The relationship between increased Body Mass Index and primary headache disorders in a group of Antiretroviral therapy induced overweight and obese patients

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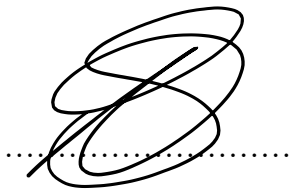
A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfillment for the degree of Master of Medicine in the division of Neurology

Johannesburg 2023

I. DECLARATION

I, Annsureeka Ganesh, 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.



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The 28th of June 2023.

II. DEDICATION

To my parents and husband for their tireless support and continuous belief in me.

III. PRESENTATIONS ORIGINATING FROM THIS RESEARCH

Nil

IV. ETHICAL CONSIDERATIONS

Permission for this cross-sectional 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: M191057).

V. ABSTRACT

Introduction: Primary headache disorders are highly prevalent and may be found co-morbid with other diseases, including Human Immunodeficiency Virus (HIV). Recent literature has suggested a relationship between increased Body Mass Index (BMI) and primary headaches, although the exact mechanisms are largely unknown and likely diverse. Weight gain following initiation of Antiretroviral therapy (ART) has recently emerged as a complication amongst people living with HIV. This unique population with primary headaches may exhibit an artificially-induced state of obesity, which forms the basis of this study in order to describe the relationship between increased BMI and primary headache disorders.

Methods: This was a cross-sectional study involving HIV positive patients on ART who had primary headaches. Participants who fulfilled inclusion criteria were enrolled in the study during their routine clinic visits. An anonymous interviewer-based questionnaire was used to record clinical and demographic data. Participants' height and weight were measured in order to calculate BMI. Fischer's exact test was used to investigate the association between the presence of primary headache, severity and frequency of headache and increased BMI. A p-value of less than 0.05 was considered evidence for statistical significance.

Results: There was a statistically significant association between female gender and increased BMI (OR 6.02, 95% CI, 1.32-26.21, p-value <0.02). Multivariate regression analysis demonstrated a higher risk of increased BMI amongst participants with features of tension type headache when compared to those with migraine, however this was not statistically significant (OR 2.47, 95% CI, 0.25-24.88, p-value 0.44). There was no statistically significant relationship

between increased BMI and the presence of primary headache, type of primary headache, severity, or frequency of headache in this study.

Conclusion: This study did not find any statistically significant relationship between increased BMI and primary headache disorders, nor any of their associated characteristics. This may be due to the small sample size, and further studies are needed to corroborate these findings.

VI. ACKNOWLEDGMENTS

My sincere gratitude to Professor G. Modi for his expert guidance and supervision of this MMed.

I would like to thank Dr M. Edoo and the staff at Themba Lethu Clinic, as well as the participants of the study for their consent, and time.

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IX. ABBREVIATIONS

ART	Antiretroviral therapy
AZT	Zidovudine
CD4	Cluster of differentiation 4
CNS	Central nervous system
DALY	Disability adjusted life years
DTG	Dolutegravir
EFV	Efavirenz
FDC	Fixed dose combination
FTC	Emtricitabine
GBD	Global Burden of Disease
HAART	Highly Active Anti-retroviral Therapy
HIV	Human immunodeficiency virus
ICHD	International Classification of Headache Disorders
InSTI	Integrase strand inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
NRTTI	Nucleoside reverse transcriptase translocation inhibitors
PI	Protease inhibitors
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organisation
YLD	Years lived with disability

1. PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction

Recent literature has identified a relationship between primary headache disorders and increased Body Mass Index (BMI), likely owing to shared pathophysiology [1-7]. The direction, causation and implications of this relationship are, however, still unknown, and require further investigation to establish the significance of this relationship. To date, there are no studies that describe the burden of primary headache disorders, or their relationship to BMI, within South Africa [4].

Primary headaches are a common group of non-communicable disorders that are known to cause significant disability [8-10] and pose great socioeconomic burden [11]. The most common types of primary headaches are migraine and tension type headache [1, 12, 13]. The lifetime global prevalence of tension type headache and migraine have been estimated at 46% and 14% respectively [1]. The occurrence of primary headaches spans all racial, gender, and age groups. Primary headaches may also occur with other co-morbidities, including human immunodeficiency virus (HIV) [14-16] and obesity [1-7, 17].

Overweight and obesity are defined by the World Health Organization (WHO) as "abnormal or excessive fat accumulation that may impair health" [18]. BMI is the most widely used classification, however, it does not exclude non-fat mass, and may not be solely indicative of one's fat content [18]. Overweight refers to BMI greater than 25 kg/m^2, and obesity refers to BMI greater than 30 kg/m^2 [18]. Obesity is a global pandemic which, like primary headache disorders, similarly spans genders, age groups and racial backgrounds. It may also be co-morbid with other disorders, including primary headaches [1-7, 17] and HIV [19-30].

Despite the suppressed state of immunity and known risk of secondary causes of headache amongst people living with HIV, primary headaches are the most common type of headache disorders within this population [15, 16]. The widespread implementation of Antiretroviral therapy (ART) has resulted in improved immunity, as well as a surge in artificially induced increased BMI amongst many patients [19-30]. This metabolic occurrence has been noted across various drug classes, both individually and in combination with each other. There is much to be determined regarding the effects and significance of increased BMI within this population, however, it may have similar implications for co-morbidities associated with obesity [19, 20], including primary headache disorders [19-30].

The emerging state of drug-induced increased BMI amongst HIV positive individuals on ART presents a unique opportunity to study the relationship between increased BMI and primary headache disorders, and forms the basis of this study.

1.2 Headache disorders in the general population

1.2.1 Background and Epidemiology

Headaches are amongst the most common neurological disorders worldwide [8-10]. The global prevalence of active headache disorders is estimated at 52% [13], of which the most prevalent headache disorder is tension type headache [1, 12]. According to the Global Burden of Disease analysis (2016) [10], 1.89 billion people suffered from tension type headache and 1.04 billion people had migraine.

The significance of these values was detailed further in the Global Burden of Diseases, Injuries and Risk Factors Study (2019) [8], in which headache disorders ranked third in years lived with disability (YLD) across all ages and genders. Headache disorders were amongst the top five

disorders resulting in disability adjusted life years (DALY) for both genders in the reproductive age group (25-49 years old), with migraine causing the highest DALY in women under the age of 50 years old [8].

These statistics illustrate the magnitude of primary headache disorders, and their impact on quality of life [8, 9]. To date, there are a paucity of studies regarding primary headache disorders within the South African context [4].

1.2.2 Classification of headache disorders

The International Classification of Headache Disorders (ICHD) [31] is an evidence-based guideline on diagnosis and classification of headache disorders. It was originally published in 1989, with the latest edition (ICHD-3) updated in 2018. The ICHD-3 classifies headache disorders into two main categories according to aetiology: primary and secondary headaches [31].

1.2.3 Primary headache disorders

Primary headaches are defined as headaches caused by independent pathophysiology, and not as a symptom of another disorder [31]. The most common primary headaches are tension type headache and migraine [1, 10, 12]. Trigeminal autonomic cephalalgias are rare in comparison, of which, cluster headache is the most common [32]. Other primary headaches include primary cough headache, primary exercise headache, new daily persistent headache, and hypnic headache [31].

Current practice allows for diagnosis and treatment of primary headaches in patients who fulfil diagnostic criteria proposed by the ICHD-3, provided they do not have atypical features that

may suggest secondary causes of headache [12, 31, 33]. Features that may warrant further investigations are commonly referred to as red flags. These may include alterations in level of consciousness, fever, meningism, features suggestive of raised intracranial pressure including papilloedema, and focal neurological signs [34, 35].

1.2.4 Tension type headache

Tension type headache is the most common primary headache experienced in the general population [1, 10, 12, 32]. It has been referred to as the "featureless headache" [12], with pain quality described as a dull, pressing ache, of mild to moderate severity. The headache is located bilaterally, usually occurring without the consortium of features that accompany migraine [12, 31]. Tension type headache may be experienced across various age groups, including older individuals, with some studies estimating tension type headache to be found in up to 50-80% of individuals over the age of 65 [36].

Tension type headache is classified as infrequent if headache occurs on less than 1 day per month, frequent if they occur between 1-14 days per month for more than 3 months, and chronic if headache occurs on more than 15 days per month for at least 3 months [31]. Defining the frequency of headache is of great importance, as it provides a quantifiable measurement that can be used to monitor response to treatment and guide further management.

The pathogenesis of tension type headache is diverse, owing to environmental, psychosocial, and genetic factors. Physiologically, activation of peripheral myofascial nociceptors have been shown to be of importance in episodic headaches, and sensitization of central pathways may result in chronicity [12, 31, 32].

1.2.5 Migraine

Migraine is classified into two main categories in the ICHD-3: migraine with aura and migraine without aura [31]. Aura refers to a group of reversible symptoms, most often visual in nature, which may precede the onset of the headache. The aura of migraine is thought to be due to the process of neuronal depolarization, known as cortical spreading depression [33]. Migraineurs usually experience a consortium of symptoms that include photophobia, phonophobia, nausea, and vomiting. These features may accompany a typically unilateral, throbbing headache of moderate to severe pain [31].

Migraine occurs most commonly during the reproductive years, and has a well-recognized female predominance [32, 37]. Like tension type headache, migraine may also be experienced by older individuals, either as a continuation of a previously existing headache disorder, or a de novo headache [38, 39]. Although there is no consensus as to what age group "elderly" refers to, studies suggest that the lifetime prevalence of migraine in persons older than 55 years is approximately 20-34% [36].

According to the ICHD-3 [31], the frequency of migraine may be classified as episodic or chronic. Chronicity refers to headache occurring on 15 or more days per month for more than 3 months, on which at least 8 days per month have features of migraine [31].

Migraine has an intricate pathophysiology that is thought to revolve around the trigemino-vascular complex. Once activated by the process of cortical spreading depression, the trigemino-vascular complex induces the release of numerous vasoactive peptides. This leads to a cascade of events, including inflammation and hormonal dysregulation, that generate migraine and may lead to other systemic effects [5, 33].

1.2.6 Secondary headache disorders

Secondary headaches are caused by underlying pathology that activates pain sensitive pathways in the cranial region [40]. Approximately 18% of individuals who suffer from headaches have a confirmed secondary cause, of which 7.4% are caused by overuse of medications [35]. Other secondary causes of headaches include infections, neoplasm, trauma, and toxins [31, 32].

Headache due to an underlying central nervous system (CNS) infection (meningitis, abscess etcetera) can often be recognized by the clinical triad of headache, fever, and vomiting. These symptoms may be accompanied by the previously mentioned red flags: changes in level of consciousness, meningism and focal neurological signs. The headaches are usually acute and resolve within three months of effective treatment of the infection. Rarely, they may become chronic, resulting in persistent headaches of varying character [31].

When a concern for a secondary cause of headache is present, further investigations may be performed to establish the underlying causative factor and guide appropriate management. These may include biochemical parameters, such as blood tests and cerebrospinal fluid analysis, as well as radiological imaging.

1.2.7 Differentiating between primary and secondary headaches

The conundrum of whether a headache is classified as primary, secondary, or both, can be approached using three main considerations as per the ICHD-3 [31]:

- A new headache that occurs in close temporal relationship to a known cause of secondary headache is classified as secondary.

- A pre-existing headache that becomes chronic due to a known secondary cause of headache is classified as both primary and secondary.
- A pre-existing headache that becomes worse in terms of severity and frequency due to a known cause of a secondary headache is classified as both primary and secondary.

Primary headaches may occur exclusively or in the presence of other headache disorders. The presence of other headache disorders may exacerbate the features of a pre-existing primary headache or cause a new, independent headache, that co-exists with a pre-existing primary headache.

1.3 Headache disorders amongst people living with HIV

1.3.1 Pathophysiology and types of headaches

The pathophysiology of headaches in people living with HIV is largely dependent on the cause and type of headache. Headaches may occur independent of HIV, as in the case of primary headache disorders, or secondarily due to the neurovirulent properties of HIV, sequelae of the immunocompromised state, or side effects of medications [41].

HIV is a neurotropic virus that may cause headache through various mechanisms which include CNS inflammation, and dysregulation of pain and neurotransmitter pathways. These mechanisms have been shown to overlap with aspects of the pathophysiology of primary headache disorders [41]. Neurotransmitter dysregulation may result in reduced levels of serotonin in people living with HIV, similar to that which occurs with migraine [33], and may lead to impaired pain control pathways. Calcitonin gene-related peptide (CGRP) is key in facilitating pain transmission in migraine [33], and infection with HIV has been shown to cause the release of CGRP by inducing cell death [41].

The diagnosis and management of headaches in people living with HIV may be approached using a similar classification system to determine whether primary headache, secondary headache, or both, exists. Numerous studies have noted primary headaches to be the most prevalent headache disorder amongst people living with HIV [14, 15, 16], and the advent of ART is likely to have further reduced the burden of secondary causes of headaches due to impaired immunity [42, 43]. There has, however, been no consensus as to which type of primary headache disorder is most common amongst people living with HIV; migraine or tension type headache [14, 15, 16]. Whilst there are no unique characteristics of primary headaches in people with HIV, the term "HIV headache" was described by Brew and Miller [44] to denote a headache with similar features to that of tension type headache.

The definitive distinction between migraine and tension type headache has been recognized by the ICHD-3 [31] as a potential challenge, due to shared pathophysiology, and several authors have described overlapping clinical features [14, 15]. Primary headaches in people with HIV have been described as severe, non-throbbing, bilateral in location, with relatively infrequent nausea and vomiting, in keeping with the description of tension type headache by Brew and Miller [44]. Several studies have aimed to explore primary headache disorders amongst people with HIV.

Mirsattari et al [16] conducted a retrospective chart analysis describing headache characteristics in a group of patients with HIV. One hundred and fifteen HIV positive patients were included, of which 44 (38%) patients experienced headaches. Twenty nine (65.9%) patients experienced primary headaches, with a prevalence of 25.2%. Migraine was most common (n=22, 76%) followed by tension type headache (n=4, 14%) and cluster headache (n=3, 10%). Secondary headaches were found in 15 (34%) patients. This study was conducted between 1990-1996 when the use of ART was neither routine, nor common. The authors concluded that primary

headaches were the most common type of headache amongst people living with HIV, independent of immune status, in keeping with the other studies [14, 15]. Furthermore, Mirsattari et al [16] suggested that investigations such as radiological imaging or cerebrospinal fluid analysis were not routinely required for the diagnosis, regardless of immune status.

This differs from other studies [45, 46], which have suggested further investigations for patients who are severely immunocompromised, although the yield for significant causative findings have been demonstrably low [45-47]. This study was important in demonstrating the prevalence of primary headaches, independent of immune status, in an era prior to widespread use of ART. The limitations of this study include the retrospective nature and small sample size, as well as investigations not being performed in all patients in order to definitively exclude secondary causes of headache.

In a cross-sectional study describing headache characteristics in HIV positive individuals, Kirkland et al [15] proposed that patients on ART had an improved state of immunity, which influenced the types of headaches they experienced. One hundred and seven participants reported headaches, with 96.3% (n=103) participants experiencing primary headaches. The most prevalent type of primary headache disorder was migraine (n=88, 82.2%), followed by tension type headache (n=15, 14%), in keeping with the findings of Mirsattari et al [16]. Interestingly, however, patients with migraine most commonly reported severe pain of bilateral location, and non-throbbing quality, with relatively infrequent reports of nausea (31.1%) and vomiting (13.6%). These characteristics overlap with many features associated with tension type headache, as described in other studies [14, 44]. Most of the patients who experienced primary headache disorders were on ART (93.5%) and had CD4 cell counts greater than 500 cells/mm^3 (n=74, 69.2%). Severity of immunosuppression correlated with increased severity, frequency,

and disability related to headache. Secondary headaches were found to have a low prevalence in this population, in accordance with other studies [14, 16, 45-47]. The possibility exists that the improved state of immunity, conferred by the widespread use of ART in this study, may have reduced the burden of secondary headaches, particularly those due to infection [42, 43]. Other studies [16], however, have not shown any relationship to immune status. As previously described by Mirsattari et al [16], routine neuroimaging has a low yield for significant secondary causes of headache in patients with typical characteristics, therefore was not utilized in this study. This may, however, be considered a limitation, as secondary causes of headaches were not definitively ruled out.

Gnonlonfoun et al [14] described the prevalence and associated characteristics of primary headache disorders in 493 HIV positive individuals in Benin, West Africa. In this cross-sectional study, primary headaches were diagnosed by a neurologist using the ICHD-2 criteria, and patients who demonstrated phenomenology concerning for secondary causes of headaches were excluded. One hundred and twenty four (25.2%) participants experienced primary headaches, a similar prevalence to that reported by Mirsattari et al [16]. Ninety-six (77.4%) participants had tension type headache, 52 (41.9%) participants had migraine, and 3 (2.4%) participants had cluster headache. These findings differ from previous studies by Kirkland et al [15] and Mirsattari et al [16] regarding the most prevalent primary headache type, although overlapping clinical features between migraine and tension type headache may account for this discrepancy [14, 15]. Other studies [48, 49] have similarly shown tension type headache to be most common in people living with HIV, which could be due to tension type headache being the most prevalent headache type in the general population [1, 10, 12, 32]. Gnonlonfoun et al [14] suggested that ART may inhibit specific neurotransmitters that are involved in migraine pathogenesis, which may account for the atypical migraine characteristics reported by Kirkland

et al [15]. This study is important in describing headache characteristics in HIV positive individuals in Africa, which carries the largest burden of the HIV pandemic [50]. A limitation of this study was that secondary causes of headache were not actively excluded. Whilst many studies suggest that routine investigations in individuals with typical headaches are not warranted [16, 34, 45, 47], more than half the participants (68.6%) in this study met criteria for the WHO HIV clinical stage 3, and this advanced state of immune suppression may have increased the risk for significant causes of secondary headache, as suggested by other studies [45, 46].

1.3.2 Investigation of headache disorders in HIV positive individuals

Current guidelines regarding investigation of headache suggest that patients with typical characteristics of primary headache, may be diagnosed and treated without further investigations, provided they do not display concerning features for secondary causes of headaches [32, 34]. To date, there are no specific guidelines regarding investigations of typical headaches presenting in HIV positive individuals, although the British HIV association [51] suggest that neurological fallout, and evidence of poor immunity with headache, should prompt appropriate neuroimaging and biochemical investigations.

The routine neuroimaging for headaches has yielded unimpressive results for significant causes of secondary headaches. Graham et al [45] retrospectively reviewed the findings of brain images in HIV positive individuals who presented with headaches. Two hundred and four contrast and non-contrast computerised topography (CT) scans from 178 HIV positive individuals were reviewed. One hundred and twenty eight (62.7%) scans were negative for secondary causes of headaches. Positive scans included space occupying lesions (n=14, 6.9%), white matter lesions (n=4, 2%), and atrophy only (n=58, 28.4%). With the exception of 3 individuals, all who had positive scans correlated with CD4 cell counts less than or equal to 200 cells/mm^3. This study

was conducted prior to the era of routine ART use, and all patients were ART naïve. CD4 cell count was considered an important predictor of CT scan outcome, although the majority of positive results related to cerebral atrophy; an entity not considered a significant secondary cause of headache [31]. Graham et al [45] demonstrated statistically significant negative results for routine neuroimaging in typical headache presentations. Despite the low yield, and many studies demonstrating the low prevalence of secondary headaches even in immunocompromised states [14, 16], the authors suggested that neuroimaging be performed in patients with CD4 cell counts less than 200 cells/mm^3. Limitations of this study include the retrospective nature, as well as failure of imaging protocols to specifically review sinuses and orbital spaces, which may have contributed to secondary causes.

Glifford et al [46] devised a clinical prediction rule for HIV positive individuals with headaches, in order to identify which patients warranted immediate neuroimaging. In this retrospective review, neuroradiological data from 364 patients who presented with headache between 1986 and 1996 were included. Patients were classified into low (n=35, 9.6%), intermediate (n=242, 66.5%) and high (n=87, 23.9%) risk categories. These were based on clinical criteria and immunological status, defined by CD4 cell count. Forty (11%) patients had abnormal CT scans of the brain, however space occupying lesions were only diagnosed in 19 (5.2%) individuals. The majority positive scans were found in the high risk group (n=18, 21%), and no positive scans were found in the low risk group. The overall positive imaging findings were, however, only found in a minority of patients, and not statistically significant, in keeping with previous studies [45, 47]. Glifford et al [46] concluded that routine neuroimaging is unnecessary in HIV positive individuals who present with typical primary headaches, but that investigations should be guided by both clinical and immunological parameters. This study is particularly helpful in resource-constraint settings where imaging facilities are not readily available, and allows for

clinical stratification to enable the appropriate management of patients. Limitations include the retrospective nature of the study design, as well as the limited use of ART as this study took place prior to routine ART use. Currently, ART usage is widespread, effective in improving immunity, and has likely reduced the burden of infective causes of secondary headache within this population [42].

Many studies [14, 15, 16] have suggested that primary headaches are the most common type of headache in people living with HIV. Routine neuroimaging for headache has a low yield for significant causes of secondary headache in individuals without atypical or high risk features [45, 46], and the indication for investigations should be guided by clinical suspicion, as it is in individuals without HIV.

1.4 Anti-retroviral therapy and Body Mass Index

1.4.1 Epidemiology of ART usage

7,2 million people were estimated to be living with HIV in South Africa in 2017 [52]. Of this population, an estimated 90% had been diagnosed and 61% were on ART, 47% of whom were virally suppressed [52]. The widespread use of ART has demonstrably been crucial in managing the HIV pandemic. However, along with an improved state of well-being, the issue of increasing BMI within this population has emerged [19]. This has led to the rise of other disorders that are co-morbid with obesity [19], including primary headache disorders.

1.4.2 Weight gain in people living with HIV

1.4.2.1 Effects of HIV on weight gain

As the exact pathophysiology of weight gain in people living with HIV is largely unknown, prognosis regarding reversibility, progression, clinical sequelae, and treatment thereof are

currently unknown. HIV, itself, is thought to induce changes within infected cells, which secrete pro-inflammatory cytokines that lead to alterations in adipocyte metabolism. This results in decreased adipocytokines, which have a protective role against the inflammatory state of obesity, and may result in insulin resistance. This process, known as lipotoxicity, may also be present in HIV positive patients in the absence of ART [25]. Inhibition of glucose transport through the blockade of insulin-sensitive glucose transporter (GLUT4) may also result in dysregulation of glucose metabolism and contribute to insulin resistance [24, 25].

An important bacterial lipopolysaccharide that is produced in the gastrointestinal system, and circulates systemically, has been found to be increased in HIV positive patients on ART. This lipopolysaccharide is thought to cause the release of inflammatory cytokines by binding to the toll-like receptor 4. A state of inflammation and insulin resistance is then induced, which subsequently leads to an increase in adipose tissue [24]. Some studies [25] indicate leptin levels may be reduced as CD4 cell counts increase, suggesting that ART may hamper the satiating effects of leptin. This may lead to increased hunger and potentially result in weight gain.

1.4.2.2 ART and weight gain

There are five main classes of drugs that constitute ART: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase translocation inhibitors (NRTTI), protease inhibitors (PI), and integrase strand inhibitors (InSTI). All classes, to varying degrees, have been associated with changes in fat metabolism and total body weight. This effect is present with individual drug use, as well as when drugs are used in combination, with drugs from the InSTI class associated with most noticeable weight gain. Weight gain has also been notably greater after initiation of ART compared to switching between classes [19, 22, 27]. Although the exact mechanism by which ART

drugs cause weight gain is largely unknown, and likely diverse, proposed theories include changes in energy metabolism, and altered adipocyte and neurotransmitter function [19, 20, 24, 25].

The 2019 South African ART clinical guidelines [21] detail indiscriminate eligibility of all patients with HIV for starting ART, in order to reduce HIV-associated complications. One of the most significant changes was the introduction of Dolutegravir (DTG), an InSTI, in all regimens. DTG is generally well tolerated, with mild gastrointestinal side effects, and has a high genetic predisposition against resistance. It has, however, been associated with significant weight gain [19, 22, 27, 28]. Risk factors for significant weight gain include female gender, black race, lower baseline CD4 cell counts and higher baseline HIV viral loads, and particularly when DTG is used in combination with other drugs, such as tenofovir alafenamide (TAF) [19, 22].

Weight gain due to ART has been described in numerous studies, and may occur during any phase of treatment [19-30]. In a pooled analysis of 8 randomized controlled trials, Sax et al [22] analysed weight gain of more than 5000 HIV positive individuals following ART initiation. Median pre-initiation BMI was 24.8 kg/m^2, and almost half of all participants were overweight (31.4%) or obese (16.3%). Baseline weight was higher in more recent trials, with a corresponding larger amount of weight gained during the trial period. The greatest weight gain was seen in the first 48 weeks following initiation of ART. Risk factors for weight gain were similar to those found in other studies [19, 22, 27], including female gender, black race, lower baseline BMI, lower baseline CD4 cell count (less than 200 cells/mm^3) and higher HIV viral load (greater than 100 000 copies/mL), as well as use of newer ART regimens which included InSTI drugs. Possible explanations for weight gain include the return-to-health phenomena associated with immune reconstitution following ART initiation, better gastrointestinal tolerability of newer regimens, and melanocortin-4 receptor (MC4R) interactions with DTG.

MC4R modulates leptin in the CNS, and may be involved in the regulation of caloric intake. Although the only notable change amongst the participants was the introduction of ART drugs, other factors that may have accounted for weight gain, such as lifestyle habits, were not controlled, and the possibility that these may have impacted weight gain cannot be excluded [22].

A retrospective study by Bakal et al [29], and a large prospective study by Kintu et al [30] had similar findings to Sax et al [22]. In both studies by Bakal et al [29] and Kintu et al [30], most of the participants had normal baseline BMI (n=969, 61.8% and n=45 231, 57% respectively). These studies are important in showcasing the surge in weight gain in patients of normal BMI, as it is now more common for ART to be initiated earlier in the disease process, when patients are less likely to be emaciated.

Bakal et al [29] demonstrated that individuals who were underweight at baseline had the greatest annual increase in BMI (0.6 kg/m^2/year), and that most participants of normal and increased BMI at baseline gained enough weight to transcend BMI classes throughout the study period. The most important determinant in weight gain was the use of an InSTI drug as the core drug, boasting a risk of development of obesity of more than 7 fold [29]. Limitations of this study lie in its retrospective nature, limiting the data to only that which was recorded at the time, thus, only BMI was able to be calculated. Fat mass and distribution may have been additional important entities to measure [24, 25].

Kintu et al [30] proposed alternative societal reasons that may contribute to weight gain following ART initiation. African society is thought to favour the phenotypic appearance that often accompanies high BMI, especially in women. It was proposed that in order to deflect from the

yoked stigmata of cachexia and HIV, patients may be actively increasing their caloric intake in an attempt to gain weight [30]. Strengths of this study include the prospective nature and large study population, however the exclusion of certain ART drug classes that are well known to cause weight gain, such as the InSTI class, is an important limitation of this study.

Eckard et al [26] studied the association between weight and fat gain, changes in basal metabolic rate, and caloric intake, in HIV positive individuals following ART initiation. A total of 30 participants were included, with an average age of 27.8 years. The majority of participants were male (n=23, 77%) and of black race (n=22, 73%). The mean baseline (pre-initiation) BMI was 24.7 kg/m^2, with 13 individuals having an increased BMI (n=3, 10% overweight and n=10, 33% obese). Weight, total body fat and truncal fat demonstrated an overall increase from baseline to 12 month follow up. There was no statistical significance between the use of TAF or DTG, diet, or change in basal metabolic rate. Higher baseline metabolic rate was found to be the most significant factor which correlated with an increase in weight and fat mass, regardless of gender and immunological status. Despite other studies [19, 22, 27] proposing low baseline CD4 cell count and high HIV viral load as risk factors for weight gain, the authors of this study found no statistically significant correlation amongst these parameters. This study is important in demonstrating the independent effect of ART on BMI, increasing both weight and, specifically, fat content. One of the major limitations of this study was the small sample size, making the findings difficult to apply to the general population.

The relationship between ART drug class and weight changes amongst newly initiated HIV positive patients was assessed in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [27]. A total of 22 972 participants were included in the study, 49% of whom were initiated on a NNRTI, 31% on PI and 20% on InSTI-based regimens

respectively. Participants who were started on an InSTI-based regimen gained the most weight over the 5 year study period. DTG demonstrated the most significant weight gain (7.2kg) compared with other drugs in the InSTI class. 32% of individuals who had normal baseline BMI became overweight following the initiation of an InSTI-based regimen. This transition was also seen in the PI group (29%) and NNRTI group (25%), albeit to lesser degrees, similar to other studies [28, 29].

The ADVANCE trial [28], conducted in Johannesburg, South Africa, randomized 1053 participants into three different treatment groups to compare efficacy of ART regimens (measured by HIV viral load suppression by week 48). Treatment groups consisted of a combination of drugs; DTG, TAF and FTC or DTG, TDF and FTC or EFV, TDF and FTC (standard care group). Significant weight gain by week 48 was found in all groups, and the mean gain in fat composition of both trunk and limbs was higher in females than males across all ART groups. Two of the three groups were given regimens containing DTG, and both these groups had higher weight gain, in keeping with findings from previous studies [22, 27, 29]. The group taking the TAF, FTC, DTG regimen experienced a 6 kilogram (kg) increase in weight and there was a 14% increase in new obesity (from baseline to week 48). The group receiving the TDF, FTC, DTG regimen experienced a 3kg increase in weight and 7% new obesity. The group without DTG (standard care group); TDF, FTC, EFV, gained the least amount of weight (1kg, 6% new obesity). Both the NA-ACCORD [27] and ADVANCE study [28] had limitations. Both studies included pregnant women, which likely influenced weight gain, and other lifestyle factors that may have caused weight gain were not controlled.

1.5 Obesity and primary headache disorders

1.5.1 Epidemiology and Classification of Obesity

68% of adult women and 31% of adult men were estimated to be overweight or obese in South Africa in 2017 [53]. Total body obesity is defined by the WHO as BMI greater than or equal to 30 kg/m^2 in the adult population [54]. Obesity can further be classified according to severity. Class 1 obesity pertains to a BMI of 30 to 34.9 kg/m^2, class 2 obesity pertains to BMI of 35 to 39.9 kg/m^2 and class 3 (extreme or severe obesity) refers to BMI greater than or equal to 40 kg/m^2 [54].

1.5.2 Pathophysiology of obesity and primary headaches

There are many hypotheses regarding the pathophysiology thought to underlie the association between obesity and primary headaches, which are shared by both HIV positive and negative individuals. These include systemic inflammation, endothelial and adipocytokine dysfunction, and hormonal dysregulation [5].

1.5.3 Orexin

The central regulation of feeding revolves around the hypothalamus. Orexigenic and melanin concentrating hormone are neuropeptides. These are produced in the lateral hypothalamus, and increase food intake. Orexin A and B have also been found to exhibit analgesic properties. Increased levels of Orexin A have been found in the cerebrospinal fluid of patients with chronic daily headaches and migraine. The possibility exists that there is a relationship between resistance to the analgesic properties of Orexin and headaches. Increased levels of Orexin A have been described amongst individuals with more frequent and more severe headaches. This may further reduce satiety and lead to weight gain [5]. The hypothalamus has also been implicated in the prodromal phase of migraineurs, accounting for the food cravings and

changes in mood and sleep cycle. Functional imaging supports this proposition, demonstrating activation of the hypothalamus during acute migraine attacks [5].

1.5.4 Serotonin

Serotonin is a neurotransmitter that increases in response to eating, thereby signaling satiety, whilst decreased levels conversely promote feeding [5]. Low levels of serotonin may result in increased hunger that leads to weight gain and generation of headache, particularly migraine. Interictal levels of serotonin have been demonstrably lower in migraineurs, suggesting that low serotonin levels may activate the trigemino-vascular complex and lead to the generation of migraine [33]. Notably, drugs that are included in the management of migraine, such as selective serotonin reuptake inhibitors (SSRI), aid in increasing circulating levels of serotonin, thus preventing migraine, whilst also promoting decreased hunger [5].

1.5.5 Adipocytokines

Adipocytokines is the term used to include inflammatory cytokines that are produced in the state of obesity, as well as adipokines that are hormones secreted by adipose tissue that facilitate the metabolic interaction between adipose tissue and other organs [55].

Leptin is an adipokine that exhibits major satiating effects. It is inhibited by testosterone and conversely increased by ovarian sex steroids, thus there are higher levels in females than males. Obese individuals have higher circulating levels of leptin, which may suggest resistance. There are conflicting theories regarding leptin levels in migraineurs. Episodic migraine sufferers have higher levels of leptin, which may be due to the involvement of leptin in the acute inflammatory phase [5]. High levels of leptin have also been observed specifically in women who have migraine with aura, which may be due to the higher state of inflammation related to aura [56].

However, in chronic migraine sufferers, leptin levels have been shown to be lower, which may be due to long-term exposure to the inflammatory state [5].

Adipose tissue expansion has been associated with an increased inflammatory response, including a chronic low-grade state of inflammation [55]. Tumor Necrosis Factor (TNF)- alpha has been associated with insulin resistance and inhibition of adipocyte differentiation. It has also been found to be increased in patients who suffer from episodic migraines, along with other inflammatory markers such as Interleukin-6 and Interleukin-10. This suggests overlap between the inflammatory pathogenesis of obesity and headaches [5].

There is evidence to suggest a biochemical relationship between primary headaches, specifically migraine, and obesity, which appears to be multi-faceted [1, 5]. The direction of this relationship regarding whether obesity is an inciting or exacerbating factor, or a consequence of the pathophysiology underlying headaches, is yet to be determined.
Congruent with these proposed underlying mechanisms, studies have consistently demonstrated a positive correlation between primary headaches and increased BMI.

Keith et al [2] analyzed 11 datasets to determine the relationship between increased BMI and headaches. They found an association between the prevalence of headache and increasing BMI in women. Class 1 obesity (BMI greater than 30 kg/m^2) was associated with a 35% increased risk of headache, whereas class 3 obesity (BMI greater than 40 kg/m^2) conferred an 80% risk. This risk occurred amongst all types of primary headache and was not found to be specific for migraine. This could be due to the above-mentioned pathophysiology, particularly the adipocytokine effects of leptin in women [5]. Despite the large sample size, a major limitation of

this study was that it included data from women only, therefore would be difficult to apply these findings to the general population.

The risk of chronicity of headaches with increased BMI was demonstrated in a longitudinal study by Scher et al [3]. Telephonic interviews were conducted, involving 1192 adults with headaches. Data from the initial interview showed that obesity was 34% more common amongst participants who had chronic headaches. Participants who had episodic headaches with obesity were five times more likely (OR=5.28) to have transitioned to chronic headaches than their non-obese counterparts at the follow up interview. Other factors found to increase risk of progression to chronic daily headaches included female gender, white race, and lower socioeconomic status. The authors concluded that obesity was a risk factor for the development of chronic headaches. One of the major limitations of this study included the telephonic nature of data collection. Height and weight were not measured using standardized methods, which may have influenced the accuracy of BMI.

In a population-based study in 2007, Bigal et al [4] found an association between increased BMI and headache. The frequency, severity, and level of disability related to headache were studied in patients who were assessed with migraine, probable migraine, and severe episodic tension type headache. Although the prevalence of migraine was not shown to have any relationship to BMI, the frequency of migraine increased with escalating classes of obesity. “Very frequent migraines” (10 to 14 headache days per month) were found in 7.4% of overweight participants, 8.2% of obese participants and 10.4% of severely obese participants, compared to 6.5% of individuals with normal BMI. Disability, based on the migraine disability assessment test (MIDAS), was found in 32% of individuals with normal BMI compared to 40.9% who had severe obesity. This study demonstrated the positive correlation between migraine severity,

frequency, and disability with increased BMI, but showed no statistical significance for other types of primary headaches. The shared metabolic dysregulation underlying both obesity and migraine pathophysiology may account for these findings [5, 55]. Despite the strength of the large sample size in this study, this study had several limitations. Self-reporting of data during telephonic interviews may have resulted in bias, influencing data and outcomes. Secondary causes of headaches, that may have accounted for worsening headache characteristics, were also not definitively ruled out.

In a cross-sectional study by Peterlin et al [6], the prevalence of self-reported migraines in subjects aged 20-55 years, with and without obesity, was evaluated. Measurements of obesity included both total body obesity (BMI) and abdominal obesity (measured using waist circumference, as defined by the WHO [57]). The prevalence of migraine was increased amongst both men and women with increased BMI, whilst the prevalence of migraine in individuals with abdominal obesity was only found to be increased amongst women. These findings demonstrate no significance between different measurements of obesity and may suggest systemic effects of obesity that intersect with the pathophysiology of migraine [6]. Shortcomings of this study included self-reporting of migraine (headache type was not verified) and not definitively excluding secondary causes of headache.

1.6 Conclusion

Primary headache disorders are highly prevalent amongst individuals with, and without, HIV [8-10, 14-16]. They may cause significant disability and pose great burden on social, economic, and medical well-being [8, 9]. Recent studies have demonstrated a relationship between primary

headaches, particularly migraine, and increased BMI, which may be due to shared pathophysiology [3-7]. With the advent of ART, and the marked immune reconstitution that accompanies it, HIV positive patients are increasingly experiencing metabolic changes that result in increased BMI [19-30]. This newly emerging state of artificially-induced obesity within this unique population provides a platform to investigate the relationship between primary headache disorders and increased BMI amongst HIV positive individuals on ART.

1.7 Objectives

To investigate the relationship between primary headache disorders and increased BMI in a group of HIV positive patients on ART. To describe associated headache characteristics with increasing classes of obesity.

1.8 Methods

1.8.1 Study design

Cross sectional, observational study investigating the relationship between primary headache disorders and increased BMI in HIV positive patients on ART.

1.8.2 Study setting

Patients will be recruited from the Neurology and HIV clinic at Charlotte Maxeke Academic Hospital (CMJAH) and Helen Joseph Hospital (HJH), situated in the city of Johannesburg, Gauteng province, South Africa.

1.8.3 Study population

Inclusion criteria

- Patients from CMJAH and HJH
- Age 18-60 years old
- HIV positive patients on ART
- Primary headache disorder
- Signed consent form

Exclusion criteria

- HIV positive patients who are not on ART
- Patients with known secondary causes of headaches
- Patients younger than 18 or older than 60 years of age
- Patients declining participation or unable to give consent
- Patients unable to stand unassisted for measurements
- Pregnancy

HIV positive patients with primary headache disorders will be offered participation to the study during their routine clinic visit. Consent will be sought from the patient after explaining the purpose of the study and the process. Clinical screening for red flag characteristics will be done to exclude secondary causes of headaches. These include the presence of meningism, focal neurological signs, changes in mental state and features suggestive of raised intra-cranial pressure, including papilloedema. Should the presence of a secondary cause for headache be concerning, further investigations will be performed to exclude a secondary cause (as per standard/best medical practice) before the patient is considered for participation.

Participants' demographic and clinical information will be collected on an interviewer-administered questionnaire (Appendix A), and patients will receive participant numbers to ensure anonymity and confidentiality. Using an amended version of the ICHD-3 criteria for primary headaches (Appendix B), details regarding headache type, frequency, and severity according to a numerical pain scale (Appendix C) will be documented. Body Mass Index will be calculated using the standardized formula: weight (kilograms) divided by height (meters) squared. The participant's weight and height will be measured without shoes, and down to one basic inner layer of clothing, using a SECA medical platform scale (measured in kilograms) and height measured with a stadiometer (measured in centimeters and converted to meters).

1.8.4 Study variables

The dependent variable is BMI, and specifically increased BMI. BMI will be categorized as "not increased BMI" and "increased BMI". "Not increased BMI" will include individuals with underweight (BMI less than 18.5 kg/m^2) and normal BMI (BMI 18.5-24.9 kg/m^2), whilst "increased BMI" will include individuals who are overweight (BMI 25-29.9 kg/m^2), mildly obese (class 1 obesity, BMI 30 to 34.9 kg/m^2), moderately obese (class 2 obesity, BMI 35 to 39.9 kg/m^2), and severely obese (class 3 obesity, BMI greater than or equal to 40 kg/m^2).

The independent variables will be headache characteristics, type of headache, severity and frequency of headache with increased BMI.

1.8.5 Duration

Data will be collected over a period of two and a half years.

1.8.6 Statistical analysis

1.8.6.1 Sampling method

A convenience method of sampling will be used.

1.8.7 Sample size

A minimum sample size of 100 participants will be needed to detect an effect at 5% level of significance and 80% statistical power, under the assumption that the relative risk of primary headache disorders in HIV positive patients is 15%, and at least 20% of patients on ART could be overweight or obese [20, 58].

1.8.8 Data collection and analysis

All data will be recorded on a standardized data sheet during the consultation (Appendix A). Data will be converted to a digital format which will then be used for statistical analysis. For the descriptive analysis, numerical variables will be summarized using means and standard deviations, or medians and interquartile ranges, based on the distribution of the values. Categorical variables will be described using tables of frequencies and percentages. Where necessary, graphs will be used for visualization of data. To investigate the correlation between increased BMI, primary headache, and its characteristics, a Chi-square test will be performed to assess the association with primary headache, where BMI is used as a categorical variable. 95% confidence intervals, and p-values will be generated and interpreted. P-values of less than 0.05 will be considered evidence of statistical significance. The goodness-of fit test will be used to assess how well the regression model fits the analyzed data. All statistical analyses will be done with the assistance of a statistician, using Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

1.9 Ethics

Ethical approval will be sought from the Human Research Ethics Committee. Ethical considerations include informed consent in the form of a typed document that participants may take home to read should they wish, as well as verbal discussion regarding consent during the time of consultation. Consultation for participation will take place in a private setting within the clinic. Should language barriers occur, appropriate translation through members of staff in a confidential manner will ensue. All data obtained will be confidential, and participants' identities shall remain anonymous for purposes of this study.

1.10 Funding

This study will be self-funded.

1.11 Timeline

This study will take place over the course of 2.5 years. A Gantt chart demonstrating the estimated timeline is illustrated below.

	Sept 2019	**Oct-Nov 2019**	**Jan 2020-February 2022**	**April 2022-May 2022**	**June 2022**
Protocol assessment					
Ethics application and approval					
Data collection					
Data analysis					

Manuscript report					

Gantt chart demonstrating estimated time line

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2 Manuscript

Introduction

Primary headache disorders are highly prevalent, and one of the leading causes of disability and socioeconomic strain worldwide [1-3]. They may be experienced across various demographics [4, 5] and with other co-morbidities, including Human immunodeficiency virus (HIV), in which they are the most commonly encountered headache type [6-8]. Recent literature has demonstrated a relationship between increased Body Mass Index (BMI) and primary headache disorders, although there is much to be determined regarding the direction and implications of this relationship [9-15]. To date, there are a paucity of studies regarding primary headache disorders in South Africa [16], and none which investigate their relationship with increased BMI.

South Africa carries a dual burden of HIV and obesity. With 7.2 million people estimated to be living with HIV in 2017, South Africa has the largest HIV pandemic in the world [17]. In 2016, 68% of adult women and 31% of adult men were estimated to be overweight and obese [18]. A surge in obesity has also been recognized amongst people living with HIV who use Antiretroviral therapy (ART), which may have similar implications as other obese states, such as effects on primary headaches [19, 20]. This newly emerging state of drug-induced obesity amongst people living with HIV provides us with a unique platform to investigate the relationship between primary headache disorders and increased BMI. This study describes the relationship between increased BMI and primary headaches in a group of HIV positive individuals on ART, and determines the effects of increasing BMI on headache characteristics.

Methods

Study design

This was a cross-sectional, observational study evaluating the relationship between primary headache disorders and increased BMI in a group of HIV positive patients on ART, and was conducted over 2.5 years (January 2020 to June 2022).

Study setting

Participants were recruited from the Neurology and HIV outpatient clinics at Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital in Johannesburg, South Africa.

Study sampling

A convenience sampling method was used. A minimum sample size of 100 participants was needed to detect an effect at 5% level of significance, and 80% statistical power, under the assumptions that the relative risk of primary headache disorders in HIV positive patients is 15%, and at least 20% of patients on ART could be overweighted or obese [20, 37].

Study methods

HIV positive patients on ART who experienced headaches were invited to participate during their routine clinic visit. Participants were required to fulfil inclusion criteria of having primary headaches and being between 18 to 60 years of age. Exclusion criteria consisted of confirmed secondary causes of headaches, or atypical clinical characteristics that warranted further investigation; fever, meningism, focal neurological deficit and features suggestive of raised intracranial pressure. Where there was concern for secondary cause of headache, investigations (as per standard/best medical practice) were performed to exclude alternative diagnoses. Pregnant women, and patients who were unable to stand unassisted for BMI measurements were also excluded. The details and purpose of the study were explained to each participant,

after which a consent form was signed. This study was conducted in private consultation rooms in the respective clinics. Information was collected in a confidential manner, using participant numbers to ensure anonymity. Demographic and clinical information were collected using an interviewer-administered questionnaire (Appendix A), which was then converted to a digital format for statistical analysis. Participants were interviewed using an amended version of the ICHD-3 criteria for primary headaches (Appendix B). The participants' weight and height were measured as per standard practice using a SECA medical platform scale (measured in kilograms), and height measured with a stadiometer (measured in centimeters, converted to meters). Body Mass Index (BMI) was then calculated using the formula: weight (kilograms) divided by height (meters) squared.

Ethical considerations

Ethical approval was obtained from the Human Research Ethics Committee (Appendix D) Ethical considerations included informed consent, and an information sheet in the form of a formal typed document, that participants were allowed to take home to read, as well as a verbal discussion regarding consent during the time of consultation. This study took place within the private consultation rooms of the outpatient clinics during routine visits. All data obtained remains confidential, and participants' identities remain anonymous for purposes of this study. Where language barriers occurred, appropriate translation was facilitated through members of staff in a confidential manner. This study did not involve any invasive medical procedures.

Statistical analysis

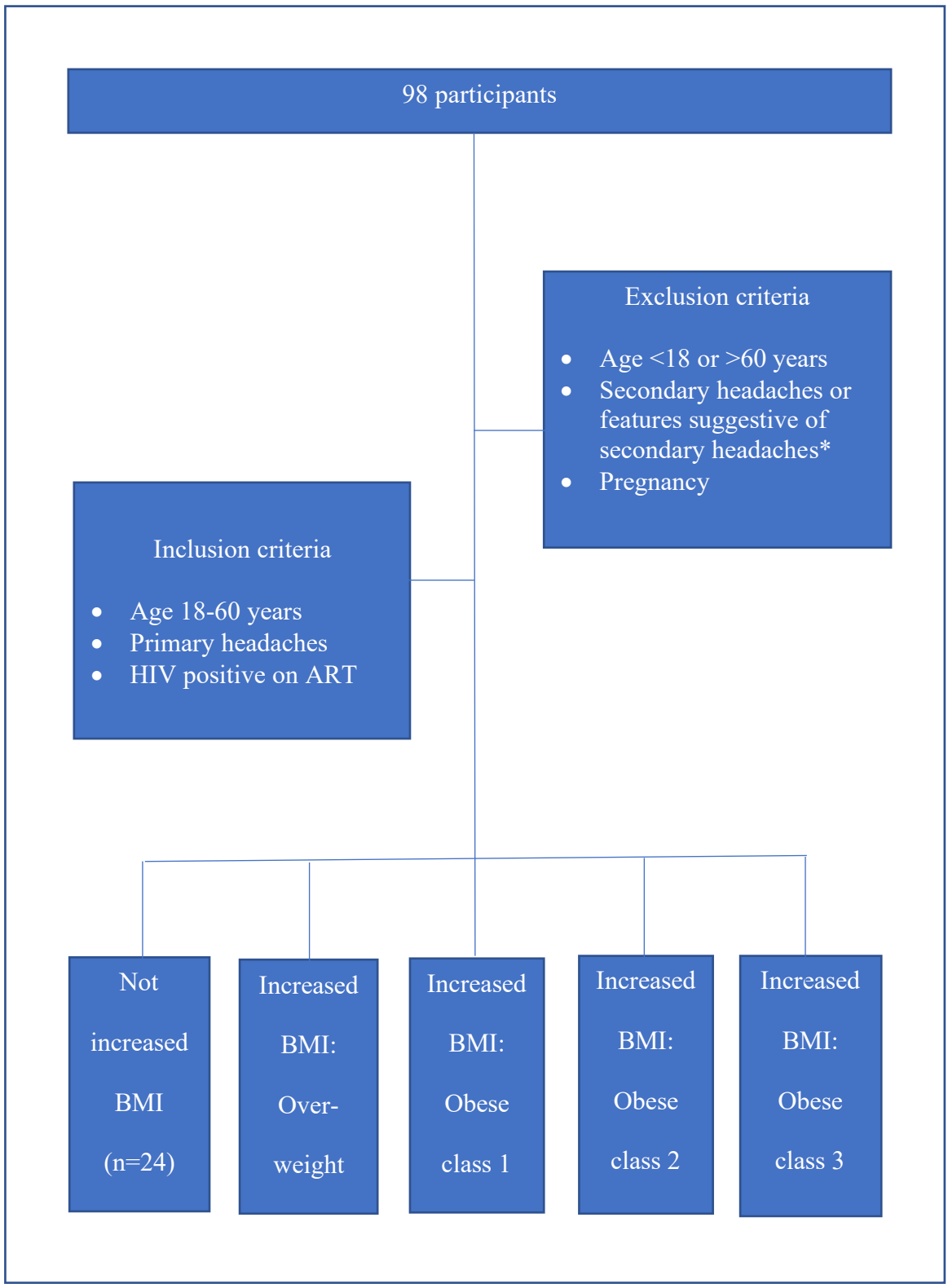
Data was recorded on a standardized data sheet during consultation and secured in an electronic file. Statistical analysis was performed using Stata 16 (StataCorp. 2019. Stata Statistical

Software: Release 16. College Station, TX: StataCorp LLC). For the descriptive analysis, numerical variables were summarized using medians and interquartile ranges based on the distribution of the values, while categorical variables were described using tables of frequencies and percentages. The BMI was calculated according to the following formula: weight (kilograms) divided by height (meters) squared. We defined 5 categories based on BMI: Not increased BMI – included underweight and normal BMI (less than 18.5-24.9 kg/m^2), and increased BMI groups; overweight (25-29.9 kg/m^2), obese class 1 (30-34.9 kg/m^2), obese class 2 (35-39.9 kg/m^2), and obese class 3 (greater than 40 kg/m^2). To investigate the independent association between BMI and primary headache (severity, frequency and type of primary headache), Fischer's exact test was performed. P-value of less than 0.05 was considered evidence for statistical significance. BMI was categorised into "Increased BMI" and "Not increased BMI" (not increased BMI included overweight and all obese classes) for the regression analysis. Logistic regression analysis was performed to determine the factors associated with increased BMI. The minimum sample size for a meaningful result was 100.

Results

A total of ninety eight (98) participants were included in the study. All participants were HIV positive on ART, and experienced primary headache disorders. A flow diagram illustrating the participation data is included (Figure 1).

Figure 1: Study participant flow diagram



*Clinical features included focal neurological deficit, changes in level of consciousness, meningism, signs and symptoms of raised intracranial pressure, including papilloedema. Severity, frequency, and type of primary headache were assessed in each BMI group.

Table 1 shows demographic and clinical information of the participants. The median age was 43 years (interquartile range 38-47), and the majority of participants were between 40 to 49 years old (n=59, 60.2%), and of female gender (n=73, 74.5%). Most participants used a fixed dose combination (FDC) ART regimen (n=78, 79.6%). Twenty one (21.4%) participants used a Dolutegravir (DTG)-containing regimen. The median CD4 cell count was 493.5 cells/mm^3 (interquartile range 285-701), with the majority of participants having a CD4 cell count greater than 200 cells/mm^3 (n=72, 73.5%). Most participants were virologically suppressed with HIV viral load less than 50 copies/mL (n=69, 70.4%). Fourteen (14.3%) participants had unknown immunological and virological data. The majority of participants had an increased BMI (n=74, 75.5%) with a median BMI of 29.8 kg/m^2 (interquartile range 25.1-33.7). The category of "increased BMI" referred to overweight (n=26, 26.5%), obese class 1 (n=28, 28.6%), obese class 2 (n=9, 9.2%) and obese class 3 (n=11, 11.2%).

Table 1: Demographic characteristics, n=98

Characteristic	**N=98**	**%**
Age (years), median (IQR*)	43 (38-47)	
Age group (years)		
19-29 years	10	10.2
30-39 years	18	18.4
40-49 years	59	60.2
>-50 years	11	11.2
Gender		
Female	73	74.5
Male	25	25.5

ART Regimen		
Unknown	13	13.3
FDC (non-DTG)	57	58.2
FDC (DTG)	21	21.4
Other	7	7.1
CD4 cell count (cells/mm^3), median (IQR*)	493.5 (285-701)	
CD4 cell count (cells/mm^3)		
Less than 200	12	12.2
Greater than 200	72	73.5
Unknown	14	14.3
HIV Viral load (copies/mL)		
Less than 50	69	70.4
Greater than 50	15	15.3
Unknown	14	14.3
BMI (kg/m^2), median (IQR*)	29.8 (25.1-33.7)	
BMI groups		
Not increased	24	24.5
Increased: overweight	26	26.5
Increased: obese class 1	28	28.6
Increased: obese class 2	9	9.2
Increased: obese class 3	11	11.2

*IQR: Interquartile range

The relationship between the severity of headache pain and BMI is presented in Table 2. Severity was graded numerically (out of a total score of 10) on the utilized pain scale; mild (0-

3), moderate (4-6) and severe (7-10). Severe pain was reported by 41 (41.8%) participants across all BMI groups, with most of these participants being overweight (n=11, 26.8%) and obese (class 1) (n=11, 26.8%). Two participants elected not to comment on severity of pain. There was no statistical significance between severity of headache and increased BMI.

Table 2 Association between BMI and headache severity, n=98

Severity	**Mild**	**Moderate**	**Severe**	**Unknown**	**P-value**
BMI group	n (%)	n (%)	n (%)	n (%)	0.903
Not increased	6 (40)	8 (20)	10 (24.4)	0	
Increased: overweight	3 (20)	11 (27.5)	11 (26.8)	1 (50)	
Increased: obese class 1	4 (26.7)	12 (30)	11 (26.8)	1 (50)	
Increased: obese class 2	2 (13.3)	3 (7.5)	4 (9.8)	0	
Increased: obese class 3	0	6 (15)	5 (12.2)	0	

The relationship between the frequency of headache and BMI is shown in Table 3. Frequency of headache was classified as “chronic” and “episodic” (more, or less, than 15 headache days per month for more than 3 months, respectively). Eleven (11.2%) participants were unsure of frequency, 28 (28.6%) participants reported chronic headaches, and 59 (60.2%) participants reported episodic headaches. Twenty one (75%) participants who reported chronic headaches had increased BMI, with the majority of participants having class 1 obesity (n=9, 32.1%). Forty four (74.6%) participants who had episodic headaches had increased BMI, with most of these participants also having class 1 obesity (n=17, 28.8%). There was no statistical significance between frequency of headache and increased BMI (p-value 0.362).

Table 3: Association between BMI and headache frequency, n=98

Frequency	Chronic	Episodic	Unknown	P-value
BMI group	n (%)	n (%)	n (%)	0.680
Not increased	7 (25)	15 (25.4)	2 (18.2)	
Increased: overweight	6 (21.4)	16 (27.1)	4 (36.4)	
Increased: obese class 1	9 (32.1)	17 (28.8)	2 (18.2)	
Increased: obese class 2	1 (3.6)	7 (11.9)	1 (9.1)	
Increased: obese class 3	5 (17.9)	4 (6.8)	2 (18.2)	

The relationship between type of primary headache and BMI is presented in Table 4. Migraine was the most common headache disorder overall (n=51, 52%). Tension type headache was found in 46 (46.9%) participants, and 1 (1%) participant had features suggestive of trigeminal autonomic cephalalgia. Thirty six (78.2%) participants with tension type headache had increased BMI, with the majority of participants being overweight (n=13, 28.3%). Thirty seven (72.5%) participants with migraine had increased BMI, the majority of whom had class 1 obesity (n=16, 31.4%). There was no statistical significance between the type of primary headache and BMI group (p-value 0.476).

Table 4: Association between BMI and headache type

Headache type	TTH	Migraine	Others	P value
BMI group	n (%)	n (%)	n (%)	0.476
Not increased	10 (21.7)	14 (27.4)	0	
Increased: overweight	13 (28.3)	13 (25.5)	0	
Increased: obese class 1	11 (23.9)	16 (31.4)	1 (100)	
Increased: obese class 2	7 (15.2)	2 (3.9)	0	
Increased: obese class 3	5 (10.9)	6 (11.8)	0	

A multivariate analysis of factors associated with increased BMI was performed and is presented in Table 5. Participants with tension type headache were more likely to have increased BMI (all categories) when compared with those who had migraine, however this was not statistically significant (OR 2.47, 95% CI, 0.25-24.88, p-value 0.44). There was statistical significance between gender and BMI (p-value <0.02); the odds of increased BMI was 6.02 higher in females compared to males (OR 6.02, 95% CI, 1.32-26.21). There was no statistical significance amongst the other variables.

Table 5: Multivariate logistic regression of BMI and explanatory variables

Variables	Odds Ratio	[95% CI]	P-value
Gender			
Male	Ref		
Female	6.02	1.32-26.21	0.02

Age group (years)			
19-29	Ref		
30-39	0.98	0.05-20.40	0.98
40-49	0.47	0.03-8.18	0.61
>-50	1.00	-	-
HIV viral load (copies/mL)			
Less than 50	Ref		
Greater than 50	0.89	0.07-10.79	0.93
CD4 cell count (cells/mm^3)			
Less than 200	Ref		
Greater than 200	0.56	0.05-6.58	0.64
Headache Type			
Migraine	Ref		
TTH	2.47	0.25-24.88	0.44
Severity			
Mild pain	Ref		
Moderate pain	7.73	0.84-70.98	0.07
Severe pain	4.71	0.49-45.52	0.18
Frequency			
Chronic	Ref		
Episodic	1.60	0.19-13.83	0.67
Unknown	0.99	0.11-8.92	0.99

Discussion

This study describes the relationship between primary headache disorders and increased BMI in a group of HIV positive individuals on ART, and is, to the author's knowledge, the first of its kind.

A total of ninety-eight (98) participants were included in this cross-sectional analysis. All participants were HIV positive on ART and had primary headaches. The majority of participants were female (n=73, 74.5%). This female predominance is likely due to the increased prevalence of primary headache disorders in females, particularly in migraine [2-5], which was the most common type of headache disorder in our study (n=51, 52%). This female predominance may also be due to the inherent nature of this study population, as there is a disproportionately higher prevalence of HIV infection amongst women [17]. The median age was 43 years old, with the majority of patients in the 40 to 49 year age group (n=59, 60.2%). Eleven (11.2%) participants were between the age of 50 to 59 years old, 4 of whom experienced headaches for at least 10 years prior to participation in the study. This is in keeping with literature acknowledging that primary headaches are most prevalent within the reproductive years, but commonly continue into older age groups [4, 5, 21].

All participants were on ART, most of whom used a fixed dose combination (FDC) drug (n=78, 79.6%), with 21 (21.4%) participants using a DTG - containing regimen. The median CD4 cell count was 493.5 cells/mm^3, with the majority of participants having a CD4 cell count greater than 200 cells/mm^3 (n=72, 73.5%). Most participants were virologically suppressed with HIV viral load less than 50 copies/mL (n=69, 70.4%). Fourteen participants (14.3%) had unknown immunological and virological data. Widespread national access, and progression in ART programs, have resulted in improved immunity amongst people living with HIV [22], and likely

account for these findings within our study population. Only 21 participants used a DTG-containing regimen, which is likely owing to the recent introduction of this drug class into first line therapy in South Africa [32]. Numerous studies [19, 20, 23-31] have demonstrated the metabolic effects of ART that lead to weight gain, particularly with the InSTI class of drugs. Studies [28, 25, 26] have also suggested that lower baseline CD4 cell count, and higher HIV viral load, may be associated with increased weight gain following ART initiation. In our cohort, baseline immunological, virological, and BMI status were unavailable, thus, the effects of ART on these parameters over time were unable to be assessed. The possibility exists that improvements in immunity, and subsequently escalation in BMI, following the initiation of ART, may have had deleterious effects on participants' headache. We did not control for other factors that may contribute to weight gain, such as lifestyle factors. Studies [25-27] have, however, suggested that the effects of ART on weight gain may be independent, despite the exact pathophysiology being largely unknown, and likely complex.

Previous studies [9, 12, 13] suggested a positive correlation between increased BMI and headache severity and frequency, likely due to overlapping pathophysiology. Scher et al [13] and Bigal et al [12] demonstrated a positive correlation between chronicity of headaches and increased BMI. Bigal et al [12] further noted a positive relationship between increasing classes of obesity and the frequency of migraine, although this was not significant for other headache types. Bigal et al [12] also described a positive relationship between severity, level of disability caused by migraine, and increased BMI. These findings were only seen amongst individuals with migraine and were not significant for other headache types. Our study did not demonstrate any statistical significance between severity, or frequency, of headache and BMI (p-value 0.903 and 0.362, respectively). This may be due to the small sample size compared to other studies.

The definitive distinction between migraine and tension type headache may be challenging, due to overlapping clinical features [7, 35]. Patients with primary headaches may also experience more than one type of primary headache, particularly as frequency and severity escalate [4, 35]. The cause for commonality of features may be multifactorial. Studies [4] have suggested an overlap in pathophysiological mechanisms, particularly those that cause worsening of severity, and frequency, in tension type headache, which may result in tension type headache presenting with features similar to those of migraine. Other studies [7, 8] have also noted intersecting features between primary headaches. Gnonlonfoun et al [8] proposed that ART may result in inhibition of neurotransmitters that are involved in migraine pathogenesis, and the possibility exists that primary headaches in this population may present with less distinctive features, similar to those seen in tension type headache.

The shared pathophysiology, and association, between primary headache disorders and increased BMI, has been most widely recognised in migraine, however limited data exists with regard to tension type headaches [36]. In our study, migraine was the most common type of primary headache (n=51, 52%), followed by tension type headache (n=46, 46.9%) and trigeminal autonomic cephalalgia (n=1, 1%). Thirty six (78.2%) participants with tension type headache had increased BMI, with the majority of participants being overweight (n=13, 28.3%). Thirty seven (72.5%) participants with migraine had increased BMI, with the majority of participants having class 1 obesity (n=16, 31.4%). Participants with tension type headache were more likely to have an increased BMI when compared to participants with migraine, although this was not found to be statistically significant (OR 2.47, 95% CI, 0.25-24.88, p-value 0.44). We found no statistical significance between headache type and BMI, which may be due to the small sample size. The possibility exists that increasing frequency and severity of tension type headache may share phenotypical characteristics similar to migraine due to

overlapping pathophysiology, thus having a similar relationship between migraine and increased BMI.

The majority of participants in our study had increased BMI (n=74, 75.5%), with a median BMI of 29.8 kg/m^2, corresponding to being overweight. Twenty six (26.5%) participants were overweight, whilst the majority of participants who were obese had class 1 obesity (n=28, 28.6%). The odds of increased BMI in females was found to be statistically significant (p-value <0.02, OR 6.02) when compared to males. This may be accounted for by our unique study population, as both HIV and primary headache disorders are most prevalent amongst females [3, 17]. Keith et al [33] found the prevalence of headache disorders in a group of women to be higher in those with increased BMI, and for this risk to escalate with increasing classes of obesity, which may be due to the effects of leptin on obesity in women [9]. Peterlin et al [10] similarly found a higher prevalence of migraine with increased BMI, as well as abdominal obesity, in both genders of the reproductive age group. The pathophysiology of this relationship between obesity and primary headaches is likely multi-factorial, yet is still largely unknown. There is a complex biochemical interplay amongst neurotransmitters that regulate appetite, and mediate pain, and the metabolic and inflammatory effects of adipose tissue [9, 10, 25, 26, 34]. We found a similarly higher prevalence of increased BMI within our study population, however this was not statistically significant, likely owing to the small sample size when compared to other studies. The increased BMI seen in this study population may be due to the effects of ART, as mentioned in other studies [19-31], however it is not possible to confirm this as baseline BMI prior to ART initiation was not available. We were also unable to exclude other causes as we did not control for other lifestyle factors that may contribute to weight gain.

Conclusion

There are a paucity of studies demonstrating the burden of primary headache disorders in South Africa, and none which describe the relationship between increased BMI and primary headaches. Despite most participants in this study having increased BMI, we found no statistical significance between the prevalence, severity, frequency or type of primary headache, and increased BMI, likely due to the small sample size.

We conclude that there is no relationship between primary headache disorders and increased BMI. Further studies that encompass larger cohorts are required to confirm these findings, to evaluate the relationship between increased BMI and primary headache disorders, and potentially guide future management.

Limitations

Our study had several limitations. A single interviewer (neurology registrar) recruited, interviewed, and assessed all participants, which may have resulted in observer bias. Use of a second interviewer in future studies may alleviate this issue.

Primary headaches and BMI are dynamic and can change with time. The cross-sectional nature of this study did not allow for investigation into this aspect of the relationship. Future studies of a prospective, longitudinal nature may be beneficial in further evaluating this relationship.

The small sample size of our study did not achieve statistical significance, and larger studies are required to corroborate our findings.

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3 Appendices

Appendix A: Interviewer-administered Questionnaire

Participant number	
Age	
Gender	
Race	
HIV/ART characteristics	
Regimen of ART&class of drugs	
Year/month of initiation	
Time of onset of headache after ART initiation	
Obesity characteristics	
Weight (kg)	
Height (m)	
BMI (kg/m^2)	
Headache characteristics	
Type of headache	
Atypical features (if applicable)	
Severity (Numerical pain scale)	

Appendix B: Criteria for Migraine and Tension type headache (adapted from ICHD-3)

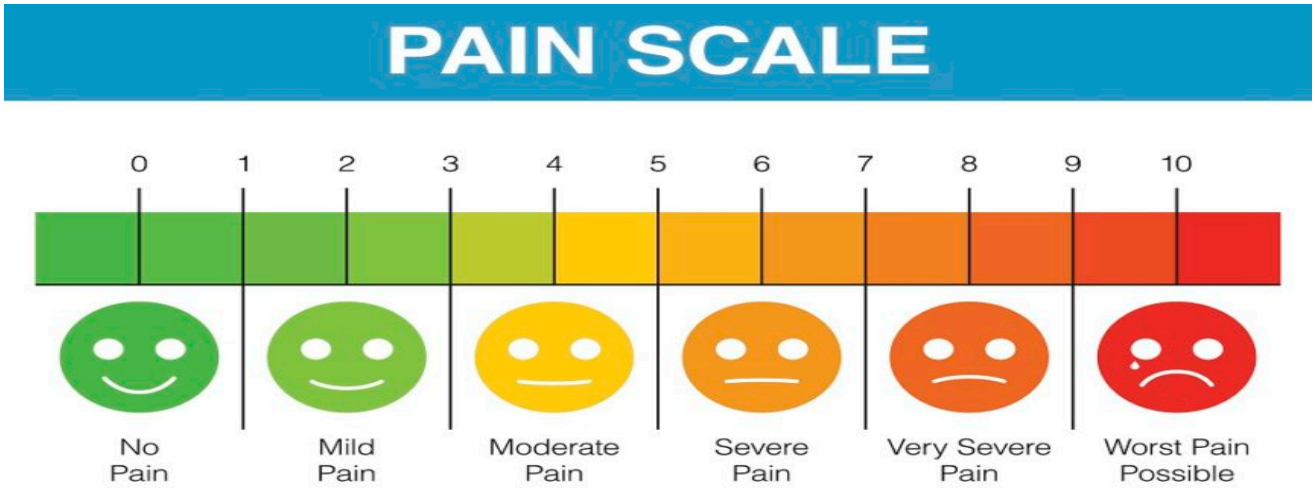
Migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1) unilateral location
    2) pulsating quality
    3) moderate or severe pain intensity
    4) aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
D. During headache at least one of the following:
    1) nausea and/or vomiting
    2) photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Tension-type headaches

A. Headaches Lasting from 30 minutes to 7 days
B. At least two of the following four characteristics:
    1) bilateral location
    2) pressing or tightening (non-pulsating) quality
    3) mild or moderate intensity
    4) not aggravated by routine physical activity such as walking or climbing stairs
C. Both of the following:
    1) no nausea or vomiting
    2) no more than one of photophobia or phonophobia
D. Not better accounted for by another ICHD-3 diagnosis.

Appendix C: Numerical Pain Scale [38]



Appendix D: Ethics Approval Certificate

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M191057

NAME: (Principal Investigator)	Dr A Ganesh
DEPARTMENT:	School of Clinical Medicine Department of Neurosciences Division of Neurology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The relationship between increased Body Mass Index and primary headache disorders in a group of antiretroviral therapy induced overweight and obese patients
DATE CONSIDERED:	2019/10/25
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Professor G Modi
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical
DATE OF APPROVAL:	2020/01/06

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

Appendix E: Turnitin Plagiarism Report

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Submission ID	1984555917
Submission Date	19-Dec-2022 06:19PM (UTC+0200)
Submission Count	1
File Name	Final_manuscript_19_Dec_2022.d...
File Extension	docx
File Size	1.4M
Character Count	85136
Word Count	14731
Page Count	73

Final manuscript 19 Dec 2022.docx.pdf
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The relationship between increased Body Mass Index and primary headache disorders in a group of Antiretroviral therapy induced overweight and obese patients

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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

Johannesburg 2022