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Global NeuroAIDS Roundtable

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REVIEW

Global NeuroAIDS Roundtable

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Abstract In May 2012, the Division of AIDS Research at the National Institute of Mental Health (NIMH) organized the "Global NeuroAIDS Roundtable" in conjunction with the 11th International Symposium on Neurovirology and the 2012 Conference on HIV in the Nervous System. The meeting was held in New York, NY, USA and brought together NIMH-funded investigators who are currently working on projects related to the neurological complications of AIDS (NeuroAIDS) in Africa, Asia, Eastern Europe, and Latin America in order to provide an opportunity to share their recent findings and discuss the challenges encountered within each country. The major goals of the roundtable were to evaluate HIV-associated neurocognitive impairment and determine if it may be directly attributable to distinct HIV subtypes or clades and to discuss the future priorities for global NeuroAIDS research. At the "Global NeuroAIDS

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Roundtable", presentations of preliminary research indicated that HIV-associated neurocognitive impairment is prevalent in all countries examined regardless of which HIV clade is present in the region. The only clear-cut difference between HIV-1 clades was in relation to subtypes A and D in Uganda. However, a key point that emerged from the discussions was that there is an urgent need to standardize neurocognitive assessment methodologies across the globe before definitive conclusions can be drawn regarding the relationship between HIV clade diversity and neuropathogenesis. Future research directions were also discussed at the roundtable with particular emphasis on the potential of viral and host factor molecular interactions to impact the pathophysiology of HIV-associated neurocognitive disorders (HAND) from a global perspective.

Keywords Human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) · Acquired immunodeficiency syndrome (AIDS) · HIV clade · NeuroAIDS · HIV-associated neurocognitive disorders (HAND) · Neuropathogenesis

Introduction

In May 2012, the Division of AIDS Research at the National Institute of Mental Health (NIMH) organized the "Global NeuroAIDS Roundtable" in conjunction with the 11th International Symposium on Neurovirology and 2012 Conference on HIV in the Nervous System. This meeting brought together NIMH-funded investigators who are currently working on the neurological complications of HIV/AIDS (NeuroAIDS) projects in Africa, Asia, Eastern Europe, and Latin America in order to provide an opportunity to share their recent findings and challenges encountered at their specific countries. The major goals of the roundtable were to examine HIV-associated neurocognitive impairment and determine if it may be directly attributable to distinct HIV subtypes or clades from a global perspective and to discuss the future priorities for global NeuroAIDS research.

Africa region roundtable

Dr. Sacktor presented data evaluating the impact of HIV-1 clade or subtype on the risk of dementia among adults in Uganda (Sacktor et al. 2009). In the USA, HIV-1 clade B is the predominant HIV subtype, whereas in sub-Saharan Africa HIV-1 clades A, C, and D are the predominant subtypes. Dr. Sacktor studied the relationship between HIV-1 subtype and the severity of HIV-associated cognitive impairment in 60 HIV-1 positive (HIV+) adults with advanced immunosuppression (mean CD4 T lymphocyte count= 127cells/mm^3) initiating highly active antiretroviral therapy (HAART) in Uganda at risk for HIV-associated cognitive impairment who received neurological, neuropsychological, and functional assessments. Subtype assignments were generated by sequence analysis of the viral genome using a portion of the gag and gp41 regions. Thirty-three HIV+ individuals were infected with HIV-1 subtype A, 2 with subtype C, 9 with subtype D, and 16 with recombinants of HIV-1 clades A and D (A/D recombinants). Eight of 9 (89 %) HIV+ individuals with subtype D had HIV-associated dementia compared to 7 of 33 (24 %) HIV+ individuals with subtype A (p=0.004).

These results suggest that in untreated HIV+ adults with advanced immunosuppression at risk for HIV-associated cognitive impairment, HIV-associated dementia may be more common among those patients with HIV-1 subtype D than those with subtype A. Studies are currently underway to evaluate HIV+ individuals with moderate immunosuppression. Further studies are needed to confirm this observation in other patient populations including HIV+ adults verses children, and urban verses rural settings, and to define the mechanism by which HIV-1 subtype D leads to an increased risk of neuropathogenesis

Dr. Boivin then presented data comparing neuropsychological function by HIV-1 subtype (A versus D) in Ugandan children. HIV subtype was determined by application of the multiregion hybridization assay from plasma HIV RNA (MHA). The MHA is particularly useful for identifying recombinant forms as two different targets dispersed across the HIV genome are simultaneously assessed. HIV-1 subtype was determined in 54 children (37 A, 16 D, 1 C; Boivin et al. 2010). Subtype A infections had higher log viral loads (median 5.0 versus 4.6, P=0.02). Children with HIV-1 subtype A performed more poorly than those with HIV-1 subtype D on all measures of neuropsychological function, especially on the Kaufman Assessment Battery for Children, second edition, even when adjusting for viral load levels. The primary outcome variables were the global scores of sequential processing (memory; P=0.01), simultaneous processing (visual–spatial analysis; P=0.005), learning (P= 0.02), and test of variables of attention visual attention (P=0.04). Based on these findings, it was concluded that children infected with HIV-1 subtype A demonstrated poorer neurocognitive performance compared to those children infected with subtype D. Subtype-specific neurocognitive deficits may reflect age-related differences in the neuropathogenesis of HIV-1. This may have important implications for when to initiate HAART and the selection of drugs with greater penetration into the central nervous system (CNS). Dr. Boivin's group is presently replicating these findings both in terms of neurodevelopmental assessment of Ugandan HIV-infected children less than 5 years of age and neuropsychological assessment of HIV-infected children between 5 and 12 years of age. They are also

exploring the sensitivity of the relationship between HIV subtype and neurocognitive effects when determining subtype from the HIV-1 Tat gene region. Although HIV-1 subtype D may be predisposed to CXCR4 tropism, HIV-1 subtype A strains can also acquire this phenotype in advanced disease. This may lead to a more virulent form of HIV disease during critical periods of brain and behaviorial development in children gestationally, peri- and postnatally. What is more, many potential target cell types express both CCR5 and CXCR4 co-receptors of HIV-1. In HIV-1 subtype C infection, the viral regulatory protein Tat has been implicated as another variable affecting the development of HAND in adults (Ranga et al. 2004). They are now trying to confirm if the HIV-1 Tat gene serves a modifying role in the development of encephalopathies in Ugandan children infected by HIV-1 subtypes A versus D.

Dr. Kanmogne presented preliminary data showing increased neurocognitive impairment (NCI) among AIDS patients in Cameroon compared to seronegative controls or HIV-infected individuals without AIDS (Kanmogne et al. 2010). She also presented data on comparative analysis of the circulating recombinant HIV-1 subtype CR02_AG, and HIV-1 subtypes A, G, and B. The recombinant HIV-1 CRF02_AG is predominant in West and Central Africa, but has also been spreading beyond Africa. Preliminary data from Dr. Kanmogne and colleagues also showed that Tat proteins from HIV-1 subtype B and CRF02_AG induced differential effects on human brain endothelial cells in vitro with subtype B significantly increasing the expression of cytokines and matrix metalloproteinases compared to Tat protein from HIV-1 CRF02_AG (Kanmogne et al., manuscript in preparation). Studies are underway to determine the effects of HIV genotype on viral replication and NCI in infected individuals in Cameroon.

Dr. Royal discussed his data from Nigeria where patients are currently recruited into NeuroAIDS studies at two sites in Abuja, the capital city. In previous studies, patients were examined for cognitive impairment using the International HIV Dementia Scale (IHDS) and it was found that, among treatment-naïve infected subjects, a cutoff of 9 correlated with an increased frequency of clinical impairment, as demonstrated by a Karnofsky status scale score of <50 (Royal et al. 2012). The strains of virus that account for approximately 90 % of infections in Nigeria are HIV-1 subtypes G and CRF_AG. In preliminary studies involving seven patients, it was found that all of four patients infected with CRF_AG were cognitively normal whereas two of three patients infected with subtype G demonstrated evidence of NCI. Studies are now underway that involve examining patients using a detailed neuropsychological battery. To date, these studies demonstrate the presence of impairment in infected individuals compared to seronegatives in speed of information processing, learning, executive functions, memory, and on the overall battery. Studies are ongoing to determine the population-based frequency and incidence of NCI, the effect of antiretroviral therapy and the links for monocyte-derived virus with impairment among infected individuals.

Dr. Wood discussed data relating to his studies examining HIV-1 clade C effects on neuropsychological function as well as his neuropathology studies in Zambia. Over 200 postmortem brains have been collected from individuals who died of AIDS in Zambia. Brain sections collected were cortex (frontal, parietal, temporal, occipital), sub-cortex (basal ganglia), hippocampus, and brain stem. So far, from their preliminary analysis, they found a high frequency of meningitis in addition to viral expression in brain. Mycobacterium tuberculosis (MTB) and fungus were evident in most of the analyzed tissues. The findings support previous reports indicating that HIV-1 subtype C does not induce HIV encephalitis (HIVE) since the most common finding was meningitis and only one case was found consistent with HIVE. Though these preliminary findings can be biased since most cases were obtained from individuals that died at the hospital, were HIV-1 positive, and the stage of HIV disease of these selected cases had not been determined. The high prevalence of opportunistic infections (OIs) found could indicate that these cases were in late-stage disease; however, in a region where high MTB is endemic and fungal infections are prevalent, this also cannot be definitely concluded. Therefore, it is likely that OIs, together with HIV-1, play a role in the development of neuropathology. They are now continuing to analyze additional brain specimens and to determine the correlation between HIV-1 disease progression with OIs, meningitis, and HIV-1 neuroinvasiveness. Dr. Wood also presented preliminary findings from neuropsychological evaluations and found 22 % impairment in HIV-1 clade C-infected subjects based on IHDS (Holguin et al. 2011).

Dr. Paul presented studies from Cape Town, South Africa where HIV-1 clade C is predominant and his findings revealed significant impairments on tests of cognitive function among HIV-positive individuals. Further, work from their group in South Africa suggests that structural magnetic resonance imaging abnormalities are evident among individuals infected with HIV-1 clade C, with reduced volumes in the total white matter, thalamus, and total gray matter. Preliminary data also suggest that volumes of the thalamus and putamen are smaller among individuals infected with HIV-1 clade C than individuals infected with HIV-1 clade B when compared with respective seronegative control groups (unpublished work). Collectively, the neuropsychological and neuroimaging studies provide evidence that HIV-1 clade C has significant neurotoxic consequences and additional work is needed to determine the specific mechanisms associated with these brain abnormalities.

Dr. Clifford discussed his studies relating to HIV-2, which is endemic in West Africa and results in chronic retroviral infection that is not rapidly fatal in most cases. Neurological involvement that is common in HIV-1 has not been widely assessed in HIV-2, and potentially could be a model of chronic retroviral infection of the CNS. Evaluation of neurological manifestations in HIV-2 compared with matched negative patients from two West African cohort studies were carried out supported by an R21 grant to Washington University in St. Louis, MO, USA. The cohorts included the Medical Research Council Laboratories supported community cohort in Caio, Guinea–Bissau and the sex worker cohort in Dakar, Senegal. Cross-sectional evaluations were performed by trained teams in each of the cohort centers. The IHDS was a common tool for assessing CNS performance. Data from the Caio cohort has been published (Choi et al. 2011). In Dakar, HIV-2 positive and negative populations were well matched, except for CD4 counts that were lower in HIV positives. No evidence of performance deficits was detected in HIV-2 positives compared to negative subjects. Similarly, on exam, there was no evidence of excess peripheral sensory neuropathy measured by distal vibratory sense or pin prick sensations, nor in neuropathic signs or symptoms. No myelopathy was found in this population screened to exclude HTLV-1 affected patients. These findings were qualitatively similar to what was found in the Guinea–Bissau cohort. A combined analysis is planned. In summary, Dr. Clifford's studies found little evidence of clinically significant central or peripheral neurologic dysfunction in chronically HIV-2 infected patients. While these immunologically intact HIV-2 patients do not have serious neurologic dysfunction, more subtle dysfunction not detected by the relatively coarse tests cannot be ruled out. Additionally, they cannot rule out development of these problems after longer exposure and progression of immunodeficiency.

The project succeeded in training teams at two African sites to perform quantitative evaluations and in translational research methodology. The foundation created with this project has already generated several large, collaborative West African translational research projects. These include the West African Network for Tuberculosis, AIDS and Malaria funded by the European and Developing Clinical Trial Partnership and the West African Platform for HIV Intervention Research funded by the Global Health Research Initiative of the International Development Research Centre of Canada. Thus, significantly augmented research will be carried out in this region, in part spurred by the work and investment in this project.

Asia region roundtable

Dr. Marcotte presented preliminary findings from collaboration between investigators at the University of California-San Diego, USA and the National AIDS Research Institute in Pune, India. This study is enrolling approximately 250 HIV seronegative controls and 250 HIV+ participants; assessing them using a comprehensive neuropsychological (NP) test battery and following them annually as they initiate HAART. The investigators are developing both baseline and longitudinal NP normative data. Analyses of the baseline data indicate that when examining age, education, and gender-adjusted *T* scores, there is a stair-step effect of disease status on cognition. Individuals with HIV-1, but without an AIDS diagnosis, perform significantly worse than controls, and the group with AIDS performs worse than both of the other groups. There is a slight increase in the prevalence of overall NP impairment in the non-AIDS group (<10 % higher than controls), with the greatest impairment (~40 %) seen in the AIDS cohort. Overall, early indications are that the neuropsychological impairment rates are not dramatically different from those seen in HIV-1 clade B. At 1 year, preliminary analyses suggest modest cognitive benefits of starting HAART in the non-AIDS and AIDS groups. Ongoing analyses are also focused on investigating the role of viral genetics and host factors (genetics, biomarkers) in the development of HAND.

Dr. Kumar gave a brief summary of his investigations carried out on HIV-1 clade C-infected individuals in Bangalore (South India) and Chandigarh (North India). Since HIV-1 Tat protein structure in clade C infection has serine replacing cysteine (impacting on monocyte transmigration into the brain), it had been believed that cognitive deficits may not be occurring among HIV-1 Clade C-infected individuals. However, it was shown that in India, occurrence of neurocognitive deficits among HAART naïve, HIV-1 clade C-infected individuals was similar to that occurring in the West with HIV-1 clade B infection (Gupta et al. 2007). It was also reported that inflammatory cytokines and virological markers were significantly increased in cerebral spinal fluid (CSF) of infected individuals (Kamat et al. 2009). A critical gap for research in India is the lack of normative data from HIV negative comparison groups. Dr. Kumar's group has recently obtained normative neurocognitive data from a group of 200 non-infected individuals and their findings are being published soon.

Dr. Pardo provided details of collaborative studies underway at the National Institute of Mental Health and NeuroSciences (NIMHANS) in Bangalore, India and the National Brain Research Centre in Manesar, India. Neuropathological studies of opportunistic infections in NeuroAIDS at NIMHANS have disclosed a high frequency of cryptococcal disease (32 %) and toxoplasma encephalitis (25 %) among 170 autopsy cases from patient's naïve to HAART. All of these patients were infected with HIV-1 clade C (Mahadevan et al. 2007). Immunopathological studies

performed at Dr. Pardo's lab also showed that infiltration by T regulatory CD4 cells (Tregs), a critical cell population for regulation of immune response, was particularly decreased in brain tissues from Indian patients with OIs as compared with brain tissues of patients from the USA with OIs infected by HIV-1 clade B. These findings may suggest a potential pathogenic role for the dysregulation of Tregs in patients with OIs and that the Tregs may be influenced by the HIV-1 clade.

Dr. Heaton presented data from a study that evaluated the rates, predictors, and consequences of neurocognitive impairment and neurocognitive decline over time, in two distinct groups of HIV-infected (HIV+) adults in China: former plasma donors (FPDs) in rural Anhui province, who were exposed to HIV due to use by some commercial blood collection companies of nonsterile methods during the 1980s and early 1990s and heroin injection drug users (IDUs) who were recruited from government-mandated methadone treatment programs in the more urban and affluent Yunnan province. Large samples of demographically comparable HIV uninfected (HIV−) controls were recruited from the respective risk groups in both provinces. Compared to their IDU counterparts, the HIV+ FPDs were older, much less educated, and had much lower family incomes; they also had HIV infection much longer, were more likely to have AIDS and to be taking HAART, had lower nadir and current CD4 cell counts, and were more likely to have neurocognitive impairment at baseline (35 % vs. 22 %). The lower rates of neurocognitive impairment in HIV+ IDUs vs. FPDs were seen only in those with early stage disease (non-AIDS, 15.8 % for IDUs versus 28.9 % for FPDs); those with more advanced disease (AIDS) had higher rates of impairment regardless of their infection risk group (38.6 % for IDUs and 40.0 % for FPDs). Neurocognitive impairment in both groups was associated with low nadir CD4 cell counts and more complaints of cognitive difficulties in everyday life; in Yunnan IDUs impairment was related to duration of infection, AIDS status, unemployment, decreased independence in activities of daily living, and depressed mood; in HIV+ Anhui FPDs, impairment was related to being on HAART and having low current CD4 levels.

Anhui FPDs were followed for up to 4 years and Yunnan IDUs up to 3 years. Thirty-one HIV+ (no HIV−) participants across both provinces died during the study; compared to HIV+ who completed the longitudinal study, those who died had higher HIV viral loads at baseline, as well as greater neurocognitive impairment, more depressed mood, and were less likely to be married. Over the follow-up period, HIV− controls and HIV+ IDUs and FPDs had comparable rates of neurocognitive improvement (all 10 %), but the HIV+ were much more likely to show neurocognitive decline (26 % for IDUs and 39 % for FPDs, vs. 12 % for controls).

These studies demonstrate that HIV infection, especially with advanced disease, was associated with increased rates of neurocognitive impairment and neurocognitive decline over time in these Chinese cohorts. Neurocognitive impairment increased the likelihood of everyday functioning difficulties and early mortality.

Dr. Sithinamsuwan discussed her studies relating to the characterization of neurocognitive impairment among individuals infected with HIV-1 clade CRF01_AE in Thailand. This clade accounts for about 90 % of HIV infection in Thailand. This work was completed primarily within the South East Asia Research Collaboration with Hawaii (SEARCH) in Bangkok, Thailand among several trials: SEARCH 001 and SEARCH 002 (ClinicalTrials.gov Identifier NCT00864292 and NCT00713752, respectively), and SEARCH 005.

The result from SEARCH 001 illustrated that depressive symptoms were more frequent in HAD (n=15) compared to nondementia cases (n=15; Valcour et al. 2007). They also identified a pattern of neuropsychological testing impairment in HIV-1 clade CRF01_AE, with substantial impairments noted in verbal learning, memory and visuospatial skills compared to a matched nondementia group. As expected, all of these areas improved after initiation of HAART; however, the HAD group tended to have less complete recovery compared to the nondementia group. The deficits noted in psychomotor speed, learning, and memory were consistent with findings from HIV-infected subjects infected with HIV-1 clade B. In contrast to other clades, they did not identify a predominance of motor deficits in this cohort, which may suggest a potential difference by HIV-1 clade; however, cultural factors, severity of disease, or clade-specific influences may all play a role.

The SEARCH 005 study investigated the frequency of neurocognitive impairment and psychiatric co-morbidity among 64 Thais who had been maintained on non-nucleoside reverse transcriptase inhibitor-based HAART with undetectable plasma viral load for years within the 2NN cohort. Their goal was to demonstrate frequent impairment despite monitored and persistently suppressed plasma HIV RNA. This study identified HAND in 37.5 % of enrollees: 20.3 % with asymptomatic neurocognitive impairment (ANI), 15.6 % with mild neurocognitive disorder (MND) and 1.6 % with HAD (Pumpradit et al. 2010). The rate appeared to be somewhat lower than that described in the USA (47 % prevalence of HAND) from the CHARTER study; however, the CHARTER cohort included a substantial number of individuals with detectable plasma HIV RNA known to impact cognition (Heaton et al. 2010). The authors concluded that HAND remained frequent even in well-controlled Thai individuals, presumably infected with HIV-1 clade CRF01_AE virus.

Dr. Letendre discussed a randomized phase 4 clinical trial in China comparing a better-penetrating HAART regimen (zidovudine–lamivudine–nevirapine) to a worse-penetrating

comparison HAART regimen (tenofovir–lamivudine–efavirenz) on the prevention of HAND. The project is based at two HIV clinics in Beijing, China and has a targeted enrollment of 250 subjects, 233 of whom have been randomized as of May 2012 (ClinicalTrials.gov Identifier: NCT01340950). The project will investigate the impact of immune activation and viral hepatitis on the relationship between treatment arms and incident neurocognitive decline over 96 weeks of observation. The project also includes an exploratory pharmacogenomics aim and has received supplemental funding for lumbar punctures and magnetic resonance spectroscopy. The final primary endpoint visit is expected to occur in the third quarter of 2013.

Latin America, Eastern Europe, and global multisite studies roundtable

Dr. Brew described studies related to assessing HIV-1 related neurologic disease in the Asia Pacific region. He outlined the activities of the Asia Pacific NeuroAIDS Consortium (APNAC) which has performed cross-sectional outpatient and inpatient studies in Thailand, Papua New Guinea, Fiji, Malaysia, Cambodia, Indonesia, China, and Hong Kong (Wright et al. 2008). While the majority of the sites are known to have mixed HIV clade populations, this is not the case in the Papua New Guinea site where HIV-1 clade C is overwhelmingly dominant. Across the APNAC sites, neurocognitive impairment was found to be common among the 658 participants (161 HIV-negative matched controls) with rates of moderate to severe disease across the region of 12 %, not dissimilar to rates in developed countries. When the whole spectrum of HAND was included the figures ranged from 25 to over 50 %, again very similar to the developed countries. The rates varied according to region rather than any obvious influence of HIV-1 clade; the variability likely related to some selection bias in the populations studied. Importantly, however, when Papua New Guinea is considered, the rates were 53 % for ANI/MND and 18 % for HAD. Symptomatic sensory neuropathy was found in approximately 20 %, similar to data from developed countries. These data argue strongly against any significant impact of HIV clade on HAND and neuropathy and particularly argue against any mitigating effect of HIV-1 clade C on HAND.

Dr. Robertson discussed findings from the AIDS Clinical Trials Group (ACTG) A5199. The International Neurological study (Robertson et al. 2011) which compared the neurological and NP effects of three HAART regimens in 860 HIV-1-infected participants in the resource-limited settings (RLS). The goal of the study was to assess prevalence of HIV-related neuropsychological and neurological dysfunction in RLS, to assess whether there was any neurocognitive advantage between initial recommended treatment regimens for RLS, and to assess incidence of HIV-related neuropsychological and neurological dysfunction in RLS on antiretroviral treatment.

Participants from Brazil, India, Malawi, Peru, South Africa, Thailand, and Zimbabwe were randomized to three HAART treatment arms: A (lamivudine-zidovudine plus efavirenz, $n=289$), B (atazanavir, emtricitabine, and didanosine–EC $n=293$), and C (emtricitabine–tenofovir–disoproxil fumarate plus efavirenz, $n=278$) as part of the ACTG PEARLS study (A5175). Standardized neurological and NP screening examinations (grooved pegboard, timed gait, semantic verbal fluency, and finger tapping) were administered every 24 weeks from February 2006 to May 2010. Associations with neurological and neuropsychological function were estimated from linear and logistic regression models using generalized estimating equations. There was an extensive period of follow-upon HAART for over 3 years with the median weeks on study at 168 ($Q1=96$, $Q3=192$) for the 860 participants.

The study detected no significant differences in neuropsychological and neurological outcomes between randomized HAART regimens. Significant improvement occurred in neurocognitive and neurological functioning over time after initiation of HAART. The etiology of these improvements is likely multifactorial, reflecting reduced HIV-1 infection of the CNS, better general health and practice effects. This study suggests that treatment with either of the WHO-recommended first-line antiretroviral regimens in resource-limited settings will improve neuropsychological functioning and reduce neurological dysfunction (Robertson 2011).

Significant country variation was noted in neuropsychological and neurological variables, which are likely multifactorial including site differences in culture and education. Differences in underlying HIV subtype are present and cannot be excluded as the cause of the country variation in neuropsychological and neurological outcomes as of yet. Specific subtyping of the study participants is underway and will yield more conclusive results.

Dr. Achim presented data derived from studies (in collaboration with Dr. Victor Babes Hospital in Bucharest) of a long-term cohort of young adults in Romania who were infected with HIV-1 clade F as children. In a preliminary study using a sample of 49 HIV+ and 20 HIV− participants and comparing raw score neuropsychological performance, they saw moderate-to-large effect sizes across all neuropsychological measures, with significant differences in the neurocognitive domains of fluency, speed of processing, attention/working memory, executive functioning, and motor skills. Since Romanian-specific normative data do not exist, it is difficult to establish "impairment" within individual participants. However, in order to at least estimate impairment rates in their pilot feasibility study, they applied normative data (adjusting for age, education, and gender)

that were gathered in the USA from a Spanish-speaking cohort (using Spanish language measures), since, unlike typical US norms, these provide adequate adjustments for individuals with lower levels of education. Using this approach, *T* scores for the Romanian controls were generally around 50, which is what one would expect if the norms were appropriate for the study group. Using data corrected with these norms, they calculated a global deficit score (GDS), which provides an estimate of overall cognitive functioning. Worse cognitive performance results in a higher GDS. A GDS score of >0.71 was the cutoff point where 15 % of HIV− controls were classified as impaired (mirroring the procedure used in their US studies). Using this score, they found that 47 % of the HIV+ cohort was classified as having neurocognitive impairment.

All HIV+ participants had a current CD4 cell count greater than 200. In order to examine whether there was a relationship between CD4 cell levels and cognition, they split the group at a CD4 cell count of 350 (the current guideline for starting antiretroviral treatment). Using the GDS as an estimate of overall cognitive functioning, within the HIV+ group there was no difference between those with a current CD4 <350 (GDS=0.91; n=15) and those with a CD4 cell count >350 (GDS=0.94; n=29). However, there was a trend for those with a nadir CD4 <200 (GDS=1.04; n=34) to have a higher GDS than those who never dropped below 200 (GDS=0.65; n=13, p=0.11).

The results of this feasibility study suggest that the translated neuropsychological measures are valid and sensitive to the effects of HIV-associated brain injury in this Romanian cohort. The HIV+ participants had worse neurocognitive functioning than the HIV− group, despite being matched in terms of socioeconomic background. Thus, even though the participants in this study were long-term survivors of infection that occurred during early childhood and had up to a decade of effective antiviral treatments that currently render them immunocompetent with good viral suppression, a significant proportion still have evidence of HAND. Importantly, their findings are not only of interest in the Romanian context, as worldwide it is estimated that 2.3 million children under the age of 15 are living with HIV.

Dr. Ellis discussed studies of neurocognitive impairment using a comprehensive neuropsychological assessment and the IHDS in HIV-1 clade B- and C-infected individuals from the same geographic region in southern Brazil. They studied 52 HIV+ and 40 HIV−/HCV− subjects from 2007 to 2011 in Curitiba, Brazil. All the HIV+ participants were recruited through the Hospital de Clinicas UFPR and Parana State Health Secretary; HIV− participants were recruited from blood banks. Blood and CSF were collected from all HIV+ participants. All participants were evaluated with an adaptation of the HIV Neurobehavioral Research Center (HNRC) neuropsychological battery for testing in Brazilian Portuguese, as well as the IHDS. HIV+ (n=52) and HIV− participants (n=40) were comparable on demographic characteristics. Among HIV+ participants, median CD4 nadir was 90 [IQR 36–266] and median log10 plasma HIV RNA was 1.68 [IQR 1.68–3.52]. Clade B (n=27)- and C (n=25)-infected individuals were similar with respect to demographic and HIV disease variables with the exception of plasma viral load, which was lower in clade B subjects than in clade C (median [IQR], 1.7 [1.7, 1.9] vs. 2.9 [1.7, 3.8]; p=0.008); clade B-infected individuals were also more likely to be on HAART (81 % versus 56 %). HIV+ individuals had a significantly higher rate of neurocognitive impairment than HIV- by the GDS (60 % vs 17 %). Impairment rates among HIV-1 clade B- and C-infected individuals did not differ significantly (65 % vs. 55 %). There was no significant difference in IHDS scores or in IHDS impairment rates between HIV-1 clade B- and C-infected individuals (11.0 [9.0–12.0] vs. 12 [9.8–12]; p=0.21; 44 % vs. 28 %, p=0.22; Cohen's d=0.17), even after adjusting for plasma viral load (p=0.83). In summary, the HNRC NP battery was successfully adapted for use in Brazilian Portuguese speakers. When ascertained using comparable methods, clade B and C HIV infections in the same geographic region did not differ in their rates of neurocognitive impairment. Similarly, the prevalence of pleocytosis, an indirect marker of intrathecal cellular chemotaxis, did not differ between clade B and C infections.

Discussion

Drs. Grant, Clifford, and Valcour provided a summary of the key findings presented at the "Global NeuroAIDS Roundtable" and led a discussion focused on future directions for the field. Dr. Grant stated that data from at least 11 countries were presented and HAND was prevalent in all these regions. However, HAND was not associated with HIV-2 infection based on studies conducted by Dr. Clifford's group in West Africa. With regard to the impact of HIV-1 clade on HAND, the results depended on the subtypes that were compared and were somewhat mixed. The indirect data presented comparing HIV-1 clade B and clade C indicated a similar clinical prevalence of HAND. For example, when impairment rates in India and Thailand were compared to rates found in prior studies in the USA, the rates were found to be similar. In a more direct and compelling comparison of HIV-1 clade B and C in the same populations in Brazil, Dr. Ellis found the same rates of neurocognitive impairment across these two clades. In a comparison of different clades, Dr. Sacktor in his studies in Uganda found that HIV-1 associated dementia was more common among those patients with subtype D than those with subtype A. A potential mechanism driving this

difference may be related to co-receptor usage. For example, HIV-1 clades A and C use the CCR5 co-receptor for viral entry which is nonsyncytium inducing, macrophage tropic, and associated with slower viral growth. Whereas HIV-1 subtype D is dual tropic and CXCR4 T cell tropic strains have more rapid viral growth and replication causing more rapid HIV disease progression. The differences in neurocognitive impairment seen between HIV-1 subtypes A and D may in part be linked to HIV disease progression.

In direct contrast to this adult data from Uganda, Dr. Boivin presented studies which indicated that in children infected by HIV-1 poorer neurocognitive performance was demonstrated with subtype A when compared to subtype D. HIV-1 subtype A is associated with CCR5 tropism and this may confer the advantage of infecting macrophages associated with an encephalitis disease outcome. In sensitive periods of the development of children, CCR5–tropic strains may be more "encephalopathogenic". If this is true, it does raise some very important questions about the effects of HIV-1 clades and other factors that may operate differently in the context of neurodevelopment verses a mature nervous system.

A number of issues need to be considered while interpreting the data presented relating to HIV clade diversity and neuropathogenesis at the "Global NeuroAIDS Roundtable". Many speakers spoke of the importance of using standardized methods for neurocognitive assessments as a current challenge to addressing the question of the effects of HIV-1 clade on HIV-associated neurocognitive impairment. An interesting example was in Dr. Royal's presentation where in his pilot work he had a rate of 22 % cognitive impairment using the IHDS and then he had a rate of about half of people impaired using a more comprehensive battery that had been standardized. This finding demonstrates an important limitation of using shorter-screening batteries to identify individuals with neurocognitive impairment. In addition, neurocognitive assessment batteries need to take into account local cultural, language, and socioeconomic factors when determining rates of neurocognitive impairment.

It is also critical to delineate the type of neurocognitive impairments that are being defined in relation to HIV-1 clades and those delineated by HAND. HAND encompasses asymptomatic neurocognitive impairment, minor cognitive disorders and HIV-associated dementia. The earlier studies demonstrating HIV-1 clade differences were studying the more severe HIV-associated dementia cases from patients in India infected with HIV-1 clade C. Thus, HIV-1 clade differences, if present, may only be apparent if similar types of impairment stratifications are compared.

The treatment status of the patients and the types of HAART regimens being administered also needs to be taken into account when assessing the impact that HIV-1 clades have in inducing neurocognitive impairment. HAART is known to make a difference in neurocognitive outcomes and different drug combinations have distinct characteristics with respect to their CNS penetration.

Another issue to consider is that HIV-1 subtype C viruses may demonstrate heterogeneity based on their geographic origins. New emerging data suggests it is important to group clade C into CC vs. CS variants since geographic differences in their distribution have been found (Prasad et al., personal communication). These viral variants may have differential impacts on neurocognitive outcomes.

There was also a discussion about future research areas to better define the potential mechanisms of HIV-1 clade specific effects on HAND. Some of the areas for future research include (1) identification of HIV clade specific neurovirulent and/or neurotropic signature sequences; (2) delineation of potential viral clade specific differences in interaction with co-morbid conditions; (3) study of HIV clade specific developmental effects in relation to neuropathogenesis; (4) assessment of the differential impact on neurocognitive outcomes resulting from unique interactions of antiretroviral medications with different viral clades; (5) study of HIV clade specific differences in LTR transactivation; (6) assessment of the impact of variations in HIV clade on establishment of viral set points; and (7) study of a potential pathogenic role for HIV-1 clade specific dysregulation of Tregs in patients with OIs.

Conclusions

The preliminary findings presented at the "Global NeuroAIDS Roundtable" indicated that HIV-associated neurocognitive impairment is prevalent in all countries examined despite the HIV-1 subtype distribution in the region. The only clear-cut difference between HIV-1 subtypes on neurocognitive impairment was seen in relation to subtypes A and D in Uganda. However, a key point emerging from the discussions was that there is an urgent need to standardize neurocognitive assessment methodologies across the globe before definitive conclusions can be drawn regarding the relationship between HIV-1 clade diversity and neuropathogenesis. A number of research directions were also discussed particularly with reference to studies of potential mechanisms of interaction of viral and host factors in the pathophysiology of HAND from a global perspective.

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