A STUDY OF "P300 EVALUATION IN ASYMPTOMATIC

HIV INFECTED PATIENTS"

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CERTIFICATE

This is to certify that the Dissertation entitled, **"A STUDY OF P300 EVALUATION IN ASYMPTOMATIC HIV INFECTED PATIENTS"** is the bonafide record work done by Dr.S.Sakthi Velayutham under our guidance and supervision in the Institute of Neurology, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, submitted as partial fulfilment for the requirements of D.M. Degree examination Branch I NEUROLOGY, AUGUST 2011, under The Dr.M.G.R. Medical University, Chennai.

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DECLARATION

I solemnly declare that this dissertation titled **"A STUDY OF P300 EVALUATION IN ASYMPTOMATIC HIV INFECTED PATIENTS"** is done by me in the Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of Prof. Dr. K.Bhanu, M.D., D.M., Professor of Neurology, and Prof. Dr. R.M. Bhoopathy, M.D., D.M., Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfilment of the university requirements for the award of the degree of D.M.Neurology.

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CONTENTS

INTRODUCTION

The HIV/AIDS epidemic is a major global public health crisis with an estimated 40 million adults and children living with HIV infection [1]. HIV Associated Neurocognitive Disorders (HAND) is characterized by cognitive, behavioral, and motor dysfunction and occurs in 10-15% of HIV-seropositive individuals with advanced infection [2] in the US .The frequency of HAND is largely unknown in resource-limited countries, although preliminary surveys suggest a relatively high frequency of cognitive dysfunction [3].

If a similar proportion were to be seen on a global scale, then HIV dementia would be the most common cause of dementia worldwide in patients under the age of 40 years. Despite the availability of HAART, HIV-related neurological disorders continue to represent substantial personal, economic and societal burdens. [4,5]

Frequently a set of patients show subclinical neurocognitive impairment, which does not fulfill the criteria for HIV Associated Dementia proposed by the American Academy of Neurology (AAN). [6]

These patients do not exhibit recognizable functional restriction in daily activities and may be missed in conventional screening and Neuropsychological testing. But they progress to frank dementia eventually

unless it is identified earlier and checked by effective Anti Retroviral Therapy.

Early recognition of subclinical neurocognitive impairment is essential to prevent the transformation to frank dementia which is associated with significant morbidity and mortality. The diagnosis of neurocognitive impairment is dependent upon a clinical history and a detailed Neuropsychological testing which is time consuming, language and education dependent, and often not available in developing countries. [7]

Continuous high level replication of HIV virus leads to virus and immune mediated killing of CD4 T lymphocytes , resulting in CD4 depletion. As the disease progresses, CD4 count declines and this has been proved in many studies.[8]

Evoked Response Potential (ERP) testing like P300 evaluation may show abnormalities in patients with subclinical neurocognitive impairment [9] and may help in identifying patients with subclinical impairment which has therapeutic implications.

With this background, this study of, " P300 evaluation in asymptomatic HIV infected patients" to explore subclinical electrophysiological abnormalities was conducted at Institute of Neurology,

Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

Correlation of CD 4 profile with P300 latency was also analyzed in the study as it has been shown earlier that CD4 count has an inverse correlation with P 300 latency. [10]

REVIEW OF LITERATURE

Decline in mental processes is a common complication of HIV infection.

HIV-Associated Neurocognitive Disorders (HAND)

HIV can mimic the effects of other neurocognitive disorders. An accurate diagnosis must differentiate from among a number of diseases that present similar symptoms. Some conditions that share symptoms include: depression, encephalitis, substance abuse, thyroid disorder, Alzheimer's, Parkinson's, Huntington's, pick's, Creutzfeldt-Jacob, cerebrovascular disease. Symptoms may include: delirium, memory impairment, apathy, social withdrawal, psychosis, seizures, behavioral changes, disinhibition, tremors, ataxia, repetitive movements, imbalance, hypertonia, visual impairment, etc.

The neurologic consequences of HIV were recognized early in the epidemic. AIDS dementia complex (ADC) was the term used to collectively describe the effects of HIV on the CNS. Today, the term ADC is a being displaced by standards that focus more on how HIV is currently affecting neurocognitive status and less on end stage disease.

Currently, highly active antiretroviral therapy (HAART) is still effectively suppressing the life threatening opportunisitic infections which are the hallmark of AIDS. HIV^+ patients are living longer before their condition

meets AIDS criteria. The incidence of the more severe form of neurocognitive disorder, HIV-associated dementia (HAD), has also decreased but improved testing and awareness has shown that HIV has a neurologic effect long before a diagnosis of AIDS. Regardless of HAART, the neurocogitive effects of HIV are still associated with the stage of HIV disease.

In 1991 the AIDS Task Force of the American Academy of Neurology published definitions to guide the diagnosis of HIV associated neurocognitive disorders (HAND). They defined two levels of HAND: HIV-associated dementia (HAD) and minor cognitive motor disorder (MCMD).

In 2007, the National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke proposed an updated standard for diagnosing HAND. The new proposed criteria creates an additional category; HIV-associated asymptomatic neurocognitive impairment (ANI). It also modifies the name and criteria for what was called MCMD to mild cognitive disorder (MCD).

Table - 1

Recent proposed diagnostic standards for HAND :	
HIV-associated asymptomatic neurocognitive impairment (ANI) diagnostic criteria	
Cognitive impairment must be attributable to HIV and no other etiology, i.e:	• Dementia • Delirium • Depression • CNS neoplasm • CNS infection • Cerebrovascular disease • Substance abuse etc.
Impairment involves at least two cognitive domains and result in neuropsychological testing performance at least 1 SD below the appropriate mean age/education norm.	• Information processing speed • Sensory/motor skills • Short-term and long-term memory • Ability to learn new skills and solve problems • Attention, concentration, and distractibility • Logical and abstract reasoning functions • Ability to understand and express language • Visual-spatial organization Visual-motor coordination • Planning, synthesizing and organizing abilities

Table - 2

Mild Cognitive Disorder (MCD) diagnostic criteria (modified for elucidation)	
Cognitive impairment must be attributable to HIV and no other etiology, i.e:	• Dementia • Delirium • Depression • CNS neoplasm • CNS infection • Cerebrovascular disease • Substance abuse, etc • Information processing speed • Sensory/motor skills • Short-term and long-term memory • Ability to learn new skills and solve problems • Attention, concentration, and distractibility • Logical and abstract reasoning functions • Ability to understand and express language • Visual-spatial organization Visual-motor coordination • Planning, synthesizing and organizing abilities
Patient or caregivers report that cognitive deficit interferes with:	home making or social activity, Mental acuity, work efficiency,

Table - 3

HIV-associated dementia (HAD) diagnostic criteria	
Cognitive impairment must be attributable to HIV and no other etiology, i.e:	• Delirium • Depression • CNS neoplasm • CNS infection • Cerebrovascular disease • Substance abuse, etc.
Impairment involves at least two cognitive domains and result in neuropsychological testing at least 2 SD below the appropriate mean age/education norm.	• Information processing speed • Short-term and long-term memory • Ability to learn new skills and solve problems • Attention, concentration, and distractibility • Logical and abstract reasoning functions • Ability to understand and express language • Visual-spatial organization Visual-motor coordination • Planning, synthesizing and organizing abilities
Cognitive impairment <u>significantly</u> interferes with:	• work • home life • social activities • ADL's
Cognitive impairment should be validated by neuropsychological testing, i.e.:	• Mini-mental state examination (MMSE) • Memorial Sloan-Kettering (MSK) scale • HIV dementia Scale (HDS)

Although the specific symptoms vary from person to person, they may be part of a single disorder known as AIDS dementia complex, or ADC. Other names for ADC are HIV-associated dementia and HIV/AIDS encephalopathy.

It is a metabolic encephalopathy induced by HIV infection and fueled by immuneactivation of brain macrophages and microglia.[11] These cells are actively infected with HIV and secrete neurotoxins of both host and viral origin.

Histopathologically, it is identified by the infiltration of monocytes and macrophages into the central nervous system (CNS), gliosis, pallor of myelin sheaths, abnormalities of dendritic processes and neuronal loss.[11][12]

The essential features of ADC are disabling cognitive impairment accompanied by motor dysfunction, speech problems and behavioral change. Cognitive impairment is characterised by mental slowness, trouble with memory and poor concentration.

Motor symptoms include a loss of fine motor control leading to clumsiness, poor balance and tremors. Behavioral changes may include apathy, lethargy and diminished emotional responses and spontaneity. ADC typically occurs after years of HIV infection and is associated with low CD4+ T cell levels and high plasma viral loads. [13]

Common symptoms include decline in thinking, or “cognitive,” functions such as memory, reasoning, judgment, concentration, and problem solving.

- Other common symptoms are changes in personality and behavior, speech problems, and motor (movement) problems such as clumsiness and poor balance.

- When these symptoms are severe enough to interfere with everyday activity, a diagnosis of dementia may be warranted.

AIDS dementia complex typically occurs as CD4+ count falls to less than 200 cells/microliter. It may be the first sign of AIDS. With the advent of highly active antiretroviral therapy (HAART), the frequency of ADC has declined from 30-60% of people infected with HIV to less than 20%. HAART may not only prevent or delay the onset of AIDS dementia complex in people with HIV infection, it can also improve mental function in people who already have ADC.

Dementia only exists when neurocognitive impairment in the patient is severe enough to interfere markedly with day-to-day function. That is, the patient is typically unable to work and may not be able to take care of him or herself. Before this, the patient is said to have a mild neurocognitive disorder.

Diagnostic criteria

Marked acquired impairment of at least two ability domains of cognitive function (e.g. memory, attention): typically, the impairment is in multiple domains, especially in learning, information processing and concentration/attention. The cognitive impairment is ascertained by medical history mental status examination or neuropsychological testing.

1. Cognitive impairments identified in 1. interfere markedly with day-to-day functioning.

2. Cognitive impairments identified in 1. are present for at least one month.

3. Cognitive impairments identified in 1. do not meet the criteria for delirium, or if delirium is present, dementia was diagnosed when delirium was not present.

4. No evidence of another, pre-existing aetiology that could explain the dementia (e.g. another CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurological disease, severe substance abuse compatible with CNS disorder.[14]

While the progression of dysfunction is variable, it is regarded as a serious complication and, untreated, can progress to a fatal outcome. Diagnosis is made by neurologists who carefully rule out alternative

diagnoses. This routinely requires a careful neurological examination, brain scans (MRI or CT scan) and a lumbar puncture to evaluate the cerebrospinal fluid. No single test is available to confirm the diagnosis, but the constellation of history, laboratory findings, and examination can reliably establish the diagnosis when performed by experienced clinicians. The amount of virus in the brain does not correlate well with the degree of dementia, suggesting that secondary mechanisms are also important in the manifestation of ADC.

AIDS Dementia Complex (ADC) is not a true opportunistic infection. It is one of the few conditions caused directly by HIV itself, but it is not quite as simple as that because the central nervous system can be damaged by a number of other causes:

- opportunistic infections - there are many
- Primary cerebral lymphoma or metastasis of other AIDS-related cancers
- direct effects of HIV in the brain
- toxic effects of drug treatments
- malnutrition

Many researchers believe that HIV damages the vital brain cells, neurons, indirectly. According to one theory, HIV either infects or activates cells that nurture and maintain the brain, known

as macrophages and microglia. These cells then produce toxins that can set off a series of reactions that instruct neurons to kill themselves. The infected macrophages and microglia also appear to produce additional factors chemokines andcytokines - that can affect neurons as well as other brain cells known as astrocytes. The affected astrocytes, which normally nurture and protect neurons, also may now end up harming neurons. The HIV virus protein gp120 inhibits the stem cells in the brain from producing new nerve cells.[15]In the neuronal cells, the HIV gp120 induces mitochondrial-death proteins like caspases which may influence the upregulation of the death receptor Fas leading to apoptosis.[16] Researchers hope that new drugs under investigation will interfere with the detrimental cycle and prevent neuron death.

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 absolutely mute. Paraparetic or paraplegic with fecal and urinary incontinence.

There is no “typical” course of the ailment. Sometimes it remains relatively mild; other times it may be severe or progress rapidly. Some people

experience only cognitive disturbances or mood shifts, while others struggle with a combination of mental, motor and behavior changes. How much these changes disrupt a person's day-to-day life differs from one individual to the next and from one stage of the disease to another.

In part because it varies so much from person to person. HIV Associated Dementia (HAD) is one of the most poorly understood aspects of HIV disease. However, since people coping with HIV often need to take many medications on a complicated timetable, maintain a regular schedule of doctors' appointments, keep track of paperwork for insurance and other benefits, and perform additional tasks that demand significant organizational and cognitive skills, a diagnosis of HAD can present obstacles to their ability to maintain control over their lives and their health, and a challenge to caregivers, partners and others who want to help.

HIV is often accompanied by cognitive impairments which are typically assessed through standard neurometric test batteries.[17,18] Early detection of neuro- psychological impairment in HIV is important since more sensitive measures of subclinical changes in cognitive impairments might lead to earlier treatment that could reduce, minimize, or possibly reverse cognitive deficits associated with infection. Previous studies however, have reported discrepant results regarding the severity of cognitive decline associated with the asymptomatic and symptomatic stages of HIV-infection. [19,20]

These equivocal reports of the clinical stage in which cognitive deficits are detected in HIV-infected individuals may be due to the fact that neurological dysfunction was assessed by different methods.

Standardized neurometric tests have long been used in both clinical and research applications for the assessment of cognitive function. [21]

These paper and pencil type neurometric tests continue to serve an important role in non-invasive assessment of a variety of psychological conditions in HIV patients. Though widely accepted and used in the field, their ability to detect subclinical changes and degree of specificity of deficit is somewhat limited.

One promising addition to the standard neurometric approach is the use of physiological measures which discriminate different levels of cognitive impairment between and within certain clinical categories. The event related potentials (ERP) of the electroencephalogram (EEG) are associated with subclinical changes in cognitive functioning in HIV-infected individuals. Specifically, components of the ERPs that result in a longer P300 latency with or without N1, P2, and N2 latency prolongation and/or smaller amplitude of P300 waveforms, when compared to a control group, are shown to be related to cognitive deficit. [22,23]

Diagnosis:

Many factors can cause the same symptoms as HAD, so making a correct diagnosis is a complex and challenging task. Depression, other psychiatric disturbances, reactions to medication and nutritional deficiencies can all lead to similar symptoms, as can infections common among people with AIDS, including toxoplasmosis, lymphoma, progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis.

An accurate diagnosis of HAD, therefore, requires a comprehensive examination that generally includes a mental status test, a brain scan, and lab tests on the cerebrospinal fluid (a fluid that bathes the brain and spinal cord), which is obtained through a procedure known as a spinal tap or lumbar puncture.

A mental status exam can help identify whether a person is suffering memory loss, difficulties with concentration and other thinking processes, mood swings and other symptom.

A structured demographic assessment, medical history, and neurological examination. The neuropsychological testing battery covered six domains including verbal memory (Rey Auditory Verbal Learning test), constructional praxis (Rey Complex Figure Copy test), psychomotor performance (Digit Symbol test, Trail Making test), motor speed (Grooved Pegboard test), frontal systems (Verbal Fluency, Odd Man Out tests), and

reaction time [California Computerized Assessment Package (CALCAP)] [24-26]. An age and education adjusted z score was used to quantify performance for each of the neuropsychological tests . Functional performance and depression symptomatology also are assessed. These assessments are used to assign a Memorial Sloan Kettering (MSK) dementia stage [27], by a consensus conference including a neurologist (N.S.) and neuropsychologist.

The neuropsychological testing battery may include the World Health Organization (WHO) University of California Los Angeles (UCLA) Verbal Learning test for verbal memory [28]. This test is similar to the Rey Auditory Verbal Learning test (RAVLT) in that it uses a list-learning task.

The Timed Gait and Grooved Pegboard tests were used to assess motor performance. The Digit Symbol test [29] and the Color Trails test [30] were used to assess psychomotor speed performance. The Color Trails 1 and 2 are similar to the Trail Making test except that to minimize cultural bias, no letters or written instructions are used. Both Color Trails 1 and 2 consist of several numbered circles colored in pink or yellow; in Color Trails 1, each number is represented by only one color, whereas in Color Trails 2, each number is printed twice, once in pink and once in yellow. In Color Trails 1, the participant is instructed to draw a line between the numbered circles one after the other, following the number sequence. In Color Trails 2, the participant must maintain the sequence of numbers and alternate between pink

and yellow. Digit span forward and backward was used to assess attention. The functional assessment included the Karnofsky Performance Scale [31]. These assessments were used to assign a MSK dementia stage of 0, 0.5, or ≥ 1 by a consensus conference. In addition, electrophysiological evaluation such as ERP(P-300) evaluation may be helpful in detecting subtle neurocognitive abnormalities which may not be picked up by conventional neurometric tests. This physiological test and neurometric tests are complementary to each other in evaluation of neurocognitive disorders in HIV affected patients.

The healthcare provider will often ask that the test be repeated to ensure accuracy. Initially these changes can be barely noticeable; it takes a skilled clinician to pinpoint changes at the earliest phase of the condition. A formal diagnosis requires that the behavior/memory changes be corroborated by a third party.

CT and MRI brain scans can reveal whether someone has suffered damage to brain tissue and can help rule out other possible causes of the symptoms. And the cerebrospinal fluid of people with HAD frequently contains high levels of HIV as well as greater amounts of certain proteins, although such findings suggest rather than prove that someone is suffering from the syndrome.

Because no single test definitively answers the question of whether someone has HAD, the final diagnosis is made by weighing all the evidence

together. Compounding the difficulty is the fact that HAD can sometimes coexist with AIDS-related infections or other factors, and determining the exact cause of each particular symptom can be virtually impossible. Time and repeated measures are helpful in confirming a diagnosis.

Treatment:

Although there is no cure for HAD, AZT, an anti-HIV drug approved by the Food and Drug Administration in the late 1980s, can help improve cognitive functioning in people with HIV. While many drugs are not able to penetrate the brain, AZT and some other antiretrovirals has been shown to cross the blood-brain barrier, which is one reason why AZT may improve symptoms of HAD. A major problem, however, is that although larger doses of AZT apparently work best, people with HAD or advanced cases of AIDS may be highly sensitive to the potentially toxic side effects of the drug.

There are several other anti-HIV drugs—d4T, abacavir, and nevirapine, for example—that are known to cross the blood-brain barrier. Some specialists believe that these drugs may also prove effective in treating HAD, although the benefits have not been definitively proven. Much more study on treating HAD is necessary before any firm conclusions can be reached.

In addition to treating HAD itself, it is important to find ways to treat the symptoms, when possible. Anti-depressants, anti-psychotics, and anti-

anxiety drugs can help relieve some of the mental distress people with HAD may experience. However, some of these medications may cause complications when taken along with antiretroviral therapy or other drugs, so caution is needed in choosing the best approach. Consultation with an AIDS-knowledgeable psychiatrist is recommended.

ROLE OF COGNITIVE EVOKED POTENTIAL IN HAND

Long latency evoked potentials (ERP), are related to cognitive processing and are referred to as cognitive evoked potentials, event-related potential (ERP), P3, P300. Apart from Neuropsychological testing, P300 evaluation is found to be useful in detecting HIV associated Neurocognitive disorders. More importantly, P300 evaluation has been found to be useful in detecting early cognitive impairment in a proportion of neurologically asymptomatic HIV patients, which may have huge impact in the management. More effective therapy with Anti-Retroviral therapy can be introduced quite early in the course, which will prevent the transformation into frank dementia.

COGNITIVE EVOKED POTENTIAL

Long latency evoked potentials (EPs) are related to cognitive processing and are referred to as cognitive evoked potentials, event-related potential (ERP), P3, P300, and endogenous EP. The event-related potentials differ from short latency evoked potentials by the following characteristics:

Endogenous stimuli elicit ERP, whereas short latency evoked potentials are elicited by exogenous stimuli.

1. Endogenous evoked potentials require attention and patient's cooperation, whereas short latency evoked potentials in most instances can be elicited without patient's cooperation, during sleep and under anesthesia.

2. Endogenous evoked potentials have a longer latency, higher amplitude, and lower frequency of waveform compared to short latency EPs.

3. Endogenous evoked potentials are not influenced by frequency and intensity of stimuli as opposed to short latency EPs.

P300:

P300 is the most frequently investigated ERP appearing at about 300 ms following task-related stimuli. The terms P3 and P300 ms are used interchangeably. P3 is a symmetrical wave maximum over the midline, central and parietal regions with a latency varying between 250 ms and 600 ms depending on the stimulus and the subject parameters.

P3 can be elicited by any stimulus, the most common being an unexpected or infrequent stimulus (oddball paradigm). This involves presentation of unexpected, infrequent stimuli randomly interspersed among frequent stimuli. The character of unexpected stimuli differs from the

common stimuli in terms of frequency or intensity. The unexpected stimulus may even be the absence of stimuli in a train of regularly spaced stimuli [32].

Two factors, (i) stimulus infrequency or unexpectedness and (ii) attention to task relevance operate independently. There is a suggestion that unexpectedness of stimulus and attention to it produce different EPs [33]. Independence of task relevance in infrequent stimulus elicits a P_3, which was referred by squires as P_{3a}. This wave form occurs slightly earlier and has a more frontal distribution than the parietal maximum P_{3b} components wave, which is best elicited by attending to a task relevant stimulus. Probably the routinely obtained P_3 represents a sum of these components (P_{3a} and P_{3b}). The other long latency components, i.e., N1, P2, N2, and slow waves are clinically less useful.

Subject

An acoustically and electrically shielded room is required for P_3 study. The subject is explained the procedure with emphasis on remaining awake and alert during the test. The procedure is done after cleaning the scalp. The subject may comfortably sit or lie down supine in a couch with eyes fixed to avoid blinking. The subject is asked to mentally count the numbers of the target stimuli or to respond to the target stimuli or to respond to the target stimuli by raising the finger or pressing a button, which allows the assessment of accuracy of responses.

Electrode Placement:

After cleaning the scalp with antiseptics solution Surface recording electrodes are placed at Fz, Cz, Pz, and are referred to link mastoid, linked ear, nose or noncephalic reference. The ground electrode is placed at Fpz. Additional electrodes may be placed to monitor eye movements, which may be time locked to the target stimuli. The electrode impedance is kept below 5kΩ.

Stimulus:

Any stimulus auditory, visual, olfactory, somatosensory or pain can be used for eliciting P_3. The P_3 elicited by different stimuli is fairly similar though slight difference in latency and topography may be present. Auditory stimuli are most frequently used in clinical practice for eliciting P_3.

The stimuli are delivered using oddball paradigm where two types of stimuli: target (infrequent) and nontarget (frequent) are used. The target stimuli comprise 15-20 % of total stimuli, which appear randomly. The patient is asked to count mentally or raise the finger or press a button in response to target stimuli.

The sequence of presentation of target and non-target stimuli is important. If the target stimuli appear at the fixed interval then it does not remain unexpected and influences the amplitude of P_3. It is therefore,

important to use a random or pseudorandom sequence contains a random sequence of target and nontarget with conditions on the stimuli sequence so that no two-target stimuli appear consecutively. A pseudorandom sequence is preferred over random sequence because of the effect of local sequence probability.

The stimulus intensity of 60-80 dB is delivered binaurally at a rate of 1 Hz.

Machine Setup and Running the Test:

The low pass filter is kept between 30 Hz and 100 Hz and high pass filter between 0.3 Hz and 1 Hz with sweep time of 1s. The EEG is amplified 10,000 times and the evoked potential waveforms are computed separately for all rare and frequent stimuli.

WAVEFORM IDENTIFICATION AND MEASUREMENT

The positive and negative waveforms are designated as P and N, respectively (P2 and P3) waves. These are labeled by their average latency in normal individuals, i.e., P3 appears around 300 ms after the stimulus. Precise measurement of P3 latency and amplitude is difficult because of its variable morphology and broad configuration. P3 is composed of two components: P3a and P3b. Ideally, both the components should be measured although in

clinical practice only P3 measurements are done. There are two ways of measuring P3 latency.

1. Point of maximum P3 amplitude

2. Intersectional extrapolation – the ascending and descending limbs of P3 are extended to the point of intersection, which is measured as P3 latency.

P3 amplitude is measured from prestimulus base to-peak – to –peak from N2 . Generally P3 amplitude decreases as the latency increases. [34] The normal values of different waveforms of cognitive evoked potential are given below.

Normative data of cognitive evoked potential (U.K.Misra,Clinical Neurophysiology)

Table - 4

Waveforms	**Latency (peak) (mean ± SD) ms**	**Amplitude (base-peak) (mean ± SD) µv**
Cz		
N1	102.0 ± 16.9	9.3 ± 3.5
P2	172.1 ± 20.0	3.6 ± 2.5
N2	232.1 ± 39.2	7.3 ± 4.1
P3	346.9 ± 38.1	9.2 ± 5.0
Fz		
P3	346.5 ± 38.0	6.6 ± 3.6
Pz		
P3	346.2 ± 41.1	9.6 ± 3.8

P-300 recording

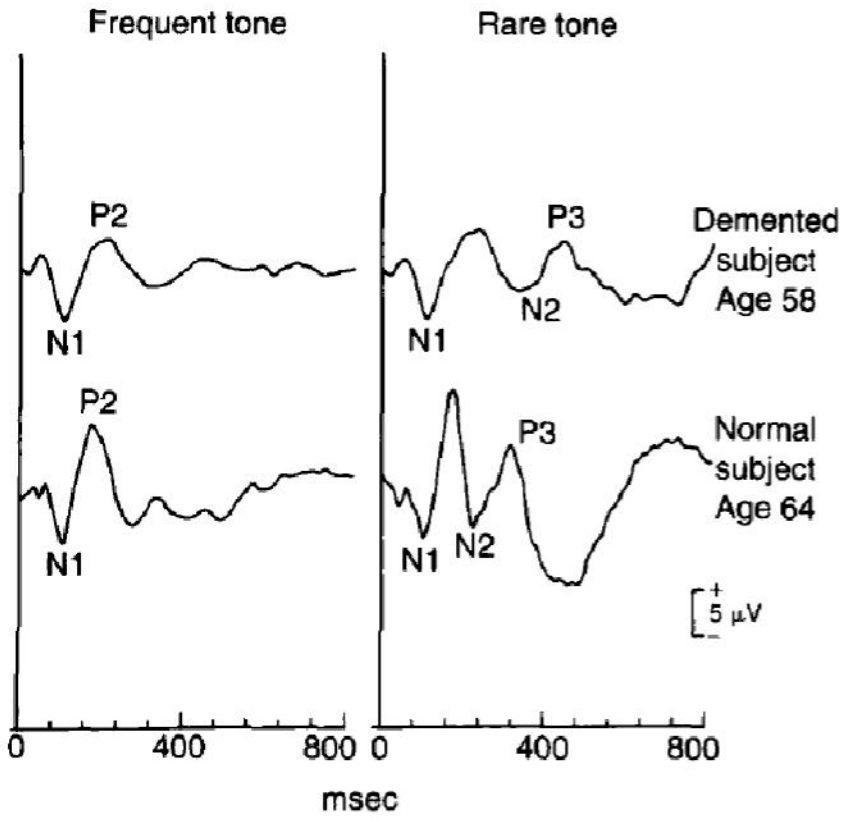


FIGURE 1. Long-latency evoked potentials recorded from the vertex in two subjects of similar age, one of whom was demented. The top row shows the response recorded from the demented subject. The bottom row shows the response recorded from the normal subject, The waveforms on the left are the responses to the frequent tone and those on the right are to the rare tone. The latency and amplitude of the N1 and P2 components are similar in the two subjects, but the later event-related components are small and delayed in the response from the demented subject. (Aminoff, Electrodiagnosis in Clinical Neurology)

GENERATORS OF P3

The exact origin of P3 is still not known. Different areas of brain such as inferior parietal lobule, frontal lobe, hippocampus, medial temporal lobe, insula, and other limbic structures have been reported to contribute to scalp recorded P3. Despite suggestion regarding the generation of P3 by medial temporal lobe and hippocampus, later studies have disproved the role of medial temporal lobe by demonstrating the presence of P_3 in patients with temporal lobectomy or bilateral hippocampal and temporal lobectomy or bilateral hippocampal and temporal lobe lesions . Normal P_3 , was also recorded in a patient who had bilateral medial temporal lobe involvement following herpes simplex encephalitis.

Recent studies employing fMRI and magnetoencephalography have been utilized to study the generators of P3. Combined ERP and fMRI study, P3a was attributed to frontal area and insula, whereas P3b to parietal and inferior temporal areas; thus pointing to the involvement of distinct attentional subsystems in target and distracter processing .

In dementia, prolongation of P3 latency compared to normal has been reported. The frequency of abnormality has ranged between 30 % and 80%.[34] P3 may be helpful in differentiating behavioral abnormalities in dementia and those because of psychiatric disturbances. P3 is expected to be normal in psychiatric patients as opposed to patients with dementia.

There have been many studies with differing results on the role of P_3 in the diagnosis of dementia. In the early stage of dementia, the P_3 may be normal or marginally altered, which undermines the value of P_3 as a clinical diagnostic test of dementia. In a study on 27 demented patients whose Mini Mental Scale Examination (MMSE) score was below 25; 80% patients had prolonged P3 exceeding 2 Standard Error of Estimate (SEE) above age latency regression time. Moreover, there was no significant difference in normal individuals and nondemented controls .

In 18 demented patients with MMSE score below 20 and 7 with psychogenic illness, 56% of demented patients and none of psychogenic patients had prolonged P3 latency exceeding mean by 2 SEE in another study, 35 senile-depressed patients were compared with 39 normal subjects. Mean latency of P2 and P3 were shorter in senile-depressed compared to control, but in Alzheimer's disease N2 and P3 were prolonged.[35]

Degree of dementia has been correlated with P3 in several studies. Blessed Dementia Scale Score, a marker of degree of dementia and delta activity in EEG were not significantly related to P3 latency. Sequential studies of P3 in dementia have revealed increase in P3 latency with disease progression [36]. Patients with infarctions without dementia have normal P3 latencies. The sensitivity of P3 in vascular dementia is about 50 %, which is similar to Alzheimer's disease.

HIV Infection

Patients with HIV infection often complain of cognitive disturbance, which may be due to AIDS dementia complex, HIV- associated encephalopathy or due to CNS opportunistic infections. In asymptomatic HIV patients there is a low frequency of P3 abnormalities, which may range from 0% to 30 %.[37,38] In symptomatic HIV patients (CDC stage II-IV), N2, P3 complex abnormalities occur in 33-80% patients. These abnormalities include latency prolongation, reduction of amplitude, or loss of waveforms. The effect of antiretroviral therapy has been monitored by P3.

In a longitudinal study, change in latency and amplitude was more frequent in HAART therapy group compared to mono, duo therapy or control group. This study highlights the important role of HAART therapy in improving cognition in HIV patients. The P3 abnormality inversely correlated with CD4 count. [39]

VARIABLES AFFECTING P_3

A number of variables may affect P_3 latency and amplitude, hence they require careful attention to avoid misinterpretation.

1. AGE

The P3 latency increases with increasing age. There is an increase in mean latency by about 1-1.5 ms/year after the age of 20 years. There are

conflicting reports on the influence of age on the amplitude of P3, however probably the amplitude decreases after the age of 80 years

2. ATTENTION

Decrease in alertness is associated with reduction in amplitude . Drowsiness or inattention decreases P_3 amplitude or may even obliterate it. However, P_3 can be recorded in stage II sleep but disappears in slow wave sleep. P_3 amplitude increases with correctly recognized stimuli compared to incorrect ones.

3. TASK

The latency increases as the discrimination of task becomes harder. [40] If the subject is asked to attend to target stimulus it results in higher amplitude P3 compared to a situation in which such instruction was not given.

Since 1991, investigators have used the term Minor Cognitive Motor Disorder (MCMD) to describe neurological and neuropsychological symptoms and signs which are not severe enough to meet criteria for frank dementia. It is estimated that 20-30% of individuals with advanced HIV infection (CD4 cell counts < 200 mm3) may show evidence of some impairment of cognitive or motor performance. In recent years the significance of these "minor" abnormalities has become better understood; however, it is still uncertain whether a "predementia syndrome" can be clearly

characterized, and if it can, whether aggressive early treatment can forestall the development of frank dementia.

The incidence and prevalence of MCMD are poorly understood. This is primarily because diagnostic criteria are relatively new, and insufficient epidemiological research data only are available. The rate of MCMD is low in medically asymptomatic HIV infection (5%) but increases to about 25% during the symptomatic phases of the disease. In contrast, frank HIV dementia was detected in 0.8% of medically asymptomatic individuals, in 2.6% of symptomatic, and 7.0% of those with clinically-defined AIDS.

MCMD may be associated with increased mortality, because of behavioral disturbances and poor adherence to anti retroviral therapy and this increased risk of death applies not only to those who become frankly demented. Mayeux and colleagues, for example, reported earlier death in those who were neuropsychologically impaired but not demented. In addition to its possible prognostic significance, MCMD also has a clear impact on function. For example, in a cohort of individuals with advanced HIV infection, functional performance was significantly worse among those with MCMD than among HIV-infected individuals without neuropsychological impairment.

MCMD may not necessarily progress to frank dementia. In fact, some individuals with MCMD may improve when retested, possibly indicating some reversibility in the neurologic dysfunction. Why some people improve

over time remains an open question. While the most obvious answer may be "practice effect" and other sources of error in neuropsychological measurement, another possibility is that the mildest form of brain disorder associated with HIV might actually have a fluctuating course, somewhat akin to what is found in demyelinating disorders. It is clear now that even during the lengthy asymptomatic phase of HIV infection, bursts of viral replication occur, and there is no true viral latency. These "viral bursts" might be accompanied by further brain seeding influencing neuro-psychological performance.

In summary, although information on the "real life" implications of HIV-associated MCMD remains fragmentary, the available data indicate that such impairments may be associated with reduced work efficiency, greater likelihood of development of frank dementia, and earlier mortality.

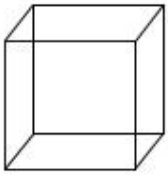
The implication is that screening of individuals with advanced HIV infection, who are at risk for HIV dementia and MCMD, is probably warranted. Simple bedside tests such as the HIV Dementia Scale (included below), which was developed in the Moore Clinic for the early detection of dementia, are particularly useful.

In general, a score of 10 or less is suggestive of HIV associated cognitive impairment or dementia and would warrant additional neurologic consultation.

In this setting, ERP testing such as P300 evaluation gains importance as it may reveal abnormalities in the form of prolongation of P300 latency much before overt dementia sets in.

HIV Dementia Scale (devised by Power.C)

Max Score	Score	
		Memory-Registration Give four words to recall (dog, hat, green, peach) - 1 second to say each. Then ask the patient all 4 after you have said them.)
4	( )	**Attention** Anti-saccadic eye movements: 20 (twenty) commands. ____ errors of 20 trials. less than or equal to 3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; > 6 errors = 0)
6	( )	**Psychomotor Speed** Ask patient to write the alphabet in upper case letters horizontally across the page (use back of this form) and record time: ____ seconds. less than or equal to 21 sec = 6; 21.1 - 24 sec = 5; 24.1 - 27 sec = 4; 27.1 - 30 sec = 3; 30.1 - 33 sec = 2; 33.1 - 36 sec = 1; > 36 sec = 0)
4	( )	**Memory - Recall** Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct after prompting.
2	( )	**Construction** Copy the cube below; record time: ____ seconds. (< 25 sec = 2; 25 - 35 sec = 1; > 35 sec = 0)



Total Score: ____/16

AIM OF THE STUDY

1. To evaluate P-300, an endogenous long latency evoked response potential (ERP) in asymptomatic HIV patients without apparent, clinical neurocognitive disturbances and to correlate it with age matched healthy controls to study subclinical abnormalities.

2. To study HIV Dementia Scale (HDS) score in those neurologically asymptomatic HIV infected patients and to correlate it with P300 abnormalities .

3. To study CD4 profile in those neurologically asymptomatic HIV patients and to correlate it with electrophysiological findings.

MATERIALS AND METHODS

In this cross sectional study, 50 HIV patients, who were neurologically asymptomatic, attending Rajiv Gandhi Government General Hospital, ART clinic and Medicine OPD , and 60 age matched healthy controls were enrolled from January 2009 to March 2011. An informed consent was obtained prior to the study.

Detailed history was taken , and meticulous neurological examination was done to rule out clinical neurocognitive disturbances. Those patients who were asymptomatic after history and examination were included in the study and those with disturbances were excluded.

Then the subjects were asked to perform the Moore clinic HIV Dementia Scale testing, (maximum score- 16) recommended by American Academy of Neurology. Patients who scored less than or equal to10 were excluded from the study and those who scored more than 10 alone were taken for the study.

In the patients who scored more than 10, the maximum score on the HIV Dementia scale was noted.(possible score- 10.5 to 16)

After the HIV Dementia scale testing, P-300 evaluation was done for those patients after obtaining due consent. P-300 analysis was done using auditory “ODDBALL PARADIGM” technique. The parameters considered

were N1 latency, P2 latency, N2 latency, P3 latency and N2-P3 amplitude. Recording over Cz was taken into consideration.

HIV Dementia scale score was correlated with P-300 latency to demonstrate any statistically significant correlation.

Then the other parameters, N1, P2, N2, P3 latencies and P3 amplitude were analyzed statistically in both the patient group and the control group to find out abnormal values, in the form of prolongation of latency of N1, P2, N2, P3 waves or reduction in the P3 amplitude and eventually identifying patients with abnormal P3 findings, who have subclinical neurocognitive impairment , revealed by neurophysiological methods.

And also CD4 count was done for the patient group which was then correlated with P-300 latency to look for any statistically significant correlation between these two parameters.

Inclusion criteria:

1. HIV positive patients with or without ART therapy, irrespective of duration of illness.

2. HIV positive patients with or without Anti Tuberculous Treatment

3. HIV positive patients with or without prophylaxis for opportunistic infections.

4. Age 15 years and above were included.

Exclusion criteria:

1. Patients in moribund state.

2. Patients with apparent features of Dementia

3. Patients with clinical neurological deficits.

4. Patients with space occupying lesions, opportunistic infections in brain.

CD4 T cell count, complete hemogram, renal and liver function tests and neuroimaging (CT-Brain or MRI Brain as required) were done.

After obtaining the results data analysis was done using SPSS statistical package.

RESULTS AND DATA ANALYSIS

50 HIV positive asymptomatic patients and 60 age matched controls were enrolled.

In the patients group 34 (68%) were males and 16 (32%) were females.

In the control group 36 (60%) were males and 24 (40%) were females.

Sex Distribution:

Table - 5

Sex	Patients	Controls
Male	34 (68%)	36 (60%)
Female	16 (32%)	24 (40%)

In the patients group, 35 (70%) were in the 30-40 age group.

4 (8%) were in the <30 age group.

11 (22%) were in the >40 age group.

In the control group, 38 subjects (63.4%) were in the 30-40 age group.

5 subjects (8.3 %) were in the <30 age group.

17 subjects (28.3 %) were in the >40 age group.

SEX DISTRIBUTION

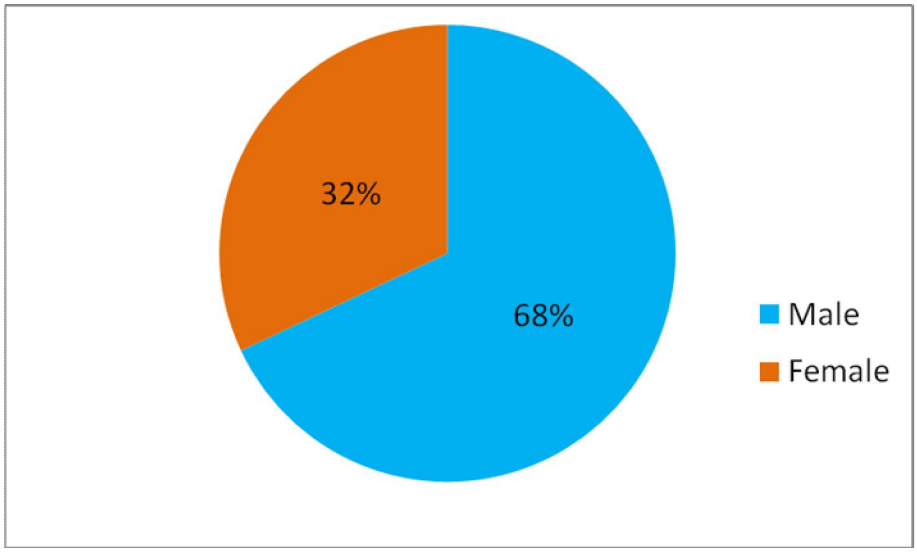


FIGURE 2 : PATIENTS

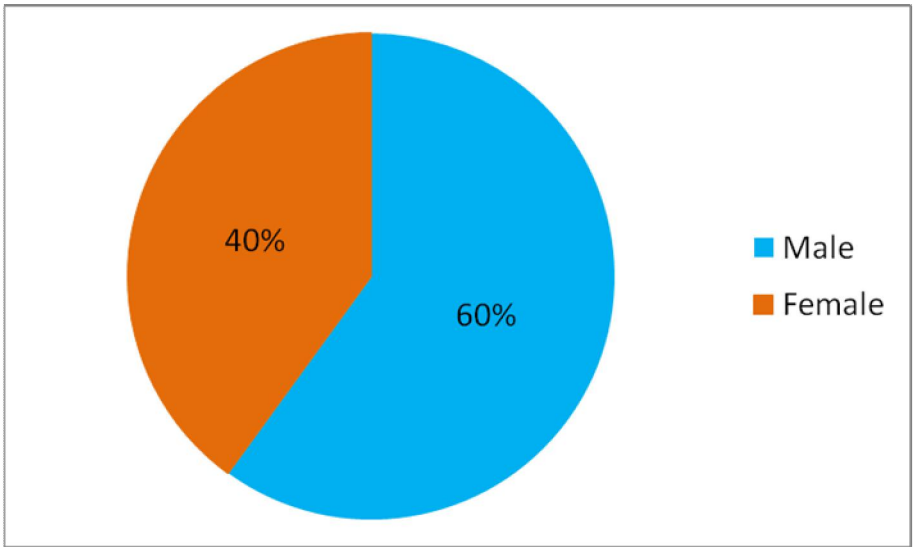


FIGURE 3 : CONTROLS

AGE DISTRIBUTION

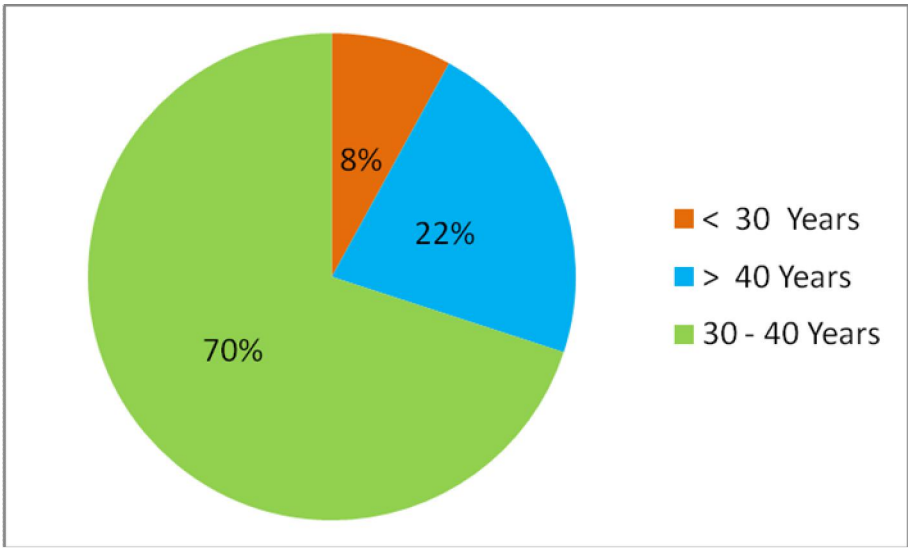


FIGURE 4 : PATIENTS

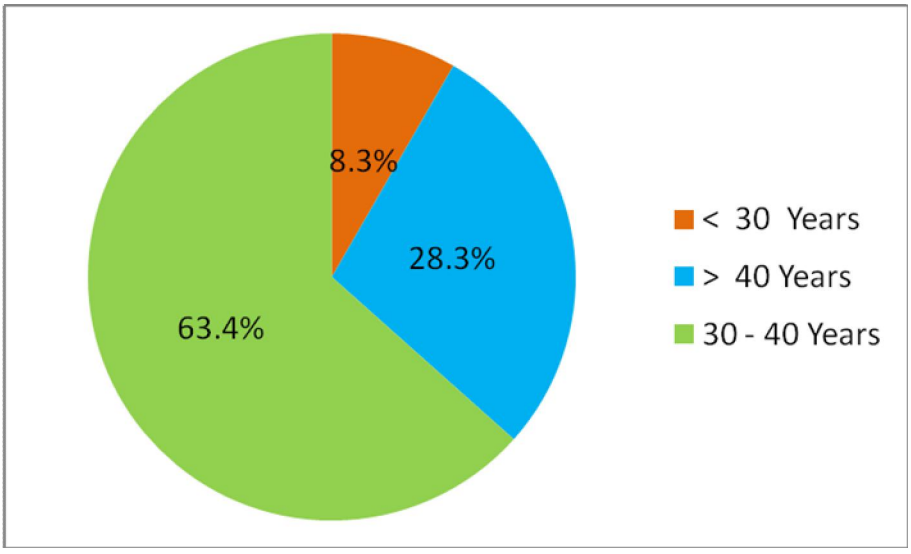


FIGURE 5 : CONTROLS

PATIENTS VS CONTROLS

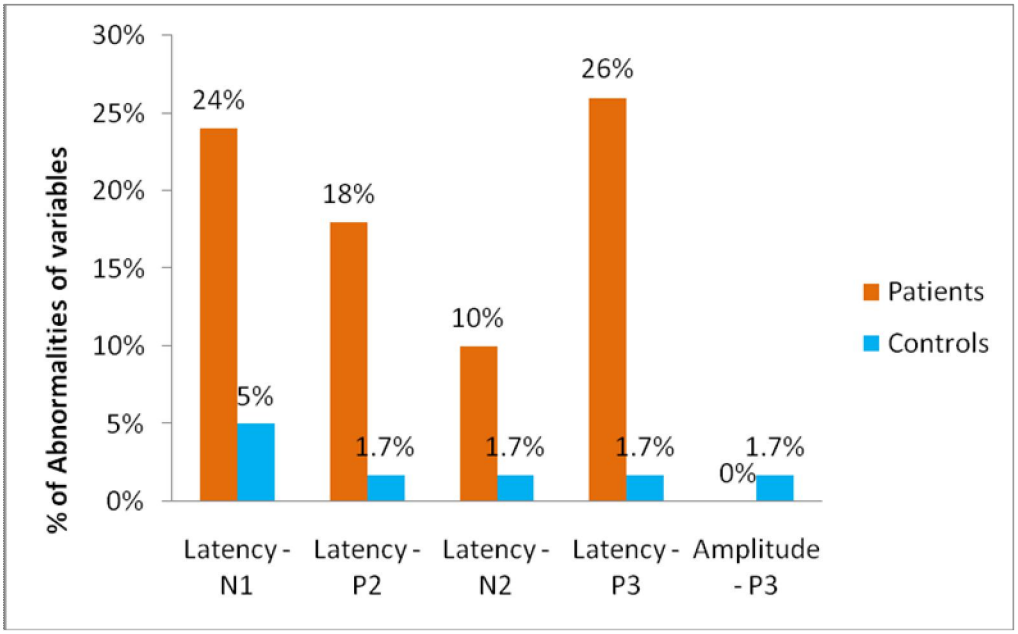


FIGURE 6 : P 300 ABNORMALITIES

AGE DISTRIBUTION:

Table – 6

Age group, in years	Patients	Controls
<30	4(8%)	5(8.3%)
30-40	35(70%)	38(63.4%)
>40	11(22%)	17(28.3%)

Pearson Correlation analysis was done to demonstrate statistically significant correlation between variables; and 'T' test was done to demonstrate significance.

SUBJECTS = HIV

Correlation (a) Pearson Correlation

Table - 7

	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,amp micV	CD4+
DUR ILL YRS	1	-.546(**)	.637(**)	.527(**)	.497(**)	.658(**)	-.471(**)	-.416(**)
HIV DS SCORE	-.546(**)	1	-.727(**)	-.565(**)	-.571(**)	-.633(**)	.659(**)	.528(**)
P3, N1 L ms	.637(**)	-.727(**)	1	.620(**)	.680(**)	.746(**)	-.715(**)	-.649(**)
P2 L ms	.527(**)	-.565(**)	.620(**)	1	.641(**)	.758(**)	-.518(**)	-.557(**)
N2 L ms	.497(**)	-.571(**)	.680(**)	.641(**)	1	.793(**)	-.759(**)	-.721(**)
P3 L ms	.658(**)	-.633(**)	.746(**)	.758(**)	.793(**)	1	-.771(**)	-.747(**)
tP-3,AM micV	-.471(**)	.659(**)	-.715(**)	-.518(**)	-.759(**)	-.771(**)	1	.716(**)
CD4+	-.416(**)	.528(**)	-.649(**)	-.557(**)	-.721(**)	-.747(**)	.716(**)	1

** Correlation is significant at the 0.01 level (2-tailed).

SUBJECTS = Control

(Correlations (b) Pearson Correlation

Table - 8

	HIV DS SCORE	**P3, N1 L ms**	**P2 L ms**	**N2 L ms**	**P3 L ms**	**P-3,AM micV**
HIV DS SCORE	1	-.121	-.019	-.234	-.224	.113
P3, N1 L ms	-.121	1	.278(*)	.748(**)	.771(**)	-.570(**)
P2 L ms	-.019	.278(*)	1	.291(*)	.275(*)	-.244
N2 L ms	-.234	.748(**)	.291(*)	1	.594(**)	-.498(**)
P3 L ms	-.224	.771(**)	.275(*)	.594(**)	1	-.658(**)
P-3,AM micV	.113	-.570(**)	-.244	-.498(**)	-.658(**)	1

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

a Cannot be computed because at least one of the variables is constant.

T- tests were significant ($P < 0.05$) for P3 latency in all age groups.

T-Test

AGE = <30 years

Table - 9

	SUBJECTS	N	Mean	Std. Deviation	Std. Error Mean	't'	Sig
HIV DS SCORE	HIV	4	14.63	.479	.239	.610	NS
	Control	6	14.92	.861	.352		
P3, N1 L ms	HIV	4	94.8000	4.33590	2.16795	.507	NS
	Control	6	97.0000	7.81665	3.19113		
P2 L ms	HIV	4	169.8000	7.47975	3.73988	1.183	NS
	Control	6	176.3333	9.14367	3.73289		
N2 L ms	HIV	4	218.6000	23.68347	11.84173	.997	NS
	Control	6	233.8000	23.56845	9.62178		
P3 L ms	HIV	4	307.6000	3.55903	1.77951	2.864	p<0.01
	Control	6	320.4167	8.32356	3.39808		
P3,AM micV	HIV	4	9.6500	.50000	.25000	1.480	NS
	Control	6	11.1833	1.99240	.81339		

AGE =30-40 years `T' Test for Significance

Table - 10

	SUBJECTS	N	Mean	Std. Deviation	Std. Error Mean	't'	Sig
HIV DS SCORE	HIV	35	13.47	1.218	.206	3.956	p<0.01
	Control	36	14.58	1.150	.192		
N1 L ms	HIV	35	105.2611	17.31848	2.92736	2.344	p<0.05
	Control	36	97.5861	9.15155	1.52526		
P2 L ms	HIV	35	174.7789	16.82438	2.84384	.714	NS
	Control	36	172.5222	8.64969	1.44162		
N2 L ms	HIV	35	234.9009	39.36446	6.65381	.052	NS
	Control	36	234.4806	27.38022	4.56337		
P3 L ms	HIV	35	337.9666	44.04266	7.44457	2.423	P<0.05
	Control	36	323.3750	14.20783	2.36797		
P3,AM micV	HIV	35	6.8740	2.50880	.42406	7.031	p<0.01
	Control	36	10.4194	1.66782	.27797		

AGE >40 years `T' Test for Significance

Table - 11

	SUBJECTS	N	Mean	Std. Deviation	Std. Error Mean	't'	Sig
HIV DS SCORE	HIV	11	12.59	.861	.260	4.299	p<0.01
	Control	18	13.92	.772	.182		
P3, N1 L ms	HIV	11	123.0s455	15.16999	4.57393	3.344	p<0.01
	Control	18	104.7056	13.81033	3.25513		
P2 L ms	HIV	11	180.8636	21.45499	6.46892	1.041	NS
	Control	18	174.2444	12.93210	3.04812		
N2 L ms	HIV	11	265.8273	30.64947	9.24116	1.302	NS
	Control	18	252.1500	25.37160	5.98014		
P3 L ms	HIV	11	374.0636	55.85177	16.83994	2.881	p<0.01
	Control	18	332.5444	20.42940	4.81526		
P3,AM micV	HIV	11	5.0909	1.48893	.44893	6.220	p<0.01
	Control	18	9.2722	1.89638	.44698		

1.Duration of illness was correlated with HIV dementia score. There was a significant inverse correlation between these two variables. There was a significant inverse correlation between those two variables. As the duration of disease increased, the HIV dementia scale score decreased.[-.536(**)].

2. Duration of disease also had inverse correlation with CD4 count [-.416(**)]

3. Duration of disease also had inverse correlation with P3 amplitude [-.471(**)].

4. Duration of disease had direct correlation with N1[.637(**)], P2[.527(**)], N2[.497(**)],P3[.658(**)] latencies. As the disease progressed, decline in CD4 count and P3 amplitude was noted , while N1, P2, N2 and P3 latencies prolonged.

HIV dementia scale score was correlated with variables:

HDS score was directly correlated with CD4 count.[.528(**)] in patient group. Those patients with high HDS score had increased CD4 count while there was no correlation between the two variables in the control group.

HDS score was inversely correlated with N1, P2, N2 and P3 latencies and directly correlated with P3 amplitude in the patient group while no such correlation existed in the control group.

P3[-.747(**)], N2 [-.721(**)], P2[-.557(**)] , N1[-.649(**)] latencies had an inverse correlation with CD4 count. As the count decreased, the latencies of the positive and negative waves also prolonged. Reduction in P3 amplitude was noted with decreasing CD4 count. We had not done CD4 count in control group and such correlations could not be derived.

DURATION OF ILLNESS IN YEARS IN HIV PATIENTS

Table - 12

DUR ILL YRS			SUBJECTS	Total
			HIV	
	1	N	5	5
		%	10.0%	10.0%
	2	N	6	6
		%	12.0%	12.0%
	3	N	8	8
		%	16.0%	16.0%
	4	N	11	11
		%	22.0%	22.0%
	5	N	8	8
		%	16.0%	16.0%
	6	N	6	6
		%	12.0%	12.0%
	7	N	3	3
		%	6.0%	6.0%
	8	N	3	3
		%	6.0%	6.0%
Total		N	50	50
		%	100.0%	100.0%

Minimum duration of illness was one year and maximum duration was eight years.

Of the HIV-infected patients, the percentage of patients who showed an abnormal latency of the P300-components of ERPs exceeding the mean value + 2 SD of ERP latencies from age-matched healthy subjects were noted.

Standard deviation of P3 variables for the different a ge groups

Table - 13

AGE		P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,AM micV
<30	Mean	97.0000	176.3333	233.8000	320.4167	11.1833
	Std. Deviation	7.81665	9.14367	23.56845	8.32356	1.99240
	Mean + 2SD	112.63	194.62	280.94	337.06	15.17
30-40	Mean	97.5861	172.5222	234.4806	323.3750	10.4194
	Std. Deviation	9.15155	8.64969	27.38022	14.20783	1.66782
	Mean + 2SD	115.89	189.82	289.24	351.79	13.76
>40	Mean	104.7056	174.2444	252.1500	332.5444	9.2722
	Std. Deviation	13.81033	12.93210	25.37160	20.42940	1.89638
	Mean + 2SD	132.33	200.11	302.89	373.40	13.06

a SUBJECTS = Control

age 1=<30 years , age2=30-40 years, age 3= > 40 years

In the patient group 12 patients (24%) had abnormally prolonged N1 latency values (> 2 SD), while only 3 (5%) had abnormal values in the control group.

The mean, SD, mean+2SD, values of N1 for age groups of patients given below

Table - 14

<30	Mean	97.0000
	SD	7.81665
	Mean + 2SD	**112.63**
30-40	Mean	97.5861
	SD	9.15155
	Mean + 2SD	**115.89**
>40	Mean	104.7056
	SD	13.81033
	Mean + 2SD	**132.33**

Table - 15

N1 latency patients vs controls

			SUBJECTS		Total
			HIV	Control	
N1 latency	< 2SD	N	38	57	95
		%	76.0%	95.0%	86.4%
	>2SD	N	12	3	15
		%	24.0%	5.0%	13.6%
Total		N	50	60	110
		%	100.0%	100.0%	100.0%

In the patient group, 9 (18%) patients had abnormally prolonged P2 values (>2 SD), whereas only one (1.7%) patient had abnormal value.

The mean, SD, mean+2SD, values of P2Latency for Patients age groups given below.

Table - 16

AGE		P2 L ms
<30	Mean	176.3333
	SD	9.14367
	Mean + 2SD	**194.62**
30-40	Mean	172.5222
	SD	8.64969
	Mean + 2SD	**189.82**
>40	Mean	174.2444
	SD	12.93210
	Mean + 2SD	**200.11**

Table - 17

P2 Latency patients vs controls

			SUBJECTS		
			HIV	**Control**	**Total**
P2 latency	< 2SD	N	41	59	100
		%	82.0%	98.3%	90.9%
	>2SD	N	9	1	10
		%	18.0%	1.7%	9.1%
Total		N	50	60	110
		%	100.0%	100.0%	100.0%

In the patient group, 5 (10%) patients had abnormally prolonged N2 values (>2 SD) while, in the control group, only one (1.7%) had abnormalvalue.

The mean, SD, mean+2SD, values of N2Latency for patients

Table - 18

AGE		N2 L ms
<30	Mean	233.8000
	SD	23.56845
	Mean + 2SD	**280.94**
30-40	Mean	234.4806
	SD	27.38022
	Mean + 2SD	**289.24**
>40	Mean	252.1500
	SD	25.37160
	Mean + 2SD	**302.89**

Table - 19

N2 latency patients vs controls

			SUBJECTS		
			HIV	**Control**	**Total**
N2 latency	< 2SD	N	45	59	104
		%	90.0%	98.3%	94.5%
	>2SD	N	5	1	6
		%	10.0%	1.7%	5.5%
Total		N	50	60	110
		%	100.0%	100.0%	100.0%

In the patient group, 13 patients had abnormally prolonged P3 latency values(>2 SD), whereas only one patient had abnormal value.

The mean, SD, mean+2SD, values of P3 Latency for age groups given below:

Table - 20

AGE		P3 L ms
<30	Mean	320.4167
	SD	8.32356
	Mean + 2SD	**337.06**
30-40	Mean	323.3750
	SD	14.20783
	Mean + 2SD	**351.79**
>40	Mean	332.5444
	SD	20.42940
	Mean + 2SD	**373.40**

Table – 21

P3Latency patients vs controls

			SUBJECTS		Total
			HIV	Control	
P3 latency	< 2SD	N	37	59	96
		%	74.0%	98.3%	87.3%
	>2SD	N	13	1	14
		%	26.0%	1.7%	12.7%
Total		N	50	60	110
		%	100.0%	100.0%	100.0%

In the patient category, no patient had a P3 amplitude value > 2 SD, while in the control group, one person (1.7%) had an abnormal value.

The mean, SD, mean+2SD, values of P3Amplitude for age groups given below:

Table - 22

AGE		**P-3,amp micV**
<30	Mean	11.1833
	SD	1.99240
	Mean + 2SD	**15.17**
30-40	Mean	10.4194
	SD	1.66782
	Mean + 2SD	**13.76**
>40	Mean	9.2722
	SD	1.89638
	Mean + 2SD	**13.06**

Table - 23

P3 Amplitude patients vs controls

			SUBJECTS		Total
			HIV	Control	
P3 Amplitude	< 2SD	N	50	59	109
		%	100.0%	98.3%	99.1%
	>2SD	N	0	1	1
		%	0%	1.7%	.9%
Total		N	50	60	110
		%	100.0%	100.0%	100.0%

DISCUSSION

HIV Associated Neurocognitive Impairment is a less recognized entity, in HIV affected patients, though it is associated with considerable morbidity and mortality, especially in developing countries. This is probably due to behavioral disturbances and poor adherence to drug therapy.

Asymptomatic patients, may not exhibit overt restriction in day to day functioning. So these patients do not seek medical attention and as a result frequently progress to frank dementia.

Even Neuropsychological screening tests may not show features of dementia. Under such circumstances, P300 evaluation gains grounds as an important tool to demonstrate subclinical neurocognitive abnormalities , which will help in early institution of effective Anti-Retroviral Therapy to prevent frank dementia.

In this study, P-300 abnormalities were noted in a proportion of neurologically asymptomatic HIV patients. Abnormal latency prolongation of both early and late components of P300 was noted in those patients.

24% (12 patients) had abnormal N1 latency values (> 2 SD)

18% (9 patients) had abnormal P2 values. (>2 SD)

10% (5 patients) had abnormal N2 values. (>2 SD)

26% (13 patients) had abnormal P3 values.(>2 SD).

But the P3recorded did not show statistically significant decreased amplitude in patients.

In this study, P3 latency was found to be prolonged in 26% of patients, who were clinically asymptomatic as evidenced by more than 10 score in the HIV dementia scale.

This finding was concordant with other studies.

Goodin DS, Aminoff MJ, in their study, " Long latency event-related potentials in patients infected with human immunodeficiency virus " observed, in patients infected with human immunodeficiency virus (HIV) , a proportion of neurologically asymptomatic patients showed P3 latency prolongation abnormalities .[37]

As in other subcortical dementias, patients with the HIV Associated Neurocognitive Disorders had a prolongation of the early components of the ERP, particularly the NI component, in addition to the prolongation of later N2 and P3 components that occurs in other dementing disorders.

Importantly, Bungener and colleagues have confirmed these general findings.[38] In addition, almost one-third of the asymptomatic patients infected by HIV have ERP changes similar to those with overt dementia,

which suggests that these patients may be at particular risk for cognitive difficulties developing in the future.

Thus, it may be that the recording of ERPs will permit early recognition of HIV encephalopathy and thereby help to identify patients with a poor prognosis or in need of more aggressive management.

Similarly, this study also showed that in addition to the abnormalities in the cortical components of P3,(N2, P3 latency prolongation), N1 and P2 subcortical components also showed latency prolongation, reiterating the point that HIV dementia is basically a subcortical variety. P3 latency prolongation was noted in 26% of asymptomatic patients.

But this study failed to show a statistically significant reduction in P3 amplitude in HIV infected subjects.

Another study done by Jaime L. Tartar et al, pointed out that a physiological measure of the EEG, the P3 component of the auditory ERP, is an early indicator of cognitive decline in HIV-persons. Differences in P3 amplitude measures suggest that the available amount of attentional resources are reduced in HIV infection and the P3 latency measures indicate that speed of processing is compromised as well.

The present finding that otherwise asymptomatic patients display cognitive impairments is suggestive that traditional neurometric tests might

not be sensitive to the processes affected by early cognitive impairments. Because HIV invades the CNS early in the course of the disease physiological methods of assessing cognitive impairments may be of great importance for the early diagnosis and treatment.

In another study, G. Arendt et al, [41] found that N2, P3 latency prolongations and P3 amplitude reduction were proportionate to degree of dementia. Clinical bradykinetic symptoms and time-dependent psychometric abilities correlated with N2 and P3 latency prolongations.

In yet another study, Gil R et al [42] observed endogenous event-related potentials (and especially the P300 component) have delayed latencies relative to normal controls in patients with dementias of diverse aetiologies. Moreover, the subcortical varieties of dementia tend to affect also the early-stage N1 and P2 components whereas both types of dementias affect the later-stage N2 and P3 components. Several studies have shown that endogenous, but also early, components of long latency auditory evoked potentials are prolonged in latency in HIV-demented patients. However, these changes may also be present in class II and III patients and may permit the early recognition of HIV encephalopathy.

In another study, Polich J, et al [43] found that P300 amplitude was smaller, and latency was marginally longer for the HIV patients compared to control subjects.

P300 latency correlated positively with increases in the patient HIV viral load. P300 group differences were consistent with declines in cognitive capability, and P300 latency increased with increased viral load. HIV infection negatively affected central nervous system function as measured by cognitive ERPs in a manner that suggests decreased arousal and increased fatigue in HIV patients.

Bahman Jabbari et al[44] performed Event Related potentials (ERPs) along with neurological and neuropsychological evaluation, in 73 neurologically asymptomatic HIV infected subjects. The results were compared with 50 age- and sex-matched controls. Event-related auditory evoked potentials were performed in 39 subjects. They were abnormal in 5 subjects initially (12%) and in 6 subjects (15%) by the last examination and more commonly in advanced stages of the illness with lower T4 counts. This data shows the evolution and association of electrophysiological abnormalities in early HIV infection and suggests a predictive value for ERP in HIV infected asymptomatic individuals.

HIV dementia scale (HDS) score done for both patients group and control group showed a negative correlation between HDS score and duration of illness. As the duration of illness increased, a decline in the HDS score was noted

But this sort of correlation could not be observed in the control group.

Duration of illness had a direct correlation with N1, P2, N2, P3 latencies and inverse correlation with P3 amplitude. This is probably due to the impact of HIV proliferation on the brain tissue.

There were correlations between HDS score and N1, P2, N2, P3 latencies in the patient group. These latencies prolonged with declining score in the HDS scale while it did not show any such correlation in the control group.

P3 amplitude had a direct correlation with HDS score and patients with high HDS score had proportionately large P3 amplitude. Some of the patients with high HDS score had abnormal P3 latency prolongation .

In this study, Pearson correlation analysis showed an inverse correlation between CD4 count and P3 latency. Patients with low CD4 cell count had increased P3 latency values. This finding had been already observed in the study done by Hussted et al, in 2002 who demonstrated P300 abnormalities. In particular, P3 latency was inversely correlated with CD4 count, patients with low CD4 count had abnormal prolongation of P3 latency. [10]

CONCLUSION

1. P-300 evaluation is an useful neurophysiological tool in detecting subclinical neurocognitive impairment in a proportion of asymptomatic HIV positive patients.

2. Abnormal P3 latency prolongation was noted in 26% of asymptomatic HIV patients in the study, which is an indicator of subclinical cognitive impairment.

3. In addition to P3 latency prolongation, the early subcortical N1, P2, and N2 latencies were also prolonged in a proportion of patients, reiterating the point that HIV dementia is basically a subcortical variety.

4. Early detection of subclinical neurocognitive impairment will help in intensifying Anti Retroviral Therapy which may modify or halt the progression of dementia in HIV patients.

5. P-300, neurophysiological testing may be complementary to neuropsychological screening tests, like HIV dementia scale, as patients who failed to show significant abnormalities in HDS score had abnormalities during P-300 evaluation.

6. CD4 cell count is inversely correlated with P-300 latency. However, this is a small study and large scale studies need to be done to confirm this observation.

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PROFORMA

Name **Age** **Sex** **Education**

Address

Occupation

OP no **MIN no** **ART no** **D.O.R:**

Duration of illness

Initial presentation

Date of diagnosis **spouse affected: Y/N**

CLINICAL FEATURES:

MMSE score:

HMF disturbances

Executive function: Y/N

Apathy Y/N

memory : Y/N, (working, recent, remote)

Language: motor/ sensory

reading/ writing/ copying

dysarthria:Y/N

apraxia

Ideational Y/N **Ideomotor Y/N**

Dressing Y/N **Constructional Y/N**

R/L Confusion Y/N

hemineglect :Y/ N

Visuospatial disorientation; Y/N,

Delusion/hallucination: Y/N

Hemianopia/quadrantanopia: Y/ N

Cranial neuropathy: if any

Spinomotor:

Weakness:

Wasting

Ataxia : Truncal/ Appendicular: R /L/ Bilateral

Involuntary movements: if any

Sensory: Y/N, Type: Romberg : P/N

Gait:

Signs of meningeal irritation: Y/N

Peripheral nerves: PR- BP-

Comorbidities:

Diabetic :Y/N Hypertension: Y/N CAD: Y/N

Tuberculosis : Y/ N CKD: Y/N

Opportunistic infections: ---------- ,----------,----------,----------
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Any other illness:

alcoholism smoking

INVESTIGATIONS : CD 4 COUNT;

Hematology TC : DC: P L E B HB : ESR:

sugar urea creatinine Na k Ca

LFT: ECG : CXR :

CSF analysis (If needed):

CT BRAIN :

MRI BRAIN :

EEG :

P-300 EVALUATION:

WAVE	LATENCY milli second	AMPLITUDE micro volt
N1		
P2		
N2		
P3		

HIV DEMENTIA SCALE

REGISTRATION 4 WORDS:

ATTENTION TEST: ANTISACCADE [0-4]	
PSYCHOMOTOR[0-6]	
RECALL [0-4]	
CONSTRUCTION[0-2]	
TOTAL SCORE	

TREATMENT :

ART: Y/ N

DURATION:

ART DETAILS;

OI PROPHYLAXIS:

OTHER TREATMENT:

HIV PATIENTS

S.NO	AGE	SEX	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,Amp micV	CD4+	CT BRAIN	MRI BRAIN	ART
1	36	1	4	12	111.46	209.38	268.75	350.12	6.82	456	NO	NO	yes
2	37	2	1	14	82.4	160.4	200.5	312.3	8.4	522	NO	NO	yes
3	33	1	4	12.5	125	164	240	322.9	3.16	457	NO	NO	yes
4	35	1	1	13	114.58	171.88	284.38	332.29	2.47	424	NO	NO	yes
5	38	1	6	12	120.6	224.6	312	442.32	2.34	322	NO	NORMAL	yes
6	37	1	5	12.5	90.6	170.4	258.6	376.4	6.4	376	NORMAL	NO	yes
7	42	1	4	14	108.3	166	280.4	304	8.4	606	NO	NO	yes
8	38	2	1	14	102	160.4	248.4	322.4	5.3	512	NORMAL	NO	yes
9	41	2	3	11.5	112	170.7	268.6	314	6.3	852	NO	NO	yes
10	38	1	4	15.5	90.8	168.3	283.5	356.2	3.8	422	NO	NO	yes
11	43	1	2	14	102.7	156	260.2	342	6.3	511	NO	NO	yes
12	34	2	7	12	132.4	198.4	286.3	412.8	2.4	254	NO	NORMAL	yes
13	36	1	6	15	90.6	174.2	223.5	312.6	7.4	867	NO	NO	yes
14	39	1	2	14.5	88.4	162.4	200.6	316	6.8	765	NO	NO	yes
15	32	1	2	13	90.4	171.4	244	304	8.2	542	NO	NO	yes
16	42	1	8	12.5	137.3	174	322	437.8	3.8	322	NO	NO	yes
17	39	1	7	12	142	200.3	331.4	476.4	2.6	342	NO	NORMAL	yes
18	32	2	3	14	88.4	150	200.4	306	8.4	744	NO	NO	yes
19	43	2	6	13.5	126.8	160.8	260.7	340.7	4.4	422	NO	NO	yes
20	34	1	3	14.5	90.4	173	222.6	352	6.4	480	NO	NO	yes
21	42	1	4	12.5	100.2	162.4	206.6	322.8	5.4	658	NO	NO	yes
22	38	2	5	11.5	145	190.4	302.2	390.4	3.2	344	NORMAL	NORMAL	yes
23	29	1	2	15	92	164.8	212	306.2	9.4	732	NO	NO	yes
24	39	1	8	12.5	112	178.4	224.6	322.2	6.4	658	NORMAL	NORMAL	yes
25	36	1	1	15.5	91.4	150	190.4	306.4	10.4	720	NO	NO	yes
26	33	2	2	13.5	92.6	160.4	188.4	302	7.6	680	NO	NO	yes
27	52	1	6	12.5	138	190.8	240.6	368	4.4	432	NO	NORMAL	yes

S.NO	AGE	SEX	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,Amp micV	CD4+	CT BRAIN	MRI BRAIN	ART
28	35	1	4	15	100.4	168	198	306.4	9.2	603	NO	NO	yes
29	36	2	5	11.5	122	172.4	212.6	332.4	7.9	687	NO	NO	yes
30	31	1	3	14.5	88.2	168.8	204	312.3	9.4	723	NO	NO	yes
31	46	1	5	12	132.4	180.4	238	364.6	4.6	412	NO	NO	yes
32	32	2	4	15	88.4	174	196.2	306.2	9.8	982	NO	NO	yes
33	28	1	3	15	90.2	176	242	307.8	10.4	580	NO	NO	yes
34	34	1	4	14.5	94.4	166.4	202.8	322.4	8.4	564	NO	NO	yes
35	28	2	3	14.5	98.6	162	188.4	304	9.4	842	NO	NO	yes
36	39	1	6	12	146.2	212.4	306.2	422	4.4	322	NO	NORMAL	yes
37	34	1	5	13.5	100.2	162.4	222	308.4	8.2	788	NO	NO	yes
38	32	2	4	14	108.2	158.4	182.4	310.6	9.4	688	NO	NO	yes
39	38	1	3	14	112.4	176.4	221.6	322.2	6.4	526	NO	NO	yes
40	37	1	2	13	98.2	184.2	212	310.4	8.4	634	NO	NO	yes
41	27	2	3	14	98.4	176.4	232	312.4	9.4	742	NO	NO	yes
42	46	2	8	12	120.2	202.2	288.6	422.4	5.4	428	NO	NO	yes
43	36	1	4	14.5	102.6	182.4	204.6	320	9.4	562	NO	NO	yes
44	32	1	1	15	106.2	172	223.2	298.8	10.2	568	NO	NO	yes
45	38	2	5	11.5	112	168.8	240.4	388.8	4.4	442	NO	NO	yes
46	53	1	5	12	132.6	224	288.3	456	3.2	324	NO	NORMAL	yes
47	35	1	6	13	112.9	168	220.2	318.4	8.8	424	NO	NO	yes
48	32	2	5	13.5	102	168.4	230.8	322	9.2	568	NO	NORMAL	yes
49	44	1	7	12	143	202.2	270.1	442.4	3.8	380	NORMAL	NO	yes
50	37	1	4	13.5	88.8	176	234	311.8	8.6	547	NO	NO	yes

CONTROLS

S.NO	AGE	SEX	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,Amp micV	CD4+	CT BRAIN	MRI BRAIN	ART
51	35	1		15.5	90.4	160.4	202.4	312.6	12.4				
52	38	1		14	94	168.2	212	316.3	9.4				
53	26	2		14	92.4	174.3	200.8	328.2	8.4				
54	36	2		15	96.3	160.8	206	312.2	9.8				
55	38	1		13.5	88.4	158.9	198	321	12.6				
56	24	2		15.5	94	176.4	221.4	332	10.4				
57	56	1		13	94.2	198.4	223.4	332.4	8.4				
58	32	1		15	92	162.4	200.7	310	11.2				
59	39	2		13.5	89.3	182.8	231	312	10.3				
60	48	1		14	98.8	162.1	241.6	322	8.4				
61	44	1		14.5	92.4	176	232.2	308.2	12.4				
62	35	1		13	89.4	174.2	223.4	320.2	10.4				
63	32	2		14	92.8	182.2	212.8	312.7	9.8				
64	38	2		13.5	104.7	188	267.5	345.2	9				
65	33	1		15.5	100.2	186.6	258.9	332	10.5				
66	46	2		14	88	167.4	210.4	316.4	9.4				
67	31	1		15.5	92	162.6	210.4	312	12.4				
68	48	1		16	96.4	170.4	223.4	318.4	10.4				
69	38	2		15	112.4	190.4	254	324.4	9.3				
70	34	2		16	92.4	167.4	232.4	308	12.4				
71	37	1		15.5	100.6	182.3	244.4	312.8	13.8				
72	31	1		14.5	88.3	173.4	242.4	320.4	12.6				
73	43	1		15	92.4	174.2	258	310.4	11.6				
74	42	2		13.5	92	164.4	245.4	322.6	9.4				
75	44	1		14	102.4	188.4	267.8	333	8.8				
76	32	1		14	98.4	176.4	270.3	340.4	9.4				
77	45	2		13	92	160.6	240.2	312.8	10.4				

S.NO	AGE	SEX	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,Amp micV	CD4+	CT BRAIN	MRI BRAIN	ART
78	33	1		16	87.2	168.4	254	308.9	8.6				
79	35	2		15	98.2	182.7	245.4	312.8	10.4				
80	52	1		14	121	196.4	274.8	356.3	7.4				
81	39	2		16	98	167.3	256	322.4	8.9				
82	28	2		15.5	92	172.4	248.4	314.8	9.8				
83	56	1		13	112.4	158.5	287.2	332.4	8.4				
84	25	2		14.5	110.3	184.3	267	312.6	12.4				
85	44	2		14	100.2	172.4	250.3	326	11.8				
86	35	1		13.5	116.4	167.3	278.3	345.3	9.8				
87	39	1		14	121.2	182	290.4	345.7	8.2				
88	36	2		15.5	89.4	167	200.4	308.4	13.4				
89	42	2		14.5	93.8	158	212.4	309.7	12.8				
90	28	1		14	90.6	162.4	222.2	322	13.8				
91	33	2		15	89.4	173.6	200.4	322.5	12.8				
92	38	1		14.5	112.4	168.4	228.8	356.3	7.8				
93	48	1		14	116.3	172.2	254.4	367.8	8.3				
94	37	2		11.5	92.9	172.4	224.4	316.8	9				
95	35	1		15	96.3	158	245.1	312	10.3				
96	33	1		15.5	90.4	169.4	232	322.8	11.2				
97	37	2		16	88.7	174.6	226.2	309.4	10.4				
98	56	1		13.5	134	162.4	284.8	360.4	7.8				
99	42	1		13.5	117.2	177.8	274	356.8	6.7				
100	47	1		13	120.4	188.4	268.4	332.8	7.8				
101	33	1		15	98.4	178	200.3	323	13.2				
102	36	2		12	99	167.3	212.4	300.9	10.4				
103	25	1		16	102.7	188.2	243	312.9	12.3				
104	34	1		14.5	109.3	167	284	342.2	10.2				
105	38	2		14	103.7	165.4	265.4	332	9.8				
106	33	1		13	112.4	178.4	275.2	345.8	8.2				

S.NO	AGE	SEX	DUR ILL YRS	HIV DS SCORE	P3, N1 L ms	P2 L ms	N2 L ms	P3 L ms	P-3,Amp micV	CD4+	CT BRAIN	MRI BRAIN	ART
107	54	1		14	120.8	188.4	290	367.4	6.7				
108	31	2		16	89.4	182	200.4	322	9.6				
109	38	1		16	90.4	176.2	221	335.9	10.2				
110	35	1		14	108.4	168.4	234.6	344.2	7.4				

sex: 1-male
2-female

YRS-Duration of illness in years

HIV DS SCORE-HIV Dementia Scale score

HIV-Human Immuno Deficiency Virus

Amp-Amplitude
L-Latency
ms-milliseconds
micV-Microvolts

ART-Anti Retroviral Therapy