ASSESSING BRAIN COMPUTED TOMOGRAPHY FINDINGS OF HIV-INFECTED ADULTS PRESENTING WITH PRIMARY HEADACHES IN JOHANNESBURG, SOUTH AFRICA

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in the division of Neurology

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i. DECLARATION

I, Kerena Gengan, do hereby declare that this research report is my own unaided work. It is being submitted for the degree of Master of Medicine in the division of Neurology. This research report is submitted in the publishable format as recognized by the Faculty of Health Sciences. I further declare that this work has not been submitted for any other examination or degree at this or any other University.

……

The ……. day of …… 2019

ii. DEDICATION

To my beloved uncle, Dr Poobalan Govender, who was my greatest supporter.

iii. PRESENTATIONS ORIGINATING FROM THIS RESEARCH

- Oral presentation at the Joint Congress of the Neurological Association of South Africa and African Academy of Neurology, East London International Convention Centre, 28 February 2019.

iv. ETHICAL CONSIDERATIONS

Permission for this prospective study was obtained from Professor G. Modi (Head of Division of Neurology, Department of Neurosciences, University of the Witwatersrand) and the Human Research Ethics Committee of the University of Witwatersrand (clearance number – M161117).

v. ABSTRACT

Introduction: Despite the high prevalence of Human Immunodeficiency Virus (HIV) infected individuals in South Africa, there are currently no studies which investigate primary headaches in this population.

The primary aim of this study was to describe the computed tomography (CT) brain findings of HIV-infected individuals with primary headache. The study also aimed to evaluate any associations between demographic factors, HIV-related factors and CT brain findings.

Methods: This was a prospective study. Adult HIV-infected individuals who met the International Classification of Headache Disorders (ICHD)3 beta criteria for primary headache disorders were included in the study. Demographic information, HIV-related information and headache characteristics were collected. All participants had CT brain scans performed. Fischers' exact test was used to test for any significant associations between demographic factors, HIV-related factors and CT findings. A P-value < 0.05 was considered significant.

Results: Eighty-six participants were included in the study. Ten (12%) participants had abnormal CT brain scans. The abnormalities included calcified granulomas, cerebral atrophy, periventricular white matter ischaemic changes and an arachnoid cyst. There were no statistically significant associations found between CT findings and age, sex, headache type, headache severity, viral suppression, CD4 count and presence or absence of antiretrovirals (ARVS). There was a statistically significant association between co-morbidities and CT findings (30% vs. 83%; p= 0.001).

Conclusion: In HIV-infected individuals with ICHD3 beta defined primary headache, there is a low prevalence of abnormalities on CT brain scans. HIV-infected individuals with co-morbidities are more likely to have abnormal CT brain scans. HIV, by itself, is not associated with abnormal CT brain scans in individuals with primary headaches.

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x. ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
ARVs	Antiretrovirals
AZT	Zidovudine
CD4	Cluster of differentiation 4
CNS	Central nervous system
CT	Computed tomography
DTG	Dolutegravir
EFV	Efavirenz
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HIV	Human Immunodeficiency Virus
ICHD	International Classification of Headache Disorders
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography

MRV	Magnetic Resonance Venography
NNRTI	Non-nucleoside reverse transcriptase inhibitor
RPV	Rilpivirine
TDF	Tenofovir
TTH	Tension type headache
WHO	World Health Organisation

1 PROTOCOL AND EXTENDED REVIEW OF THE LITERATURE

1.1 Introduction

With 7.1 million people living with Human Immunodeficiency Virus (HIV) in South Africa, HIV is this country's most serious health issue[1]. Headache, a highly debilitating condition, is frequently experienced by these individuals [2]. Headache in HIV-infected individuals can occur at any stage of the illness and has a broad differential diagnosis. Studies documenting headache in HIV-infected individuals done prior to the widespread effective use of anti-retroviral drugs showed a higher prevalence of secondary headache with cryptococcal meningitis being a leading cause of headache[3,4]. Studies in which patients did not have significant immunosuppression showed primary headache to be the chief cause of headache[5].

Computed tomography (CT) scans of the brain are pivotal to the management of secondary headache in HIV-infected individuals as these patients may have life threatening conditions causing their headache. The importance of CT brain scans in defined primary headache is less clear. To date no previous studies has investigated the CT brain findings in HIV-infected individuals with International Classification of Headache Disorders (ICHD) defined primary headache[6]. This study describes the CT brain findings of HIV-infected individuals with ICHD 3rd edition beta version (ICHD3 beta) defined primary headache and evaluates the relationship between state of immune suppression and CT findings. Additionally, this study determines the effect of demographic factors and headache related factors on CT findings in these individuals.

1.2 Human Immunodeficiency Virus (HIV)

1.2.1 HIV Epidemiology

In 2017 there were 36.9 million people living with HIV worldwide and approximately 5000 new infections per day[7]. South Africa, with an HIV prevalence of 11.2 % has the largest HIV epidemic in the world[8]. South Africa has in addition, the largest treatment programme in the world, accounting for 20% of people on antiretroviral therapy (ARVs) globally and has one of the largest domestically funded programmes therefore impacting the economy of the country[8]. HIV impacts the health of individuals and the health and wealth of households, aggravating pre-existing poverty. The negative consequences of HIV are therefore far reaching

1.2.2 HIV Central Nervous System (CNS) Pathogenesis

HIV-1, an RNA virus, causes profound cluster of differentiation 4 (CD4) depletion via reduction of gut-associated memory T cells and chronic immune activation, which results in fatigue of homoeostatic T-cell responses and progressive immunodeficiency. The main target of HIV-1 is the CD4 receptor and specific chemokines are secondary receptors. HIV can also infect CD4 negative cells for example astrocytes. Subgroups of HIV-1 are T-tropic viruses that prefer replication in T lymphocytes and use CD4 and CXCR4 as chemokine receptors, and M-tropic viruses which prefer replication in macrophages and uses CCR5 as a chemokine receptor. M-tropic viruses are the most common type in the brain.

Once integration of the HIV provirus into the host cell genome occurs, the HIV virus can be latent for years with memory CD4 T lymphocytes and macrophages serving as reservoirs. The brain serves as a reservoir due to the sequestration of HIV in macrophages and because the blood brain barrier can prevent penetration of antiretroviral drugs (ARVS). Chronic immune activation with dysregulation of macrophages and overproduction of proinflammatory chemokines and cytokines within the CNS leads to the development of some of the neurological manifestations of HIV, notably HIV-associated dementia[9].

1.2.3 Neurological manifestations of HIV

The neurological consequences of HIV are frequent and may occur at any stage of the disease. HIV-infected individuals first present with neurological manifestations in 10-20% of cases, and over 50% have neurological disease during the course of their illness[10]. Neurological complications of HIV can be divided into primary complications and secondary complications. Primary complications are due to the direct effects of HIV and include the spectrum of HIV-associated neurocognitive disorders, HIV-associated vacuolar myelopathy, HIV transverse myelitis, HIV-associated sensory neuropathies and aseptic meningitis. Headache may occur during seroconversion or with aseptic meningitis.

Secondary neurological complications of HIV are the result of immunodeficiency and the acquisition of opportunistic infections. The common opportunistic infections encountered are cryptococcal meningitis, CNS toxoplasmosis, tuberculosis meningitis, primary central nervous system lymphoma, cytomegalovirus encephalitis and radiculomyelitis and progressive multifocal leukoencephalopathy. ARVs also cause neurological side effects including nucleoside reverse transcriptase inhibitor (NRTI) induced neuropathy, zidovudine

(AZT) induced myopathy and, efavirenz (EFV) induced psychosis, vivid dreams and cerebellar ataxia. Anti-retroviral drugs may also cause headache. Efavirenz, abacavir, nevirapine and raltegravir all cause headache[11].

1.2.4 Management of HIV

Antiretroviral therapy is recommended for all HIV-infected individuals regardless of their CD4 count[12,13]. First line regimens in South Africa are:

Tenofovir (TDF) + emtricitabine (FTC) or lamivudine (3TC) + efavirenz (EFV) or

TDF + FTC or 3TC+ dolutegravir (DTG) or

TDF + FTC or 3TC + rilpivirine (RPV)[14].

Monitoring for treatment failure with viral load testing is pivotal after initiation of ARVs. Viral load testing should be performed 6 and 12 months after initiation of treatment and annually thereafter. Virological failure is defined as having a viral load >1000copies/ml on two occasions,3 months apart, with adherence support occurring during the 3 months[15]. CD4 count should be measured at baseline pre-treatment and as clinically indicated. Advanced HIV disease is defined by a CD4 count < 200 cells/mm3 or a World Health Organisation (WHO) clinical stage 3 or 4 event[15]. Immunological failure is defined by a CD4 count at or below 250 cells/mm3 following clinical failure or persistent CD4 levels below 100 cells/mm3[15].

1.3 Headache

1.3.1 Headache Background

Headache is among the commonest conditions treated by the medical fraternity. Headache causes substantial individual distress and morbidity and societal and economic burden due to work absence. The Global Disease Study found headache to be the second leading cause of years lived with disability worldwide[16]. This debilitating disorder has a global prevalence of 46%[17]. In Sub-Saharan Africa, there is conflicting data regarding the prevalence of headache. A population based rural study in Tanzania demonstrated an overall headache prevalence of 12% over 1 year whilst a population-based study in Zambia reported a 1year prevalence of 72%[18,19]. Research improving understanding, investigation and treatment of this highly prevalent disorder is necessary.

1.3.2 Primary versus Secondary Headache

Primary headache disorders are those without an underlying medical condition. Primary headaches are diagnosed when clinical characteristics fulfil the diagnostic criteria devised by the International Headache Society[6]. A detailed history of headache characteristics and a normal clinical neurological examination is required to make the diagnosis of a primary headache. The diagnosis of primary headache disorders is not established by any laboratory study or imaging procedure. Investigations assist in excluding other causes of headache.

Primary headaches are divided according to their phenomenology. The commonest primary headaches seen in clinical practice are tension type headaches, migraine and cluster headaches. The Global Burden of Diseases study 2010 found tension type headache to be the second most prevalent condition in the world (22%) and migraine the third most prevalent (15%)[20]. In sub-Saharan Africa population-based studies have shown the prevalence of

migraine (18 vs 23%) and tension type headache (21 vs 23%) to be similar in both Ethiopia and Zambia[18,21]. There are currently no studies detailing the prevalence of different primary headaches in South Africa.

Secondary headache occurs as a result of underlying pathology. Secondary headache is diagnosed when a new headache occurs with another disorder capable of causing headache or when a pre-existing headache becomes chronic or worsens in relation to another disorder capable of causing headache[6]. The causes of secondary headaches are multiple. Common causes of secondary headache include infection, trauma and vascular disease. Headache due to a psychiatric condition is also considered a secondary headache. Causes of secondary headache need to be actively excluded as these may be life threatening.

1.3.3 The International Classification of Headache Disorders

The International Headache society published the first edition of The International Classification of Headache Disorders (ICHD1) in 1988[6]. ICHD1 was formulated using expert opinion. After revision due to new evidence and changes in the opinions of experts, the ICHD2 criteria was published in 2004. The ICHD 3rd edition, β version was published in 2013 following new scientific research[6]. The beta version of the ICHD3 allowed for field testing before the final ICHD3 was published in 2018. These operational diagnostic criteria have been used extensively in research and have been shown to be both sensitive and specific for the diagnosis of primary headaches[22,23].

Patients are given a diagnosis according to the headache phenotype currently present or present within the last year. If a headache fulfils two different diagnostic criteria additional

information is used to determine which is the most likely diagnosis. Patients need to experience a specified minimum number of headache attacks to be diagnosed with a particular headache type. Headaches are classified and coded into types and subtypes and need to meet requirements set in the criteria.

The classification divides the primary headaches into migraine, tension type headache, trigeminal autonomic cephalalgias and other primary headache disorders. Other primary headaches include primary exercise headache, primary cough headache, primary headache associated with sexual activity, primary thunderclap headache, cold-stimulus headache, external-pressure headache, primary stabbing headache, nummular headache, hypnic headache and new daily persistent headache. The two major subtypes of migraine are migraine without aura and migraine with aura[6]. Tension type headache (TTH) is divided into episodic and chronic types and episodic type is further subdivided into frequent TTH and infrequent TTH[6].

1.3.4 Headache in HIV-infected individuals

The second commonest site of pain in HIV-infected individuals is the head and neck and headache is the presenting manifestation of Acquired Immunodeficiency Syndrome (AIDS) in 12.5% to more than 55% of patients[2,24]. In HIV-infected individuals potentially life threatening, treatable causes of secondary headache should be excluded. HIV-infected individuals may have secondary headaches due to a multitude of opportunistic infections such as CNS toxoplasmosis, progressive multifocal leucoencephalopathy and cryptococcal meningitis or due to mass lesions for example primary CNS lymphoma and bacterial

abscesses. Headaches in HIV-infected individuals may also be caused by antiretroviral drugs and HIV related aseptic meningitis.

Headaches in hospitalized HIV-infected individuals are more likely due to a serious condition than headache in outpatients[3,25]. Goldstein et al found significant underlying disease in 40 (82%) of 49 patients in a study of hospitalized patients, whereas Singer found tumour and opportunistic infections in only 4% of outpatient HIV-infected individuals presenting with headache[3,25]. However, overall primary headache is more common than secondary headache in HIV-infected-individuals[5].

1.3.5 Primary Headache in HIV-infected individuals

Primary headaches are frequently experienced by HIV-infected individuals[5]. A retrospective chart review of 115 HIV-infected patients by Mirsattari et al revealed a prevalence of 44% for headache, with primary headaches and secondary headaches accounting for 66% and 34% of all headaches respectively[5]. Kirkland et al also demonstrated a higher prevalence of primary headaches compared to secondary headaches following interviews of 200 HIV-infected patients[26]. The majority of patients in this study (88%) were on anti-retroviral therapy with a mean CD4 count of 443 cells/mm, possibly accounting for the low prevalence of secondary headaches due to lower prevalence of opportunistic infections. The limitation of the study was that secondary headaches were only diagnosed by a review of medical records and temporal relationship to headache. No neuroimaging was performed to definitively exclude underlying pathology. Despite South Africa having the largest epidemic of HIV in the world there have been no studies investigating primary headache in this population.

1.4 Investigation of Headache

1.4.1 Neuroimaging

1.4.1.1 CT brain scans in the investigation of headache

Neuroimaging whether computed tomography (CT) or magnetic resonance imaging (MRI) is indispensable for the investigation of headache. MRI is not widely available in developing countries and CT brain scans are usually the first-line investigation for patients with headache in this setting. CT brain scans are chiefly performed to detect intracranial lesions for example tumours and also to exclude treatable causes of headache for example cerebral abscesses. Neuroimaging is also requested when there are medico-legal concerns or at a patient's request. Both patients and doctors are reassured when neuroimaging reveals no abnormalities.

The potential complications associated with CT scans include an allergic reaction to iodine contrast media, exposure to ionizing radiation, false positive studies causing patient anxiety and false reassurance from an inadequate study. CT scans are performed at a substantial cost. In South Africa the cost of a CT brain scan is between R3000 to R5000[27]. In the South African public sector access to Computer Tomography (CT) is limited with only 1.7 units available per million population[28]. The judicious use of this expensive imaging modality in such a resource limited setting is therefore important.

1.4.1.2 The utility of CT brain scans for the investigation of primary headache

Primary headaches are by far more prevalent than secondary headaches which raises concerns about routine neuroimaging in all patients with headache. Botella et al attempted to determine which clinical features in patients with non-acute headache were associated with significant abnormalities on neuroimaging, significant abnormalities being tumours, vascular malformations, Chiari malformations, hydrocephalus, large arachnoid cysts, intracranial

haemorrhage and acute cerebral infarcts[29]. The headache types in their group of 1876 patients were migraine (49%), tension-type (35.4%), cluster (1.1%), posttraumatic (3.7%) and indeterminate headache (10.8%). The total yield of significant abnormalities was 1.2% and the yield in patients with a normal neurological examination was 0.9%. Incidental findings of pineal cysts, intracranial lipomas and arachnoid cysts were found in 14 patients (0.75%). The yield of neuroimaging studies was higher in the group with indeterminate headache (3.7%) than in the migraine (0.4%) or tension-type headache (0.8%) groups. The conclusion was made that although the yield of significant abnormalities was small, clinical features did not enable abnormalities on neuroimaging to be ruled out. The HIV status of the patients in the study was not documented.

An evidence-based guideline on neuroimaging in non-acute headache published by the US Headache Consortium came to the conclusion that in patients with headaches other than migraine, and a normal neurological examination, it was not possible to predict the probability of significant neuroimaging abnormalities[30]. A meta-analysis performed by the consortium found that patients with a normal neurological examination and migraine had a low rate of significant neuroimaging abnormalities of 0.18%. The meta-analysis included studies utilizing both CT and magnetic resonance imaging (MRI). The recommendation made by the consortium is that neuroimaging is not usually warranted for patients with migraine and a normal neurological examination unless patients have atypical headache features or an additional risk factor. The consortium could not make a recommendation regarding the use of neuroimaging in tension type headache due to insufficient evidence. No recommendation was made regarding neuroimaging in HIV-positive patients with primary headache.

The European Headache Federation published a consensus on the technical investigation of primary headache in 2016[31]. The consensus, based on expert opinion, recommends MRI brain for migraine with persistent unilateral aura and brainstem aura. MRI, Magnetic Resonance Angiography (MRA) and Magnetic Resonance Venography (MRV) is recommended for persistent aura without infarction and migrainous infarction. MRI brain is also recommended for the trigeminal autonomic cephalalgias, primary cough headache, hypnic headache, exercise headache, thunderclap headache and headache associated with sexual activity. MRI brain was favoured over CT brain in these instances. CT scans may replace MRI in the emergency setting. The consensus also states that if patients suffer from an anxiety disorder and have fears about a brain tumour CT scans may be performed to allay these fears. The consensus states that HIV infection may point to an underlying cause for headache but does not offer specific recommendations regarding the use of CT scans in HIV-infected individuals with primary headache. No guidelines exist regarding the use of CT Brain scans in HIV-infected persons with primary headaches. Current practice involves scanning all HIV-infected persons with headache regardless of headache type.

1.4.2 Lumbar Puncture in the investigation of headache

Lumbar punctures are primarily performed to exclude causes of secondary headache for example meningitis, idiopathic intracranial hypertension and subarachnoid haemorrhage. The European Headache Federation recommends performing lumbar punctures on patients with chronic migraine, frequent tension type headache and chronic tension type headache, primary exercise headache, primary stabbing headache, primary headache associated with sexual

activity, primary thunderclap activity and new daily persistent headache[31]. The European Headache Federation acknowledges that HIV infection points to a possible secondary headache however does not institute any guidelines about performance of lumbar punctures in this instance. There are no studies documenting the lumbar puncture findings in HIV-infected individuals with primary headache.

1.5 CT brain scans in HIV-infected individuals

CT scans of the brain have proven to be indispensable in the management of HIV-infected patients presenting to the emergency department with headache. Tso et al conducted a retrospective review of imaging and medical records of HIV-infected patients who visited the emergency department of the University of Maryland Medical Centre with neurological complaints[32]. Their cohort consisted of 146 patients who were known to have HIV or had risk factors for HIV infection. The 146 patients visited the emergency department 169 times with headache being the most common complaint. Of the 169 cranial CTs obtained, 85 (50%) were normal, 49 (29%) showed atrophy only and 35 (21%) demonstrated focal lesions. Twenty-five patients with a non-focal presentation had lesions on CT. New findings were found on repeat CT in seven patients. Tso et al proposed that CT is indicated in every HIV-infected individual with neurological symptoms and that repeat scans are necessary even in patients with recent scans. Patients were recruited via CT reports, it is therefore likely that not all patients who presented with headache were scanned as scans were ordered at the attending physicians' discretion. The HIV status of 32 patients remained unknown.

Graham et al reviewed CT scans of HIV-infected patients with headache uncomplicated by altered mental state, meningism, focal neurological signs and symptoms suggestive of subarachnoid haemorrhage, and correlated the scans with the CD4 counts of the patients[33]. Of the 204 CT scans performed, 128 (62.7%) were negative, and 76 (37.3%) were positive. Atrophy contributed to 58 (76.3%) of abnormal scans. Mass lesions and white matter changes were seen in 23% (18/204) of scans. All participants with mass lesions or white matter changes had a CD4 count <200 cells/mm. It is therefore likely that patients with high CD4 counts have a paucity of CT brain abnormalities. This study did not look at the correlates of viral load and CT brain findings of those with uncomplicated headaches. None of the patients were on highly active antiretroviral therapy (HAART). Another limitation of the study was that headache types were not classified in this study.

Gifford et al devised a clinical prediction rule which divided 364 HIV-infected patients with headache into three groups based on clinical criteria and CD4 count[34]. The low risk group, comprising of patients with CD4≥200 cells/mm and no focal neurological signs, altered mental status or seizures, had no abnormal CT scans. In the intermediate group (patients with CD4<200 cells/mm, no focal neurological signs, no seizures, no altered mental status), 22% had abnormal CT scans whilst in the high risk group (patients with focal neurological signs, altered mental status or seizures regardless of CD4 count), 21% of patients had an abnormal head CT. Overall, 40 (11%) patients had abnormal CTs. Definite intracranial mass lesions were diagnosed in 19 (5%) patients and possible intracranial lesions (other than atrophy) were diagnosed in 21(6%) patients. In a second group of 93 outpatients who presented with headache, Gifford et al found focal brain lesions in 3 patients (3%)[34]. A major limitation was that not all the patients in this group had CT scans done. The possibility exists that patients

with better immunological status do not require routine CT scans as part of the workup for primary headaches due to a low yield of abnormal scans. Patients in this study were not on HAART.

In a retrospective review of neuroimaging findings of HIV-infected patients in the pre-HAART and post-HAART eras Matinella et al found that cerebral lesions were detected in 53/243 patients (21.8 %) in the pre-HAART era and far fewer patients in the HAART era (61/801, 7.6 %, $p<0.001$)[35]. The HIV viral load of patients were not measured and therefore the frequency of cerebral lesions in virally suppressed versus unsuppressed HIV-infected patients on HAART could not be established.

1.6 Conclusion

Primary headaches appear to be more prevalent than secondary headaches in HIV-infected patients[5]. However, no studies describing CT findings in HIV-infected patients with primary headache exist. The available literature demonstrates that mass lesions, atrophy and white matter changes are seen in patients with isolated headache with varying frequencies. It is unknown how frequently these CT changes are seen in HIV-infected patients with defined primary headache. This study describes the CT findings in HIV-infected patients with ICHD3 beta defined primary headaches hence addressing this gap in the literature. As a secondary endpoint, the study evaluates CT brains in virally suppressed and unsuppressed patients and patients with differing CD4 counts presenting with primary headaches.

1.7 Study Objectives

- To assess the computed topography brain findings of HIV-infected patients with primary headaches (as defined by the International Classification of Headache disorders, 3rd Edition)
- To evaluate differences in the computed topography brain findings in virally suppressed versus virally unsuppressed HIV-infected patients with primary headaches

1.8 Methods

1.8.1 Study Design

This is a cross sectional study conducted over six months. A cross-sectional analysis of CT brains will be evaluated in HIV-infected patients meeting ICHD3 criteria for primary headaches.

1.8.2 Study Setting

The study will be conducted at the Neurology outpatients departments and ARV clinics at Charlotte Maxeke Johannesburg Academic Hospital, Helen Joseph Hospital and Chris Hani Baragwanath Hospital

1.8.3 Study Methods

All HIV-infected patients with primary headaches who meet eligibility criteria will be asked to volunteer in the study. Written informed consent for study participation will be obtained. A data sheet will be used to collect demographic, HIV and headache-related information. Non-

contrast CT brains will be performed on all patients enrolled into the study and contrast CT scans will be performed if indicated. CT brains will be reviewed by an independent radiologist. Lumbar punctures will be performed on all patients to exclude a secondary cause. Severity of headache will be assessed using the 4-point Verbal Rating Scale.

1.8.3.1 Eligibility Criteria

Inclusion Criteria

- HIV positive patients who have headaches that fulfill ICHD3 criteria for primary headache disorders

Exclusion Criteria

- Age < 18 years
- History of seizures
- Previous head injury
- Fever
- Neck stiffness
- Symptoms of raised intracranial pressure
- Presence of focal neurological signs
- Abnormal findings on fundoscopy
- Renal dysfunction
- Iodine allergy

1.8.4 Statistical Methods

1.8.4.1 Sampling Method

- Convenience sampling method

1.8.4.2 Sample Size Calculation

- Statistical software used for sample size calculation :Statcal/ Epi Info 7.1
- Number of HIV positive patients seen over 6 months estimated at 15 000
- Estimated frequency of primary headache among HIV patients = 20% (6, 13)
- Acceptable margin of error 5%, 95% confidence interval
- No clusters and design effect =1
- Sample size (minimum) =242

1.8.4.3 Sample Selection

- All patients meeting the inclusion criteria

1.8.5 Data Collection and Analysis

- A data sheet (included in appendix) will be completed for each patient
    - Demographic information: age, race, sex, HIV related information: Date of diagnosis, treatment or not, duration of ARV regimen, CD4 count, viral load count
    - Headache related information: type, duration and severity
    - CT Brain: findings normal or abnormal
- All CT scans will be reviewed by a registrar in radiology followed by a radiologist

- CT findings will be stratified into normal and abnormal findings and significant associations will be tested using Fischers Exact test
- Abnormal findings will be stratified into focal brain lesions, white matter changes and cerebral atrophy and additional findings
- P- value< 0.05 will be considered significant. A statistician will be consulted regarding performing actual data analysis

1.9 Ethics

- The protocol will be submitted for ethics approval to the Human Research Ethical Committee of the University of Witwatersrand
- Consent, including consent for a contrast CT scan, will be obtained from all study participants
- Data confidentiality will be maintained by assigning participants study numbers
- Sample selection bias

1.10 Funding

- Self-funded

1.11 Timing

- Patients will be recruited and enrolled into the study over a 6-month period. Data collection will occur simultaneously. Thereafter, data analysis and manuscript write-up will commence.

Figure 1: Gantt chart showing the proposed timeline of the study

	October 2016	November 2016	Jan-June 2017	July-Sept 2017	Sept-Dec 2017
Protocol Assessment					
Ethics application					
Data Collection					
Data Analysis					
Manuscript write-up					

1.12 References (Extended Literature Review)

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2 MANUSCRIPT

INTRODUCTION

There are 7.1 million people living with the Human Immunodeficiency Virus (HIV) in South Africa[1]. Headache, a highly debilitating condition, is frequently experienced by these individuals[2]. Studies documenting headache in HIV-infected individuals done prior to the widespread effective use of anti-retroviral drugs showed a higher prevalence of secondary headache with cryptococcal meningitis being a leading cause of headache [3,4]. Studies in which patients did not have significant immunosuppression showed primary headache to be the chief cause of headache[5]. Despite South Africa having the largest epidemic of HIV in the world, there are currently no studies which investigate primary headache in this population.

Computed tomography (CT) of the brain is pivotal to the management of secondary headache in HIV-infected individuals as these patients may have life threatening conditions causing their headache. The importance of CT brain scans in defined primary headache is less clear. Current consensus recognises that HIV infection may point to an underlying cause for headache but does not offer specific recommendations regarding the use of CT scans in HIV-infected individuals with features suggestive of a primary headache[6,7]. To date no studies have investigated the CT brain findings in HIV-infected individuals with International Classification of Headache Disorders (ICHD) defined primary headache[8]. This study describes the CT brain findings of HIV-infected individuals with ICHD3 beta defined primary headache and evaluates the relationship between the stage of immune suppression and CT findings. Additionally, this study determines the effect of demographic factors and headache related factors on CT findings in these individuals.

METHODS

Study Design

This was a prospective study evaluating the CT brain scans of HIV-infected patients meeting ICHD3 beta criteria for primary headaches. The study was conducted over a six-month period from 1 January 2017 to 30 June 2017.

Study setting

Patients were recruited from the Neurology outpatient departments and ARV clinics at Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital, in Johannesburg, South Africa.

Study sampling

Convenience sampling was used. A sample size of 242 was calculated based on a margin error of 5%, 95% confidence level and primary headache prevalence in HIV infected individuals at 20%[5].

Study methods

HIV positive patients who had headaches that fulfilled the ICHD3 beta criteria for primary headache disorders were recruited for the study. Participants were 18 years or older. Exclusion criteria for participation were history of seizures or previous head injury, fever, neck stiffness, symptoms of raised intracranial pressure, the presence of focal neurological signs and abnormal findings on fundoscopy.

A data sheet was used to collect demographic information, headache related information and HIV-related information. A detailed history of headache was taken from patients. Information included type and duration of headache, headache frequency, and severity of headaches. Headache type was classified according to the ICHD3 beta criteria for primary headaches[8]. Severity of headache was assessed using the 4-point Verbal Rating Scale (VRS). HIV-related information that was documented included duration of disease, cluster of differentiation 4 (CD4) count and HIV viral load performed within the preceding 6 months, presence or absence of ARV use and duration of ARV use.

All participants had non-contrast and/or contrast CT brains performed. All CT brains were reviewed by an independent radiologist. Lumbar punctures were performed in patient who consented to having the procedure performed. The cerebrospinal fluid was analysed by the National Health Laboratory Services. Cerebrospinal fluid was examined for protein content, glucose levels and presence of cells. Gram staining, india ink testing, investigation for cryptococcal antigen and tuberculosis. Gene Xpert testing was also performed on cerebrospinal fluid specimens.

Ethical considerations

Written informed consent, including consent for a CT brain, was obtained from all participants. Identifying markers were replaced with study numbers to maintain participant confidentiality. The study was approved by the Human Research Ethics Committee of the University of Witwatersrand, ethics clearance number: M16117.

Statistical analysis

Demographic information was described quantitatively using frequencies and percentages. CT findings were described categorically as normal or abnormal and then further stratified. Fischers exact test was used (as some variables had a frequency <5) to establish any significant associations between age, sex, co-morbidities, headache type, headache severity and CT findings. Fischers exact test was also used to determine if any significant association existed between HIV viral load suppression and CT findings and CD4 count and CT findings as some variables were < 5. A P- value< 0.05 was considered significant.

RESULTS

Eighty-six participants were included in the study. Table 1 shows the demographic characteristics and clinical HIV information of the participants. The median age of participants was 39 years. The majority of participants were between 30 to 39 years old (40%) and female (96%). The median time since HIV diagnosis was 96 months with majority of the cohort on ARVs (96%). The median CD4 count was 542 with 88% of the cohort being virally suppressed. Majority of the cohort did not have a co-morbidity (66%). Of those who had a comorbidity hypertension was the most common (60%).

Table 1: Demographic and clinical characteristics

	(n=86)	
Characteristic	**Number**	**%**
Age in years, median (IQR)*	39	(35 - 48)
Age group		
18-29	6	7%
30-39	40	46%
40-49	22	26%
50+	18	21%
Sex		
Female	83	96%
Male	3	4%
Time since HIV diagnosis in months, median (IQR)**	96	(60 - 149)
On ARV therapy		
No	3	4%
Yes	83	96%
Duration on ARVs in months, median (IQR)*	84	(50 - 120)
CD4 count, median (IQR)*	562	(411 - 770)
CD4 categories		
<200	9	11%
>200	77	89%
Viral load (Suppressed/unsuppressed)		
Suppressed	76	88%
Unsuppressed	10	12%
Co-morbidities (Y/N)		
No	66	77%
Yes	20	23%
Type of comorbidity		
Carcinoma of the breast	2	10%
Dilated Cardiomyopathy	1	5%
Hypertension	12	60%
Pulmonary Hypertension	1	5%
Pulmonary Tuberculosis	1	5%
Scleroderma	1	5%
Systemic lupus erythematosus	1	5%
Tuberculosis of the breast	1	5%

* Median and Interquartile Ranges (IQR) presented

Of the 86 participants, 81 (94%) had tension-type headaches. Majority of the tension type headaches were frequent tension-type headaches 68 (84%). Only 5 (6%) participants had migraine, of which all had migraine without aura.

The reported tension-type headaches were predominantly of moderate severity 53 (65%), whilst the majority of migraine was rated as severe.

The median duration of tension-type headache was 24 months (8; 60) while that of migraine was 64 months (24; 108). The median headache episodes per month were 4 for both migraine and tension-type headache.

Table 2: Headache characteristics

	(n=86)	
Characteristic	**Number**	**%**
Headache Type		
Migraine	5	6%
Tension-type	81	94%
ICHD3 Classification		
Migraine		
Migraine without Aura	5	100%
Tension-type		
Chronic tension-type headache	10	12%
Frequent tension-type headache	68	84%
Infrequent tension-type headache	3	4%
Severity 4-point VRS		
Migraine		
Moderate	2	40%
Severe	3	60%
Tension-type		
Mild	13	16%
Moderate	53	65%
Severe	15	18%
Headache duration in months		
Migraine duration, median (IQR)*	64	(24 - 108)
Tension-type duration, median (IQR)*	24	(8 - 60)
Headache episodes per month		
Migraine episodes, median (IQR)*	4	(1 - 4)
Tension-type episodes, median	4	(3 - 12)

(IQR)*

* Median and Interquartile Ranges (IQR) presented

Table 3 shows the brain computed tomography findings of the participants. Overall, 12% of participants had abnormal CT scans, 8% of these abnormalities were seen on pre-contrast scans and 10% of these abnormalities were seen on post contrast scans. Five percent of participants had focal brain lesions, 2% had white matter changes and 7% had cerebral atrophy. The abnormal CT findings were: calcified granulomas, cerebral atrophy, periventricular white matter changes and an arachnoid cyst. One participant had both cerebral atrophy and periventricular white matter changes.

Table 3: Brain Computed Tomography (CT) findings

	(n=86)	
Characteristic	**Number**	**%**
CT Normal/Abnormal		
Abnormal	10	12%
Normal	76	88%
Pre-contrast CT(normal/abnormal/not done)		
Abnormal	8	9%
Normal	56	65%
Not done	22	26%
Post contrast CT(normal/abnormal/not done)		
Abnormal	9	10%
Normal	67	78%
Not done	10	12%
Focal brain lesion (Y/N)		
No	83	95%
Yes	3	5%
White matter changes (Y/N)		
No	84	98%
Yes	2	2%
Cerebral Atrophy (Y/N)		
No	80	93%
Yes	6	7%
CT scan Abnormal Findings		
Calcified granuloma left parietal lobe	1	1%
Cerebral Atrophy	6	7%
Periventricular white matter ischaemic changes	2	2%
Right ambient cistern arachnoid cyst	1	1%
Calcified granuloma left temporal lobe	1	1%
None	76	88%

* Median and Interquartile Ranges (IQR) presented

Lumbar punctures were performed on 61 participants, all of which were normal. The median cerebrospinal fluid protein was 0.26. Nine out of the ten participants with abnormal brain computed tomography findings had lumbar punctures performed and these were all normal (results not shown on tables).

Table 4: CT findings by viral suppression

	Viral load				
	Suppressed		Unsuppressed		
CT Findings	**(n=76)**	**Col %**	**(n=10)**	**Col %**	**p-value***
CT Normal/Abnormal					
Abnormal	9	12	1	10	1.000
Normal	67	88	9	90	
Pre-contrast CT(normal/abnormal/not done)					
Abnormal	7	9	1	10	1.000
Normal	49	65	7	70	
Not done	20	26	2	20	
Post contrast CT(normal/abnormal/not done)					
Abnormal	8	10	1	10	1.000
Normal	59	78	8	80	
Not done	9	12	1	10	
Focal brain lesion (Y/N)					
No	73	96	10	100	1.000
Yes	3	4	0	0	
White matter changes (Y/N)					
No	74	97	10	100	1.000
Yes	2	3	0	0	
Cerebral Atrophy (Y/N)					
No	71	93	9	90	0.535
Yes	5	7	1	10	

*p-value from Fisher's exact test

There were no statistically significant associations between any of the CT variables and viral suppression (Table 4).

Table 5: CT findings by CD4 categorization

	CD4 categories				
	< 200		> 200		
CT Findings	**(n=9)**	**Col %**	**(n=77)**	**Col %**	**p-value***
CT Normal/Abnormal					
Abnormal	2	22	8	10	0.280
Normal	7	78	69	90	
Pre-contrast CT(normal/abnormal/not done)					
Abnormal	2	22	6	8	0.224
Normal	6	67	50	65	
Not done	1	11	21	27	
Post contrast CT(normal/abnormal/not done)					
Abnormal	2	22	7	9	0.294
Normal	6	67	61	79	
Not done	1	11	9	12	
Focal brain lesion (Y/N)					
No	9	100	74	96	1.000
Yes	0	0	3	4	
White matter changes (Y/N)					
No	9	100	75	97	1.000
Yes	0	0	2	3	
Cerebral Atrophy (Y/N)					
No	7	78	73	95	0.117
Yes	2	22	4	5	

*p-value from Fisher's exact test

There were no statistically significant associations between any of the CT variables and CD4 categories (Table 5).

There was a statistically significant association between the presence of co-morbidities and abnormal CT findings (p-value = 0.001). The majority of the participants with abnormal CT findings had co-morbidities (Table 6). Other factors were not associated with CT findings.

Table 6: Several characteristics by CT findings

Characteristic	CT Findings: Abnormal (n=10)	Col %	Normal (n=76)	Col %	p-value*
Headache severity VRS					
Mild	2	20	11	14	0.222
Moderate	8	80	47	62	
Severe	0	0	18	24	
Age group					
18-29	1	10	5	7	0.182
30-39	2	20	38	50	
40-49	3	30	19	25	
50+	4	40	14	18	
Sex					
Female	10	100	73	96	1.000
Male	0	0	3	4	
Co-morbidities(Y/N)					
No	3	30	63	83	0.001
Yes	7	70	13	17	
On ARV therapy (Y/N)					
No	0	0	3	4	1.000
Yes	10	100	73	96	
Headache type					
Migraine	1	10	4	5	0.470
Tension-type	9	90	72	95	
ICHD3 classification					
Chronic tension-type headache	1	10	9	12	0.861
Frequent tension-type headache	8	80	60	79	
Infrequent tension-type headache	0	0	3	4	
Migraine without aura	1	10	4	5	

*p-value from Fisher's exact test

DISCUSSION

This study describes the CT brain findings of HIV-infected individuals with primary headache fulfilling ICHD3 beta criteria. We found abnormalities on CT brain scans in 12% of our study participants demonstrating that in HIV-infected individuals with ICHD3 defined primary headache there is a low prevalence of abnormalities on CT brain scans. There are no previous studies documenting abnormal CT brain findings in HIV-infected individuals with defined primary headache. However, studies investigating undefined headache in HIV-infected individuals found CT abnormalities ranging from 34% to 50% [5,9,10]. In the general population the yield of CT abnormalities in primary headache is 2%[11]. Although CT brain abnormalities in HIV-infected individuals with primary headache are infrequent, this study demonstrated a higher prevalence of abnormalities than in the general population.

Three (5%) participants had focal brain lesions. Two of these participants had calcified granulomas which are lesions indicative of previous infection and one participant had an incidental finding of an arachnoid cyst. The focal brain lesions were not due to an active opportunistic infection and were not causing mass effect or raised intracranial pressure. Two participants (2%) had white matter changes which were periventricular and possibly as a result of hypertension in these patients. Cerebral atrophy was found in 6(7%) of CT brain scans. These CT findings did not warrant treatment and none were life threatening. The abnormalities found could not account for the headache these participants experienced.

The majority of participants, 76(88%), had suppressed HIV viral loads on anti-retroviral therapy. Prior studies investigating primary headache in HIV-infected individuals did not document participants' HIV viral loads [5,12]. This study showed that there were no statistically significant associations between abnormal CT findings and viral suppression. Additionally, no statistically significant association was found between CD4 count and abnormal CT findings. Seventy-seven (89%) of our participants had a CD4 count >200 cells/mm and the median CD4 count of participants was 562 cells/mm. In the cohorts investigated by Mirsattari et al and Kirkland et al participants had lower CD4 counts[5,12]. Mirsattari et al found the mean CD4 count of migraineurs to be 321 cells/mm whilst participants with tension-type headache had a mean CD4 count of 90 cells/mm[5]. In the study by Kirkland et al, the mean CD4 count was 326 cells/mm[12]. Our study was conducted in the era of widespread and efficient use of ARVs thereby accounting for the difference in degree of immune suppression in patients with primary headache.

A statistically significant association between having co-morbidities and abnormal CT findings (p-value = 0.001) was found in this study. The commonest co-morbidities in previous studies documenting primary headache in HIV-infected individuals were anxiety, depression and insomnia. Hypertension was the most frequent co-morbidity in our cohort. This is consistent with the high prevalence of hypertension in the general population[13]. Hypertension causes abnormalities on CT brain scans specifically periventricular white matter changes and cerebral atrophy. The association between abnormal CT findings and co-morbidities in our cohort could be due to the high frequency of hypertension.

The majority of participants in our cohort were female (96%) which is in contrast to other studies investigating primary headache in HIV-infected individuals which documented a male predominance[5,12,14]. In the study by Mirsattari et al 28 of 29 (97%) of participants with primary headache were male, whilst Kirkland et al found a slight male predominance of 52%. The female predominance found in our study is however in keeping with primary headache demographics in the general population[15,16].

The prevalence of TTH peaks between the ages of 30 and 39 years and the prevalence of migraine increases with age until a peak is reached during the fourth decade of life[15,16]. The median age of participants in our cohort was 39 years old, with the majority of participants in the 30-39 age group which is in keeping with current literature.

There is conflicting data regarding the most prevalent primary headache semiology in HIV-infected individuals. Mirsattari et al and Kirkland et al both found migraine to be the commonest headache type[5,12]. Participants in their cohorts had lower CD4 counts suggesting that migraine is more common with a greater degree of immune suppression.

All sixty-one lumbar punctures performed in our study were normal. In the study by Mirsattari et al only 8 lumbar punctures were performed on participants and the majority were normal[5]. Evers et al also performed lumbar punctures on a small subgroup of 24 participants and found that the group of participants with tension type headache had lower protein and fewer inflammatory changes in CSF than the group of participants without tension type headache[14]. The paucity of CSF changes may signify that HIV is not the cause of the headache in individuals with primary headaches.

CONCLUSION

Despite primary headache being highly prevalent in HIV- infected individuals there is a paucity of data surrounding this health issue, especially in the South African context. Our study found that in HIV-infected individuals with ICHD3 beta defined primary headache, there is a low prevalence of abnormalities on CT brain scans. The abnormalities were unrelated to the degree of immunosuppression. However, HIV-infected individuals with co-morbidities were found to be more likely to have abnormal CT brain scans. This phenomenon may be explained by the high prevalence of hypertension in our cohort.

We conclude that HIV, by itself, is not associated with abnormal CT brain scans in individuals with ICHD3 beta primary headaches. Further studies are needed to corroborate these findings with the aim to reduce unwarranted and costly investigation of primary headache in HIV-infected individuals.

LIMITATIONS

The major limitation of our study is the small sample collected. During the time allocated for recruiting patients only eighty-six participants met inclusion criteria. The small sample does not enable us to propose a shift in practice when encountering an HIV-infected individual with primary headache, all such individuals should continue to be investigated for a possible underlying cause of headache. Larger neuroradiological studies are needed to corroborate our findings so that unnecessary investigations are in future curtailed, reducing costs to patients and society.

Participants were recruited, interviewed, diagnosed and assigned a primary headache classification by a single neurology registrar which may have resulted in observer bias. Further studies require a second interviewer to prevent this problem.

The cross-sectional nature of the study is a limitation as headache can change in severity, frequency and semiology and patients may develop cerebral atrophy and other abnormalities on CT scans as the HIV disease progresses.

The small number of participants with severe immunosuppression in our study may be seen as a limitation however this is reflective of the advancements that have been made in HIV diagnosis and treatment.

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3 APPENDICES

Appendix i: Data Collection Sheet

Demographic Data	
Study Number	
Age	
Sex	
Telephone Number	
Headache History	
Date of Onset	
Type	
Episodes per month	
Severity (VRS-4)	
No Pain- 0	
Mild Pain -1	
Moderate Pain- 2	
Severe Pain- 3	
HIV History	

Date of diagnosis	
ARVS (Yes or No)	
Duration of ARVS	
CD4	
Viral load	
Co-morbidities (Yes/No)	
Diabetes	
Hypertension	
Other	
CT Findings (Radiologist Review)	
Normal/Abnormal	
Findings (Yes/No):	
Focal brain lesions	
White matter changes	
Cerebral Atrophy	
Additional Findings	
CSF Findings	
Protein	
Glucose	
Neutrophils	
Lymphocytes	
Gram Stain	
Gene Xpert	
India Ink	
Clat	
Other	

Appendix ii: Ethics Clearance Certificate

R14/49 Dr Kerena Gengan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161117

NAME: (Principal Investigator)	Dr Kerena Gengan
DEPARTMENT:	Neurology Charlotte Maxeke Johannesburg Academic Hospital Chris Hani Baragwanath Academic Hospital Helen Joseph Hospital
PROJECT TITLE:	Assessing Brain Computed Topography Findings of HIV Infected Adults Presenting with Primary Headache in Johannesburg, South Africa
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G. Modi
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Appendix iii: Plagiarism Report

Turnitin Originality Report

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