A STUDY ON PATTERN OF NEUROPSYCHOLOGICAL PERFORMANCE IN HIV POSITIVE PATIENTS AND IMPACT OF ANTIRETROVIRAL THERAPY IN COGNITIVE IMPAIRMENT

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MADURAI.

CERTIFICATE

This is to certify that the dissertation entitled a **"A STUDY ON PATTERN OF NEUROPSYCHOLOGICAL PERFORMANCE IN HIV POSITIVE PATIENTS AND IMPACT OF ANTIRETROVIRAL THERAPY IN COGNITIVE IMPAIRMENT"** is a bonafide record of work done by **Dr. Abdul Rahuman** in the Department of Psychiatry, Government Rajaji Hospital, Madurai Medical College, Madurai, under the direct guidance of me.

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ABBREVIATIONS

H.I.V - Human Immuno Deficient Virus

AIDS - Acquired Immuno Deficient Syndrome

ICTC - Integrated councelling and treatment centre

ART - Anti Retroviral Therapy

ICD - International classification of Diseases

DSM - Diagnostic and Statistical Manual

CONTENTS

INTRODUCTION

HIV infection is a global pandemic, with cases of AIDS reported in nearly every country in the world. Infection with the human immunodeficiency virus-type-1 (HIV-1) can have a significant impact on the central nervous system (CNS) as well as on the immune system. Michael Gottlieb(1981) diagnosed with Pneumocystis carinii pneumonia in a gay man and some rare cases of Kaposi's sarcoma were diagnosed during the same period. All these patients were strangely immuno deficient—their immune systems could not fight off even simple infections. Other opportunistic infections accompanied these diagnoses.

The initial diagnosis was given the incriminating acronym GRID, Gay Related Immunodeficiency Disease. Since male homosexuals and intravenous drug users were frequent blood donors, for both altruistic and financial reasons, the blood supply was quickly tainted. Suddenly hemophiliacs living outside the usual risk areas, who needed Factor VIII, which was extracted from the whole blood of thousands of donors, came down with the same symptoms. During 1982 AIDS was diagnosed among hemophiliacs and injection drug users (IDUs). Later the first case of heterosexual transmission was identified in USA.(centers for disease control and prevention, 1983).

The first studies performed by the CDC in 1981 traced the sexual contacts of a small group of 40 patients suffering from KS, PCP, and/or other opportunistic infections. All cases could be traced to the single index case, called Patient Zero, a French Canadian flight attendant Gaetan Dugas. Although Dugas was not the first person to show symptoms of HIV infection, he was the center of this particular cohort of diseased individuals. The earliest fully documented case of HIV dates back to 1959. A Congolese man's blood sample from a medical study was preserved, found, and then analyzed in 1998. It was verified that he had been HIV+. Other suspected, but unverified because of the lack of either blood or tissue samples, cases date back as early as 1934.

Since the identification of HIV in 1981 ,neurologists described several HIV-related central nervous system (CNS) syndromes within the first several years of the epidemic. Mental health professionals from nursing, social work, psychology, and psychiatry followed the plight of patients of the epidemic and helped to mobilize interest and galvanize a response. Initially, much of the work focused on grief and loss issues, as well as supportive psychotherapy, but quickly broadened to recognize a number of specific psychiatric conditions, including acquired immune deficiency syndrome (AIDS) dementia, Cognitive Impairment, the

associated AIDS mania, increased rates of major depression, and psychiatric consequences of CNS injuries.

Neuropsychiatric disorders in HIV can be either primary or secondary. Primary complications are those that can be attributed directly to the infection of the central nervous system by the virus, or to imuno pathological events precipitated by HIV infection. Primary HIV-related brain disorders include HIV-related dementia and minor cognitive disorder.

Immune suppression can lead to a variety of secondary complications affecting the brain, including opportunistic infections (e.g. cerebral toxoplasmosis and progressive multifocal leucoencephalopathy) and tumours (e.g. cerebral lymphoma). Secondary complications in the form of acute and subacute syndromes (e.g. delirium) often occur as a result of cerebrovascular complications and toxic states induced by various therapeutic agents.

Five percentage of newly diagnosed AIDS cases and 60% in late AIDS have been found to be impaired, (Tozzi et al, 2005, Cysique et al ,2004, Yepthomi et al ,2006). Neuropsycholgical impairment caused by HIV was found in the areas of attention and concentration, abstraction, learning, memory, psychomotor and cognitive processing speed in several

studies.(Bornstein et al., 1993; Heaton et al., 1995; McArthur and Seines, 1997, Glen et al, 2005).

Age, CD4 count, Education, Employment are the some of the factors predicting the development of cognitive impairment, proposed by few literatures.

Pharmacologic treatment strategies for cognitive disorders can be divided into four types: 1) antiretroviral therapies, 2) therapies aimed at immunological measures or inflammatory mediators, 3) therapies aimed at bolstering the response of the brain to the onslaught of the infection (e.g., neurotransmitter manipulation), and 4) nutritional therapies. Most controlled studies have investigated the efficacy of antiretroviral therapies, and while these studies have advanced our knowledge about interventions for cognitive disorders, several key factors required to be considered. First is the fact that most published studies to date report on the treatment strategy of administering a single antiretroviral agent. Their findings are therefore difficult to interpret in light of the multi drug regimens that are now the standard of care in developed countries. Second, the reports vary widely with regard to the study population, since some studies enrolled subjects on the basis of established criteria for HIV-associated dementia or minor cognitive motor disorder but other studies enrolled cognitively impaired subjects without Specifying

whether they also met criteria for a clinical disorder. Third, the range of HIV clinical severity also varied widely in study subjects. Whether antiretroviral agents penetrate the blood-brain barrier sufficiently to adequately suppress viral replication is a key issue that requires further study.

Scope of this study:

This study focused on the primary neuropsychiatric disorders of HIV and cognitive impairment in particular. There is some evidence to suggest that CD4 count was an important predictor of the development of immune deficiency and subsequent cognitive impairment. .This study aims to corroborate on the prevalence of cognitive impairment in HIV patients and to know whether CD4 count are correlated with the impairment and the effect of antiretroviral therapy in the cognitive impairment

Plan of the study:

The present study has been planned as follows

Review of Literature

Methodology

Results and Interpretation

Discussion

Conclusion

REVIEW OF LITERATURE

HIV was originally recognized through a series of case descriptions involving young homosexual men with Pneumocystis carinii pneumonia in the early 1980s in Los Angeles. Subsequently, it became clear that these patients had severe immune system compromise and were vulnerable to infections that had been seen in other immuno compromised individuals. Recent estimates indicate that up to 40 million people are infected worldwide, and another 20 million have died from HIV disease. Currently, 750,000 babies are born each year with HIV infection. Some estimate that 16,000 new infections occur each day, and that one individual is infected with HIV approximately every 10 seconds. (UNAIDS ,2008).

In 2006 UNAIDS estimated that there were 5.6 million people living with HIV in India, which indicated that there were more people with HIV in India than in any other country in the world(UNAIDS 2007). However, NACO disputed this estimate, and claimed that the actual figure was lower. (NACO, 2006). In 2007, following the first survey of HIV among the general population, UNAIDS and NACO agreed on a new estimate – between 2 million and 3.6 million people living with HIV. (NACO,UNAIDS,WHO-2007).The figure was

confirmed to be 2.4 million in 2008 (NACO,2007).This puts India behind South Africa and Nigeria in numbers living with HIV.

In terms of AIDS cases, the most recent estimate comes from August 2006, at which stage the total number of AIDS cases reported to NACO was 1, 24, 995. Of this number, 29% were women, and 36% were under the age of 30 (NACO, 2007). These figures are not accurate reflections of the actual situation, as large numbers of AIDS cases go unreported.(NACO, 2007).Overall, around 0.3% of India's population is living with HIV While this may seem a low rate, India's population is vast, so the actual number of people living with HIV is remarkably high. There are so many people living in India that a mere 0.1% increase in HIV prevalence would increase the estimated number of people living with HIV by over half a million. (Kumar et al, 2006).

Epidemiological studies in India show that HIV-C is the most prevalent virus and men are roughly four times more infected than women and that rural inroads are evident (Panda, 2006).According to NACO(2007) , Southern states like Tamilnadu, Andhra Pradesh, Karnataka were harboring more than half of the HIV patients. In Andhra, the HIV prevalence at antenatal clinics was 1.26% in 2006 - higher than in any other state - while the general population prevalence was 0.97% in

2005-2006. The vast majority of infections in Andhra Pradesh are believed to result from sexual transmission. HIV prevalence at STD clinics was 24.4% in 2006. In Karnataka the average HIV prevalence at antenatal clinics has exceeded 1% . Among the general population, 0.69% was found to be infected in 2005-2006. The average HIV prevalence among female sex workers in Karnataka was 8.64% in 2006, and 19.20% of men who have sex with men were found to be infected. In Maharashtra, 2005-2006 survey found an infection rate of 0.62% in the general population of Maharashtra. This state is home to around one in five of all people living with HIV in India. Some small North eastern states like Manipur, Mizoram contributed significantly in the development of HIV in IV drug abusers. The 2005-2006 survey found that 1.13% of the general population of Manipur was infected - the highest of all states surveyed(NACO,2007).

Tamil Nadu

When surveillance systems in the southern Indian state of Tamil Nadu, home to some 62 million people, showed that HIV infection rates among pregnant women were rising - tripling to 1.25% between 1995 and 1997 .Tamil Nadu State AIDS Control Society (TANSACS) had been set up in 1994, through this organization all HIV related activities were

carried out.The HIV prevalence at antenatal clinics in Tamil Nadu was 0.25% in 2006, though several districts still have much higher rates. The general population survey of 2005-2006 found a rate of 0.34% across the state. Prevalence among injecting drug users was 24.20% in 2006 - the highest of all states and union territories(NACO,2007).

In Madurai, the annual report of ART centre revealed that 2274 HIV cases were registered during 2005, of which 1568 were males and 706 were females. The ART centre, Madurai was started in 2004, since it's inception about 10,000 cases were registered till September 2008.Among them about 4,000 patients received Anti retroviral Therapy.

HIV is a single-stranded ribonucleic acid (RNA) virus that selectively infects immune cells, particularly T lymphocytes and macrophages. RNA viruses use several strategies to infect cells and reproduce themselves. HIV is one member of a class of RNA viruses called retroviruses, all of which carry the enzyme reverse transcriptase (RNA-dependent deoxyribonucleic acid [DNA] polymerase) in the viral particle and depend on this enzyme for successful infection. Reverse transcriptase synthesizes viral DNA from the viral RNA strand. This DNA is then transported into the nucleus of the cell and directs the production of more viral RNA using the cell's synthetic machinery. This

DNA also may become inserted into the cellular DNA (where it is referred to as a provirus) and lie dormant, only to be activated at a much later time.

HIV binds to specific recognition proteins found on the surface of certain cells of the immune system. Once bound, the virus is taken into the cell. At the same time, the outer coating of the viral particle is removed. The enzyme reverse transcriptase carried within the viral particle then begins the process of transcribing the viral RNA into DNA. This DNA moves to the nucleus of the cell where it directs the cell machinery to produce large quantities of viral messenger RNA (mRNA). The viral RNA then uses the cell's own machinery to produce the proteins required to make viral particles and other viral proteins. The viral particles are assembled around viral RNA, and the mature virions bud outward from the cell's surface. Finally, viral particles are cleaved from the cell surface and released into the host to infect other immune cells. (Adamson et al,1996; Johnson et al,1996; Seilhan et al,1997; Thompson et al,2001).

The mechanism of HIV-associated cognitive–motor disorder is not fully understood. Although the productive HIV infection of the CNS is

probably essential, most investigators conclude that indirect mechanisms play a role. (Johnson et al, 1996; Adamson et al, 1996).

Products released by activated macrophages are prime candidates for neurotoxic mechanisms. The known neurotoxicity of tumor necrosis factor-_ (TNF_) and other studies demonstrating its expression in association with HIV encephalitis have suggested that this cytokine represents a critical factor in the pathophysiology of neurological dysfunction in HIV. (Wesselingh et al 1993; Seilhean et al, 1997;Thompson et al ,2001).

Susan et al (2002) proposed the following mechanisms. (1)The predominant cognitive-impairing component of HIV-1 is its viral coat glycoproteins, (2) gp120 impairs memory by overstimulating pathways that normally sustain memory, (3) the cognitive effect of gp120 is mediated by its protein core, and (4) gp120 likely impairs memory by affecting the cholinergic/VIPergic system.

Acquired Immunodeficiency Syndrome (AIDS) is a clinical syndrome resulting from the collapse of cell mediated immunity secondary to infection with the Human Immunodeficiency Virus-Type 1 (HIV-1). The most common gross anatomical changes associated with AIDS include brain atrophy with sulcul widening and ventricular enlargement. Human immunodeficiency virus (HIV) appears to have a

predilection for subcortical structures, especially the frontal-subcortical systems (e.g., the basal ganglia).(Ketzler S et al ,1990;,Kuru K et al,1990;Everall I et al,1991;Wiley C et al,1991). Damage to these structures can cause specific motor and cognitive abnormalities, including poor fine-motor precision, memory deficits, and difficulties performing complex cognitive tasks.(Villa G et al,1993;Heaton R et al,1995).Damage to these systems can also cause significant neuro psychiatric syndromes, including depression, obsessive-compulsive disorder, mania, and apathy.(Hymas et al,1991;Cummings et al,1993).Another study revealed high rates of depression (60%), dysthymic disorder (25%), and anxiety disorders (25%) among persons seeking HIV related mental health services in the public sector (Lyketsos et al,1996). That study found high rates of comorbid substance use disorders, with nearly 50% of all patients having a diagnosis of alcohol or drug dependence. Another clinical study in Madurai indicated that about 34% of HIV patients had depression. (Venkobao Rao, 1993)

One aspect of sub cortical neurological disease is the presence of motor and cognitive retardation including deficits in mental speed, spontaneity of action, spontaneity of speech for comment or question, initiative, and enthusiasm(Mapou et al,1993;Perkins et al ,1995).

Histopathological analyses reveal white matter abnormalities, multinucleated giant cells of macrophage origin, microglial nodules, and diffuse reactive astrocytosis to be present in 70 to 90% of the brains of patients with AIDS who come to autopsy (Wiley 1994; Hardy et al 1999).

HIV induced minor cognitive-motor disorder or mild neurocognitive disorder is a less severe neurocognitive disorder emergent in earlier HIV infection .The symptoms of minor cognitive-motor disorder are often overlooked, as they may be very subtle, but they are essentially mild manifestations of the same symptoms seen in HIV-associated dementia: cognitive and motor slowing. Often, the disorder is discovered as a result of a singular minor complaint by a patient, such as taking longer to read a novel; dysfunction when performing fine motor tasks. The disorder is confirmed when mild impairments are present in at least two of the following domains: verbal/language, attention, memory (recall or new learning) abstraction, and motor skills.

Definitional Criteria for HIV-Associated Minor Cognitive Motor Disorder is as follows (American Academy of Neurology, 1991).

Probable Diagnosis (must meet all four criteria)

1. Acquired cognitive/motor/behavioral abnormalities, verified by both a reliable history and by neuropsychological tests.

2. Mild impairment of work or activities of daily living.

3. Does not meet criteria for HIV dementia or HIV myelopathy.

4. No other etiology present.

Prevalence data for minor cognitive-motor disorder are variable, often suggesting up to 60 percent prevalence by late-stage AIDS. Prevalence in earlier stages is not well defined, but the disorder has been anecdotally reported preceding a diagnosis of AIDS by 11 years. Subtle neuropsychological impairment may be found in 22%–30% of otherwise asymptomatic patients with HIV infection (Whilkie et al, 1990; White et al ,1995)

Early in the AIDS epidemic, some patients presented with rapidly progressing neuro cognitive disturbances, leading to an intensive search for etiology. Several CNS opportunistic conditions were identified, including cytomegalovirus (CMV) encephalitis, progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, cryptococcal meningitis, and CNS lymphoma. However, a subset of patients remained for which no identifiable pathogen could be found, and it was deduced that HIV itself was the causative factor behind the dementia. Autopsy studies of demented AIDS patients revealed characteristic white matter changes and demyelinization, microglial nodules, multinucleated giant cells, and perivascular infiltrates but a marked absence of HIV within neurons. This has led to the current theories of neuronal loss through

action of macrophages and microglial cells, through activation of cytokines and chemokines that trigger abnormal neuronal pruning, or through both. It appears that basal ganglia and nigrostriatal structures are affected early in the dementia process, with diffuse neuronal losses following. Typical late findings show an approximate 40 percent reduction in frontal and temporal neurons. (Ketzler et al ,1990).

Mild cognitive impairment refers to the transitional period between normal cognition and dementia, but is not an extension of normal ageing. Subjects with mild cognitive impairment have subtle but measurable cognitive impairment that is not severe enough to interfere with independent living.

Prevalence data for minor cognitive-motor disorder are variable, often suggesting up to 60 percent prevalence by late-stage AIDS. Whether minor cognitive-motor disorder predisposes to HIV-associated dementia is also of some debate. It appears that some patients may continue to have minor problems, whereas another group progresses to frank dementia. (Glen Treisman et al, 2005).

Neuro ICONA (Italian Cohort Naïve Antiretroviral) study done in 2002 over 395 HIV Positive patients naïve to HAART with no severe psychiatric disorders using the following tests - Timed gait-motor speed,

Digit symbol test-selective attention, WHO/ULCA Auditory verbal learning test-verbal memory, Color Trails 2 –sustained attention,cognitive flexibility revealed that the prevalence of cognitive impairment was 17.9percentage.(Starace et al, 2002)

Mccutchan et al (2007) studied 286 patients by using Trail making A , B and Digit symbol Test found that over one quarter(27%) of participants exhibited impairment at their initial neuropsychological assessment, a rate twice that expected in a normal population.

Rodriguez et al s(2007) data indicate that prevalence of neuropsychological impairment in stage A(asymptomatic) was 33%., 41.2% in stage B (low symptomatology patient) and of 70.7% in stage C (AIDS patients).The pattern of neuropsychological impairment was consistent with fronto-subcortical type alterations.

Another study done on Neurocognitive impairment and survival in a cohort of HIV-infected patients (Tozzi et al, 2005) revealed that among the 412 enrolled patients, 224 (54.4%) were neurocognitively impaired and 188 (45.6%) were neurocognitively unimpaired. Patients were administered measures of neurocognitive function (a battery of 17 neuropsychological tests), clinical and neurological evaluation, laboratory testing, and brain imaging studies. They also suggest that HIV-associated

neurocognitive impairment (NCI) was recognized as an independent risk factor for death.

Kevin Robertson et al study (2007) on pattern of neuropsychological impairmernt among HIV patients in Uganda demonstrated a relative decline in measures of verbal learning and memory, speed of processing, attention and executive function compared to HIV negative controls. This is a similar pattern to what has been found in the USA, Europe and Australian settings ,and would suggest that the pattern of neuropsychological loss will be the same with clade A and D HIV infection, (Miller et al ,1990),(Heaton et al 1995) In turn, this would suggest that HIV clade A and D have the same underlying pattern of neuropathology. There is no significant difference in the fine and gross motor tests between HIV positive and negative groups.

A Prospective case control study by Odiase et al (2007) with a total of 288 randomly selected subjects, comprising 96 HIV-positive symptomatic patients, 96 HIV-positive asymptomatic patients and 96 HIV-negative controls. The Recognition Memory Test and Choice Reaction Time tasks, components of the computer-assisted neuropsychological tests battery- the Iron Psychology 'FePsy' were used for cognitive assessments indicated that HIV positive patients had

psychomotor slowing , impaired attention and significant memory impairment.

Wig et al(2004) studied 70 HIV patients and showed that 42% of subjects had HIV associated Mild Neurocognitive disorder. 1.02% had HIV associated Dementia and 1.02% had HIV associated Delirium .They also found that there was no significant association on multivariate stepwise regression analysis between cognitive functions and age, sex, and duration of disease, BMI, hemoglobin level except CD4 counts.

Yepthomi et al's (2006) data collected in Chennai-based study with a sample of 30 treatment-naïve HIV-positive individuals with a median CD4 cell count of 97, and 30 age and education matched healthy controls obtained from the same region of India revealed significant differences on most cognitive tests, with lower performances obtained by the HIV-positive individuals. These results suggest that cognitive difficulties are present among individuals with the clade C virus in India, with as many as 56% of the patients with advanced HIV meeting the criterion for impairment in two cognitive domains.

Gupta et al (2007) using Standardized neuropsychological tests in a sample of 119 adults infected with clade C HIV-1 who were not on antiretroviral medications. Neuropsychological test performance was compared with gender-, age-, and education-matched normative data

derived from a sample of 540 healthy volunteers and a matched cohort of 126 healthy, HIV-1-seronegative individuals. Among the seropositive subjects, 60.5% had mild to moderate cognitive deficits characterized by deficits in the domains of fluency, working memory, and learning and memory. None of the subjects had severe cognitive deficits.

Venkoboa Rao's study (1993) in Madurai, with 67 HIV infected patients revealed that abnormality in visuo-motor function was detected in 68% of subjects. On the memory scale 54% were found to have verbal impairment, or non-verbal impairment or both.

Predictors of Cognitive Impairment:

Age, CD4 count, Education, Employment are the some of the predicting factors in the development of cognitive impairment ,proposed by few literatures .

AGE:

Older HIV individuals are 2 to 4 times more susceptible for development of cognitive impairment. According to Michael Garter(2004) 88% of HIV-positive patients aged under 40 had normal or equivocal cognitive function, only 56% of HIV-positive individuals over 50 met this criteria.

Von Gorp et al (1994) did a cross-sectional observational study recruited 67 HIV-positive patients aged over 50, and 52 HIV-positive patients aged under 35. Both groups of patients underwent neuropsychological assessment and had CD4 cell counts and their plasma and CSF viral loads measured. HIV treatment histories were also obtained. They found an increased risk of cognitive impairment in HIV-positive individuals aged over 50. Dementia was present in 22% of HIV-positive patients over 50 at study baseline and 9% of HIV-positive individuals under 50 at the same study point.

Valcour et al (2004) indicated that despite having lower HIV viral loads in plasma and cerebrospinal fluid, HIV-positive patients aged 50 and above had a higher burden of neuropsychological impairment.

Current estimates suggest that 10% of adults with AIDS are over 50 years old and about 3% are over 60 years old.(Shipp et al, 1991;CDC 1994, 1996; Chen et al., 1998). Becker et al (1997) found that test Performance declined with age.

Sacktor et al (2007) done a study in One hundred thirty-three older (age >or= 50 years) HIV+ individuals and 121 younger (age 20 to 39 years). The older HIV positive.(total) cohort had greater impairment in tests of verbal memory, visual memory, verbal fluency, and psychomotor speed compared to the Young HIV positive(total) cohort.

After adjusting for differences in education, older HIV positive patients with dementia (n = 31) had a greater deficit in the Trail Making test Part B (P = 0.02) compared to younger HIV positive patients with dementia (n = 15). Age was associated with lower performance in tests of memory, executive functioning, and motor performance in older HIV+ individuals with and without cognitive impairment (total cohort), compared to younger HIV+ individuals.

Several theoretical models can be advanced that provide a rationale for expecting that age and HIV infection would interact. First, from the perspective of a brain or cognitive reserve capacity model (Satz, 1993), aging and HIV infection are considered as co-risk factors that reduce cognitive reserve capacity. The greater the reduction in reserve, the more likely that an impairment threshold will be crossed producing an observable neurocognitive deficit. Second, at a more specific conceptual level, perhaps aging and HIV infection have a common or significantly overlapping neuropathological locus therefore impairing the same neurocognitive processes. For instance, Hinkin et al. (1990) reported that the level and pattern of performance on neuropsychological testing was similar in a sample of young adults diagnosed with AIDS (mean age = 38 years) and a group of older neurologically normal HIV seronegative adults (mean age = 70 years). The similar performance, despite an age

difference greater than 30 years, was attributed to a common mechanism, disruption of subcortical-frontal white matter connections. Similarly, behavioral slowing, a fundamental symptom of both aging and HIV infection, has been ascribed to basal ganglia dysfunction in both older (Bashore, 1993) and HIV-infected (Martin, 1994) adults. A third possible mechanism is that of a general slowing of cognitive operations. In other words, the uniform slowing of all cognitive operations produce the performance deficits observed in specific tasks. There is evidence for general slowing with age (Cerella, 1985; Salthouse, 1985)

EDUCATION

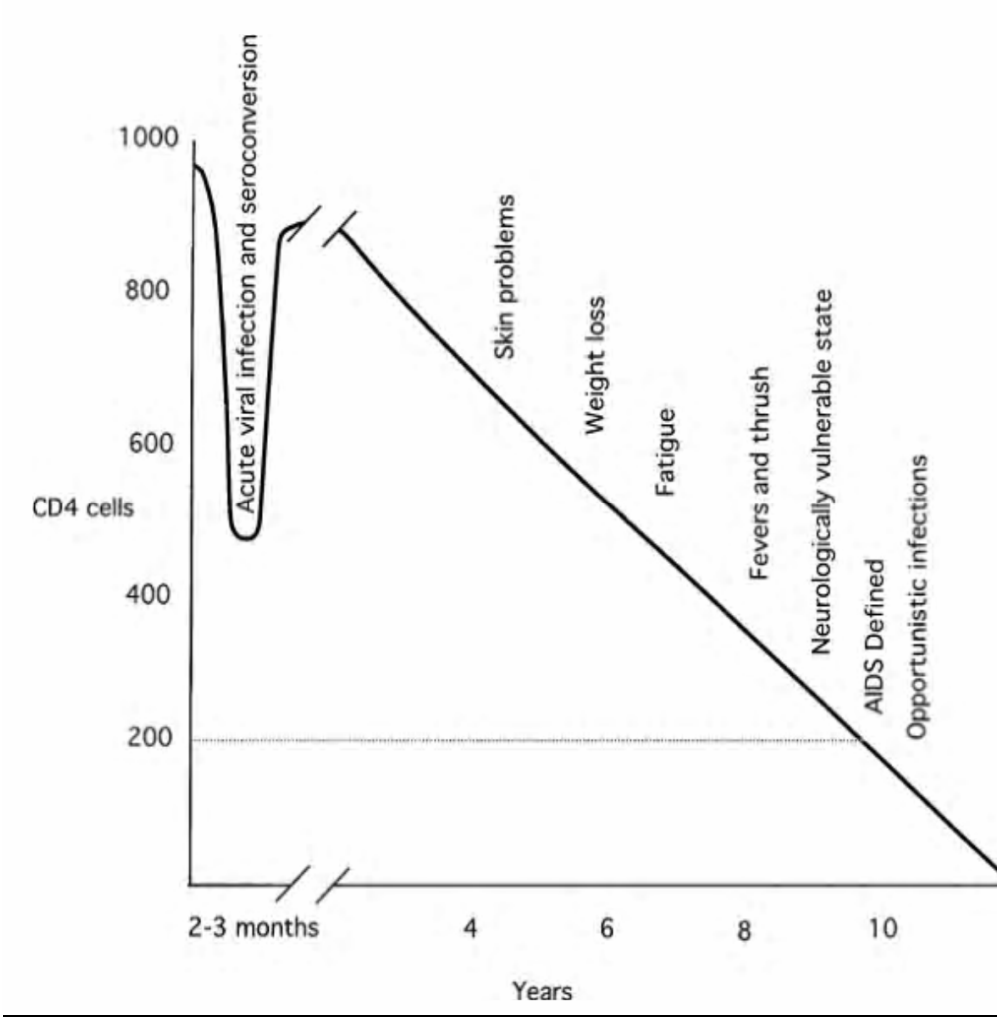
Starace et al ’s(2002) Neuro ICONA study revealed that Global NeuroPsychological impairment was significantly more frequent (25.5%)in subjects with lower educational level(i.e. <8years of education) than >8years of educated subjects(9.7%).Ryan et al(2005) also gave a similar results in their study done with 200 subjects.

UNEMPLOYEMENT:

Starace et al (2002) suggest that the impairment was more (28.2%) in unemployed than in employed subjects (10.3%).Similarly the impairment also lead to unemployment. Tozzi et al, 2004 with seventy subjects revealed that the health –related quality of life scores including social, occupational functioning was low in cognitively impaired patients.

CD4 COUNT

The CD4 count can be used to track the progress of the infection and the status of the immune system. The average person has approximately 1,000 CD4 lymphocytes per mm^3 (or μL) of blood. Before the development of effective treatment for HIV, the average patient's CD4 cell count dropped approximately 100 CD4 cells per mm^3 (or μL) per year, and, thus, over a 10-year course was completely decimated. The immune system becomes quite compromised as the CD4 cell count drops below 200 per μL, and "cellular" immunity diminishes and is finally lost. As shown in the following diagram, untreated patients with HIV infection have a brief severe decline in CD4 count immediately after infection. As the immune response to HIV begins the CD4 count returns to normal levels but then begins a slow decline. The CD4 count decreases by approximately 100 cells per year of infection in the average untreated patient. Over time, the effectiveness of immune function declines, and the patient may develop the conditions shown in the Figure. In the years before the development of effective treatment, this graph served as a kind of grim road map that ended inevitably in the death of the patient. (John Bartlett, 2005).



Gupta et al(2007) conducted a study to assess cognitive functioning in a sample of 119 adults infected with clade C HIV-1 who were not on antiretroviral medications their performance was compared with gender-, age-, and education-matched normative data derived from a sample of 540 healthy volunteers and a matched cohort of 126 healthy, HIV-1-seronegative individuals. Among the seropositive subjects, 60.5% had mild to moderate cognitive deficits characterized by deficits in the domains of fluency, working memory, and learning and memory..

Although the most immuno suppressed group (CD4 count < 200 cells/mm3 or viral load > 1,000,001 copies) was small, their rate of impairment in visual working memory was greater when compared to groups with better immune function.

Konov (2007) supported the above findings with the following association between CD4 count cut-offs and the percentage of cognitive impaired subjects.

CD 4 Count	**Percentages**
</=200 vs. >200	73.1 vs. 52.6
</=250 vs. >250	66.7 vs. 53.3
</=300 vs. >300	63.9 vs. 56.5
</=350 vs. >350	57.1 vs. 62.5

Wig et al (2004) found that there was a significant negative correlation between CD4 count and time taken on Trail making part A, B and significant positive correlation between CD4 count and scores of block design and digit symbol (both imply poor performance with lower CD4 (<200cells) cell count.

McCutchan et al (2007) documented improved performance on neuropsychological tests after initiating HAART .They also indicated

that this improvement was marginally associated with the continued or improving control of plasma HIV-RNA levels, but not with concurrent levels of immune recovery (CD4 lymphocyte counts).

Odease et al ‘s (2007) data collected from the following study with a total of 288 randomly selected subjects, comprising 96 HIV-positive symptomatic patients, 96 HIV-positive asymptomatic patients and 96 HIV-negative controls. The Recognition Memory Test and Choice Reaction Time tasks, components of the computer-assisted neuropsychological tests battery- the Iron Psychology 'FePsy' were used for cognitive assessments. The results supported McCutchan’s(2007) finding and stated that impaired ability for sustained attention was present irrespective of the CD4+ level relative to controls.But HIV-positive subjects with CD4+ counts < 200/microl and between 200 and 499/microl had significant memory impairment ($p < 0.001$ and $p < 0.001$ respectively) but there was no significant impairment among those with count > or = 500/microl.

Salawu et al (2008) studied with a selected population of 60 heterosexual asymptomatic treatment-naive HIV-positive subjects, They administered the Community Screening Instrument for Dementia (CSI-D) to assess language, memory, registration, attention and calculation, recall, praxis and orientation. HIV positives differed from individually matched

control subjects in certain measures of language expression, registration, attention and calculation, orientation to time, motor response and total CSI-D scores. The CD4 cell count of the HIV-seropositive subjects had no significant correlation with the cognitive test scores.

AIDS dementia complex:

AIDS dementia complex (ADC; also known as HIV dementia, HIV encephalopathy and HIV-associated dementia) is a common neurological disorder associated with HIV infection and AIDS. It is a metabolic encephalopathy induced by HIV infection and fueled by immune activation of brain macrophages and microglia.(Gray et al,2001).These cells are actively infected with HIV and secrete neurotoxins of both host and viral origin. The essential features of ADC are disabling cognitive impairment accompanied by motor dysfunction, speech problems and behavioral change.

ADC stage characteristics:

Stage 0 *(Normal)* Normal Mental and Motor Function

Stage 0.5 *(Subclinical)* Minimal symptoms of cognitive or motor dysfunction characteristic of ADC, or mild signs (snout response, slowed extremity movements), but without impairment of work or capacity to perform activities of daily living (ADL). Gait and strength are normal.

- **Stage 1** *(Mild)* Evidence of functional intellectual or motor impairment characteristic of ADC, but able to perform all but the more demanding aspects of work or ADL. Can walk without assistance.
- **Stage 2** *(Moderate)* Cannot work or maintain the more demanding aspects of daily life, but able to perform basic activities of self care. Ambulatory, but may require a single prop.
- **Stage 3** *(Severe)* Major intellectual incapacity - cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output. And/or motor disability - cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well.
- **Stage 4** *(End Stage)* Nearly vegetative. Intellectual and social comprehension and responses are at a rudimentary level. Nearly or absolutelymute. Paraparetic or paraplegic with urinary and fecal incontinence. . (Atkinson et al,1995).

Prevalence of ADC is between 10-20% in Western countries(Grant et al,2005) and has only been seen in 1-2% of Indian HIV patients.(Satishchandra et al,2000;Wadia et al ,2001).Whether minor cognitive-motor disorder predisposes to HIV-associated dementia is also

of some debate. It appears that some patients may continue to have minor problems (Mandal et al, 2008), whereas another group progresses to frank dementia. (Masliah et al, 1996).

ANTIRETROVIRAL THERAPY AND COGNITION

A neurologically active regimen was defined as one with 3 or more antiretroviral drugs known to penetrate the CNS in effective concentration. Individuals with advanced HIV infection receiving 3 or more neuroactive drugs showed a higher probability of reaching an undetectable cerebrospinal viral load. Seven antiretroviral drugs were defined as neuroactive drugs: nevirapine, efavirenz, stavudine, zidovudine, lamivudine, abacavir, and indinavir. **Principles for selecting the first-line regimen (NACO, 2007)**

1. Choose 3TC (lamivudine) in all regimens
2. Choose one NRTI to combine with 3TC (AZT **or** d4T)
3. Choose one NNRTI. (NVP or EFV)

In our ART center, Govt. Rajaji hospital, Madurai the combination of ZIDOVUDINE (300mg), LAMIVUDINE (150mg), NEVIRAPINE (200mg) was considered as a preferred regimen and administered in most of the patients.(NACO,2007).

Zidovudine (AZT) :

Zidovudine, (also known as AZT or ZDV) was the first drug approved for the treatment of HIV, is an anti-HIV treatment in a class of drugs called nucleoside reverse transcriptase inhibitors (NRTIs). The lowest effective dose of AZT has not been determined, and the currently recommended dose is 300-600 mg per day. Side effects can be anaemia , leucopenia, lip, mouth and tongue sores, bone marrow damage confusion, loss of speech or appetite, muscle aches, fever abnormal bruising or bleeding.

LAMIVUDINE(3TC)

Lamivudine (also known as 3TC), is an anti-HIV treatment in the class of drugs called Nucleoside Reverse Transcriptase Inhibitors(NRTIs).The recommended dosage of Lamivudine is 150 mg twice a day. There is also a 300 mg once a day formulation. Lamivudine has few side-effects, mainly nausea, vomiting, headaches, and rare cases of hair loss. Although not as commonly as with some other anti-HIV drugs, Lamivudine can cause peripheral neuropathy. A set of rare but serious side effects of nucleoside analog anti-HIV drugs is called lactic acidosis and severe hepatomegaly with steatosis (an enlarged fatty liver). Women, especially those who are oveweight, are particularly at risk

NEVIRAPINE

Nevirapine falls in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class of antiretrovirals. Both nucleoside and non-nucleoside RTIs inhibit the same target, the reverse transcriptase enzyme. The most common adverse effect of nevirapine is the development of mild or moderate rash (13%).Severe or life-threatening skin reactions have been observed in 1.5% of patients, including Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity. Nevirapine may cause severe or life-threatening liver toxicity, usually emerging in the first six weeks of treatment.

Since the introduction of Antiretroviral therapy, particularly after the concept of HAART (Highly active antiretroviral therapy) the debate regarding the effectiveness of HAART in the Neuropsychological impairment in HIV Patients continue in various part of the world.

Sacktor et al (1998) studies the effect of HAART in the cognitive impairment due to HIV. They were studied 474 homosexuals and followed from 1995 to 1997 after giving HAART. The results showed that relative to antiretroviral naïve patients, HAART participants showed better performance over the course of one year in psychomotor speed and Trail making part B.

Deutscha et al's(2001) data support the view that twice as many subjects (eight out of 22,36%) in the pre-HAART group developed new neuropsychological impairment than in the post-HAART group (four out of 24, 17 %). For all subjects, inclusion was restricted to those completing a detailed battery of neuropsychological tests at baseline and follow-up visits. These tests encompassed eight domains: abstraction/flexibility, attention/speed of information processing, learning, memory, verbal, perceptual-motor, motor, and sensory functioning.

Starace et al (2002) showed that Neuropsychological deficit was found in 14.0% of subjects on HAART vs. 10.7% of subjects who were not taking HAART. In patients with AIDS, neuropsychological deficit was found in 37.1% of subjects on HAART Vs 33.3% of subjects who weren't undergoing HAART regimen.

Tozzi et al (2004) studied 70 subjects on HAART and concluded that cognitive impairment in patients receiving HAART was associated with reduced HRQoL.(Health Related Quality of Life). Identifying cognitive impairment may provide motivation for additional treatment to help patients to compensate for deficits in functioning.

Lucette et al (2004) done a study with 97 HIV positive patients.Among them 41 subjects on Neuroactive HAART and 56

subjects on HAART.The results showed that both groups did not differ from one another on neuropsychiatric performance,but both groups were impaired compared with controls and the neuroHAART group showed significantly better memory performance ,unrelated to plasma viral load,than the HAART group.

Parson et al (2006) investigated the relationship between HIV-associated neurocognitive impairment and quality of life. HAART failures experienced slower psychomotor processing, and had increased self-reports of physical health complaints and substance abuse. Contrariwise, HAART successes experienced improved mental processing, demonstrating the impact of successful treatment on functioning.

A Large scale longitudinal study done by McCutchan et al (2007) Of 433 advanced AIDS patients with documented immune reconstitution (CD4 lymphocyte counts < 50 before and > 100 cells/microl after HAART), 286 had brief assessments of cognition (Trailmaking A/B and Digit Symbol Tests) at least once, no confounding neurological conditions, and available neuropsychological norms with comprehensive demographic corrections revealed that improved performance on neuropsychological tests was documented over a 2-year period 3-5 years after initiating HAART. This improvement was marginally associated

with the continued or improving control of plasma HIV-RNA levels, but not with concurrent levels of immune recovery (CD4 lymphocyte counts).

Bartlett (2008) studied 284 participants with a baseline prevalence of neuropsychiatric impairment (NPI) of 27%. Sequential analysis showed NPI decreased significantly to 16% at week 48 and 14% at week 96 after HAART. The author concluded that patients who responded to HAART for prolonged periods had stable or improving cognition, although continuing neurological recovery was incomplete on HAART.

But the following studies raise the question about the effectiveness of HAART on cognitive impairment due to HIV.

Dore et al (1999) collected data of All initial ADI (AIDS defining illness)cases in Australia over the period 1992-1997 . Three initial ADI groups were established: 1) ADC –AIDS DEMENTIA COMPLEX ,2)other predominantly central nervous system (CNS) ADIs (toxoplasmosis and cryptococcosis); and 3)non-CNS ADIs. For each ADI grouping, the proportion of total ADls, and median CD4 cell count in the pre-HAART era were compared with the HAART era. They concluded that a proportional increase in ADC compared with other ADIs and a marked increase in the median CD4 cell count at ADC diagnosis have occurred since the introduction of HAART in Australia. These

changes suggest that HAART has a lesser impact on ADC than on other ADIs, with the poor CNS penetration of many antiretroviral agents a possible explanation.

Wig et al(2004) from AIIMS done a follow up study and compared the patients on ART and without ART, but found no significant difference in cognitive performance.

Tozzi et al (2005) study raise concerns regarding the clinical relevance of CNS involvement as potent antiretroviral therapies become less effective.

Giancola et al (2006) studied 165 HIV-1 infected patients exposed to a stable highly active antiretroviral therapy (HAART) regimen and indicates that the use of stable HAART, including multiple drugs that have good CSF penetration, was not associated with neuropsychologic performance. To prevent independent replication of HIV in CSF with better control of a relevant reservoir of HIV is one of the crucial aims of therapeutic strategy.

Nath and Sacktor (2006) opined that highly actively antiretroviral therapy may need to be optimized in patients with HIV-associated cognitive impairment to achieve maximal central nervous system penetration; however, this therapeutic strategy may not be sufficient for halting the process. In some instances, the antiretroviral drugs themselves

may become the problem. New strategies for neuro protection that also target host genes which control HIV replication are being developed.

All of the above studies indicated the various opinions about cognitive impairment in HIV patients , the predictors of the impairment and the impact of ART in the cognitive impairment. With this background the present study was conducted in our local setting to know about the various features of HIV induced cognitive impairment.

MATERIALS AND METHODS

AIM OF THE STUDY:

To assess the prevalence and pattern of Neuropsychological impairment among HIV patients and to study longitudinally if ART (Anti retroviral therapy) has any impact on the Neuropsychological decline.

OBJECTIVES:

1. To assess the prevalence of cognitive impairment in HIV positive patients.

2. To know the pattern or type of cognitive impairment in the same patients.

3. To study the association between CD4 count and the level of impairment in cognition.

4. To know the effect of Antiretroviral therapy in the cognitive decline due to HIV.

The Detailed review about the relationship between cognitive impairment in HIV, CD4 count, and Antiretroviral Therapy reveal certain areas of agreement and certain areas of disagreement. The present study is a longitudinal study based on a hypothesis –verification design with use of validated structured tools and definite statistical design.

Methodology of the study was approved by the Institute Ethical Committee of Govt. Rajaji hospital. Study was conducted at ART-

Centre, Govt.Rajaji hospital, Madurai from the period of January 2008 to September 2008. Randomization was achieved by choosing consecutive patients who satisfied the following criteria.

INCLUSION CRITERIA

1. Seropositive patients diagnosed by ELISA Test.
2. Patients age should be between 18 years and 50 years.
3. He/She should be a literate. (Able to read and write)
4. Patient should be clinically stable to attend the interview.
5. Those who gave consent for initial study and for follow-up.

EXCLUSION CRITERIA

1. He /She should not suffer from present or past psychiatric illness including substance induced disorder.
2. Patient should not have present or past neurological disorders.
3. Patients with history of Head injury.
4. He /She should not suffer from any sensory – motor impairment.
5. Patients with severe medical illness or chronic drug intake that would interfere with the ability to perform the study.

HYPOTHESIS:

The following hypothesis were formulated

1. There will be a significant difference in the performance of Neuropsychological functions between index and control groups.

2. HIV causes cognitive impairment in various domains especially in Attention, Mental speed, Motor speed, Memory, Intelligence.

3. Performance became poor if the age increases.

4. Lower CD4 count associates with poor performance.

5. Duration after HIV positivity is positively correlated with cognitive impairment.

6. Antiretroviral therapy has a positive impact in the cognitive impairment.

OPERATIONAL METHODS

The Medical officer in ICTC identified the cases for the study on the basis of HIV positivity by ELISA then the author selected the subjects randomly based on the inclusion criteria. After ascertaining the fitness of the patient for a detailed neuropsychiatric interview, the patient was explained about the nature of the study. Confidentiality was assured. After obtaining the consent from the patient, the interview was held either in a single setting or in multiple setting as needed or on the request of the patient. This enabled the researcher to have co-operative and reliable interview with the patient. Since CD4 count 250 cells is the cut off range to start ART in HIV patients (followed in our ART centre), 30 consecutive patients with CD4 count less than 250 cells were assigned

as index cases and 30 patients with CD4 count more than 250 cells were taken as controls. After screening them for socio- demographic and illness-related details, Psychiatric evaluation, Neurological assessment and neuro-psychological evaluation (sometimes on more than two sessions) were done with the following tools. Then Anti retroviral therapy with 3 drugs (Zidovudine,Lamivudine,Nevirapine) were instituted to the index Cases since they had the CD4 count of less than 250 cells. Re-evaluation was performed in both groups after 3 months.

TOOLS USED:

1. MINI-International Neuro-psychiatric Interview (Sheehan and Lecrubier ,1992)
2. Standard progressive matrices (Raven, 1989)
3. Finger tapping test (Spreen and Stauss, 1998.)
4. Digit symbol substitution Test (Wechsler,1981)
5. Color Trails Test (D' Elia et al,1996)
6. Digit vigilance Test (Lezak, 1995)
7. PGI Memory scale (Pershad, 1977)

1.M.I.N.I(Mini Intenational Neuropsychiatric Interview)

The M.I.N.I.(1990) is the most widely used psychiatric structured diagnostic interview instrument in the world. The M.I.N.I. has been translated into 43 languages and is used by mental health professionals

and health organizations in more than 100 countries. The M.I.N.I. is a short, structured diagnostic interview that was developed in 1990 by psychiatrists and clinicians in the United States and Europe for DSM-IV and ICD-10 psychiatric disorders. It includes modules for 23 disorders and features questions on rule-outs, disorder sub typing, and chronology. It also features a number of algorithms to handle hierarchical rule-outs in the event that the patient had more than one disorder at a time. With an administration time of approximately 15 minutes, the M.I.N.I. is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies. The M.I.N.I. has been validated against the much longer Structure Clinical Interview for DSM diagnoses (SCID-P) in English and French and against the Composite International Diagnostic Interview for ICD-10 (CIDI) in English, French and Arabic. It has also been validated against expert opinion in a large sample in four European countries (France, United Kingdom, Italy and Spain).In India during 2005 a study on attempted suicide by Chandrasekeran et al used the MINI scale .Recently Venketsubramanian et al (2007) used this instrument to diagnose schizophrenia in their study on Relationship between Insulin growth factor and Schizophrenia.

2. STANDARD PROGRESSIVE MATRICES

Raven's Standard Progressive Matrices(1936) (often referred to simply as Raven's Matrices) are multiple choice tests of abstract reasoning, also used for assessment for intelligence. Originally developed by Dr John C. Raven in 1936. In each test item, a candidate is asked to identify the missing segment required to complete a larger pattern. Many items are presented in the form of a 3x3 or 2x2 matrix, giving the test its name. The booklet comprises five sets (A to E) of 12 items each (e.g. A1 through to A12), with items within a set becoming increasingly difficult, requiring ever greater cognitive capacity to encode and analyze information. All items are presented in black ink on a white background. The actual scores obtained by people living in most countries with a tradition of literacy - from China, Russia, and India through Europe to Kuwait - are very similar at any point in time. Adequate standardization, ease of use (without written or complex instructions), and minimal cost per person tested are the main reasons for its widespread international use in most countries of the world.

3.FINGER TAPPING TEST

The Finger Tapping Test is used to measure motor speed. There are several brain structures mediating motor speed. The prefrontal cortex mediates motor planning; the supplementary motor area mediates

initiation of motor acts, while the premotor cortex, basal ganglia and the cerebellum mediate fine motor control. Motor speed reflects the efficiency of this integration. The Finger Tapping Test measures the speed with which the index finger of each hand can tap. It consists of a tapping key mounted on a box. The Subjects taps the tapping key with the index finger of each hand. The subject is instructed to tap the key as fast as he/she without moving body or shoulder. The subjects is given a total of 5trials lasting 10 seconds each. The average number of taps over five trials forms the score of that hand. This test takes about 5minutes.

4.DIGIT SYMBOL SUBSTITUTION TEST

The Digit Symbol Substitution (Wechler, 1981) is a test of visuo motor coordination, motor persistence, sustained attention and response (mental) speed. Mental speed is a composite measure, which requires rapid processing of information also requires coordination of different areas of the brain. The test consists of a sheet in which numbers 1 to 9 are randomly arranged in 4 rows of 25 squares each. The subject substitutes each number with a symbol using a number-symbol key given on the top of the page. The time taken to complete the test forms the score. Errors made are noted down. The test takes about 6-7minutes.

5.COLOR TRAILS TEST

The color trails test (D'Elia et al,1996) was developed by the WHO as part of Multicenter study on HIV infection. The Test is an analogue of the Trail making test and is considered to be free from the influence of language. It has two parts .Part 1 requires sustained attention, perceptual tracking and simple sequencing while part 2 requires mental flexibility in addition to the above. The test is considered as a measure of focused attention because in both parts of the test, the subject has to ignore irrelevant numbers while scanning for the number, which is next in sequence. In each part a practice form precedes the test.

6. DIGIT VIGILANCE TEST:

The Digit Vigilance Test (Lezak, 1995) consists of numbers 1 to 9 randomly ordered and placed in rows on a page. There are 30 digits per row and they are closely packed. The same level of attention is required over a period of time. The subject has to focus on the target digits 2 and 8 amongst other distracter digits. Time taken and number of errors were taken as scores. Inability to sustain and focus attention leads to both increased time to complete the test as well as errors.

7. PGI MEMORY SCALE: (Persad 1997; Persad and Wig 1979)

It's a Battery of Memory tests was constructed and standardized in 1977(Persad 1997; Persad and Wig 1979) in India. Authors observe that

while constructing the test efforts were made to ensure that it is not unduly dependent on intelligence and is equally valid for both sexes and applicable and acceptable to illiterate and unsophisticated subjects who constitute the majority of subjects in Indian hospitals and clinics. The instruction and administration are simple. The scale consists of ten subsets and intercorelation between them are moderate to negligible. Performance is not affected by scores in intelligence. The test-retest reliability ranged between 0.70 and 0.84 for psychotic groups. 0.48 and 0.84 for normal group.

STATISTICAL DESIGN:

The following statistical methods were used in this study.

Central tendencies and the dispersion of the variables were studied using descriptive statistical methods such as mean, standard deviation. Comparison of the mean values between the groups was done using student's t test and intra group comparison of the variables during the follow-up was studied by using paired t test. The significance of association between predictors and the neuropsychological testing was made out by Pearson's coefficient of correlation. The significance of cognitive decline in the index group over three months in comparison to

that of the controls was studied by using Analysis of Covariance (ANCOVA).

LIMITATIONS OF THE STUDY

1. A larger sample size in both index and control groups could have made the results more generalisable.
2. Consecutive follow up of the groups periodically for a longer period could have enabled a more detailed study of pattern of decline and the possible protective effect of ART.

RESULTS

TABLE-1. SOCIODEMOGRAPHIC VARIABLES OF INDEX PATIENTS AND CONTROLS

	Index Group (N=30)	Controls (N=30)
AGE in years		
a)21 to 35	20	16
b) 35 to 50	10	14
INCOME		
Above Rs 2500	11	8
Below Rs 2500	19	22
SEX		
Men	23	22
Women	7	8
DOMICILE:		
Rural	15	20
Urban	15	10
MARITAL STATUS		
Married	25	26
Single	5	4
OCCUPATION		
Salaried	21	20
Self-Employed	9	10
EDUCATION:		
7 to 10^{TH} STD	22	23
Above 10^{TH} STD	8	7

Table I shows the Demographic variables of both subjects and control groups. It shows that about 66% (20 out of 30) of the index patients are less than 35 years. In control groups about 53% peoples are less than 35 years. Both groups represent the most affected age group.

Both group consists of about 75% of male members and indicating the high prevalence and awareness of male population. In the index groups rural and urban people represent almost equal (50%) percentage where as in the control group rural people slightly predominate.

About 80% in both groups are married and in both groups about 30% in both groups are self/un employed others are working as salaried individual.

Lowest education in both groups are 7^{th} standard, about 26% in both groups are studied above 10^{th} standard.

TABLE-2. Comparison of disease related variables of index and control groups

	CASES (N-30) MEAN (S.D)	CONTROLS(N-30) MEAN (S.D)	't'
CD-4 COUNT	190.89(79.4)	361.70(68.3)	9.45**
DURATION in months	16.89(12.6)	10.93(6.8)	2.71**
BLOOD UREA	24.33(7.7)	25.13(5.2)	0.49
BLOOD SUGAR	96.03(16.3)	98.53(14.0)	0.56

Df = 58 **** p < .01**

Table -2 shows the comparison of disease related variables indicated that CD4 count was lower and duration of illness longer for the index group and the difference was statistically significant. Blood urea and blood sugar did not differ significantly.

TABLE-3 Comparison of neuropsychological performance of index and control groups

	CASES (N-30) MEAN(S.D)	CONTROLS (N-30) MEAN (S.D)	't'
Raven's Matrices	18.86(4.8)	20.13 (4.7)	1.65
Finger Tapping			
Right	29.70(3.3)	28.80(2.7)	1.37
Left	29.00(3.5)	27.60(2.3)	1.91
Digit Symbol test	7.76(2.9)	5.43(1.8)	1.44
Color Trail			
1	4.10(1.5)	3.16(0.6)	3.24**
2	7.20(2.1)	5.96(1.2)	2.90**
Digit Vigilance			
Time	4.33(1.1)	3.83(1.3)	1.66
Error	1.16(1.5)	0.50(0.7)	2.36*
PGI Memory Scale	75.43(9.6)	79.00(7.2)	1.72

Df = 58. * p < .05; ** p < .01.

Table – 3 : Comparison of neuropsychological performance of index and control groups showed that in color trail test 1 and 2 and in Digit Vigilance-Error score statistically significant differences were observed. Even though Index patients scored lower in Raven's matrices and PGI memory scale scores and had longer duration in Finger Tapping 1 and 2 and Digit Vigilance-Time than the controls, the differences were not statistically significant .

TABLE 4 Correlation between disease variables and neuropsychological performances among the index patients

	AGE	DURATION	CD-4
Raven's Matrices	0.04	0.26	-0.05
Finger Tapping			
Right	0.11	-0.13	0.13
Left	0.12	-0.14	0.18
Digit symbol	0.27	-0.06	-0.21
Color Trail test			
One	0.25	0.04	-0.28
Two	0.31	0.03	-0.24
Digit Vigilance			
Time	0.42**	-0.31	-0.19
Error	-0.08	0.02	-0.14
PGI Memory Scale	-0.21	0.07	0.31

Values refer to Pearson's γ.

* $p < .05$; ** $p < .01$.

Values given with * are statistically significant.

Correlation between neuropsychological performance and disease-related variables showed that Digit Vigilance-Time was significantly correlated with age and other associations were not statistically significant.

TABLE-5 -Comparison of the cognitive scores in index patients both during initial evaluation and three months after ART

	CASES (N-30) MEAN(S.D)	FOLLOWUP (N-30) MEAN (S.D)	Paired 't'
Raven's Matrices	18.86(4.8)	19.07(4.6)	2.26*
Finger Tapping			
Right	29.70(3.3)	29.53(3.0)	1.40
Left	29.00(3.5)	28.83(3.26)	1.30
Digit Symbol test	7.76(2.9)	7.40(2.0)	2.01
Color Trail			
1	4.10(1.5)	4.03 (1.4)	1.14
2	7.20(2.1)	6.87(2.0)	2.27*
Digit Vigilance			
Time	4.33(1.1)	4.3(1.7)	0.37
Error	1.16(1.5)	0.77(1.1)	1.98
PGI scale	75.43(9.6)	75.50(9.1)	0.23

Table 5 showed the comparison of the cognitive scores in index patients both during initial evaluation and three months after ART, indicated that there was a stasticaly significant differnces were noticed in Raven's test and color trail test two.There was notable differences in Digit vigilance error and digit vigilance scores,but they are not statisticaly significant.

TABLE-6 Comparison of neuropsychological performance scores of control patients both during initial and follow up visits (after 3 months)

	CONTROLS (N-30) MEAN (SD)	FOLLOWUP (N-30) MEAN(SD)	PAIRED ' t'
Raven's Matrices	20.13 (4.7)	20.37(4.3)	0.74
Finger tapping			
Right	28.80(2.7)	28.70(2.7)	1.13
Left	27.60(2.3)	27.67(2.3)	1.00
Digit Symbol test	5.43(1.8)	5.43(1.9)	0.00
Color Trail			
1	3.16(0.6)	3.13(0.7)	1.00
2	5.96(1.2)	6.00(1.3)	0.57
Digit vigilance			
Time	3.83(1.3)	3.80(1.3)	1.00
Error	0.50(0.7)	0.57(0.77)	1.14
PGI scale	79.00(7.2)	79.10(7.3)	0.83

Table-6 showed the Comparison of neuropsychological performance scores of control patients both during initial and follow up visits (after 3 months).It indicated that there was some negligible differences in the scores of Raven's matrices and PGI memory scale but they were not statistically significant. Almost no changes were noted in the scores of digit vigilance and digit symbol substitution test.

TABLE-7 Comparison of neuropsychological functions of index group and the control group over three months' followup.

	Cases Mean (S.D)	Followup Mean (S.D)	Controls Mean (SD)	Followup Mean(SD)	F
Raven's Matrices	18.86(4.8)	19.07(4.6)	20.13 (4.7)	20.37(4.3)	0.27
Finger Tapping					
Right	29.70(3.3)	29.53(3.0)	28.80(2.7)	28.70(2.7)	0.01
Left	29.00(3.5)	28.83(3.26)	27.60(2.3)	27.67(2.3)	0.53
Digit Symbol test	7.76(2.9)	7.40(2.0)	5.43(1.8)	5.43(1.9)	0.05
Color Trail					
1	4.10(1.5)	4.03 (1.4)	3.16(0.6)	3.13(0.7)	0
2	7.20(2.1)	6.87(2.0)	5.96(1.2)	6.00(1.3)	2.32
Digit Vigilance					
Time	4.33(1.1)	4.3(1.7)	3.83(1.3)	3.80(1.3)	0.01
Error	1.16(1.5)	0.77(1.1)	0.50(0.7)	0.57(0.77)	1.33
PGI scale	75.43(9.6)	75.50(9.1)	79.00(7.2)	79.10(7.3)	0.27

Df-58 *<0.5,p*<0.01

TABLE-7 showed the Comparison of neuropsychological functions of index group and the control group over three months' followup, none of the variables were significant.

DISCUSSION

Neurocognitive changes have been documented along various dimensions, with varying severity in different stages of HIV-AIDS disease. Atkinson and Grant (1994) reported an annual rate of HIV dementia in 7 to 14% of the patients and that psychopathology due to milder form of cognitive impairment occurred in half of the patients with frank AIDS. Though during early stages, the impairments were mild, they exerted a summated decline in the individual's behavioral adaptation, vocational efficiency and quality of life (Edwin et al, 1999). Different cognitive functions showed a different lag in onset and have a differing course of decline (Gupta et al, 2007; Skolasky et al, 2007). Some of these changes were amenable to earlier management with anti retroviral therapy (Cysique et al, 2004).

Previous studies have documented the nature and extent of neuropsychological changes in different phases of the disease but there were differences in considering ART as preventive of further deterioration of the impairments. Hence, the study was based on Hypothesis verification design. The index group and control group were identified with definite homogenization and comparability. Measures of impairment were frequently-used neuropsychological tools, previously used in native population and with an acceptable validity.

The present study was conducted on the most immuno-suppressed group (CD4 count < 250 cells) and the socio-demographic profile of predominantly middle aged, married men of average education from both rural and urban domicile. Since most of the people attending ICTC had similar socio economic profile, these patients may be considered as representative of the those attending the ICTC. Comparability between the two groups was maintained.

Comparison of the physical parameters showed that CD4 count and duration of the illness were significantly different. The difference in CD4 count was expected as it formed the criteria for the difference between the index patients and controls. Longer duration of the illness in these patients indicated that increasing immuno-suppression was the resultant of length of the illness. Biochemical parameters like blood urea, sugar in both groups did not vary significantly.

Comparison of neuropsychological performance of the patients with the controls showed that patients were significantly poor in Colour Trail test 1 and 2 and made more errors in Digit Vigilance test. Colour trails test is a measure of sustained attention. Increasing error-proneness in Digit Vigilance further indicated their inability to sustain attention. Disturbances in attention have been identified as a hallmark of early

disturbance and rapid decline in HIV related neuro-cogntive disturbances (Edwin et al, 1999; Cysique et al, 2002; Cysique et al, 2004). Correlations between illness-variables and decline in attention have been recognized as resulting in secondary memory disturbances (Carey et al, 2006) but in our study no significant impairment in memory was noted. Though during early stages, the impairments were mild, they exerted a summated decline in the individual's behavioral adaptation, vocational efficiency and quality of life (Tozzi et al, 2004).

The pattern of neuropsychlogical deficits found in this study is similar to what has been found in USA, Uganda and Australia where HIV Clades A,B,D are highly prevalent.(Janssen et al,1992; Portegies et al,1993; Kevin Robertson,2007). In India, clade C is the predominant one and underlying neuropathology is same in various clades.

Correlations between illness-variables and neuropsychological performance did not show any statistically significant association, except between duration in Digit Vigilance Test and age of the individual. Sacktor et al (2007) observed similar differences in aged HIV patients and concluded that age was associated with lower performance interests of memory, executive functions and motor performance. They attributed such differences to changes due to advanced age itself or due to age-

associated co-morbidities. The CD4 cell count of the HIV-seropositive subjects had no significant correlation with the cognitive test scores. The results were similar to the findings of Villa et al (1996). Wig et al (2004) and Salowu (2008) found that there was a negative correlation between CD4 count and attention. According to Odiase et al (2007) there was impaired ability for sustained attention irrespective of the CD4 level relative to controls.

Comparison of cognitive scores in the index patients before and after 3 months of ART found a significant difference in Standard progressive matrices and in color trail 2 indicated that there was a definite change in attention as well as in mental flexibility. Similar comparison in the control didn't show difference in any of the tests. Thus, significant improvements in the index group were unlikely to be a derivative of practice effects. Early changes in response to ART were also observed in other studies especially in attentional functions (Cysique et al, 2004).

Analysis of Covariance between the groups considering their performances in the initial assessment and at three months' follow-up showed that the improvements in index group were not significantly more than the improvements of the control group in any of the dimensions of neuropsychological functions. Incremental changes observed in the index

group during follow-up were not sufficiently incremental to attain statistical significance. The insufficiency could be a resultant of the short duration of follow-up and might become prominent in continued follow-up evaluations (Sacktor et al, 2005). The possibility of improvement is explainable as resulting from any of neuropsychological reconstructive processes and if provable in long term follow-up studies could point to an effective way of preventing neuro-cognitive decline.

CONCLUSION

This longitudinal study has the objective to analyse the pattern of neuropsychological impairment in HIV positive patients and the impact of Antiretroviral Therapy on Cognitive impairment.The findings in the study bring to light certain observations which, inspite of the limitations in the study,may be generalizable. It has been inferred that

1.There was significantly more impairment in neuroopsychological functons in the index patients in comparision to controls.

2. Signifcant impairment in both sustained and focused attention was noted from our study.

3.No significant difference was noted in Mental speed,Motor speed and Memory.

4.Age and duration after postivity were possitvely correlated with neuropsychologcal performance.

5.CD4 count has no positive correlation with the cognitive scores.

6.Antiretroviral Therapy improves the neuropsychologcal performance especialy in sustained attention as well as in mental flexibility.

Neuropsychological deficits particularly in attention were likely to influence the patients activities of daily living and ability to maintain

employment. Early recognition and treatment of cognitive dysfunction by involving psychiatrist as a team member in the ART or by mandatory opinion of the psychiatrist for all HIV positive patients may lead to a better outcome. Further studies to characterize HIV associated cognitive impairments and their impact in daily living and employment are necessary.

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APPENDICES

APPENDIX-I

PROFORMA

S.No : Date:

Name :

Address :

Age :

Sex : Male/Female In Patient / Outpatient

Education :

Occupations :

Income :

Marital Status :

Handedness :

Regarding HIV

CD4 Count :

WHO Staging I / II / III / IV :

Clinical Observations

Sensory Function of

Vision / Hearing / Touch :

Motor Functions :

H/O Com Medical Illness :

H/O Substance Dependence :

H/O Head Injury :

H/O Mental Illness :

Family History : Mental Illness / Neurological Illness____

Lab Investigations

Blood Urea :

Blood Sugar :

SGOT :

SGPT :

Case History

APPENDIX-II

MINI NEUROPSYCHIATRIC INTERVIEW

GENERAL INSTRUCTIONS:

The M.I.N.I. was designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Validation and reliability studies have been done comparing the M.I.N.I. to the SCID-P for DSM-III-R and the CIDI (a structured interview developed by the World Health Organization). The results of these studies show that the M.I.N.I. has similar reliability and validity properties, but can be administered in a much shorter period of time (mean 18.7 ± 11.6 minutes, median 15 minutes) than the above referenced instruments. It can be used by clinicians, after a brief training session. Lay interviewers require more extensive training.

GENERAL FORMAT:

The M.I.N.I. is divided into modules identified by letters, each corresponding to a diagnostic category.

•At the beginning of each diagnostic module (except for psychotic disorders module), screening question(s) corresponding to the main criteria of the disorder are presented in a gray box.

•At the end of each module, diagnostic box(es) permit the clinician to indicate whether diagnostic criteria are met.

RATING INSTRUCTIONS:

All questions must be rated. The rating is done at the right of each question by circling either Yes or No. Clinical judgment by the rater should be used in coding the responses. Interviewers need to be sensitive to the diversity of cultural beliefs in their administration of questions and rating of responses. The rater should ask for examples when necessary, to ensure accurate coding. The patient should be encouraged to ask for clarification on any question that is not absolutely clear.

The clinician should be sure that each dimension of the question is taken into account by the patient (for example, time frame, frequency, severity, and/or alternatives).Symptoms better accounted for by an organic cause or by the use of alcohol or drugs should not be coded positive in the M.I.N.I.

APPENDIX-III

STANDARD PROGRESSIVE MATRICES

Raven's Standard Progressive Matrices (often referred to simply as Raven's Matrices) are multiple choice tests of abstract reasoning, also used for assessment for intelligence. In each test item, a candidate is asked to identify the missing segment required to complete a larger pattern. Many items are presented in the form of a 3x3 or 2x2 matrix, giving the test its name. The booklet comprises five sets (A to E) of 12 items each (e.g. A1 through to A12), with items within a set becoming increasingly difficult, requiring ever greater cognitive capacity to encode and analyze information. All items are presented in black ink on a white background.

APPENDIX-IV

DIGIT SYMBOL SUBSTITUTION TEST

1	2	3	4	5	6	7	8	9
-	⊥	⊃	L	∪	O	^	x	=

2 1 3 7 2 4 8 1 5 4 2 1 3 2 1 4 2 3 5 2 3 1 4 6 3

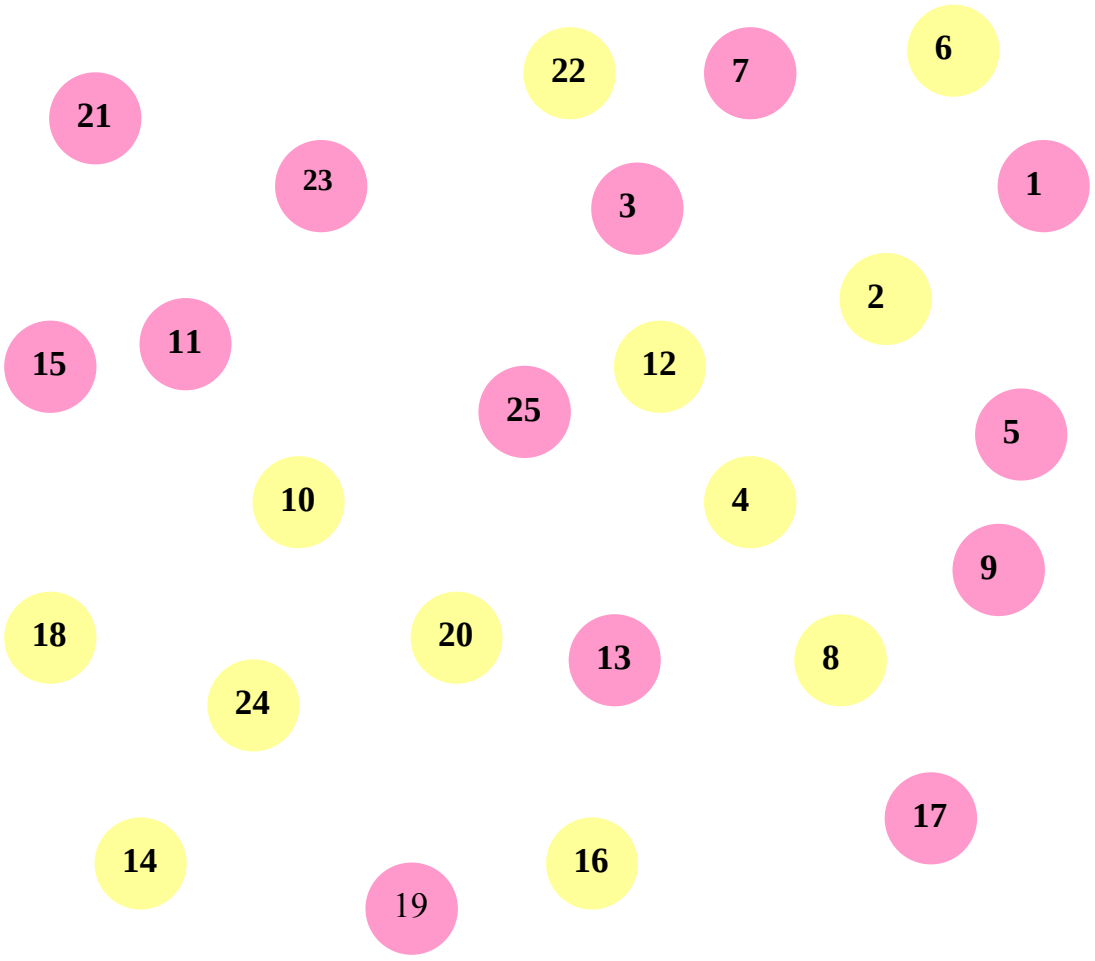
1 5 4 2 7 6 3 5 7 2 8 5 4 6 3 7 2 8 1 9 5 8 4 7 3

6 2 5 1 9 2 8 3 7 4 6 5 9 4 8 3 7 2 6 1 5 4 6 3 7

9 2 8 1 7 9 4 6 8 5 8 7 1 8 5 2 9 4 8 6 3 7 9 8 6

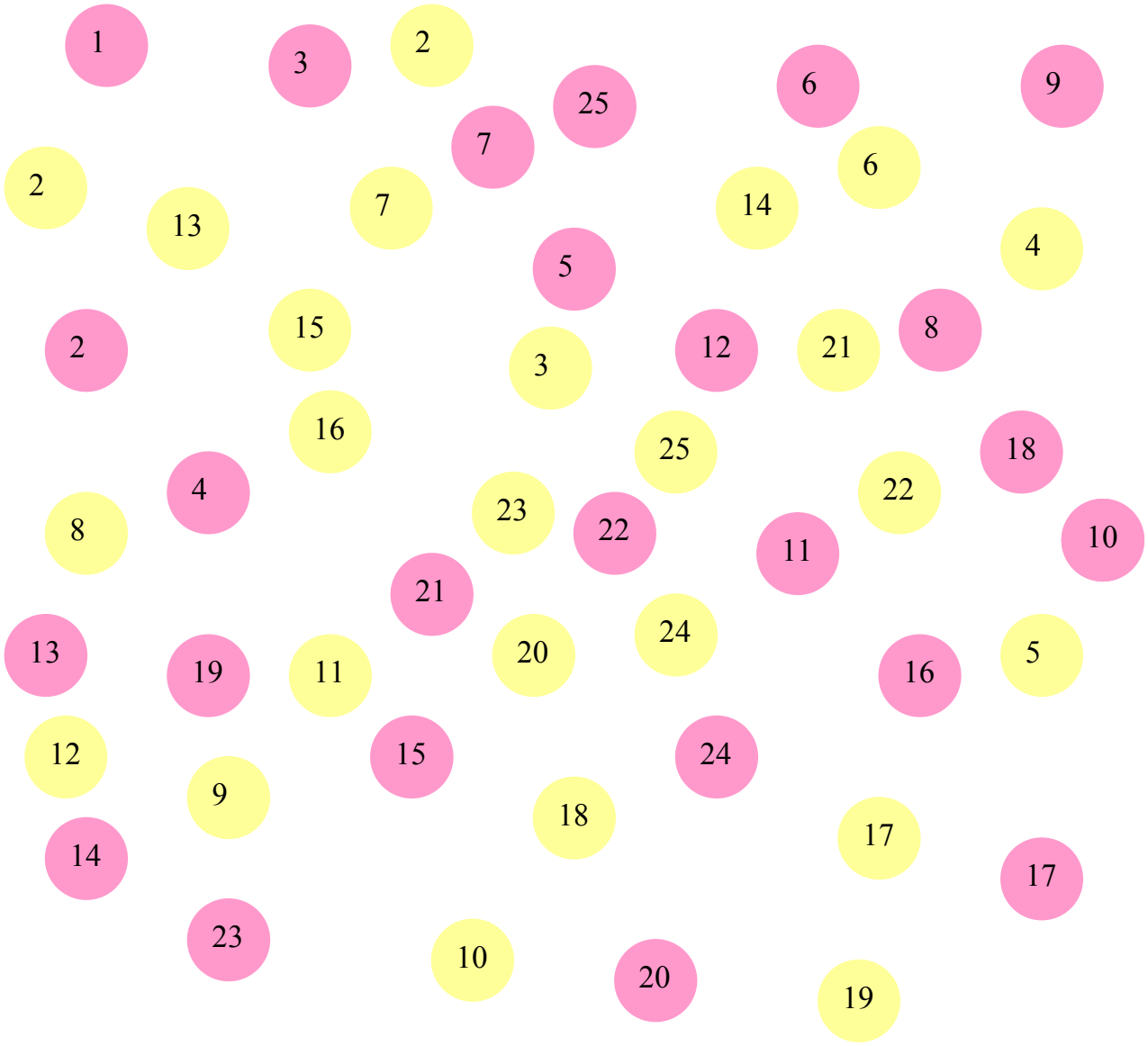
APPENDIX-V

COLOR TRAIL TEST -ONE



APPENDIX-VI

COLOR TRAIL TEST-TWO



APPENDIX-VI

DIGIT VIGILANCE TEST

"2" and "8"

6 2 6 7 2 3 1 3 8 5 5 5 8 1 7 9 1 7 2 7 4 5 7 6 1 3 9 6

2 7 1 5 2 7 9 1 9 4 6 9 5 7 1 8 9 5 6 5 4 2 1 1 6 9 7 5

9 4 6 9 5 7 1 8 9 5 6 5 4 2 7 1 5 2 7 9 1 7 1 1 1 4 2 8

5 1 8 3 4 2 6 9 9 9 6 7 8 6 7 1 7 1 3 4 3 9 8 4 2 7 1 5

1 9 7 9 7 1 6 7 8 6 5 5 7 2 9 6 5 9 5 4 7 3 2 4 5 6 1 4

4 6 8 4 1 4 1 7 2 4 7 1 7 6 7 5 4 9 8 7 5 6 2 1 6 9 3 1

7 8 6 7 1 7 1 3 4 3 9 8 6 5 1 8 3 4 2 6 9 9 6 1 6 4 3 9

4 9 3 8 7 2 5 4 4 8 7 6 4 1 4 7 2 6 8 7 5 6 3 2 6 4 4 6

4 8 6 4 7 5 4 4 7 9 7 3 6 8 6 5 4 7 4 3 4 9 2 5 3 5 4 7

4 9 3 3 8 1 8 4 2 6 5 6 6 1 7 2 4 2 9 7 9 7 6 1 5 1 4 1

APPENDIX-VII

PGI MEMORY SCALE

PGI Memory Scale:

I. Remote Memory

1. Age
2. Birth Place
3. a) When were you married?

   b) When did you start working?

   c) When did you stop your education?
4. What's your last child age / brother's age?
5. When did you first came to GRH?
6. When did you visit the ward for the first time? (ART)

/6

II. Recent Memory

1. Supper last night?
2. Breakfast this morning?
3. Name of this month?
4. Day is to-day?

5. Whom did you meet yesterday?

/5

III. Mental Balances

1. A, B, …… Z (or) A,B,C,.....
2. 20-0 in reverse
3. 40-3 in reverse

/3

IV. Attention and Concentration

1. DF

(a) 5-7-3 (b) 4-7

5-3-87 6-5-8

4-6-4-95 29763

2. DB

8 -5 2-8

4 3 7 8-5-1

8 5 6 3 3 7 5 9

4 7 2 9 1 6 1 5 8 3

V. Delayed Recall (Repeat after one minute)

(1) Umbrella	(2) Fish
Flower	Lamp
Clock	Rupee
Picture	Taj
Pencil	Doll

/10

VI. Immediate Recall

1. Rama getup from the chair, opened the door and wentout

/3

2. The patient was laid on the couch, Examined, Prescription was written and asked to come next day

/4

3. No water in Mohan's House, took the bucket went to the top he street, filled it with water at returned

/5

VII. Verbal Retention for Similar Pairs

		Trial-1	Trial-2	Trial-3	
1. UWm	×				
2. CÉlé	LNlé				
3. Bi	ùTi				
4. TLp	CWî				
5. Lñlé	ùYsû[				
Total		/5	/5	/5	/15

VIII. For Dissimilar Pairs

		Trial-1	Trial-2	Trial-3	
1. úUû_	Lñlé				
2. UWm	EVWm				
3. Å[dá	L¼]m				
4. áZkûR	LNlé				
5. L]î	BZm				
Total		/5	/5	/5	/15

IX. Visual Retention (Cards 1 to 3 = 1 scores each (6)

4 = 3 scores (3)

5 = 4 scores (4)

Total = /13

1. Card -1
2. Card -2
3. Card -3
4. Card -4
5. Card -5

X. Recognition (Total 10)

No. of Objects Correctly Recognized (-)	-	
No. of Objects Wrongly Recognized	-	
Total Score	-	/10