eighty-two percent of the sample adhered more than 95% of the time, however, only 3.5% reported complete adherence. In a study of nevirapine (NVP), hepatotoxicities were observed in 64/385 (17%) of those treated with NVP and 0/83 of those treated with efavirenz (EFV) in combination with stavudine (d4T)/lamivudine (3TC) or emtricitabine (FTC). Hepatotoxicities in the NVP were higher females (20%) than in males (12%) In the national roll-out program, 2 first-line regimens were selected. Regimen 1 contains D4T+3TC+EFV or NVP and regimen 2 contains ddI+AZT+Kaletra. When patients are on Rifampicin, increased doses of EFV and Kaletra are recommended. With Immune Reconstitutions Syndrome (IRIS) in this setting, 12 cases of TB have been noted, the only predictor for the syndrome was a high fever within the first 4 weeks.

HIV-related neurological disease in Africa

Stroke in Africa

Dr. Kumwenda presented research on causes of stroke like illness in HIV seropositive adults at Queen Elizabeth Central Hospital in Blantyre, Malawi (Kumwenda *et al*, 2004). The study involved a descriptive survey of 104 patients (50 males and 54 females) who were diagnosed as having stroke and were stratified by patient status. Stroke diagnosis was based on rapid onset neurological deficits (>24 hours) within the previous 7 days, with deficits lasting more than 24 hours and no other etiology for the symptoms and signs. Patients meeting entry criteria had full physical examination complete blood count and differential, random blood sugar, VDRL test, HIV test (rapid), toxoplasmosis serology, CT scan of brain, echocardiogram, doppler carotid scan, ECG, and CSF examination. Fifty-one percent (64% women, 40% men) were HIV-positive. There was a relationship between age and the likelihood of HIV infection in the stroke patients, the mean age was 38 years for the HIV-positive and 59 years for the HIV-negative patients, and 79% of the 16–49 age group was HIV-positive. While the CT scans were usually compatible with occlusive disease in both groups, hemorrhage was seen more commonly in the older HIV-group. Of those patients who had CSF studies, 9 (14%) had elevations of lymphocyte count, 2 had positive India ink preparation for *Cryptococcus*. Twenty-one percent had positive serum serology for toxoplasmosis but only one had a positive CSF IgG. None had positive syphilis serology. It was concluded that testing for HIV status should be conducted in all patients presenting with stroke, and was particularly important in young patients.

Cryptococcal meningitis

Dr. Kanyama (2004), from Lilongwe, Malawi discussed cryptococcal meningitis, Cryptococcal infection is the most common cause of meningitis and the third commonest reason for neurologic disease in HIV infection in sub Saharan Africa. In up to 90% of patients with cryptococcal meningitis it constitutes the first presentation of AIDS-defining disease. Untreated cryptococcal meningitis is almost 100% fatal; mean survival after presentation is 4 days in Blantyre, 14 days in Harare, and 10 days in Zambia. Even with monotherapy treatment with fluconazole, there is a 35% mortality in inpatients in Lilongwe. Altered mental status, cranial nerve involvement, high CSF pressure and a high number of organisms in the CSF are indicators of poor prognosis. While CSF evaluation generally shows elevated white cell count, high protein, and low glucose, these parameters are occasionally normal. Dr. Kanyama stressed the need for more research on the impact of fluconazole monotherapy on the treatment of cryptococcal meningitis in resource-limited settings, the need for accurate and rapid laboratory evaluation and an overwhelming need for widespread use of HAART to reduce the mortality and morbidity associated with cryptococcal disease.

Toxoplasmosis

Dr. Amod (2004) from Durban, South Africa discussed the commonest opportunist infection causing focal brain disease in AIDS patients, toxoplasmosis. *Toxoplasma* seropositivity varies by geographic location, and may be as high as 75% of the population. Early studies indicate that up to 47% of seropositive patients who are HIV-infected will develop disease. The CNS is the target in 80%, the retina in 5%. Pneumonitis, myocarditis, and disseminated multi-organ involvement are less common. The clinical presentation is generally of subacute onset over days to weeks. Up to 70% have headache and fever and up to 60% have focal neurological signs, particularly hemiparesis and cranial nerve palsies. Confusion and lethargy are present in up to 40% and seizures also occur in up to 40%. Neuroradiological findings suggestive of toxoplasmosis include multiple contrast enhancing lesions, particularly in the basal ganglia or corticomedullary junction, and surrounding edema with mass effect and ventricular distortion. Primary prophylaxis has been shown to decrease the incidence of TE in HIV-infected patients. In resource limited settings prophylaxis should be instituted for CD4 count of < 200. Intensive treatment should be given to patients with neurological disease in the face of IgG positivity with CD4 count < 100 and/or multiple lesions on brain imaging. The recommended treatment and prophylaxis is cotrimoxazole in appropriate doses.

Neurosyphilis

Dr. Marra (2004) provided a presentation on neurosyphilis. In the developed world, syphilis occurs in epidemics. Currently, most cases are in men who have sex with men, many of whom are HIV-infected. Syphilis is endemic in the developing world. The WHO estimates that there are 12 million cases of syphilis worldwide per year, and that syphilis is responsible for approximately 150,000 deaths. Most cases and deaths occur in the Africa and Asia. Since the advent of effective antibiotic therapy for syphilis, early neurosyphilis (asymptomatic, meningitis, stroke) is more common than late neurosyphilis (general paresis and tabes dorsalis). Symptomatic meningitis, as well as stroke and dementia could be mistaken for primary HIV-associated complications in Africa. The CSF-Venereal Disease Research Laboratory (VDRL) test is specific but not sensitive for the diagnosis of neurosyphilis. When it is negative, diagnosis may be based solely on CSF pleocytosis. HIV itself may cause mild CSF pleocytosis that might be mistaken for neurosyphilis. CSF-FTA and elevated CSF B cells assessed by FACS are helpful in distinguishing between these 2 causes of mild CSF pleocytosis. Recommended treatment is high dose intravenous aqueous crystalline penicillin or intramuscular procaine penicillin plus probenecid, for 10–14 days in each case. Ceftriaxone may be an effective alternative treatment for neurosyphilis in HIV-infected patients. HIV-positive patients are less likely to normalize the CSF VDRL after neurosyphilis treatment, particularly if the CD4 count is <200. Dr. Marra stressed the need for further research to identify “neuroinvasive” *T. pallidum* phenotypes in blood, to prospectively confirm the FACS data, and to identify additional factors that predict response to neurosyphilis treatment in HIV-infected and -uninfected patients.

Cerebral malaria

Dr. Taylor (2004) working in Blantyre, Malawi discussed cerebral malaria in African children. Cerebral malaria collectively involves the clinical manifestations of *Plasmodium falciparum* malaria that induce changes in mental status and coma. Dr. Taylor reviewed the life cycle of *plasmodium falciparum*, and discussed the epidemiology of malaria in Africa. Most symptomatic cases occur in those under 10 years of age. According to Dr. Taylor, the following three intersecting clinical syndromes are responsible for virtually all the deaths in African children: metabolic acidosis manifesting as hyperpnea, cerebral malaria, and severe anemia. The prevalence of HIV is 35% in those with severe malarial anemia while the prevalence of HIV is 21% in those cerebral malaria. With cerebral malaria in children, there is generally rapid recovery, the deficits are reversible. Approximately 10% of those are left neurological sequelae, but there is 15–20% mortality rate. Although progress has been made in antimalarial treatment, no

significant reduction in mortality has occurred. Dr. Taylor noted that the Blantyre Coma Score was developed in Blantyre, has some utility in predicting severity of outcome of fatal *falciparum* malaria in African children.

Tuberculosis

Dr. Laloo (2004), from Durban, South Africa presented discussed central nervous system tuberculosis in human immunodeficiency virus-infected patients. Tuberculosis accounts for up to one-third of AIDS deaths worldwide. Escalating tuberculosis case rates over the past decade in many countries in sub-Saharan Africa are largely attributable to the HIV epidemic. In KwaZulu Natal, South Africa, almost two thirds of the tuberculosis cases are HIV+, with about a 50% cure rate. DNA fingerprinting confirmed a significant proportion of reinfection. The experience in King Edwards Hospital in Durban, South Africa has been that TB has accounted for 21% of the Paradoxical worsening of tuberculous symptomatology and lesions may occur following antituberculous therapy. A comparison study of neuro-TB in developed vs developing world was reviewed, and found higher tuberculosis in a Mexican site compared to the United States. (Trujillo, 1995), but a higher frequency of CNS lymphoma. In those with Neuro-TB, residual hydrocephalus is common and infarction occurs in more than 50%. The multiple manifestations of neuro TB include meningitis, tuerculoma, brain abscess, encephalitis, myeloradiculopathy, spinal cord abscess, and vertebral TB. In South Africa, TB is the fourth leading cause of intracranial mass lesion. Dr. Laloo discussed the possibility that a paradoxical response associated with enhanced tuberculin signs and symptoms may occur after the initiation of combination antiretroviral therapy in HIV-infected TB patients. Furthermore, the signs and symptoms after the initiation of combination antiretroviral therapy may have important public health implications.

Neuroassessment issues

Dr. Jelsma (2004), in Cape Town, South Africa, presented preliminary data on different aspects of development in children with HIV. In South Africa, 5.6% of children between the ages of 2–14 years are infected with HIV. Although MTC is available, not all mothers participate. Although the transmission rate is about 15% when breast feeding, bottle feeding not always a socially or economically viable option. Prior to HAART, 16–19% had neurological impairment and prior estimates indicated that over 90% of children would experience neurological symptoms (Belman, 1988). Prior studies have shown motor and mental delay in HIV+ African children, including studies in Uganda (Dutarl, 1999), Zaire (Biovin), and Rwanda. School performance suffers with 56% found to language impairments

(Papola, 1994), and poorer intellectual and achievement scores (Bachanas, 1998). In a studies from Cape Town, participants were selected from HAART clinics, (73 children with HIV were selected, 33 female/40 male) and Well-Baby clinics (99 HIV seronegative children were selected, 50 female/49 male). As expected, the children with HIV showed significant developmental delay in motor tasks, mental tasks, language tasks, and nutrition as compared to controls. Confounding factors include poverty, parental ill health, and maternal depression. Longitudinal studies are required to investigate whether these developmental delays improve with continued HAART therapy. The language differences make translation and instrument issues important, and these become important in assessment. For instance there is the same word for "blue" and "green" in one culture where there is little attention paid to colors. Investigators have to take care when using assessment tools not developed for the specific population.

Dr. Holding and colleagues (2004) from Kenya presented "Moving Tests Between Contexts: Neuropsychological Assessments in Rural Populations." Dr. Holding noted that there are difficulties moving intellectual, academic, and neuropsychological assessments into environments and populations that these tests were originally normed in. Test modification includes administration, content and structure; translating test language does not automatically or adequately adapt a test to a different culture. Care must be taken to modify and pilot tests in order to reduce error variance, and increase reliability and sensitivity. Secondly, some functional measures should be included to help "validate" tools both for the study population and the scientific audience. The authors presented problems they have faced with test administration, test content, and structure. Essential elements of test administration were covered, establishing rapport in a setting where children do not often interact with adults one-to-one and especially adults outside of their community or village, communicating at the child's level of language complexity, reducing fatigue from travel time to the testing location, and explaining the nature of the study to the children to reduce fears. In any study that uses many examiners, standardization of the administration process is necessary. One hurdle the group found in this study was the need for correction of incomplete records. Translation and back translation of test items, and replacement of items that are culturally unfamiliar is necessary. Because most residents of rural settings are not familiar with psychological assessment, it is imperative to find innovative methods to explain the research goals, follow-up, and consent.

Dr. Boivin (2004), working in Uganda, discussed neuropsychological assessment of executive frontal lobe functions in the African context. In prior studies in Zaire, Dr. Boivin presented global cognitive change

between HIV positive children and HIV negative controls on the Kaufman (Boivin *et al*, 1995, in *Health Psychology*). Assessment of frontal lobe function is vitally important in HIV/AIDS ARV clinical trials. Frontal lobe impairment, or Executive Syndrome, may represent the most sensitive area in the progression of HIV brain infection and in gauging the benefits of antiretroviral therapy intervention within the clinical trials context. Several considerations must be made when assessing participants' frontal lobe function in resource-limited countries, including: quality of prenatal care, antiretroviral treatment, quality of home environment, and potentially confounding health histories including cerebral malaria and progressive encephalopathy. Neuropsychological tests developed for high-resource settings can be adapted for use with both children and adults in the African context.

AIDS dementia complex in Africa

Dr. Gretchen Birbeck presented pilot work on HIV-Dementia among Hospice Patients in Zambia (Birbeck *et al*, 2004). The study was an exposure-control study at Kalingalinga Hospice in Lusaka. The HIV Dementia Scale, Trails Making A & B, Neuropsychiatric Inventory (NPI), Caregiver Dependence Scale, and a locally adapted Mini Mental Status Examination were used to assess HIV-dementia. These measures were translated from English into Nyanja and Bemba and pilot tested in local markets for cultural acceptability prior to use in clinics and hospitals. Forty-seven participants were recruited with a mean age of 34.7 (23-58), 63% female, 25% widowed, 17% divorced, 40% had less than primary education, and the caregiver was almost always female [mother (33%), sister (33%), spouse (22%), aunt (6%)]. Memory problems were found in 52% of participants, and reported cognitive problems (as changes in thinking) were noted in 33% of the participants, by self-report or family members. The mean MMSE score was 24.2 (range 6-28). Gait problems were found in 58%. The cultural unacceptability of the NPI became apparent when family members refused to discuss issues of aggression, agitation, hallucinations, or depression in any abstract terms. The researchers concluded that culturally valid instruments are necessary to assess functional status, neuropsychiatric symptoms, and neurological outcomes. Also, functional outcome measures could elucidate the true social and economic impact of NeuroAIDS.

Dr. Noeline Nakasujja presented on the Assessment of Neuro-AIDS and complications in Uganda. This study assessed the prevalence of HIV-Dementia and Minor Cognitive Motor Disorder (MCMD) in an ambulatory Sub-Saharan HIV clinic. The study provided validity data for a rapid screening test, the International HIV dementia scale (IHDS) for

detecting HIV-D in an African population. The study also measured the prevalence of HIV sensory neuropathy in the same population. Eighty-one HIV+ individuals received detailed demographic, neuropsychological, neurological, and functional assessments which were adapted for use in this setting including translation into Luganda for some measures. Those with active CNS infections were excluded. Seventy-six HIV-individuals were evaluated to establish age and education matched controls for neuropsychological testing. HIV+ individuals with advanced infection showed impaired verbal memory, psychomotor, and functional performance compared to HIV-individuals, suggesting that HIV dementia as well as sensory neuropathy are common (HIV-D—30%, neuropathy—40%) among HIV+ individuals in an Infectious Disease clinic in Uganda. For HIV-D, the sensitivity of the IHDS was 80% and specificity was 57% (using a cutoff of ≤ 10), suggesting that the IHDS may be a useful tool for nonneurologist personnel to screen for cognitive problems in developing countries.

Neurological studies in resource-limited settings

Very little is known about the prevalence of ADC and milder neuropsychological dysfunction in HIV-infected people in resource-limited settings. Reports from these countries are few, and the findings have been somewhat inconsistent. The prevalence of ADC in Sub-Saharan Africa has been reported to be as low as 3% (Belec *et al*, 1989) to as high as 54% (Howlett *et al*, 1989). Differences in sampling and assessment procedures likely contribute to the observed disparities. The World Health Organization (WHO) conducted one such study of HIV-associated cognitive impairment using standardized assessment procedures on 602 HIV-positive and 353 HIV-negative individuals. The study sites included Bangkok, Thailand; Kinshasa, Zaire; Nairobi, Kenya; and São Paulo, Brazil. In physically symptomatic individuals, impairment rates of 19.1% (Zaire), 15.3% (Kenya), 18.4% (Thailand), and 13.0% (Brazil) were found (Maj *et al*, 1994). Based on the neurological examination, substantial rates of neurological impairment in symptomatic individuals were found (41% Zaire, 40% Kenya, 66% Thailand, and 54% Brazil).

ACTG 5199: The international neurological study

To date, there has been no systematic investigation of the effects of antiretroviral on cognitive functioning in resource limited settings. In the developed world,

cognitive impairment is relatively common in HIV-infected individuals who have not been treated with antiretroviral therapy (McArthur *et al*, 1993). Most HIV-seropositive individuals in resource-limited settings have not had antiretroviral regimen and are likely at the same or greater risk for ADC than their infected counterparts with access to HAART in the developed world. NIMH has funded the first study to investigate cognitive improvement with antiretroviral treatment in resource limited settings through the NIAID AIDS Clinical Trials Group, ACTG 5199: The International Neurological Study. This study will enroll 960 subjects at 12 international sites including Blantyre and Lilongwe, Malawi; Harare, Zimbabwe; Johannesburg and Durban, South Africa; Pune and Chennai, India; Port au Prince, Haiti; Rio de Janeiro and Porto Alegre, Brazil; Lima, Peru; and Chiang Mai, Thailand. The combined total number of people infected in the geographic areas represented by the ACTUs/AIACTUs and in the proposed sites within the International Neurology Consortium are in excess of 30 million. A5199 will conduct neuropsychological and neurological assessments to determine the prevalence of ADC and HIV-1-associated neurological OIs in untreated HIV-1-infected individuals at baseline; and determine the impact of HAART on the incidence of ADC and HIV-1-associated neurological OIs, and change in neurocognitive functioning with treatment.

The burden of neurological disease

HIV-associated cognitive impairment is associated with substantial impact on even the simplest activities of daily living. The burden of neurological disease on families and communities is substantial, with both an impact in terms of loss of productivity and income for the diagnosed, but also for those who take the primary responsibility as caretakers. In resource-limited settings with high rates of HIV-infection, the toll is likely devastating, but remains to be documented (Schifitto *et al*, 2001; Tozzi *et al*, 2004).

Funding opportunities

Dr. Kopnisky, from the National Institute of Mental Health's Center for Mental Health Research on AIDS (CMHRA), provided an overview of the structure of the National Institutes of Health, and discussed funding mechanisms available to investigators pursuing research in African settings (Kopnisky, 2004). Traditionally, research partnerships between a U.S. investigator and an investigator in a developing country are encouraged. Other NIH Institutes and Centers are also involved in supporting international research; moreover, the mission of the Fogarty International Center is to

actively support international research and training to reduce the disparities in global health. The CMHRA international research agenda includes: fostering new collaborations between U.S. and other PIs to enhance HIV prevention, disseminate proven interventions, facilitate development of investigators worldwide, and encourage U.S. PIs to work internationally. The CMHRA recognizes the

enormous global burden of disease posed by mental illness and brain disorders, and the coincident burden of infectious disease (HIV) and its sequelae on the CNS, families, and communities. They are committed to supporting basic and behavioral research with the goal of alleviating the suffering from mental illness and the effects of HIV and other opportunistic infections and coinfections on the brain.

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