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Neuropsychiatric Manifestations of HIV Infection and AIDS

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1. Introduction

Acquired Immune Deficiency Syndrome (AIDS) was first reported in the United States in 1981 and has since become a major worldwide epidemic. AIDS is caused by the human immunodeficiency virus (HIV). By killing or damaging cells of the body's immune system, HIV progressively destroys the body's ability to fight infections and certain cancers. The term AIDS applies to the most advanced stages of HIV infection.

Statistics on the world epidemic of HIV/AIDS indicates that 39.5 million people are living with HIV/AIDS worldwide. Of these, 24.7 million (63%) live in Sub-Saharan Africa, a region that is home to just 10% of the world's population (UNAIDS/WHO report, 2006).

HIV is a retrovirus, which is immunosuppressive, predisposing the individual to opportunistic infections and certain neoplasm (Wiley, 1994). In addition to impairment in immune functions, evidence has suggested that HIV is neurotropic. It should therefore be anticipated that neuropsychiatric complication might be common in HIV positive individuals during all phases of HIV related illness.

Over the years, researchers have developed antiretroviral drugs to fight both HIV infection and its associated infections and cancers. Currently available drugs do not cure people with HIV infection or AIDS, and they all have side effects that can be severe. Because no vaccine for HIV is available, the only way to prevent infection is to avoid behaviours that put a person at risk of infection, such as sharing needles and unprotected sex.

It is believed that neuropsychiatric disorders account for over 15% of the world's disease burden. Due to the recent advances in antiretroviral therapy, the life expectancy of people living with HIV has increased, and thus clinicians are more likely to encounter the neuropsychiatric manifestations of the disease. In as many as 20% of HIV infected individuals, neurologic or neuropsychiatric symptoms may be the presenting features, prior to other medical symptoms of AIDS. Despite improvement in and combination of antiretroviral therapy, neuropsychiatric complications still occur in as many as 50% of people living with HIV and are mostly undiagnosed and untreated. Assessment and management of mental disorders is integral to an effective HIV/AIDS intervention program. Mental health professionals will increasingly be called upon to assist in the management of people living with HIV/AIDS. Thus psychiatrists will need to be familiar with disorders that are prevalent in HIV infection. It is now estimated that 40-70% of patients with AIDS develop clinical neurologic abnormalities. The most common neurologic manifestations are minor cognitive motor disorder (MCMD) and HIV-associated dementia (HAD). On the other hand, depression is the most common psychiatric condition in people living with

HIV/AIDS with estimated life time prevalence in the range of between 21% and 61% (Elliot et al, 1998). This category of psychiatric disorders presents diagnostic challenges because of the many neurovegetative confounding factors that are present in association with HIV illness. In both cases, the impact of these syndromes on seropositive patients is significant and appropriate intervention is required, the key to optimal treatment resting with early diagnosis and aggressive treatment.

Initially, the neuropsychiatric manifestations of HIV/AIDS were attributed to psychological reactions to a systemic illness, the effects of psychosocial stressors associated with the disease, or the consequences of opportunistic infections or neoplasms within the central nervous system (CNS). It is now recognized that the psychiatric sequelae of HIV infection and AIDS are numerous and have etiologies that involve neurobiological and psychosocial factors. These include the direct or primary effects of HIV on nervous tissue, the consequences of secondary viral and nonviral opportunistic infections, tumors, cerebrovascular disease, and the complications of systemic therapies for AIDS and associated disorders.

Some previous studies have indicated that Neuropsychiatric disorders in people living with HIV/AIDS are associated with disease progression, poor adherence to antiretroviral drugs, increased incidence of high risk sexual behavior with the potential for further HIV transmission, and deterioration in their quality of life.

Mental and neurological disorders have an intertwined relationship with HIV and AIDS, yet sadly are often overlooked when HIV interventions are planned and implemented. Several important aspects of HIV care and treatment place psychiatrists at the forefront of this epidemic, these include:

- psychiatric disorders (including substance use) can increase an individual's risk of acquiring sexually transmitted diseases, including HIV;
- pre-existing mental disorders (including substance use) can predate and/or complicate HIV-related illness;
- neuropsychiatric complications and psychiatric illness can affect adherence to antiretroviral therapy regimens;
- new antiretroviral treatments and combination therapies can affect the CNS and/or contribute to the development of psychiatric side effects/symptoms;
- individuals with waning immunity and high viral loads may be at particular risk for the HIV-related CNS complications that can cause acute mental status changes;
- the proportion of mental health and/or substance abuse disorders among people living with HIV/AIDS is nearly 5 times greater than the proportion found in the general population;
- persons living with a severe mental illness are disproportionately vulnerable (as high as 23%) to infection with HIV and other sexually transmitted diseases;
- psychiatric syndromes can be especially challenging to recognize and accurately diagnose in the medically ill; and
- as HIV/AIDS becomes increasingly a chronic disorder with the improvement of treatments and longer survival times, the need for comprehensive psychiatric care and services is expected to rise.

2. Biology and pathophysiology of HIV infection

HIV is a lentivirus, a subgroup of retroviruses. As with other retroviruses, HIV has rapid rate of genetic mutation. This family of viruses is known for latency, persistent viremia,

infection of the nervous system and weakening of the host immune responses. HIV-1 is the form of the virus that causes disease in most part of the world. HIV-2 discovered in 1986, causes a relatively small proportion of cases clustered in West Africa. HIV has high affinity for CD4 T lymphocytes and monocytes. When HIV binds to CD4 cells, it becomes internalized. The virus replicates itself by generating a DNA copy using reverse transcriptase enzyme. Viral DNA becomes incorporated into the host DNA, enabling further replication (Green, 1991, Stebbing et al, 2004). HIV causes the lysis of CD4 lymphocytes. These cells are critical in cell-mediated immunity. The course of HIV infection is characterized by latency. Unfortunately, profound immune deficiency eventually develops, as CD4 cell count drops below 200 cells per mm³. At this point, the patient becomes vulnerable to opportunistic infections and malignancies (Centers for Disease Control, 1982). Progression from HIV to AIDS occurs at a median of 11 years after infection. In the recent past, most patients would not survive more than 1 to 2 years after diagnosis of AIDS. However, since the introduction of antiretroviral drugs and prophylaxis against opportunistic pathogens, death rates from AIDS have begun to decline significantly.

3. Treatment of HIV infection

Treatment is accomplished through numerous combinations of antiretroviral agents belonging to the following groups: Nucleoside analogue reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors and nucleoside analogues. In the mid-1990s, several investigators studied combination therapies of two reverse transcriptase inhibitors and a protease inhibitor. This therapy was later referred to as Highly Active Antiretroviral Therapy (HAART). HAART dramatically reduced viral load and often resulted in an increase in CD4 cell count. The current goal of treatment is to reduce viral load to undetectable levels and maintain such remission without interruption. Evidence suggests that the therapies suppress replication but do not eradicate HIV from all parts of the body, particularly lymphoid tissue and the brain. Not all patients who initiate antiretroviral therapy respond. The lack of clinical response is likely explained by problems with adherence, suboptimal antiretroviral treatment potency, and genetic mutation of HIV strains (Descamps et al, 2000). Many patients experience substantial side effects, and it is not uncommon for changes to be made in antiretroviral regimens because of such side effects. Adverse effects include lipodystrophy, hyperlipidemia, nephrotoxicity, bone marrow suppression, neuropathy and elevation of blood glucose to possibly diabetes mellitus levels (Deeks et al, 1997). Patients often experience nausea, vomiting, diarrhea, sleep disturbances and rashes.

Adherence is of utmost concern with antiretroviral treatment because even minor deviations from the prescribed regimen can result in viral resistance and permanent loss of efficacy for existing medications (Practice guidelines for HIV treatment, 2000). Studies of antiretroviral treatment continue to indicate that a near-perfect adherence is needed to adequately repress viral replication (Demasi et al, 2001).

As the world HIV epidemic spreads increasingly among disadvantaged persons with limited resources who have multiple comorbid disorders, significantly more psychosocial stressors, and less access to ongoing primary or mental health care, these individuals are at risk of not receiving the recommended treatment for HIV infection. Services for HIV patients must balance medical interventions with the emotional, economic, and social supports required for good quality of life and prevention of further transmission (Practice guidelines for HIV treatment, 2000).

4. Etiology of the neuropsychiatric manifestations of HIV/AIDS

4.1 Impact of HIV on the Central Nervous System (CNS)

Clinical evidence for direct infection of the CNS by HIV emerged in the mid- 1980s, when patients began to survive their presenting opportunistic infections but went on to develop neuropsychiatric syndromes that could not be attributed to CNS opportunistic infections and neoplasm. Additional evidence included signs of neuro-cognitive impairment in adults, loss or arrest of developmental milestones in children, ability to culture HIV from the cerebrospinal fluid, neuropathological lesions of the brain at autopsy, and abnormalities observed through brain imaging techniques, including cerebral atrophy (Deeks et al, 1997).

HIV invades the CNS early in the course of infection entering by way of macrophages, which along with microglial cells are largely responsible for HIV replication within the CNS. While HIV does not infect neurons in the CNS, it causes neuronal death by causing the elaboration of neurotoxins which in turn induce a variety of inflammatory factors that cause apoptosis, or programmed cell death of neurons (Swindells et al, 1999).

The pathogenesis of HIV infection within the brain and its relationship to neurologic and psychiatric complications remains obscure, but there is evidence that cellular and molecular components of the immune system are involved (Bloom & Rausch, 1997).

Several different mechanisms may explain the effects of HIV on the CNS. Researchers have hypothesized that pathogenesis begins with viral penetration of the CNS and associated loss of integrity of the blood-brain barrier. This may allow cellular and non-cellular inflammatory components of the immune system to enter the CNS, resulting in damage to neurons and non-neuronal support cells (Rabkin & Ferrando, 1997).

Some studies have examined viral load and CD4 cell counts, measures typically used to monitor immunologic function in patients with HIV infection, as potential markers of CNS injury and vulnerability to CNS complications. A study that followed viral loads and CD4 cell counts in a large cohort of HIV-infected men without AIDS found that relatively high plasma HIV RNA (> 3000 copies/ml) and low CD4 T-lymphocyte counts (< 500 x 10⁶ cells/l) were predictive of both dementia and neuropathy (Childs et al., 1999). The authors suggested that effective suppression of HIV may reduce the risk of developing these neurological complications.

Based on evidence of basal ganglia dysfunction in HIV-associated dementia (Berger & Nath, 1997), some researchers proposed that microvascular abnormalities would be found in the basal ganglia of patients with this condition (Berger, 2000). Using time-course magnetic resonance imaging, these investigators observed increased enhancement, both immediate and late, in the basal ganglia of individuals with HIV infection and moderate-to-severe dementia, relative to HIV patients without dementia. These data suggested that increases in regional cerebral blood volume and disruption of the blood-brain barrier have an etiologic role in the development of HIV-associated dementia.

Most HIV DNA in the brain has been found in macrophages/microglia, often near apoptotic neurons, suggesting that cytokines produced by the infected cells might contribute to neuronal destruction (Shapshak et al., 1995). Macrophages may infiltrate the CNS by interacting with the endothelial cells that form the blood-brain barrier, causing endothelial cell damage and disrupting the barrier (Nottet, 1999). Chemokines (cytokines that act as macrophage attractants) and their receptors on neurons and glial cells appear to play a central role in HIV entry into the CNS and eventual cellular destruction (Gabuzda & Wang, 2000; Zheng, 1999). Synaptic damage, without neuronal loss, has been observed in patients with mild HIV-

associated cognitive disorders. Using synaptic density as an indicator of damage in post-mortem brain samples from HIV-infected patients, Everall and colleagues found that reduced synaptic density correlated significantly with ante-mortem neuropsychological functioning, and stressed that early diagnosis and treatment could potentially reverse synaptic damage and prevent cognitive decline (Everall et al., 1999). Loss of subcortical neurons in the brain of people infected with HIV may be associated with the experience of depression.

Evidence is accumulating to suggest roles for several HIV proteins, including glycoprotein 120 (gp120), HIV-1 negative factor (Nef), and transactivating protein (Tat), in HIV-induced neuropathogenesis. For example, the viral envelope protein gp120 appears to bind to rat dorsal root ganglia and human neuroblastoma cells (Apostolski et al., 1993), and in rats exposure to gp120 has been shown to cause swelling and increase tumor necrosis factor in the sciatic nerve trunk, induce astrocyte and microglial infiltration into the spinal cord, and cause neuropathic pain behaviours (Herzberg & Sagen, 2001). *In vitro*, studies have shown that Nef induces macrophage chemotaxis (Koedel et al., 1999) and acts as a potent neurotoxin (Trillo-Pazos et al., 2000). Astrocytes treated with Tat *in vitro* produced pro-inflammatory cytokines and chemokines that may contribute to neuronal injury (Galey et al., 2001). Tat also stimulates macrophage production of metalloproteinases, enzymes that are expressed at increased levels in certain neurologic diseases and in the brain tissues of patients with AIDS (Johnston et al. 2000). Although the significance of these laboratory findings for patients with HIV or AIDS remains to be clarified, it is probable that many of these mechanisms combine to produce the neurologic and psychiatric changes seen with HIV infection and AIDS. Identifying and characterizing the mechanisms involved may open new avenues for prevention and treatment.

4.2 Psychosocial factors

The psychosocial stress associated with a socially stigmatizing terminal illness and frequent infections carries with it tremendous emotional upheaval in vulnerable individuals. There is usually a sense of loss of health, financial security, independence and relationships in HIV infected persons. This is made worse when relevant social support is missing (Katalan et al, 1989).

Specific crisis points and psychosocial factors can precipitate psychiatric disorders especially anxiety and depression in HIV-infected persons. These crisis points includes- learning of HIV positive status, disclosure of HIV status to family and friends, introduction of medication, occurrence of any physical illness, recognition of new symptoms/ progression of disease, necessity for hospitalization, death of a partner, diagnosis of AIDS, changes in major aspects of lifestyle, necessity for making end of life and permanency decisions (HIV clinical guidelines, 2000).

5. Neurologic manifestations of HIV

HIV is classified among the lentiviruses, a family of viruses characterized in part by their tendency to cause chronic neurologic disease in their animal hosts. It is not surprising, then, that neurologic complications of HIV infection are common and not confined to opportunistic infections. All levels of the neuraxis can be involved, including the brain, meninges, spinal cord, nerve, and muscle. Neurologic disease is the first manifestation of symptomatic HIV infection in roughly 10-20% of persons, while about 60% of patients with advanced HIV disease will have clinically evident neurologic dysfunction during the course

of their illness (Koppel et al., 1985). The incidence of subclinical neurologic disease is even higher: autopsy studies of patients with advanced HIV disease have demonstrated pathologic abnormalities of the nervous system in 75-90% of cases (De la Monte et al., 1987). HIV has been cultured from brain, nerve, and cerebrospinal fluid (CSF) from persons at all stages of the disease, including those without neurologic signs or symptoms. Positive HIV cultures in CSF do not predict the presence or development of neurologic signs or symptoms later on. The development of neurologic manifestations of AIDS depends on a number of factors, such as antiretroviral treatment history, degree of immunosuppression, and the molecular biology of the viral strain, particularly its neurovirulence (McGuire & Greene, 1996). Host factors, including genetic makeup, undoubtedly play a role in selective vulnerability to neurologic manifestations.

The initial infection of the nervous system by HIV is usually asymptomatic, although acute aseptic meningitis, encephalitis, and inflammatory polyneuropathy have all occurred in this setting. Despite its potential to cause disease at all levels of the nervous system, HIV does not directly infect central or peripheral neurons, astrocytes, or oligodendroglial cells. Latent or low level HIV infection in the CNS is maintained by virus-infected cells of the monocyte/macrophage lineage. "Indirect effects" of macrophage activation--such as dysregulation of cytokines and chemokines, free-radical (oxidative stress) injury, and secretion of soluble factors that are potently neurotoxic, have been implicated as effectors of nervous system injury in HIV.

5.1 Minor cognitive impairment

Despite evidence of early infection of the CNS, symptoms of cognitive impairment typically occur late in symptomatic HIV disease, usually in the setting of severe immunosuppression (Miller et al., 1990).

Cognitive impairment has long been recognized as part of manifestation of human immune deficiency virus infection. These changes include loss of cognitive flexibility, difficulty in problem solving, mental slowness and difficulty in concentration. There are also difficulties in memory which manifest as delayed recall. Despite the wide spread use of highly active antiretroviral therapy (HAART), at least in developed nations and some developing nations, cognitive impairment and other neurological complications of HIV infection persist with devastating personal and socioeconomic consequences. Even though neurons are rarely infected by human immunodeficiency virus especially at early stage of the infection, neuronal loss is quite common in patient with HIV infection.

Although as many as 40% of patients with HIV/AIDS will have some form of cognitive impairment even before the development of full dementia, only a small percentage (5-10%) may go on to develop dementia itself. Various type of cognitive impairment in HIV infection has been documented and the American academy of Neurology (AAN) published a diagnostic criteria for HIV associated dementia (HAD) and minor cognitive motor disorder (MCMD); which include motor, affective and behavioural abnormalities, consistent with the early description of AIDS dementia complex.

5.2 AIDS Dementia Complex (ADC)

Some investigators hold that increased HIV proliferation in the brain is necessary for the development of ADC. Others propose that a macrophage-initiated cascade of events can lead to brain dysfunction and clinical dementia, even in the absence of high viral load in the

brain. Activated macrophages, whether infected with HIV or not, are capable of secreting potent neurotoxins, inducing pro-inflammatory cytokines, and generating oxygen free radicals that can damage cells and lead to neuronal dysfunction or death (Glass et al., 1995). A particular subtype of monocyte/macrophages derived from the peripheral blood was found to be greatly increased among patients with AIDS dementia compared with both HIV infected and uninfected controls. Soluble factors from these macrophages were found to be highly neurotoxic--that is, they killed human brain cells in culture (Pulliam et al., 1997).

Although the incidence of nearly all nervous system opportunistic infections has declined dramatically in the era of potent antiretroviral therapy, the impact on the incidence and prevalence of HIV-associated cognitive impairment including frank ADC--has been low. The prevalence of ADC in HIV-infected individuals with higher CD4 counts (200-350 cells/ μ L) actually appears to have increased since 1996. Pathologically, the prevalence of HIV-associated brain disease, or encephalopathy, is rising despite suppressive antiretroviral therapy (Neuenburg et al., 2002). Poor penetration of the blood-brain barrier by many of the antiretroviral drugs, particularly the protease inhibitors, has been suggested as a reason for the persistence of ADC.

There is some evidence that, despite the poor CNS penetration of most antiretrovirals, effective antiretroviral therapy may attenuate the neurotoxicity of circulating monocytes/macrophages. Among individuals with ADC receiving effective antiretroviral regimens, macrophage-derived soluble factors were found to be less neurotoxic than observed prior to the availability of combination antiretroviral therapy (Pulliam et al., 1997).

The major difference between "HIV associated dementia complex" and "HIV associated minor cognitive/ motor disorder" is the severity of impairment in activities of daily living. That is, by definition, dementia must have cognitive impairment severe enough to interfere with occupational or social functioning. In "HIV associated minor cognitive/motor disorder," activities of daily living are generally intact with the possible exception of mild difficulties in the most demanding activities.

The initial features of HIV associated dementia include an overall slowing in cognition (i.e., bradyphrenia) and movement (i.e., bradykinesia) as well as difficulties in motor dexterity and coordination, forgetfulness, poor concentration, and marked apathy. Although dysphoric mood is not a common feature, the pronounced slowing and apathy may appear as if the patient is depressed. Furthermore, assessing other aspects of depression (e.g., weight loss, cognitive disturbance and insomnia) is difficult for patients with this disorder due to shared symptomatology that may be indistinguishable from the psychiatric symptoms.

Later in the course of HIV associated dementia, the patient may exhibit myoclonus, bowel and bladder incontinence, and, eventually, mutism and a vegetative state. Once these advanced features are present, death is typically imminent.

Because the above initial symptoms are similar to those seen in other patient groups with subcortical impairment (e.g., Parkinson's disease, progressive supranuclear palsy, multiple sclerosis) and because of the neuroimaging findings of subcortical neuropathology, HIV associated dementia was originally described as a subcortical dementia. However, in light of the more recent findings of cortical atrophy and higher cortical function deficits in AIDS patients, this characterization may not fully describe the spectrum of neuropsychiatric deficits associated with HIV infection and AIDS.

Antiretroviral therapy may be helpful in treating Minor Cognitive /Motor Disorder and HIV associated dementia and should be recommended for all patients, unless there are contraindications. The ability of particular antiretroviral drugs to penetrate the blood-brain barrier may be less important to treatment success than the overall potency of the regimen and the ability of the patient to adhere to it.

Studies from the 1980s showed that zidovudine monotherapy was beneficial in patients with HAD, so some clinicians include it in the ART regimen for anyone with neurocognitive impairment. Others suggest using at least 2 drugs that cross the blood-brain barrier (eg, zidovudine, stavudine, abacavir, lamivudine, and nevirapine). Efavirenz, didanosine, and lamivudine cross to a lesser degree. As a class, protease inhibitors (PIs) have poor blood-brain barrier penetration. Nevertheless, patients have shown neurocognitive improvement while taking PI-containing regimens, perhaps because of indirect effects on HIV activity in the CNS.

When present, depressive symptoms should be treated with low dosages of selective serotonin reuptake inhibitors (SSRIs).

Antipsychotic medications may be useful in treating agitation and hallucinations, but patients with these conditions are often extremely sensitive to anticholinergic adverse effects and extrapyramidal symptoms. Newer neuroleptic or antipsychotic agents, such as olanzapine and risperidone, have lower rates of significant side effects compared with older drugs. The starting dosage of olanzapine is 2.5 mg orally at bedtime; that for risperidone is 0.5-1 mg orally at bedtime. Note that these drugs may interact with antiretroviral medications, especially ritonavir, and can cause weight gain and other metabolic adverse effects. Avoid benzodiazepines, which tend to increase confusion and decrease concentration.

Psychostimulants such as methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) have been used to improve attention, concentration, and psychomotor function. Dosages of methylphenidate start at 5 mg for a test dose, then 2.5-5.0 mg twice daily, increasing by doses of 5 mg every other day until the desired effect is achieved. Usual dosages are in the range of 20-30 mg per day. Monitor blood pressure, heart rate, and symptoms of restlessness, agitation, nausea, and psychosis.

For a patient who is knowledgeable about HIV, a dementia workup or diagnosis often precipitates a crisis, with an increased risk of suicide. Carefully screen for depression and suicidality, and treat these if they develop.

Behavioral management strategies may assist the patient with early manifestations of dementia to continue living with some degree of independence and safety in the home. Memory aids such as posted notes, calendars, alarmed pill-boxes, and other environmental cues may help.

It is critical to enlist the support of family members and significant others at an early stage of the illness. Because the disease is frightening and may be progressive, the patient and members of the support system need assistance in anticipating and planning for the future. Plans for assisted living or other in-home custodial care should be made early. Severe or late dementia causes fear, misunderstanding, and frustration for both the patient and care givers. All involved will require help from visiting nurses, social workers, hospice workers, and physicians. Recommend the preparation of an advance directive for the patient with early manifestations of dementia.

5.3 Overview of clinical neurologic disease

5.3.1 Cerebral symptoms and signs

Apart from dementia, HIV-infected patients are at risk for a wide range of neurologic diseases. Cerebral signs and symptoms are the most common. Global cerebral disease can present with altered mental status or generalized seizures, whereas focal disease often produces hemiparesis, hemisensory loss, visual field cuts, or disturbances in language use. Fungal, viral, and mycobacterial meningoencephalitis are the most common causes of global cerebral dysfunction, and progressive multifocal leukoencephalopathy (PML), primary CNS lymphoma, and toxoplasmosis account for the majority of focal presentations. As the epidemic has progressed, the epidemiology of CNS complications has changed. In general, availability of effective antiretroviral regimens has been associated with a dramatic decline in incidence and severity of opportunistic infections of the CNS. Even before the availability of these regimens, the incidence of CNS toxoplasmosis had declined among patients receiving trimethoprim-sulfamethoxazole prophylaxis against *Pneumocystis*. Unfortunately, antiretroviral regimens have not demonstrably decreased the prevalence of PML, and the incidence among individuals with higher CD4 counts may be increasing. However, the prognosis of this once uniformly fatal disease has improved dramatically, with long-term remissions now fairly common among patients receiving antiretroviral therapy (Berger et al., 1998).

5.3.2 Syndromes affecting cord, nerve roots, and muscle

Viral and, rarely, fungal and parasitic opportunistic infections can affect the spinal cord. Systemic lymphoma can infiltrate nerve roots and meninges, occasionally causing a mass lesion within the cord. In addition, HIV itself is associated with a spastic paraparesis similar to that seen with vitamin B12 deficiency. Peripheral nerve injury is very common, particularly a painful distal neuropathy seen late in HIV infection. About 35% of hospitalized patients with advanced HIV disease have peripheral neuropathy (Hall et al., 1991).

Although myalgias or muscle pains are a frequent complaint, frank muscle disease is less common. Both inflammatory myopathies and a toxic myopathy secondary to zidovudine have been observed. More recently, a syndrome of acute neuromuscular weakness, often associated with lactic acidosis, has been described in association with several nucleoside analogue reverse transcriptase inhibitors, including zidovudine (AZT), stavudine (d4T), didanosine (ddI), and lamivudine (3TC), either alone or in combination. Any patient on antiretroviral therapy presenting with a "Guillain-Barré-type" picture of ascending neuromuscular weakness should be tested for lactic acidosis and evaluated with electromyography and nerve conduction studies.

Among patients infected with HIV, serious neurologic disease may present with relatively trivial symptoms and signs. Therefore, a high index of suspicion must be maintained to detect disease early in these patients. A careful neurologic examination to attempt anatomic localization is necessary to guide further laboratory and imaging studies. Because multiple neurologic diseases often coexist in patients, close follow-up is needed even if a presumptive diagnosis has been made. A change in clinical condition often necessitates a thorough reevaluation.

5.3.3 Pain

There is growing awareness that pain from a variety of etiologies commonly complicates HIV disease. In general, patients with AIDS have pain comparable in prevalence and intensity to

pain in patients with cancer, with similar mixtures of neuropathic and visceral-somatic etiologies. However, although efforts to improve malignant pain management have benefited many patients with cancer, pain in patients with AIDS is dramatically undertreated.

Aggressive pain treatment can be the single most important and most challenging intervention in the care of patients with HIV disease. In a recent U.S. study, only 15% of ambulatory AIDS patients with severe pain received adequate pain management. The principles of pain assessment and treatment in the patient with HIV/AIDS are not fundamentally different from those in the patient with cancer and should be followed.

These principles are described in the WHO analgesic ladder (WHO clinical guidelines, 1994), a well-validated, stepwise approach to pain management related to pain severity. Therapy ranges from nonopioid analgesics and adjuvants to systemic weak and strong opioids to intraspinal drug delivery for refractory severe pain. Opioids, except in quite high doses, can be ineffective in neuropathic pain; adjuvants (namely, tricyclics, anticonvulsants) are often more successful. Where neuropathic pain is refractory to such therapies, pain management specialists should be consulted.

5.4 Specific neurologic conditions

5.4.1 Neuromuscular disorders

A wide range of peripheral nervous system disorders develop in patients with HIV infection, leading to pain, sensory symptoms, and muscle weakness. Both "primary" HIV associated nerve disorders, and those secondary to opportunistic processes are well described. In addition, certain antiretroviral drugs may cause or exacerbate peripheral neuropathies.

Classification of Neuromuscular Disorders

Four types of neuropathy are important to recognize in clinical practice, either because of their high prevalence or their therapeutic implications, or both. They are:

1. Distal symmetric polyneuropathy (DSPN)
2. Mononeuropathy multiplex
3. Chronic inflammatory demyelinating polyneuropathy
4. Progressive lumbosacral polyradiculopathy

The incidence of neuropathy increases with declining CD4 cell count and advancing systemic HIV disease. Familiar causes of neuropathy, such as nutritional deficiency and diabetes mellitus, account for only a small percentage of the neuropathy in these patients. Toxicity of therapeutic drugs, notably zalcitabine (ddC) is responsible for some cases of neuropathy, or for progression; however, antiretroviral toxicity is probably overdiagnosed as a primary cause of HIV-associated neuropathy.

Proper recognition of the different types of peripheral nerve dysfunction is essential for patient management. Except for the few neuropathies with known causes, most of these disorders are characterized on the basis of clinical features alone. The rate of symptom progression, the degree of weakness relative to sensory loss, and the severity of immunosuppression guide the differential diagnosis. The electrophysiologic features of nerve conduction and electromyographic studies remain the gold standard for diagnosis, and may lead to different therapeutic options.

5.4.2 Myopathy

Symptomatic primary muscle disease is uncommon in patients with HIV infection. A polymyositislike syndrome occurs rarely, with few cases encountered even in large referral

centers. A secondary myopathy attributable to the muscle toxicity of AZT emerged in the latter half of the 1980s with widespread use of the drug. The hallmark of myopathy is diffuse, symmetric weakness of "proximal" muscles, hip or shoulder girdle muscles, with a sparing of sensory and autonomic functions. Difficulty with squatting, rising from a chair, or walking upstairs is often the presenting symptom of myopathy. Some patients have myalgia and muscle tenderness, but these complaints are also common in patients without myopathy. In patients receiving AZT, discontinuation of the drug may result in clinical improvement of myopathy. Muscle pain and serum creatine kinase levels decrease first, followed by a more delayed improvement in strength. Some patients may tolerate rechallenging with lower doses of AZT, although the use of other antiretroviral therapy is probably preferable (Dalakas et al., 1990).

5.4.3 Spinal cord disorders

Clinically significant spinal cord disorders are less common in HIV disease than are peripheral nervous system diseases. The neurologic signs of myelopathy such as increased tone and hyperreflexia in the legs and Babinski signs (extensor plantar responses) may be elicited even in the absence of subjective complaints. In most cases, such asymptomatic signs reflect mild HIV-associated spinal cord disease that may or may not progress. Patients with symptomatic myelopathy usually complain first of clumsy gait and urinary hesitancy. The clinical course is typically one of slow progression, and most patients remain ambulatory. A more fulminant course may be seen with wheelchair dependence within a few months. Upper extremities are affected very late, if at all. Baclofen (10-30 mg three times daily) or tizanidine (4 mg three times daily) may attenuate leg spasticity and reduce leg cramps. Painful dysesthesias may be treated with "neuropathic pain" adjuvants, such as lamotrigine or desipramine.

5.4.4 Intracranial disorders

The CNS disorders in the setting of HIV disease can be divided into four general categories: a) primary infection of the brain by HIV; b) opportunistic infections by parasitic, fungal, viral, and bacterial organisms; c) CNS neoplasms; and d) complications of systemic disorders.

Primary HIV Infection of the Brain: HIV Associated Dementia Complex has already been discussed above.

5.4.5 Intracranial opportunistic infections

CNS toxoplasmosis has been the most common cause of intracerebral mass lesion in HIV-infected patients. Its incidence has declined dramatically among patients receiving PCP prophylaxis, and further declined among patients treated with effective antiretroviral therapy. Earlier reports described frequencies of 3-40%, reflecting the considerable regional variation in exposure to the parasite. CT scan of the brain usually shows multiple ring-enhancing lesions with predilection for cortex and deep gray-matter structures such as the basal ganglia. The cerebellum and brain stem are less commonly involved. Radiologic appearance can vary markedly; single lesions and lesions with diffuse enhancement, as well as nonenhancing lesions can appear.

5.4.6 Aseptic meningitis

Patients with aseptic meningitis often present initially with headache and occasionally with altered mental status or cranial neuropathies. Many patients with this syndrome probably

have primary HIV meningoencephalitis. In investigating symptoms such as headache, altered mental status, and cranial neuropathy, aseptic meningitis must be a diagnosis of exclusion.

5.4.7 Viral encephalitis

Among the opportunistic viral infections of the CNS, the most important are the herpes viruses: herpes simplex types 1 and 2 (HSV-1 and -2), herpes varicella-zoster (VZV), and CMV. Each can cause a meningoencephalitis with mental status changes and focal neurologic findings. Diagnosis is complicated by the low yield of CSF viral cultures in herpesvirus encephalitis in general. In general, the onset of headache, fever, and seizures should, in the absence of other clear etiologies, prompt empiric treatment for herpes simplex encephalitis with acyclovir (10.0 to 12.5 mg/kg intravenously every 8 hours).

5.4.8 Fungal encephalitis

Candida Albicans, which commonly infects the oral mucosa of patients with HIV disease, can cause a meningoencephalitis, usually in the setting of fungemia. Microabscesses are the usual pathologic findings in the brain. Mucormycosis, especially among injection drug users, and aspergillosis have been reported causes of meningoencephalitis in patients with advanced HIV disease.

5.4.9 Systemic neoplasms

Although Kaposi sarcoma (KS) is the most common systemic neoplasm in HIV disease, it rarely spreads to the CNS. Among the systemic cancers, non-Hodgkin lymphoma is the most important cause of neurologic dysfunction in HIV disease and invades the CNS by spreading along the leptomeninges. Common signs and symptoms include cranial nerve palsies and polyradiculopathy and less commonly, myelopathy due to epidural metastasis with spinal cord compression.

5.4.10 Central nervous system lymphoma

Primary CNS lymphoma (PCNSL) is a fairly common cause of cerebral mass lesions in patients with advanced HIV disease. The most common signs and symptoms are confusion, lethargy, and personality changes, usually with focal deficits, such as hemiparesis, hemisensory loss, ataxia, and aphasia. Seizures are less common, but not rare.

5.4.11 Metabolic encephalopathy

Metabolic encephalopathy occurs frequently in patients with advanced HIV disease. Adverse reactions to therapeutic drugs, hypoxia, electrolyte imbalance, and multiorgan failure are common etiologies. Efavirenz can cause a transient encephalopathy for a few weeks after initiation of therapy. In the cachectic patient or in patients with significant liver disease or history of protracted vomiting, Wernicke encephalopathy due to thiamine deficiency should be considered.

5.4.12 Stroke

Cerebral infarction and transient ischaemic attacks are seen infrequently in HIV infected patients, with a reported incidence ranging from 0.5% to 8.0%. Based on a case control

study, this incidence is less than that among age-matched young adults with other terminal illnesses. Among patients with advanced HIV disease, cerebral ischemic disease is more common than hemorrhagic stroke.

6. Psychiatric manifestations of HIV infection

Recognizing the psychiatric manifestations of HIV disease can be complicated by the complex biologic, psychological and social circumstances associated with this illness, and psychiatric symptoms often go unrecognized and untreated (Evans et al., 1999). The significance of these findings is magnified by emerging evidence that certain symptoms, such as depression, may be associated with an increase in mortality rate among HIV-seropositive women and with disease progression in HIV-seropositive men.

The psychiatric sequelae of HIV infection and AIDS are numerous and have etiologies that involve neurobiological and psychosocial factors. These include the natural and expected grief response to being diagnosed with a terminal illness, later reactions to disability and illness, exacerbation of preexisting psychiatric illness, development of new primary psychiatric symptoms and syndromes, and the neuropsychiatric manifestations of HIV associated neurological illness.

It is understandable that individuals who receive notification of positive HIV test results will be emotionally distressed as they adjust to the knowledge of their HIV serostatus. The severity of the acute distress will vary from individual to individual. Whereas some individuals may react with little distress, others may be at increased risk of suicide. Thus, it appears that although individuals are often distraught after receiving positive HIV test results, after an adjustment period lasting weeks to a few months, most will cope well and will show a reduction in anxiety and depressive symptoms. Consequently, it appears that symptoms of depression and anxiety should not be considered "normal" in asymptomatic HIV infection. Rather, significant symptoms should warrant careful clinical evaluation.

6.1 Depressive disorder in patients with HIV/AIDS

Depressive symptoms are the commonest psychiatric complication of chronic medical illnesses (Practice guidelines for HIV treatment, 2000). Studies have shown that the prevalence of depression in people living with HIV/AIDS is 2 to 3 times higher than that in the general population (Bing et al, 2001). Depressive disorder is the most common psychiatric condition in people living with HIV/AIDS with estimated life time prevalence in the range of between 21% and 61% (Elliot et al, 1998). A recent meta-analysis of data from ten studies examining the prevalence of depression among HIV-infected individuals reveal a two-fold increase in rates of depression compared with HIV-negative individuals (Ciesla et al, 2001). The current estimates may represent an underestimation as there is evidence that depression may be under diagnosed in the context of HIV medical care (Steven et al, 2003). Previous research has also shown that depression in patients with HIV/AIDS may be associated with disease progression (Cook et al, 2004), reduced compliance with antiretroviral treatment (Rabkin et al, 2002), and as a result of additional illness burden, lead to a reduction in the quality of life (Sherbourne et al, 2000). Depressed individuals with HIV use significantly more health care and related services (Williams et al, 2005). Despite all of these important evidences, depression remains underrecognized, underdiagnosed and undertreated in medical clinics. Thus, recognizing and treating depression is important

because of its association with poor self-care and worse health outcomes in those with HIV (Paterson et al, 2000).

The relationship between depression and HIV/AIDS may be complex. Firstly, populations at risk for HIV infection have elevated rates of major depression. High rates of major depression have been found in homosexual men (Sittirai et al, 1993) and patients with substance use disorders (Mc Kinon et al, 1996). Secondly, major depression is a risk factor for HIV infection by virtue of its impact on behavior, intensification of substance abuse, exacerbation of self-destructive behaviors, and promotion of poor partner choice in relationships. In this way, depression can be seen as a vector of HIV transmission. Patients with depression have also been shown to be at increased risk for disease progression and mortality. Thirdly, HIV increases the risk of developing major depression through a variety of mechanisms, including direct injury to subcortical areas of the brain, chronic stress, stigma, worsening social isolation, bereavement, debilitation and intense demoralization (Zisook et al, 1998). Although direct evidence for a relationship between worsening HIV disease and the development of depression is limited, there are several studies that support this link, particularly the study based on the Multicenter AIDS Cohort Study showing that there is a two and half fold increase in rates of depression as patients CD4 cell count falls below 200 cells per mm³.

Symptoms of depression include persistent sadness, loss of interest, decreased energy and appetite, low concentration, sleep problems, guilt/worthlessness feelings, psychomotor retardation or agitation, and suicidal ideations. In addition to significant distress, symptoms of depression can also cause other health-related functional and quality of life impairments.

6.2 Mania

Higher rates of mania have also been noted with progression of HIV infection. In early HIV infection, 1%-2% of patients experience manic episodes (Lyketsos & Treisman, 2001), which is only slightly higher than the rate in the general population. However, after the onset of AIDS, 4%-8% of patients appear to experience mania (Lyketsos et al., 1993). This increased frequency of mania around the time of onset of AIDS has been closely associated with cognitive changes or dementia and is thought to be a secondary manic syndrome due to HIV infection of the CNS. In a 17-month chart review, among the 8% of patients with manic episodes, counts of helper/inducer lymphocyte (CD3+/CD4+) cells were significantly higher in those with a history of mood disorder, suggesting that mania may be a direct effect of HIV on the CNS (Lyketsos et al., 1993). In a case-control study of 19 patients with HIV-associated mania and 57 HIV-seropositive controls, AIDS dementia was significantly more common in patients with mania, which suggests a strong association between HIV neuropathology and manic symptoms (Mijch et al., 1999). Sometimes referred to as "AIDS mania," this condition is phenomenologically different from the typical manic syndrome of bipolar disorder in both its symptom profile and severity, and it is often characterized by irritability rather than euphoria.

6.3 Anxiety

Anxiety is common in patients with HIV seropositivity. Individuals with pre-existing disorder may be at increased risk for exacerbation of symptoms, due to the numerous stresses of HIV positivity. Concern over possible progression of HIV disease, the impact of

illness on social status, friends, family and work, as well as existential concerns all may result in significant anxiety.

6.4 Psychosis

Psychosis is a recognized, but relative to the mood disorders, an uncommon psychiatric manifestation of AIDS. Even less commonly, antiretroviral therapy may precipitate psychosis. For example, there have been anecdotal reports of psychosis associated with ganciclovir and efavirenz. Paranoid delusions, and auditory hallucination have been reported most frequently and manic symptoms and catatonia have also been described. Psychosis has been found more frequently in patients with AIDS-related neurocognitive impairments and can be a manifestation of psychiatric conditions such as delirium, affective disorders, or schizophrenia, but it also may occur in the absence of these conditions. Estimates of the prevalence of new-onset psychosis in patients with HIV range from 0.5 to 15% (which is considerably higher than would be expected in the general population).

6.5 Delirium

Delirium is a frequent consequence of the severe medical illnesses or treatment that occurs over the course of AIDS. Behavioural manifestations include agitation, psychosis, aggressive behaviour, mutism and marked withdrawal. The delirium in AIDS is usually indistinguishable from the delirium resulting from any other serious acute medical illness.

6.6 Substance abuse

Abuse of variety of substances, including alcohol, and other illicit drugs may be common in groups at high risk of HIV infection. Continued abuse of substances may have many adverse consequences, including interference with patients adherence to needed medical treatment, increased risk of behaviour that could result in further transmission of HIV (such as unsafe sex while intoxicated, sharing needles etc.), as well as morbidity related directly to the use of the substance. It is therefore necessary to do a careful assessment for an existing substance use disorder in HIV positive patients.

6.7 Suicide

Several epidemiological studies suggest that AIDS patients are at increased risk of death by suicide. The relative prevalence is estimated to range from 7 to 36 times the rate in demographically similar control populations. Other studies, however, have not found patients with AIDS to have higher suicidal ideation, especially when comparing persons with AIDS to other medically or neuropsychiatrically ill patients.

HIV infection may exacerbate psychiatric conditions, including major depression, bipolar disorder, and schizophrenia. One study of patients who had schizophrenia before they were diagnosed with HIV infection found that the patients had more severe depressive episodes and reduced tolerance to psychopharmacologic medications (including benzodiazepines and neuroleptics) after infection than before. Although methodological issues make such studies difficult, more research is needed to understand better the role of HIV infection in worsening pre-existing psychiatric disorders.

Various complications of HIV infection including opportunistic infections of the CNS, tumors, systemic disease, and adverse effects of medications may mimic psychiatric illnesses, producing symptoms that resemble mania, depression, psychosis, or drug

intoxication. In all cases, any underlying medical problem should be addressed. The acute onset of psychiatric symptoms in a patient with no such prior history should prompt a complete neuropsychiatric evaluation, toxicology and laboratory screens, and when appropriate, neuroimaging studies and lumbar puncture to help identify possible causes.

7. Assessment and treatment of psychiatric disorders in people living with HIV/AIDS

A comprehensive history from the patient and/or caregiver is needed. There should be special focus on the history of the current complaint, past psychiatric history, past and present substance abuse history, full medical history and sexual risk history and the patient's adherence to previous treatment regimens. Of equal importance is identification of social support systems.

A mental status examination (MSE) of the patient's level of cognitive (knowledge-related) ability, appearance, emotional mood, and thought patterns at the time of evaluation should be conducted. In the psychotic patient one needs to focus specifically on the behaviour and appearance of the patient. His or her speech and speed of thoughts should be assessed, and mood symptoms, affect, suicidality and neuro-vegetative symptoms evaluated. Perceptual disturbances, thought form, thought content and finally insight and judgment also need to be assessed.

A comprehensive and meticulous physical and neurological examination should be performed to exclude any organic causes for the presenting psychiatric symptoms. One should first examine for signs of delirium and rule out HIV-associated cognitive disorders. Medical diagnoses should first be considered and only after that should a psychiatric diagnosis be entertained.

Differential diagnosis needs to consider the presence of a pre-existing psychiatric illness, use of illicit substances and the presence of cognitive impairment.

Assessment and treatment of psychotic disorders in people living with HIV/AIDS (PLWHA) can be very challenging. A useful delineation may be to divide psychosis in the PLWHA into: (i) psychiatric disorders predating HIV infection; (ii) new-onset psychotic disorders; and (iii) disorders associated with medical conditions (delirium) or substance intoxication or withdrawal, and those that are likely to be complications of treatment (i.e. antiretrovirals or antituberculosis drugs). A good history, mental state and physical examination is usually important in making this delineation. Laboratory investigations are crucial in the assessment of delirium and substance intoxication.

The choice of antipsychotic drugs depends largely on the patient, presenting symptoms, past response, potential side-effect profile, possible drug interactions, cost, and pill burden of the chronically ill patient. Many patients with new-onset psychosis or psychosis associated with various medical conditions may only require short-term treatment with antipsychotic medication. However, some patients may require long-term maintenance treatment with antipsychotic agents, and here special attention must be paid to the following factors. The typical antipsychotics are commonly used in resource-constrained settings. Here low doses of haloperidol or chlorpromazine can be used. Vigilance is required with regard to extrapyramidal side effects. Newer atypical antipsychotics such as Risperidone or Olanzapine are now widely used in the treatment of psychotic disorders in HIV/AIDS. They have lower propensity to cause extrapyramidal side effects.

The impact of depression on the course of HIV has initiated the application of specific psychosocial and pharmacologic treatments targeting individuals with HIV and comorbid depression. Pharmacotherapy is the mainstay of treatment of moderate to severe depression. Several studies have demonstrated efficacy of various antidepressant agents in HIV patients, but no single antidepressant has been found superior in treating HIV-infected patients as a group (Olatunji et al, 2006).

Aside from how well the pharmacology of the antidepressant matches a patient's disease, the engine that drives effectiveness is patient adherence. The general rule is to start at low doses of any medication and titrate up to a therapeutic dose slowly, so as to minimize early side effects that may act as obstacles to adherence. Patients who show partial response to antidepressant after adequate dosage and duration should be offered an augmentation strategy. The choice of an antidepressant is largely based on their side effect profile. Some of the antidepressant drugs that are useful in treatment of depression in patients with HIV/AIDS include Amitriptyline, Imipramine, Clomipramine, Fluoxetine, Paroxetine, Sertraline, Fluvoxamine and Venlafaxine (Elliot et al, 1998). The use of psychostimulants such as Methylphenidate and Dextroamphetamine has also been found effective (Wagner et al, 2000).

Some clinicians often wonder about the interaction of antidepressants and HAART. Some interactions may occur but two points deserve emphasis. Firstly, because depression is associated with reduction in adherence to HAART, untreated depression may be equally or more detrimental to disease progression than any medication interaction. Secondly, experience in working with comorbid HIV and depression has not shown clinical significance to antidepressant-HAART interaction.

Psychosocial intervention is an integral part of treatment for depression in patients with HIV/AIDS. A combination of psychosocial intervention and medication was shown to be more effective for patients than either modality alone. Among the individual psychotherapies, interpersonal psychotherapy, cognitive-behavioral psychotherapy and supportive psychotherapy are effective in treatment of depression in patients with HIV/AIDS (Markowitz et al, 1995). A social intervention such as social support group therapy is also effective (Kelly et al, 1993).

Identifying and treating depression in patients with HIV/AIDS could result in substantial improvement in quality of life and potentially increase medication adherence, which would in turn affect illness severity and progression.

Treatment of anxiety disorders in HIV/AIDS also requires a combination of psychosocial intervention and medication. Adequate counseling and relaxation techniques are sufficient to treat mild anxiety associated with the various crisis points in the course of HIV/AIDS. For the more severe anxiety disorders, antidepressants and cognitive behavioural techniques are useful.

Every patient with HIV/AIDS presenting with psychiatric disorder must also be assessed for suicidal risk and cases where risk is high, patients should be hospitalized for detailed evaluation and appropriate treatment.

Substance abuse is a common problem in patients with HIV/AIDS. Physicians should have a high index of suspicion while assessing patients. When present, motivational interviews are important. Patients with severe problems who are motivated should be hospitalized for detoxification and appropriate pharmacological and psychosocial treatment.

8. Neurologic and psychiatric complications of antiretroviral drugs

Much progress has been made in treating HIV infection in the last several years and people infected with HIV are now living longer, healthier lives. What was once considered a progressive, ultimately fatal disease has become, in developed countries, a chronic condition that often can be managed long term.

In large part, this change has resulted from the introduction of protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), and non-nucleoside reverse transcriptase inhibitors (NNRTI) in highly active antiretroviral treatment (HAART) regimen. Now, carefully selected combinations of these agents can bring viral loads below detectable levels, increase CD4 T-lymphocyte counts, and improve immune function.

Investigators have realized that HIV cannot be completely eradicated with the treatments that are currently available and that long-term HAART may have side-effects that are severe or health-complicating enough to require modification or temporary cessation of treatment. Even when the virus is virtually undetectable in the blood, it appears to remain sequestered in host reservoirs that are inaccessible to HAART and may provide a source for viral rebound if therapy is withdrawn. With the treatments currently available, HAART will probably need to continue for the patient's lifetime, and clinicians need a thorough understanding of the health implications associated with long-term HAART, the potential complications of HIV infection even in the absence of overt illness, and the strategies for maintaining treatment adherence and minimizing treatment side-effects.

Unfortunately, complications of HAART and complications of HIV infection, particularly in patients with advanced disease and AIDS, overlap significantly. Among health risks that may be associated with HIV or HAART are neurologic complications (such as myelopathy, neuropathy and neuropathic pain, changes in cognition, and dementia), and psychiatric complications (such as mania, depression, schizophrenia, and substance abuse and dependence). CNS complications in patients with HIV, including psychiatric syndromes, delirium, seizures, and cognitive impairment, may in some cases reflect consequences of treatment with antiretroviral drugs that penetrate the CNS. For example, zidovudine and efavirenz, both considered attractive choices for patients with CNS complications because they have good CNS penetration, are themselves associated with potentially significant neuropsychiatric complications. Peripheral neurologic complications including neuropathic pain, neuropathic weakness, and denervation syndromes have been attributed to various toxic and metabolic factors in association with antiretroviral treatment. In managing neurologic complications, it is important to distinguish, when possible, between symptoms related to the HIV disease process and side-effects of HAART. To make such distinctions, clinicians need to understand which antiretroviral agents may cause neurologic and psychiatric symptoms.

Zidovudine, a nucleoside analogue that inhibits replication of HIV by interfering with viral reverse transcriptase, was the first agent to significantly reduce mortality and opportunistic infections in HIV-infected patients. Zidovudine has been found effective at high doses in slowing the progression of AIDS dementia, and can penetrate the blood-brain barrier. Zidovudine is therefore an attractive choice in HAART regimens targeting dementia and other CNS complications of HIV. However, its CNS penetration may also explain the confusion, agitation, and insomnia in up to 5% of people who took zidovudine for one year. In addition, there are anecdotal reports of psychiatric symptoms, including mania and depression, in patients treated with zidovudine. Several case reports document manic

episodes in association with zidovudine treatment, even in patients with no previous psychiatric history. In some patients, mania was severe enough to necessitate hospitalization. In recent years, fewer problems have been reported, in part because zidovudine is now used in lower doses (approximately of 600 mg/day (or 300 mg twice a day) versus the up to 2000 mg/day doses used in the pre-HAART era.

The mechanisms involved in zidovudine-associated psychiatric effects are unknown. For some patients, dose reduction is beneficial, but for others, discontinuation may be necessary. Discontinuing zidovudine treatment has been shown to rapidly reduce manic symptoms (and symptoms returned upon reintroduction of the drug, suggesting a causal relationship). However, patients have been able to resume zidovudine treatment if they also received treatment for mania.

Other adverse neurologic effects of zidovudine treatment are insomnia, myalgia, and severe headaches. Zidovudine also has been associated with seizures, particularly in cases of overdose, which have on rare occasions been fatal. Because HIV infection is associated with similar neurological problems, it is important to exclude other causes before attributing them to zidovudine treatment. However, the severity of these side-effects suggests the need to closely monitor patients taking this drug.

Neurologic symptoms associated with other NRTI may include headache, malaise, and fatigue; for most patients, these symptoms are not severe enough to discontinue HAART. A more serious side-effect is peripheral neuropathy and may be seen with didanosine, zalcitabine, or stavudine treatment but not with zidovudine treatment. The mechanism is unknown, but in vitro studies have shown that zalcitabine, stavudine, and didanosine but not zidovudine - inhibit nerve growth factor (NGF)-stimulated differentiation of a neuronal cell line.

For patients with peripheral neuropathy, symptomatic treatment with ibuprofen or topical analgesic creams can sometimes be effective. Tricyclic antidepressants have been used to manage pain in patients with HIV-associated peripheral neuropathy. In clinical practice, we have found that Tricyclic antidepressants can be partially effective, but for many patients, the pain of neuropathy can be severe, irreversible, and debilitating. Therefore, patients with HIV who develop neuropathy require careful evaluation to determine the risks and benefits of continuing NRTI treatment. In some cases, decreasing dosage may help, but in others, the contributing drug must be discontinued.

Three NNRTIs - efavirenz, delavirdine, and nevirapine - are currently available for the treatment of HIV infection. They are usually prescribed in combination with NRTI. Clinical trials of delavirdine and nevirapine revealed few adverse events affecting the CNS; therefore, the relatively more substantial CNS side-effects seen in clinical trials of efavirenz were unexpected.

CNS side-effects observed with efavirenz include dizziness, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalization, hallucinations, insomnia, and abnormal or vivid dreams. For most patients, these side-effects resolve within 6-10 weeks of starting treatment, but for some patients, symptoms seem to wax and wane over a long term. For most patients, these disturbances diminished or resolved within 2 months. Neither dose reduction nor dose splitting shortened or reduced the intensity of symptoms.

Psychiatric effects also have been noted with efavirenz, though they occur less frequently than neurologic effects. When efavirenz-associated psychiatric effects occur, they may be serious and may include anxiety, depression, and suicidal ideation.

Clinicians should advise patients of possible CNS effects of efavirenz, and should watch for changes in behavior, cognition, or mood. If side-effects persist or patients find them intolerable, a switch in HAART regimen may be appropriate. Although efavirenz is often a first-line treatment, many patients receive it after experiencing treatment failure on earlier HAART regimens. Therefore, patients who switch to efavirenz and then experience neurologic or psychiatric side-effects may have limited options for future antiretroviral treatment. It is important to carefully consider risks and treatment alternatives for these patients.

The combination of HIV Protease Inhibitor with the older antiretroviral agents brought about substantial decreases in viral loads and opportunistic infections with concomitant increases in CD4 T-cell counts. As a result, HIV-associated morbidity and mortality has declined dramatically in recent years.

Although PI may have neurologic side-effects, they tend to be variable and less prominent than those seen with NRTI or NNRTI. Neurologic symptoms may occur more often with ritonavir or ritonavir/saquinavir combination treatments than with indinavir treatment.

9. Consequences of neuropsychiatric problems in patients with HIV/AIDS

Some previous studies have indicated that Neuropsychiatric disorders in people living with HIV/AIDS are associated with disease progression, poor adherence to antiretroviral drugs, increased incidence of high risk sexual behavior with the potential for further HIV transmission, and deterioration in their quality of life. Thus, the place of psychiatrists in the treatment and care of patients with HIV/AIDS is crucial.

There is a consistently strong evidence from high income countries that adherence to Highly Active Antiretroviral Therapy is lowered by depression, cognitive impairment, alcohol use and substance use disorders. A study in Ethiopia showed that depression was associated with less than 95% self reported adherence (Ambebir et al., 2008). Previous research has also shown that depression in patients with HIV/AIDS may be associated with reduced adherence with antiretroviral treatment (Byakika-Tusuiime et al., 2009; Dimatteo et al., 2000; Mugavero et al., 2000; Phyllips et al., 2002; Rabkin & Goetz 2002) and disease progression (Cook 2004; Paterson 2000). They concluded that identifying and treating depression in these patients may improve medication adherence.

In a study of women who were medically eligible to receive Highly Active Antiretroviral Therapy (HAART), its non receipt was associated with substance use. Furthermore, other epidemiological studies indicate that the presence of drug use disorder can complicate the management of HIV illness and compromise adherence to HIV medication and secondary preventive efforts (HIV clinical resource 2009).

HIV-infected subjects in several studies reported "forgetting" as one of the most common reasons for poor adherence to antiretroviral drugs. It is also possible that HIV-associated neurocognitive disturbances, which are common and more prominent as the disease advances, might be responsible for some of the cases of poor medication adherence. Other studies have reported a significantly greater risk of poor adherence to HAART in HIV-infected persons with neurocognitive impairment (Hinkin et al. 2002).

Depression has been associated with immune suppression and other health outcomes in studies of individual with and without chronic disease (; Herbert & Cohen 1993; Rover et al., 1991). Studies have documented association between depression and HIV progression (Lesserman et al., 1997; Lesserman et al, 1999), HIV-related symptoms (Leketsos et al., 1993)

and mortality (Lesserman et al., 1997). Some studies found that HIV-sero-positive gay men who reported depressive symptoms demonstrated immunological changes associated with HIV activity and progression, for example CD4, CD8 cell count proliferate.

Some studies have compared pattern of neuropsychiatric disorder especially the neurocognitive impairment at various level of CD4 cell counts namely 200, 250, 300, 350 and 400 cells /ml and found that there is generally worsening trend of neurocognitive impairment as the CD4 cell count decreases and therefore recommended the serial determination of CD4 cell count in HIV infected patient and screening for neuropsychiatric syndromes in those with CD4 count values of less than 350 cell/ml (Bornstein et al., 1992; Heaton et al., 1995; Miller et al., 1990).

Research has shown that neuropsychiatric disorders in patients with HIV/AIDS complicates help seeking, diagnosis, quality of care provided, treatment and its outcome and adherence (World Health Organization report, 2008). Regardless of aetiology, the co morbidity of mental illness and HIV poses special challenge for HIV care. Individual with these co morbidity face even greater barriers to care than those with HIV alone. Once in care, their treatment is more complex (Francine et al., 2009). Mental and substance use disorders in HIV/AIDS affects help seeking behaviour or uptake of diagnostic and treatment services for HIV and AIDS.

People with alcohol use disorders are more likely than the general population to contract HIV. Similarly, rates of alcohol problems are high among HIV/AIDS patients (Petry, 1999). Lifetime prevalence rates of alcohol use disorders ranging from 29% to 60% have been found among HIV positive populations (Bryant, 1998). This is 2 to 4 times higher than in the general population. Alcohol use is associated with high-risk sexual behaviors and intravenous drug use which are two major modes of HIV transmission.

In persons already infected, the combination of heavy drinking and HIV has been associated with increased medical and psychiatric complications, delays in seeking treatment (Samet et al., 1998), difficulties with HIV medication adherence (Cook et al., 2001; Wagner et al., 2001), and poorer HIV treatment outcomes (Lucas et al., 2002). Decreasing alcohol use in people who have HIV or who are at risk for becoming infected reduces the spread of HIV and the diseases associated with it.

People who abuse alcohol are more likely to engage in behaviors that place them at risk for contracting or transmitting HIV. A history alcohol use has been correlated with a lifetime tendency toward high-risk sexual behaviors, including multiple sex partners, unprotected intercourse, sex with high-risk partners (e.g., injection drug users, prostitutes), and the exchange of sex for money or drugs (Avins et al., 1994; Boscarino et al., 1995; Malow et al., 2001; Windle, 1997). There may be many reasons for this association. For example, alcohol can act directly on the brain to reduce inhibitions and diminish risk perception (Cooper, 2002; Fromme et al., 1999; MacDonald et al., 2000).

Decreasing alcohol use among HIV patients not only reduces the medical and psychiatric consequences associated with alcohol consumption but also decreases other drug use and risky sexual behavior and hence reduces HIV transmission (Lucas et al., 2002). Thus, alcohol and other drug abuse treatment can be considered primary HIV prevention as well (Metzger et al., 1998).

With improved treatments and longer survival times for persons with HIV infection, the maintenance and improvement of their functioning and well-being (collectively referred to as "health-related quality of life") have become major goals of treatment. The World Health

Organization (WHO) defined quality of life (QOL) as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment (WHOQOL Group, 1995).

We know from studies of patients and general populations that mood disorders, particularly depression, have a substantial negative impact on a person's health-related quality of life (Jia et al, 2004). In fact, for most domains of functioning and well-being, depression is more debilitating than most medical conditions (Sherbourne et al, 2000). In a study conducted by Sherbourne et al (2000) to assess the impact of psychiatric conditions on health related quality of life, they recruited a national probability sample of persons with HIV, receiving medical care in the United States. Subjects were screened for psychiatric conditions and their health-related quality of life was assessed. They found that 36% of subjects screened positive for a current depressive disorder and 26% for dysthymia. Subjects with a probable diagnosis of any mood disorder had significantly worse functioning and well-being than those without a mood disorder diagnosis on all health-related quality of life measures, including the physical and mental health composites. These findings substantiate the considerable additional illness burden associated with mood disorders in HIV infected people.

This chapter is intended to help create awareness about mental health problems and its consequences in patients with HIV/AIDS, so as to facilitate routine screening of mental disorders and mental health integration in the comprehensive care of people living with HIV/AIDS.

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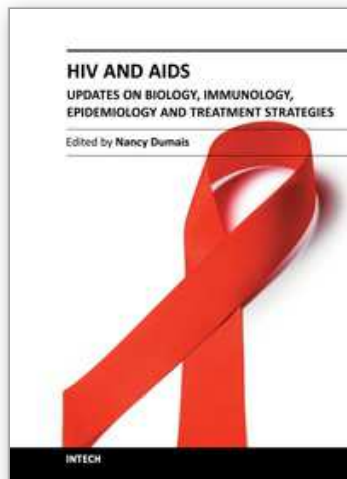
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The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, “From the laboratory to the clinic,” and the second part, “From the clinic to the patients,” represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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