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Chapter 8

Neurological Manifestations of HIV-1 Infection and Markers for HIV Progression

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Additional information is available at the end of the chapter

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1. Introduction

Human immunodeficiency virus, or HIV, is the virus that causes acquired immune deficiency syndrome (AIDS). The acquired immunodeficiency syndrome (AIDS) was first described in 1981 in USA. In 1983, human immunodeficiency virus type-1 (HIV-1) was isolated, and in the following year it was demonstrated clearly that it was the causative agent of AIDS. The disease is a major health problem in many parts of the world. The high prevalence and striking diversity of neurological disorders complicating AIDS were recognized in 1983 (Snider et al., 1983). AIDS was associated with distinct neurological syndromes, such as dementia, myelopathy and painful neuropathy that appeared to result from the HIV itself. Over the last 30 years, there has been increasing recognition of the role that auto antibodies play in neurological disorders. During the past decade, AIDS has become a global health problem with 182,000 000 cases reported from 152 countries. It is estimated that nearly five to ten million people are infected worldwide with HIV-1. With a mean incubation period from time of infection to the development of AIDS of eight to 10 years, it is projected that nearly all HIV-1-infected individual will develop AIDS within the next 15 years (Quinn, 1990). It has become increasingly evident that the vast majority of HIV-1 infected people will eventually develop AIDS or an AIDS-related condition (De Wolf and Lange, 1991) with a median time of progression to AIDS of 7-10 years from infection in adults (Lui *et al*., 1988; Bacchetti and Moss, 1989) and shorter periods in infants and elderly patients (Medley et al., 1987; Auger et al., 1988; Lagakos & DeGruttola, 1989). In the United States alone, 104, 210 cases of AIDS and more than 61,000 deaths have been reported. Sexual, parenteral as well as perinatal transmission routes have remained the major modes of transmission, although the proportion of cases within each risk behaviour category has changed. Recently, there has been a dramatic increase in the proportion of AIDS patients who have acknowledged as IV drug user or have heterosexual contact with other individuals at high risk for HIV infection (Quinn, 1990).

In Sub-Saharan Africa, 22.5 million people living with HIV (68% of the global infections) and 1.6 million AIDS death in 2007 (76% of the AIDS deaths worldwide). In recent years, global efforts have increased substantially. The most encouraging improvements have been in Sub-Saharan Africa where the number of people being treated with anti-retrovirals has increased tenfold from 2003 to 2006 (Peters et al., 2008). The decline of HIV infection in some regions was partially offset by a rise in new infections in other parts of the globe, particularly in Asia and Eastern Europe (Delpech & Gahagan, 2009). It was estimated that over 5 million people in South Asia living with HIV/AIDS. Almost 90% of those infected live in India. Other countries in the region such as Bangladesh, Pakistan and Nepal have a low HIV prevalence in general population (Abeysena & De Silva, 2005).

2. Back ground of immune defence mechanisms

Humoral immunity and complement system: immunity that is mediated by secreted antibodies produced in the cells of the B lymphocyte. Cell mediated immunity : is an immune response that does not involve antibodies but rather involves the activation of macrophages, natural (NK), antigen-specific cytotoxic T-lymphocytes.

2.1. Causes of immunosuppression primary: Antibody deficiency, combined antibody

Antibody deficiency, combined antibody and cellular deficiency, Complement deficiency. Acquired: Extremes of age, Diabetes, Chronic alcoholism, HIV infection, Connective tissue diseases, Organ failure (renal, hepatic), Malignancy, Iatrogenic (chemotherapy, radiotherapy, Transplantation). HIV is a retrovirus that primarily infects vital organs of the human immune system such as CD4+ T cells (a subset of T cells), macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells (Alimonti et al 2003).

2.2. Cells affected

The virus entering through which ever route and acts primarily on the following cells: Lymphoreticular system: CD_4+ T-Helper cells, Macrophages, Monocytes, B-lymphocytes, Certain endothelial cells and Central nervous system: Microglia, Astrocytes, Oligodendrocytes, and Neurones.

2.3. Relation of CD4 T cell count

Neurologic Complications increase with decline in CD_4 T cell count. CD_4 T cell count > 500/μl – Earlystage – Demyelinating Neuropathies, CD_4 T cell count 200 to 500 – Mid stage – Dementia - VZV radiculities and CD_4 T cell count <200 –advance stage → Dementia, Myelopathy, Painful-neuropathy.

2.4. Immune deficiency & clinical disease

Clinical manifestations, Susceptibility to infections, Lymphoreticular malignancies, autoimmune disease.

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3. Neurological menifestations of HIV-1 infections

HIV is neuroinvasive, it does not directly infect neurons. The major brain reservoirs for HIV infection and replication are microglia and macrophages. Astrocytes can be infected but are not a site of active HIV replication. HIV-associated neurologic complications are indirect effects of viral neurotoxins (viral proteins gp120 and tat) and neurotoxins released by infected or activated microglia, macrophages and astrocytes. Neurologic manifestations occur over the entire spectrum of HIV disease. Fifty to 70% of patients experienced acute clinical syndrome 1 to 6 wks after infection, Neuro Manifestations occur in 10% involves Multiple Parts of nervous system. Some Monophonic illness Meningitis, Meningioencephalitis, Seizures, Myelopathy, Cranial and Peripheral Neuropathy linked to primary HIV and recover within 1 week. Neurological opportunistic infections and malignancies predominated in early reports, but it became also clear that AIDS was associated with distinct neurological syndromes, such as Acute/subacute diffuse encephalopathy Progressive dementia, Focal mass lesions, Acute stroke like presentation, Meningitis, Multiple cranial neuropathies and Acute/subacute myelopathy.

3.1. HIV encephalopathy

(AIDS Dementia Complex or HIV associated Dementia) is a late complication of HIV infection and progresses slowly over months seen in pts with CD_{4T} cell Count >350cells/μl. Dementia is a major feature but aphasia, apraxia and afnofia uncommon, motor abnormality like unsteady gait, poor balance, tremor and in late stage develop apathy & lack of initiative – leads to vegetative state mania (table 1). Neuro imaging: MRI & CT demonstrate cerebral atrophy, Basal ganglia calcification in children. CSF: MonoNucleatz cells increase, Protein increase, RNA can be detected and HIV can be cultured. Infective: CMV ventriculoencephalitis, Varicella encephalitis, Herpes encephalitis, Toxoplasma encephalitis (rare).

Stage	0	Normal	Normal Mental Motor function
Stage	0.5	Subclinical or equivocal	Absent or equivocal symptoms No impairment of work Slow ocular extremity movements Snout response present
Stage	I	Mild	Able to perform all balance demanding aspects Functional ,intellectual and motor impairment present
Stage	II	Moderate	Able to perform basic activities but not demanding aspects Requires single prop
Stage	III	Severe	Major intellectual incapacity Motor disability cannot walk unassisted
Stage	IV	End stage	Nearly Vegetative urinary and facial incontinence

Table 1. Clinical staging of HIV Encephalopathy

Treatment:

Combination anti retro viral therapy is beneficial and rapid improvement in cognitive function.

3.2. HIV-associated dementia

The major direct effect of HIV infection on the immune system is the profound and progressive loss of CD4 lymphocytes. This leads to impaired cellular immunity, and a dysregulation of macrophages, with the overproduction of a variety of proinflammatory cytokines and chemokines (Griffin, 1997). HIV can enter the nervous system early after infection, but productive infection is rarely detectable before immunosuppression has developed. Based upon phylogenetic analysis of HIV gp160, the route of central nervous system (CNS) infection appears to primarily involve infected monocytes (Liu et al., 2000) as well as free viral particles and HIV proteins crossing a disrupted blood–brain barrier. The presentation of HIV-D includes cognitive, behavioral, and motor dysfunction, and suggests a predominant subcortical involvement (Navia et al., 1986). In the early stages, memory loss, mental slowing, reading and comprehension difficulties, and apathy are frequent com plaints (Fig. 1) (Mc Arthur et al., 2003).

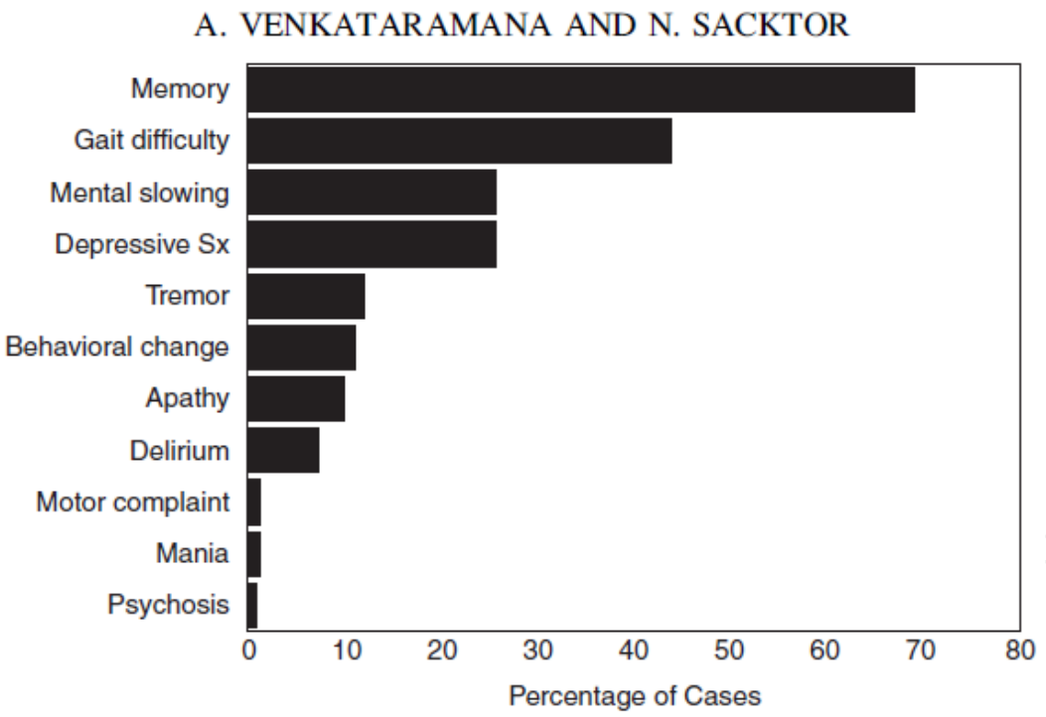

Figure 1. Frequency of symptoms in HIV dementia among 300 subjects personally examined at JHU HIV Neurology program (McArthur et al., 2003).

The cognitive deficits of HIV- D are characterized primarily by (1) memory loss that is selective for impaired retrieval; (2) impaired ability to manipulate acquired knowledge; (3) personality changes including apathy, inertia, and irritability; and (4) general slowing of all thought processes. Gait disturbance and impairment of fine manual dexterity are common early manifestations. Examination findings include impaired rapid movements of eyes and limbs,

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diffuse hyperreflexia, frontal release signs, and sometimes Parkinsonism (Mirsattari et al., 1998). A recent study suggests that antiretroviral drug combinations with drugs that have better CSF penetration are associated with greater CSF viral load suppression and may be associated with greater improvement in neuropsychological test deficits compared to antiretroviral drug combinations with drugs that have poor CSF penetration (Letendre et al., 2004). Antiretroviral drugs with the highest CSF:plasma ratios or with profound effects on viral replication in the periphery with a resulting decrease in virus entry into the CNS (e.g., zidovudine, stavudine, abacavir, nevirapine, efavirenz, and indinavir) are likely to be the most efficacious for the treatment of HIV-D. Affective: Apathy (depression-like features), Irritability, Mania, new onset psychosis. Behavioral: Psychomotor retardation (slowed speech or response time), Personality changes, Social withdrawal. Cognitive: Lack of visuospatial memory (misplacing things), Lack of vasomotor coordination, Difficulty with complex sequencing (difficulty in performing previously learned complex tasks), Impaired concentration and attention-Impaired verbal memory (word-finding ability), Mental slowing. Motor: Unsteady gait, loss of balance, Leg weakness, dropping things, Tremors, poor handwriting and decline in fine motor skills.

3.3. HIV associated neuropathy

Symptomatic neuropathies occur in approximately 10% to 15%. Pathologic evidence of peripheral nerve involvement is present in virtually all end-stage AIDS patients. The most common complaints are numbness, parethesias and painful dysestesias. Zanetti et al., (2004) reported mild distal dysestesia that neither interfered with the activities of daily living nor required specific therapy. The main neurological sign was distal symmetric sensory alteration (in 97.1% of the patients) in the four limbs but mainly in the feet. The etiology and pathogenesis of peripheral neuropathy associated with HIV infection is uncertain. It can be caused by the direct or indirect action of HIV and antibody production, or secondary to infections (CMV, MAC), toxic effects of certain drugs (isoniazid, vincristine, d4T, ddi, ddC), or nutritional deficiencies (vitamin B12) (Rizzuto et al., 1995; Dalakas et al., 1988; Figg, 1991; Browne et al., 1993; Pike, 1993; Abrams et al., 1994; Kieburtz et al., 1991; Norton et al., 1996; Gill et al., 1990; Simpson et al.,1995). Almost all patients with HIV that had diagnosis of peripheral neuropathy were taking drugs probably neurotoxic (ddi, d4t,ddC isoniazid) (Zanetti et al., 2004) to determine the effect of 5 weeks of individualized acupuncture treatment, delivered in a group setting, on pain and symptoms of peripheral neuropathy associated with HIV infection. In addition, the acupuncture regimen reduced pain/aching/burning and pins/needles/numbness in the upper and lower limbs (Phillips et al., 2004).

3.4. HIV related to myelopathy with polyradiculopathy

The most common cause of spinal cord disease in AIDS patients is AIDS-associated myelopathy, with a reported prevalence of 20% to 55% in different series (Gray et al., 1990; Henin et al., 1992; Petito et al., 1985; Goldstick, 1985; Dal et al., 1994; Artigas et al., 1990). Clinical symptoms and signs of myelopathy included spastic paraparesis, gait disturbance, urinary problems, and impotence in males, hyperreflexia, and a variable degree of sensory loss. A

clinical rating of the severity of the myelopathy was established by a neurologist blinded to the MR findings. The myelopathy was rated as mild, moderate, or severe: mild if there were only subjective complaints of leg stiffness, heaviness, cramps, or subjective bladder dysfunction (not incontinence), together with objective findings of increased tone, hyperreflexia, or extensor plantar responses; moderate if there was objectively demonstrable weakness of the lower extremities or incontinence; and severe if the patient was not independently ambulatory. The MR findings of the spinal cord were subsequently correlated with the clinical rating of the severity of the myelopathy. June et al, 1999, reported spinal cord MR features were abnormal in 18 (86%) of the 21 patients (table 2). The most common finding was spinal cord atrophy, seen in 15 patients (71%) (Fig 2).

MR Findings in the Spinal Cord	No. of Patients	Clinical Rating of Severity of Myelopathy, No. (%)		
		Mild	Moderate	Severe
Normal MR findings	3	2 (66.7)	0	1 (33.3)
Cord atrophy	15	3 (20.0)	9 (60.0)	3 (20.0)
Intrinsic cord signal abnormality	6	1 (16.7)	2 (33.3)	3 (50.0)
Atrophy plus cord signal abnormality	3	1 (33.3)	0	2 (66.7)

Table 2. American Journal of Neuroradiology 20:1412-1416 (9 1999)

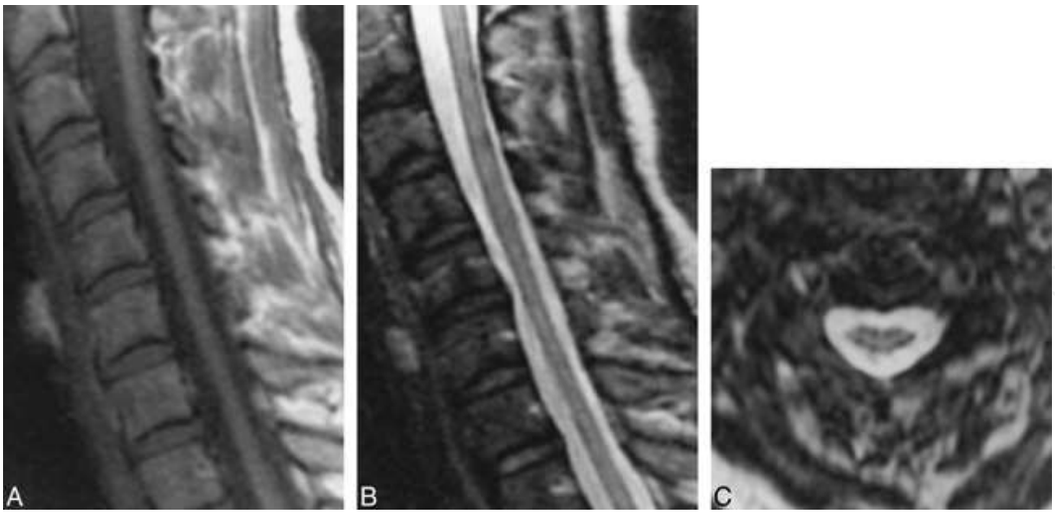

Figure 2. American Journal of Neuroradiology 20:1412-1416 (9 1999)

AIDS-associated myelopathy is characterized pathologically by discrete or coalescent intramyelin and periaxonal vacuolation, with cellular debris and lipid-laden macrophages, in the white matter of the spinal cord. The axons are usually intact, but in severe vacuolization, they may become disrupted. It typically involves the lateral and posterior columns of the cervical

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and thoracic cord (Henin et al., 1992; Petito et al., 1985; Dal et al., 1994; Tan et al., 1995). The effect of HAART on improving the symptoms or slowing the progression of HIV-associated myelopathy is not known. A pilot study using high doses of oral L-methionine led to improvement in clinical and electrophysiologic features of the disease in an open-label clinical trial (Dorfman et al., 1997). Uncontrolled clinical experience no benefit from corticosteroids and intravenous immunoglobulin (IVIG).

3.5. HIV-Associated Neuromuscular Weakness Syndrome (HANWS)

Toxic events secondary to use of HAART can be observed globally. Recently, Simpson et al. 2004, reported a heterogeneous syndrome termed the HIV-associated neuromuscular weakness syndrome (HANWS) which seems to be related to hyperlactatemia and stavudine and/or didanosine exposure. Rapidly ascending neuromuscular weakness syndrome," associated with lactic acidosis syndrome in HIV-infected patients. Majority dramatic motor weakness developed over days to weeks (resembling GBS ▪ respiratory failure and death in several patients. Systemic symptoms included nausea, vomiting, weight loss, abdominal distention, hepatomegaly, and lipoatrophy. Stavudine, Lamivudine and Efavirenz are most commonly used ARV agent. Muscle weakness worsened even after discontinuation of ARV therapy. Rapidly progressive sensorimotor polyneuropathy and myopathy observed. In recent years, a spectrum of metabolic and morphologic alterations has emerged among HIV-infected patients receiving HAART. Additionally, neurological syndromes, such as antiretroviral toxic neuropathy, have been clinically well characterized (Höke & Cornblath, 2004; Keswani et al., 2002). Diagnostic information find out by severe axonal neuropathy, increase Serum lactate level twice times than normal, decrease Serum bicarbonate and arterial pH level, increase serum CPK level. Electrophysiology; EMG-NCV: severe axonal neuropathy in most of the cases, demyelinating features may be seen admixed or in isolation and myopathic features may be noted. Nerve and Muscle Biopsy: Important in evaluating patients with HANWS. Mitochondrial studies with morphology assessment and mitochondrial DNA (mtDNA) quantification may be needed to further elucidate the role of mitochondrial toxicity in this syndrome Treatment: As was observed in this report, the antiretroviral most often associated with HANWS was stavudine. Avoiding stavudine or didanosine, the nucleosides with the highest association with mitochondrial toxicity, may be a satisfactory alternative in the long run. The treatment of HANWS is controversial and important since this is potentially a fatal syndrome. Our experience reinforces the recommendation that early interruption of HAART and clinical support is beneficial. Initiate systemic treatment for lactic acidosis syndrome and supportive treatment for the neurologic component in a monitored setting. Neuromuscular weakness - corticosteroids, intravenous immunoglobulins, vitamins (B1, B12), and plasmapheresis have been used (Luciano et al., 2003).

3.6. Toxoplasmosis

Toxoplasmosis is the leading cause of focal central nervous system (CNS) disease in AIDS. CNS toxoplasmosis in HIV-infected patients is usually a complication of the late phase of the disease. Toxoplasmosis has been an indicator disease for AIDS since the early days of the

human immunodeficiency virus (HIV) epidemic (Horowitz et al., 1983; Luft et al., 1984). CNS toxoplasmosis begins with constitutional symptoms and headache. Later, confusion and drowsiness, seizures, focal weakness, and language disturbance develop. Without treatment, patients progress to coma in days to weeks. On physical examination, personality and mental status changes may be observed. Seizures, hemiparesis, hemianopia, aphasia, ataxia, and cranial nerve palsies may be evident. Occasionally, symptoms and signs of a radiculomyelopathy predominate. Serologic studies in patients with CNS toxoplasmosis may demonstrate rising titers of anti-toxoplasma immunoglobulin G (IgG) antibodies, CD4 counts < 100 cells mm^{-3} and CSF findings are non-specific. Detection of T.gondii DNA by PCR has only moderate sensitivity. MRI typically reveals multiple enhancing lesions with perifocal oedema and mass effect in the basal ganglia and gray white matter interface of the cerebral hemispheres. Any part of the brain can be affected, mostly solitary in appearance. Standard therapy consists of pyrimethamine, sulfadiazine, and folinic acid in combination. Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative regimen (Dedicoat et al., 2006). A Cochrane data base review failed to find a significant difference between standard therapy and TMP-SMZ. Clindamycin can be used in patients allergic to sulfa drugs. Effective antiretroviral therapy is equally important (Dedicoat et al., 2006; Fung et al., 1996; Bertschy et al., 2006; Behbahani et al., 1995). Most common cause of cerebral mass lesion, Sub acute course with fever, headache, confusion or cognitive disturbances with focal deficits, Seizures 24 – 29 %, rarely psychotic features. Imaging – Multiple mass lesions at grey – white junction & basal ganglia, CSF – Non specific, Antibody to T. Gondi, PCR recently developed.

3.7. AIDS related primary CNS lymphoma

A relationship between congenital or acquired immune deficiency (AIDS) and lymphoma was first recognised more than 30 years ago. An association between non-Hodgkin's lymphoma (NHL) and the acquired immune deficiency syndrome became evident in the early 1980s. Lymphoma occurring in the HIV-infected individual may be systemic, may primarily involve the central nervous system, or may be localised in the body cavities. Systemic lymphoma is the most common presentation, accounting for approximately 80% of all cases. The histology usually is diffuse large cell, immunoblastic, or small non-cleaved cell lymphoma. Primary CNS lymphoma accounts for approximately 20% of all cases. Most patients are profoundly immunosuppressed and typically have a CD4 lymphocyte count below 50/ml. Approximately two-thirds or more of them have AIDS-defining conditions prior to the development of primary CNS lymphoma (Gill et al., 1985; Goldstein, 1991). The lesions are typically few in number (1–3), large (2–4 cm), and contrast enhances approximately 50% of the time (Fine & Mayer 1993). Lesions are most common in the cerebrum, but also occur frequently in the cerebellum, basal ganglia and brain stem, and are nearly always found to be multifocal at autopsy (Loureiro et al., 1988; MacMahon et al., 1991). The lymphoma cells tend to be distributed along vascular channels as perivascular cuffs, are of B cell origin, display large cell and immunoblastic histologies. Subacute presentation with headache, impaired cognition, focal cerebral dysfunction. D/D – Toxoplasmosis, PML. Imaging – Multiple enhancing periventricular or subependymal lesions, CSF – EBV nucleic acid in CSF being studied. NHL are of higher grade and advanced stage. Response and tolerance to chemotherapy is poor. Systemic lymphoma in

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patients with HIV infection is a potentially curable disease, although the potential for cure is less than in immunocompetent individuals. Appropriate use of supportive care is an important component of therapy (Table 3) (Sparano, 2001).

Indication	Drug(s)
Primary infection prophylaxis	
Pneumocystis carinii, Toxoplasma	TMP-SMZ 1 DS QD
Oral and/or oesophageal candidiasis	Fluconazole 100 mg QD
MAI Complex (CD4 < 50/ul)	Azithromycin 1200 mg weekly
Secondary infection prophylaxis	
Herpes simplex infections	Acyclovir 400 mg BID or 200 mg TID
Cytomegalovirus infection	Ganciclovir 1 g TID
Mycobacterium–avium complex	Clarithromycin 500 mg BID plus ethambutol 15 mg/kg QD, with or without rifabutin 300 mg QD
Toxoplasma gondii	Sulphadiazine 1–1.5 gm q6h, pyrimethamine 25–75 mg QD, Leucovorin 10–25 mg QD — QID
Cryptococcus neoformans	Fluconazole 200 mg QD
Salmonella bacteraemia	Ciprofloxacin 500 mg BID
Haematopoietic growth factors	
For selected patients in whom the risk of febrile neutropenia ⩾40%	G-CSF 5 mcg/kg or GM-CSF 250 mcg/M^2 s.c. daily beginning after completion of chemotherapy and continue until neutrophil recovery
Antiretroviral agents	
Selecting patients for therapy	Follow NIH guidelines (http://www.hivatis.org)
Role of therapy in controlling malignancy	
Kaposi's sarcoma	Essential
Lymphoma	Unknown
Other tumours	Unknown
Factors influencing selection of agents	
May be used with myelosuppressive drugs	Didanosine, zalcitabine
Avoid with myelosuppressive drugs/regimens	Zidovudine
Avoid with neurotoxic drugs/regimens	Didanosine, zalcitabine, stavudine
May alter the metabolism of cytotoxic drugs metabolised by cytochrome p450 enzymes	All protease inhibitors and non-nucleoside RTIs

QD. Daily; TID, three times daily; BID, two times daily; QID, four times daily; s.c., subcutaneous; G CSF, granulocyte colony stimulating factor; GM,CSF, granulocyte-macrophage colony stimulating factor, NIH, national institute of health; RTIs, reserve transcript inhibitors.

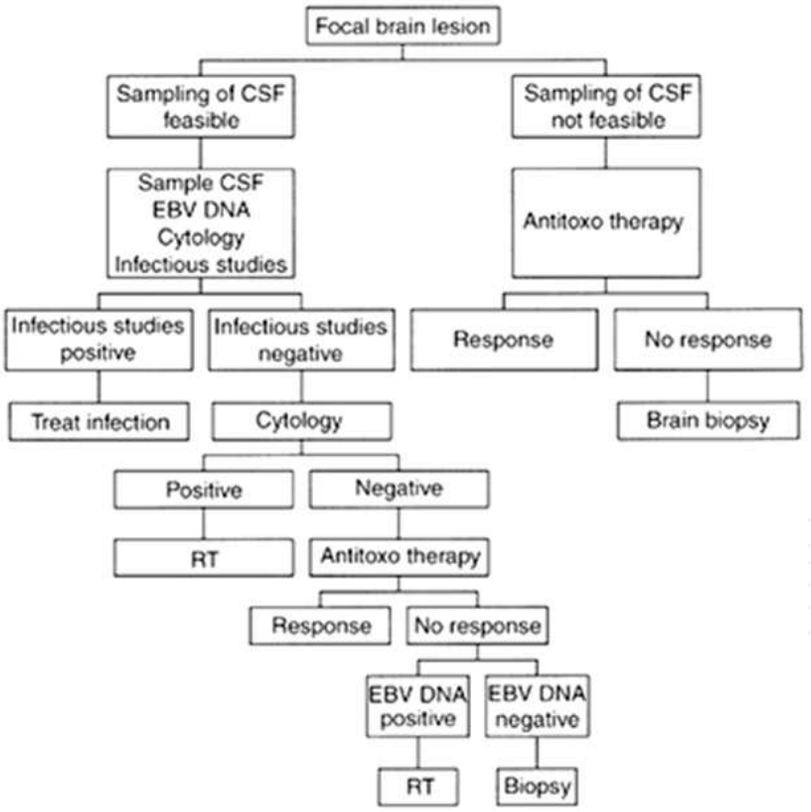
Table 3. Suggested supportive care for the patient with HIV infection and lymphoma or other malignancies. European Journal of Cancer 37 (2001) 1296–1305

Appropriate supportive care and CNS prophylaxis might improve outcome. In patients with HIV infection, the differential diagnosis of a patient with focal brain lesions includes PCNSL, cerebral toxoplasmosis, and other infections. Focal brain lesions have also been described in conjunction with relapsed systemic lymphoma (Desai et al., 1999). A proposed algorithm for the diagnostic approach to a patient with HIV infection and focal brain lesions is shown in Fig. 3.

3.8. HIV related progressive multifocal leukoencephalopathy

Progressive Multifocal Leukoencephalopathy (PML) is a rare demyelinating disease (focal neurological disease & cognitive impairment) of the CNS caused by reactivation of JC virus (JCV) 1. Radiographic evidence of white matter disease with subcortical involvement – 'scalloped' appearance. CSF – Non specific. Primary infection occurs in childhood and the virus remains latent in the kidney or lymphoid organs thereafter. In the setting of cellular immunosuppression, the virus may spread to the central nervous system, leading to a lytic infection of oligodendrocytes and subsequent demyelination. Classically, PML was observed in patients with advanced HIV infection, lymphoproliferative disorders and transplant

recipients. There is no specific treatment for PML, but the survival in HIV-infected PML patients has increased substantially during the last decade. Before the introduction of highly active antiretroviral therapy (HAART), only 10% patients with PML lived for more than a year. In contrast, recent studies have shown at least 50% one-year survival of HIV- infected PML patients (Falco et al., 2008; De Luca et al., 2008). However, the prognosis of PML associated with other immunosuppressive conditions remains poor. Immune recovery associated with HAART has resulted in a better prognosis for HIV-infected PML patients. The prompt institution of HAART in HIV infected PML patients is the most effective therapeutic approach in increasing survival in this group. Several studies have shown that PML survival increased from 10 to 50% in the last decade (Falco et al., 2008; De Luca et al., 2008; Cinque et al., 2003; Bamford et al., 1989; Du Pasquier et al., 2004; Koralnik et al., 2004; Gasnault et al., 2003; Antinori et al., 2003). In a recent study, JCV-peptide loaded dendritic cells from PML patients, HIV-infected individuals and healthy control subjects could elicit a strong cellular immune response mediated by CD8+ cytotoxic T lymphocytes cell response *in vitro* (Marzocchetti et al, 2009), which suggests that autologous dendritic cell-based immunotherapy could be a potential therapeutic option for PML.



CSF, cerebrospinal fluid
Antitoxo, antitoxoplasmosis
RT, radiotherapy

Figure 3. Algorithm for management of HIV – infected individuals with focal brain lesions European Journal of Cancer 37 (2001) 1296–1305

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3.9. Neurological approach to immunocompromized patients due to HIV-1

Central nervous system pathogens in specific immunocompromised-host (HIV-1) categories based upon presentation like Meningitis, Meningoencephalitis, and Encephalitis. Cryptococcal meningitis is seen in populations but cryptococcomas are much more frequent in the latter. Encephalitis and cerebral abscesses usually do not produce cerebrospinal fluid (CSF) changes unless the lesion communicates with the ventricular or subarachnoid spaces. Discrete white matter lesions have a narrower differential including calcineurin-induced demyelination usually in the posterior territory and progressive multifocal leukoencephalopathy (JC papova virus) which is characteristically nonenhancing and without mass effect. Meningoencephalitis due to Toxoplasma gondii continues to be the predominant pathogen in HIV-1 disease even with highly active antiretroviral therapy (HAART) exposure (Peter K. Linden, 2009).

3.10. Neurogenic manifestation of HIV infection in children

Twenty percent of children present with severe symptoms or die in infancy, Prognosis is related to: a) Greater inoculation of HIV b) Earlier infection with immature immune system c) Immune escape from mother. Asceptic Meningitis or Meningoencephalitis does not occur in infants. Acquired Microcephali, cerebral vasculopathy and basal ganglia, Calcification are unique in children. OIS are rare in children, here absolute CD_4T cell count less helpful. HIV-DNA PCR on peripheral blood lymphocytes can help to diagnosis. Avoid vaginal delivery, plan caesarean section and avoid breast feeding.

4. Markers for HIV progression

A combination of different markers is required to predict plasma human immunodeficiency virus type 1 (HIV-1) disease progression (Fahey et al., 1990; Saves et al., 2001). Levels of plasma HIV-1 RNA and CD4 + cell count are highly predictive of progression to AIDS or death (Hughes et al., 1997; Mellors et al., 1997; Saves et al., 2001). However, variations of these markers do not explain all variations of disease progression and the relative prognostic value of laboratory markers of HIV disease are not the same at different stages of the disease. Therefore the use of markers of immune activation has been suggested (Graham, 1996; Saves et al., 2001). CD4+ cell count (CD4) and RNA viral loads (RNA) are the two most commonly used prognostic markers of the clinical progression of HIV infection for HIV infection (Hammer et al., 2006; Gilks et al., 2006). Besides, there are various additional markers for HIV progression such as CD8+ cell count, anti-HIV antibodies, p24 antigen, hemoglobin concentration, platelet concentration as well as erythrocyte sedimentation rate (ESR). Various predictors for progression to AIDS among HIV-positive homosexual men have beed identified. These include low absolute number and/or percentage of CD4+ lymphocytes, low CD8+ cell count, low concentration of anti-HIV antibodies, p24 antigenaemia, decreased concentration of haemoglobin, increased titre of IgG antibody to cytomegalovirus, raised serum IgA and IgM values, raised concentrations in the serum of interleukin-2 receptor, neopterin and beta2-microglobulin (Gafa et al., 1993). Among these markers, the percentage of CD4+ cells was

found to be the best predictor of HIV progression (Fahey et al., 1990), followed by serum concentrations of neopterin and beta2-microglobulin, IgA, interleukin-2 receptors and p24 antigen. Only a few studies have the predictive values of these serological markers which have been evaluated in cohorts of IVDUs (Gafa et al., 1993). De Wolf & Lange, (1993) observed that several laboratory markers become most noticeably established as predictors of progression from asymptomatic HIV-1 infection to AIDS: (1) Decline in antibody reactivity to HIV core proteins p24 and p17; (2) Appearance of persistent HIV-1 p24 antigenemia; (3) Declining numbers and percentages of peripheral blood CD4-positive lymphocytes; (4) Elevated serum beta2-microglobulin concentration and (4) Elevated serum and urine neopterin concentrations.

4.1. Immunological and virological markers

Based upon scientific literature, immunological and virological markers have been proven as prognostic indicators for progression of HIV disease. The most widely studied marker, the CD4 + lymphocyte count was found to be the best single indicator of the stage of the illness (Zeller et al., 1996). HIV infects CD4+ T lymphocytes selectively and causes the destruction of CD4+ T cells directly as well as indirectly leading to gradual loss of the CD4 T cell numbers in peripheral circulation. Hence, the CD4+ T cell counts are being used to monitor the disease progression in HIV infection, to decide the threshold for initiation of anti-retro viral therapy, to monitor the efficacy of Anti Retrroviral treatment and to initiate prophylactic treatment for opportunistic infections (OIs) (Atlh Nicholson, 1997; Pattanapanyasat & Thakat, 2005). Measuring the CD4+ lymphocytes count remains the most effective means of evaluating of the clinical prognosis of patients infected with Human Immunodeficiency Virus (HIV) (Stein et al., 1992). This measurement has been universally accepted as a uniform means for the clinical staging of patients infected with HIV and those progressing to AIDS (Levine et al., 2000) and for the determination of the commencement of antiretroviral therapy and for monitoring the response to antiretroviral therapy (Evans-Gilbert et al., 2004).

4.2. CD4+ cell count

CD4+ T lymphocyte play a central regulatory role in the immune response. The decrease in CD4+ T cell numbers can compromise the normal immune functions of the body. Hence, the number of CD4+ T cells in the circulation provides important information regarding the immune competence of an individual (Thakar et al., 2011). HIV primarily targets CD4 cells. As HIV disease progresses, CD4 cell counts decline, typically by about 30-100 cells/μl per year (depending on viral load), leaving a person increasingly vulnerable to infections and cancers. People with CD4 cell counts above 500 cells/μl generally have relatively normal immune function and are at low risk for opportunistic infections (Hammer et al., 2006). The clinical staging of HIV disease and the relative risk of developing opportunistic infections have historically relied on the CD4 cell count as the principle laboratory marker of immune status (Kleinman et al., 1998; Patton et al., 2003). HIV disease is commonly categorized on the basis of three levels of immunodeficiency: relative immune competence (CD4 cell count > 500/μl; ≥ 29%), early immune suppression (CD4 cell count between 200/μl and 500/ μl); 4%-28%) and severe immune suppression (CD4 cell count <200/μl and 500/ μl); <14%) (CDC, 1993).

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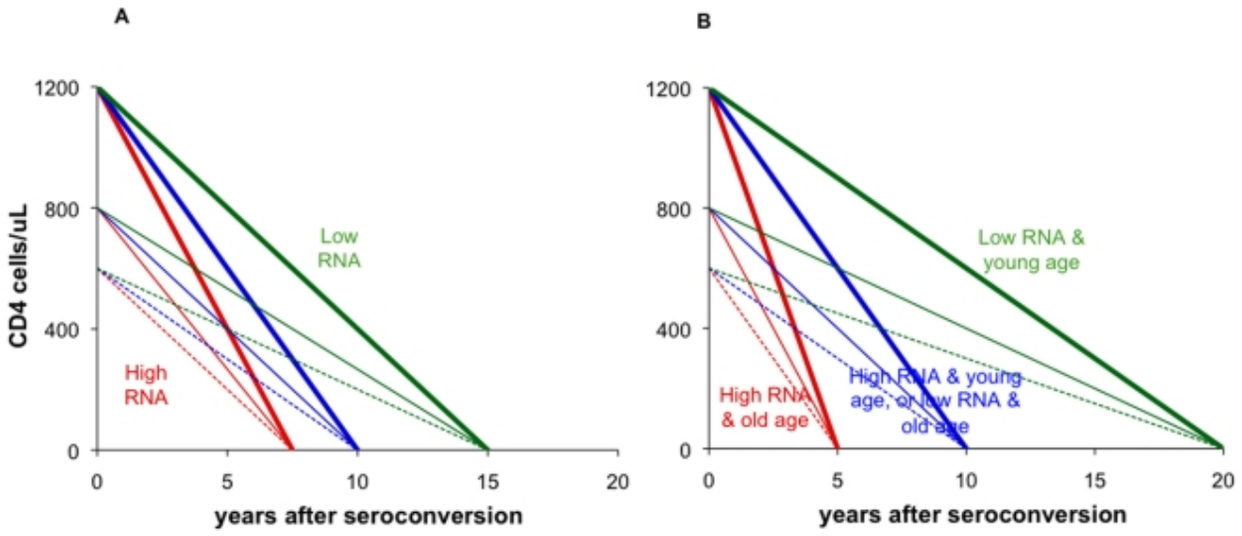

Figure 4. Schematic natural history model of HIV-1 replication driving rates of CD4 decline and clinical progression (Korenromp et al., 2009)

4.3. CD8+ cell count

There are two types of T cells carry the CD8 surface molecule: T-suppressor cells, which inhibit immune responses, and killer T cells (also known as cytotoxic T lymphocytes, or CTLs), which target and kill infected or cancerous cells. As with CD4 cells, a variety of factors can cause CD8 cell counts to fluctuate. CD8 cell counts typically rise over time in people with HIV, but (unlike CD4 cells) CD8 cell numbers do not independently predict disease progression, and their relation to immune status is not well understood (Vajpayee & Mohan 2011).

4.4. CD4 and CD8 cell percentage

Because absolute CD4 and CD8 cell counts are so variable, some physicians prefer to look at CD4 or CD8 cell percentages, the proportion of all lymphocytes that are CD4 or CD8 cells. Percentages are usually more stable over time than absolute counts. A normal CD4 cell percentage in a healthy person is about 30-60 per cent, while a normal CD8 cell percentage is 15-40 per cent (Taylor et al., 1989).

4.5. CD4/CD8 cell ratio

The CD4/CD8 cell ratio is calculated by dividing the CD4 cell count by the CD8 cell count. A normal CD4/CD8 cell ratio is about 0.9-3.0 or higher, there are at least 1-3 CD4 cells for every CD8 cell. In people with HIV this ratio may be much lower, with many more CD8 cells than CD4 cells (Giorgi, 1993).

4.6. HIV viral load

Viral load tests measure the amount of HIV RNA in the blood. The presence of RNA indicates that the virus is actively replicating or multiplying. Along with the CD4 cell count, viral load

is one of the most valuable measures for predicting HIV disease progression and gauging when anti-HIV treatment is indicated and how well it is working. Viral load is expressed either as copies of RNA per milliliter of blood (copies/ml) or in terms of logs. A log change is an exponential or 10-fold change. For example, a change from 100 to 1,000 is a 1 log (10-fold) increase, while a change from 1,000,000 to 10,000 is a 2 log (100-fold) decrease. If the level of HIV is too low to be measured, viral load is said to be undetectable, or below the limit of quantification. However, undetectable viral load does not mean that HIV has been eradicated; people with undetectable viral load maintain a very low level of virus. Even when HIV is not detectable in the blood, it may be detectable in the semen, female genital secretions, cerebrospinal fluid, tissues, and lymph nodes (Calmy et al., 2004; Petti et al., 2006; WHO, 2006). In primary HIV infection, patients may present with flu-like symptoms which usually occur during the first weeks of HIV-1 infection. It is associated with peak levels of HIV-1 RNA viremia, which subsequently declines until reaching a set point, where levels remain for months to years. Initial studies suggested that those with more symptomatic acute infection and longer duration of illness have faster rates of progression to AIDS (Koenig et al., 2006). A viral load of 100,000 copies/ml or more is considered high, while levels below 10,000 copies/ml are considered low. Research has consistently shown that higher viral loads are associated with more rapid HIV disease progression and an increased risk of death. Current U.S. HIV treatment guidelines (Koenig et al., 2006) recommend that people should consider starting treatment if their viral load is above 55,000 copies/ml (revised upward from 10,000 copies/ml in the previous guidelines). Importantly, most studies that have correlated viral load and HIV disease progression have been done in men; more recent research indicates that women may progress to AIDS at lower viral load levels, suggesting that the treatment threshold should perhaps be revised downward for women (Monica et al., 2002).

4.7. Beta2-microglobulin (β2-microglobulin)

β2-microglobulin is a low molecular weight protein that forms light chain of the class I major histocompatibility complex (MHC) which present on the surface of most somatic cells including T and B lymphocytes as well as macrophages (Cresswell et al., 1974; Lawlor et al., 1990; De Wolf and Lange 1991). It exhibits amino acid homology with the constant region of immunoglobins (Dar & Singh, 1999; Fauci & Lane, 1998; Quin & Benson, 1994). Circulating β_2-MG is generated during normal MHC I turnover (Lawlor et al., 1990) and thus is not specific to HIV-related cell death. Stimulation of lymphoid cells increases β2-microglobulinproduction. Elevated serum concentration are seen in renal failure, hepatitis, rheumatoid arthritis, myeloproliferative disorders, lymphoproliferative disorders, infectious mononucleosis, influenza A and cytomegalovirus infection (De wolf and Lange, 1991). Free β2-microglobin can be measured in both serum and urine and levels of urine β2-microglobin correlate with the degree of progression of HIV disease. It spikes in acute infection, declines and then rises during the infection. Levels of β2-microglobin are elevated in a variety of conditions characterized by lymphocyte activation and/ or lymphocyte destruction; *e.g*. lymphoproliferative syndromes, autoimmune diseases, viral infection and in patients with renal diseases. It can be measured in serum or plasma by using radio immunoassay radio immunoassay (RIA) or competivive ELISA based tests. B2-microglobin measurement has several advantages as a

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laboratory assay to help determine prognosis. By contrast with CD4 cell count which requires special procedures for specimen handling and processing, β2-microglobin can be measured with a serological assay and equipment available in many laboratories (Vajpayee & Mohan, 2011). Increased concentrations of this molecule are predictive of progression of HIV infection to AIDS (Moss et al., 1988).

4.8. Neopterin

Neopterin (6-D- erythrohydroxy-propylpterin) is a low molecular weight compound derived from an intermediate product of the *de novo* biosynthesis of tetrahydrobiopterin from guanosine triphosphate (GTP) (Dar & Singh, 1999; Fauci & Lane, 1998; Quin & Benson, 1994). It is an early marker of HIV infection. The levels rise further on progression from pre AIDS to clinical AIDS (Vajpayee & Mohan 2011). It is produced by macrophages after stimulation with gamma interferon. The levels have also been found to be associated with progression of HIV-1-related disease (Fuchs et al., 1988; Melmed et al., 1989; Kramer et al., 1989; De Wolf and Lange 1991) but the predictive value is slightly inferior to that of β2-microglobulin levels. Since neopterin levels are stimulated by HIV infection, measurement of neopterin levels can be useful in monitoring progression and evaluating antiviral therapy (Vajpayee & Mohan 2011).

4.9. Additional markers

Haematological manifestations of HIV infection are common and more frequently occur with progression of the disease. Therefore the complete blood count (CBC) is one of the important haematological parameters which need to checked for HIV patients. They may have low blood cell counts (cytopenias) due to chronic HIV infection or as a side effect of medications, particularly drugs that damage the bone marrow, where all blood cells are produced. Blood cell counts are typically reported as the number of cells per μl of blood (cells/μl) or as a percentage of all blood cells. HIV patients should be checked for CBC for every six months, and more often if they are experiencing symptoms or taking drugs associated with low blood cell counts (De Santis et al., 2011; Olayemi et al, 2008).

4.9.1. Red and white blood cells

Anemia is common in HIV positives. HIV itself and various OIs such as *Mycobacterium avium* complex (MAC) can affect red blood cells and their oxygen-carrying capacity (Volberding et al., 2003; Owiredu et al., 2011). People with HIV infection should be especially concerned with neutrophil and lymphocyte levels, in particular CD4 and CD8 cell counts. Neutrophils normally make up about 50-70 per cent of all white blood cells. Various anti-HIV drugs, OI medications [including ganciclovir (Cytovene), used to treat cytomegalovirus, or CMV], and cancer chemotherapies that suppress the bone marrow may lead to neutropenia (Firnhaber, 2010).

4.9.2. Platelets

Platelets are necessary for blood clotting. A normal platelet count is about 130,000-440,000 cells/μl. Low platelet counts (thrombocytopenia) - which can lead to easy bruising and excessive

bleeding may be caused by certain drugs, autoimmune reactions, accelerated destruction by the spleen, or HIV disease itself (Torre & Pugliese, 2008). In 2012, Parinitha & Kulkarni study the haematological changes in HIV infection with correlation to CD4+ cell count. In their study, they found that among 250 patients studied, anaemia was seen in 210 (84%) of cases. Thrombocytopenia occurs in 45 (18%) cases. Majority of cases (70%) had CD4+ cell counts below 200 cells/mm3. Fifty-four cases (21.6%) had CD4 cell counts between 200 to 499 cells/mm3 and 21 (8.4%) cases had CD4 count more than 500 cells/mm3. In patients with CD4 counts less than 200 cells/mm3, anaemia was seen in 91.4% cases, leucopenia in 26.8% cases, lymphopenia in 80% cases and thrombocytopenia in 21.7% cases.

5. Summary

The prevalence of neurological associated with HIV-1 is estimated at 15 to 50% of patients (Dalakas et al., 1988; Cornblath et al., 1988; So et al., 1988; Monte et al., 1988; Gabbai et al., 1990). But it may be almost 100% when a pathological study is performed (Rizzuto et al., 1995; Gabbai et al., 1990). The etiology and pathogenesis of neurological disease associated with HIV infection is uncertain. It can be caused by the direct or indirect action of HIV and antibody production, or secondary to infections (CMV, MAC), toxic effects of certain drugs (isoniazid, vincristine, d4T, ddi, ddC), or nutritional deficiencies (vitamin B12) (Rizzuto et al., 1995; Dalakas et al., 1988; Figg et al., 1991; Browone et al., 1993; Pike et al., 1993; Abram et al., 1994; Kieburtz et al., 1991). HIV seropositive patients may be overlooked or misdiagnosed. A discerning clinical analysis may be helpful in the diagnosis of this common disease and several laboratory markers become most noticeably established as predictors of HIV-1 infection.

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