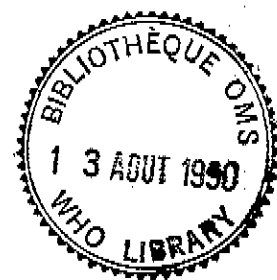

GLOBAL
PROGRAMME
ON AIDS

REPORT OF THE SECOND CONSULTATION
ON THE NEUROPSYCHIATRIC ASPECTS
OF HIV-1 INFECTION

GENEVA
11-13 JANUARY 1990



WORLD
HEALTH
ORGANIZATION

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SUMMARY

A consultation on the neuropsychiatric aspects of HIV-1 infection was held at the WHO Headquarters in Geneva from 11 to 13 January 1990, within the framework of the collaborative initiatives currently carried out by the Global Programme on AIDS (GPA) and the Division of Mental Health (MNH) of WHO.

The purpose of the meeting was:

- a) to review the currently available scientific evidence concerning neuropsychiatric disorders occurring in HIV-1 infected subjects, with special regard to the new information which appeared in the literature during the past two years;
- b) to discuss the research activities which have been undertaken or planned in this area within the GPA/MNH collaborative programme;
- c) to develop operational diagnostic criteria for HIV-1 associated neuropsychiatric disorders, to be tested and used in research and clinical practice.

The review of the available scientific evidence showed that a wide range of neurological and psychiatric disorders can occur in subjects with HIV-1 infection. With the further spreading of the epidemic, it is likely that an enormous burden of neuropsychiatric problems will face the health care systems of many countries. It is very urgent, therefore, to produce projections about the number of persons who will suffer from these problems in the next five and ten years, and to undertake action concerning the training of staff and the provision of care to those who will be affected.

On the other hand, the experts attending the consultation pointed out that the presently available information about HIV-1 associated neuro-psychiatric disorders mainly derives from studies carried out in Western countries and in samples of homosexual or bisexual men with a high educational level. The generalizability of the findings obtained in these populations is uncertain, and well-designed investigations in other geographic and socio-cultural contexts, as well as in other at-risk populations, are clearly needed. It was recognized that the WHO multicentre study on neuropsychiatric aspects of HIV-1 infection, currently ongoing in five continents, represents an important step in this direction.

The participants in the meeting agreed that a syndrome consisting of cognitive and motor impairment, which in some cases appears to be directly related to the infection of the brain with HIV-1, can now be reliably described. It was suggested that this syndrome be called from now on "HIV-1 associated cognitive/motor complex", and operational diagnostic criteria for it were provided.

After careful consideration of the presently available neuropsychological studies, it was concluded that, according to the weight of current evidence, otherwise healthy HIV-1 infected subjects (stages II and III according to the Centers for Disease Control (CDC)) are not more likely to present a clinically

significant cognitive impairment than persons not infected with HIV-1. It was confirmed, therefore, that there is no justification for HIV-1 serological screening of asymptomatic persons as a strategy to detect such impairment in the interest of public safety.

Several recommendations were made at the end of the consultation. Among other things, it was recommended that WHO: 1) should continue to promote research to obtain information on the prevalence and natural history of HIV-1 associated neuropsychiatric disorders in different geographic contexts; 2) should make projections on the expected number of cases of these disorders and on the consequent expected burden on health care services; 3) should collaborate with governments in their effort to develop appropriate care for persons suffering from these disorders.

1. INTRODUCTION

It is well established that neurological and psychiatric disorders frequently occur in subjects with ARC and AIDS: in fact, approximately 65% of those who die of AIDS exhibit significant mental and neurological impairment in the terminal phase of the illness (26), and pathological changes in the central and peripheral nervous systems have been reported in the autopsy of up to 90% of AIDS cases (29). Furthermore, acute stress reactions and adjustment disorders are common in otherwise asymptomatic HIV-1 infected subjects, especially immediately after discovery of seropositivity (18).

In view of these facts, the Global Programme on AIDS (GPA) and the Division of Mental Health (MNH) of WHO implemented a collaborative programme specifically focused on HIV-1 associated neurological and mental health problems. Within this programme, several research activities have been undertaken or planned, which aim to explore:

- a) the prevalence and natural history of HIV-1 associated neurological and psychiatric disorders at the different stages of HIV-1 infection, in various at-risk populations, and in different geographic and socio-cultural contexts;
- b) the projected impact of HIV-1 associated neurological and psychiatric disorders on health care services in the mid-to-late 1990s;
- c) the effects of psychosocial factors (including life events, social support and coping strategies) on cellular immunity in HIV-1 infected subjects.

Other planned GPA/MNH joint initiatives concern the relationship between HIV-1 infection and drug abuse and the psychological responses of physicians and nurses dealing with AIDS patients.

The above initiatives complement those carried out by the Social and Behavioural Research Unit of GPA (such as the project on psychological counselling for persons with HIV-1 infection and the survey on sexual behaviours and AIDS-related knowledge, attitudes, beliefs and practices).

Besides the above-mentioned activities, GPA and MNH decided to convene, at regular intervals, meetings of experts, in order to:

- a) review the currently available research evidence concerning neurological and psychiatric aspects of HIV-1 infection;
- b) discuss the progress of the collaborative programme.

The first of these meetings took place in Geneva from 14 to 17 March 1988 (45), and the second was held, again in Geneva, from 11 to 13 January 1990. The present document is a report of the latter consultation.

This meeting was attended by 13 experts from 10 countries (see Annex 1). Dr B. Osuntokun (Nigeria) acted as Chairman, and Drs R. Janssen (USA) and J. Perriens (Zaire) were the rapporteurs.

Besides the review of the research evidence in the field and the discussion on the progress of the programme, a third objective of the consultation was the development of operational diagnostic criteria for HIV-1 associated neuropsychiatric disorders, designed to allow comparison between research findings obtained by different groups and to facilitate communication in clinical settings.

An outline of the research evidence reviewed during the consultation is provided in Section 2 of the present report. Section 3 summarizes the implications of this evidence as concerns HIV-1 serological screening, training of staff and provisions for care, and research needs. Section 4 lists the recommendations made at the end of the consultation.

Further information about the GPA/MNH research project on the neuropsychiatric aspects of HIV-1 infection, which is already ongoing, is provided in Annex 2, while the operational diagnostic criteria for HIV-1 associated neuropsychiatric disorders, developed at the consultation, are presented in Annex 3. Finally, Annex 4 reproduces the ICD-10 research criteria for dementia, panic disorder and generalized anxiety disorder, to which reference is made in the above-mentioned operational diagnostic criteria, and Annex 5 provides an outline of the WHO staging system for HIV-1 infection, currently in development.

2. THE EVIDENCE

2.1 Introduction

This part of the report reviews the current evidence concerning HIV-1 associated neuropsychiatric disorders (section 2.2) and the results of neuropsychological testing in otherwise healthy HIV-1 seropositive subjects (groups II and III according to the Centers for Disease Control (CDC)) (section 2.3).

2.2 HIV-1 associated neuropsychiatric disorders

The neuropsychiatric disorders which have been found to be associated with HIV-1 infection can be classified as follows:

A) HIV-1 associated cognitive/motor complex

- HIV-1 associated dementia
- HIV-1 associated myelopathy
- HIV-1 associated minor cognitive/motor disorder

- B) HIV-1 associated mental and behavioural disorders
- Delirium
 - Acute psychotic disorders
 - Affective disorders
 - Adjustment disorders
 - Acute stress reactions
 - Suicide
- C) Other HIV-1 associated central nervous system (CNS) disorders
- Progressive encephalopathy of childhood
 - Meningitis
- D) HIV-1 associated peripheral nervous system disorders
- Inflammatory polyneuropathy
 - Predominantly sensory neuropathy
 - Myopathy
- E) Neurological disorders due to opportunistic processes in HIV-1 infected subjects
- Progressive multifocal leukoencephalopathy
 - Cerebral toxoplasmosis
 - Cryptococcal meningitis
 - Cytomegalovirus neuropathy
 - Other syndromes due to opportunistic infections
 - Primary CNS lymphoma

2.2.1 HIV-1 associated cognitive/motor complex

This category includes conditions marked by cognitive, motor and behavioural abnormalities which in some cases appear to relate directly to an effect of HIV-1. A variety of terms have been used to describe these clinical entities. In this report we use a new terminology, including a general term to encompass all the conditions (HIV-1 associated cognitive/motor complex), and additional terms to segregate subsets of patients on the basis of severity and prominence of cognitive or myelopathic deficits (HIV-1 associated dementia, HIV-1 associated myelopathy, and HIV-1 associated minor cognitive/motor disorder).

In this scheme the term HIV-1 associated cognitive/motor complex replaces the previous term AIDS dementia complex (ADC); the term HIV-1 associated myelopathy includes the clinical syndrome corresponding to the pathologically identified vacuolar myelopathy; the term HIV-1 associated minor cognitive/motor disorder corresponds to the ADC stage 1 of the classification by Price et al. (33), as well as to what was referred to as "neurobehavioural abnormalities other than dementia" in the report of the March 1988 Consultation (45), and as HIV-1 associated neurocognitive disorder in a recent investigation (14). The HIV-1 associated cognitive/motor complex may be pathogenetically heterogeneous, but clinically it appears as a continuum, with differences between the subtypes being principally quantitative rather than qualitative.

It should be specified, however, that progression from the minor cognitive/motor disorder to either dementia or myelopathy is not inevitable, and that the manifestations of the former condition may even resolve completely.

2.2.1.1 HIV-1 associated dementia

Individuals with this condition suffer from a cognitive disturbance of a severity which is in line with accepted definitions of other dementias (e.g. that of ICD-10). This group comprises patients previously included in the ADC stages 2-4 but now designated by ICD-10 guidelines as mild, moderate and severe (see ICD-10 definition, Annex 4).

The dementia is of the subcortical type, being characterized by psychomotor slowing, inattentiveness and volitional torpor. However, in functional terms, these deficits interfere with memory and information processing sufficiently to confer major disability with respect to work and activities of daily living.

Individuals with HIV-1 associated dementia typically complain of forgetfulness, slowness, poor concentration, and difficulties with problem solving and reading. Behaviourally, 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.

The prevalence and natural history of this disorder are presently imprecisely defined. However, it is clear that the prevalence increases with advancing HIV-1 related systemic disease and immunosuppression.

According to a number of studies of AIDS patients the point prevalence of HIV-1 associated dementia ranges between 8 and 16% (16,19,22,39). However, in an autopsy series of cases referred to neurologists, this figure was as high as 66% (32). 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 associated dementia can be the presenting manifestation of HIV-1 infection and thus lead to the diagnosis of AIDS. Available evidence suggests that this occurs in 0-3.3% of AIDS patients (15,16).

Pathologically, this condition is frequently characterized by multinucleated-cell encephalitis, and evidence of productive HIV-1 infection of macrophages, monocytes, and multinucleated cells resulting from the fusion of these two cell types. However, HIV-1 associated dementia and multinucleated-cell encephalitis are not synonymous, since one-third to one-half of patients with the former condition will exhibit only central astrogliosis and myelin pallor at pathological examination.

Neuropsychological testing characteristically reveals abnormalities in many assessments, but particularly in attention, rapid sequential problem solving and motor speed.

Computerized tomography (CT) and magnetic resonance imaging (MRI) nearly always detect brain atrophy with enlargement of the cerebral sulci and ventricles. MRI may additionally exhibit increased signal on T2 weighted images in the central white matter and, at times, in diencephalic nuclei.

In about one-third of patients p24 antigen can be detected in cerebrospinal fluid (CSF). Moreover, CSF beta-2-microglobulin, neopterin and quinolinic acid levels are often elevated, although it is premature to imply that they are diagnostic markers.

Accumulating evidence suggests that HIV-1 associated dementia may be ameliorated by zidovudine (AZT) therapy (30,37). It is worth pointing out, however, that the only placebo-controlled trial of this drug for the treatment of the above condition was not successful due to problems of patient recruitment.

There are no definite risk factors for the development of HIV-1 associated dementia, although it has been suggested that its frequency may increase with age (15). It is uncertain whether otherwise asymptomatic HIV-1 seropositive subjects who exhibit more subtle abnormalities, referred to in section 2.3, are at any increased risk of developing the syndrome. HIV-1 associated dementia often progresses rapidly to severe deterioration and death, but may also have prolonged stable phases, or may fluctuate, with reversible deterioration occurring in concomitance with opportunistic infections, such as Pneumocystis carinii pneumonia. Not enough data are available to determine course and outcome of the syndrome in patients without opportunistic infections and neoplasms.

2.2.1.2 HIV-1 associated myelopathy

In this condition motor symptoms and signs, particularly involving the legs, predominate, indicating major spinal cord dysfunction. These patients are so spastic, ataxic or weak that fully independent ambulation is precluded. Motor abnormalities are not confined to the legs: hands are affected, although less severely, and abnormalities above the spinal level are frequently present (e.g., increased jaw jerk, snout or other release reflexes). Cognitive dysfunction is commonly also present. However, in this group of patients gait disturbance is disproportionately severe and dominates the clinical picture.

This myelopathy is diffuse rather than segmental and thus is not characterized by a sensory or motor "level". It is characteristically painless. Its pathological substrate is usually vacuolar myelopathy and its pathogenesis is uncertain.

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 HIV-1 associated myelopathy exceeds 20% among autopsied AIDS cases in New York and New Jersey (29). The lower prevalence observed in clinical and autopsy series from other centres may depend upon case selection

or autopsy technique. It is useful to point out that subjects with HIV-1 infection are also at risk for HTLV-1 infection, which can cause a spastic paraparesis not unlike HIV-1 associated myelopathy.

Only anecdotal reports of the occurrence of HIV-1 associated myelopathy in otherwise asymptomatic (CDC Groups II and III) persons have appeared. Thus, the incidence of the condition in these subjects is probably quite low; however, prospective studies will be needed to assess this matter. No risk factors for the development of this condition after HIV-1 infection have been identified. The effect of AZT or other anti-viral agents in its treatment is unknown.

2.2.1.3 HIV-1 associated minor cognitive/motor disorder

This entity encompasses the less severe spectrum of HIV-1 associated cognitive/motor complex, corresponding to ADC stage 1 and to HIV-1 associated neurocognitive disorder (14).

The characteristic symptoms and signs and neuropsychological test abnormalities are qualitatively similar to those of HIV-1 associated dementia but quantitatively less severe. Thus, frequent symptoms include forgetfulness, slowness of thinking, reduced concentration, gait and at times hand clumsiness, and reduced drive or motivation. Signs on neurological examination may include slowness of response, poor concentration, difficulty in rapid repetitive movements, and minor gait instability. Diagnosis should be made with great caution in drug abusers, in whom the meaning of subjective complaints concerning cognitive functioning and of abnormal neuropsychological performance may be different than in homosexual and bisexual men.

The prevalence and incidence of this disorder are uncertain. Recently, it has been found to occur in 42% of homosexual men with ARC (14). Clinical experience suggests that the disorder may be non-progressive or indolent: indeed, many individuals may not progress to dementia, and sometimes the symptoms may even resolve completely.

Neuropsychological tests show abnormalities which are similar to those of HIV-1 associated dementia, but are less frequent and less marked. Cerebral atrophy by CT or MRI is not frequently present. CSF infrequently contains detectable p24 antigen. Beta-2-microglobulin, neopterin and quinolinic acid may be mildly elevated.

2.2.2 HIV-1 associated mental and behavioural disorders

2.2.2.1 Delirium

Delirium has been described within the context of HIV-1 dementia and of the aseptic meningitis which may develop upon seroconversion (32). Moreover, its occurrence in AIDS patients may be related to hypoxia (for instance, from Pneumocystis carinii pneumonia), cryptococcal meningitis, systemic infections (such as staphylococcal bacteremia), space-occupying lesions of the brain (such as CNS lymphoma or brain abscesses due to toxoplasmosis), metabolic derangements (disorders of fluid, electrolyte or acid-base balance), and the use of psychotropic drugs (especially tricyclic antidepressants, whose central anticholinergic activity seems to be more pronounced in such patients).

The clinical picture of delirium is characterized by clouding of consciousness with reduced capacity to shift, focus and sustain attention to environmental stimuli; perceptual disturbances (misinterpretations, illusions and hallucinations); disorientation and memory impairment; incoherent speech; insomnia; increased (more rarely decreased) psychomotor activity. The syndrome usually develops over a short period of time (hours to days) and its intensity tends to fluctuate during the course of a day. Complete recovery is the rule in delirium occurring at the time of seroconversion. Delirium superimposed on HIV-1 dementia may aggravate its course.

There is no available estimate of the prevalence and incidence of delirium in HIV-1 infection. Management of the syndrome consists of treating the underlying cause, maintaining fluid and electrolyte balance and nutrition, providing sedation and correction of disturbances of sleep-wake cycle, supplying a quiet environment and a nursing support directed towards re-orientation.

2.2.2.2 Acute psychotic disorders

Hallucinations (either visual or auditory) and delusions (either persecutory or grandiose) are not infrequent in patients with ARC or AIDS. They may occur within a context of cognitive impairment, which may be sometimes subtle or fluctuating, or they may be initially the only psychopathological manifestations, being followed later by such symptoms as disorientation, clouding of consciousness, memory and concentration disturbances. In both these cases, a diagnosis of organic brain syndrome (dementia or delirium) is usually warranted (18).

There are, however, also reports of patients with asymptomatic HIV-1 infection, ARC or AIDS who developed acute psychotic disorders without any evidence of cognitive impairment throughout the episode (4,12,13,40).

It is unclear whether these syndromes may be (43): 1) one of the possible reactions to the diagnosis of HIV-1 infection or AIDS; 2) an effect of drugs used or abused by the patient; 3) the result of the chance association of psychosis and HIV-1 seropositivity; 4) an event precipitated by HIV-1 infection in predisposed subjects; 5) a direct consequence of HIV-1 infection of the brain.

The incidence and prevalence of either psychotic symptoms or syndromes in subjects with HIV-1 infection, as compared with the general population, are completely unknown. The response of these syndromes and symptoms to neuroleptics has been found to be frequently favourable. Nevertheless, AIDS patients have been regarded to be overly sensitive to extrapyramidal side effects of antipsychotic drugs.

2.2.2.3 Affective disorders

2.2.2.3.1 Depression

A depressive syndrome not fulfilling ICD-10 criteria for severe depressive episode or DSM III-R criteria for major depression may occur at any point in the course of HIV-1 infection, but more frequently in the period following the identification of HIV-1 seropositivity (adjustment disorder with predominant depression) or in the initial stage of HIV-1 associated dementia. It is

important to emphasize that depressive symptoms may be difficult to differentiate from some manifestations of ARC (fatigue, anorexia, weight loss, loss of libido, sleep disorders).

Major depression has been reported in subjects with HIV-1 infection, but estimates concerning its prevalence have been quite divergent. These discrepancies probably reflect the small size of the subject samples and the different sources from which they were recruited. It is also important to stress that the vulnerability to depression may be different in the various groups at risk for HIV-1 infection. Atkinson et al. (1) reported that a history of major depression was significantly more frequent in a sample of homosexual men as compared with a socio-demographically matched group of heterosexuals.

Major depression in HIV-1 infected subjects may be: 1) a reaction to the psychosocial problems related to HIV-1 infection and AIDS; 2) a direct consequence of HIV-1 infection of the brain (in view of the predilection of HIV-1 for limbic areas, which are believed to control emotional experience); 3) an event precipitated by HIV-1 infection in a predisposed subject; 4) the result of the chance association of affective illness and HIV-1 seropositivity.

For otherwise asymptomatic persons, there is no evidence that depression need be treated differently from what is done in persons not infected with HIV. However, patients suffering from an organic brain syndrome from any cause are susceptible to delirium induced by tricyclic antidepressants: 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 antidepressants should be considered.

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.

2.2.2.3.2 Mania

A few cases of hypomania or mania in subjects with HIV-1 infection have been also described. In some of them, cognitive impairment was associated or soon developed, thus suggesting a diagnosis of organic brain syndrome; in some others, cognitive impairment did not appear throughout the episode.

It is unclear whether these cases may be: 1) the result of the chance association of bipolar affective disorder and HIV-1 seropositivity; 2) an effect of drugs used or abused by the patient; 3) an event precipitated by HIV-1 infection in predisposed subjects; 4) a direct consequence of HIV-1 infection of the brain.

2.2.2.4 Adjustment disorders

Adjustment disorders consist of a morbid (that is, excessive in length and/or intensity) response to the diagnosis of HIV-1 infection or AIDS, or more generally to the stress associated with the disease.

Their occurrence is conditioned by several factors: 1) subject's coping strategies; 2) previous history of psychiatric disorders; 3) family, occupational and social acceptance; 4) availability of adequate counselling, especially before and after HIV-1 serologic testing (24).

The clinical picture of adjustment disorders may be dominated by depression, anxiety, somatic complaints, or disturbances of conduct. Their duration is very variable, and may be of several months.

Adjustment disorders have been reported to represent the most frequent diagnosis in patients with ARC or AIDS referred for psychiatric consultation. They have been found to be more frequent in subjects with ARC than those with AIDS, which finding has been ascribed to the greater level of uncertainty about the future in subjects with mid-stage manifestations of the disease (41).

Management of adjustment disorders has been found to benefit from behavioural and cognitive psychotherapy on an individual or group basis (24). Pharmacological treatment of depression and anxiety may be useful, although the above mentioned sensitivity of patients with ARC and AIDS to anticholinergic side effects should be taken into account in the prescription of tricyclic antidepressants, and the high liability to drug abuse of some subjects with HIV-1 infection should be considered in prescribing benzodiazepines.

2.2.2.5 Acute stress reactions

These reactions are particularly frequent immediately after the discovery of seropositivity, but may occur in any phase of HIV-1 infection, especially when changes occur in the individual's clinical state.

They include expressions of despair, anger, guilt, withdrawal, fear, and may involve the appearance of somatic symptoms, that can be interpreted by the subject as evidence of a physical decline.

In type, severity and duration these reactions are similar to reactions to other major life events or diseases in the context of the culture. They do not usually lead to chronic functional impairment.

Acute stress reactions are aggravated in the context of poor social support, lack of occupational or financial flexibility, or pre-existing personality disorder.

Management of these reactions is based on supportive counselling, with liaison psychology/psychiatry as appropriate.

2.2.2.6 Suicide

HIV-1 infection and AIDS have been found to be associated with a high risk of suicide. Marzuk et al. (21), in a study of the suicide rate in New York City in 1985, reported that the relative risk of suicide in men with AIDS aged 20-59 years was 36.3 times that of men in the same age range without this diagnosis, and 66.15 times that of the general population.

The suicide rate reported in this study may be underestimated, since there may have been suicide victims in whom the diagnosis of AIDS was not reported or even not suspected, as well as AIDS patients in whom suicide was not recognized as the cause of death.

Psychosocial factors which may precipitate suicide in AIDS patients include the social stigma related to the illness, the withdrawal of family support, diminished or lost occupational functioning, long-term dependency, loss of friends or lovers (often due to AIDS), and the spectre of an inexorable terminal illness that may lead to pain, disfigurement and emaciation. The presence of concomitant psychiatric syndromes, especially depression and delirium, may increase the rate of suicide in AIDS patients. It is uncertain whether suicidal risk is higher in drug users.

The risk of suicide has been found to be particularly high in the period following the discovery of HIV-1 seropositivity, which confirms the importance of pre- and post-test counselling.

2.2.3 Other HIV-1 associated central nervous system disorders

2.2.3.1 Progressive encephalopathy of childhood

Children can 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.

The incidence of encephalopathy is unknown, but 11.5% of pediatric AIDS cases reported to CDC from 1 September 1987 to 31 December 1988 had this condition (15). Some recent studies have found a significant improvement of the encephalopathy after treatment with AZT.

2.2.3.2 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 variation of HIV-1 associated 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% (19). 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.

2.2.4 HIV-1 associated peripheral nervous system disorders

2.2.4.1 Inflammatory polyneuropathy

HIV-1 associated inflammatory polyneuropathy (IP) may be observed at any stage of HIV infection. It may present as (5,17): 1) a subacute, multifocal peripheral, sensory-motor neuropathy (mononeuritis multiplex) which predominates in the lower limbs but may also affect cranial nerves; 2) an inflammatory subacute, roughly symmetrical sensory-motor polyneuropathy; 3) a typical acute Guillain-Barré syndrome, with facial diplegia, in which respiratory failure is uncommon.

This condition may be immune-mediated, representing immune dysregulation, rather than resulting from direct nerve damage by HIV-1. Other viruses, such as herpes group viruses, may also be of relevance in its pathogenesis.

Except for CSF pleocytosis, the clinical and laboratory features of IP are indistinguishable from those of demyelinating neuropathies occurring in the absence of HIV-1 infection.

The majority of cases of IP present in the early stages of HIV-1 infection (CDC Groups II and III), and the disease may, therefore, be the first manifestation of HIV-1 infection (3). However, the disorder is uncommon.

Risk factors for the development of IP after HIV-1 infection are unknown and it is unclear whether the syndromes appear in all of the groups at risk for HIV-1 infection.

Most patients affected by IP recover spontaneously. Steroids, with or without plasmapheresis, have been used for their treatment, but controlled studies of their effectiveness are lacking. The use of high-dose intravenous immunoglobulin has been also proposed.

2.2.4.2 Predominantly sensory neuropathy

Predominantly sensory neuropathy (PSN) in the HIV-1 infected persons normally presents with paresthesiae and dysesthesiae, primarily affecting the balls of the feet and the toes symmetrically. Usually there is minimal weakness, depressed ankle jerks and impaired vibratory sensation. 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, or cytomegalovirus (CMV) infection (9), may be of importance.

The 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 of PSN is symptomatic. Some patients respond to tricyclic antidepressants or to topically-administered capsaicin, although the effectiveness of these drugs has not been systematically studied. The value of AZT in the treatment of PSN is unknown.

It is important to mention that a distal symmetrical axonal polyneuropathy may be observed in patients treated with dideoxyinosine (DDI) or dideoxycytidine (DDC).

2.2.4.3 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 (EMG) 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 (6), 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, in severe cases, immunosuppressive therapy.

Several patients receiving long-term AZT demonstrate evidence of myopathy, with proximal weakness, muscle pains, muscle wasting, mild elevation of CK levels, and myopathic features on EMG. There are no specific clinical, EMG, enzymological or biopsy findings that can reliably distinguish this condition from HIV-1 associated myopathy. The diagnosis is suggested by improvement within 4-6 weeks after interruption of treatment.

2.2.5 Neurological disorders due to opportunistic processes in HIV-1 infected subjects

There are a number of opportunistic infections or neoplasms that can affect patients with HIV-1 infection and immunosuppression. By definition, the presence of these illnesses is diagnostic of AIDS.

Some of the most important of these opportunistic conditions are: progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, cryptococcal meningitis, CMV neuropathy, CNS tuberculosis, herpes zoster encephalitis, CMV encephalitis, varicella zoster radiculitis, and primary CNS lymphoma.

The contribution of other infectious tropical diseases, such as malaria or trypanosomiasis, as opportunistic infections of the nervous system in HIV-1 infected patients is unknown.

2.2.5.1 Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an unusual infectious CNS disease caused by the papovavirus JC. Affected patients present with dementia, blindness, dysphasia, hemiparesis, ataxia and focal deficits which may progress rapidly to 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 areas of myelin loss. These histopathological findings are pathognomonic. Monoclonal antibody staining or electron microscopy can reveal the causative agent.

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 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 in the United States.

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.

2.2.5.2 Cerebral toxoplasmosis

Cerebral toxoplasmosis in AIDS patients results from the reactivation of latent brain infection with the opportunistic intracellular parasite Toxoplasma gondii. Patients most frequently present with focal neurological signs.

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 direct visualization on light or electron microscopy. Radiological studies frequently reveal 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.

Presumptive diagnosis of CNS toxoplasmosis can be based on response to empiric therapy with pyrimethamine and sulfadiazine.

Although serologic tests for toxoplasmosis are unreliable, determination of intrathecal synthesis of anti-toxoplasma antibodies can be helpful (31).

By December 1989, 4,776 cases of cerebral toxoplasmosis had been reported to 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 is the first clinical manifestation of illness. The CDC data suggest that 1.9% of AIDS patients first present with this condition.

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 the above 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.

2.2.5.3 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, fever and photophobia are most common. Diagnosis is made by CSF analysis with cryptococcal cultures, cryptococcal antigen titers or India ink staining.

By December 1989, 7,505 cases of AIDS-related cryptococcal meningitis had been reported to CDC; the prevalence among AIDS patients in the UCSF series was 5.3%. Many AIDS patients who develop cryptococcal meningitis have this illness as their first clinical manifestation of AIDS. According to CDC data, this occurs in 5.4% of AIDS patients.

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 can result in a significant response with resolution of clinical symptoms and control of the disease. The major therapeutic problem involves toxicity of these agents and recurrent disease. The use of ketoconazole derivatives for maintenance therapy is under investigation. Lifelong suppressive treatment may be required in most patients.

2.2.5.4 CMV neuropathy

CMV neuropathy should be considered when a severe, multifocal neuropathy, predominating in the cauda equina territory, develops late in the course of AIDS. Neuropathy is usually associated with CSF pleocytosis with polymorphonuclear reaction and other manifestations of CMV infection (retinitis, colitis, pneumonitis).

2.2.5.5 Other syndromes due to opportunistic infections

2.2.5.5.1 CNS tuberculosis

CNS tuberculosis is caused by reactivation of latent infection with Mycobacterium tuberculosis. The most common presentations are meningitis, paraplegia, and brain abscess. The relation of these illnesses to HIV-1 infection is likely but requires further study. Diagnosis of CNS tuberculosis can be made by one of several available antigen detection tests (7). There are effective standard treatment regimens for CNS tuberculosis. The optimal duration of therapy is unknown.

2.2.5.5.2 Other viral CNS diseases

Herpes simplex, CMV and varicella zoster virus may all cause meningoencephalitis in HIV-1 infected subjects. Diagnosis and treatment are difficult. CMV is a major cause of retinitis which can lead to blindness. It is easily diagnosed by its characteristic findings on funduscopic examination (i.e., 'cotton-wool spots').

Herpes zoster is caused by reactivation of a latent infection with varicella zoster virus. The diagnosis is easily made by clinical examination. Rarely, it is associated with transverse myelitis and encephalitis. Management is symptomatic, although acyclovir could be helpful in severe cases.

2.2.5.6 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 non-enhancing 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's sarcoma or other tumours).

At UCSF, 25 of 1,286 patients had CNS lymphoma (1.9%). CDC data suggest that in 0.5% of AIDS patients in the United States, CNS lymphoma is the first AIDS-defining illness. 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.

2.3 Results of neuropsychological testing in otherwise healthy HIV-1 seropositive subjects

At present there is disagreement as to whether abnormalities as measured by neuropsychological testing occur with increased frequency in otherwise healthy HIV-1 infected persons (CDC Groups II and III).

Several published studies have not demonstrated an increase of this frequency. McArthur et al. (23) found no differences in performance on neuropsychological tests between 270 asymptomatic HIV-1 seropositive homosexual/bisexual men (14%) and 193 seronegative homosexual men (15%) in the Multicenter AIDS Cohort Study (MACS). These observations have been confirmed by an analysis of over 700 HIV-1 seropositive men in CDC groups II/III in the MACS (25). Janssen et al. (14) studied 74 HIV seropositive and 157 HIV seronegative homosexual/bisexual men (CDC Groups II and III) in the San Francisco City Clinic study and found no significant difference in performance on neuropsychologic tests (13% and 12% respectively). Goethe et al. (10) studied 83 healthy HIV-1 seropositive men (Walter Reed Class I and II) in the United States Air Force and found no significant difference in the frequency of neuropsychological abnormalities between seropositives (8%) and seronegative controls (0%). Selnes et al. (38), in a longitudinal study of approximately 200 HIV-1 seropositives tested semiannually for up to two years, found no significant decline in neuropsychological performance. Tross et al. (42) also found no significant increase in abnormal test results in 16 asymptomatic seropositives compared to 20 seronegatives. Several unpublished studies have also found no significant difference between asymptomatic seropositives and seronegative controls (27,36).

Other published studies have reported differences in performance on neuropsychological tests by asymptomatic seropositives compared to seronegatives. Grant et al. (11), in a study of sixteen seropositive men (CDC Groups II and III) in San Diego, demonstrated an increase in the prevalence of neuropsychological abnormalities in seropositives (44%) compared to seronegative controls (9%). Perry et al. (28), in a study of 20 seropositive homosexual men, found a significant increase in neuropsychological abnormalities (50%) in seropositives compared to age- and education-matched controls (15%). Ayers et al. (2) have also reported finding neuropsychological impairment in seropositive subjects without any clinical symptoms. Wilkie et al. (44) found significant neuropsychological test impairment in 52 asymptomatics compared to 13 seronegative controls. Several unpublished studies have also found subtle neuropsychological abnormalities (8,34).

Interpretation and comparison of the results of the studies available in this area are made difficult by several factors (18): 1) differences in the functional domains assessed by the various authors and in the instruments used to assess similar domains; 2) occasional use of unstandardized tests; 3) dissimilarity of the populations and of the sample sizes; 4) different approaches used in the analysis of data and in the definition of thresholds for abnormality; 5) different attention to confounders (such as psychiatric symptomatology, alcohol or drug abuse, prescribed medication, history of childhood learning disabilities or of CNS traumas); 6) possible heterogeneity of asymptomatic HIV-1 seropositives from the immunological viewpoint (it has been reported that subjects with immunological decline may have a worse cognitive performance); 7) insufficient attention to social, educational and above all cultural characteristics of the subjects likely to affect results.

The studies in which no increase of the frequency of abnormal neuropsychological findings could be demonstrated among HIV-1 seropositive individuals included in all over 1,100 subjects, while the studies showing such increase included in all about 250 subjects. Thus, although the topic remains controversial, the weight of current evidence suggests that the great majority of persons in CDC Groups II and III do not have an impaired performance on neuropsychological tests. On the other hand, the abnormalities on these tests found in some studies have not been shown to be associated with clinically significant neuropsychiatric impairment.

Most of the information regarding neuropsychological function in HIV-1 infected individuals is derived from studies in a single risk group, well-educated homosexual or bisexual men in industrialized countries, and therefore the same conclusions may not be readily applied to other risk groups, or to groups with different levels of education or with different frequencies of confounding factors such as the use of alcohol and other drugs.

3. IMPLICATIONS OF THE EVIDENCE

3.1 Implications concerning screening

The weight of currently available evidence suggests that otherwise healthy HIV-1 infected individuals (CDC groups II and III) are not more likely to have a clinically significant cognitive impairment than persons not infected with HIV-1. Hence, there is, at the present time, no justification for HIV-1 serological screening of asymptomatic persons as a strategy for detecting such impairment in the interest of public safety. This policy statement needs to be continually reviewed in the light of studies currently in progress or planned.

It is recognized that in AIDS- and HIV-1 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 were 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.

Protection of the public by preventing accidents is an important policy goal. 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, alcohol or drug abuse, and psychiatric disorder. Therefore, from the viewpoint of public safety, the critical issue is not the cause of impaired job performance, but the ability to detect impairment whatever the cause.

Given the evidence evaluated at the consultation, denial of access to employment or 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 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.

3.2 Implications concerning training of staff and provisions for care

As the incidence of AIDS steadily increases, an enormous burden of neuropsychiatric problems will face the health care system of many countries. 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 to far exceed the number of persons with Parkinson's disease.

Much less is known on the impact of AIDS on the medical services in developing countries, as very little information on the incidence of neuropsychiatric dysfunctions among AIDS patients in these countries is available.

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.

The consultation recommended that the HIV-1 related burden of neuropsychiatric disorders on the health care system be determined and that adequate projections of their evolution be made to plan for future health care needs.

The fundamental need is to ensure that appropriate support and treatment services are available and accessible, not only to patients with clinical illness, but also 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, 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, 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, psychiatrists and psychologists 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 present report should be widely disseminated to health workers to help ensure that informed advice is provided to HIV-1 infected persons.

3.3 Implications concerning research needs

The main general research issues arising from the above review of currently available evidence can be summarized as follows:

- 1) Although several neuropsychiatric disorders have been found to be associated with HIV-1 infection, the existence of a causal relationship between the infection and the disorder is in most cases not conclusively demonstrated. For instance, on the basis of presently available epidemiological data, the association of psychosis and HIV-1 seropositivity can be expected to occur by chance in 750 new cases every year within the population of the United States, or even more frequently if one considers that subjects at high risk for HIV-1 infection and individuals with a first psychotic episode share many features. This number largely exceeds that of actually reported cases of HIV-1 associated psychotic disorders since the epidemic has started and throughout the world.
- 2) The clinical characterization of some HIV-1 associated neuro-psychiatric disorders until the present has not been precise, which has hampered the comparability among the results obtained by the different research groups. It is to be hoped that the operational diagnostic criteria suggested at this consultation will contribute to the resolution of this source of disagreement in research findings.

- 3) The currently available information about HIV-1 associated neuropsychiatric disorders mainly derives from studies carried out in Western countries and in samples of well-educated homosexual or bisexual men. The generalizability of the findings obtained in these populations is uncertain, and well-designed investigations in other geographic and socio-cultural contexts, as well as in other at-risk populations, are clearly needed. The WHO multicentre study on neuropsychiatric aspects of HIV-1 infection, presently ongoing on five continents, is expected to address this issue.
- 4) Very few longitudinal studies focusing on HIV-1 associated neuropsychiatric disorders have been carried out until now, so that the natural history of these conditions is largely unknown. Also in this case, the above mentioned WHO study could provide important data.
- 5) Data on the prevalence and incidence of the various HIV-1 associated neuropsychiatric conditions are at present either lacking or conditioned by the type of facilities where the investigations have been conducted. Large nationwide surveys, like that focusing on HIV-1 associated dementia, recently completed by the CDC in the USA, would be extremely useful.
- 6) For some HIV-1 associated neuropsychiatric disorders, currently available information derives almost completely from the evaluation of small size samples of patients (or even single cases), without - or with inadequate-control groups. It should be kept in mind that the selection of appropriate control groups is of paramount importance. One recommendation is to have the subject serve, whenever possible, as his/her own control over time.
- 7) The prevalence of several psychiatric disorders is apparently higher in some groups at risk for HIV-1 infection than in the general population, which confirms the importance of the selection of appropriate controls (if HIV-1 seronegative subjects are used, they should share with HIV-1 seropositives the risk factors for the infection) and the caution which must be observed in making any assumption about the causal relationship between HIV-1 infection or disease and observed psychopathology.
- 8) The comparability of the research findings obtained by different groups is presently further hampered by the use of different evaluation instruments, mainly but not only in neuropsychological testing. Some of these instruments, in addition, are of uncertain reliability, and very few of them have been found to be suitable for use in a cross-cultural context. WHO is currently testing a comprehensive instrument for the assessment of HIV-1 associated neuropsychiatric disorders, including a neuropsychological battery which is designed to be easily administrable and culturally non-specific.
- 9) The frequent concomitance with HIV-1 infection of other infectious processes with possible neuropsychiatric complications represents another important research problem. Whether adequate prevention or treatment of the above processes may have an impact on the progression of HIV-1 associated neurological and psychiatric disorders remains uncertain.

- 10) There is currently no consensus on the nature and prevalence of neurological abnormalities in symptomatic HIV-2 infection, although some data have been reported. A better characterization of these abnormalities from both the clinical and the neuropathological viewpoint would be extremely useful for both practical and theoretical reasons.
- 11) The usefulness of anti-viral chemotherapy not only in the treatment of some HIV-1 associated neurological disorders but also in their prophylaxis remains open to debate. A particularly important issue is whether such treatment, when performed in asymptomatic HIV-1 seropositive subjects, significantly delays or modifies the expression of HIV-1 associated cognitive motor complex. Moreover, the effects of these drugs (both the therapeutic and the adverse ones) should be considered as confounding variables in studies carried out in this area.
- 12) Studies on neuropsychiatric aspects of HIV-1 infection have major public policy implications. Therefore, it is essential to avoid premature disclosure of data to the media prior to rigorous scrutiny of peer review. In international collaborative studies, it is important that investigators agree prior to the beginning of the investigation as to the manner of publication.
- 13) Confidentiality is a vital concern in studies of persons with HIV-1 infection. In all studies in this area, forms linking personal identifiers and data must be kept in a locked file and be available only to the principal investigator. This is of paramount importance not only for the persons themselves, but also to ensure the successful recruitment and the continued participation of study subjects.
- 14) The development of indicators of the quality of services dealing with neurological and mental health aspects of HIV-1 infection is an important research issue. Such quality should be assessed in terms of efficacy (capacity to produce the desired effects), efficiency (relation between the actual impact of care and the costs), equity (distribution of services in accordance with the objectives of care and with the perceived needs of the population), accessibility (removal of financial and other obstacles to the use of the available services), adequacy (supply of a sufficient number of services in relation to the needs and demand), acceptability (provision of services which are concordant with the social and cultural expectations of the users) and scientific-technical level.
- 15) The experience of care for HIV-1 infected subjects suggests several possible research topics. On the one hand, it would be extremely useful to develop and test algorithms for the management of the most frequent neuropsychiatric problems associated with HIV-1 infection. These should be suitable for application even in very busy clinical contexts, especially of developing countries, where the availability of diagnostic tools and of medication may be very limited. On the other hand, it would be worthwhile to explore some issues concerning caregivers, such as the patterns of emotional responses of health

workers dealing with AIDS patients, the utility of mutual support groups for these workers, and the evidence among them of the syndrome of demoralization, fatigue and anxiety with somatization called "burnout".

- 16) It is very urgent to produce projections about the number of persons who will suffer from HIV-1 associated neurological and mental health problems in the next five and ten years. This would help the decision makers in planning strategies for care, as well as education and training programmes for personnel.

4. RECOMMENDATIONS

4.1 Recommendations concerning the action of WHO

The consultation made the following recommendations concerning the action of WHO:

- 1) The Organization should continue to promote research to obtain information on the prevalence and natural history of HIV-1 associated neuropsychiatric disorders in different geographic and socio-cultural contexts.
- 2) It should continue to promote research on the pathogenesis, predictors and possible markers for HIV-1 associated neuro-psychiatric disorders, with particular attention to dementia and cognitive/motor abnormalities.
- 3) It should continue efforts in the development of research methodology, with special regard to standardization of neuropsychological testing in a cross-cultural context.
- 4) It 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.
- 5) It should make projections of the expected number of cases of HIV-1 associated neuropsychiatric disorders and on the consequent expected burden on health care services for the next 5 and 10 years.
- 6) It should promote research specifically focused on practical aspects of management of HIV-1 associated neurological and psychiatric disorders, including the development and testing of algorithms for the diagnosis and treatment of these conditions, and the assessment of psychological problems of physicians and nurses who take care of HIV-1 subjects.
- 7) It should promote education and training for the development of psychological support systems for care providers and family members of HIV-infected persons.
- 8) It should collaborate with governments in their effort to develop health care services for the treatment of patients with HIV-1 associated neuropsychiatric disorders.

4.2 Recommendations concerning action to be undertaken at country level

Concerning action to be undertaken at country level, the consultation made the following recommendations:

- 1) Health workers should be made aware of the wide range of neuropsychiatric conditions associated with HIV-1 infection and of the fact that, according to the weight of existing information, the frequency of clinically significant cognitive impairment is not significantly increased (over the levels found in HIV-1 uninfected people) until or unless patients develop ARC or AIDS.
- 2) Health services should prepare to deal with a large burden of neuropsychiatric illness, much of it severe, in patients with ARC and AIDS; planning should commence immediately.
- 3) Governments should be aware of the increased demand for neuropsychiatric care as the HIV-1 epidemic progresses. They have the responsibility to ensure that medical services receive proper support to be able to cope with their increased work load, and that training programmes for key categories of health workers are soon implemented.
- 4) Services in which HIV-1 serology is performed should in every case be able to provide pre- and post-test counselling. Moreover, in planning the development of counselling services, the special needs of families of HIV-1 infected subjects and of the staff dealing with AIDS patients should be taken into account.
- 5) Governments and health workers should be aware of the high priority of research concerning the neurological and mental health aspects of HIV-1 infection, and of its immediate policy and care implications. This research should be adequately encouraged, supported and funded at country level, taking into account that the uncertain generalizability to the various geographic and socio-cultural contexts is one of the main limitations of the currently available scientific evidence in the field.

LIST OF PARTICIPANTS IN THE CONSULTATION

Dr G. Goodwin, MRC Brain Metabolism Unit, Royal Edinburgh Hospital, Morningside Park, Edinburgh EH10 5HF, United Kingdom

Dr E. Gussev, Division of Neurological Diseases, Second Medical Institute, ul. Ostroviliana 1, Moscow 117437, USSR

Dr R. Janssen, Division of Viral and Rickettsial Diseases, Centers for Disease Control, 1600 Clifton Road, Atlanta GA 30333, United States of America

Dr E. Katabira, MRCP, Mulago Hospital, Department of Medicine, Makerere University, P.O. Box 8933, Kampala, Uganda

Dr J. McArthur, Department of Neurology, Johns Hopkins Hospital, Meyer Building, Rm 6109, 600 N. Wolfe Street, Baltimore MD 21205, United States of America

Dr Mitsuhiro Osame, Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Kagoshima City, 1208-1 Ushuku, 890 Japan

Dr B. Osuntokun, Neurology Unit, Department of Medicine, University of Ibadan, Ibadan, Nigeria

Dr J. Perriens, Mama Yemo Hospital, Projet SIDA, Kinshasa, Zaire

Dr R. Price, Department of Neurology, University of Minnesota, Medical School, Box 295 UMHC, Minneapolis MN 55455, United States of America

Dr G. Said, Neurology Unit, Bicêtre Hospital, 78, rue du Général Leclerc, 94275 Le Kremlin Bicêtre, France

Dr P. Satz, Department of Neuropsychology, Neuropsychiatric Institute, and Hospital Center for the Health Sciences, 760 Westwood Plaza, Los Angeles CA 90024-1759, United States of America

Dr Thiravat Hemadchudha, Neurology Division, Department of Medicine, Chulalongkorn University Hospital, Bangkok 10500, Thailand

Dr M. Zaudig, Inpatient Department, Max-Planck Institute for Psychiatry, Kraepelinstrasse 10, 8000 Munich 40, West Germany

Annex 1

WHO Secretariat

Dr P. Crocchiolo, GPA/BMR
Dr J. Esparza, GPA/BMR
Dr M. Maj, MNH/GPA
Dr J. Mann, Director, GPA
Dr N. Sartorius, Director, MNH
Dr F. Sonnenburg, GPA/BMR
Dr R. Widdus, Chief, GPA/PCD

OUTLINE OF THE WHO MULTICENTRE STUDY ON THE
NEUROPSYCHIATRIC ASPECTS OF HIV-1 INFECTION

Background

This study follows on from the first two recommendations that were made at the Consultation on Neuropsychiatric Aspects of HIV Infection held in Geneva in March 1988, i.e.:

- 1) that WHO should promote research to obtain information on the natural history, pathogenesis, predictors and possible markers for HIV-1 related neuropsychiatric disorders;
- 2) that WHO should promote the development and standardization of research methodology, and in particular:
 - (a) promote the definition or creation of a standard broadly based battery for assessment of HIV-1 related neuropsychiatric abnormalities;
 - (b) promote the development of an easily administered and culturally non-specific measure of neuropsychological function.

Objectives

The objectives of the study are:

- 1) to determine the prevalence of neuropsychiatric abnormalities at the different stages of HIV-1 infection, in various at-risk populations, and in different geographic and socio-cultural contexts;
- 2) to characterize these abnormalities and assess their natural history;
- 3) to search for possible correlations of neuropsychiatric findings with somatic manifestations and immunological aspects of HIV-1 infection.

Design

The study is currently ongoing in six centres (Bangkok, Thailand; Kinshasa, Zaire; Los Angeles, USA; Munich, West Germany; Nairobi, Kenya; Sao Paulo, Brazil). In each of them, the main investigation will be carried out on at least 100 HIV-1 seropositive asymptomatic subjects (CDC groups II and III), 50 subjects with HIV-1 associated somatic manifestations not meeting CDC criteria for AIDS, 50 subjects with AIDS by CDC criteria, and 100 age-, sex- and education-matched HIV-1 seronegative controls. Subjects will be recruited from outpatient medical sites. In each subject, a comprehensive instrument for the collection of neuropsychiatric data (including a battery of neuropsychological tests) will be administered at baseline and at one-year intervals (six-month intervals for AIDS patients and relevant controls) for three years.

Annex 2

What has been done

The protocol for the study and the relevant evaluation instruments (including a newly developed battery of neuropsychological tests which is expected to be culturally non-specific) have been finalized. A training workshop for the neurologists and the psychiatrists participating in the study has been held in Atlanta from 27 November to 4 December 1989. The pilot phase of the investigation has started on 2 January 1990.

Timetable for the future

A training workshop for the neuropsychologists participating in the study will take place in Nairobi from 12 to 15 March 1990. The pilot phase of the investigation will be completed by 30 April 1990. A meeting of the Heads of the centres will be held during the Sixth International Conference on AIDS, San Francisco, USA in June 1990. The main phase of the study will start after this meeting and will last until June 1993.

OPERATIONAL DIAGNOSTIC CRITERIA FOR HIV-1 ASSOCIATED
NEUROPSYCHIATRIC DISORDERS

HIV-1 ASSOCIATED COGNITIVE/MOTOR COMPLEX

HIV-1 ASSOCIATED DEMENTIA

- A. The general ICD-10 criteria for dementia (see Annex 4) have to be met, with the following modifications:
- (1) Decline in memory may not be severe enough to impair activities of daily living.
 - (2) Decline in motor function may be present and is verified by clinical examination (abnormal gait, slowed rapid movements, limb incoordination, hyperreflexia, hypertonia, or weakness) and when possible formal neuropsychological testing (e.g., timed gait, grooved pegboard, finger tapping). This motor function impairment should not be entirely caused by myelopathy, peripheral neuropathy, or other physical illness.
 - (3) The minimum requested duration of symptoms is one month.
 - (4) Aphasia, agnosia and apraxia are unusual.
- B. Laboratory evidence for systemic HIV-1 infection needs to be present (ELISA test with specificity of at least 95%, or Western blot, or PCR, or culture).
- C. No evidence of another etiology from history, physical examination or laboratory tests should be present. Specifically, lumbar puncture, CT or MRI should be done to exclude active CNS opportunistic processes. Determination of serum cryptococcal antigen is probably adequate for excluding cryptococcal meningitis. If neuroimaging studies (CT, MRI) are not available, "possible" should be added to the diagnosis to identify its level of certainty.

HIV-1 ASSOCIATED MYELOPATHY

- A. Both of the following are required:
- a. Symptoms of lower extremity weakness, incoordination, or urinary incontinence in the absence of back pain.
 - b. Signs of lower extremity spasticity, weakness, hyperreflexia, or the presence of Babinski signs.
- B. Laboratory evidence of systemic HIV-1 infection needs to be present (see above).
- C. No other possible cause of myelopathy is present (spinal cord tumours, compressive lesion, multiple sclerosis, other myelopathies). If the presence of these conditions cannot be assessed, or if other potential etiologies are present, but not thought to be the cause of myelopathy, the diagnosis should be "possible HIV-1 associated myelopathy".

Annex 3

The severity of HIV-1-associated myelopathy should be graded as follows:

Stage 1: needs walking assistance (walker, cane)

Stage 2: confined to bed or wheelchair or urinary incontinence

HIV-1 ASSOCIATED MINOR COGNITIVE/MOTOR DISORDER

- A. Evidence of at least one subjective cognitive symptom persisting more than one month, among the following:
 - (1) impaired memory
 - (2) impaired concentration
 - (3) mental slowing
 - (4) apathy
- B. Abnormality on clinical exam (slowed fine motor tests, abnormal reflexes) or on neuropsychological testing (tests of attention, speed of information processing, motor speed, memory, visuospatial skills).
- C. The subject is able to perform all but the more demanding aspects of work or ADL. Social activities are mildly impaired but not to the degree making the person dependent on others, or person's performance at work is mildly impaired and person is able to maintain usual job. The subject can feed self, dress, and maintain personal hygiene, handle money, shop, use public transportation, or drive a car, but complex daily tasks such as bill writing and checkbook balancing or keeping track of appointments or medications may be occasionally impaired. Problems cause interference with usual activities several times per week, occasionally requiring minor assistance. Can walk without assistance.
- D. Laboratory evidence of HIV-1 systemic infection (see above).
- E. No other explanation. Must rule out depression, and symptoms should not be thought to be related to intravenous drug use (IVDU). Does not meet criteria for HIV-1 associated dementia or myelopathy.

HIV-1 ASSOCIATED DELIRIUM

- A. Impairment of consciousness and reduced ability to direct, focus, sustain, or shift attention.
- B. At least three of the following:
 - (1) disturbances of perception, including illusions and/or hallucinations;
 - (2) disorganized thinking;
 - (3) impairment of immediate recall and recent memory, with relatively intact remote memory;

- (4) disorientation in time, place or person.
- C. At least one of the following:
 - (1) rapid, unpredictable shifts from hypoactivity to hyperactivity;
 - (2) increased reaction time;
 - (3) increased or decreased flow of speech;
 - (4) enhanced startle reaction.
- D. At least one of the following:
 - (1) insomnia or reversal of the sleep-wake cycle;
 - (2) nocturnal worsening of symptoms;
 - (3) disturbing dreams and nightmares which may continue as hallucinations or illusions after awakening.
- E. Rapid onset and diurnal fluctuations of the course of the symptoms.
- F. Total duration up to six months but typically from a few days to four weeks.
- G. Laboratory evidence of systemic HIV-1 infection (see above).
- H. No evidence of organic factors (other than those related to HIV-1 infection) that can be reasonably presumed to be responsible for the symptoms in A-D.

Subcategories:

HIV-1 ASSOCIATED DELIRIUM NOT SUPERIMPOSED ON DEMENTIA

HIV-1 ASSOCIATED DELIRIUM SUPERIMPOSED ON DEMENTIA

HIV-ASSOCIATED ACUTE SCHIZOPHRENIA-LIKE PSYCHOTIC DISORDER

- A. An acute onset of delusions, hallucinations, marked disorder in the form of thought, or any combination of these. The time interval between the first appearance of any psychotic symptom and the presentation of the fully developed disorder should not exceed two weeks.
- B. (1) At least one of the following:
 - a) Thought echo, thought insertion or withdrawal, and thought broadcasting.
 - b) Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations, and delusional perception.

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- c) Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.
- d) Persistent delusions of other kinds that are culturally inappropriate or implausible, such as religious or political identity, superhuman powers and ability (e.g., being able to control the weather, or being in communication with aliens from another world).

(2) or at least two of the following:

- a) Persistent hallucinations in any modality, when accompanied by either fleeting or half-formed delusions without clear affective content, or by persistent over-valued ideas, or when occurring every day for weeks or months on end.
- b) Breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech, or neologisms.
- c) Catatonic behaviour, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.
- d) Marked apathy, paucity of speech, and blunting or incongruity of emotional responses. It must be clear that these are not due to depression or to neuroleptic medication.

- C. The total duration of the disorder does not exceed one month.
- D. The criteria for dementia or delirium are not fulfilled.
- E. The criteria for mania or depressive episode are not fulfilled.
- F. Laboratory evidence of systemic HIV-1 infection (see above).
- G. No evidence of organic factors (other than those related to HIV infection) that can be reasonably presumed to be responsible for the syndrome.

HIV-1 ASSOCIATED OTHER ACUTE PSYCHOTIC DISORDER

Criteria A, and C to G for the previous category are fulfilled, but criterion B is not.

HIV-1 ASSOCIATED DEPRESSIVE EPISODE, MILD SEVERITY

- A. At least two of the following symptoms:
 - (1) Depressed mood to a degree that is definitely abnormal for the subject, present for most of the day and almost every day, largely uninfluenced by circumstances, and sustained for at least two weeks;
 - (2) Loss of interest or pleasure in activities which are normally pleasurable;
 - (3) Decreased energy and increased fatiguability.

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- B. Additional symptom or symptoms from the following to give a total of at least four:
- (1) Loss of confidence and self-esteem;
 - (2) Unreasonable feelings of self-reproach or excessive and inappropriate guilt;
 - (3) Recurrent thoughts of death or suicide, or any suicidal behaviour;
 - (4) Complaints or evidence of diminished ability to think or concentrate;
 - (5) Change in psychomotor activity, with agitation or retardation;
 - (6) Sleep disturbance of any type;
 - (7) Change in appetite (decrease or increase) with corresponding weight change.
- C. The duration of the episode is at least two weeks.
- D. The criteria for dementia or delirium are not fulfilled.
- E. Laboratory evidence of systemic HIV-1 infection (see above).
- F. No evidence of organic factors (other than those related to HIV-1 infection) that can be reasonably presumed to be responsible for the syndrome.

HIV-1 ASSOCIATED DEPRESSIVE EPISODE, MODERATE SEVERITY

- A. At least two of the symptoms listed in A for depressive episode, mild severity.
- B. Additional symptoms from those listed in B for depressive episode, mild severity to give a total of at least six.
- C. Same as C for depressive episode, mild severity.
- D. Same as D for depressive episode, mild severity.
- E. Same as E for depressive episode, mild severity.
- F. Same as F for depressive episode, mild severity.

HIV-1 ASSOCIATED SEVERE DEPRESSIVE EPISODE WITHOUT PSYCHOTIC SYMPTOMS

- A. All three of the symptoms listed in A for depressive episode, mild severity.
- B. Additional symptoms from those listed in B for depressive episode, mild severity, to give a total of at least eight.
- C. Absence of delusions, hallucinations or depressive stupor.

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- D. Same as C for depressive episode, mild severity.
- E. Same as D for depressive episode, mild severity.
- F. Same as E for depressive episode, mild severity.
- G. Same as F for depressive episode, mild severity.

HIV-1 ASSOCIATED SEVERE DEPRESSIVE EPISODE WITH PSYCHOTIC SYMPTOMS

- A. The criteria for the previous category are met, with the exception of criterion C, since delusions, hallucinations or depressive stupor are present.

Subcategories:

HIV-1 ASSOCIATED SEVERE DEPRESSIVE EPISODE WITH MOOD CONGRUENT PSYCHOTIC SYMPTOMS

HIV-1 ASSOCIATED SEVERE DEPRESSIVE EPISODE WITH MOOD INCONGRUENT PSYCHOTIC SYMPTOMS

HIV-1 ASSOCIATED ADJUSTMENT DISORDER

- A. Experience of an identifiable stressor related to HIV-1 infection, such as learning that one is HIV-1 seropositive or that one has AIDS, within one month of the onset of symptoms.
- B. Maladaptive reaction to the stressor, as indicated by either of the following:
 - (1) Impairment of occupational (or school) functioning or in usual social activities or relationships with others;
 - (2) Symptoms are in excess of an expectable reaction to the stressor.
- C. Symptoms do not persist for more than six months.
- D. The criteria for previous categories of specific mental disorders and ICD-10 criteria for panic disorder or generalized anxiety disorder (see Annex 4) are not fulfilled.
- E. Laboratory evidence of systemic HIV-1 infection (see above).

Subcategories:

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH PREDOMINANT DEPRESSION

The predominant manifestations are symptoms such as depressed mood, tearfulness, feeling of hopelessness.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH PREDOMINANT ANXIETY

The predominant manifestations are symptoms such as nervousness, tension and worry.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH MIXED EMOTIONAL REACTIONS

The predominant manifestation is a combination of depression and anxiety or other emotions.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH PREDOMINANT SOMATIC COMPLAINTS

The predominant manifestations are physical symptoms, that cannot be interpreted as directly linked to HIV-1 infection.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH PREDOMINANT DISTURBANCE OF CONDUCT

The predominant manifestation is a conduct which violates societal norms, such as truancy, vandalism, reckless driving or fighting.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER WITH MIXED DISTURBANCE OF EMOTIONS AND CONDUCT

The predominant manifestations are both emotional symptoms and disturbances of conduct.

HIV-1 ASSOCIATED DISORDER WITH PREDOMINANT SOCIAL WITHDRAWAL

The predominant manifestation is social withdrawal, without significant depression or anxiety.

HIV-1 ASSOCIATED ADJUSTMENT DISORDER, NOT OTHERWISE SPECIFIED.

HIV-1 ASSOCIATED ACUTE STRESS REACTION

- A. Exposure to an exceptional stressor related to HIV-1 infection, such as learning that one is HIV-1 seropositive or that one has AIDS.
- B. Exposure to the stressor is followed by an immediate onset of symptoms (within one hour).
- C. Two groups of symptoms are given: the reaction is graded as mild if only group 1 is fulfilled, moderate if group 1 plus at least two symptoms of group 2 are fulfilled, severe if group 1 plus at least four symptoms of group 2 are fulfilled, or if dissociative stupor is present.
 - (1) At least four of the following symptoms:
 - a) Palpitations or pounding heart (not merely occasional extra-systoles).
 - b) Hot or cold sweats or flushes.
 - c) Trembling or shaking of limbs.
 - d) Dry mouth (not due to medication or dehydration).
 - e) Discomfort or pains in the chest or epigastrium (e.g., "butterflies" or churning in the stomach).

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- f) Difficulty in breathing or feelings of choking.
 - g) Feelings of dizziness, unsteadiness or light-headedness.
 - h) Feeling faint, unreal, "not really here".
 - i) Feeling of loss of emotional control or going mad, or impending death.
 - j) Muscle tension, aches and pains in the limbs.
 - k) Restlessness and inability to relax.
 - l) Feeling keyed up, or on edge, or mentally tense.
 - m) A sensation of a lump in the throat, or difficulty with swallowing.
 - n) Exaggerated response to minor surprises or being startled.
 - o) Difficulty in concentrating or mind going blank, because of worrying or anxiety.
 - p) Persistent irritability.
 - q) Difficulty getting to sleep because of worrying.
 - (2) a) Withdrawal from expected social interaction.
 - b) Narrowing of attention.
 - c) Apparent disorientation.
 - d) Anger or verbal aggression.
 - e) Despair or hopelessness.
 - f) Inappropriate or purposeless overactivity.
 - g) Uncontrollable and excessive grief (judged by local cultural standards).
- D. Without the current presence of any other disorder in ICD-10 (except for F41.1, generalized anxiety disorder, and F60, personality disorders), or not within three months of the end of any other ICD-10 disorder.
- E. The symptoms must begin to diminish after not more than 48 hours.
- F. Laboratory evidence of systemic HIV-1 infection (see above).

HIV-1 ASSOCIATED PROGRESSIVE ENCEPHALOPATHY OF CHILDHOOD

- A. At least one of the following progressive findings present for at least 2 months:
- a. Loss of developmental milestones or intellectual ability.
 - b. Impaired brain growth (acquired microcephaly and/or brain atrophy demonstrated on CT or MRI).
 - c. Symmetrical motor deficits manifested by two or more of the following: paresis, abnormal tone, pathologic reflexes, ataxia, or gait disturbance.
- B. Evidence for systemic HIV-1 infection:
- a. Infants and children < 15 months
 - i) virus in blood or tissues (culture or PCR)
or
 - ii) HIV-1 antibody
and
evidence of cellular and humoral immune deficiency
or
symptoms meeting CDC case definition for AIDS
 - b. Children \geq 15 months
 - i) antibody or virus in blood or tissues (Western blot or PCR or culture).
- C. No evidence of other etiology.

If criteria A and B are met, but C is not, the diagnosis should be defined as "possible".

HIV-1 ASSOCIATED INFLAMMATORY POLYNEUROPATHY

- A. Subacute progressive (or relapsing) motor and/or sensory dysfunction of more than one limb of a peripheral nerve nature.
- B. Develops over at least one month.
- C. Lumbar puncture shows elevated protein, mononuclear pleocytosis and non-reactive VDRL.
- D. EMG/NCV studies, when available, confirm the presence of peripheral neuropathy, with features of both axonal loss and demyelination.
- E. Laboratory evidence of HIV-1 systemic infection (see above).

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- F. No evidence of other etiology. Must rule out mutilation of the hands or feet, retinitis pigmentosa, ichthyosis, history of drug or toxic exposure known to cause a similar peripheral neuropathy, or family history of a genetically based peripheral neuropathy, sensory level, or unequivocal sphincter disturbance.

If criteria A-E are met, but F is not, the diagnosis should be defined as "possible".

HIV-1 ASSOCIATED PREDOMINANTLY SENSORY NEUROPATHY

- A. Distal limb sensory symptoms (feet > hands) of a peripheral nerve nature, e.g., numbness, burning or pain.
- B. Clinical examination confirming a distal, relatively symmetric polyneuropathy in which sensory abnormalities predominate.
- C. Electrodiagnostic studies, when available, indicative of a predominantly axonal polyneuropathy.
- D. Laboratory evidence of systemic HIV-1 infection (see above).
- E. No evidence of other etiology. Nerve biopsy may be indicated to rule out certain etiologies such as amyloid or leprosy, but is not a requirement.

If criteria A, B and C are met, but E is not, the diagnosis should be defined as "possible".

HIV-1 ASSOCIATED MYOPATHY

- A. Symptoms of proximal lower and/or upper extremity weakness, documented by physical examination.
- B. CPK elevated two-fold over normal for laboratory.
- C. Laboratory evidence of systemic HIV-1 infection (see above).
- D. No other etiology. EMG and muscle biopsy may be necessary to rule out certain other etiologies. To distinguish from AZT myopathy, should not improve after withholding of AZT therapy.

If criteria A and B are met, but D is not, the diagnosis should be defined as "possible".

EXCERPT FROM ICD-10: RESEARCH CRITERIA FOR DEMENTIA, PANIC DISORDER
AND GENERALIZED ANXIETY DISORDER

F00-F09 ORGANIC, INCLUDING SYMPTOMATIC, MENTAL DISORDERS

DEMENTIA

A. Evidence of a dementia, of a specified level of severity, based on the presence of each of the following:

- (1) A decline in memory which causes impaired functioning in daily living. The decline is most evident in the learning of new information and, in more severe cases, the recall of previously learned information is also affected. The impairment applies to both verbal and non-verbal material. The decline should be objectively verifiable and not based on subjective complaint. This should be achieved by obtaining a history from an informant and/or by neuropsychological testing. The level of severity should be assessed as follows:

Mild impairment: A degree of memory loss sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living. The main function affected is the learning of new material, but in early or mild cases, the medium and long term memory may be affected little or not at all. For example, the individual has difficulty in registering, storing and recalling elements in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.

Moderate impairment: A more severe degree of memory loss. Only highly learned or very familiar material is retained. New information is retained only occasionally and very briefly. The individual is unable to recall basic information about where he lives, what he has recently been doing, or the names of familiar persons. This degree of memory impairment is a serious handicap to independent living. An associated finding may be the intermittent loss of sphincter control.

Severe impairment: Severe memory loss with only fragments of previously learned information remaining, the subject fails to recognize even close relatives. There is no retention of new information. The individual is not able to function in the community without close supervision: there is gross decline in personal care and loss of sphincter control.

- (2) A decline in intellectual abilities characterized by deterioration in thinking and in the processing of information, again of a degree leading to impaired functioning in daily living. Evidence for this should be obtained when possible from interviewing an informant and from a neuropsychological examination (if an estimate of premorbid intelligence can be made). To obtain both is desirable. Deterioration from a previously higher level of performance should be

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established, as by demonstration that the current level of handling and comprehension of ideas is incompatible with what might have been expected before. The level of intellectual impairment should be assessed as follows:

Mild impairment: The decline in intellectual abilities causes impaired performance in daily living, but not to a degree making the individual dependent on others; or there is a decline in performance in the individual's accustomed work, including work in the home, which is conspicuous to others. More complicated daily tasks or recreational activities cannot be undertaken.

Moderate impairment: The decline in intellectual abilities makes the individual unable to function without the assistance of another in daily living, including shopping and handling money. Within the home, only simple chores are preserved. Interests are very restricted and poorly sustained. Work outside the home cannot be conducted or has to be closely supervised.

Severe impairment: The decline precludes not only independence from the assistance of others, but is characterized by an absence, or virtual absence, of intelligible ideation.

The overall severity of the dementia is best expressed as the level of memory or intellectual impairment, whichever is the more severe (e.g., mild memory impairment and moderate intellectual impairment indicates a dementia of moderate severity).

- B. Absence of clouding of consciousness during a period of time long enough to enable the unequivocal demonstration of A. There may nevertheless be superimposed episodes of delirium in the course of a dementing illness. If a case presents with delirium, the diagnosis of dementia should be deferred because the impairment of thinking, memory and other higher functioning could be wholly attributed to the delirium itself.
- C. A deterioration in emotional control, social behaviour or motivation. The change in emotional control may manifest itself as a depressive change in character, as unconcern or unawareness or as increased irritability. Social behaviour may become coarsened, with disregard for dress or eating habits, or unaccustomed coarseness in speech. The change in motivation is usually characterized by inertia or apathy.
- D. For a confident clinical diagnosis, A should have been clearly present for AT LEAST SIX MONTHS; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

The diagnosis is further supported by evidence of damage to other higher cortical functions, such as aphasia, agnosia, apraxia, and of disintegration of social behaviour and a progressive change in personality, in which reduced spontaneity is a conspicuous early feature.

F41 OTHER ANXIETY DISORDERSF41.0 Panic disorder (episodic paroxysmal anxiety)

- A. Recurrent panic attacks, that are not consistently associated with a specific situation or object, and often occurring spontaneously (i.e., the episodes are unpredictable). The panic attacks are not associated with marked exertion or with exposure to dangerous or life-threatening situations. The range of individual variation of both content and severity is so great that two grades, moderate and severe, are specified with a fifth character:
- F41.00 Panic disorder - moderate degree: AT LAST THREE PANIC ATTACKS IN A THREE-WEEK PERIOD.
- F41.01 Panic disorder - severe degree: AT LAST FOUR PANIC ATTACKS PER WEEK OVER A FOUR-WEEK PERIOD.
- B. A panic attack is a discrete episode of fear and other symptoms which starts abruptly, soon reaches a peak, and lasts at least some minutes. AT LEAST ONE out of symptoms (1)-(4) must be or have been present, either currently or at some time since the onset of the disorder, PLUS AT LEAST ONE MORE symptom from any of symptoms (1)-(9):
- (1) Palpitations or pounding heart (not merely occasional extra-systoles).
 - (2) Hot or cold sweats or flushes.
 - (3) Trembling or shaking of limbs.
 - (4) Dry mouth (not due to medication or dehydration).
 - (5) Feeling of loss of emotional control or going mad or impending death.
 - (6) Discomfort or pains in the chest or epigastrium (e.g. "butterflies" or churning in the stomach).
 - (7) Difficulty in breathing, or feelings of choking.
 - (8) Feelings of dizziness, unsteadiness or light-headedness.
 - (9) Feeling faint, unreal, "not really here".
- C. Not due to a physical disorder, or other mental disorders such as schizophrenia and related disorders (F20-29), affective disorders (F30-39), or somatoform disorders (F45).
- D. The panic attacks do not occur consistently in association with specific objects or situations (F40.0-F40.2).

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F41.1 Generalized anxiety disorder

- A. A period of AT LEAST SIX MONTHS with prominent anxiety, worry and feelings of apprehension (whether justified or not), about everyday events and problems.
- B. If another diagnosis can be made, the focus of worry and anxiety is not a constituent symptom, for instance, any of the phobic disorders (F40.0-F40.2), or obsessive-compulsive disorder (F42).
- C. At least four of the following symptoms are usually present when worrying:
 - (1) Palpitations or pounding heart (not merely occasional extra-systoles).
 - (2) Hot or cold sweats or flushes.
 - (3) Trembling or shaking of limbs.
 - (4) Dry mouth (not due to medication or dehydration).
 - (5) Discomfort or pains in the chest or epigastrium (e.g. "butterflies" or churning in the stomach).
 - (6) Difficulty in breathing, or feelings of choking.
 - (7) Feelings of dizziness, unsteadiness or light-headedness.
 - (8) Feeling faint, unreal "not really here".
 - (9) Feeling of loss of emotional control or going mad, or impending death.
 - (10) Muscle tension, aches and pains in the limbs.
 - (11) Restlessness and inability to relax.
 - (12) Feeling keyed up, or on edge, or mentally tense.
 - (13) A sensation of a lump in the throat, or difficulty with swallowing.
 - (14) Exaggerated response to minor surprises or being startled.
 - (15) Difficulty in concentrating or mind going blank, because of worrying or anxiety.
 - (16) Persistent irritability.
 - (17) Difficulty getting to sleep because of worrying.
- D. The disorder does not meet the full criteria for panic disorder (F41.0).
- E. Not sustained by a specific organic disorder, such as hyperthyroidism, excess consumption of amphetamine-like substances, or withdrawal from benzodiazepines.

OUTLINE OF THE WHO STAGING SYSTEM FOR HIV INFECTION (IN DEVELOPMENT)

With the worldwide spread of the AIDS epidemic, the need for a universally applicable staging system of HIV infection and disease is strongly felt by clinicians. Main purposes of such a system are:

1. to improve clinical management of the patients;
2. to establish a correct prognosis;
3. to help in designing and evaluating drug and vaccine trials;
4. to perform studies on pathogenesis and natural history of the infection.

WHO/GPA decided to address this issue by organizing a consultation on HIV-1 staging, which took place at the end of July 1989. As a result of this consultation, WHO is proposing a new staging system of HIV-1 infection, which is meant to meet the above stated requirements of universal applicability and flexibility, according to the different degrees of technology available in different areas of the world.

Opportunistic infections all pace inexorably the course of HIV-related disease; however, not all of them show the same degree of severity or of prognostic significance, nor occur with the same frequency in the course of HIV-1 infection. In fact, there are different degrees of "opportunism": the less opportunistic an infection, the more it is common; the more opportunistic, the less it is common among the "normal" population. For example, infections like Herpes zoster (less specifically prevented by T-cell function integrity) may be expected to occur earlier in the HIV-1 carrier, when his or her immune system is less deteriorated and more similar to the "normal" standard; while infections like *P. carinii* pneumonia (more specifically those prevented by T-cell function integrity) are expected to occur later, when the immune failure of the HIV-1 carrier is far more advanced. This pathogenetic correlation between progressively increasing levels of immune function deterioration and occurrence of different kinds and patterns of opportunistic infections represents the rational basis for a clinical staging system of HIV infection.

In the past, expressions like asymptomatic carrier, PGL, ARC and AIDS have been widely used to indicate, roughly, different HIV-1 infection stages. However, this is no longer, or not completely, acceptable, especially as far as AIDS is concerned, since these definitions were not given for prognostic, but rather for epidemiological surveillance purposes, as they were based on different features, symptoms or clinical pictures not necessarily coinciding with degree of severity and, hence, with prognosis. AIDS itself can be staged: in fact, we can break down the disease into different clinical pictures with significantly different prognostic value.

The course of HIV-1 infection is a continuum; within this continuum, the only clear-cut available prognostic criterion is (retrospectively established) time of survival. To consider "AIDS" as the "end-stage" of HIV-1 infection

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could be misleading, in so far as not all AIDS-indicator diseases (CDC) or symptoms (WHO) are prognostically equivalent; in fact, for clinical staging purposes, different AIDS or ARC indicators, if evaluated according to average survival time, may be assigned to different appropriate clinical stages.

In the 3-layer system proposed by WHO, clinical staging (level A) is of fundamental importance, as it represents the real "backbone" of the whole system: any HIV-1 seropositive subject can be staged according to level A anywhere in the world (stage 1 = asymptomatic/PGL; stage 2 = early disease; stage 3 = intermediate disease; stage 4 = late disease). However, as laboratory indices, wherever available, can help in refining our ability to place the HIV-1 infected individual in a well-defined prognostic stage and may even be decisive during the symptomatic incubation period, levels B and C were added to level A, including, respectively, simple "routine" laboratory markers available even in smaller institutions and more "sophisticated" parameters accessible in teaching and research hospitals. Total lymphocyte counts Hb, Ht and ESR are the main level B laboratory tests. According to recent preliminary studies, there is some evidence that total lymphocyte counts correlate well with CD4 cell counts. The presence of a small laboratory and, in some instances, of an X-ray department, may also enable the physician at level B to improve the diagnostic assessment of the patient. CD4 cell counts, Neopterin, Beta-2 microglobulin, p24Ag, etc. (level C) may further fine-tune staging. However, with the notable exception of the completely asymptomatic stage in which we necessarily have to rely on the laboratory, clinical criteria supersede the laboratory markers: thus, we wanted to underscore, on the one hand, the importance of sound clinical judgement and, on the other hand, the universal applicability of the system. Finally, the terms early and late disease (instead of mild and severe), have been chosen in order to emphasize the continuity of the gradual deterioration process which takes place in the course of HIV-1 infection.

The proposed staging classification, in order to be universally applicable, also takes into account the different degrees of accuracy attainable in diagnosing clinical markers according to different access to instrumental and laboratory diagnostic facilities. For this reason, both highly sophisticated diagnoses like cerebral toxoplasmosis or PCP and very easily identifiable symptoms like grossly evaluated weight loss or performance scale are included. There is always at least one sign or symptom which can help to classify any HIV-1 seropositive subject as belonging to a certain stage and, conversely, any HIV-1 seropositive subject can be staged, regardless of the degree of diagnostic accuracy.

In other words, the list has been conceived in such a way that HIV-1 seropositive individuals can always be staged, regardless of the degree of diagnostic refinement attained (definitive diagnosis, presumptive diagnosis, signs and symptoms only): there is always at least one feature which may fit a definite prognostic category. Of course, geographical diversity may account for differences in the prevalence of various diseases; the new staging system, however, was designed to meet, at least to a great extent, these requirements.

An example of how the new staging system could be usefully employed comes from the recent Washington meeting on clinical and surrogate end-points in drug and vaccine efficacy trials. In fact, laboratory end-points can only

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surrogate, to a certain extent, clinical end-points (severe morbidity and death). However, the crucial issue is that clinical end-points have to be defined as clearly as possible, and this clarity so far was lacking, especially because epidemiological definitions like AIDS and ARC were arbitrarily and inappropriately used for clinico-prognostic purposes. AIDS and ARC may not be used as clinical end-points, as they do not represent one well-defined stage of disease and, in fact, encompass each a variety of indicator diseases with differing degrees of clinical severity and of prognostic significance. Death is obviously the most relevant clinical end-point: any drug or vaccine which prevents death is more effective than anything else which does not: however, there is also a need to evaluate drugs and vaccines for their ability to prevent progression even in earlier stages than death. According to the new staging system, it would be possible to use end-points such as progression from stages 2 or 3, respectively, to 3 or 4. To this purpose, the clinical experience accumulated in the last years, studies on average survival times after different opportunistic infections and also the widening knowledge of the relations existing between clinical manifestations and the underlying degrees of immune deficiency were all important factors in devising the new staging system.

In this sense, we can use every occurring opportunistic infection as a reliable marker of the underlying degree of immune dysfunction and thus, as a well-defined end-point in the progressive course of the disease.

HIV testing is the necessary premise to HIV staging: this, however, should not represent a major technical or economic problem, since wherever staging may be needed (either for clinical management or for enrollment into drug or vaccine trials), availability of HIV-1 testing facilities may be taken for granted.

The proposed system, of course, has to undergo a process of validation by multiple, well-conducted cross-sectional and prospective studies. To this purpose, an appropriately formulated questionnaire has been developed to verify the feasibility of the system by correlating clinical and laboratory markers in a preliminary cross-sectional study. After having processed these preliminary data, a formal proposal of the new system will be officially made. In analogy with the WHO AIDS case definition, the new staging system will be flexible enough to eventually incorporate some proposed modifications, especially if well-conducted longitudinal studies will provide evidence for doing so in some particular geographic areas with peculiar disease patterns.

REFERENCES

1. ATKINSON, J.H. et al. Prevalence of psychiatric disorders among men infected with human immunodeficiency virus. A controlled study. *Arch. Gen. Psychiat.*, 45:859-864, 1988.
2. AYERS, M.R. et al. Performance of individuals with AIDS on the Luria-Nebraska Neuropsychological Battery. *Int. J. Clin. Neuropsychol.*, 9:101-105, 1987.
3. BERGER, J.R. et al. Neurologic disease as the presenting manifestation of AIDS. *South. Med. J.*, 80:683-686, 1987.
4. BUHRICH, N. et al. HIV infection associated with symptoms indistinguishable from functional psychosis. *Brit. J. Psychiat.*, 152:649-653, 1988.
5. CORNBLATH, D.R. et al. Inflammatory demyelinating peripheral neuropathies associated with HTLV-3 infection. *Ann. Neurol.*, 21:32-40, 1987.
6. DALAKAS, M.C. et al. Polymyositis associated with AIDS retrovirus. *JAMA*, 256:2381-2383, 1986.
7. DANIEL, T.M.. New approaches to the rapid diagnosis of tuberculous meningitis. *J. Infect. Dis.*, 155:599-602, 1987.
8. FIELD, M. et al. Subclinical cerebral dysfunction is common amongst volunteers with asymptomatic HIV infection. Abstracts IV International Conference on AIDS, 1988, Book 1, p. 379.
9. FULLER, G.N. et al. Association of painful peripheral neuropathy in AIDS with cytomegalovirus infection. *Lancet*, 2:937-941, 1989.
10. GOETHE, K.E. et al. Neuropsychological and neurological function of human immunodeficiency virus seropositive asymptomatic individuals. *Arch. Neurol.*, 46: 129-133, 1989.
11. GRANT, I. et al. Evidence for early central nervous system involvement in acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections: studies with neuropsychological testing and magnetic resonance imaging. *Ann. Int. Med.*, 107:828-836, 1987.
12. HALEVIE-GOLDMAN, B.D. et al. AIDS-related complex presenting as psychosis. *Am. J. Psychiat.*, 144:964, 1987.
13. HALSTEAD, S. et al. Psychosis associated with HIV infection. *Brit. J. Psychiat.*, 153:618-623, 1988.

Annex 6

14. JANSSEN, R.S. et al. Neurologic and neuropsychologic manifestations of human immunodeficiency virus (HIV-1) infection: association with AIDS-related complex but not asymptomatic HIV-1 infection. *Ann. Neurol.*, 26:592-600, 1989.
15. JANSSEN, R.S. et al. Epidemiology of HIV encephalopathy in the United States. Abstracts V International Conference on AIDS, 1989, p. 50.
16. LEVY, R.M. & BREDESEN, D.E.. AIDS and the nervous system. Raven Press, New York, 1988.
17. LIPKIN, W.I. et al. Inflammatory neuropathy in homosexual men with lymphadenopathy. *Neurology*, 35:1979-1983, 1985.
18. MAJ, M.. Psychiatric aspects of HIV-1 infection and AIDS. *Psychol. Med.*, in press.
19. MARSHALL, D.W. et al. Spectrum of CSF findings in various stages of HIV infection. *Arch. Neurol.*, 45:954-958, 1988.
20. MARTIN, A. et al. Patterns of neuropsychological dysfunction in a select group of HIV-positive individuals in comparison to psychiatric controls. Abstracts V International Conference on AIDS, 1989, p.463.
21. MARZUK, P.M. et al. Increased risk of suicide in persons with AIDS. *JAMA*, 259:1333-1337, 1988.
22. McARTHUR, J.C. Neurologic Manifestations of AIDS. *Medicine*, 66:407-437, 1987.
23. McARTHUR, J.C. et al. Low prevalence of neurological and neuropsychological abnormalities in otherwise healthy HIV-1 infected individuals: results from the multicentre AIDS cohort study. *Ann. Neurol.*, 26:601-611, 1989.
24. MILLER, D.. Living with AIDS and HIV. MacMillan, Houndmills, 1987.
25. MILLER, E.N. et al. Neuropsychological performance in HIV-1 infected homosexual men: the Multicentre AIDS Cohort Study (MACS). *Neurology*, 40:197-203, 1990.
26. NAVIA, B.A. et al. The AIDS dementia complex: I. Clinical features. *Ann. Neurol.*, 19:517-524, 1986.
27. O'DOWD, M.A. et al. Comparison of neuropsychological function in HIV seropositive intravenous drug abusers in a methadone maintenance program. Abstracts IV International Conference on AIDS, 1988, Book 2, p. 399.
28. PERRY, S. et al. Neuropsychological function in physically asymptomatic, HIV-seropositive men. *J. Neuropsychiat.*, 1:296-302, 1989.

29. PETITO, C.K. et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with AIDS. *N. Engl. J. Med.*, 312:874-879, 1985.
30. PIZZO, P. et al. Effect of continuous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N. Engl. J. Med.*, 219:889-896, 1988.
31. POTASMAN, I. et al. Intrathecal production of antibodies against *Toxoplasma gondii* in patients with toxoplasmic encephalitis and the acquired immunodeficiency syndrome (AIDS). *Ann. Int. Med.*, 108:49-51, 1988.
32. PRICE, R.W. et al. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science*, 239:586-592, 1988
33. PRICE, R.W. et al. The AIDS dementia complex: some current questions. *Ann. Neurol.*, 23 (Suppl):527-533, 1988.
34. REINVANG, I. et al. Neuropsychological findings in relation to immunological parameters in HIV-positive individuals. Abstracts IV Conference on AIDS, Book 1, p.390.
35. RESNICK, L. et al. Early penetration of the blood-brain barrier by HIV. *Neurology*, 38:9-14, 1988.
36. RIEDEL, R.R. et al. Psychometric evaluation shows reduced vigilance and verbal memory of HIV-positive hemophiliacs. Abstracts IV Conference on AIDS, Book 2, p. 404, 1988.
37. SCHMITT, F.A. et al. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N. Engl. J. Med.*, 319:1573-1578, 1988.
38. SELNES, O.A. et al. HIV-1 infection: no evidence of cognitive decline during the asymptomatic stages. *Neurology*, 40:204-208, 1990.
39. SNIDER, W. D. et al. Neurological complications of AIDS: analysis of 50 patients. *Ann. Neurol.*, 14:403-418, 1983.
40. THOMAS, C.S. et al. HTLV-III and psychiatric disturbance, *Lancet*, 2:395, 1985.
41. TROSS, S. et al. Psychological and social impact of AIDS spectrum disorders. Abstracts II International Conference on AIDS, 1986, p. 157.
42. TROSS, S. et al. Neuropsychological characterization of the AIDS dementia complex: a preliminary report. *AIDS*, 2:81-88, 1988.
43. VOGEL-SCIBILIA, J.E. et al. HIV infection presenting as psychosis: a critique. *Acta Psychiatr. Scand.*, 78:652-656, 1988.

Annex 6

44. WILKIE, R.L. et al. Cognition in early HIV infection. Arch. Neurol., in press.
45. WORLD HEALTH ORGANIZATION. Report of the Consultation on the neuropsychiatric aspects of HIV infection. Geneva, 14-17 March 1988.

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