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Meeting report

HIV in the brain: pathology and neurobehavioral consequences

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The National Institute of Mental Health recently sponsored a meeting to review current understanding of nervous system complications during HIV infection and to prioritize research goals. The ultimate goal of this meeting was to advance our understanding of the mechanisms underlying the neurological and neurobehavioral consequences of HIV infection, collectively referred to as neuroAIDS, in order to facilitate the identification and testing of therapeutics that will prevent or reverse these consequences. The specific objectives of this meeting were to (i) identify areas of consensus and conflict concerning the neurological and neurobehavioral complications of HIV infection; (ii) determine what questions need to be addressed next; and (iii) identify ways to design and execute studies to resolve these issues. Attendees included clinicians and basic scientists actively involved in research in this and other related areas including neuroscience, immunology, virology, neurology, psychiatry and neuropsychology.

Four workgroups were convened to address specific questions and to make recommendations for research in both the clinical and basic science of neuroAIDS. The following is a summary of the discussions and conclusions of these four workgroups. First, the clinical syndrome was discussed and recommendations were presented to standardize the methods for diagnosing and classifying HIV-induced neuropsychological impairments. This is followed by a review of the discussions of viral load, including viral strain and viral products, and their potential contribution to neuroAIDS. The CNS inflammation workgroup discussed how this may impact on CNS function. Finally, the deliberations of the participants in the therapeutics workgroup considered matters of clinical trial design, inclusion and exclusion criteria for subjects that would make them best-suited for clinical trials, and the uncertain mechanisms of pathogenesis that may be barriers to the development of effective treatments.

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The clinical manifestations of AIDS Dementia Complex, or HIV-associated motor/cognitive complex, include impairments in motor and cognitive function of varying severity. Impaired motor skills range from generalized weakness to total paralysis. Changes in cognition range from slowed information processing or forgetfulness to marked dysfunction that severely impedes daily functions. The reported incidence of neurological complications varies depending on the criteria used to assess the impairments, but 10–50% of HIV infected individuals are likely to experience neurological or neurocognitive complications during the course of their disease, with the highest probability of occurrence during late-stage disease.

In order to more precisely identify and characterize the various degree of cognitive dysfunction, it was recommended by this workgroup that a standardized classification system be employed, with the following categories: (1) neuropsychologically unimpaired, referring to performance at or above expected levels in all functional domains, or below expected levels in no more than one domain; (2) neuropsychologically impaired, referring to performance below expectations in at least two cognitive domains; (3) mild neurocognitive/minor motor disorder, where evidence indicates that the identified impairment occurs in at least two domains resulting in mild dysfunction in everyday functioning or work performance; and (4) HIV-associated dementia, where it has been demonstrated that significant neuropsychological impairment occurs in at least two domains, and results in marked dysfunction in everyday functioning or work performance. Although these categories can be broadly applied to children with HIV-infection, classifying the stage and

degree of impairment must take into account their ongoing development, and therefore may be more complex and require longitudinal data. It was agreed that the term 'dementia', which in the past has been applied to subjects with a broad range of neuropsychologic functional capacity, should be reserved for only the most severe level of HIV-related cognitive impairment. Also, in all instances, etiologies other than HIV must be ruled out.

It was recommended by this workgroup as well that diagnostic methods representing the full range of neuropsychological functioning be utilized to assess neuropsychological status in HIV-infected individuals, including verbal/language, attention/speed of information processing, abstraction, memory (learning and recall), complex perceptual-motor performance, and motor skills. It was the consensus of this workgroup that it is unlikely that an adequate comprehensive assessment of cognitive functioning, which is particularly important with mild HIV-related cognitive impairment, can be completed in less than two hours. It was also agreed that a comprehensive assessment of neurocognitive functioning should include evaluations of everyday functioning and quality of life, because assessment of everyday functioning is critical in establishing a neurocognitive diagnosis as well as in determining meaningful changes in clinical trials. Although performance-based measures to evaluate activities of daily living are available, the development of instruments that assess more challenging aspects of everyday function (e.g., work-related and driving abilities) was recommended. In addition, it is well-established that neuropsychological performance may differ as a function of age, education, gender, and race, therefore, the availability of norms incorporating these variables should be a factor when selecting tests.

For clinical trials assessing the efficacy of medications to ameliorate cognitive impairment, this workgroup recommended that neuropsychological testing should be the 'gold standard' and the psychometric properties of the neuropsychological tests should be carefully considered when designing the research protocol. The workgroup strongly recommended that a comprehensive neuropsychological assessment be performed at the beginning of any trial in order to characterize fully the subject's neuropsychological functioning. Implicit in this is the recommendation that clinical trials designed to assess CNS effects of a drug be designed *de novo* and not be added on to an existing AIDS Clinical Trial Group already in progress unless such a trial can accommodate rigorous neurocognitive assessment. It was also determined that the power of a study will be seriously compromised if subjects enter a study without adequate pre-assessment of neurocognitive status. In addition, the same neuropsychological battery should be performed as an endpoint in order to evaluate the degree to which there has been cognitive change. Additional neuropsychological assessments occurring between these two points would function primarily to monitor toxicity and disease progression, and therefore would be best served by a significantly smaller neuropsychological battery that does not include tests that are part of the baseline/endpoint battery. Due to the nature of neuropsychological testing, it was recommended that the use of frequent, brief assessments should be generally discouraged. Subjects who are repeatedly exposed to neuropsychological tests tend to overlearn the material, thus limiting the sensitivity of the instruments. While the use of alternate forms may be an option for some tests, even subjects exposed to different versions of a measure begin to develop strategies in how to approach the test, thus running the risk of changing what it is that the later administrations of the tests are measuring.

A number of surrogate markers were identified that may provide useful information regarding CNS function. Structural imaging of the brain using computerized tomography (CT) and magnetic resonance (MR) may detect CNS pathology in late stage HIV infection which may be related to neuropsychological impairment, but appear insensitive to changes early in the course of HIV. More recently developed methods such as MR spectroscopy and functional MR demonstrate increased sensitivity, but are of limited general utility due to the experimental nature, advanced technical requirements, and costs of these techniques. Single photon emission computerized tomography (SPECT) appears to detect some medication-related changes (e.g., benefits from the initiation of AZT), and is relatively available, but difficulties in quantifying the images remain, and only limited evidence exists that SPECT images correlate with neuropsychological functioning thus hampering its usefulness in HIV research. Positron emission tomography (PET) provides valuable information regarding brain metabolism, but is costly, is not appropriate for numerous repeated testings, and is not readily accessible. It was therefore concluded that most of these techinques are useful for focused studies of HIV-related CNS functioning and intermediate endpoints in treatment assessments, but are not practical as primary outcome measures for clinical trials.

Several important questions remain to be answered with respect to the clinical syndrome of HIV-associated motor/cognitive complex. How do fluctuations in neuropsychological functioning, including transitions to and from different neurocognitive diagnostic classifications, relate to virus-induced CNS perturbations and changes in medical status? How do regional changes in brain function correlate with domain-specific neuropsychological performance? In light of the new regimens of combination therapy of protease inhibitors and

nucleotide analogues, which significantly decrease systemic virus load, the relationship of systemic as well as CNS virus load to neuropsychological status becomes increasingly important to determine. Are persons treated in this way more or less likely to develop evidence of HIV encephalopathy?

Finally this workgroup recommended the initiation of new treatment trials in which neuropsychological/neurological outcomes are the primary focus. These trials should first determine if the drug enters the brain, and then incorporate comprehensive neuropsychological assessments and determination of corresponding stage of disease into the trial design. Such trials should be of two broad types: studies on neurocognitive consequences of new generation antiretrovirals, including application of multiple therapies; and studies on novel agents that act on hypothesized neuropathogenetic pathways with the goal of testing their neuroprotective/neuroremediative promise. Examples include the study of drugs acting on glutamate receptors, drugs blocking adverse cytokine effects, agents that replace neurotrophic factor deficiencies, etc.

Virus load

The events and stages of infection in the CNS, and particularly the relationship of intracerebral viral replication, virus load, and viral genotype to the development of neuropsychological disease, are important scientific issues that await resolution. There is evidence that HIV may enter the CNS early in the course of systemic infection. However, the coincident and subsequent events following HIV CNS infection remain to be elucidated. For example, virus may enter the CNS parenchyma and be eliminated without further pathologic sequelae, or a persistent viral infection may be established resulting in a progressive assault on CNS function. Alternatively, the loss of host defences as a result of systemic infection may allow unchecked systemic virus replication to give rise to neurovirulent viruses capable of extensive invasion and subsequent replication within the CNS, with attendant pathological changes and neurocognitive impairment. Identifying the critical events that occur and contribute to the development of neuropsychological impairment, and the mechanisms that lead from one stage of impairment to the next, is a formidable task, but necessary for the development of therapeutics targeted to prevent or treat this component of HIV disease.

There was strong consensus within this workgroup that determining the relationship between CNS virus load and the onset and progression of identifiable neuropsychological impairments is of paramount importance. Another critical issue is whether decreasing systemic virus load will result in a concurrent decrease in CNS viral load, or whether a drug must enter the brain to have therapeutic effects within the CNS. Although the concentration and types of viruses in the blood stream and cerebrospinal fluid (CSF) can be monitored in the course of infection, their relationship to infection of CNS tissues is unknown.

The presence of virus and the amount of virus within the CNS are currently assayed post-mortem by a variety of methods that differ in their capabilities to detect and quantitate virus. Infectious virus can only be detected in tissue culture, but because of its vascularity, it is difficult to estimate the titer of virus within the brain parenchymal tissue by this method. Northern, Southern and Western blots are relatively insensitive but quantitative, whereas PCR techniques offer exquisite sensitivity and detection but because of non-homogeneous distribution and multiple host cells, are less relevant for quantitation of virus in the CNS. Antigen (p24) capture immunohistochemistry and *in situ* hybridization with or without amplification in post-mortem tissue sections currently are the best measures of viral burden in the CNS, including the types and numbers of cells that harbor HIV and if they are or are not productively infected. All contemporary methods, however, are limited in their sampling power.

A major challenge remains to develop methods to non-invasively quantitate and localize virus within the brain early in the course of HIV infection. This is necessary to link the presence of virus causally to the occurrence and progression of neuropsychological impairment as well as to evaluate the effectiveness of antiviral treatment in the CNS. Research directed toward the development of noninvasive neuroimaging with high resolution to measure virus burden should also be encouraged.

Virus load within the CNS tissue compartment may be independent of other anatomic sites, and currently can only be assessed in end-stage disease in post-mortem material. At earlier stages, brain biopsies, even if ethically justified, sample only small discrete regions of the CNS and would provide limited information. For these reasons animal models that most closely approximate neuroAIDS are essential. The use of the non-human primate model (discussed also in the CNS Inflammation workgroup) is optimal to determine to what extent virus burden in the CSF reflects virus burden in the CNS tissues. This may in turn shed light on some of the central questions in neuropathogenesis: Does virus enter the CNS by hematogenous and/or CSF routes? Is infection of the CNS the result of trafficking of infected cells into the CNS and, if so, what types of infected cells are involved (e.g., monocyte or $CD4^+$ T lymphocytes)? What role does infection of brain endothelium and macrophage/

endothelial cell interactions play in neuroinvasion? In addition to animal models, participants agreed that questions like the latter can also be approached in appropriately designed tissue culture systems.

Considerable discussion focussed on which animal models should be used to study HIV-related neurological disease, and it was generally agreed that the best animal model depended on the question being asked. SIV infection of rhesus macaques recapitulates all aspects most germane to neuropathogenesis, such as immune depletion, motor/cognitive impairment and encephalitis, and intense collaborative efforts are necessary for its efficient utilization and to maximize the information that can be obtained from this model. Other non-human primate models have some limitations. There has been no conclusive documentation of neurological disease in baboons or pigtail macaques infected with HIV-1 or -2, or rhesus macaques infected with SIV-HIV chimeras (SHIVs), and data do not support the utility of HIV infection of the chimpanzee as a model for neuroAIDS.

Additional animal models that may not recapitulate the neurological consequences of HIV-infection as well as the SIV model but nonetheless have utility in modeling specific aspects of neuropathogenesis include feline and murine models should also be supported. This includes FIV, which invades the nervous system and causes neurological disease associated with immunosuppression, but virus burden within the CNS, neuropathological changes, and clinical manifestations of infection are minimal. Studies of chronic viral infection of the murine CNS by retroviruses in the oncogenic subfamily could lead to new ideas about how lentiviruses cause neurological disease, and transgenic models afford opportunities to examine the specific consequences of expression of HIV env and other viral genes in the CNS. Morever, HIV-infected human monocytes/macrophages can be implanted into the murine CNS to investigate mechanisms of neurotoxicity.

A number of pressing questions remain to be answered. Do specific viral strains mediate neurologic disease? Sequence analysis of CNS viral clones must be done to determine the importance of viral tropism, the regions of the virus mediating this tropism, and the mechanisms by which these regions mediate neurotoxicity and ultimately effect CNS dysfunction. How is CNS virus burden to be measured, and what is the relationship between virus detected predominantly within the CSF and the virus burden that characterizes HIV encephalitis? Paired studies measuring plasma virus burden with simultaneous CNS virus burden are necessary. The need for surrogate markers of HIV encephalitis, which at present can only be determined post-mortem, must be developed in order to establish causal events leading to CNS dysfunction. What is selecting for viral abundance within the CNS? The virus detected within the CNS is not likely a result of passive movement of cell-free virus from the blood into the CNS. Heavy virus burdens in the CNS could result from specifically neurotropic/neurovirulent viral strains, a host cell micro-environment leading to the production of abundant virus, or the absence of significant immune control of viral replication. The relative importance of these three different pathways must be determined.

CNS inflammation

The pathogenesis of HIV encephalitis, defined as viral infection of the brain, and how it relates to neurocognitive disorders and dementia remains obscure. There is, however, an emerging consensus that specific cellular elements of the immune system and the cytokines they produce are involved. The cell types most strongly implicated are cells of the monocyte family including activated microglia and infected macrophages. At this point in our understanding of HIV-induced CNS inflammation, it is important to note that while microglial activation always occurs in neuroimmunological/inflammatory disorders of the CNS, it can also occur in other conditions, such as certain neurodegenerative diseases or enzymatic deficiency disorders, and after trauma. Consequently, abnormal production of cytokines and/or chemokines may be indicative of a nascent or ongoing inflammatory response, or the manifestations of specific cell types suffering viral infection or altered metabolic processes. The cellular or chemical elements of the immune system may function in ways parallel or identical to their normal roles as the etiology of HIV-associated neurological dysfunction, with the presence, activation state, or relative levels of these cells and materials the result of a pathophysiological process leading to the neurological sequelae of HIV infection.

It was the consensus of this workgroup that research addressing the role of the blood brain barrier (BBB) in HIV infection of the CNS, HIV encephalitis, and the pathological manifestations of motor/cognitive dysfunction is of great importance and should be encouraged. Research in this area should include studies to determine how the integrity of the BBB relates to infection, and whether the extent of macrophage infiltration in the CNS and the pattern of adhesion molecule/integrin expression on cells of the BBB correlate with the progression of the neurological dysfunction. How does the virus load within the CNS correlate with the BBB status, and does that impact on neuronal function?

Neuronal dysfunction must underlie the observed motor and cognitive impairment. The use

of the SIV-infected primate animal model has allowed the identification of specific pathology accompanying CNS dysfunction. Because non-human primates can be assessed for neurological dysfunction using methodologies and assays that closely resemble that used in humans, this is an ideal model for this purpose and more efficient use of this model through facilitated collaborations was strongly recommended. A particular advantage of the non-human primate model is that animals can be sacrificed and examined when the changes that drive the motor/cognitive dysfunction actually occur.

This workgroup recognized the importance of other animal models, and recommended continued support of their use for addressing specific research questions. For example, the concept of selective neuronal vulnerability warrants further investigation, and the use of transgenics has allowed the identification of select destruction to specific neurons with over expression of certain cytokines or viral factors. The LP-BM5 infected mouse is also useful for addressing specific issues, such as changes in local neural chemistry and the resultant effects on the adjacent neural tissue.

There is little information available on the expression of neurotrophic factors in HIV-induced motor/cognitive impairment, and how these factors may affect neuronal function or viability. It was recommended that studies to determine the cellular sources, the stimuli, regulation and induction events, and the functional effects of the production of these factors be encouraged. Chemokine/chemokine receptor expression and function also requires further exploration, how they are regulated and where they are expressed in the brain, and how this relates to neuronal dysfunction. Viral proteins and their effects on neurons and glia, as well as other factors also warrants further study. The viral encoded Tat protein can affect the activity of select intracellular messengers and the production of cytokines, and may contribute to some of the pathological changes that are associated with HIV-induced neuropsychological impairments.

The role of nitric oxide (NO) also needs further exploration. NO is generated by nitric oxide synthase (NOS) and can cause damage through the formation of peroxynitrite. There are at least three forms of this enzyme, eNOS, nNOS and iNOS, representing endothelial, neuronal and immunological forms respectively. However these are not restricted to the specific cell types. nNOS may be very important in stroke and trauma, where large amounts are produced and metabolized quickly. iNOS is not normally expressed in healthy brain. Evidence indicates that NO can be associated with neuronal cell death, and increased levels of iNOS within the CNS have been correlated with encephalopathy.

One major theme that emerged from the deliberations of this workgroup is that a primary goal of research in this area should be to increase understanding of the basic mechanisms involved in the neuropathology of AIDS. Understanding the pathogenesis of HIV-induced CNS impairments requires unraveling complex interactions of the components of the nervous system and the immune system in normal conditions as well as following the introduction of the various agents in physiologically abnormal concentrations. A thorough understanding of the function of all cell types in the brain is required. Many basic questions remain unanswered. Why do only a subset of HIV infected individuals develop encephalopathy? What is the relationship of virus burden to the inflammatory response? What is the role of mononuclear macrophages in HIV CNS disease? What is the temporal relationship between the pathology identified at end stage disease and the actual onset of the motor/cognitive impairment seen throughout the disease process? Significant progress must be made toward answering some of these basic questions to advance our understanding of this complex syndrome.

Therapeutics

Drug therapy for the neurological and neurobehavioral complications of HIV infection can be targeted to either prevent the onset of symptoms or stop the progression and reverse the apparent neuronal dysfunction. In agreement with the Clinical NeuroAIDS workgroup, it was the recommendation of this workgroup that as drugs with potential efficacy in treating neuroAIDS are identified, clinical trials to assess CNS effects of a drug be designed *de novo*, and the population of subjects in the trials should be chosen based on the hypothesis to be tested and the anticipated mechanism of action of the drug.

It was the consensus of this group that studies addressing prophylaxis of HIV-associated neuropsychological dysfunction in a neurologically normal cohort are likely to be resource intensive. Although a number of predictors for the development of HIV-associated CNS dysfunction have been identified, there is insufficient information regarding the complete spectrum of potential predictors, and their predictive power. While the investigation of predictors for the development of HIV-associated motor/cognitive dysfunction is encouraged, until they are better defined, the use of this population for primary studies of the prophylaxis of HIV-induced CNS dysfunction was not viewed favorably. However, using the development of CNS dysfunction as a secondary endpoint in the context of other antiretroviral studies was encouraged, particularly in pediatric clinical trials.

The population of HIV-infected patients with mild neurocognitive/minor motor disorder was identified as ideal for assessing drug efficacy in most cases for a number of reasons. These include the availability of a larger population from which to recruit patients into studies, fewer confounding variables such as opportunistic infections or debility secondary to advanced AIDS, minimal competency issues, and better patient compliance with study regimens. Additionally, this disorder was believed more likely to be reversible than HIV dementia, and quite importantly, an improvement in cognitive function is likely to have a high impact on quality of life, for example employment, day-to-day function, etc. One precaution with this particular population is the recognition that their cognitive function can vary throughout the disease. A minority of subjects may demonstrate an improvement in level of function in the absence of specific therapeutic intervention.

Studying the population with HIV dementia represents an unique opportunity to study not only the efficacy of therapy but also potential mechanisms of the pathogenesis of HIV-associated neuronal dysfunction. It was the consensus of the group that pharmacokinetics directed at the proposed pathways of CNS dysfunction, e.g., memantine, are best performed in patients with HIV dementia. It was generally agreed however, that since HIV dementia occurs most frequently in late stage disease, this condition is less likely to be reversible. Infants and children with symptomatic HIV disease are at the highest risk for developing neurobehavioral deficits and HIV-associated encephalopathy, and should be included in drug efficacy studies.

The specific therapies can be broadly classified into: (1) antiretroviral therapies; (2) therapies directed at potential pathways in the pathogenesis of HIV-induced neuropsychological impairments (excitotoxins, cytokines, etc.; (3) factors that may contribute to HIV-induced neuropsychological impairments (including concomitant infectious diseases such as CMV and nutritional factors like vitamine B12); (4) palliative therapies (neuropharmacology/neurotransmitter therapies, such as direct and indirect dopamine agonist or alpha 2 adrenergic agonists); and, (5) therapies directed at the neuroendocrine axis. With respect to antiretroviral therapy, a comparison of drugs with and without CNS penetration was recommended to address the important question of whether the reduction of CNS viral burden is necessary in ameliorating HIV-induced motor/cognitive dysfunction.

As in the other workgroups, it was recommended that the development of animal models to evaluate the safety, efficacy, and dose ranges for this class of drugs be strongly encouraged. In addition, research on the assessment of delivery of proposed therapies for neuroAIDS to brain parenchyma is of paramount importance and attention should be given to improving mechanisms of drug delivery to the CNS. Palliative therapies were considered to be important with respect to both what they can tell us about neuropathogenesis and the improvement in quality of life.

Neuropsychometric testing (see the consensus statement from the Clinical neuroAIDS workgroup) was uniformly believed to be the 'gold standard' for evaluating and serially following patients with HIV-induced neuropsychological impairments or at risk for their development. Tests of the functional capacities of the individual were considered to be very important. It was agreed that more work needs to be done on the value of surrogate markers. Interweaving their evaluation in the context of clinical trials was strongly encouraged. Among the surrogate markers which were identified as most promising are studies of CSF/plasma virus load, MR spectroscopy and functional MRI.

The consensus of this group was that the most appropriate trial design was dependent on the hypothesis being tested. It has been well recognized during the performance of earlier studies that it is virtually impossible to standardize antiretroviral therapy. Therefore, any study of patients with HIV-induced neuropsychological impairments will likely include the best possible antiretroviral therapy. A control arm for the CNS-targeted effects with the best standard therapy is regarded as a necessity. The optimal length of therapy for the evaluation of drugs used in the treatment of HIV-induced neuropsychological impairments remains unknown and will require further assessment. Expediency, however, dictates that the duration of therapy equal or exceed the time that is considered to be the best estimate of the time to response. The inclusion of an open label phase to these clinical trials is recommended as it stimulates interest among potential participants and increases the data available to analyze. The group also agreed that a 2×2 factorial design is advantageous because of the increase in the power for statistical analysis.

The identification of specific therapies to be tested over the next 5 years was considered to be very important. Among the classes of drugs that were given high priority in this regard are: (1) NMDA receptor antagonists, (2) calcium channel blockers, (3) antioxidants, (4) PAF antagonists, and (5) anti-inflammatory agents. Small scale, phase 1 and 2 studies were believed to be of value. However, in those studies requiring large patient populations, multi center collaboration is strongly encouraged. The Neurological AIDS Research Consortium (NARC) can be regarded as a model for this type of collaborative effect. The NARC has created a framework for the investigation of AIDS related neurological complications with a large and broadly representative patient pool, a wide range of expertise including statistical support, a proven track

record in performing difficult studies. It serves as a paradigm for collaboration across institutional boundaries, receiving support from the NINDS, NIAID and NIMH.

Based on the breadth of challenges of neuroAIDS and the recognition that the performance of these clinical trials are costly in terms of time, labor, and money, the group strongly urged that there be an increase in the research and support to accomplish these aims.

Summary

In addition to what has been summarized by the individual workgroups, a number of general recommendations were made to facilitate research in this area, and efforts are underway to accomplish these goals. First, precipitated by a discussion led by the Directors of the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke, there was a strong recommendation by the participants that there be more cooperative efforts of support by the different Institutes for research in this area. This could result in an increase in multi-faceted, coordinated clinical studies that include outcome measures for neuropsychological effects of particular treatment protocols as well as provide resources to basic researchers. Second, the need for a comprehensive neuroAIDS specimen registry was identified to facilitate both the collection and distribution of HIV-infected human and SIV-infected primate blood, CSF, and brain tissue, as well as tissues and cells from other *in vivo* and *in vitro* models for neuroAIDS. Third, it was recommended that methods be developed to facilitate coordinated research efforts in the use of the SIV-infected rhesus animal model, to maximize the benefits of this highly relevant model.

The nervous system complications of HIV infection affect a significant number of HIV-infected adults and children, frequently compromising their quality of life and functional capacity. Much progress has been made since the initial description of this disease phenomenon more than 10 years ago. The pathologic alterations observed in the brains of affected individuals at death has been well described, and efforts to correlate these changes with observed dysfunction during life must continue. Identification of specific mechanisms underlying the observed CNS disease becomes more pressing as new and more potent drugs become available which dramatically decrease systemic load and offer individuals living with HIV a potential remission in the disease process and longer life expectancy. The effect of these new drugs on HIV-induced CNS disease however is not yet known, and long term suppression of systemic virus replication may in fact result in an increase in incidence of neuroAIDS as a result of unchecked CNS virus replication, as a result of patients living longer with the presence of HIV, or due to other factors not yet identified. Prevention or effective treatment of the CNS effects of HIV infection must be aggressively pursued to reduce morbidity and improve the quality of life of HIV-infected individuals.

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