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# Brain computed tomography findings in HIV-infected adults presenting with impaired mental status: determining the value of CT in a resource constrained environment.

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# BRAIN COMPUTED TOMOGRAPHY FINDINGS IN HIV-INFECTED ADULTS PRESENTING WITH IMPAIRED MENTAL STATUS: Determining the Value of CT in a Resource Constrained Environment

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Diagnostic Radiology

Johannesburg, 2013

# Declaration

I, Tanusha Sewchuran, declare that this research report is my own work. It is being submitted for the degree of MMed (Diagnostic Radiology) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Tanusha Sewchuran

On this 13th day of June 2013.

To Nic.

My soul mate, my rock, my best friend. I love you.

## Publications and presentations

This work has never been published nor presented at any local or international congresses.

# Abstract

**INTRODUCTION**: HIV/AIDS is a global health problem, with Sub-Saharan Africa the most affected. “Neuro-AIDS” refers to the extensive neuropathological manifestations of the disease. Neuroimaging of the HIV-infected individual plays a fundamental role in their work-up. Limited resources, however, drive the development of imaging protocols based on clinical signs. ‘Confusion’ may or may not represent a significant presenting sign and needs to be investigated, as it is the basis of referral of a significant number of patients for CT scanning.

**AIM**: To determine the frequency of positive findings of head CT in HIV-infected adults presenting with confusion with/without associated neurology, and correlate them with the degree of immunosuppression, presence of CSF abnormality and their ARV therapy status.

**METHOD**: CT brain scans of adult patients, who were HIV-positive and presented with confusion in Johannesburg, Gauteng, were retrospectively reviewed. The neurological status, CD4 counts, LP results and their ARV therapy status were documented.

**RESULTS**: 30% of our HIV-infected patients presented with confusion. There were 156 patients who were included. CT scans were abnormal in 81%. We found that ‘associated neurology’ was a weak predictor for abnormal CT, making it a poor screening tool. A positive LP was predictive of infection ($p=0.04$ for focal infection, $p=0.03$ for infected surface collection) and infarction ($p<0.01$) on CT. CD4 count, LP results and ARV therapy were found to be abnormal in the majority of patients.

**CONCLUSIONS**: CT was abnormal in the majority of HIV-infected patients presenting with confusion. Neurology was an unreliable clinical indicator. A positive LP was a good predictor for CT evidence of infection and infarction. The clinical parameters such as CD4 counts, LP results and ARV therapy, were abnormal in the majority of patients. If any of these parameters are abnormal in a patient with a normal CT, we believe this should motivate for further imaging with MRI.

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# 1. Introduction

## 1.1 Motivation and rationale for this study

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remain the greatest epidemics in the modern world, with the highest number of people living with AIDS in Sub-Saharan Africa (1). Whilst Southern Africa is home to less than 2% of the world's inhabitants, as many as 30% of these individuals are living with HIV/AIDS (1). Since its recognition in 1981 (2), it has become one of the fastest growing viruses known to mankind.

According to Statistics South Africa, in 2010 approximately 5.24million people inhabiting South Africa (3) and 60 million worldwide (4) were HIV-infected. There are an estimated 400 000 AIDS deaths per annum in South Africa alone (5), with nearly 25 million individuals worldwide having already succumbed to the virus (4). In comparison, a paltry 920 000 people were estimated to be receiving anti-retroviral (ARV) therapy in South Africa in 2009 (3). The virus affects both urban and rural communities, with a higher number of infected females than males. It is estimated that the average life expectancy in Sub-Saharan Africa has decreased from 55-60 years of age in the 1980's to less than 40 years old as a result of the HIV epidemic (1). This has obvious adverse effects on South Africa's developing economy.

The virus poses a multifaceted challenge to radiologists. The term 'NeuroAIDS' has been coined to describe the vast number of HIV-infected individuals experiencing neurological sequelae of the disease (6). Clinical features suggestive of neurological contamination

include headache, meningism, an altered mental status, implying change in consciousness or cognition (referred to in this report as “confusion”), visual or speech disturbance and motor, sensory or cranial nerve deficits (referred to in this report as “neurology”) (7). 90% of infected patients will have central nervous system (CNS) involvement, and approximately 10% of AIDS patients will have neurological sequelae at initial presentation (8). CNS complaints in HIV-infected patients represent approximately 20% of all visits to the emergency department (9). Following pulmonary disease, neurological manifestation is the next most common clinical complaint in AIDS (7). Consequently, imaging of the neurological system has come to play a fundamental role in the multidisciplinary management of the HIV/AIDS patient (10).

There are three main groups of neuropathological manifestations of HIV/AIDS: (11, 12)

a) Opportunistic infections
b) Neoplasms and
c) HIV-associated lesions

As a consequence of this, neuroradiology has become an essential part of the initial workup of these patients (12). The available neuroimaging literature highlights viral opportunistic infections such as cytomegalovirus (CMV), bacteria, such as tuberculosis, parasites like toxoplasmosis and fungal infections, specifically cyptococcosis and aspergillosis. Lymphoma is the most common CNS neoplasm. HIV-associated lesions consists primarily of HIV-Associated Dementia (HAD)/AIDS Dementia Complex (ADC) (11,12). In the conference, ‘Assessment of NeuroAIDS in Africa’ (June 2004) in Malawi, stroke, toxoplasmosis, cryptococcal meningitis, neurosyphillis, cerebral malaria and

tuberculosis were highlighted as the leading causes of HIV-associated neurological disease in Africa (1).

Much is known about the penetration of the virus into the central nervous system. HIV has been found to enter the blood brain barrier (BBB) early on via infected cells, primarily microglia and macrophages (2, 12). The 'Trojan Horse' theory, involving predominately monocyte and macrophage infiltration is the principle route of CNS infection (2). HIV has been found in the brain as soon as 15 days after initial infection (12).

There are a variety of imaging modalities at our disposal to assist us in detecting, diagnosing and treating the HIV positive patient (12). Most accessible would be computed tomography (CT) and magnetic resonance imaging (MRI). Single positron emission computed tomography (SPECT) and positron emission tomography (PET) are also of assistance (11) but are less accessible. Newer modalities such as magnetic resonance spectroscopy (MRS), functional MRI (fMRI), diffusion tensor imaging (DTI) and perfusion MRI (pMRI) are under investigation (13) with regard to their usefulness in the diagnosis and treatment of HIV. A suitable neuro-imaging modality to follow the pattern of the virus in the neurological system and to act as a more accurate substitute to viral load markers in monitoring its progress (13) is desirable.

MRI has been proven superior to CT when it comes to detecting neuropathology in HIV/AIDS, because of its enhanced contrast resolution (14). It has been found to be more sensitive than CT in the diagnosis of most brain parenchymal manifestations of the disease, particularly white matter disease (11, 15). FLAIR (fluid-attenuated inversion

recovery sequence) is particularly adept at delineating periventricular and subcortical pathology (12). MR Spectroscopy has shown increased levels of NAA (N-acetylaspartate) and MI (myoinositol) suggesting diffuse brain involvement (12). However, in the early stages of the disease, even MRI and CT may prove indefinite (15). CT is the most readily available cross-sectional imaging modality, is easy to use and is comparatively cheap (16). Compared to MRI, it is better suited to imaging the agitated and unstable patient because of its speed (17) and in the acute setting, it is sufficient to direct initial management of the HIV infected patient. It is also an important screening tool to determine if lumbar puncture may be performed (7). Specifically in the South African urban setting, most secondary referral institutions have CT scanners at their after-hours disposal, whereas MRI resources are severely limited (18). Specifically in the public sector in Johannesburg, MRI facilities are available only at select tertiary referral institutions and only for emergencies for after hours periods, due to human resource restrictions. The current waiting time at the Charlotte Maxeke Johannesburg Academic Hospital, for example, is 4 months for outpatient scans. This is compounded by a large patient volume from referral centres, as well as limited staff members trained in MRI.

Davenport et al demonstrated the CT and MRI findings of a variety of neuropathological manifestations of HIV (11). Atrophy and white matter changes may be observed, solid and rim enhancing lesions with oedema, meningeal enhancement, vascular bleeds and infarcts and evidence of raised intracranial pressure (ICP) can be diagnosed on CT (11). CT has proven superior in detecting calcification in healing or chronic tuberculomas (11). CT, for example, may demonstrate a rim enhancing lesion suggestive of an abscess, but a combination of MRI and MRS can further distinguish a tuberculous abscess and a

pyogenic one (12). MRI can be performed thereafter if CT proves ambiguous (16) or negative, but is unrealistic in the South African emergency after hours setting (7). With regards to AIDS Dementia Complex, both CT and MRI are relatively insensitive. CT demonstrates global atrophy and/or demyelination, whilst MRI is more sensitive to the white matter changes (11). But, more often than not, the clinical features are expressed before any imaging findings (11). Functional imaging, such as fMRI and FDG (F-18 fluorodeoxyglucose)-PET can demonstrate increased metabolism in areas of the brain early on the disease, generally before symptom manifestation (15,18). Using Thallium-201 brain SPECT in the AIDS patient can be of assistance in distinguishing lymphoma from toxoplasmosis (12). FDG-PET, on the other hand, can help distinguish focal infections and lymphoma (12).

Thus the dilemma: In a resource limited environment such as South Africa, is there real value of using CT as a first line neuroimaging modality in the HIV-infected patient? In 1999, Rothman et al proposed a new set of indications for urgent head CT in the HIV-infected individual presenting to the emergency department (9). He proposed that emergency physicians have a low threshold for requesting neuroimaging in HIV-positive patients (9). This, in part, can be attributed to the fact that the compromised immune system in HIV/AIDS may mask clinical features normally associated with similar conditions in patients with intact immune systems (17). Five clinical criteria were suggested by Rothman, namely new onset seizures, depressed or altered orientation (or confusion), a headache that had changed in quality or one that was prolonged (>3 days) or a focal neurological deficit, which warranted immediate neuroimaging (9). Their aim was to identify HIV-infected individuals requiring acute intervention, whilst attempting to restrict

the number of urgent head CT's in the emergency department (9). In 2001, a study published in the Southern African Journal of HIV Medicine stated that the majority of literature on HIV/AIDS medicine available to clinicians was in fact from Europe or America, despite Southern Africa being the epicentre of the virus (19). They also advocated CT brain scans in HIV-positive patients presenting with meningitis or encephalitis, as they were more at risk for asymptomatic focal brain lesions (19). Toxoplasmosis, pyogenic abscess and tuberculoma were found to be the most frequent causes of intracranial mass lesions in a study done on HIV-infected individuals in KwaZulu Natal (19). This was corroborated by a prospective study by M Modi et al in Soweto, Johannesburg, who established neurocysticercosis as a cause for cystic HIV-associated focal brain lesions, and toxoplasmosis and tuberculosis for solid HIV-associated focal brain lesions (20). This study found that rarer causes are primary CNS lymphoma and PML (20). These studies further advocate the need for both a high index of suspicion in the HIV-infected patient presenting with neurology, and consequently a low threshold for investigation.

Stedman's medical dictionary defines confusion as a "mental state in which reactions to environmental stimuli are inappropriate because the subject is bewildered, perplexed or disorientated". Medline plus defines confusion as being "a disturbance of consciousness characterised by the inability to engage in a logical orderly thought process". According to Wikipedia, when "pathological, it is associated with a loss of orientation to person, time and place accompanied by disturbance of memory". This is directly comparable to Rothman's criteria (9).

The HIV virus is lymphotropic and neurotropic, and swiftly crosses the BBB (7, 19). Therefore, patients afflicted with the disease are susceptible to developing an altered mental status (confusion) (17). In 2010, Ho et al suggested numerous reasons for this presenting complaint. The virus itself, a vulnerable immune system, associated systemic illness and psychiatric conditions as well as, the combined effects of treatment regimes such as Immune Reconstitution Inflammatory Syndrome (IRIS) were highlighted (17). In the local South African setting of Gauteng, requests to image the HIV-infected patient presenting with a disordered level of consciousness or confusion are frequent. The possible differential diagnoses are vast. Rothman et al found that diminished orientation to person, time or place (or confusion) in the HIV-infected individual has the greatest association with a new focal finding on neuroimaging (9).

Several studies have demonstrated that the level of immunosuppression is directly correlated to a neurological condition but also to the clinical manifestation of the patient (17, 19). The Centre for Disease Control (CDC) emphasizes the role of CD4 in determining the clinical stage of HIV (21). Table 1.1 summarises these CDC findings.

**Table 1.1: Correlation of infective agent CD4 count and clinical findings in HIV infected individuals (17)**

| Opportunistic Infection | CD4 count (cells/$mm^3$) | Clinical Features |
|---|---|---|
| HIV-associated Dementia | < 200 | Cognitive, behavioural and mental slowing (confusion) |
| Meningitis (cryptococcal, TB, syphilitic, lymphomatous, bacterial) | < 200 | Headache, altered mental status (confusion), or complications thereof |
| Toxoplasmosis | < 200 | Altered mental status (confusion), seizure |
| Drug ingestion | < 200 | Depends on type of drug ingested |
| Metabolic encephalopathies | < 200 | Renal or hepatic failure, electrolyte abnormalities |
| Primary CNS Lymphoma | < 200 | Slowly progressive focal deficit or cognitive dysfunction (confusion) |
| Progressive multifocal leukoencephalopathy | < 200 | Focal deficit (neurology) |
| CMV ventriculoencephalitis | < 100 | Cognitive impairment (confusion) with brainstem abnormalities |
| Brain abscess (bacterial or fungal) | < 100 | Progressive focal cerebral deficit (neurology) +/- headache |
| Tuberculoma | < 100 | Progressive focal cerebral deficit (neurology) |
| Angioinvasive fungi (aspergillus) | < 50 | Associated sinus infection |

Ho et al also acknowledged that an HIV-positive patient presenting with a CD4 count of <200cell/$mm^3$ was at the greatest risk of developing CNS opportunistic infections, primary CNS lymphoma and HIV-associated dementia, despite being on Highly Active Antiretroviral Therapy (HAART) (17). Comparatively, patients with higher CD4 counts (>200cells/$mm^3$) and an altered mental status were more likely to have cerebrovascular disease (17). For these reasons Graham et al also suggested limiting head CTs in infected patients to those with a CD4 <200cell/$mm^3$ presenting with CNS symptomatology (21). Patients with higher CD4 counts (>200cells/$mm^3$) would benefit more from MRI as an initial imaging modality rather than CT, as the yield of positive findings on CT were low (21). The impact of CD4 counts on the CT finding has also not been evaluated in the local setting. Graham et al documented early stage HIV as a CD4 of ≥500 cells/µL (equivalent to 500cells/$mm^3$) where patients were relatively asymptomatic (21). Middle stage disease ranged from 200-499 cells/µL with myalgia, fatigue and headaches. Late stage disease (<200 cells/µL) and advanced AIDS (<50 cells/µL) had significant AIDS defining illnesses (21). For our purposes, we re-categorised the CD4 counts as the majority of our cohort had CD4 counts below 200 cells/$mm^3$.

In the evaluation of the HIV-infected individual presenting with an altered mental status, a lumbar puncture (LP) is recommended (17). The question of performing lumbar puncture prior to neuroimaging is a controversial one. Evidence of a space-occupying lesion, haemorrhage, hydrocephalus or raised intracranial pressure often contraindicates an LP (7, 9, 17) making a case for performing CT early on. A documented difficulty in the interpretation of cerebrosoinal fluid (CSF) results in HIV-infected patients is the elevated proteins (>100mg/dL) and an associated lymphocytic pleocytosis (>50/$mm^3$) associated

with the disease (17). Important aspects of the LP analysis include the opening pressures, and protein, glucose, cell counts and cultures (17).

Ho et al reported specific CSF findings in selected HIV CNS disorders (17) summarised in table 1.2.

**Table 1.2: Correlation of selected CNS disorders and lumbar puncture results (17).**

| **CNS Disorder** | **CSF findings** |
|---|---|
| PML | ↑protein, normal glucose, mild lymphocytic pleocytosis |
| HIV-associated dementia | Normal opening pressure, normal/↑protein, normal glucose, mild lymphocytic pleocytosis |
| Primary CNS Lymphoma | ↑protein, normal glucose, lymphocytic pleocytosis |
| Cerebral toxoplasmosis | ↑protein, normal glucose, lymphocytic/monocytic pleocytosis |
| Cryptococcal meningitis | ↑opening pressure, normal/↑protein, normal/↓glucose, lymphocytic pleocytosis |
| TB Meningitis | ↑opening pressure, ↑protein, ↓glucose, lymphocytic pleocytosis |
| Syphilitic meningitis | Normal/↑opening pressure, ↑protein, normal/↓glucose, lymphocytic pleocytosis |
| CMV ventriculoencephalitis | ↑protein, normal/↓glucose, polymorphonuclear pleocytosis |

With the advent of highly active antiretroviral therapy (HAART), the incidence of neurological disease, particularly CNS opportunistic infections has significantly decreased (22). The spectrum of neurological disease in developed countries prior to the availability of ARV therapy parallels the current profile seen in developing countries due to the relative deficiency of antiretrovirals (22). Research and follow-up is difficult in the developing world because of poverty and poor infrastructure, social stigma, limited access to drugs and refrigeration, and cultural and political issues (1). Whilst large-scale treatment programs have been introduced, it is unlikely that everyone in need will be helped (23). As such, rationing of ARV therapy occurs. This again will impact the disease profile, more specifically the CNS complications manifested.

The possibility for neuropathological manifestations in the HIV-infected patient is vast. With escalating pressure to conserve resources in the South African setting, the goal is to use available clinical information to limit unwarranted CT scans and to motivate for possible MRI scanning where necessary. To this end we attempt to establish a relationship between the CT findings in an HIV-infected individual presenting with confusion, their presenting neurological complaint, CD4 count, LP CSF results and ARV therapy.

## 1.2 Aims and objectives

### 1.2.1 Aim

To determine the frequency of positive findings of head CT in HIV-infected adults presenting with confusion with/without associated neurology, to categorise these and correlate them with the degree of immunosuppression, presence of CSF abnormality and their ARV therapy status.

### 1.2.2 Objectives

1. To determine the number of abnormal brain CTs in HIV-infected adults presenting with confusion, and to categorise those with/without associated neurology
2. To categorise the CT findings and compare with those who presented with associated neurology and those who did not
3. To correlate the degree of immunosuppression using CD4 categories with the CT findings
4. To compare those patients on ARV therapy to those not on ARV's with regards to the CT finding
5. To compare LP CSF results with the CT findings.

# 2. Materials and Methods

## 2.1 Study Design

This was a retrospective, quantitative descriptive study of head CT reports, laboratory data and available clinical treatment information.

## 2.2 Study Setting

A secondary referral centre (Helen Joseph Hospital) CT scan department in Johannesburg, South Africa. This facility had a Philips Brilliance 16 slice MDCT, Eindhoven, Netherlands.

## 2.3 Study Sample

The reports of adults undergoing brain CT scans at Helen Joseph Hospital for a 12-month period (01/01/2010 to 31/12/2010) were reviewed, as were the CD4 and CSF results, as well as the ARV treatment recorded.

## 2.4 Inclusion Criteria

All HIV-infected adults (> 13 years), as indicated on head CT request form were considered. Only patients with a primary complaint of confusion documented on the CT request form were included in the study, whether or not accompanied by a history of other neurological findings, CSF results and ARV therapy information.

## 2.5 Exclusion Criteria

Patients were excluded if their HIV status was not confirmed on laboratory records.

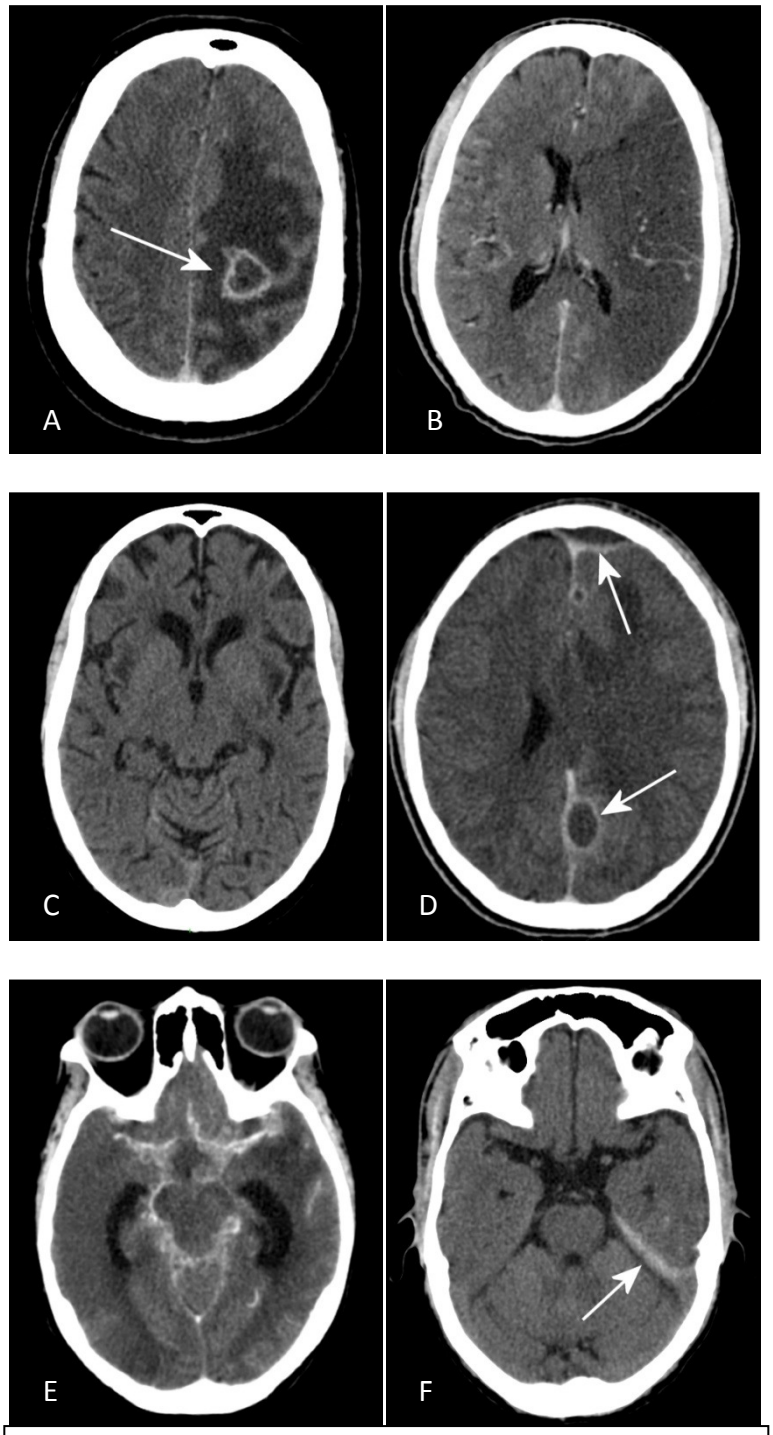
## 2.6 Measurements

A retrospective analysis of all head CT reports meeting the inclusion criteria was performed. The on-site NHLS laboratory was used to confirm the HIV status and to obtain the CD4 results. Patients who had available CSF results were considered additionally as a sub-group. Another subcategory of patients with available antiretroviral therapy information was also considered. This information was obtained from the ARV Clinic, Thembalethu, at Helen Joseph Hospital. CT findings were recorded from the final CT scan reports with the aid of a tick sheet (appendix B). Figure 2.1 shows examples of some of the pathology recorded.

Immunosuppression was categorised according to table 2.1

**Table 2.1: Categories defining degree of immunosuppression according to CD4 count**

| CD 4 Count (cells/$mm^2$) | Category |
|---|---|
| >200 | 1 |
| 101- 200 | 2 |
| 50 - 100 | 3 |
| <50 | 4 |




A: Rim-enhancing lesion with surrounding oedema
B: Infarct involving the left MCA territory
C: Global atrophy
D: Infected surface collections
E: Significant basal meningeal enhancement complicated by obstructive hydrocephalus and right temporal lobe infarct, indicating TB
F: Subarachnoid haemorrhage

**Figure 2.1 Documented CT abnormalities in HIV-infected patients presenting with confusion**

The subgroup of patients who had undergone lumbar puncture was categorised as positive or negative, based on the finding of any abnormal cells, using table 2.2 as a guide (24).

**Table 2.2. Summary of typical LP CSF findings**

| CSF Findings | Normal | Bacterial | Viral | TB |
|---|---|---|---|---|
| Cells | 0-5 | >1000 | <1000 | 25-500 |
| Polymorphs | 0 | Predominate | Early | +/- increased |
| Lymphocytes | 5 | Late | Predominate | Increased |
| Glucose | 60-80 | Decreased | Normal | Decreased |
| CSF : Plasma Glucose ratio | 66% | <40% | Normal | Decreased |
| Protein | 5-40 | Increased | +/- increased | Increased |
| Culture | Negative | Positive | Negative | +TB |

Patients were also categorised into whether they had or did not have associated neurological signs from the request card. Neurology included cranial nerve deficits, hemiplegia/hemiparesis, tremor, abnormal gait and abnormal pupils. Patients were categorised if they were or were not initiated onto ARV therapy based on the clinical information available. The CD4 category, the presence or absence of associated neurology, a positive or negative LP result, and if the patient is currently on ARV therapy was compared and correlated to the CT findings.

## 2.7 Limitations of study

There is no MRI facility at Helen Joseph Hospital. Patients requiring MRI are transferred to outlying tertiary centres. As such, we could not access MRI scans if they were done. As this was a retrospective study, some patient data was not be available because of inaccurate records, or insufficient information available on the request form.

## 2.8 Methods of Analysis

Data analysis was carried out using SAS (SAS Institute Inc., SAS Software version 9.3 for Windows, Cary, NC, USA : SAS Institute Inc. (2002-2010). A 95% confidence interval was used throughout, unless otherwise specified. Tests for significant relationships were carried out using Pearson's $X^2$ test at the 95% confidence interval. Fisher's exact test was used in the case of 2x2 tables, or where the requirements for Pearson's $X^2$ test could not be met. The strength of the associations was determined by Cramer's V (the Phi coefficient was used in the case of 2x2 tables). The absolute values of these Phi coefficients were interpreted as follows:-

| | |
|---|---|
| 0.50 and above | high/strong association |
| 0.30 to 0.40 | moderate association |
| 0.10 to 0.29 | weak association |
| Below 0.10 | little if any association. |

# 3. Results

In the one-year period (01/01/2010 to 31/12/2010), 2495 CT scans of the brain were performed at the Helen Joseph Hospital Radiology department. Of these 524 were for patients who were HIV-infected (21%). Those presenting with associated confusion numbered 156/ 524 (30%). This was our inclusion group. These confused patients were subcategorised into those with concomitant neurological features (66/156; 42%) - **'neuro'** group - and those without neurological symptoms (90/156; 58%) - **'non-neuro'** group. The median age in the study group was 37 years (IQR 31-46 yrs.). The mean age was 39.2 years with a SD of 12.3 years. There was no significant difference between the mean ages for the neurology and non-neurology groups (t-test with pooled variances: p=0.60). The male: female distributions, as well as the ages of the included patients are summarized in Table 3.1 under the specific categories.

**Table 3.1: Demographics of the overall group and sub-groups.**

| | | Overall | 'Non Neuro' | 'Neuro' |
|---|---|---|---|---|
| | | Number (%) of patients<br>156 | Number (%) of patients<br>90 | Number (%) of patients<br>66 |
| Gender | Male | 88 (56%) | 57 (36%) | 31 (20%) |
| | Female | 68 (44%) | 33 (21%) | 35 (23%) |
| Age | Median<br>Mean | 37 years<br>39 years | 39 years<br>39 years | 38 years<br>38 years |
| | Min age | 15 years | 15 years | 19 years |
| | Max age | 100 years | 100 years | 67 years |

Information on antiretroviral therapy was available in 106 /156 patients (68%). Therefore, ARV treatment status for 32% of the patients in the study was unknown. The proportion of missing data did not differ significantly between the neurology groups (test for binomial proportions, p=0.27). The ARV therapy information available is summarized in Table 3.2 below.

**Table 3.2: Antiretroviral therapy information and status for overall and subgroups.**

| Antiretroviral Therapy | Overall | 'Non-Neuro' | 'Neuro' |
|---|---|---|---|
| | Number (%) of patients<br>156 | Number (%) of patients<br>90 | Number (%) of patients<br>66 |
| ARV results available | 106 (68%) | 58 (64%) | 48 (62%) |
| ARV therapy | 73/106 (69%) | 42/58 (72%) | 31/48 (65%) |
| Not on ARV therapy | 33/106 (31%) | 16/58 (28%) | 17/48 (35%) |

For the 106 patients whose ARV treatment status was known, there was no significant association between ARV treatment status and presentation with additional neurology; "neuro group" (p=0.41). There was no significant association between being on ARV treatment at the time of the CT scan and the overall presence of CT findings (p=0.81).

CT scans were found to be abnormal in 127/156 patients (81%) – in the 'non neuro' subgroup 70/90 (78%) were abnormal and 57/66 (86%) were abnormal in the 'neuro'

subgroup. The abnormal intracranial CT findings are summarized in Table 3.3 for the overall, 'non-neuro' and 'neuro' groups.

**Table 3.3: Intracranial abnormalities on CT for the 'overall', 'non neuro' and 'neuro' subgroups.**

| CT Finding | Overall | 'Non-Neuro' | 'Neuro' |
|---|---|---|---|
| | Number of patients (%) n = 156 | Number of patients (%) n = 90 | Number of patients (%) n = 66 |
| Intracranial CT Abnormality | 127 (81%) | 70 (78%) | 57 (86%) |
| *NAD | 29 (19%) | 20 (22%) | 9 (14%) |
| White Matter Disease | 21 (13%) | 11 (12%) | 10 (15%) |
| Infection focal | 30 (19%) | 15 (17%) | 15 (23%) |
| Infection surface collection | 13 (8%) | 6 (7%) | 7 (11%) |
| Vascular bleed | 5 (3%) | 2 (2%) | 3 (5%) |
| Vascular infarct | 31 (20%) | 19 (21%) | 12 (18%) |
| Focal mass | 7 (4%) | 4 (4%) | 3 (5%) |
| Atrophy | 73 (47%) | 42 (47%) | 31 (47%) |
| Hydrocephalus | 13 (8%) | 7 (8%) | 6 (9%) |
| Other | 14 (9%) | 8 (9%) | 6 (9%) |

* NAD = no abnormality detected.
(More than one abnormality was possible per patient accounting for the numbers not adding up to the totals.)

We defined the CT scan as the gold standard for determining the sensitivity and specificity of the neurological examination as a test (i.e. 'neuro' vs. 'non neuro' groups). The results are summarized in Table 3.4 below.

**Table 3.4: The sensitivity and specificity of the neurological ('Neuro' vs. 'non-neuro') examination in predicting the presence of CT findings**

| CT finding | Sensitivity | 95% confidence interval for sensitivity | Specificity | 95% confidence interval for specificity |
|---|---|---|---|---|
| Overall | 0.49 | 0.36-0.54 | 0.69 | 0.49-0.85 |
| White matter disease | 0.48 | 0.26-0.70 | 0.59 | 0.50-0.67 |
| Infection focal | 0.50 | 0.31-0.69 | 0.60 | 0.50-0.68 |
| Infection surface collection | 0.54 | 0.25-0.81 | 0.59 | 0.50-0.67 |
| Vascular bleed | 0.60 | 0.15-0.95 | 0.58 | 0.50-0.66 |
| Vascular infarct | 0.39 | 0.22-0.58 | 0.57 | 0.48-0.66 |
| Neoplasm mass | 0.43 | 0.10-0.82 | 0.58 | 0.49-0.66 |
| Atrophy | 0.42 | 0.31-0.54 | 0.57 | 0.46-0.68 |
| Hydrocephalus | 0.46 | 0.19-0.75 | 0.58 | 0.50-0.66 |

The degree of immunosuppression, as quantified by the individual's CD4 count, was available in 125/156 patients (80%). The CD4 counts ranged from 1 to 587 cells/$mm^3$ for the overall group, with a mean of 119.5 cells/$mm^3$ (SD= 136). The median CD4 count in the study group was 59 cells/$mm^3$ (IQR 23-160). For the patients in the 'non-neuro'

subgroup the CD4 count range extended from 1 to 587 cell/mm$^3$, with a mean of 117.2 cells/mm$^3$. The 'neuro' subgroup CD4 counts ranged from 3 to 573 cell/mm$^3$, with a mean of 122.6 cells/mm$^3$.

The frequency distribution of CD4 counts is illustrated in figure 3.1 below.

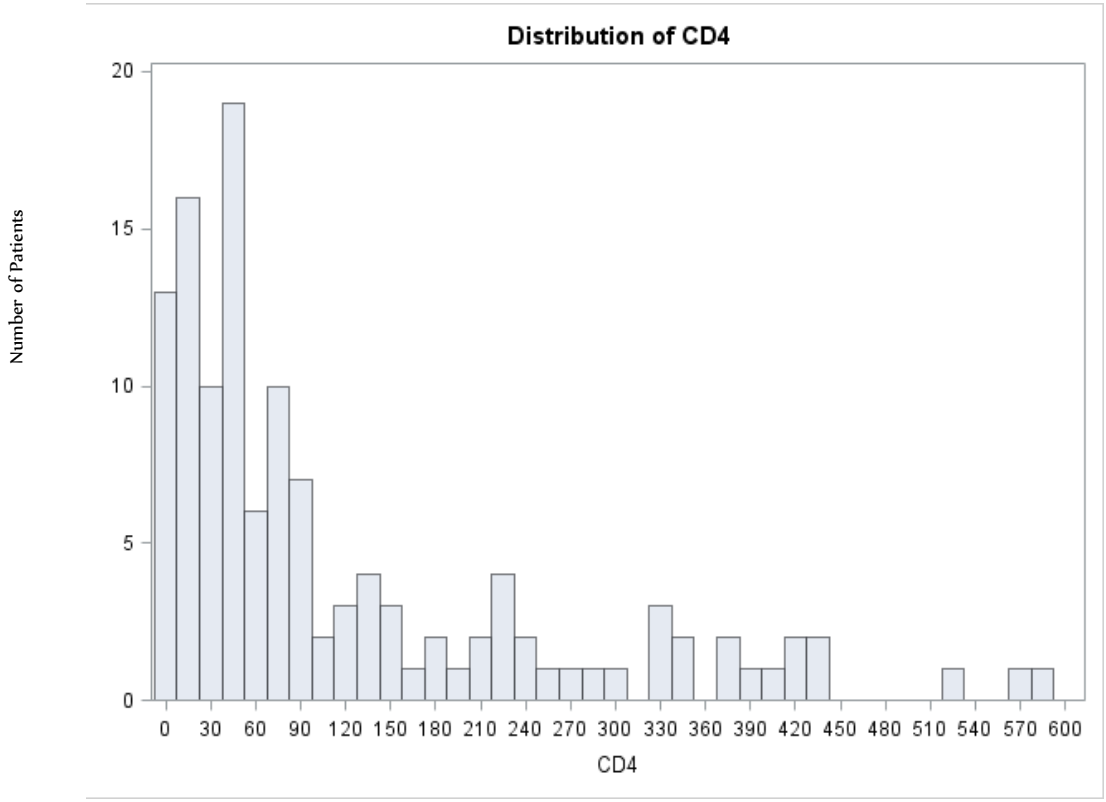



**Figure 3.1: Frequency distribution of patients according to CD4 cells/mm$^3$ counts for the 'overall' group**

Since the distribution of CD4 counts was so positively skewed, further analysis was conducted using CD4 categories, and we tested the association between CD4 counts and neurology group in terms of CD4 categories rather than absolute count, shown in Table 3.5 below.

**Table 3.5: Number of patients with CT abnormality according to CD4 category and clinical group.**

| | Overall | | | | ‘Non-Neuro’ | | | | ‘Neuro’ | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of patients with available CD4 counts (%) | | | | Number of patients with available CD4 counts (%) | | | | Number of patients with available CD4 counts (%) | | | |
| CD4 Category | 4 | 3 | 2 | 1 | 4 | 3 | 2 | 1 | 4 | 3 | 2 | 1 |
| Number of patients | 56/125 *45%* | 26/125 *21%* | 15/125 *12%* | 28/125 *22%* | 33/73 *45%* | 14/73 *19%* | 10/73 *14%* | 16/73 *22%* | 23/52 *44%* | 12/52 *23%* | 5/52 *10%* | 12/52 *23%* |
| CT Abnormality | 47/56 *84%* | 23/26 *88%* | 14/15 *93%* | 20/28 *71%* | 28/33 *85%* | 11/14 *79%* | 9/10 *90%* | 10/16 *62.5%* | 19/23 *83%* | 12/12 *100%* | 5/5 *100%* | 10/12 *83%* |
| *NAD | 9/56 *16%* | 3/26 *12%* | 1/15 *7%* | 8/28 *29%* | 5/33 *15%* | 3/14 *21%* | 1/10 *10%* | 6/16 *37.5%* | 4/23 *17%* | 0/12 *0%* | 0/5 *0%* | 2/12 *17%* |

* NAD = no abnormality detected

The CD4 count for 80% of the patients in the study was known. The proportion of missing data did not differ significantly between the 'non-neuro' and 'neuro' groups (test for binomial proportions, p=0.72).

The p-values for the tests of association between the CT findings and the CD4 categories for the overall, 'neuro' and 'non-neuro' groups are shown in table 3.6 below.

**Table 3.6: P-values of statistical significance of CD4 category correlation with CT finding**

| CT finding | Overall | 'Non-Neuro' | 'Neuro' |
|---|---|---|---|
| Overall presence of abnormality | 0.29 | 0.39 | 0.52 |
| White matter disease | 0.81 | 0.22 | 0.06 |
| Infection focal | 0.06 | 0.03 | 0.69 |
| Infection surface collection | 0.14 | 0.24 | 0.59 |
| Vascular bleed | 0.73 | 0.55 | 0.23 |
| Vascular infarct | 0.25 | 0.62 | 0.04 |
| Neoplasm mass | 0.20 | 0.42 | 0.20 |
| Atrophy | 0.03 | 0.32 | 0.04 |
| Hydrocephalus | 0.55 | 0.72 | 0.74 |
| Other | 0.41 | 0.62 | 0.39 |

There was a significant, but weak association between the presence of atrophy and CD4 category for the overall data set (Fisher's exact test: p=0.03; Phi coefficient = 0.27): a higher proportion of patients in CD4 category 3 (CD4 – 50-100) had atrophy in the 'Overall' group - demonstrated in Figure 3.2 below.

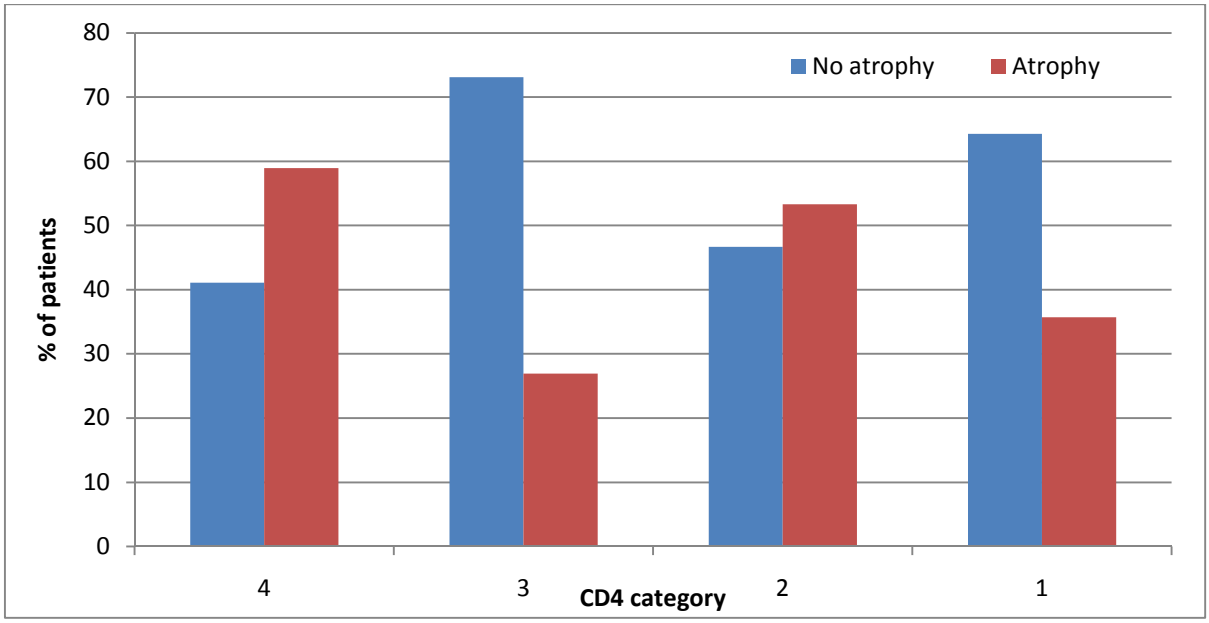



**Figure 3.2: Presence of atrophy according to CD4 categories for the 'overall' group**

There was a statistically significant but moderate association between atrophy and CD4 category for the neuro group (Fisher's exact test: p=0.04; Phi coefficient=0.41): a higher proportion of patients with category 2 and 4 disease displayed atrophy than those with CD4 categories of 1 or 3 in the 'Neurology' group, shown in Figure 3.3.

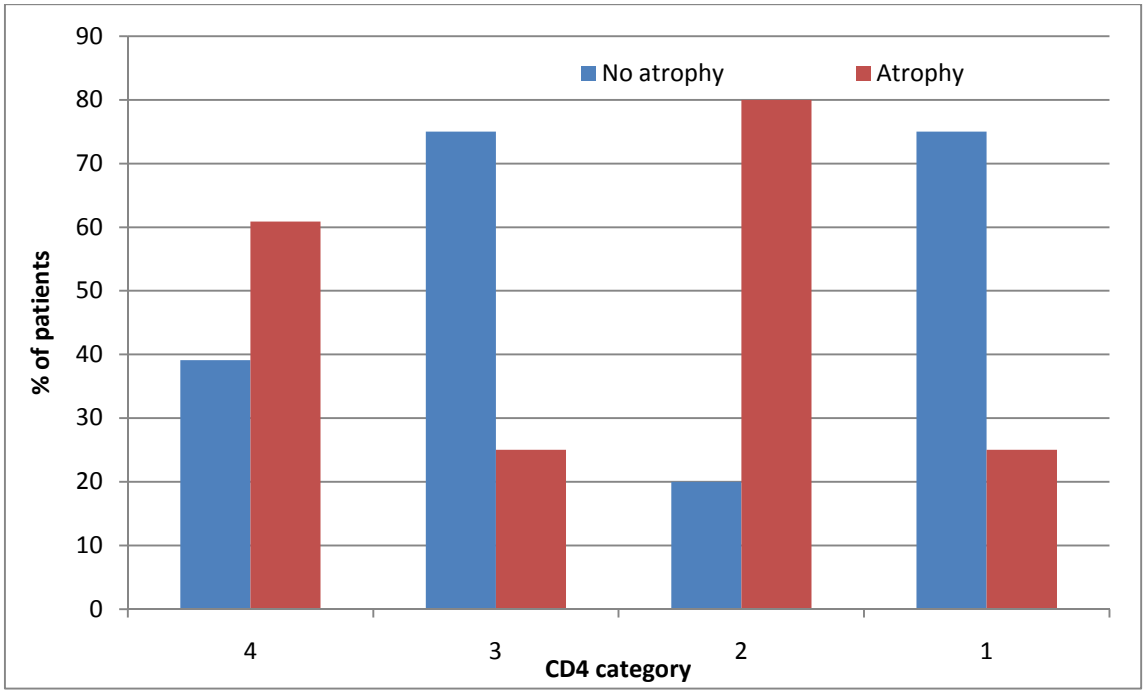



**Figure 3.3: Presence of atrophy according to CD4 category in the 'neuro' group**

There was a statistically significant (p value) and moderate association (Phi coefficient) between vascular infarct and CD4 category for the 'neuro' group (Fisher's exact test: p=0.04; Phi coefficient=0.38): a lower proportion of patients with category 4 disease displayed vascular infarcts than those with category 3 disease for the 'Neuro' group, illustrated in Figure 3.4 below.

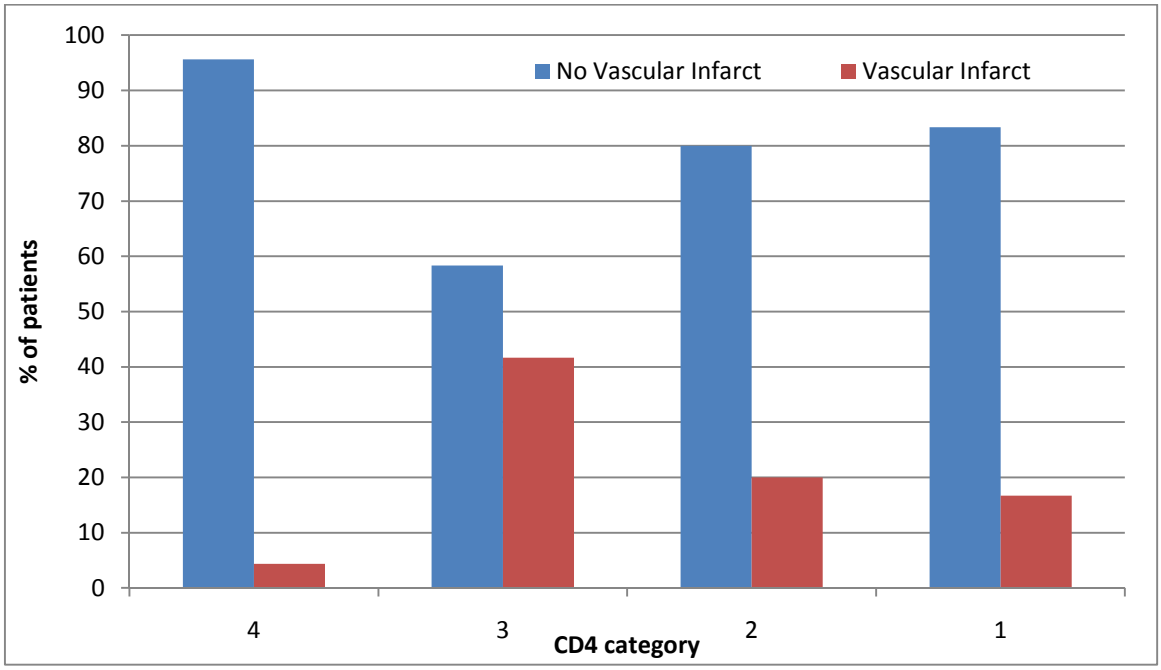



**Figure 3.4: Presence of infarcts according to CD4 category for the 'neuro' group.**

There was a statistically significant and moderate association between 'infection focal' and CD4 category for the 'non-neuro' group (Fisher's exact test: p=0.03; Phi coefficient=0.33): a higher proportion of patients with category 2 and 3 disease had this finding compared to those in the other disease stages in the 'Non-neuro' group of patients, demonstrated in Figure 3.5 below.

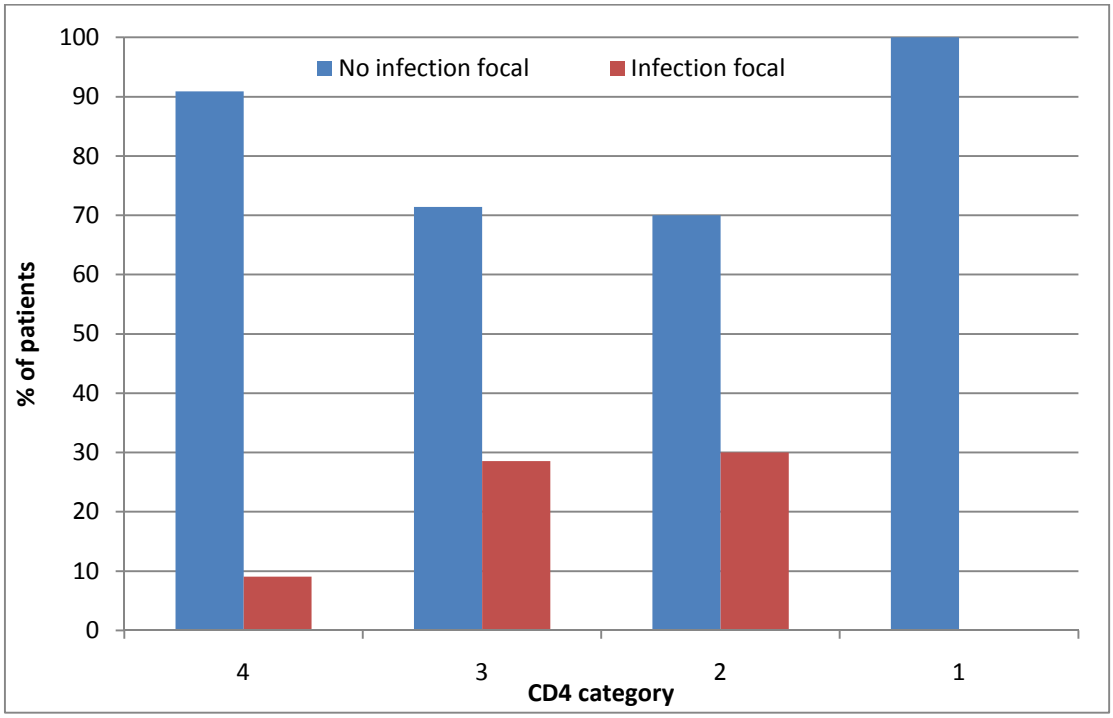



**Figure 3.5: Presence of focal infection according to CD4 category in the 'non-neuro' group**

Of the 156 patients in the study, 138 had documented lumbar puncture CSF results (88%).

The LP results are summarized according to subgroups in table 3.7 below.

**Table 3.7: Summary of lumbar puncture CSF results according to clinical groups**

| Lumbar Puncture Findings | Overall | 'Non-Neuro' | 'Neuro' |
|---|---|---|---|
| | Number (%) of patients | number (%) of patients | number (%) of patients |
| Total available | 135/156 (87%) | 80/90 (89%) | 55/66 (83%) |
| Positive | 85/135 (63%) | 48/80 (60%) | 37/55 (67%) |
| Negative | 50/135 (37%) | 32/80 (40%) | 18/55 (33%) |

The p-values for the tests of association between CT findings and the LP findings for all groups are summarized in table 3.8 below.

**Table 3.8: P-values of statistical significance correlating a positive CSF puncture result with a range of CT findings.**

| CT finding | Overall | 'Non-Neuro' | 'Neuro' |
|---|---|---|---|
| Overall | 0.17 | 0.10 | 1.00 |
| White matter disease | 0.62 | 0.75 | 1.00 |
| Infection focal | 0.04 | 0.22 | 0.18 |
| Infection surface collection | 0.03 | 0.08 | 0.65 |
| Vascular bleed | 0.55 | 1.00 | 0.33 |
| Vascular infarct | <0.01 | 0.03 | 0.02 |
| Neoplasm mass | 1.00 | 1.00 | 1.00 |
| Atrophy | 0.38 | 0.82 | 0.39 |
| Hydrocephalus | 0.09 | 0.04 | 1.00 |
| Other | 0.10 | 0.21 | 0.32 |

There was a statistically significant but weak association between 'infection focal' and LP finding for the overall data set (Fisher's exact test: p=0.04; Phi coefficient=0.18): a higher proportion of those with a positive LP CSF finding also had focal infection, compared to those with a negative LP finding in the Overall group. This is illustrated in Figure 3.6 below.

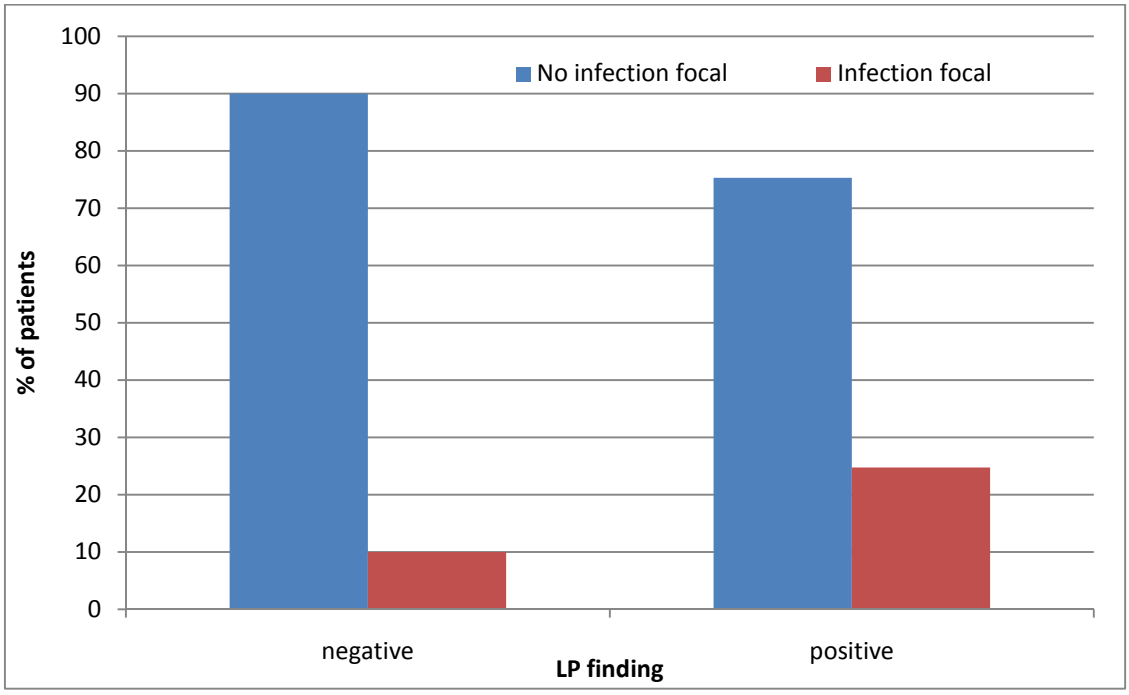



**Figure 3.6: Presence of focal infection according to LP positivity in the Overall group.**

There was a statistically significant but weak association between 'infection surface collection' and LP for the overall group (Fisher's exact test: p=0.03; Phi coefficient=0.19): a higher proportion with a positive LP had 'infection surface collection', than those with a negative LP. This is shown in Figure 3.7 below.

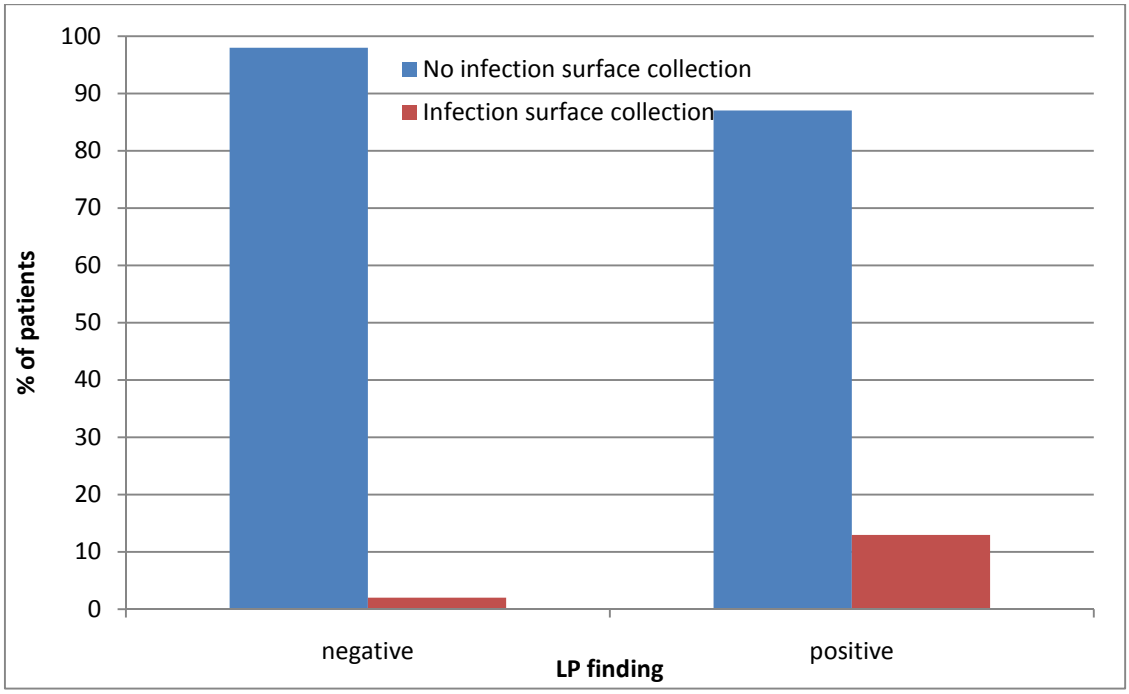



**Figure 3.7: Presence of 'infection surface collection' by LP result in the overall group**

There was a statistically significant but weak association between vascular infarct and LP CSF finding for the Overall data set (Fisher's exact test: $p<0.01$; Phi coefficient=0.27): a higher proportion of those with a positive LP CSF finding also had vascular infarct, compared to those with a negative LP CSF finding in the overall group. This is represented in Figure 3.8 below.

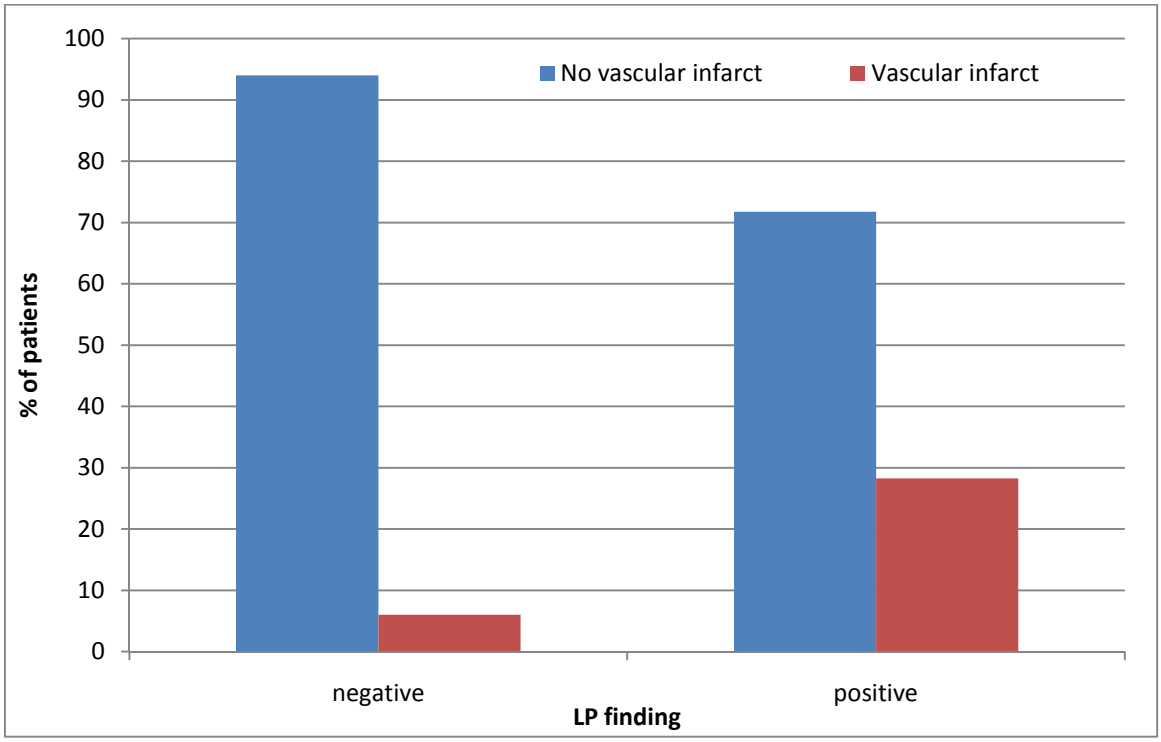



**Figure 3.8: Presence of 'vascular infarcts' by LP result for the 'overall' category.**

There was a statistically significant moderate association between 'vascular infarct' and positive LP CSF finding for the 'neuro' group (Fisher's exact test: p=0.02; Phi coefficient=0.31): all 9 cases of vascular infarct in the 'neuro' group were associated with a positive LP finding, as shown in Figure 3.9 below.

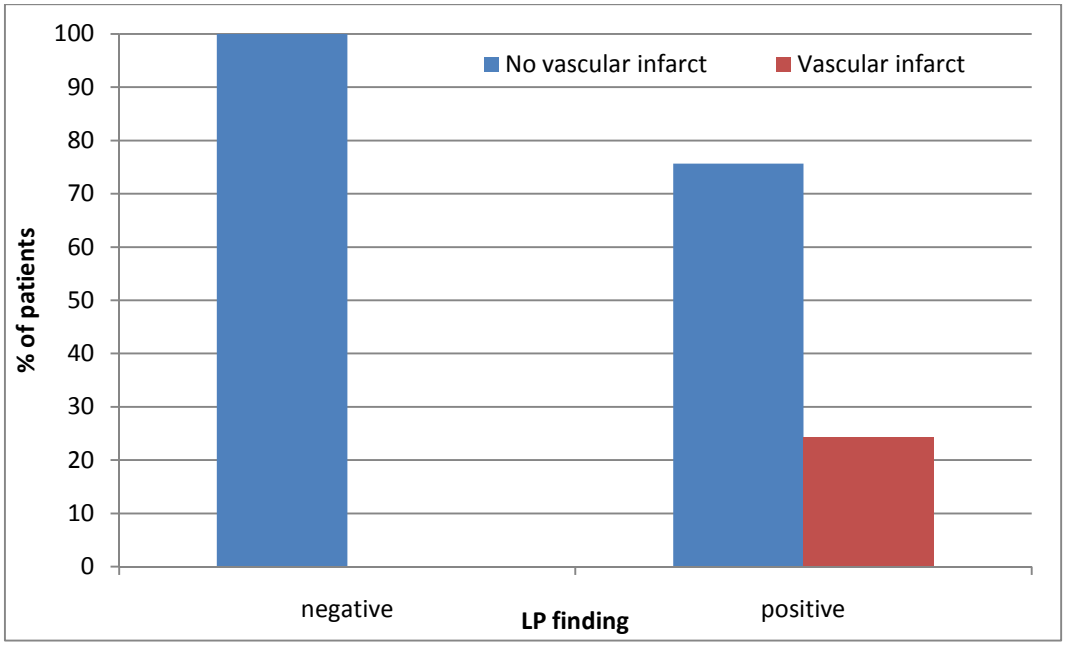



**Figure 3.9: Presence of vascular infarcts by LP result in the 'neuro group'**

There was a statistically significant but weak association between vascular infarct and positive LP finding for the 'Non-neuro' group (Fisher's exact test: p=0.02; Phi coefficient=0.27): a higher proportion of those with a positive LP result had vascular infarcts, compared to those with a negative LP result in the 'Non-neuro' group, demonstrated in Figure 3.10 below.

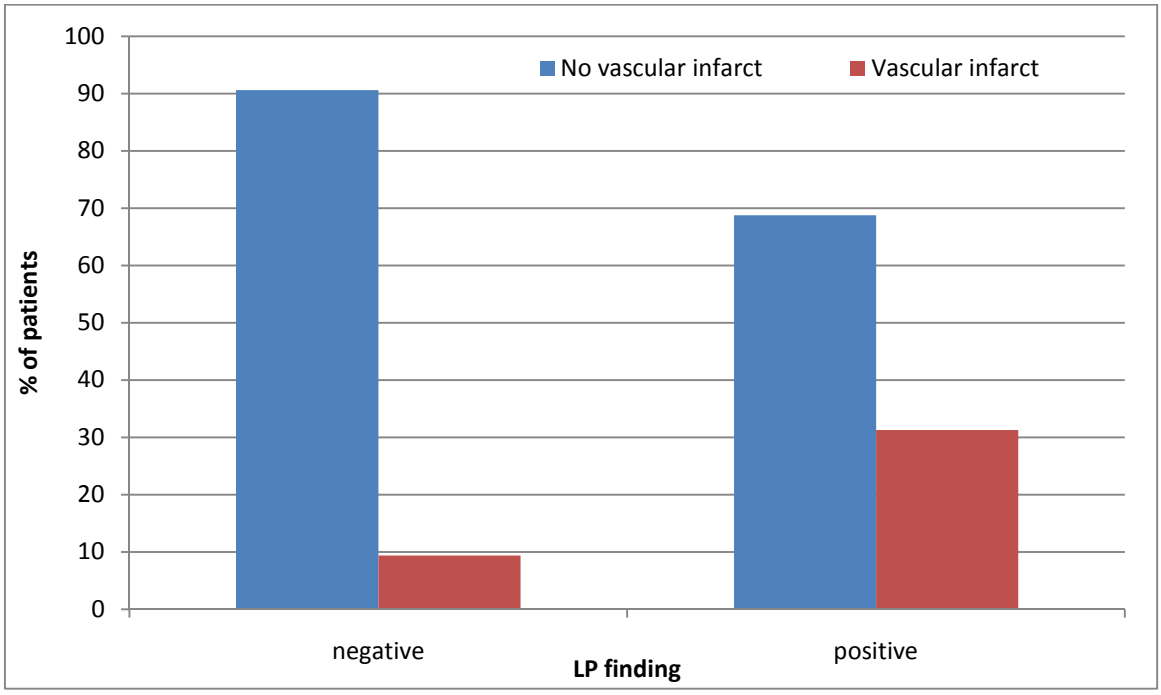



**Figure 3.10: Presence of 'vascular infarct' by LP results in the 'non-neuro' group**

There was a statistically significant but weak association between hydrocephalus on CT and abnormal LP CSF finding for the 'non-neuro' group (Fisher's exact test: p=0.04; Phi coefficient=0.25): all 7 cases of hydrocephalus in this group were associated with a positive LP CSF finding for the 'Non-neuro' group, shown in Figure 3.11 below.

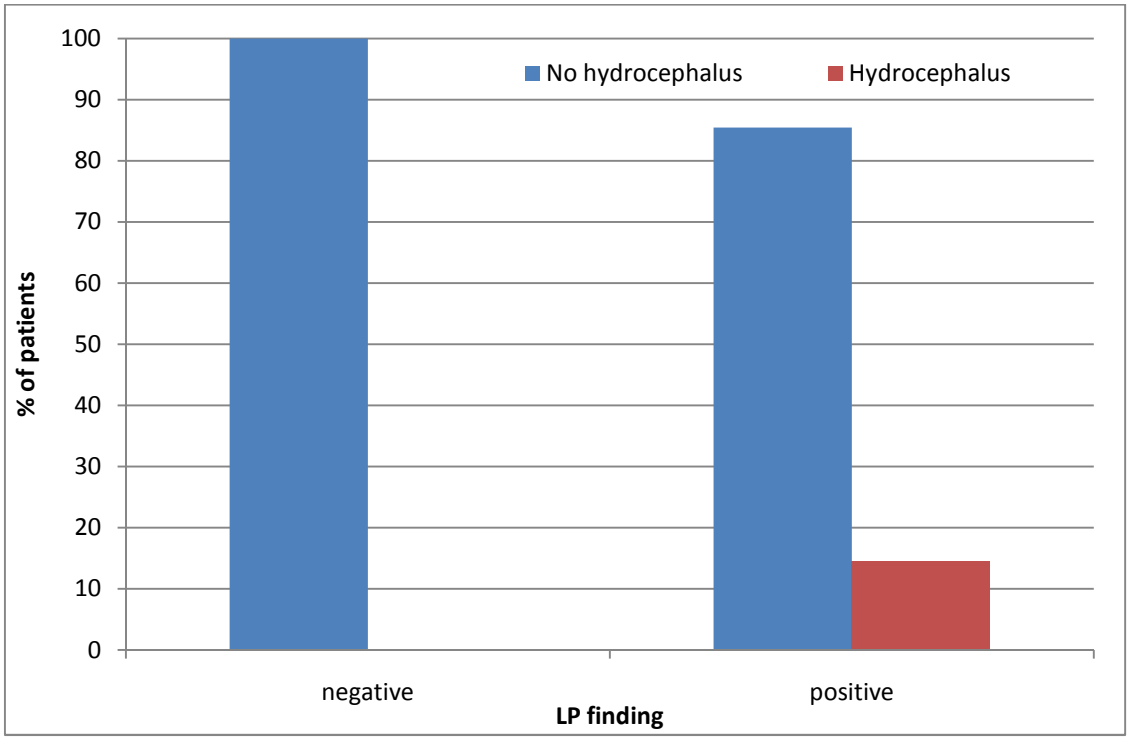



**Figure 3.11: Presence of hydrocephalus by LP result in the 'non-neuro' group**

There were 20 HIV-infected patients in total who presented without associated neurology, in whom the CT brain was normal (NAD). Their associated clinical findings are summarised in table 3.9 below.

This group of patients was evaluated individually by cross-referencing with the clinical information: the CD4 category (high (>200cells/mm3) = 1; low (<200cells/mm3) = 2, 3, 4), the LP CSF result and ARV therapy status. We determined that 14 of the 20 (70%) patients listed showed an abnormality in either one or more of the clinical/laboratory parameters.

**Table 3.9: Summary of data for 'non neuro' patients who also had normal CT scans**

| Age | Gender | CD4cells/ $mm^3$ | CD4 category High | CD4 category Low | ARV | | LP | |
|---|---|---|---|---|---|---|---|---|
| 41 | F | 283 | 1 | | Y | | - | - |
| 32 | M | 43 | | 4 | - | - | NEG | |
| 38 | M | 131 | | 2 | Y | | | POS |
| 44 | M | 41 | | 4 | | N | NEG | |
| 37 | F | 245 | 1 | | Y | | | POS |
| 52 | M | 400 | 1 | | Y | | - | - |
| 39 | M | 340 | 1 | | Y | | NEG | |
| 28 | F | - | | | Y | | NEG | |
| 21 | F | 334 | 1 | | Y | | | POS |
| 33 | F | 11 | | 4 | Y | | NEG | |
| 27 | M | 41 | | 4 | Y | | NEG | |
| 40 | M | - | | | | N | NEG | |
| 33 | F | 252 | 1 | | - | - | | POS |
| 32 | M | 13 | | 4 | | N | - | - |
| 35 | F | 5 | | 4 | - | - | NEG | |
| 41 | M | 68 | | 3 | Y | | | POS |
| 35 | M | 79 | | 3 | - | - | | POS |
| 52 | M | - | | | - | - | NEG | |
| 30 | M | - | | | Y | | NEG | |
| 44 | F | 68 | | 3 | Y | | | POS |

Key: NEG = negative; POS = positive; Y = yes; N = no

# 4. Discussion

## 4.1 Aim

The aim of this study was to formulate a general framework or management protocol to guide the appropriate use of CT brain in patients who are HIV-infected in countries with limited resources. To this end, we had hoped to use clinical and laboratory data to support or dispute the urgent need for a CT scan in these patients, specifically those presenting with confusion. Our fundamental question was: ”What is the value of CT brain scans in patients who are HIV-infected, presenting with a history of confusion, with or without associated neurology?” To determine the answer we aimed to predict, using the clinical and laboratory parameters mentioned, when the CTB would yield a positive finding. In doing so, we might be able to stop performing unnecessary CT scans, in an already resource constrained environment. Alternatively, in a scenario where neurology was present but CT scan is negative, resource allocation may be better redirected to MRI.

## 4.2 Facilities

CT facilities in the major centres in South Africa are run continually and are, as such, susceptible to extrinsic wear and tear and overuse. This becomes a significant drain on resources. In Johannesburg alone, 4 major referral hospitals, Charlotte Maxeke Johannesburg Academic Hospital, Chris Hani Baragwanath Hospital, Helen Joseph Hospital and Rahima Moosa Mother and Child Hospital serve an estimated 3.24 million people. In addition to the overwhelming trauma that presents to South African hospitals, patients with HIV/AIDS put these institutions under further strain. Sub-Saharan Africa has the

largest number of people living with AIDS (1), and over 5 million of them live in South Africa (5). The rate of infection is the highest in Sub-Saharan Africa (22).

We performed 2495 brain CT scans at our institution during the study period and 21% of these patients were HIV-infected. Our results show that confusion as a presenting feature makes up 30% of requests in HIV-infected patients. 58% of the patients in our study group had no associated neurological findings. The majority (69%) of the patients in our cohort were already on anti-retroviral therapy, suggesting that resources may be even more stretched where anti-retroviral treatment is less available.

## 4.3 Demographics

The age distribution of our study cohort was expected. The mean age of our patients was 39 years, with only 5 patients over the age of 65 years. This is comparable to the study by Rothman et al, in which 53.6% of their study population fell into the 35-44 year age group (9). This population group should be the greatest contributor to our economy and socio-economic development. Instead, the medical burden of this population group paradoxically impacts negatively on the economy.

## 4.4 CT and Neurology

Tso et al demonstrated that 55% of HIV-infected patients presenting to the Emergency Department had an altered mental status (7). In comparison 30% of HIV-infected patients presenting for CT in our institution had confusion. Of these 42% (66/156) had associated neurology.

The literature indicates that patients who are HIV-infected, confused and have associated neurology have a high chance of having an abnormal head CT (7,9). Tso showed that 25% of their patients who were HIV-infected, confused and had associated neurology had a focal lesion on CT (7). Rothman demonstrated that an HIV-infected patient with depressed/altered orientation (or confusion) had a 39 times greater relative risk of having a new focal finding on CT (9). In comparison, we found that CT scans were abnormal in 81% of our overall group of patients, and in 86% of patients with additional neurology. In their review article, Ho et al. support these findings (17).

In the 14% of our patients with associated neurology who had a normal CT scans, MRI may have demonstrated neuroimaging findings not visible on CT (e.g. acute infarction or infection). The sensitivity and specificity of using 'associated neurology' as a predictor of an abnormal CT, was weak. Neurology was found to be only moderately specific (69%) and poorly sensitive (49%) in predicting an abnormal CT (or any individual CT finding), making it a poor screening tool in HIV-infected patients with confusion.

## 4.5 CT and No Neurology

We demonstrated abnormal CT scans in 78% of our group of HIV-infected patients who did not have neurology. There were 22% of patients presenting with confusion and no neurological signs that had a normal CT. In these patients CT may not have been indicated or MRI may have demonstrated pathology that CT was not able to identify. This is an additional area where clinical parameters may play a role in dictating imaging choices, and motivate for MRI. When we used additional clinical patient parameters, 14 of the 20 (70%) patients with no neurology and a **normal** CT may have warranted further imaging with MRI, based on the following risks singly or in combination:

- A low CD4 count
- Not being on ARV therapy
- A positive LP

We think this supports the recommendations of Tso et al, who emphasized the need for a recent CD4 count and viral load, composition and duration of ARV therapy, a lumbar puncture and an adequate history as key components in the workup of the HIV-infected patient presenting with an altered mental status (7). These items should form integral parts of the request cards for CT scanning to allow radiologists to motivate for further imaging with MRI in the event of a normal CT.

## 4.6 CT and LP

In our setting, any confused patient, whether HIV-infected or not, undergoes a lumbar puncture as part of their workup. This is because of the large HIV-infected population living in Sub-Saharan Africa, and because TB is endemic here (two-thirds of TB positive cases in Kwa-Zulu Natal South Africa are HIV positive)(20). There was a statistically significant but weak association between a focal infective process on CT and a positive LP, as well as for an infected surface collection on CT and a positive LP, for the Overall group. This shows the relevance of clinical parameters predicting CNS infections in HIV-infected patients. The weakness of the association could be attributed to the fact that the radiological manifestations of the LP findings are not always present at the time of scan, or that the patient has already received first dose of antibiotics.

A statistically significant correlation between a vascular infarct on CT and a positive LP was demonstrated in all groups. This association was weak in the Overall and Non-

neurology groups, but moderate in the Neurology group. HIV infection is associated with cerebrovascular disease, most likely attributable to immune suppression (9). Offiah et al demonstrated that certain CNS infections, specifically TB and neurosyphillis, cause endarteritis or vasculitides, which result in ischaemic infarcts (25). Other causes of stroke in HIV-infected patients include cardiac sources of emboli (e.g. from HIV-associated cardiomyopathy), haematological causes (such as disseminated intravascular coagulation), drug misuse or cerebral venous thrombosis (19). A negative LP is unlikely to deter imaging in patients with visible neurology, for example in the form a hemiplegia. A positive LP should therefore motivate for further imaging (in the form of MRI) of the brain to search for pathology such as stroke even in patients without neurology and those with normal CT.

## 4.7 CT and CD4 Count

It has been well documented that the degree of immunosuppression is an accurate predictor of certain opportunistic diseases, and that with more advanced HIV-infection and a lower CD4 count, the likelihood of presenting with these opportunistic infections rises (17). Furthermore, Graham et al stated that there was an increased risk of demising of an AIDS related illness within 2 years, in patients with CD4 counts <50cells/$mm^3$ (21). Our patients' CT findings were randomly distributed amongst all CD4 categories. However, the average CD4 count of our overall group was 119cells/$mm^3$. It has been reported that CD4 counts below 200cells/$mm^3$ are more associated with opportunistic infections (17). This is relevant to us, as our patient population represents a random group of patients over a 1 year period, indicating that CD4 counts in our population were generally lower than in other populations previously studied. Rothman et al documented

in their study, that 50% of the HIV patients who had neurological complaints and were scanned, had CD4 counts <50 cells/$mm^3$ (9) compared to 45% in our study.

Tso et al found atrophy in approximately a third of their patients (7). Whilst they did not correlate it to the CD4 count, they noted that atrophy was most likely a harbinger of additional neurological diseases (7). We demonstrated a statistically significant association between atrophy and Category 3 (CD4 50-100cells/$mm^3$) patients and in the Overall group and between atrophy and Category 2 (101-200cells/$mm^3$) and Category 4 (<50cells/$mm^3$) disease in Neurology group.

A statistically significant association was demonstrated between CD4 Category 3 (101-200cell/$mm^3$) and vascular infarcts in the neurology group. Rothman et al demonstrated vascular pathology in patients in a higher CD4 category (>200cell/$mm^3$) (9).

A statistically significant and moderate association between Category 2 (101-200cells/$mm^3$) and 3 (51-100cells/$mm^3$) patients and focal infection was demonstrated in the non-neurology group. This is again comparable to previously mentioned studies, indicating opportunistic infections are more rife in the <200cells/$mm^3$ CD4 category (17). Of note, no focal infections were demonstrated in the Category 1 patients, who had CD4 counts of >200cells/$mm^3$.

## 4.8 CT and ARV Therapy

Traditionally, initiation onto antiretroviral therapy helps to slow down the progress of the disease. The immune system is boosted, helping to maintain the CD4 count at a higher degree for a longer period of time. Thus, ideally the patient on ARV therapy would be less susceptible to CNS opportunistic infections (22). In our study cohort, only 69% of our study population had been initiated onto antiretroviral therapy. Despite reports in the literature that patients on ARV therapy were less likely to develop opportunistic infections (22), we found no statistical significance between patients on ARV therapy and those not on treatment with regard to the presence of any particular CT abnormality. Despite two-thirds of our patients being on ARV's, the CD4 counts were not at levels where their immunity may be considered to have been reconstituted, substantiating a lack of IRIS findings. The overall low mean CD4 counts account for the relatively high frequency of atrophy and infection.

## 4.9 Table of Comparison

Table 4.1 below compares both similarities and differences between our study and two others, "Cranial Computed Tomography in the Emergency Department Evaluation of HIV-Infected patients with Neurologic Complaints" by EL Tso et al [7], and "A Decision Guideline for Emergency Department Utilization of Non Contrast Head Computed Tomography in HIV-Infected Patients" by RE Rothman et al [9].

**Table 4.1: Comparison between our study and other related studies**

| | Our Study | Tso et al [7] | Rothman et al [9] |
|---|---|---|---|
| Sample Size | 156 | 146 | 110 |
| HIV Status | Known positive | Known or suspected clinically | Known positive |
| Inclusion Criteria | Confusion (+/- Neurology) | Neurology (complaint) | Neurology (new / changed) |
| Study Design and Methods | Retrospective comparison of CT scans to clinical criteria to establish correlation | Prospective study using clinical parameters to determine if CT required | Prospective study using clinical parameters to determine if CT required |
| Other Laboratory Data | Correlated CD4 counts and LP results to the CT finding | Nil else | Documented CD4 counts, but no correlations |
| Confusion | 100% | 33% | 30% |
| CT Planning | Post-contrast (+/- Pre) | Pre and post-contrast | Pre-contrast only |
| Normal CT | 19% | 29% | 48.2% |
| Atrophy on CT | 47% | 33% | 27.3% |
| Focal Intracranial Lesion | 23% | 38% | 24.5% |
| LP Abnormality | 63% | 24% | Not done |
| CD4 count <200 cells/$mm^3$ | 78% | - | 78.2% |
| Criticism | Retrospective study | Not all patients proven HIV+ | Only pre-contrast CT done |

In comparison to the studies by Tso and Rothman who showed normal CT in about one third to one half of HIV infected patients with neurology, we demonstrated normal scans in only about one fifth of patients. Our study initially intended to demonstrate the wastefulness of CT imaging in confused HIV infected patients. It was designed to investigate if clinical and laboratory data (presence of neurology, CD4 counts, LP CSF and ARV therapy) could predict whether CT scanning would be positive thereby preserving wasted CT resources. CT was successful in demonstrating abnormalities in the majority of patients, and would therefore, make a good triage tool. CT had a high yield of abnormalities. Depending on resources, it can then be used either routinely, or can be motivated for depending on clinical parameters like CD4 and LP results. It is important to note, however, that our population group represents a majority of patients with CD4 counts less than 200cells/$mm^3$ (78%) and positive lumbar punctures (63%). By definition therefore, the majority of our study population were at risk of CNS abnormality. With these overwhelming positive clinical parameters, we should expect the CT scans to demonstrate pathology in HIV-infected, confused patients.

The management of an HIV-infected patient has become a significant burden in the emergency department (7). Because the differential diagnosis for these patients with CNS complaints such as confusion is so vast, neuroimaging diagnosis is necessary (7). In keeping with the emergency medicine and AIDS literature (7) we recommend CT highly for these purposes.

Rothman et al proposed a list of clinical criteria as considered indications for brain imaging: decreased or altered orientation (i.e. confusion), new seizure and headache (which is prolonged or different in quality). These clinical parameters accurately predicted 100% of focal new findings on CT in their study (9). Restricting the use of CT to patients

who met the above criteria would have resulted in a 37% reduction in CT usage in their study. They did not however take additional clinical and laboratory information such as CD4, LP and ARV therapy into consideration, as in our research.

## 4.10 Current Applications

Because of the significant proportion of positive CT abnormalities demonstrated in our study, we recommend that HIV-infected patients with confusion warrant imaging, and that negative clinical and laboratory parameters cannot be used to predict whether the CT brain scan will be normal. We do recommend using clinical and laboratory parameters for motivating for MRI in patients with normal CT, pending further research.

## 4.11 Limitations of this study

The most significant shortcoming of our work is the retrospective nature of the study. The experience of the examining physician as well as the variety and experience of reporting radiologist was therefore not standardised, which may result in significant interpretational variances in clinical findings and CT reports. In addition, the ability of the physician to determine the presence of neurological signs in a confused patient is limited. Rothman advocates imaging every HIV-infected patient with a neurological sign or symptom because subtle clinical presentations may belie significant intracranial pathology (9). The immune suppression in HIV-infected patients may mask important signs which physicians attribute to significant disease (17).

Another shortfall is the lack of suitable record keeping, specifically for CD4 counts, LP CSF results and antiretroviral therapy information, where numerous patients were lost for

those calculations. We recorded the presence of 'neurology' based on the CT referral card and not on review of clinical features listed in the patient notes. This may well have distorted the perception of prevalence and influence of clinical signs on the CT findings.

The fundamental challenge facing the emergency physician managing these complex patients in the emergency department is establishing the clinical criteria necessitating **immediate neuroimaging vs. those that can wait** until post admission or on an outpatient basis (9). The significance of individual CT findings was not considered in our study, but some CT findings such as atrophy do not have any immediate impact on management, whilst CT demonstration of an acute surface haemorrhage, acute infarction or an abscess may prompt urgent treatment. We also did not categorize urgent from non-urgent requests.

Other neuroimaging studies, which were reviewed as a background to this project, document the vast neurological manifestations of HIV/AIDS. Few are original research studies with clinical and/or laboratory data as a predictive tool in determining the possible neuropathological diagnoses.

We also do not know how many **asymptomatic HIV-infected patients** in our population would yield a neuroimaging abnormality.

## 4.12 Further Research

A prospective study comparing the individual CT and MRI findings in the HIV-infected patient is warranted. These findings should then be correlated with clinical and laboratory predictors of intracranial pathology. Better standardization of the referring physician and reporting radiologist, perhaps with the aid of a tick sheet should also be considered.

# 5. Conclusion

CT was found to be abnormal in the vast majority of HIV-infected patients presenting with confusion, whether or not they had associated neurology, showing that clinical triage was unreliable.

Laboratory parameters overall were not adequate predictors of CT abnormality, except for a positive lumbar puncture which correlated significantly with infection and infarction. This would, therefore, be a good predictor for facilities without access to CT. In centres where CT is available, scanning prior to LP is advocated, not only to identify contraindications to LP, but also because CT findings may be altered as a result of LP.

# Appendix A: Ethics Clearance Certificate

**UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG**
Division of the Deputy Registrar (Research)

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**
R14/49 Dr Tanusha Sewchuran

| | |
|---|---|
| **CLEARANCE CERTIFICATE** | M111114 |
| **PROJECT** | Brain Computed Tomography Findings in HIV-Infected Adults Presenting with Impaired Mental Status: Determining the Value of CT in a Resource Constrained Environment |
| **INVESTIGATORS** | Dr Tanusha Sewchuran. |
| **DEPARTMENT** | Department of Diagnostic Radiology |
| **DATE CONSIDERED** | 25/11/2011 |
| **M1111140DECISION OF THE COMMITTEE*** | Approved unconditionally |

**Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.**

**DATE** 25/11/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof S Andronikou

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**DECLARATION OF INVESTIGATOR(S)**

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

## Appendix B: Data Collection Sheet

| DIAGNOSIS<br>CT sign<br>---<br>PATIENT | CD4 | VL | Infection:<br>Focal | Infection:<br>Surface collection | Vascular:<br>Bleed | Vascular:<br>Infarct | Neoplasm:<br>Mass | Neoplasm:<br>Meningeal | Ventriculomegaly:<br>Atrophy | Ventriculomegaly:<br>Hydrocephalus |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | | | |
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