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Review

NeuroAIDS in Brazil

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Brazil has the largest number of HIV cases of any single country in Latin America—over 600,000. Recently, investigators have begun to characterize the extent of neurological morbidity due to HIV in this country. During 2005 and 2006, the U.S. National Institute of Mental Health cosponsored two meetings of experts aimed at summarizing existing knowledge of HIV and its neurological complications in Brazil. Topics addressed ranged from clinical neurobehavioral aspects to molecular biology. Experts attending the meeting considered fruitful directions for future research. *Journal of NeuroVirology* (2007) **13,** 89–96.

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In July 2005, the U.S. National Institute of Mental Health organized the first major meeting devoted to discussing issues relating to neurologic and neuropsychiatric complications of human immunodeficiency virus (HIV) infection in Brazil. Entitled "NeuroAIDS in Brazil," the meeting was convened at the Marina Palace Hotel in Rio de Janeiro, Brazil, and attended by leading neurologists, psychiatrists, psychologists, and Brazilian Health Ministry officials. The participants discussed findings related to central nervous system (CNS) as well as peripheral nervous system (PNS) complications of HIV infection and associated opportunistic and coinfections in Brazilian patients. Several neurologists from the United States discussed strategies and capacity-building needs for assessment of HIV-associated neurologic complications in resource poor countries. A panel discussion entitled "Priorities for NeuroAIDS Research in Brazil and the Developing World" was also convened. Among the many topics discussed, a key issue that emerged from the panel discussion was that future research efforts should be directed at understanding the importance of viral clade diversity in HIV neuropathogenesis.

A second meeting in Curitiba, Paraná, explored these issues further. This international symposium, entitled "HIV and the Nervous System: Clade Diversity" was held at the Grand Hotel Rayon in Curitiba, in Southern Brazil, on April 21 and 22, 2006. Organizers Sergio Almeida, M.D., PhD of the Federal University of Paraná (UFPR) in Curitiba and Ronald Ellis, M.D., PhD of the University of California, San Diego (UCSD), assembled investigators from more than 20 different institutions around the world. Southern Brazil is unique in that it hosts substantial proportions of two of the most prevalent HIV subtypes, clades B and C, in the same geographical region. The meeting was sponsored by the US National Institutes of Mental Health (NIMH), the UCSD HIV Neurobehavioral Research Center (HNRC), the Academia Brasileira de Neurologia, UFPR, and Fundação Araucária.

HIV epidemiology in Brazil and the governmental response

Dr. Orival Silveira of the Brazilian Ministry of Health provided an overview of the epidemiology and socioeconomic aspects of HIV-1 infection in Brazil. The Brazilian government recognized the presence of HIV in the country earlier than many other countries; attempts at an organized governmental response were launched in 1983. Following an initial exponential rise in prevalence of HIV-1 similar to that seen in many other countries in the mid-to-late 1980s, the rate stabilized at approximately 0.61% (1990 to 2003). Even with this relatively low prevalence, Brazil has the largest number of HIV cases of

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any single country in Latin America: approximately 600,000 as of 2004. Cumulative acquired immunodeficiency syndrome (AIDS) cases number 362,364. Among the factors believed to have contributed to the effective stabilization of the epidemic in Brazil was the government's response, which included strategies of prevention, harm reduction, and antiretroviral treatment.

In 1991, the government initiated distribution of AZT through the public health system, and in 1996 the Sarney Law (9313) established the right to universal access to antiretroviral therapy (ART). In 1997 to 1998, monitoring and logistic systems were established and by April, 2005, ART was being provided to 160,000 patients in Brazil. From 1997 through 2005 the total AIDS spending for the country of Brazil was $3.5 billion US dollars, with antiretroviral drugs (ARVs) making up the bulk of these expenditures ($2 billion). Of this investment, 89% came from the national budget and 11% was from a World Bank Loan. The National Network of Public laboratories consists of 82 CD4+/CD8+ laboratories, 71 viral load laboratories, and 18 genotyping centers, distributed across the country. AIDS incidence, hospitalization, and mortality growth rates were controlled, with a noticeable stabilization after 1998. In 2005, 79% of ARVs were procured by importing from multinational manufacturers, with the remaining 21% being produced locally.

HIV diversity in Brazil

Ricardo Sobhie Diaz, MD, PhD, of the Retrovirology Laboratory, Division of Infectious Diseases, at the Paulista School of Medicine, Federal University of São Paulo, summarized recent advances in scientific knowledge of HIV diversity and viral clades in Brazil. Brazilian investigators have found a large spectrum of unique B/F recombinants in the epicenter of the Brazilian epidemic in Sao Paulo, suggesting a high frequency of dual infections there. In fact, the majority of clade F viruses in Brazil are recombinant forms (Soares *et al,* 2003). With the recent introduction and significant expansion of clade C in the south of Brazil—an area where clade B infections previously predominated, B/C recombinants are becoming increasingly frequent.

Dr. Diaz presented some evidence that viral subtypes might influence responses to antiretroviral therapy. For example, clade C viruses have been shown to develop rapid resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) via the V106N mutation (Brenner *et al,* 2003), and clade F strains may show natural resistance to protease inhibitors (PIs) via the L69M mutation (Calazans *et al,* 2005). Additionally, one study demonstrated that after 48 weeks of antiretroviral therapy viral load declines were less in clade F–infected individuals than in clade B–infected patients.

Antiretroviral drug resistance testing methods in Brazil

Rodrigo Brindeiro, MD, described RENAGENO (Rede Nacional de Genotipagem), the National Genotyping Network of Brazil, which constitutes 18 laboratories spread across the country, coordinated by a central laboratory in Río de Janeiro. Local treating physicians identify HIV+ patients who may need antiretroviral resistance testing in preparation for designing a new regimen. The local physician then sends a request for resistance testing to one of hundreds of reference physicians, who in turn validate the need for resistance assays. The reference physician (Médicos de Referência em Genotipogem) then forwards the request to the laboratory, and patient samples are sent for genotypic assays. Results are fed back to local providers through the reference physicians. A government-hosted website provides algorithms to interpret the resistance genotyping results. RENAGENO has centralized systems for quality assurance, including methodologies for detecting polymerase chain reaction (PCR) contamination.

Clade B and C infections in the SCID mouse model of neuroAIDS

William R. Tyor, MD, of Charleston, South Carolina, USA, presented data on an animal model that is being used to investigate HIV subtype neuropathogenesis. The severe combined immune deficiency (SCID) mouse model of HIV encephalitis (HIVE) takes advantage of the capacity for HIV-infected human peripheral blood mononuclear cells (PBMCs) to grow in mouse brains where they are less likely to be rejected by the host immune system. Such mice develop pathology similar to HIVE, particularly when the infecting strain is a CXCR5 coreceptor–utilizing strain. Pathological features in the brains of these mice include multinucleated giant cells, microgliosis, and astrogliosis. Additionally, human monocytes become activated in the mouse CNS and express tumor necrosis factor (TNF)-α and interferon (IFN)-α. Cognitive deficits in this model are demonstrated by using the water radial arm maze, which reveals problems in both working memory and reference memory compared to control mice. Finally, neuronal death and loss of dendritic integrity can be found in the brains of these mice. When combination ART is administered to the mice, measurable reductions occur in HIV viral load, astrogliosis and TNF-α expression. However, normalization of neuronal dendritic integrity and cognitive function is not observed.

HIV clades in India: implications for the CNS

Vinayaka R. Prasad, PhD, of the AIDS International Training and Research Program at the Albert Einstein

College of Medicine, Bronx, New York, USA, reviewed recent findings on molecular differences between clade B and C viruses that may influence HIV neuropathogenesis. These clade specific differences occur in a virally encoded transactivating protein, Tat. HIV-1 Tat can recruit monocytes to the brain both via its own beta chemokine activity as well as indirectly by stimulating monocyle chemoattractant protein (MCP)-1 chemokine secretion by astrocytes. Dr. Prasad's laboratory, in collaboration with Drs. Uday Kumar Ranga (Bangalore) and Raj Shankarappa (U. Pittsburgh), examined Tat protein sequences from different subtypes and found that the dicysteine chemokine motif is polymorphic and is conserved in all subtypes except C isolates, where a Cys31 → Ser mutation is present in 90% of the subtype C sequences examined (Siddappa *et al,* 2004). The subtype C Tat protein was also defective in monocyte chemotaxis, but retained its transcriptional transactivation function (Ranga *et al,* 2004).

In collaboration with Dr. Tyor, the SCID mouse HIV encephalitis model has been used to investigate whether HIV-1 CNS infection differs by subtype. Experiments were done in which human monocytes were infected with either HIV-1 ADA (subtype B) or HIV-1 Indie (subtype C) isolates. Monocytes were then seeded into SCID mouse brains in a manner that leads to similar densities of infected cells. Mice were monitored for cognitive dysfunction using a radial arm maze (RAM). As established previously, HIV-1 ADA–infected mice made significantly more errors on the RAM compared to controls. Interestingly, the HIV-1 Indie–infected mice exhibited cognitive performance at an intermediate level between the two other groups, resulting in a lack of significant differences in errors for the clade C versus control and clade C versus HIV ADA group comparisons. Experiments to confirm these findings are currently in progress. These include the use of magnetic resonance spectroscopy (MRS) to quantify *N*-acetylaspartate as a measure of neuronal/axonal damage *in vivo.*

HIV clades in Europe and Africa: relationship to neuroAIDS

Dr. Paola Cinque of the San Raffaele Scientific Institute, Milano, Italy, reviewed findings on HIV clades in Europe and Africa and potential implications for neuropathogenesis. The prevalence of non-B subtypes in Europe has been increasing among persons infected heterosexually from 1994 to 2004. HIV-1 clade differences at the genome level could translate to biological differences that might result in altered systemic or neurological pathogenesis. Previous studies have already demonstrated clade-specific differences in transmission risk, natural history, and response to ART. For example, whereas subtype B viruses often demonstrate a switch to CXCR4 coreceptor usage in advanced disease stages, subtype A isolates rarely show CXCR4 tropism (Laeyendecker *et al,* 2006). With regard to neuropathogenesis, it is possible that clade-specific differences in Env might confer differential neurotropism or neurovirulence. For example, subtype C isolates show reduced fitness in macrophages compared to subtypes A, B, and D (Ball *et al,* 2003). Because macrophages are important in neuropathogenesis, this characteristic may confer reduced susceptibility to neurological disease with subtype C infections. However, there is not yet any direct evidence for an impact of viral subtype on the prevalence and natural history of CNS disease. Studies that address this issue must account for confounding factors such as the geographical association of certain coinfections with clade distribution across the world.

C/EBP binding sites and different HIV clades

Dr. Brian Wigdahl of Philadelphia, Pennsylvania, USA, described recent investigations focusing on subtype-specific molecular diversity in the HIV-1 regulatory region or long terminal repeat (LTR). LTR regulates HIV-1 gene expression in monocytes, and LTR-directed transcription of viral genes relies heavily on the participation of cellular transcription factors, including nuclear factor (NF)-κB, Sp, and CCAAT/enhancer binding protein alpha (C/EBP) family members. Specifically, two C/EBP binding sites within the modulatory region of the LTR have been shown to be required for efficient virus replication in cells of monocyte/macrophage lineage, even though they are not needed for replication in lymphoid cells. Two specific C/EBP configurations, 3T I and 5T Sp III, are only found in LTRs from PBMCs of patients in late-stage HIV disease, and are more common in autopsied brain tissue derived from individuals with AIDS dementia as compared to those without. Emerging data suggest that the physical position and consensus sequence of C/EBP DS3 differs among HIV-1 subtypes A, B, C, and D. These differences might in turn affect monocytic differentiation, neuroinvasion, viral replication, and ultimately manifestations of CNS disease.

HIV dual infection and the worldwide diversity of HIV

Davey Smith, MD, of the University of California, San Diego, USA, spoke on global HIV diversity and dual infection. He reviewed the strong phylogenetic evidence that HIV is a zoonotic disease, with HIV-1 originating from chimpanzees and HIV-2 from sooty mangabees. Since moving into the human population in Africa, HIV-1 has become a highly successful pathogen, infecting millions of people worldwide.

Part of its devastating success comes from its ability to diversify, which explains the numerous clades and forms that exist throughout the world. This diversification could have occurred through random mutation and selection or through recombination, or both. Recombination occurs when two different viruses infect the same person and exchange genetic material to form mosaic viral progeny. Because many recombinant forms have been identified, both circulating (CRF) and unique (URF), dual infection with HIV cannot be a rare occurrence. In fact, in many parts of Africa where multiple clades intersect, URFs represent as many as 50% of the strains. Dual infection occurs in two forms: coinfection—when an individual is infected with two different viruses at the same time—and superinfection—when an individual is infected with separate viruses at separate times.

Investigating instances of superinfection may give insight into how the immune system can protect itself from infection. Ongoing efforts to develop candidate HIV vaccines must consider these "natural" immunization failures in the hopes of better understanding the role of virus-specific CD8+ T-cell responses and other host immune responses. Emerging data suggest that the strength of neutralizing antibody responses, rather than cytotoxic lymphocyte (CTL) responses, is associated with protection from superinfection. Thus neutralizing antibody is potentially important for the design of preventative vaccines.

Neurocognitive disorders in HIV

Igor Grant, MD, Director of the HIV Neurobehavioral Research Center at the University of California, San Diego, USA, provided an overview of HIV CNS disease, focusing on neurobehavioral issues in HIV infection. HIV enters the brain early in the course of infection and can produce neurocognitive impairment (NCI) that can range in severity from subclinical to frank dementia. Those that develop NCI often have difficulties in learning new information, rapidly processing and evaluating data, and in neuromotor abilities. These consequences may be due to direct effects of viral products on neural cells, or they may represent effects of inflammatory cascades activated in the CNS. Ultimately, damage to synaptodendritic structures is evident as diminished mitogen-activated protein (MAP)-2 immunostaining in cerebral tissue collected at post mortem. During life, this can be seen by using brain magnetic resonance imaging, which reveals elevated abnormal white matter signal that has been shown to correlate with the synaptodendritic damage. Synaptodendritic injury is believed to be the substrate for NCI. Although NCI may be quite mild, it can still affect everyday functioning, such as employment, and medication management, and it is associated with shortened survival.

Although modern combination ART has reduced the incidence of NCI, prevalence remains high (30% to 60% of cases, depending on stage of HIV disease), largely due to long-term survival of treated persons. HIV-related NCI may wax and wane in severity over time, seen as transitions from mild impairment to normal neurocognitive function, or vice versa. Cofactors that may exacerbate the effect of HIV on the brain include substance abuse and concurrent hepatitis C infection. ARV treatments with CNS-penetrating agents that significantly lower cerebrospinal fluid viral load appear especially effective in reversing NCI. In addition to NCI, persons with HIV disease may suffer from mood disorders or have other psychiatric comorbidities that compromise both prevention and treatment efforts. In culturally diverse and resource-limited settings, diagnosis of NCI may require development of instruments that are specific and have normative standards for the culture in question. Efforts to prevent HIV transmission and improve adherence to treatment may be compromised by the presence of NCI and other neuropsychiatric disturbances.

Antiretroviral therapy and the CSF/CNS sanctuary

Ronald Ellis, MD, PhD of the HIV Neurobehavioral Research Center at the University of California, San Diego, USA, discussed the potential beneficial neurocognitive effects of antiretroviral therapy in light of emerging evidence that the CNS provides HIV with a sanctuary from the effects of antiretroviral medications. Although HIV-associated dementia (HAD) and milder neurocognitive disorders improve with highly active antiretroviral therapy (HAART), this recovery is incomplete in many patients. There is conflicting evidence about whether HAART regimens with better CNS penetration are necessary to obtain optimal neurocognitive improvement. Some investigators have classified the outcomes of HAART in cognitively impaired patients into three principal categories: (1) fully recovered, representing individuals who have restored normal neurocognitive functioning after HAART is initiated; (2) partially recovered, that is, individuals who have recovered to some extent, but have residual neurocognitive impairment; and (3) irreversible, representing patients with "burnt out" brain injury and persistent cognitive impairment. What proportions of patients fall into these three groups is entirely unknown, because HIV-infected individuals in the United States receive treatment independent of the presence of cognitive impairment, and no prospective clinical trial has ever attempted to optimize antiretroviral treatment for HIV neurocognitive disorders.

Nevertheless, large-cohort studies continue to identify an excess of neurocognitive impairment among HAART-treated, HIV-infected individuals, suggesting that incomplete recovery is common. Mild neurocognitive impairment (MNI) is defined as

impairment in two or more domains on neuropsychological testing using appropriate normative comparisons, in a patient with no other definitive etiology for neurocognitive impairment who may or may not be aware of cognitive difficulties. In large-cohort studies such as CHARTER (CNS HIV Antiretroviral Therapy Effects Research), this condition affects about 50% of HAART-treated, HIV+ individuals, as compared to an expected ~15% in the general population. Although the impact of this type of problem in individual patients may be quite subtle, across large groups there are substantial overall reductions in employability, competent driving, and other higher-level activities of daily living. This is true even among individuals with relatively early HIV disease, i.e., those who have never met criteria for AIDS. Mild cognitive impairment may result in inadequate adherence to antiretroviral medications, and it predicts death independent of other markers of disease severity.

Development of neuropsychological test norms in U.S. minority populations

Mariana Cherner, PhD, Assistant Professor of Psychiatry at the HIV Neurobehavioral Research Center (HNRC), University of California, San Diego, USA, spoke on the development of neuropsychological (NP) test norms for minority populations in the United States and implications for norms in the developing world. The HNRC approach to NP assessment utilizes tests that evaluate a variety of cognitive domains including learning and remembering, speeded information processing, attention/working memory, visuospatial/constructional abilities, verbal functioning, abstraction/executive functioning, motor ability, and sensory-perceptual functioning.

Age, education, and in some cases sex can affect performance on NP tests. Therefore to classify an individual as impaired one must compare their score to what would be considered normal for a person who is similar in these demographic characteristics. To do this, a normative sample is tested. Raw scores are converted to standardized scores, typically adjusted for age, years of education, and sex. Standardized scores reflect the level of performance on a common scale across tests: *T* scores (mean = 50, standard deviation = 10), where scores >55 correspond to above average performance, 54–45 average, 44–40 below average, 39–35 mild impairment, 34–30 mild-moderate, 29–25 moderate, 24–20 moderate-severe, and <20 severe impairment.

In just as age, education, and sex may affect performance, ethnicity and cultural and linguistic contexts may also affect scores, even within the same country. Thus tests developed in one part of the world may not represent a valid measure of cognitive functioning in a different region. This can be clearly shown by comparing rates of NP impairment using normative data without ethnicity adjustment to those with ethnicity adjustment. NP impairment rates in African-American and Spanish-speaking subjects using published test norms are higher than expected, with misclassification being most salient at lower levels of education. Additionally, it may be necessary to adapt the tests themselves to a new linguistic or cultural context. For example, the San Diego group translated and adapted the Hopkins Verbal Learning Test–Revised (HVLT-R), a test of verbal learning and memory, from English into Spanish, with special attention to word frequency and contextual frequency in the new language. Using a sample ($n = 180$) of Spanish speakers from the U.S. Mexico border regions of California and Arizona to generate norms, rates of impairment on the Spanish version of the HVLT-R among HIV + positive participants were similar to those in English-speaking subjects. Development of so-called "population-specific" norms requires consideration of factors such as what defines a population, and the extent to which race and ethnicity represent proxies for socioeconomic, educational, and cultural differences. These considerations are especially important in HIV, which tends to affect persons who do not conform demographically to available test norms.

Neuropsychological functioning and clade C virus in India

India has an estimated 5.1 million cases of HIV infection, the vast majority of which are HIV-1 clade C. Dr. Robert Heaton of the University of California, San Diego, USA presented work in which he and collaborators at the National AIDS Research Institute (NARI) compared the neurobehavioral effects of HIV-1 infection in India and the United States. Previous evaluations of the neurobehavioral effects of HIV in India have been limited by the lack of standardization of NP tests. Extensive linguistic, cultural, and educational differences dictate the need for country-specific tests and normative data. Dr. Heaton and colleagues have begun to address this using an approach in which Indian physicians and mental health experts first review Western tests. After excluding or adapting certain tests to suit the unique cultural and linguistic situations in India, permission is obtained from Western test publishers to translate the tests into Indian languages and dialects. Translations are validated by independent back-translations into English and comparison to the original tests. Indian and U.S. investigators then jointly train examiners and pilot studies are conducted with HIV+ and HIV− participants in India to evaluate the tests. Initial studies suggest that there are population differences in performance in some cognitive domains, but when population-specific norms are used, the prevalence of neurocognitive impairment in clade C–infected individuals in India is similar to that of clade B–infected individuals in the United States.

Drug abuse, hepatitis C, and HIV

Dr. Scott Letendre of the HIV Neurobehavioral Research Center, University of California, San Diego, USA, discussed the effects of drug use, hepatitis, and HIV on the brain. The coexistence of drug use and liver pathogens in many individuals is well recognized. There is speculation that brain injury might result from interactions between drug use and hepatitis at multiple levels, including immune responses, viral replication rates, and medication metabolism and adherence. Hepatitis C virus (HCV) is a particularly prevalent infection worldwide, with an estimated 180 million individuals having chronic HCV disease. About 3 million of these reside in the United States, where coinfection with HIV is also common, affecting about 300,000 persons. In Brazil, HCV prevalence rates range from 4.9% in the general population to 41% among prison inmates in São Paulo. Among HIV+ individuals in São Paulo, 18% are coinfected by HCV.

HCV is a member of the family *Flaviviridae*, which includes many viruses that show a predilection for causing nervous system disease, such as Japanese encephalitis, West Nile, and Dengue viruses. HCV is an enveloped, positive, single-strand RNA virus that, like HIV, can replicate at a very high rate in the cytoplasm of infected cells. Also like HIV, HCV's high mutation rate leads to substantial diversity and evasion of host immune responses. Unlike HIV, HCV has a large viral genome that does not integrate into the cell's DNA. Although there are many HCV strains, genotypes 1a and 1b predominate both in the United States and Brazil.

Although hepatocytes represent the primary targets for HCV infection, productive infection also occurs in lymphocytes and cells of the monocyte-macrophage lineage. These blood-derived cells may traffic to the brain to cause disease. Additionally, microglia and astrocytes in the CNS express receptors involved in HCV cell entry, and thus may be infectible. Increasing evidence suggests that HCV is associated with neurocognitive impairment in a substantial proportion of infected individuals. Corroborative findings include cerebral metabolite changes on magnetic resonance spectroscopy, negative-strand RNA in brain tissue, evidence of HCV replication in the cerebrospinal fluid (CSF) in some individuals and the presence of distinct HCV genotypes in brain. Neurocognitive impairment is not limited to individuals with advanced liver disease (i.e., hepatic encephalopathy). Clinically, several studies have shown that HCV/HIV coinfected individuals are significantly more likely to be neurocognitively impaired than those infected only by HIV, independent of educational attainment, IQ, depression, recreational drug use, and other confounding factors.

Methamphetamine (METH) represents an additional cofactor in HIV neuropathogenesis. METH is an easily manufactured, recreationally used drug that crosses the blood-brain barrier easily due to its high lipophilicity. In addition to acting as a "false" neurotransmitter, chronic METH use appears to damage dopaminergic and serotonergic neurons, including those in the substantia nigra. These targets of damage overlap somewhat with those involved in HIV infection, theoretically resulting in additive injury. Dr. Avi Nath's group at Johns Hopkins University has demonstrated that METH interacts with the HIV Tat protein to stimulate cellular oxidative stress in brain tissue in mice. This is accompanied by increased gene expression of TNF-α and intercellular adhesion molecule type I (ICAM-1), as well as reduced dopamine levels, in mouse striatum. Using multivariate modeling, the San Diego group has shown that the effects of METH, HCV, and HIV on neurocognitive impairment are statistically independent from one another, suggesting additive neural injury. The effects of METH use on neurocognitive function may occur through immune dysregulation, as METH users have increased levels of MCP-1 (CCL2), soluble TNF receptor type II, and soluble CD14 in CSF and plasma.

Epidemiology of drug abuse in Curitiba

Psychiatrist Marco Antonio Bessa, Coordinator of the Section on Chemical Dependence of the Brazilian Psychiatric Association, presented data on substance abuse and dependence in relation to the HIV epidemic in Brazil. In Brazil, as in much of the rest of the world, the most important drugs of abuse are the legal substances, alcohol and tobacco. Alcohol is involved in 50% of automobile accidents and 60% of domestic violence cases, and it is used by 50% of unemployed workers. Among illicit drugs in Brazil, cannabis use is the most common, whereas heroin use is comparatively rare, and cocaine is intermediate in frequency. Among Brazilians living with HIV/AIDS, the percentage of injection drug users has dropped from 29% in 1992 to 12% in 2003. During this period, sexual transmission rates for HIV grew as drug-related incidence declined.

Major depression and HIV infection

Francisco Jaime Barbosa of Curitiba, Parana, Brazil, reviewed psychiatric comorbidity in HIV infection. Major depressive disorder (MDD) is the most prevalent psychiatric disorder in HIV-infected patients, affecting up to 45% at some stage of the illness. HIV-infected individuals are diagnosed with MDD about twice as frequently as noninfected individuals. Diagnosing depression in the context of HIV can be challenging, because symptoms such as fatigue, decreased appetite, and decreased libido may be attributable to either morbidity. Co-occurring HIV and MDD are associated with greater morbidity and mortality than either alone. Depression may influence

the effectiveness of antiretroviral therapy by reducing medication adherence.

The nature of the association between MDD and HIV is a matter of debate, with some suggesting that depression is simply one manifestation of HIV brain disease, whereas others consider depression to be a primary disorder that may be exacerbated by HIV. Still others suggest that depression may represent an adjustment reaction to the diagnosis of HIV infection. HIV has profound effects on psychological health not only through its influence on physical well-being, but also by causing difficulties in interpersonal relationships, leading to marital conflicts, divorce, social exclusion, conflicts at work, loss of employment, and financial problems. Conversely, MDD is associated with impaired cellular immunity—potentially reversible with antidepressant therapy—that may exacerbate HIV disease. Stress in HIV infection is believed to increase glucocorticoid levels and reduce levels of brain-derived neurotrophic factor, which in turn can result in atrophy and death of hippocampal neurons, leading to depression and learning and memory impairments. Research has not yet provided a consensus as to whether MDD may be an initial manifestation of a cerebral disorder caused by HIV infection. Thus neuropsychological impairment may occur with or independent of MDD.

Somatostatin and psychiatric manifestations: differences with HIV clades

Dr. Ian Everall of the HIV Neurobehavioral Research Center, University of California, San Diego, USA, addressed the potential role of somatostatin in the pathogenesis of MDD in HIV. Somatostatin is a neuromodulatory transmitter found in a distinctive population of interneurons arising from the medial ganglionic eminence. Additionally, somatostatin is highly concentrated within the amygdala, a cortical structure well known for its extensive role in emotional processing. Somatostatin is involved in the regulation of striatal dopamine levels, which also influence mood. The somatostatin analog, vapreotide, antagonizes neurokinin receptors—a characteristic that is being targeted by a new class of antidepressant medications. In a recent study of gene expression in the brains of individuals dying with HIV infection, Dr. Everall and colleagues found that somatostatin gene expression was reduced both in an initial series of 4 cases with MDD compared to 11 without, as well as in an extended series of 7 cases with a history of MDD as compared to 14 without. The reduction in somatostatin gene expression was independent of the presence of HIV encephalitis. These findings suggest that somatostatin dysregulation is important in the molecular pathogenesis of major depressive disorder in the setting of HIV infection. All of the individuals in this study were from the United States and therefore presumably were infected with HIV clade B virus. Future studies will evaluate the potential role of somatostatin gene expression in major depressive disorder in the setting of infection with other HIV subtypes, including subtype C.

Peripheral neuropathy, HIV, and antiretroviral therapy in Brazil

Dr. Osvaldo Nascimento of the Universidade Federal Fluminense (UFF), Rio de Janeiro, reviewed findings on infectious peripheral neuropathies in Brazil. He recently reported on a study that categorized and compared the types of neuropathies evaluated at tertiary academic centers in North and South America. All patients were included into one of six major categories: immune mediated, diabetic, hereditary, infectious/inflammatory, systemic/metabolic/toxic (not diabetic), and cryptogenic. Infectious/inflammatory neuropathies were found to be more common in South America (14%) than in North America (5%). Among the infectious neuropathies in South America, human T-cell leukemia virus (HTLV)-1 (25%), Chagas disease (9%), and leprosy (39%) were the most common. HIV-associated sensory neuropathy (HIV-SN) has been shown to affect 30% of individuals with AIDS, and treatment is often ineffective. Recently skin biopsy with intraepidermal nerve fiber (IENF) density determination has shown reduced IENF in HIV-associated sensory neuropathy. IENF density was inversely correlated with neuropathic pain. Decreased IENF density at the distal leg was associated with lower CD4 counts and higher plasma HIV RNA levels.

Panel discussion

A panel comprising Drs. Rodrigo Brindeiro, Ricardo Diaz, Paola Cinque, Igor Grant, Ian Everall, Robert Heaton, and Ronald Ellis summarized potential future directions in collaborative research on HIV clades and neuroAIDS in Brazil. Major questions raised were as follows:

- What more can we learn about the molecular epidemiology of HIV in Brazil, particularly as regards interclade recombination and its effects on pathogenesis and response to ART?
- Is neurocognitive impairment similarly common in Brazil as in India, Europe, and the United States?
- If impairment in Brazil is more or less prevalent, is this attributable to viral factors (e.g., clade), host factors (e.g., different ethnicities, genetic backgrounds), or interactions between these two?
- Are associations between viral load in CSF, type of HAART, and neurocognitive improvement similar in Brazil as in the United States?

- What unique comorbidities interact with HIV to cause neurological complications in Brazil?
- Do clade-specific differences in C/EBP binding account for differences in pathogenesis and clinical manifestations in HIV-infected individuals in Brazil?
- What is the association between depression and neurocognitive disorders in Brazilian HIV infection?
- What are the effects of past and ongoing drug abuse on the status of HIV disease and response to ART in Brazil?

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