Journal of NeuroVirology (1997) 3, 89–101

http://www.jneurovirol.com

Meeting report

Prospects for therapy of HIV-associated neurologic diseases

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Keywords: HIV; neurology; therapy; clinical trials

Introduction

In June 1996, NINDS and Johns Hopkins University Department of Neurology organized a 1½ day workshop, 'HIV Neurologic Therapies Workshop'. The principal objective of the Workshop was to facilitate the development of innovative therapeutic strategies for dementia, neuropathy, neurologic CMV disease, and progressive multifocal leukoencephalopathy (PML). Separate groups focused on different neurologic therapies with the following goals: identifying new compounds, optimizing trial design, and prioritizing plans for the initiation of neurologic trials.

In this summary, we will review the findings and recommendations of the conference: (1) Definition of endpoints in trials of HIV dementia; (2) Antiretroviral agents for therapy of HIV dementia; (3) Inflammatory mediators and neuroprotective agents in HIV dementia and (4) Therapy for CMV encephalitis/radiculomyelitis and progressive multifocal leukoencephalopathy. A full list of Workshop participants is provided in Appendix 1 and this report attempts to synthesize the discussions and presentations contributed by these participants.

Epidemiology of neurologic diseases in HIV infection

Most information about the incidence and prevalence of neurologic diseases associated with HIV infection comes either from clinical cohorts (which have an inherent referral bias), from the surveillance data from the Centers for Disease Control and Prevention (which captures mainly the *initial* AIDS-defining illnesses and not subsequent or secondary indicator diseases), or from natural history cohort studies, such as the Multicenter AIDS Cohort Study (which may be limited to a particular risk behavior group and may have inherent selection biases). Despite these limitations, most surveys agree that neurologic involvement is relatively common, with HIV dementia affecting 15 to 20% of individuals after AIDS, with an annual incidence of 5 to 10%. HIV-associated minor cognitive motor disorder may be even more prevalent, affecting 25% of those in CDC stage C. HIV-associated sensory neuropathy is rising in prevalence, partly as a result of the toxic effects of dideoxynucleoside analogs, and is estimated to affect 20 to 30% of those with advanced HIV infection (Bacellar *et al*, 1994). Studies of temporal trends for the 'primary' HIV-associated neurologic diseases showed a significant rise in the incidence rates for sensory neuropathy between 1987 and 1992, while those for HIV dementia remained stable (see Figure 1). As yet, there is no information whether the combination therapies and protease inhibitors have had an impact on these diseases. There is universal hope that these potent antiretroviral agents, which can suppress plasma HIV viral load by 2 log or greater, might have a significant effect on HIV replication in the brain and improve dementia symptoms. However, because of the limited CNS penetration of most of the protease inhibitors, it is possible that HIV replication might be suppressed in the systemic compartment, but not within the brain (Table 1).

With data combined from different sources, the prevalence of CMV-associated neurologic disease, including encephalitis and radiculomyelitis, is estimated to be about 5% (Gallant *et al*, 1992; Moore and Chaisson, 1996). The impact of recently-introduced prophylaxis with oral ganciclovir on these rates is unstudied. Based on the ability of this regime to reduce rates of development of CMV retinitis, one might anticipate a corresponding reduction in the frequency of CNS infection. By contrast, incidence rates of PML have remained

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Received 26 November 1996; accepted 2 December 1996

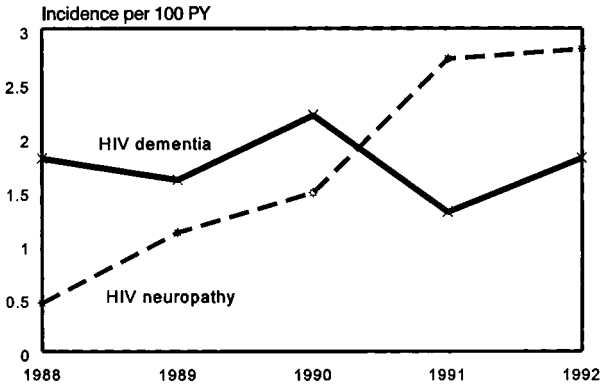

Figure 1 Annual incidence rates (per 100 person years) for HIV dementia and sensory neuropathy among HIV seropositive men in the Multicenter AIDS Cohort Study. Note rising incidence rates for neuropathy and stable rates for dementia. From Bacellar *et al* (1994).

Table 1 Epidemiology of HIV-associated Cognitive impairment

- 'Minor' cognitive/motor disorder occurs in 20% CDC stage B-C
- HIV dementia affects 15% adults/children with AIDS
- HIV dementia develops only rarely during asymptomatic phase and is an AIDS indicator disease in 3%
- Temporal trends: incidence stable through 1992, 7% p.a. after AIDS
- Risk factors: ↓↓ CD4, anaemia, injection drug use, possible female sex
- Variable progression of dementia: 30% have only slow progression or remain stable
- Rapid progression of dementia is associated with ↓ CD4, injection drug use, CNS immune activation
- Protective effect of antiretrovirals suggested from clinical trials, not from observational studies
- Uncertain effect of combination therapy and protease inhibitors

relatively stable (Bacellar *et al*, 1994), but might increase as survival times with profound immunodeficiency are extended further with potent antiretroviral combination therapy.

For further information on the epidemiology of HIV-associated neurologic disease, see Bacellar *et al* (1994), Chiesi *et al* (1996), Janssen *et al* (1992), Moore and Chaisson (1996).

Definition of endpoints in trials of HIV dementia

Functional impact of neuropsychological impairment

In reviewing the requirements for the optimal design and conduct of valid and rigorous clinical trials, previous information developed by the FDA on the assessment of anti-dementia drugs is germane. In 1989, the FDA sponsored a symposium to review methods for the evaluation of anti-dementia drugs, principally for Alzheimer's disease (Ad Hoc FDA Dementia Assessment Task Force, 1991). One of the conclusions from the symposium is as appropriate for HIV dementia as it is for Alzheimer's disease: '...Enhancement of activities of daily living or other areas of overall functioning must be demonstrated to prevent the marketing of drugs that produce statistically significant improvements in cognition, but trivial improvements in overall functioning.' Some of the principles of efficacy assessment developed by the *ad hoc* Dementia Assessment Task Force are summarized in Table 2.

Table 2 Principles of efficacy assessment: HIV dementia therapy

Requirement for randomized, placebo controlled, and blinded trials	Avoid placebo effect Balanced treatment groups
Correct selection of participants	Internal validity
Broad range of severity	Generalizability
Small number of outcome measures	Avoid Type 1 error
Assessments should measure changes in cognitive and everyday function	External (criterion) validity
Outcome: improvement or slowing of progression	Variability in course may impact on sample size

Modified from: Ad Hoc FDA Dementia Assessment Task Force, Neurobiology of Aging, 1991

The neuropsychological profiles of both mild and severe HIV dementia have been well characterized (Tross *et al*, 1988; Van Gorp *et al*, 1993). The most sensitive tests for detection of HIV dementia are those which assess psychomotor speed, memory, and reaction time. In Phase I/II studies, it is generally appropriate to include a broad battery of neuropsychological tests to assess the nature and magnitude of a drug's effect. For larger scale Phase II/III studies, short focused cognitive assessments combining global ratings and activities of daily living (ADL) scales are preferable. There is uniform agreement that test batteries for detection and monitoring of HIV dementia should sample a variety of relevant cognitive/motor domains, including psychomotor speed; immediate, recent, and long term memory; attention; and reaction time. Placebo-controlled trials are required because of the strong placebo effect simply from trial participation. Work in multiple sclerosis clinical trials suggested that the behavior of control groups in clinical trials is 'generally more favorable than their pre-enrollment behavior' presumably due in part to placebo effect and partly to regression to the mean

(Weinshenker *et al*, 1996). Neuropsychological test batteries used in trials should be clinically relevant, sensitive to change, and robust to the effects of fluctuation or practice effect. Several of the published or planned trials of HIV dementia rely on a composite of summary measure of neuropsychological performance derived from summation of scores of individual neuropsychological tests. Sidtis (1994) have shown that a summary score, derived from several neuropsychological tests, correlates well with the degree of clinical impairment using the Memorial Sloan Kettering HIV dementia severity scale (see Figure 2).

Instrumental activities of daily living (IADL), such as driving, bill paying, check writing, shopping etc, are important components of a test battery, permitting assessment of functional impact and thereby proving external (criterion) validity for any observed changes in neuropsychological performance. Several recent studies have related neuropsychological performance to measures of everyday functioning in a wide variety of disease states. For example, in Huntington's disease (a predominantly subcortical dementia similar to HIV dementia), psychomotor speed and measures of attention were significant determinants of everyday functioning in early disease (Rothlind *et al*, 1993). In Alzheimer's disease, disease severity was the strongest predictor of ADL and IADL performance. Tests of visuoperception abilities made a significant contribution to the explanatory variants in both ADL and IADL function (Hill *et al*, 1995). Cohen *et al* (1995) also showed that neuropsychological performance was sensitive to functional outcome in patients with dementia. Heaton *et al* (1978) used data from the extended Halsted-Raitan Neuropsychological Battery to accurately predict employment status in dementia, using neuropsychological and personality tests to assess likelihood of patient employment. More recently, in multiple sclerosis, Rao *et al* (1991) showed a relationship between neuropsychological performance and employment status which was independent of patients' physical and psychiatric symptoms. Finally, Acker (1986) determined that neuropsychological performance in patients following closed head injury is a significant predictor of disability and functional outcome.

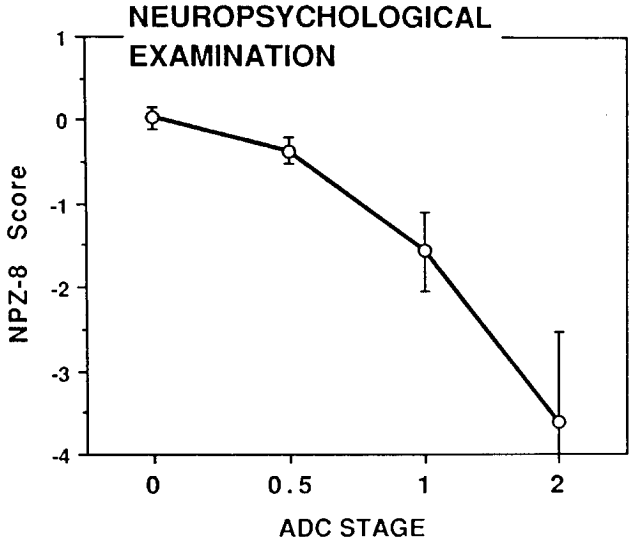

Figure 2 Close relationship between neuropsychological testing and clinical severity of HIV dementia: NPZ-8 score derived from the MACRO neuropsychological examination as a function of ADC stage. Error bars represent 95% confidence intervals for each mean. From Sidtis (1994).

In HIV infection, a number of studies have examined whether neuropsychological impairments are predictive of work disability and impairments in instrumental activities of daily living. For example, the WHO Neuropsychiatric AIDS Study found that the frequency of neurologic abnormalities and impaired functioning for everyday activities was higher in medically symptomatic individuals (CDC stage B or C), but not asymptomatic seropositive subjects, compared to controls (Maj *et al*, 1994). In a cohort of 271 HIV-positive men and women with advanced HIV infection, the majority with CD4 count less than 200, an algorithm was developed to operationalize the AAN definitions for HIV dementia and HIV-associated minor cognitive/motor disorder using standardized functional, neurological, and neuropsychological measures (The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders, 1996). It was unusual for functional deficits to occur in isolation, and usually there was a combination of neuropshychological, neurological, and functional deficits. Both minor cognitive/motor disorder and HIV dementia were associated with significantly poorer function on a self-rated scale of physical activities, the MOS Physical Functional Scale. These data confirm a strong correlation between severity of cognitive impairment and indicators of functional ability in HIV infection, even taking into account sociodemographic factors, disease severity, CD4 count, hemoglobin, and psychiatric indicators (The Dana Consortium on Therapy for HIV Dementia and Related Cognitive Disorders, 1996). In other work, Albert *et al* (1995a) showed a relationship between neuropsychological impairment and work disability, as well as modification of time use in HIV-infected individuals with neuropsychological deficits (Albert *et al*, 1995b).

Employment status and work function have been examined with respect to neuropsychological performance in HIV infection by the UCSD/HNRC group. Heaton *et al* (1994) reviewed the employment status of 289 HIV seropositive individuals and found the rate of unemployment in neurocognitively normal seropositives was 9.7%, while that among neurocognitively impaired individuals was 26.9%. After excluding any individuals with

constitutional symptoms to eliminate the effects of systemic disease, the rate of unemployment among neurocognitively normal persons was 7.9% and that among the neurocognitively impaired was 17.5%, a statistically significant twofold increase. Unemployment may be an imprecise indicator of functional impact from neurocognitive impairment and many other factors may influence employment, including financial and health insurance concerns. To our knowledge, comprehensive studies of actual types of employment and the economic impacts of cognitive impairment have not yet been completed.

The UCSD group have reported on the quality of life implications of neurocognitive impairment. They determined that there was a steady loss of quality-adjusted life-years as measured by the Quality of Life Well-being Scale (QWB) with increasing severity of neurocognitive impairment (McArthur and Grant, 1996).

Finally, it should be noted that neuropsychological testing and scales assessing ADL are accepted endpoints for trials in other dementing disorders. For example, the cholinesterase inhibitor tacrine (Cognex) was approved for therapy of Alzheimer's disease on the basis of a double blind, placebo-controlled study in patients selected for apparent responsiveness to tacrine. Smaller declines in cognitive performance and activities of daily living were measured in the tacrine group (Davis *et al*, 1992). Primary measures included the Alzheimer's disease assessment scale (ADAS) which includes both a cognitive subscale and noncognitive component. The instrumental Activities of Daily Living (IADL) was a secondary measure.

We recommend that neuropsychological test batteries and measures of everyday function remain the 'gold standards' for assessing therapy for HIV dementia. We conclude that the information from HIV dementia and other dementing illnesses proves that neuropsychological testing is both valid and reliable for assessing nervous system function.

Surrogate markers in HIV dementia trials

Work is ongoing to develop and validate alternative 'surrogate markers' for monitoring neurological disease. These are summarized in Table 3. Up to now, the 'gold standard' for detection of HIV dementia and monitoring response to therapy has been neuropsychological tests. Some of these surrogate markers have the advantage that they may be a more direct measurement of pathophysiological changes in the brain. For example, magnetic resonance spectroscopy may provide an *in vivo* measure of neuronal viability and could thus assess changes in neuronal density in HIV dementia (Barker *et al*, 1995; McConnell *et al*, 1994). Similarly, measurement of activation markers in CSF, eg, β2-microglobulin, neopterin, might reflect heightened state of immune activation within the CNS which correlates directly with the severity and rate of progression of dementia (Glass *et al*, 1995; Bouwman *et al*, 1996). Studies have shown significant changes in these markers following introduction of zidovudine therapy. Other instruments under development include functional MRI (Navia, B, personal communication) and various assays to measure CSF viral load. It is still unclear, however, whether CSF viral load is reflective of CNS viral load or simply represents trafficking lymphocytes. p300 evoked potentials have also been used to detect changes with therapy (Fein *et al*, 1995). Clearly, more work is needed to define the reliability and predictive value of these tests, however, it seems likely that at least some of them can be developed as important outcome measures for HIV dementia trials.

Table 3 'Surrogate markers' for monitoring HIV dementia therapy

Qualitative MRI:	assessment of atrophy and white matter change
Quantitative MRI:	measurement of structural change and regional atrophy
MR spectroscopy:	measurement of neuronal viability
Functional MRI:	measurement of brain activity – oxygen extraction
SPECT/PET:	measurement of brain activity
CSF analysis:	measurement of viral load, immune activations markers TNF-α, β2 microglobuin, neopterin, sTNF-2
p300 latencies	measurement of conduction and processing time

Design of clinical trials

Up to now, most trials of HIV dementia have been designed as placebo-controlled, parallel design clinical trials with a duration of 10 to 16 weeks. The optimal duration of dementia trials has been determined somewhat empirically based on open label experience and positive results from the original licensing trial which examined neuropsychological performance at weeks 8 and 16. Information beyond 4 months is clearly important to assess the durability of treatment response. However, it is often impractical to continue a placebo-controlled trial beyond this point because of relatively high drop out rates from trials of patients with advanced HIV infection and an inability to maintain a stable 'background' antiretroviral regime in an era of rapidly changing therapies. One compromise is to follow a placebo-controlled phase with a more prolonged open label extension phase. This also has the additional advantage of providing an incentive to patients to participate in a placebo-controlled study. Alternative trial designs, for example 2×2 factorial studies, may be appropriate for testing combinations of therapies and have recently been used in

one of the Dana Consortium Phase I/II studies testing thioctic acid and Deprenyl (K Kieburtz, personal communication).

In HIV dementia trials, the observed event rate influences sample size calculation significantly. For example, if the primary outcome is dementia progression, and the event rate in the placebo group is 40% and treatment intervention produces a 30% reduction, 325 patients would be required for a parallel design controlled trial. If the placebo rate is 50% and treatment induces a 30% reduction, 226 patients would be required (Weinshenker *et al*, 1996). Recent work suggests a wide variability in the rate of neurologic progression in HIV dementia, with a proportion of individuals showing prolonged cognitive stability (Bouwman *et al*, 1996). This observation means that dementia trials will need to factor in this inherent variability in calculations of anticipated progression and sample size.

Recommendations for design of treatment trials for HIV dementia

1. Neuropsychological test batteries and assessments of everyday functioning should remain primary outcome measures
2. Endpoints or outcomes should be used that are clinically-relevant and sensitive to the effects of change
3. 'Surrogate' markers of nervous system structure, function or pathophysiology should be developed and validated against existing instruments
4. Design of trials must take into account the necessity of stable antiretroviral 'background' and include incentives for participation, such as open label extension phases
5. Design of trials must take into account viability of progression of HIV dementia and the potential heterogeneity of minor cognitive/motor disorder

Antiretroviral strategies for therapy of HIV-associated dementia

Lessons from pediatric trials

Progressive encephalopathy, the childhood equivalent of HIV dementia, develops in 20 to 60% of children with HIV infection, with variable rates of progression (Belman *et al*, 1988). Several clinical trials have shown some efficacy for antiretroviral therapy in this condition. In one of the earliest and most convincing studies, Pizzo *et al* (1988) showed significant improvement in overall neurological performance, as measured by IQ scores in children receiving intravenous zidovudine. This was subsequently confirmed with oral zidovudine (McKinney, Jr. *et al*, 1991). Further information about the effect of dideoxynucleoside analogs on HIV dementia have derived from pediatric studies of ddl. Earlier studies showed improvements in neuropsychological performance related to plasma concentration of ddl (Butler *et al*, 1991). More recently, combination therapy with AZT plus ddl was found to improve survival compared to AZT alone in ACTG 152, although the combination had no superior effect on neuropsychological performance (personal communication).

There is little available information yet about the use of protease inhibitors in children. Currently, the recommended treatment for progressive encephalopathy in children is combination antiretroviral therapy with high dose AZT (15 mg/kg/day) plus ddl.

Specific recommendations for future study and treatment of progressive encephalopathy in children

1. Neurological assessment should be included as part of systemic disease protocols with the development of standardized operational definitions of neurological disease and standardized neurological examinations
2. In addition to antiretroviral therapies, additional emphasis should be placed on trials of adjunctive therapies, including immune-based therapies, eg immunomodulatory therapy; nutritional therapies, eg omega III fatty acids, carnitine; and trials for opportunistic infection prophylaxis

Treatment of HIV-associated dementia

Only one placebo-controlled clinical trial of antiretroviral therapy (with zidovudine) for HIV dementia in adults has been published. Despite the paucity of information from controlled clinical trials, in fact, a substantial amount of evidence has accumulated to indicate that HIV dementia is treatable and its deficits and functional impact are reversible in a proportion of patients. Early studies with high dose (greater than 1200 mg) zidovudine suggested that the incidence of HIV dementia was significantly lower in zidovudine recipients than in patients receiving no treatment (Portegies *et al*, 1989) and that the effect might be dose-related (Nordic Medical Research Councils HIV Therapy Group, 1992). The original licensing trial of zidovudine showed significant improvements in neuropsychological performance for individuals with advanced HIV infection; however, this trial excluded those with severe dementia. Recently, Chiesi *et al* (1996) showed a 40% reduction in risk of HIV dementia after AIDS with zidovudine. These results have not been confirmed by large US observational analyses, possibly reflecting the influence of zidovudine dose on neuroprotection. It appears that neuroprotective effects of antiretroviral monotherapy, at currently used doses, are relatively limited.

One open label study suggested that even severe dementia might respond to zidovudine therapy. Tozzi *et al* (1993) studied 30 patients with HIV dementia of varying severity and showed sustained responses in neurologic function with improvements in Memorial Sloan Kettering severity scores at 3 and 6 months (see Figure 3. The only placebo-controlled trial of zidovudine (ACTG 005) demon-

strated that zidovudine therapy improved neuropsychological performance in individuals with HIV dementia (Sidtis *et al*, 1993). 'High dose' AZT (2000 mg per day) was more efficacious than 'low dose' AZT (1000 mg per day). This trial led to the recommendation, still current, that treatment of established HIV dementia include zidovudine in highest tolerable doses (usually 800 to 1000 mg daily). Other antiretrovirals have not been studied systematically, either for neuroprotection or treatment of established dementia. There is limited information on the CNS penetration of the dideoxynucleoside analogues, although recent work suggests that ddl may achieve CSF levels of 20% of plasma (Burger *et al*, 1995). There is little available information on combination therapy, and none yet on protease inhibitors. Data from the MACS suggests some protective effect of combination therapy for dementia/wasting syndrome (Graham *et al*, 1996). ACTG 193 is an ongoing 'piggyback' study of HIV dementia in patients with advanced HIV disease with CD4 count less than 50. This study, when completed in 1997, should provide important much-needed information on the effects of currently used combination therapies in individuals at highest risk for development of HIV dementia.

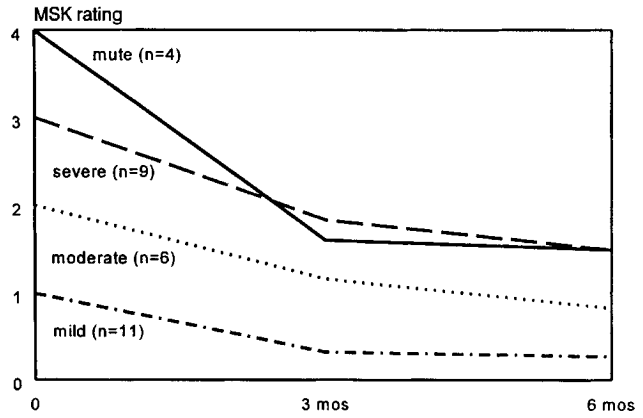

Figure 3 Open label treatment with zidovudine of 30 patients with HIV dementia of varying severity showing sustained responses in neurologic function with improvements in Memorial Sloan Kettering severity scores at 3 and 6 months. From Tozzi *et al* (1993). Note that even some severely impaired patients (MSK 3-4) showed improvements.

New agents for treatment of HAD

A widespread assumption up to now is that effective HIV dementia antiretroviral therapy must include agents with good CNS penetration. While this may indeed be a valid assumption, it should not *a priori* limit the use and study of such potent antiretroviral agents such as the protease inhibitors. Suppression of systemic infection may reduce further CNS seeding, and thus even a 'non-penetrating' protease inhibitor may have some effect. The non-nucleoside reverse transcriptase inhibitor, nevirapine (Viramune), apparently has good CSF penetration, and might be considered in antiretroviral protocols for HIV dementia. Table 4 includes the antiretroviral agents which are either in development or already in clinical trial.

Table 4 New antiretroviral agents and immune-based/neuroprotective therapies in development or clinical trial

Name	*Type*	*Plasma: CSF*	*Comments*
Antiretrovirals			
1592 (Abacavir)	Nucleoside analog	approximately 0.2	Multicenter Phase II/III trial began 8/96
Nevirapine (Viramune)	Non-nucleoside reverse transcriptase inhibitor	approximately 0.4	No controlled trials underway
Delavirdine (Rescriptor)	Non-nucleoside reverse transcriptase inhibitor	0.01	Phase I/II recently completed (Pharmacia-Upjohn)
6 chlorodideoxyguanosine	Nucleoside analog	approximately 0.2	May reduce HIV replication in chronically infected cells
VX478/141W94	Protease inhibitor	0.01	Clinical trials being considered for neurological disease
Indinavir (Crixivan)	Protease inhibitor	0.2	No clinical trials underway, but in widespread clinical use
Immune-based./neuroprotective therapies			
Memantine	NMDA receptor antagonist		ACTG 301: to start 12/96
Lexipafant	Platelet activating factor antagonist		Dana Consortium Phase I/II: to start 12/96
Prednisone	Macrophage suppression		ACTG: in development
Deprenyl	Putative anti-apoptotic agent		Dana Consortium Phase I/II study completed. Development planned

Further information about clinical Trials can be obtained from 1-800-TRIALSA, or via the World Wide Web

Recommendations for development of future antiretroviral therapies for HIV dementia

1. To develop and facilitate methods to implement more rapid development and clinical testing of new antiretroviral agents
2. To collect better information on the importance of CNS penetration of the protease inhibitors and other new antiretrovirals and the impact of potent combination therapies on CSF viral load
3. To include neurological assessments as part of routine clinical evaluations in systemic disease antiretroviral protocols and set up active surveillance and operational case definitions to capture HIV dementia as an outcome

Immune-based and neuroprotective therapies for HIV dementia

Numerous reviews have summarized the multitude *in vitro* and *ex vivo* studies of the pathophysiological mechanisms of neuronal dysfunction and death occurring with HIV dementia (see Figure 4). In addition to antiretroviral therapies, strategies focusing on blockade of aberrant immune reactions or on neuronal protective strategies may have an important adjunctive role for the treatment of HIV dementia, or its protection. In one of the most recent comprehensive reviews, Dewhurst, Gelbard, and Fine (1996) discuss the role of a number of candidate neurotoxins which may be important in causation of HIV dementia, triggering neuronal damage through common pathways involving the induction of oxidative stress and excitotoxicity. Table 5 includes the candidate neurotoxins in HIV dementia.

A number of *in vitro* model systems have been developed which may facilitate the clinical development of novel immune-based/neuroprotective

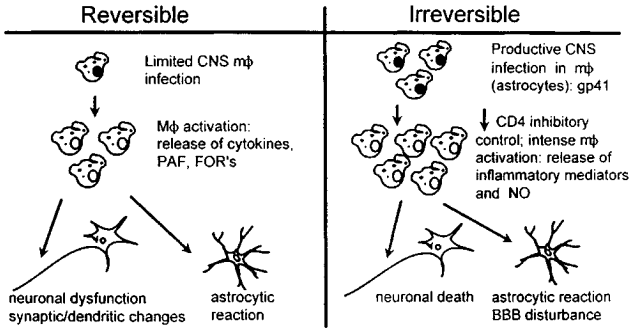

Figure 4 Hypothetical pathophysiologic mechanisms in HIV dementia. During 'reversible' phase there is limited infection of CNS macrophages and microglia, with macrophage activation and release of pro-inflammatory cytokines, platelet activating factor, and free oxygen radicals. These stimulate astrocytosis and neuronal dysfunction. During 'irreversible' phase, productive CNS infection increases, with release of neutotoxic gp41. With declining CD4 count, reduced inhibitory control leads to intense macrophage activation. Release of nitric oxide (NO) is associated with neuronal death and severe dementia.

Table 5 Candidate neurotoxins in HIV dementia (modified from Dewhurst [1996])

Molecule	*Comments*	*References*
HIV-1 gp-20	CNS injury occurs in gp120-transgenic mice; toxic to cultured human nuerons through the induction of soluble factors from microglia; stimulates glutamate efflux from human astrocytes	Lipton and Gandelman. (1995); Toggas *et al.* (1994); Koka *et al.* (1995); Benos *et al.* (1994)
gp41	Neurotoxic in mixed neuronal/glial cultures, elevated levels of brain gp41 associated with severe or rapidly progressive HAD	Adamson *et al.* (1996)
HIV-1 Tat	Infusion of HIV- Tat peptides into murine brain causes inflammatory CNS damage that is reversible upon blockade of TNF-α; HIV-1 Tat also mediates oxidative stress and is toxic to cultured human neurons	Philippon *et al.* (1994) Magnuson *et al.* (1995)
TNF=-α	Expressed at high levels in CNS of persons with HIV-1 dementia; toxic to cultured human neurons; mediates oxidative stress in human cells and activates transcription factor NF-$_K$B, which upregulates expression of HIV-1 and of cellular genes including iNOS and adhesion molecules	Wesselingh *et al.* (1993)
IL-6	CNS injury occurs in IL-6 transgenic mice; toxic to human neurons	Yeung *et al.* (1995)
PAF	PAF elevation in CSF correlates with dementia and immunosuppression in AIDS; toxic to human neurons at physiological levels	Gelbard *et al.* (1994)
Arachidonic acid and its metabolites	Present at elevated levels in CNS in HIV-1 dementia; produced by activated, HIV-1-infected human monocytes *in vitro*; inhibits glutamate uptake by rodent astrocytes	Lipton *et al.* (1995); Griffin *et al.* (1994); Volterra *et al.* (1994)
Excitotoxins glutamate	Excitotoxic tryptophan metabolites are increased in HIV-1 dementia (quinolinic acid, 3-hydroxykyurenine); NMDA receptor anatagonists block gp120-, PAF-, and Tat-toxicityin human and/or rodent neurons; non-NMDA antagonists block TNF-α and Tat-neurotoxicity in human neurons	Lipton *et al.* (1995); Magnuson *et al.* (1995); Gelbard *et al.* (1993); Gelbard *et al.* (1994); Sardar (1995)
Reactive oxygen species, nitric oxide	Inhibition of nitric oxide synthesis and/or addition of anti-oxidanrts to human and/or rodent neurons can protect against gp120- or TNF-α-mediated neurotoxicity	Lipton and Gendelman (1995); Talley *et al.* (1995)

(IB/NP) therapies. As one example of many systems, Persidsky *et al* (1996) developed a SCID mouse model system. With intracerebral inoculation of HIV-infected monocytes, many of the pathological features of HIV encephalitis can be duplicated. This is one of the systems under development which may provide a test system in which to rapidly screen candidate agents.

Several Phase I/II clinical trials of IB/NP agents have been completed for HIV dementia. These include the TNF-α antagonist pentoxifylline (McArthur *et al*, 1994); the calcium channel antagonist nimodipine (Navia *et al*, 1996); the anti-oxidant OPC14117 (Data Consortium for Treatment of HIV Dementia, 1996); the anti-oxidant thioctic acid; and the putative anti-apoptotic agent Deprenyl (K. Kieburtz personal communication). The Phase I/II studies have been conducted principally to generate information about toxicity and safety of these agents given in combination with antiretroviral therapies. For at least three of them, nimodipine, OPC14117, and Deprenyl, positive trends suggesting neuropsychological improvement have been seen.

Recommendations for development of future immune-based and neuroprotective strategies for HIV dementia and neuropathy

1. To develop rapid pre-clinical testing systems, in small animal or *in vitro*, for identification of potentially useful agents
2. To expand and facilitate an efficient system for conducting Phase I/II trials in a rapid, efficient manner
3. To design and plan Phase I/II trials in parallel with the design of larger scale Phase II/III trials so that well-tolerated agents can quickly be moved to pivotal trials of efficacy
4. To include in neurologic trials surrogate markers sensitive to changes in pathophysiological events affected by the specific intervention
5. To develop trials focusing on the impact of these types of therapies for HIV-associated sensory neuropathy and vacuolar myelopathy

Treatment of CMV-induced neurologicial disease and PML

CMV-induced neurologic disease

CMV retinitis remains the most common CNS manifestation of CMV disease; however, two discrete syndromes, CMV encephalitis and CMV radiculomyelitis, are also frequent opportunistic infections, occurring in 2 to 5% of patients with AIDS. With the availability of oral ganciclovir and its ability to prevent CMV disease, there may well be changes in the incidence of CMV encephalitis or radiculomyelitis. It remains to be seen exactly how widespread the use of oral ganciclovir will become, especially taking into account cost and the high number of capsules required for prophylaxis. A major advance in the early diagnosis of CMV encephalitis and radiculomyelitis is the detection of CMV DNA in cerebrospinal fluid. The development of PCR evaluation of the CSF for CMV has facilitated early and more definitive diagnosis. Several studies (Fillet *et al*, 1993; Cinque *et al*, 1992; Wolf and Spector, 1992; Gozlan *et al*, 1992, 1995; Cinque *et al*, 1996) confirm that a positive DMV DNA PCR is highly predictive of CMV neurological disease. For diagnosis of CMV encephalitis, CMV DNA PCR has a sensitivity of 84%, specificity of 98%, and positive predictive value of 90% (Cinque *et al*, 1996). Up to now, however, successful therapy of CMV encephalitis is only anecdotal. While there is more extensive experience with the successful treatment of CMV radiculomyelitis with antivirals (Cohen *et al*, 1993), neither syndrome has been evaluated systematically in a controlled trial. Based partly on experience with the combined use of ganciclovir and foscarnet for treatment of systemic CMV infection (Dieterich *et al*, 1993; Weinberg *et al*, 1994) and *in vitro* evidence of synergism (Manischewitz *et al*, 1990), the ACTG HIV Neurology Group has designed a PhaseI/II pilot treatment study (ACTG 305) to examine the CSF penetration and response to combined ganciclovir and foscarnet in CMV encephalitis and radiculomyelitis. The trial will include an induction phase of high dose foscarnet plus ganciclovir, followed by a maintenance phase and will examine the relationship between plasma and CSF concentrations of the two agents, drug resistance, as well as the role of quantitative CSF PCR to assess CMV viral load.

Cidofovir is a recently approved anti-CMV agent with proven efficacy against CMV retinitis. The agent has significant renal toxicity, and its efficacy for treatment of neurologic disease has not been explored.

Recommendations for CMV disease

1. To track incidence trends for CMV neurologic diseases as primary prophylaxis becomes more common
2. To rapidly complete ACTG 305 (combination of ganciclovir and foscarnet) to define pharmacokinetics of available antivirals and the utility of assays of CMV resistance and quantitative PCR
3. To develop, in collaboration with virologists and pharmacologists, newer, less toxic anti-CMV agents and move quickly to trial

Progressive Multifocal Leukoencephalopathy

PML has become a relatively common disease in AIDS, and unlike CMV disease, cannot be prevented, so its incidence is likely to rise with improvements in survival. Up to now, diagnosis has relied on brain biopsy confirmation; however, detection of JC virus in cerebrospinal fluid by PCR has a sensitivity of approximately 60 to 70% (G

Major, personal communication). This suggests that trials in the future could be conducted without a requirement for biopsy. Therapy up to now has been very limited, with scattered anecdotal reports of responses to alpha interferon, cytosine arabinoside, high dose antiretrovirals, and occasional spontaneuous remissions. The ACTG has recently closed the first controlled trial of PML (243) comparing the safety and efficacy of cytosine arabinoside in biopsy-proven PML. Sixty-two patients were randomized to receive either maximized antiretroviral therapy or maximized antiretroviral therapy with either intravenous or intrathecal cytoside arabinoside. No survival benefit was seen. The median survival was 10.6 weeks in the antiretroviral arm compared to 12 weeks in the combined Ara-C arms (no significant difference).

Replication of the JC virus relies on cellular replication machinery, as well as the JC virus large T antigen. The T antigen recruits a critical enzyme, topoisomerase-1 and RNA-primed DNA polymerization then proceeds. This DNA replication/protein complex is a rational point to target. There are theoretical reasons, based on the unique features of JC virus replication, that suggest that topoisomerase inhibitors might be effective therapies because viral replication should be more sensitive to topoisomerase inhibitors than cellular replication. Kerr *et al* (1993) have shown that the topoisomerase inhibitor camptothecin and its congener topotecan can inhibit JC virus DNA replication in glioma cells. Several campothecan analogs have been synthesized, including CPT-11, topotecan, and 9-amino-campothecan (9AC). Currently two topoisomerase-1 inhibitors are under consideration for PML trials. Topotecan, has recently been approved by the FDA for treatment of ovarian cancer under the trade name Hyacamtin. A Phase II trial of topotecan has been developed by Smith-Kline-Beecham and is ready to begin in late 1996 (W Royal, personal communication). 9AC is currently in Phase I/II testing for cancer patients who have received previous chemotherapy and a Phase I trial of 9AC in HIV-related KS is underway within ECOG. A Phase I trial in patients with HIV-associated PML has been proposed by the ACTG Neurology Group to determine toxicity and CSF penetration and to ascertain tolerable doses and toxicity.

Cidofovir, recently licensed from treatment of CMV retinitis, may have some anti-JC virus effect, but its activity needs to be confirmed further in *in vitro* studies, and nephrotoxicity may limit its application. A Phase I study is in development within the ACTG. Finally, alpha interferon, may have some efficacy for PML, based on its antiviral properties. An observational study in PML recently suggests a positive effect on survival and slowing disease progression (Huang *et al*, 1996).

In conclusion, we have reviewed previous clinical trials designed to treat HIV-associated neurological diseases, and we provide specific recommendations for the design of new clinical trials, as well as potential new therapies for HIV dementia, neuropathy, neurologic CMV disease, and PML.

Recommendations for development of therapeutic agents for PML

1. To clarify the sensitivity/specificity of CSF JCV PCR, to avoid requirement for brain biopsy in trials of PML
2. To perform *in vitro* studies and Phase I/II trials of toposiomerase inhibitors and cidofovir
3. To conduct trials of topotecan and alfa interferon
4. To develop a centralized database to collect information about open label use of anti-PML agents, diagnostic tools and natural history

Acknowledgements

To Nancy Rosenberg for her assistance in organizing the conference, and to the participants whose discussions, comments, and viewpoints contributed to this document. Supported by: NS 26643

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