

WHO/GPA/DIR/88.1
Original: English
Distr.: General

GLOBAL
PROGRAMME
ON AIDS

REPORT OF THE
CONSULTATION ON THE
NEUROPSYCHIATRIC ASPECTS
OF HIV INFECTION

GENEVA
14-17 MARCH 1988



WORLD
HEALTH
ORGANIZATION



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1. INTRODUCTION

It is well established that neurological and psychiatric disorders occur in AIDS: 70% of those who die of AIDS exhibit significant mental and neurological impairment, and pathological changes in the central and peripheral nervous system have been reported in the autopsy of up to 90% of AIDS cases (20, 46).

Recent reports have also suggested that neuropsychiatric disorders may occur earlier in the course of the HIV-1 infection and possibly even in the absence of constitutional symptoms (persons classified as Groups II or III according to the Centers for Disease Control (CDC) Classification - see Annex 3).

Accordingly, apprehensions have been raised concerning possible public health hazards that could result from neurological, cognitive or behavioural abnormalities occurring in otherwise asymptomatic HIV-1 infected individuals. In particular, such concerns have been linked to occupations or settings having the potential of endangering public safety (e.g., civil aviation, operation of nuclear reactors or heavy industrial equipment).

To examine currently available data and formulate appropriate policy responses in this complex area, a four-day Consultation (14-17 March 1988) was convened in Geneva by the WHO Global Programme on AIDS (GPA) and the Division of Mental Health (MNH). Forty-eight experts from 17 countries attended this Consultation, representing the disciplines of neurology, psychiatry, psychology, neurobiology, epidemiology, social work, occupational health, ethics, clinical research, and health policy.

The meeting, chaired by Dr A. Adams (Australia), was divided in two parts. For the first two days, available evidence on the neuropsychiatric effects of HIV-1 infection was consolidated and reviewed - with a particular focus on persons with CDC Groups II and III HIV-1 infection.

The following issues were considered:

- * What neuropsychiatric conditions are associated with Groups II and III HIV-1 infection?
- * What is known about the incidence, prevalence, course and functional impact of such neuropsychiatric effects in Groups II and III HIV-1 infected persons?
- * How does the incidence and prevalence of such problems in Groups II and III HIV-1 infection compare with that of non-HIV-1 related neuropsychiatric conditions in the general population?

In the second part of the meeting, the policy implications arising from this information were identified and considered.

In the first part of the Consultation, the working group examining the neurological data was chaired by Dr B. Osuntokun (Nigeria) with Drs J. Berger (USA) and J. McArthur (USA) as rapporteurs. A working group to examine the psychiatric/psychological evidence was chaired by Dr L. Eisenberg (USA) with Drs A. Jablensky (Bulgaria) and D. Miller (UK) as rapporteurs. During the second part of the Consultation, three working groups were established: Policy Implications, chaired by Dr L. Eisenberg (USA); Research Implications, chaired by Dr R. Levy (USA); and Health Care Implications, chaired by Dr P. Mason (UK).

2. CONCLUSIONS AND RECOMMENDATIONS

In persons with the disease AIDS or in those with the AIDS-related complex (ARC), important neuropsychiatric clinical conditions have been recognized to occur. In many cases these conditions have been linked to effects of HIV-1 in the central and peripheral nervous system. As a result, concern has been expressed about whether persons infected with HIV-1 who are otherwise healthy might experience functional neuropsychiatric impairments.

Participants at the Consultation concluded that:

"At present, there is no evidence for an increase of clinically significant neuropsychiatric abnormalities in CDC Groups II or Groups III HIV-1 seropositive" (i.e. otherwise asymptomatic) individuals as compared to HIV-1 seronegative controls.

Therefore, there is no justification for HIV-1 serological screening as a strategy for detecting such functional impairment in asymptomatic persons."

The most important outcome of these deliberations is that governments, employers and the public can be assured that based on the weight of available scientific evidence, otherwise healthy HIV-1 infected individuals are no more likely to be functionally impaired from a neuropsychiatric viewpoint than uninfected persons. Thus, HIV-1 screening would not be a useful strategy as a marker of such functional impairment in otherwise healthy persons.

These policy recommendations will be kept under continual review as additional scientific information becomes available.

The Consultation recommended that:

1. WHO should promote research to obtain information on the natural history, pathogenesis, predictors and possible markers for HIV-1 related neuropsychiatric disorders with particular attention to dementia and other neurobehavioural abnormalities;
2. WHO should promote the development and standardisation of research methodology, and in particular:
 - (a) WHO should promote the definition or creation of a standard broadly based neuropsychological test battery for assessment of HIV-1 related neuropsychiatric abnormalities including instruments or approaches which would have predictive power for changes in functional/occupational capacity;
 - (b) WHO should promote the development of an easily administered and culturally non-specific measure of neuropsychological function which could help provide data on the global extent of HIV-1 related neuropsychiatric abnormalities;
3. WHO should investigate, as a high priority, a report from Africa of the apparent occurrence of acute psychotic disorders as a possible first manifestation of HIV-1 infection and which are associated with rapid death without ARC or AIDS;

4. WHO should promote awareness among health workers of both the wide range of neuropsychiatric conditions particularly associated with late stages of HIV-1 infection and that, based on available evidence, otherwise healthy HIV-1 infected individuals are no more likely to be functionally impaired than uninfected persons.
5. WHO should continue to play an active role in the exchange of information in this field, with particular attention to the impact of new information on the policy issues described in this report.

3. THE EVIDENCE

3.1 Introduction

The neuropsychiatric diseases and disorders considered to be associated with HIV-1 infection were:

- HIV-1 dementia
- Neurobehavioural abnormalities other than dementia
- HIV-1 meningitis
- Vacuolar myelopathy
- Demyelinating peripheral nerve disease
- Mononeuritis multiplex
- Predominantly sensory neuropathy
- HIV-1 associated myopathy
- Opportunistic infections and neoplasms, including:
 - Progressive multifocal leukoencephalopathy
 - Cerebral toxoplasmosis
 - Cryptococcal meningitis
 - Primary CNS lymphoma
- Severe depressive episode (Major depression)
- Other affective disorders
- Schizophreniform and paranoid disorders
- Delirium
- Other, presumably organic, mental disorders in Groups II and III individuals
- Adjustment reactions
- Adjustment disorders

3.2 HIV-1 dementia

Individuals with HIV-1 dementia (also known as "AIDS-dementia complex", "HIV encephalopathy", or "subacute encephalitis") typically complain of forgetfulness, slowness, poor concentration, and difficulties with problem solving and reading. They may appear apathetic and exhibit reduced spontaneity and social withdrawal. In a small percentage of affected individuals the illness may initially present atypically as an affective disorder, psychosis, or seizures.

Bedside mental status examination demonstrates inattention, psychomotor slowing, impaired memory, and impairment of reasoning. Physical examination often reveals tremor, impaired rapid repetitive movements, imbalance, ataxia, hypertonia, generalized hyperreflexia, positive frontal release signs, and impaired pursuit and saccadic eye movements.

Formal neuropsychological testing shows multiple abnormalities on a variety of tests - primarily those that measure performance under time constraints, problem solving, visual scanning, perceptual and visual motor integration, learning and memory, and alternation between two or more performance rules or sets.

Children can also develop an HIV-1 associated neurodevelopmental disorder characterized by developmental delay, hypertonia, microcephaly and basal ganglia calcification. Unlike adults, the neurological involvement in children most often occurs in the absence of opportunistic infections and neoplasms.

In HIV-1 seropositive individuals or patients with clinical AIDS, characteristic symptoms as mentioned above are strongly suggestive of the diagnosis of HIV-1 dementia. However, the constellation of symptoms that characterize HIV-1 dementia is not specific. Other etiologies of dementia must be excluded, and HIV-1 serology must also be obtained before the diagnosis of HIV-1 dementia can be made. Laboratory and radiographic studies are most useful in excluding other diagnostic entities that may cause dementia in HIV-1 infected individuals. Magnetic resonance imaging (MRI) of the brain in persons with HIV-1 dementia often, though not invariably, reveals brain atrophy and white matter lesions. The cerebrospinal fluid (CSF) may reveal an increased protein content and mononuclear pleocytosis; furthermore, intrathecal synthesis of anti-HIV-1 specific IgG may be demonstrated, and HIV-1 may be isolated from the CSF. However, any of these CSF abnormalities can occur in neurologically and neuropsychologically normal HIV-1 infected individuals.

Currently there are no available data on the incidence of this disorder. According to a number of studies of AIDS patients the point prevalence of HIV-1 dementia ranges between 8 and 16% (8.2% in the UCSF study reported by Levy, et al.; 10% in the United States Air Force study presented by Marshall, et al.; 11% New York study reported by Snider, et al.; 16% of the patients reported by McArthur)(31, 35, 55, 37). However, in an autopsy series of cases referred to neurologists this figure was as high as 66% (Memorial-Sloan Kettering study reported by Price, et al.) (46). The variation among prevalence data in these studies may result from a number of factors, including sample selection, referral patterns, differences among risk groups, differences among various geographic regions and differences in applied diagnostic criteria and techniques of investigation.

HIV-1 dementia can be the presenting manifestation of HIV-1 infection and thus lead to the diagnosis of AIDS. Available evidence suggests that 0-3.3% of AIDS patients may present with HIV-1 dementia: 16 out of 1,286 cases at the University of California at San Francisco (UCSF); 10 out of 300 AIDS cases in Sydney, Australia (Cooper, personal communication); and none among a series of 30 AIDS cases seen in Japan (Tabira, personal communication).

There are no known risk factors for the development of HIV-1 dementia in HIV-1 infected persons. Whether differences in the manifestations or the course of HIV-1 dementia exist among different groups of persons at risk for HIV-1 infection is under study. It is uncertain whether those individuals with Groups II and III HIV-1 infection who exhibit more subtle abnormalities, referred to in section 3.3, are at any increased risk of developing HIV-1 dementia. HIV-1 dementia, generally, but not invariably, progresses quickly to severe deterioration and death. Not enough data are available to determine course and outcome of HIV-1 dementia in patients without opportunistic infections and neoplasms.

There is not enough evidence to confirm the efficacy of any anti-viral agent in the management of this disorder. Psychosocial interventions with patients and their carers, to help sustain quality of life, attenuate the rate of deterioration, and minimize the impact of behavioural disturbance, represent the sole and optimum management strategy at present.

3.3 Neurobehavioural abnormalities other than dementia

Neurobehavioural abnormalities (other than dementia) are not specific and can only be related to HIV-1 infection if after thorough evaluation they cannot reliably be ascribed to any particular disorder or etiology.

Neurological, cognitive or behavioural problems may occur singly or in combination and include difficulty with concentration, memory, speech, or language, persistent headaches, incoordination, weakness, diplopia, vertigo, apathy, anxiety or depression.

Abnormalities detectable by neuropsychological tests can include motor slowing, poor concentration, impairments in rapid sequencing and processing, abstracting ability, learning and recall, complex perceptuo-motor performance or language abilities. These abnormalities are usually mild, are insufficient to establish a diagnosis of dementia by the International Classification of Diseases (ICD 10) clinical criteria and, by patient report, rarely interfere with job performance in the absence of other AIDS-related illnesses.

The abnormalities are detected by history, physical examination, neuropsychological tests and laboratory evaluation with particular emphasis on neuropsychological testing. Abnormalities detected by such evaluation are non-specific, and it is not clear whether they are pathognomonic of HIV-1 infection. To establish their presence, functional disorders, such as adjustment reaction and depression or organic brain dysfunction, (e.g., due to substance abuse, metabolic disorder or head trauma, must be ruled out.

The reported prevalence of abnormality as measured by neuropsychological testing is 9-18% for HIV-1 seronegative controls; 20% (Price, et al.) to 54% (Grant, et al.) for ARC patients and 35% (Memorial-Sloan Kettering study reported by Price, et al.) to 87% (San Diego study reported by Grant, et al.) for AIDS patients. Incidence rates for these abnormalities in HIV-1 seropositive (CDC Groups II and III) populations are unknown, but will be obtained through currently ongoing prospective studies.

At present, there is disagreement as to whether abnormalities as measured by neuropsychological testing occur with increased frequency in otherwise healthy HIV-1 (CDC Groups II and III) infected individuals. Point prevalence of these abnormalities is not clearly known and varies according to diagnostic criteria, neuropsychological test batteries, sample selection, and rates of confounding factors in different studies.

In a study of 650 homosexual/bisexual HIV-1 seropositive men (CDC Groups II and III) in Baltimore, Los Angeles, Chicago, and Pittsburgh, no differences in the prevalence of neurological symptoms or in performance on neuropsychological testing were found when seropositive individuals were compared to uninfected controls (10% in both groups) (unpublished data from the ongoing Multicenter AIDS Cooperative study presented by McArthur et al.).

A study of 85 homosexual/bisexual men (CDC Groups II and III) in San Francisco showed no difference in the prevalence of neurological abnormalities or of abnormal performance on neuropsychological tests between seropositives (15%) and controls (18%) (Ongoing CDC/San Francisco Cohort study, unpublished results reported by Janssen et al.).

A third study of 83 healthy, HIV-1 seropositive men (Walter Reed Class I and II) in the United States Air Force (35, in press) showed no significant difference in the frequency of neurological abnormalities or neuropsychological deficits between seropositives (8%) and seronegative controls (0%).

However, a study of sixteen seropositive men (CDC Groups II and III) in San Diego (18) demonstrated an increase in the prevalence of abnormalities in neuropsychological tests in seropositives (44%) compared to seronegative controls (9%). Unpublished data from an ongoing longitudinal study by this group indicate that about one-third of thirty HIV-1 seropositive persons examined to date have some neuropsychiatric impairment compared to 10% of HIV-1 negative controls (data presented by Grant).

The data from the first three studies referred to above involved over 800 men and have shown no increase in neurological and neuropsychological abnormalities in HIV-1 infected, otherwise healthy persons, when compared to HIV-1 seronegative controls. The data from the fourth of the studies mentioned above are based on a small series but raise the possibility of some increase in neuropsychological abnormalities in such persons. The weight of current evidence suggests that CDC Groups II and III persons do not have an increased frequency of neuropsychological abnormalities; however, the presence of divergent findings means that a final conclusion is not possible at present.

There are no known risk factors or predictors of neurobehavioural abnormalities in persons infected with HIV-1. The natural history of these abnormalities is also unknown. It is not known whether they are transient and reversible, persistent or progressive. It is also unknown whether these abnormalities predict subsequent neurological or mental deterioration.

It is possible to offer specific therapy in the form of supportive care and referral to psychological specialists when appropriate. Psychogenic factors may account for some of the observed mild cognitive defects, and as such are amenable to psychological interventions. It should be noted that in the opinion of several participants in this Consultation, psychoactive medication such as anti-depressants might cause more frequent and severe side effects in HIV-1 infected persons compared with uninfected individuals.

3.4 HIV-1 related meningitis

An acute "aseptic" meningitis occurring shortly after infection appears to represent a primary response of the nervous system to HIV-1 infection. Symptoms compatible with acute meningeal inflammation include headache, retro-orbital pain, meningismus, fever, photophobia, cranial neuropathies, and rarely, transient encephalopathy (but not progressive dementia). Typically, the acute symptoms are self-limited, require no special treatment, and resolve within 1 to 4 weeks.

A more indolent variant of HIV-1 related meningitis with only headache and persistent low-grade CSF pleocytosis has been recognized. This type of meningitis can only be attributed to HIV-1 infection after the exclusion of other possible causes.

The illness is defined by symptoms and signs as described above in the presence of CSF mononuclear pleocytosis exceeding five white blood cells per cubic millimeter.

The incidence of clinically apparent meningitis seems to be low but no systematic studies have been carried out. Symptomatic meningitis may occur as part of acute infection with HIV-1 (CDC Group I) or can occur in persons in CDC Groups II and III. In persons in CDC Groups II and III, the incidence of "silent" CNS involvement, manifested by CSF lymphocytic pleocytosis, intrathecal synthesis of anti-HIV-1 specific antibodies, and/or HIV-1 isolation, may exceed 50%. The significance of these findings is uncertain.

Acute "aseptic" meningitis is usually self-limited. Likewise, "silent" CSF abnormalities may "normalize" as the patient moves into later stages of the disease (i.e. CDC Group IV). It is uncertain whether either the acute symptomatic meningitis or the "silent" CSF abnormalities are associated with the later development of progressive dementia.

3.5 Vacuolar myelopathy

Vacuolar myelopathy appears to be a condition associated with HIV-1 infection. Typically, the clinical manifestations of this disease include a slowly progressive spastic paraparesis, sensory ataxia, sphincter disturbance and impaired distal sensation without a clearcut sensory level. The myelopathy may be subtle, or masked by other neurological disorders, (e.g. concurrent myelopathy and peripheral neuropathy). While the myelopathy is generally associated with HIV-1 dementia, the pathological changes observed in these two conditions are very different, suggesting different pathogenic mechanisms for the two processes. It has not been established that the vacuolar changes result directly from spinal cord infection with HIV-1.

Myelography and spinal MRI are usually normal. CSF examination reveals non-specific abnormalities including mononuclear pleocytosis, elevated total protein, and HIV-1 isolation.

The prevalence of vacuolar myelopathy exceeds 20% among autopsied AIDS cases in New York and New Jersey (44). However the lower prevalence observed in clinical and autopsy series from other centres, may depend upon case selection or autopsy technique.

Only anecdotal reports of the occurrence of vacuolar myelopathy in otherwise asymptomatic (CDC Groups II and III) persons have appeared. Thus, the incidence of the condition in CDC Groups II and III persons is probably quite low; however, prospective studies will be needed to assess this matter. The course and outcome of this condition in CDC Groups II and III persons is unknown; in particular it is unknown whether the course of vacuolar myelopathy is different in the earlier stages of HIV-1 infection compared with the later stages. No risk factors for the development of this condition after HIV-1 infection have been identified. The effect of zidovudine (formerly AZT) or other anti-viral agents in the treatment of vacuolar myelopathy is unknown.

3.6 Demyelinating peripheral nerve disease

HIV-1 associated demyelinating peripheral nerve disease typically presents as either an acute demyelinating motor neuropathy (a Guillain-Barré-like syndrome) or as a more chronic syndrome with predominantly motor weakness (10). This condition may be immune-mediated, representing immune dysregulation, rather than resulting from direct nerve damage from HIV-1. Other viruses, such as herpes group viruses, may also be of relevance in its pathogenesis.

The diagnosis of this disorder requires:

- (a) HIV-1 seropositivity.
- (b) Clinical features such as hypo- or areflexia, weakness, and vibratory loss.
- (c) Electrophysiological abnormalities including conduction block and marked slowing of nerve conduction velocities.
- (d) CSF abnormalities including a marked pleocytosis which often distinguishes HIV-1 related demyelinating neuropathies from those not associated with HIV-1.
- (e) Nerve biopsy which reveals the typical changes of inflammatory demyelinating neuropathy, mononuclear-macrophage infiltration and internodal demyelination.

The clinical and electrophysiological features of demyelinating neuropathies associated with HIV-1 infection are indistinguishable from demyelinating neuropathies occurring in the absence of HIV-1 infection.

The majority of cases of demyelinating neuropathies present in the early stages of HIV-1 infection (CDC Groups II and III) (11) and the disease may, therefore, be the first manifestation of HIV-1 infection (5). However, the disorder is uncommon.

Risk factors for the development of demyelinating neuropathies after HIV-1 infection are unknown and it is unclear whether the syndrome appears in all of the groups at risk for HIV-1 infection.

Most patients with these demyelinating neuropathies recover spontaneously. Steroids, with or without plasmapheresis, have been used for their treatment, but controlled studies of their effectiveness are lacking.

3.7 Mononeuritis multiplex

There is no consensus on the range of manifestations of mononeuritis multiplex occurring in HIV-1 infected individuals. However, several reports have described individuals with multiple mononeuropathies, some with accompanying cranial neuropathies and others with central nervous system signs. Several patients have developed a more widespread peripheral neuropathy with features of chronic inflammatory demyelinating neuropathy. The etiology of mononeuritis multiplex occurring in HIV-1 infected persons is unknown and could be related to concurrent infection (e.g., with hepatitis B virus).

The diagnosis of mononeuritis multiplex in a person with HIV-1 infection requires the clinical features of mononeuropathy to be present as well as pathological changes on nerve biopsy (vasculitic changes and centronfascicular degeneration).

The incidence of this disorder in persons with HIV-1 infection, regardless of Group classification is rare. Some HIV-1 infected individuals with mononeuritis multiplex progress to develop generalized neuropathy, but too few patients have been studied so far to generalize about course of the illness. There is no proven therapy for mononeuritis multiplex.

3.8 Predominantly sensory neuropathy (PSN)

Predominantly sensory neuropathy (PSN) in the HIV-1 infected person normally presents with acral paresthesiae and dyesthesiae, primarily affecting the balls of the feet and the toes symmetrically. Usually there is minimal weakness; however, ankle jerks are depressed and vibratory thresholds are elevated. Some patients with predominantly sensory neuropathy have a selective degeneration of the gracile tract in the spinal cord at autopsy and it has been proposed that the syndrome represents HIV-1 infection and damage of the dorsal root ganglia. Other factors, including toxic and nutritional factors, may be of importance.

Diagnosis of PSN involves electrophysiological studies which reveal a neuropathy affecting both sensory and motor fibers, characteristic of axonal degeneration. Pathological evaluation of nerve biopsy specimens reveals axonal loss and mild inflammatory changes.

Approximately 20% of patients with AIDS and fewer patients with ARC develop PSN. Distal symmetrical peripheral neuropathies in the general population, particularly in the elderly, may be common and PSN may not be sufficiently characteristic to be considered pathognomonic of HIV-1 infection. PSN only rarely occurs in HIV-1 infected, otherwise healthy, persons (CDC Groups II and III).

The only known treatment for PSN is symptomatic. While their use has not been systematically studied, some patients respond to tricyclic anti-depressants or to topically-administered capsaicin. The value of zidovudine (formerly AZT) in treatment for PSN is unknown.

3.9 HIV-1 associated myopathy

HIV-1 associated myopathy is characterized by a subacute, predominantly proximal muscle weakness with myalgias, excessive fatigue, and an increased serum creatine kinase (CK) level. Electromyographic features parallel those observed with polymyositis. Muscle biopsies may reveal myofiber degeneration and regeneration, and perivascular and interstitial inflammation. A self-limited myopathic process may also be observed at the time of seroconversion to HIV-1. The diagnosis is established in an HIV-1 seropositive person on the basis of the clinical features, elevated muscle enzymes, electromyographic criteria and muscle biopsy findings.

The incidence of this disorder in people infected with HIV-1 is unknown but the clinical syndrome is rare. HIV-1 myopathy may occur as the presenting manifestation of the infection (12), but the frequency of such presentation is not known.

There are no known risk factors for the development of myopathy after HIV-1 infection. The course and outcome of HIV-1 myopathy are not known. No form of treatment has been proven to be effective. On the basis of anecdotal evidence some investigators have suggested using immunosuppressive therapy.

3.10 Opportunistic infections and neoplasms

There are a number of opportunistic infections or neoplasms that can affect the patient with HIV-1 infection and immunosuppression. By definition, the presence of these illnesses will result in the diagnosis of AIDS. Thus, while they may arise as the initial illness in CDC Groups II and III patients, once the illnesses have developed, the patients carry the diagnosis of AIDS (Group IV).

Several of the most important of these opportunistic conditions are: progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, cryptococcal meningitis, and primary CNS lymphoma.

3.10.1 Progressive multifocal leukoencephalopathy (PML)

PML is an unusual infectious CNS disease caused by the papovavirus John Cunningham (JC). Affected patients present with dementia, blindness, dysphasia, hemiparesis, ataxia and focal deficits which slowly progress until death.

Characteristic radiological findings of this disease include white matter lesions without mass effect. Biopsy or autopsy reveals focal loss of myelin and the presence of bizarre glial cells with characteristic inclusions surrounding these areas of myelin loss. These histopathological findings are pathognomonic. Monoclonal antibody staining or electron microscopy can reveal the causative agent (JC).

Eight of 1,286 AIDS patients at UCSF had PML (0.6%) and preliminary reports from the University of Miami indicate that PML may occur in up to 3.8% of their AIDS patient population.

PML may be the initial clinical manifestation of HIV-1 infection in a small number of cases. PML was the initial manifestation of AIDS in three patients at UCSF, (0.2% of all AIDS patients); data from Miami suggest that a similar proportion of their patients with PML had this disease as their initial clinical manifestation of AIDS. CDC data suggest that PML was the initial manifestation of AIDS in 0.8% of all AIDS cases.

There are no known factors that increase the risk of developing PML following HIV-1 infection. There are no known effective therapies for PML. The prognosis is grave; mean survival after the onset of symptoms is less than two months.

3.10.2 Cerebral toxoplasmosis

Cerebral toxoplasmosis in AIDS patients results from the reactivation of latent brain infection with the opportunistic intracellular parasite Toxoplasma gondii.

Definitive diagnosis of this infection can be made by evaluation of biopsy material. *Toxoplasma* organisms can be identified by touch preparation, peroxidase-antiperoxidase staining or by direct visualization on light or electron microscopy. Radiological studies reveal frequently multiple bilateral ring enhancing lesions but these are difficult to distinguish from findings in other AIDS-related CNS diseases so that specific diagnosis by radiological criteria is impossible. Clinical findings are also nonspecific. Response to empiric therapy with pyrimethamine and sulfadiazine is considered by some to be an appropriate method to establish the diagnosis of toxoplasmosis.

By October 1987, 838 cases of cerebral toxoplasmosis had been reported to the CDC. Between 2% and 13% of AIDS patients develop cerebral toxoplasmosis depending upon patient risk group and geographic location. Autopsy data suggest it may occur in as many as one-third of AIDS patients.

In a substantial proportion of AIDS patients with cerebral toxoplasmosis, this disease was the first clinical manifestation of illness; overall, however, the percentage of AIDS patients first presenting with cerebral toxoplasmosis is small. Thus, while cerebral toxoplasmosis was the initial manifestation of AIDS in 44% of patients at UCSF with cerebral toxoplasmosis, only 1.8% of all patients with AIDS at UCSF presented with cerebral toxoplasmosis. The CDC data suggest that 5.4% of AIDS patients first present with cerebral toxoplasmosis.

Risk factor analysis for the development of toxoplasmosis has only been performed for AIDS patients in the United States. In the United States, AIDS patients from Haiti and Florida are at increased risk of developing this opportunistic infection. These risk factors are independent of each other. As this illness appears to result from the recrudescence of a latent infection, variations among different geographic locales may reflect prior rates of infection with the organism related to the endemicity of toxoplasmosis in these areas.

Therapy with pyrimethamine and sulfadiazine can result in a complete resolution of symptoms and control of the disease. In patients intolerant of sulfa drugs, clindamycin, although of unproven efficacy, may be the second line chemotherapeutic agent. Lifelong treatment is necessary in most patients. Survivals of up to 18 months have been reported.

3.10.3 Cryptococcal Meningitis

Meningitis caused by infection with the common soil fungus Cryptococcus neoformans is a well known clinical entity. Symptoms of meningitis, including headache, stiff neck, fevers and photophobia are most common. Other signs and symptoms have been described in section 3.4 (31). Diagnosis is made by CSF analysis with cryptococcal cultures, cryptococcal antigen titers or India ink staining.

By October 1987, 2,473 cases of AIDS-related cryptococcal meningitis had been reported to the CDC; the prevalence among AIDS patients in the UCSF series was 5.3%. While many AIDS patients who develop cryptococcal meningitis have this illness as their first clinical manifestation of AIDS, the proportion of AIDS patients who first present with cryptococcal meningitis is

small. Thus, in 34% of all cases of cryptococcal meningitis in AIDS patients at UCSF the condition was the initial manifestation of AIDS representing 1.8% of all AIDS patients. CDC data suggest that 6.1% of AIDS patients have cryptococcal meningitis as their first AIDS-defining illness.

In the United States, the prevalence of reported cryptococcal meningitis is highest in New York and New Jersey. This appears related to the increased proportions of intravenous drug users and blacks among the AIDS patients in these areas; these two factors appear to be independent of each other and each is associated with an approximately two-fold increase in relative risk.

Treatment with amphotericin B, with or without 5-flucytosine, can result in a significant response with resolution of clinical symptoms and control of the disease. The major therapeutic problems involves toxicity of these agents and recurrent disease. Therapy with ketoconazole derivatives for maintenance therapy is under investigation. Lifelong suppressive treatment may be required in most patients.

3.10.4 Primary CNS lymphoma

Primary malignant lymphomas of the brain are rare but well characterized tumours, involving proliferation of atypical lymphocytes, usually in a perivascular distribution. Radiological studies tend to reveal contrast enhancing mass lesions although nonenhancing CNS lymphomas have been identified. Lesions are more frequently unifocal than multifocal. The radiological picture is similar to that of other focal processes in patients with AIDS. Definitive diagnosis is made by brain biopsy. Response to radiation therapy may suggest the diagnosis but is not definitive (e.g., such response may be obtained in the rare cases of metastatic Kaposi sarcoma or other tumours).

At UCSF, 25 of 1,286 patients had CNS lymphoma (1.9%). Of patients with CNS lymphoma at UCSF, 48% presented with lymphoma as the first AIDS-defining illness; this represents 0.9% of all AIDS patients at UCSF. CDC data suggest that 1.5% of AIDS patients in the United States first present with CNS lymphoma. Epidemiological studies have not revealed risk factors for development of CNS lymphoma.

Early studies suggested that this disease was untreatable and rapidly progressive. However, according to one recent study, the tumours of patients in otherwise good general health appear to respond to early aggressive radiation therapy which may increase the length and quality of life. Without this therapy mean survival is about two months.

3.11 Severe depressive episode / Major depression

Depression (severe depressive episode according to ICD-10, or major depression according to DSM-III-R) is a common mental disorder in most populations and can be regarded as a well established clinical entity for which explicit, internationally applicable diagnostic criteria have been developed (27). The diagnosis can be made reliably on clinical grounds, taking into account the present mental state, previous history and family history. In the general population, the incidence of new cases per year is about 5 per 1000 (51). The period prevalence, however, is much higher and may amount to 5% of the adult population over a 6-month period, according to data reported from the US Epidemiologic Catchment Areas (ECA) study (48). The lifetime risk determined in a Swedish prospective longitudinal study (21) was about 40% for females and 20% for males; the male/female ratio in most populations is 1:2 or 1:3.

Depression may occur at any point in the course of an HIV-1 infection, but according to clinical reports, there is a clustering of such illnesses: (a) in the period following the identification of HIV-1 seropositivity (as a reactive state linked to the realization of the health threat, loss of self-esteem, and guilt; see section 3.16); and (b) in the initial stage of HIV-1 dementia, where affective disturbance may precede the onset of the cognitive abnormalities.

Depressive illnesses occur in CDC Groups II and III persons but data on their incidence and prevalence are currently lacking. The reported frequency (43, 13) among HIV-1 seropositive persons who were referred to a psychiatric consultation was 15-17%. There are at present much larger unanalysed series of observations on HIV-1 seropositive individuals with psychiatric symptoms; analysis of this material should permit an estimation of the prevalence of major depression in HIV-1 seropositive populations.

However, even if the incidence of depression in persons in CDC Groups II and III is higher than in the general population, a difference (unless excessive) will be difficult to demonstrate in view of the high baseline rate of occurrence of depressive disorders. Another potential difficulty in attributing mood disorders to HIV-1 is the possibility that groups at risk of becoming infected might consist of persons who are more likely to suffer from depression than members of the general population. Additionally, the differential diagnosis of depression in an HIV-1 seropositive individual is difficult because its symptoms may mimic features of ARC (weight loss, sleep disturbance, loss of libido) or dementia (slowing of mental processes, impaired concentration, subjective complaints of memory deterioration). Nevertheless, such differentiation should be attempted because of its important implications for prognosis, treatment and management.

Very little is known at present about the course and outcome of depression in CDC Groups II and III persons. The available case reports indicate that its onset is usually gradual; sudden incapacitation due to unrecognized depressive illness is unlikely. The risk of depression in an HIV-1 seropositive person may be augmented by psychosocial factors (lack of social support). The frequency of suicide and attempted suicide associated with depression in HIV-1 seropositive populations is not known although HIV-1 seropositive persons do fulfill prospective criteria for elevated suicidal risk (53). A recent report by Marzuk et al. (36) suggests that Group IV patients are at increased risk of committing suicide.

For otherwise asymptomatic persons, there is no evidence that their depression need be treated differently from depression in seronegatives. However, patients suffering from an organic brain syndrome from any cause are susceptible to delirium induced by tricyclic anti-depressants: it may be necessary to start treatment with a smaller dose and increase the dose more gradually than in other patients. If a therapeutic dose of tricyclics cannot be tolerated, non-tricyclic anti-depressants should be considered, with monitoring.

The above considerations about diagnosis, treatment and management are of particular relevance to general practitioners and emergency room physicians, because only a minority of the depressive persons who are also HIV-1 seropositive are likely to make a first contact with a psychiatrist.

3.12 Other affective disorders

There are anecdotal reports of manic episodes in HIV-1 seropositive individuals but it is not known whether these are causally linked to HIV-1 infection of the nervous system or are the expression of a bipolar affective illness in a person who happens to be seropositive.

3.13 Schizophreniform and paranoid disorders

There are several case reports (28, 34, 57) of acute psychotic illnesses with hallucinations, paranoid or grandiose delusions, and thought disorder in individuals who could be classified as CDC Groups II and III. On the basis of such reports the etiology of these illnesses cannot be clearly attributed to HIV-1 infection, and further research is needed to establish whether acute schizophreniform or paranoid psychosis could be a neurobehavioural manifestation of HIV-1 infection.

3.14 Delirium

Delirium is a well defined entity, and the ICD-10 diagnostic guidelines and research criteria ensure its reliable identification. Delirium may develop in a variety of physical illnesses, infectious and parasitic diseases, intoxications, and as a complication of head injury. It is particularly common among the elderly where it usually occurs in the context of cerebrovascular disease or dementia. The incidence of deliria is higher in the developing countries in association with the higher frequency of infectious and parasitic diseases.

In HIV-1 infection, single cases of short-lived delirium have been described in association with the aseptic meningitis which may develop upon seroconversion (38). Cases of delirium in the early Groups II and III individuals are probably quite rare. Delirium is apparently much more common in HIV-1 dementia where it is superimposed on cognitive deficits and may aggravate the clinical picture (47). However, estimates of incidence are not available at present.

The course of the delirious episodes that may sometimes occur at the time of seroconversion is benign (complete recovery within hours or days). However, there is no return to pre-morbid functioning when delirium develops in the context of HIV-1 dementia. It is not known whether the development of a delirium may worsen the overall course of HIV-1 dementia, but this possibility cannot be excluded. Delirium should be regarded, therefore, as a serious complication in the course of HIV-1 dementia. Its occurrence should be prevented to the extent possible by providing good general care to HIV-1 seropositive persons with early dementia; its manifestations should be appropriately treated.

3.15 Other mental disorders

There have been a number of individual case reports referring to acute illnesses of mixed symptomatology in HIV-1 infected persons (e.g., combining delusions and hallucinations, affective symptoms, and impaired sensorium). Such illnesses cannot be unequivocally classified but the primary etiology appears organic and is likely to be HIV-1 related. More epidemiological data are required before incidence can be assessed.

An observation of potential significance, reported from Tanzania (50), concerns the apparent occurrence of acute psychotic disorders in HIV-1 seropositive individuals. These disorders apparently were the first manifestation of HIV-1 infection and resulted in rapid deterioration and death within weeks or months, without development of ARC or AIDS. The clinical picture in these cases is not dementia but an acute hallucinatory psychosis with gross excitement. The nature of these illnesses needs further investigation; no autopsies have thus far been performed.

3.16 Adjustment reactions

Adjustment reactions are common experiences in those recently diagnosed with HIV-1 infection and represent reactions to learning that one has HIV-1 infection. They involve expressions of despair, grief, guilt, anxiety, protest, depression and hypochondriasis. In type, severity and duration these reactions are similar to reactions to other major life events or disease in the context of the culture. They do not usually lead to chronic functional impairment. Factors which have a significant bearing on the severity and duration of such reactions include perceived stigma and the extent of social support.

Adjustment reactions may occur in up to 90% of those seen with the recent diagnosis of HIV-1 infection; thus, these reactions occur in CDC Groups II and III individuals. The impact of adjustment problems may be reduced by anticipatory support offered through pretest counselling and patient preparation. These reactions are most common after diagnosis and may recur or appear for the first time with changes in the individual's clinical status.

In Groups II and III persons, adjustment reactions may last several weeks or longer if the patient has insufficient support or counselling and medical management. Adjustment reactions are aggravated in the context of poor social support, poor or non-existent family support, lack of occupational or financial flexibility, and in persons with a history of personality disorders and/or drug or alcohol dependencies. Adjustment reactions in family members and loved ones of people with HIV-1 infection are also extremely common and probably exacerbate or prolong adjustment reactions in the infected person.

Supportive counselling is the treatment of choice, with liaison psychology/psychiatry as appropriate. Counselling should include management of environmental issues including relationships, social and occupational concerns.

3.17 Adjustment disorders

Many reports have not differentiated between adjustment reactions and disorders.

Adjustment disorders feature chronic functional distress or impairment and involve a morbid (excessive in length and/or intensity) response to the stress of HIV-1 infection identification or diagnosis.

The incidence and prevalence of adjustment disorders in CDC Groups II and III individuals is not known. Adjustment disorders may be more frequent in persons with prior psychiatric histories (57, 52). These adjustment disorders may last many months. They are frequently amenable to psychological therapy

or medication, subject to the constraints of dosage and tolerance of side effects described in section 3.11. The same risk factors exist for the development of adjustment disorders as for adjustment reactions, including prior psychiatric disturbance. In general, treatment is the same as for adjustment reactions; however, hospital admission may be required during a severe decline in clinical status.

3.18 Summary of the evidence

There are a wide range of neuropsychiatric diseases and disorders associated, more or less clearly, with HIV-1 infection. For persons with AIDS and for some with ARC all areas of the nervous system are susceptible to damage or dysfunction due to HIV-1 or to opportunistic infections or meningitis. However, based on the review of currently available scientific and medical data, there is no evidence for an increase of clinically significant neuropsychological abnormalities in CDC Groups II or III HIV-1 seropositive persons compared to HIV-1 seronegative controls.

4. POLICY IMPLICATIONS

4.1 HIV-1 serological screening

Since there is no evidence that otherwise healthy HIV-1 infected individuals (CDC Groups II and III) are more likely to be functionally impaired than persons not infected with HIV-1, there is, at the present time, no justification for HIV-1 serological screening as a strategy for detecting such functional impairment in asymptomatic persons in the interests of public safety.

This policy statement needs to be continually reviewed in the light of studies currently in progress or planned.

It is recognised that in AIDS and HIV related issues public concern has been aroused and might be susceptible to excessive influence by anecdotal or single case reports. For example, if a bus, train or air accident occurred and the driver/pilot was an asymptomatic HIV-1 seropositive person, the conclusion might be drawn - inaccurately given the weight of existing evidence - that HIV-1 infection led to a neurological, cognitive or behavioural abnormality which was responsible for the accident.

It needs to be emphasized that single instances and anecdotes cannot and should never replace meticulous analysis of all the available evidence as a basis for reaching conclusions regarding cause and effect and for policy formulation.

4.2 Safety related occupations

Protection of the public by preventing accidents is an important policy goal. The review of existing data has led to the statement that there is no evidence that asymptomatic HIV-1 infected individuals pose special problems in safety related occupations. The application of performance and functional standards currently recommended for use either in industry (e.g. for airline pilots, crane drivers, etc.) or for assessing individual capacity to perform daily activities (e.g. for driving a car) represents the most effective strategy to detect meaningful dysfunction due to any cause. A vast range of conditions may impair performance, including stress, fatigue, disruption of circadian rhythms, aging, substance abuse, and psychiatric disorder (Annex 2).

Therefore, from the standpoint of public safety, the critical issue is not the cause of impaired job performance, but the ability to detect impairment whatever the cause. This highlights the importance of reviewing the effectiveness of performance testing in a variety of situations where public safety is involved. There is a continuing need to bring together psychiatrists, neurologists, clinicians, epidemiologists, neuropsychologists, industrial psychologists, occupational health personnel and safety experts to ensure that test procedures used in screening for functional impairment of central nervous system function are refined and validated. In this regard, it is essential to determine precisely the correlation between tests of neuropsychological function and actual job (functional) performance.

If neuropsychological testing was to be used to establish criteria for functional/occupational assessment of individuals with HIV-1 infection in Groups II and III persons, there should be evidence to indicate:

- (a) a clear and reliably assessed association between neuropsychological abnormalities and HIV-1 seropositivity based upon comparison of HIV-1 seropositives with appropriately selected seronegative persons; and
- (b) a clear and reliably assessed association between neuropsychological abnormalities as determined by testing and functional performance directly relevant to occupational tasks.

4.3 Social consequences of screening

Given the evidence evaluated by this Consultation, denial of access to employment or the freedom to engage in everyday activities for otherwise healthy persons solely on the basis of HIV-1 serological status would represent a violation of human rights and lead to broad and destructive social implications.

It is also necessary to draw attention to the complexity and possible social consequences of screening which are unrelated to public safety. The "Report of the Meeting on Criteria for HIV-1 Screening Programmes, Geneva 20-21 May 1987 (WHO/SPA/GLO/87.2)" should be consulted by those concerned with the broader considerations and implications of screening.

The Consultation recognized that HIV-1 screening of prospective or existing employees could be implemented by employing agencies for reasons other than public safety and unrelated to neuropsychological function. For example, an individual industry could consider introducing HIV-1 screening solely to promote its public relations image as being concerned with public safety. In other cases, should a considerable training and financial investment be involved, employees might be screened so as to exclude those who, if HIV-1 infected, have an increased likelihood of reduced life expectancy.

In summary, while the continued refinement of functional tests to detect early neuropsychiatric impairment in occupational groups is to be encouraged, there is no justification at this time for the addition of HIV-1 serological screening to these tests in the name of public safety.

5. RESEARCH IMPLICATIONS

5.1 Introduction

This Section discusses the research implications arising from the consolidation and review of available evidence and the formulation of policy implications. Methodological issues in currently available studies and proposals for the design, execution and interpretation of ongoing and future studies are discussed. As HIV-1 dementia and neurobehavioural abnormalities have been identified as the most important issues for HIV-1 Groups II and III persons, research requirements for these are separately discussed. Nevertheless, similar research implications arise for other HIV-1 related neuropsychiatric disorders. Finally, as studies are undertaken regarding the neuropsychiatric aspects of HIV-2 infection, similar methodological considerations will apply.

5.2 Methodological issues

5.2.1 Relationship of testing to functional capability

A critical methodological issue complicating the current research is whether an abnormality on neuropsychological testing has relevance to individual or general job performance or activities of daily living. Furthermore, minor abnormalities in test performance might not predict inability to carry out a particular job. HIV-1 infection may involve variable nervous system pathology; accordingly, there may be highly variable and diverse neuropsychological consequences. Thus, limited and/or highly focused testing or screening batteries may be insufficiently sensitive; testing over a broad range of functions may be necessary. There is a need to attempt to define or create a standard neuropsychological test battery for assessment of HIV-1 infected persons. Such a battery of tests should ideally include instruments or approaches which have shown value in predicting functional capacity or performance.

5.2.2. Difficulties encountered in analysis and comparison of existing studies.

There is great variation in the design of the available studies. The studies to date have used diverse neuropsychological tests to evaluate HIV-1 infected people. Different definitions of abnormality have been used and different criteria adopted for establishing these abnormalities. Some studies have estimated mean population scores on neuropsychological tests while others have determined the number of individuals relative to the size of the group who have performed abnormally on these tests. Most studies have used single point testing rather than longitudinal assessment. In some studies, all patients with HIV-1 infection, regardless of clinical status (asymptomatic infection, ARC and AIDS) have been presented together; this is inappropriate and prevents clarification of the relevant issues.

The selection of appropriate controls has also been a problem in some studies. The stress associated with the recent diagnosis of HIV-1 infection and the lifestyle of many HIV-1 infected persons makes the use of normative data from the general population or even from uninfected individuals (individuals without the stress associated with the knowledge of HIV-1 infection) problematic.

The size and homogeneity of the populations in the currently available studies are insufficient to allow generalizations regarding the presence of neuropsychological abnormalities among persons in CDC Groups II and III. Furthermore, some of these studies have not eliminated the confounding influence of possible coexisting psychiatric or neurological disease. In addition, it is not known if the severity of HIV-1 related brain disease correlates with the degree of cognitive impairment; only some of the studies currently available address the concomitant neurological status of the patient. Finally, current state-of-the-art screening for mental status and psychiatric abnormalities are predominantly western culture-specific.

Therefore, the standardization of methodology is of prime importance. In particular, there is an urgent need to develop an easily administered (i.e. by field workers), culturally non-specific measure of neuropsychological function. Use of this kind of instrument could help provide data on the nature and extent of HIV-1 related neuropsychiatric abnormalities on a global basis.

5.3 Experimental Design

5.3.1 Study populations

It is important that study populations be representative of all risk behaviour groups, geographic locations, socio-economic and cultural settings.

It is critical that patients with concomitant psychiatric or neurological disease be studied separately. It is also important to note that patients will be increasingly treated with anti-viral drugs. As such, future studies need to take into account the effects of these drugs as well as their complications as confounding variables.

5.3.2 Control groups

The selection of appropriate control groups is of paramount importance. One recommendation is to have the patient serve as his or her own control over time (see section 5.3.4). In designing future studies, the following control groups could be included:

- (a) HIV-1 seronegative individuals with the same risk factors;
- (b) HIV-1 seronegative individuals with the recent diagnosis of life threatening illnesses;
- (c) HIV-1 seronegative individuals outside usual risk behaviour groups but closely matched on sociodemographic and educational characteristics;
- (d) Individuals with similar rates of alcohol use, drug use, and level of education;
- (e) HIV-1 seronegative patients with other causes of immunosuppression.

5.3.3 Neuropsychological test instruments

The appropriate choice of neuropsychological test instruments, including methodology, frequency of administration, and interpretation are of major importance for future studies. Test batteries should demonstrate a relationship to clinical and functional status. The evaluation of existing neuropsychological tests and the development of a core battery for use in future studies is required.

This core battery might well be used with all risk behaviour groups and in various geographical and cultural areas, with additional tests of specific value in the evaluation of discrete populations. Tests should be selected as a function of the hypothesis in question; very sensitive tests might be used to detect subtle abnormalities while highly specific tests might be used to characterize the exact nature of cognitive impairment.

Agreement should also be sought on the quantitative evaluation of group mean data or individual variation from control population norms of these neuropsychological tests and the criteria for abnormality on each test need to be standardized.

Neuropsychological tests should not be performed in isolation from carefully designed psychiatric, neurological, laboratory and radiological studies. There is a need for systematic, longitudinal studies using widely available and well validated psychiatric evaluation measures to establish the incidence, prevalence and nature of psychiatric disease among HIV-1 infected persons.

The possible presence of the abnormalities which have been observed in individuals with HIV-1 dementia must be investigated in CDC Groups II and III individuals. Some such investigations could include:

- (a) Careful assessment of ocular mobility using eye tracking and electronystagmographic techniques;
- (b) Studies of balance and equilibrium;
- (c) Studies of thresholds of sensory perceptions;

An attempt to correlate the presence of cognitive abnormalities, if observed, with abnormalities of magnetic resonance images of the brain, CSF parameters, immunological abnormalities and nutritional factors should be made. Furthermore, a systematic analysis of the psychosocial influence of the family and care-givers of these study patients on the development and progression of cognitive abnormalities should be explored.

5.3.4 Longitudinal measures

It is imperative that future studies be designed so that longitudinal measures will be performed. While the possibility of a learning effect on performance has been raised, this should not prevent repeat testing. Indeed, improvement on subsequent testing may not be seen in patients with cognitive dysfunction and the absence of a learning effect may be significant. The interval between measurements is an important variable and needs to be explicitly stated. Shorter intervals between measurements may be more sensitive to subtle progression of disease.

If during the course of the study individuals progress in terms of their systemic illness, they will no longer be in Groups II or III and as such the data may not be comparable to that derived from patients remaining in Groups II or III. Such progression should be taken into account for analyzing these data. This progression should not, however, be reason for terminating the study as considerable information might be derived from these patients.

5.3.5 Data analysis

Several issues relating to data analysis have already been discussed. If abnormalities on neuropsychological tests are detected then it becomes critical to define and quantitate the criteria needed to relate these abnormalities to clinically and functionally relevant situations and to theoretical understanding. Clearly the more sensitive the neuropsychological test the more difficult it may be to find relevant external criteria for this test. The particular features of job performance that may be reflected by neuropsychological testing need to be identified and quantified before evaluating the implications of abnormal neuropsychological test results.

5.3.6 Reporting of data

Studies of neuropsychiatric aspects of HIV-1 infection have major public policy implications. Therefore, it is essential to avoid premature disclosure of data to the media or in other ways prior to the rigorous scrutiny of peer review. Reporting of data should be subject to the accepted standards of peer review; data should be published in recognized scientific journals. In international collaborative studies, it is important that investigators agree prior to the beginning of the study as to the manner of publication.

Confidentiality is a vital concern in studies of persons with HIV-1 infection. All data collection and analysis must be performed in such a manner as to ensure the confidentiality of the study participants. This is of paramount importance not only for the persons themselves, but to ensure the successful recruitment and continued participation of study subjects.

5.4 Research into HIV-1 Dementia

The most important issues to be clarified regarding HIV-1 dementia include natural history, pathogenesis, predictors of disease and possible markers of disease.

Studies are required to describe the incidence and prevalence of HIV-1 dementia in all affected risk groups and diverse geographic locations. Studies are needed to determine at what stage of HIV-1 infection dementia may occur and to correlate dementia with other coexistent factors, such as immune status, CSF abnormalities and depression. These studies will help to answer the question whether dementia develops de novo or follows other milder cognitive disturbances (continuity versus discontinuity model of HIV-1 related cognitive dysfunction).

The pathogenesis of HIV-1 dementia is poorly understood. Most investigators agree that HIV-1 infection of the brain plays an important role. The exact manner whereby this infection results in the clinical syndrome of dementia is not known but may involve direct cytotoxicity, neuronal dysfunction, alteration of CNS trophic factors or neurotransmitters, immunological phenomena, or other mechanisms.

The implications of fully understanding the pathogenesis of HIV-1 dementia may include the ability to predict the populations at increased risk, the natural history of the illness and efficacy of treatment modalities. One particular issue involves the site of viral infection in the brain; the access of anti-viral agents to this site is an important issue that needs to be addressed by those developing anti-HIV-1 agents.

More work needs to be done in identifying the epidemiological (cultural, genetic, geographic), social, biological, psychiatric, neurological, neuropsychological, and demographic aspects of this disease. These may have predictive value for both the development of disease, its severity, and its rate of progression.

Because HIV-1 dementia requires exclusion criteria for its diagnosis, it is essential that attempts be made to identify markers for this illness. These potential markers might include CSF immunological factors, neurotransmitter levels, specific viral markers, brain imaging information or other currently unrecognized factors.

The value of different types of psychological support in the management of this illness needs to be evaluated. The type and degree of psychological support may be different for HIV-1 dementia than for other psychiatric illnesses. The value and potential risk of treatment of concomitant psychiatric disorders with anti-depressants, neuroleptics, or other pharmacological agents needs to be investigated. In particular, the effect of these agents upon symptoms referable to HIV-1 dementia needs to be evaluated. The value of anti-HIV-1 agents in the treatment of HIV-1 dementia has not been well studied. Careful controlled studies of these anti-viral agents need to be performed. There is a greater role for the use of animal models than has been previously employed.

5.5 Research into neurobehavioural abnormalities other than dementia

An identical set of issues to those raised for HIV-1 dementia exists for the milder neurobehavioural abnormalities in the setting of HIV-1 infection. Of critical importance is the determination of whether such neurobehavioural abnormalities represent distinct disorders or are early symptoms which progress to HIV-1 dementia. Careful natural history and pathogenetic studies are needed to address this issue. Development of a staging system for neurobehavioural abnormalities may facilitate more complete and specific studies in the future.

In addition, it is not yet known whether these neurobehavioural abnormalities are permanent or reversible. Interventions of potential value in the treatment of these abnormalities should be investigated.

6. HEALTH CARE IMPLICATIONS

6.1 Care/management

As the incidence of AIDS steadily increases, an enormous burden of neuropsychiatric illness will face the health care system of many countries. In the USA in 1986, there were approximately 8,000 neurologically symptomatic AIDS patients; this number is predicted to rise to 54,000 in 1991. By 1991, the number of neurologically symptomatic AIDS patients in the USA is expected

to be nearly half as many as the number of all patients with epilepsy and will far exceed the number of persons with Parkinson's disease. As these figures relate only to patients with manifest AIDS and neurological dysfunctions, this is an underestimation of the impact of HIV-1 infection on neurology services.

The impact of AIDS on mental health care is difficult to ascertain and predict. Most, if not all patients with AIDS experience significant problems in adjusting to a probably fatal illness and psychological or psychiatric assistance will be required in many cases. In addition, a substantial proportion of AIDS patients will have major psychiatric disorders and/or may become demented; these patients will frequently require psychiatric assessment and care.

Finally, the large number of persons infected with HIV-1 but without signs of systemic illness creates a unique problem.

Against this background the Consultation considered issues relating to the management of HIV-1 seropositive persons presenting with neuropsychiatric disorders. The Consultation recognized that these conditions present as medical and social phenomena with the following features:

- (a) Fear of AIDS in individuals and the profound implications for the individual following the discovery that he or she is infected;
- (b) The psychological impact of self-interpretation of everyday cognitive failures in an infected individual aware of the long term possibility of the onset of dementia;
- (c) The concerns and anxieties of significant others (family, lover, co-worker etc.) for an individual with apparent neurobehavioural problems;
- (d) The tolerance of the community which may vary widely depending on its previous experience with AIDS cases or with its education regarding the modes of transmission of the virus will heighten the need to handle infected individuals with compassion and understanding.

6.2 Access to care

The fundamental need is to ensure that appropriate support and treatment services are available and accessible, not only to individuals with clinical illness, but to asymptomatic individuals as soon as they become aware that they are infected. Not only is it important that infected individuals have access to care, but it is essential that all health care workers be aware of the possible range of neuropsychiatric disorders that may present or develop. In this manner, health care workers will be able to respond with appropriate attitudes, understanding and therapy and recognize these problems at the earliest possible stage and refer patients on to appropriate care as required.

HIV-1 infected persons may seek access to care through self-referral or referral by significant others who may have noticed changes in the individual's behaviour. Self-referrals include those who are already experiencing symptoms and those who are asymptomatic but concerned about their health. There is a need for health services to be able to respond to those experiencing acute adjustment and stress reactions as the result of learning of their seropositive status. These services will require trained psychiatrists, neurologists, psychologists, counsellors and social workers.

It is already clear from the experience of some countries that it will not be possible to deal with the neuropsychiatric aspects of the HIV-1 epidemic by relying only on those neurologists, psychologists and psychiatrists who have expressed a particular interest in HIV-1 infection and AIDS. It is inevitable that most, if not all, neurologists, psychiatrists and psychologists will need to become involved in managing HIV-1 infected persons. Therefore, there is an urgent need for training programmes for key categories of health workers.

The impact of the AIDS epidemic on hospital services is already a major concern to which must now be added the additional burden of caring for a growing number of AIDS patients with dementia. If pharmacological therapies result in the prolongation of life but do not have an effect on the incidence of dementia, hospitals and/or hospices may become involved in caring for large numbers of patients with HIV-1 dementia. The extent to which these people can be cared for at home is debatable and it may be necessary to plan for long term inpatient care.

Existing services for ambulatory patients may need to be reassessed with regard to the appropriate mix of staffing and with regard to the provision of specialized diagnostic equipment in order to detect and manage HIV-1 related neuropsychiatric conditions.

In relation to support services for patients and their families the further strengthening of community services, counselling services, voluntary agencies and self-help groups is essential.

The report of this Consultation should be widely disseminated to health workers to help ensure that informed advice is provided to HIV-1 infected persons.

In summary, there are two major policy implications for the care and management of HIV-1 infected persons arising from this Consultation:

1. Health workers should be made aware of both the wide range of neuropsychiatric conditions associated with HIV-1 infection and that the weight of existing information indicates that functional impairment is not significantly increased (over the levels found in HIV-1 uninfected people) until or unless patients become clinically ill with ARC or AIDS.
2. Health services need to prepare to deal with a large burden of neuropsychiatric illness, much of it severe, in patients with ARC and AIDS; planning should commence immediately.

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ANALYSIS OF CONTRIBUTION OF
NEUROPSYCHIATRIC IMPAIRMENT TO ACCIDENTS

Accidents and critical situations involving casualties or potential hazards to individuals and groups are common events on a global scale, and their prevention by technological, legislative and public health measures is a priority social and political concern. The size of the problem can be illustrated by the estimate that worldwide, the annual number of traffic casualties is in excess of seven million (including at least 250,000 deaths), and that over 50% of these casualties occur among persons younger than 35 years old (3).

Epidemiological methods have been applied to the study of accidents, and an important conclusion stemming from such research is that in majority of instances multiple causation is involved. In order to obtain a valid estimate of the potential for any single factor, such as cognitive-neurological impairment due to HIV-1 infection, to contribute significantly to the overall probability of accidents of a given type, it would be necessary to place clinical and epidemiological knowledge about that factor in the broader context of multiple causality.

The most common behavioural factors in the causation of air transportation, road traffic, and industrial accidents (i. e. the types of accidents that may affect large numbers of persons) are: human (operator) error; the use of alcohol and other psychoactive substances; life stress; and mental disorders. Each will be briefly reviewed.

1. Human error. The liability to errors in perception and judgement, temporary fluctuations of attention, and failures in motor coordination is a "normal" feature of the neurobehavioural make-up of human beings. While such "mental lapses" are of no consequence in most social situations, their risk potential may be dramatically increased in many man-machine interactions, especially those calling for high-speed of decision making under conditions of cognitive overload. The dissociation between reaction time (which may be within normal limits) and the so-called cognition time, required for stimulus processing under such conditions, may be of critical importance in high-performance jobs, such as aircraft operation. It has been estimated that at least then 25% of all accidents involving passenger-carrying aircraft are primarily explicable in terms of human error (22). Such factors have been estimated to be responsible for about 65% of the traffic accidents in a major metropolitan area. (4). It should be noted that the probability of human error can be sharply augmented by the synergistic effects of fatigue and circadian rhythm desynchronization (e.g. due to shiftwork or jet lag) (33).

2. Alcohol use. Even in low doses, alcohol has significant effects on reaction time, perception, information processing, motor coordination and judgement. Notwithstanding individual variation and tolerance, alcohol is a major risk factor in automobile, aircraft, and industrial accidents. Alcohol dependent persons are 4.5 times as likely to die in a motor vehicle accident compared with matched non-alcoholic persons (61), and reduced driving capability due to intoxication has been found to be the principal cause in 67% of the accidents in which alcohol was implicated (1, 30).

Alcohol is a major risk factor in aircraft accidents. A toxicological investigation of 1,345 general aviation pilots in the US, who had been killed in accidents during 1968-1974, established elevated alcohol blood levels in 19.5% (41); an earlier study in the UK provided evidence (post mortem liver histology) of alcohol abuse in 4.5% of all aircrew who were killed in accidents between 1955 and 1979 (22).

3. Use of other psychoactive drugs. Considering that in the developed countries the average psychotropic drug consumption is of the order of 50 to 150 defined daily doses (DDD) per 1000 population, it is understandable that psychoactive drug use is among the major risk factors involved in accidents. The magnitude of the hazard has been examined in a controlled study of traffic accident casualties, which established that the relative risk of a fatal accident for persons using minor tranquilizers was 4.9 (54). Benzodiazepines, a number of "over-the counter" preparations containing antihistamines, beta-blockers, as well as a broad range of illicit drugs may impair performance, and their effects can be synergistically augmented by alcohol use.

4. Life stress. Stressful life events, including bereavement and other loss, changes in social and occupational position, and other events straining the coping capacity of the individual, may increase the liability to error. Persons who had experienced recent life stress were found to have an increased risk of fatal traffic accidents.

5. Mental disorders. There is epidemiological evidence that depression and anxiety disorders are very common in the general population. Up to 5% of the adult population may be experiencing episodes of depression and anxiety within a given year, and the lifetime risk may be in the order of 20% in males and over 40% in females (21). Depression is associated with a slowing down of mental processes and motor activity, and may be seriously incapacitating to a person operating high-performance equipment. The accident risk is also increased for persons with personality disorders and a history of psychiatric treatment for alcohol abuse.

This brief review highlights the existence of many conditions which are: (a) significantly more common than asymptomatic HIV-1 infection and (b) of a demonstrated potential to impair performance.

Given the conclusion of this Consultation, screening of personnel for HIV-1 antibodies is not an effective accident risk reduction strategy. Such screening should also be seen in the context of its possible negative consequences (e.g. psychosocial stress potential, or the creation of an illusory sense of improved safety leading to a reduced vigilance regarding other risk factors) which is likely to outweigh any minimal gains. The alternative approach, for which a sound scientific base can be provided, consists in programmes aiming to upgrade safety of operations by systematic, periodic targeted examinations of personnel, which should include neuropsychological investigations and behaviour assessment.

SUMMARY OF CDC CLASSIFICATION SYSTEM FOR HIV INFECTION

GROUP I	Acute infection
GROUP II	Asymptomatic infection ¹
GROUP III	Persistent generalized lymphadenopathy ¹
GROUP IV	Other disease
Subgroup A	Constitutional disease
Subgroup B	Neurological disease
Subgroup C	Secondary infectious diseases
Category C-1	Specific secondary infectious diseases listed in the CDC surveillance definition for AIDS ²
Category C-2	Other specified secondary infectious diseases ²
Subgroup D	Secondary cancers
Subgroup E	Other conditions

1 Patients in Groups II and III may be subclassified on the basis of a laboratory evaluation.

2 Includes those patients whose clinical presentation fulfills the definition of the acquired immunodeficiency syndrome used by Centers for Disease Control for national reporting.

Source: Centers for Disease Control. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome, Morbidity and Mortality Weekly Report, 1987, 36 (suppl 1S)

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