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Research Submission

Headache Among Patients With HIV Disease: Prevalence, Characteristics, and Associations

Kale E. Kirkland, PhD; Karl Kirkland, PhD; W. J. Many Jr, MD; Todd A. Smitherman, PhD

Background.—Headache is one of the most common medical complaints reported by individuals suffering from human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), but limited and conflicting data exist regarding their prevalence, prototypical characteristics, and relationship to HIV disease variables in the current era of highly active antiretroviral therapy (HAART).

Objectives.—The aims of the present cross-sectional study were to characterize headache symptoms among patients with HIV/AIDS and to assess relations between headache and HIV/AIDS disease variables.

Methods.—Two hundred HIV/AIDS patients (49% female; mean age = 43.22 ± 12.30 years; 74% African American) from an internal medicine clinic and an AIDS outreach clinic were administered a structured headache diagnostic interview to assess headache characteristics and features consistent with International Classification of Headache Disorders (ICHD)-II diagnostic semiologies. They also completed 2 measures of headache-related disability. Prescribed medications, most recent cluster of differentiation (CD4) cell count, date of HIV diagnosis, possible causes of secondary headache, and other relevant medical history were obtained via review of patient medical records.

Results.—One hundred seven patients (53.5%) reported headache symptoms, the large majority of which were consistent with characteristics of primary headache disorders after excluding 4 cases attributable to secondary causes. Among those who met criteria for a primary headache disorder, 88 (85.44%) met criteria for migraine, most of which fulfilled ICHD-II appendix diagnostic criteria for chronic migraine. Fifteen patients (14.56%) met criteria for episodic or chronic tension-type headache. Severity of HIV (as indicated by CD4 cell counts), but not duration of HIV or number of prescribed antiretroviral medications, was strongly associated with headache severity, frequency, and disability and also distinguished migraine from TTH.

Conclusions.—Problematic headache is highly prevalent among patients with HIV/AIDS, most of which conform to the semiology of chronic migraine, although with some atypical features such as bilateral location and pressing/tightening quality. A low frequency of identifiable secondary causes is likely attributable to reduced frequency of opportunistic infections in the current era of HAART. Disease severity is strongly predictive of headache, highlighting the importance of physician attention to headache symptoms and of patient adherence to treatment.

Key words: headache, migraine, human immunodeficiency virus, acquired immune deficiency syndrome

From the Department of Psychology, University of Mississippi, Oxford, MS, USA (K.E. Kirkland and T.A. Smitherman); University of Alabama School of Medicine, UAB Health Center—Montgomery, Montgomery, AL, USA (K. Kirkland and W.J. Many Jr).

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Address all correspondence to T.A. Smitherman, Department of Psychology, University of Mississippi, 302D Peabody, University, MS 38677, USA, email: tasmithe@olemiss.edu

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Abbreviations: AIDS acquired immune deficiency syndrome, AZT azidothymidine, HAART highly active antiretroviral therapy, HIT-6 Headache Impact Test, HIV human immunodeficiency virus, MAO Montgomery AIDS Outreach, MIDAS Migraine Disability Assessment Questionnaire, MOH medication overuse headache, SDIH-R Structured Diagnostic Interview for Headache-Revised Brief Version, TTH tension-type headache, UAB University of Alabama School of Medicine

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Recent estimates indicate that over 1.1 million Americans are infected with human immunodeficiency virus (HIV), the precursor to acquired immune deficiency syndrome (AIDS),[1] a disease that disproportionately affects African Americans and Hispanic Americans. HIV has consistently been linked to frequent but varying headache patterns.[2,3] Headache is one of the most common medical complaints among HIV patients,[4-6] with 38-61% suffering from problematic headache.[2,3,7-9] The potential for headache susceptibility is increased in this population due to heightened risk of supervening opportunistic encephalic infections such as cryptococcal meningitis, cerebral toxoplasmosis, or neurosyphilis that occur as HIV progresses,[10-12] as well as from complications stemming from maintenance on complex drug regimens[13,14] and high rates of comorbid medical conditions.[15] Diagnosis of secondary headache conditions is often inhibited by high costs of confirmatory medical procedures such as lumbar punctures and magnetic resonance imaging and computerized tomography scans. In addition to these secondary causes of headache, it is recognized that headache in some HIV patients is a symptom of the initial infection itself, in which case symptoms include a dull, bilateral ache but lack consistent descriptions of duration, site, and response to treatment (International Classification of Headache Disorders, [ICHD]-II Code 9.3, "Headache Attributed to HIV/AIDS").[5,10,16]

Beyond these secondary causes of headache, primary headache disorders such as migraine and tension-type headache (TTH) commonly occur among HIV patients, and some studies suggest they are more common than secondary headache disorders among this population. Mirsattari and colleagues studied 115 HIV patients from 1990 to 1996 and observed that of those with headache (38%), primary headache disorders were twice as common as were headaches attributable to secondary causes associated with HIV.[3] Other researchers have also observed a high frequency of primary headache disorders among HIV patients, although conflicting findings exist regarding the relative prevalence of migraine vs TTH. For instance, some investigators have found that TTH is more common than migraine (46% vs 16%) and worsens as HIV progresses,[2] while others have observed that migrainous typologies greatly outnumber those of TTH or cluster headache (76% vs 14% vs 10%, respectively).[3]

Collectively, the few existing studies on headache typologies among HIV clinic patients portray a very mixed picture that highlights considerable variability of headache symptomatology. Prior studies on headache and HIV disease occurred almost exclusively before the widespread use of antiretroviral (ARV) combinations. Undoubtedly, the most notable advance in HIV treatment in the last 15 years is the advent of highly active ARV therapy (HAART), which was developed in the mid-1990s but not widely promulgated until the early to mid-2000s. HAART is an aggressive treatment strategy intended to suppress viral replication and slow disease progression that typically involves combinations of multiple ARVs, most commonly 2 nucleoside/nucleotide reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor or protease inhibitor. HAART has indeed revolutionized the treatment and prognosis of HIV disease, delaying the progression to AIDS and reducing transmission, mortality, and rates of opportunistic infections.[17] However, data are lacking regarding the prevalence and diagnostic characteristics of headache among HIV patients in the current HAART era.

The present study endeavored to identify headache prevalence and semiologies of clinic patients with HIV/AIDS and to assess relations between headache

(frequency, severity, disability) and HIV disease variables (CD4 count, duration of disease, concurrent ARVs) in order to foster greater clinical recognition of headache characteristics and treatment options among HIV patients. One goal was thus simply to describe the modal features and diagnostic semiologies based on reported headache symptoms. A second goal was to identify HIV disease variables predictive of headache characteristics and disability. Regarding associations between disease variables, we hypothesized that higher headache frequency, severity, and disability would be associated with lower CD4 counts (greater disease severity) and longer duration of HIV.

METHODS

Study Sites and Participants.—Participants were 200 adults patients diagnosed with HIV/AIDS who attended 1 of 2 outpatient medical clinics in Montgomery, AL, between December 2009 and June 2010. Patients participated as they presented for routine medical evaluations for purposes of monitoring their HIV/AIDS status at either the University of Alabama School of Medicine's (UAB) Montgomery Internal Medicine Residency Program or the Montgomery AIDS Outreach (MAO) Program. These sites were chosen because Montgomery County has the highest per capita rate of HIV infection in the state of Alabama[18] and because the population is composed mostly of African Americans (54.3%),[19] who are diagnosed with HIV at 7.6 times the rate of Caucasian Americans.[1] The UAB Internal Medicine Residency Program is a 3-year graduate medical training program accredited by the Accreditation Council for Graduate Medical Education and utilizes Baptist Medical Center–South in Montgomery as its primary teaching hospital. MAO is a private, nonprofit, community-based service organization that offers testing, patient education, medical treatment, mental health counseling, and prevention education for individuals with HIV.

Measures.—*Structured Diagnostic Interview for Headache-Revised, Brief Version (SDIH-R).*—The SDIH-R is a structured diagnostic interview designed to establish headache diagnoses according to the operational criteria of the ICHD-II.[10] The present study employed a revised version of the original SDIH[20] that accords with ICHD-II criteria and included supplemental questions about headache symptoms in relation to HIV infection. Headache diagnoses were made based on the semiology of the reported headache symptoms (after exclusion of documented secondary causes) and in accordance with strict adherence to ICHD-2 criteria and review of patient medical records. Chronic migraine was diagnosed in accordance with ICHD-II revised appendix criteria for chronic migraine.[21] HIV/AIDS or associated opportunistic infections were considered secondary causes of headache when patient medical records revealed the presence of CNS infections (eg, toxoplasmosis, meningitis, encephalitis) at the onset of or prior to headache symptoms, in which case headache secondary to infection was diagnosed. Headache frequency (days per month) and headache severity (0-10 pain ratings) were also obtained from the SDIH-R questions.

Measures of Migraine-Related Disability.—The Migraine Disability Assessment Questionnaire (MIDAS)[22] and Headache Impact Test (HIT-6)[23] were administered to assess headache-related disability. The MIDAS is a 5-item questionnaire that quantifies headache-related disability in terms of missed days of work or school, housework, and nonwork (family/leisure) activities over the past 3 months. It is widely used and has satisfactory internal consistency, high test–retest reliability, and good concurrent validity.[24] Scores range from 0 to 270, with scores of 11-20 indicative of moderate disability (Grade III) and scores of greater than 20 indicative of severe disability (Grade IV). The HIT-6 assesses headache-related disability using a Likert scale format instead of number of disabled days. It complements the MIDAS because it inquires also about pain severity, rest, and emotional upset related to headache. The HIT-6 has been found to be a reliable, valid, and internally consistent measure of headache impact in research on headache populations.[23,25] Scores range from 36 to 78, with greater scores indicating higher disability. Recent research has supported the joint use of the MIDAS and HIT-6 to inform statements about headache-related disability and suggested that they are differentially influenced by headache frequency (MIDAS) and headache severity (HIT-6).[26]

Patients also completed a demographic questionnaire inquiring about relevant demographic variables (gender, marital status, race, sexual orientation). Most recent CD4 cell counts, date of HIV diagnosis, and all prescribed medications and comorbid diagnoses were obtained via review of patient medical records. Number of prescribed ARVs was calculated by summing the number of prescribed agents, such that 1 pill containing multiple ARVs or classes of ARVs was tallied according to the number of discrete agents therein.

Procedure.—This study was approved by the institutional review boards at both the University of Mississippi and the UAB School of Medicine. Participants were recruited during their routine medical examinations at both aforementioned clinics over continuous weeks until complete data were obtained on 200 individuals. All presenting patients who had a diagnosis of HIV or AIDS and attended either clinic on a day that research personnel were present (2 days/week) were invited to participate. Prior to participation, they provided written informed consent; a total of 36 participants declined to participate. After informed consent was obtained, 1 of the 2 primary researchers (1st and 2nd authors) administered the SDIH-R orally in a private setting in order to assess headache symptoms. After completion of the SDIH, the participants completed the MIDAS and HIT-6; these measures were administered orally to approximately 120 patients who had a reading level below 7th grade as determined by prior administration of the Reading Scale of the Wide Range Achievement Test.[27] (Administration of this measure is part of standard clinic protocol due to documented low reading proficiencies in Central Alabama.[28,29])

Statistical Analyses.—A priori power analyses indicated that 150 participants were sufficient to support statistical analyses comparing headache vs non-headache patients for the present study, assuming a large effect size, power of 0.80, and alpha level of 0.05. Statistical analyses were conducted using PASW by SPSS version 17.0. Descriptive statistics was used to report the prevalence of headache symptoms among HIV patients. *t*-Tests for independent samples were used to compare headache and non-headache patients on demographic and HIV disease variables of interest; given the number of comparisons, a conservative Bonferroni correction was applied ($P = .05 / 10 = .005$). Pearson correlations were used to assess relations between CD4 counts, HIV duration, and headache severity/disability. A series of univariate analyses of variance (ANOVAs) was used to assess differences between various headache diagnoses (chronic migraine vs episodic migraine vs TTH) on clinical variables of interest; here again, a Bonferroni correction was applied to control for familywise error ($P = .05 / 6 = .008$). Tukey HSD post hoc tests were used to assess differences between specific groups for the significant ANOVAs. Effect sizes are reported in R^2 values (correlational analyses) and partial eta-squared (η^2) values (univariate ANOVAs).

RESULTS

Participant Characteristics.—Of the 200 patients, 101 were male, 98 were female, and 1 identified as transgendered. Their mean age was 43.22 (SD = 12.30), with ages ranging from 18 to 85. One hundred forty-eight (74.0%) were African American, 42 (21.0%) were Caucasian, 7 (3.5%) were Hispanic/Latino, and the remaining 3 were of other ethnicities. Regarding sexual orientation, 148 (74.0%) identified as heterosexual, 43 (21.5%) identified as homosexual, and 9 (4.5%) identified as bisexual. Level of education varied considerably among the sample: 32.5% had not completed high school and 10.0% had completed college.

Patients had been living with HIV for an average of 99.70 (SD = 69.29) months, with a range from 2 to 282 months. Characterization of HIV/AIDS disease severity was made according to the World Health Organization's (2007) classification for immunological staging based on most recent CD4 counts (number of CD4 cells per mm^3 of blood), which represents the primary laboratory indicator of immune system functioning among HIV patients.[17] Seventy-four participants (37.0%) were classified as not significant (CD4 counts of 500 or greater), 40 (20.0%) were classified as mild (CD4 of 350-499), 58 (29.0%) were classified as advanced (CD4 of 200-349), and 28 (14.0%) were classified as severe (CD4 below 200, meeting criteria for AIDS). The mean CD4 count of the entire sample

was 443.48 (SD = 261.58). Current ARV guidelines suggest CD4 counts be measured every 3-4 months in clinical settings; the mean time since last CD4 measurement for participants in this study was 43.52 (SD = 35.06) days. Nearly all patients in the sample (93.5%) were prescribed ARVs at the time of data collection, 88% of whom were prescribed 3 or more ARVs consistent with HAART regimens. Participants carried an average of 2.19 (SD = 1.48) comorbid diagnoses. Besides headache, other prominent medical diagnoses were hypertension (38%), major depressive disorder (20%), hepatitis (14%), hypercholesterolemia (9%), diabetes (8.5%), anxiety disorders (6%), asthma (6.5%), and bipolar disorder (4%).

Headache Prevalence, Features, and Semiologies.— *Headache Prevalence.*—Of the 200 HIV/AIDS participants, 107 (53.5%) reported having headaches. Notably, only 39% of patients had been diagnosed with a headache disorder previously. Four participants' headaches were attributable to secondary causes based on review of medical records and temporal relationship with headache symptoms (2 with toxoplasmosis, 1 with meningitis, and 1 with post-traumatic headache); these individuals were thus excluded from subsequent group comparisons. A minority of patients reporting non-pulsating pain described their typical headache as a bilateral ache (14/103; 13.59%) potentially suggestive of HIV as a secondary cause; however, these symptoms were not considered to be attributable to initial infection because the mean duration of HIV among these individuals was over 11 years (M = 137.07 months, SD = 69.77; Range = 32-251 months). Further, nearly all of these patients also reported severe pain intensity, aggravation by activity, and both phonophobia and photophobia. As such, the 103 patients reporting headache symptoms without documented secondary causes were assigned diagnoses consistent with semiologies of ICHD-II primary headache disorders.

Common features of the 103 primary headache semiologies were high frequency (M = 16.84 days/month, SD = 10.57), severe intensity (M = 7.83/10, SD = 1.60), bilateral pain distribution (65.05%), aggravation by activity (78.64%), photophobia (78.64%), and phonophobia (82.52%). Patients were evenly split between those reporting pulsating vs non-pulsating characteristics (51.46% vs 48.54%). Nausea (31.07%) and vomiting (13.59%) were relatively infrequent. Most patients (82.52%) reported that their headaches began subsequent to their HIV diagnosis; the majority of patients with preexisting headache (n = 18) reported that their headaches had not increased in frequency (11/18) or severity (14/18) after diagnosis with HIV. Consistent with high severity and frequency of headaches, the participants reported extremely severe headache-related disability on both the MIDAS (M = 132.13, SD = 91.52) and HIT-6 (M = 68.58, SD = 10.63).

Table 1.—Demographic Characteristics of the Primary Headache vs Non-Headache HIV Patients

Variable	Headache (n = 103)	Non-Headache (n = 93)
Mean CD4 count (SD)	326.70* (222.85)	585.51 (228.48)
Mean age (SD)	43.28 (11.65)	43.16 (13.26)
Gender (% female)	47.60	50.50
Race (% African American)	74.80	73.10
Marital status (% single)	66.00	59.10
Sexual orientation (% heterosexual)	66.00	82.80
Mean education (SD)	11.51 (1.67)	11.71 (2.01)
% Smoker	77.70*	5.40
Mean no. prescribed ARVs (SD)	3.22 (1.24)	3.42 (1.13)
Duration of HIV in months (SD)	103.07 (72.15)	95.84 (65.14)

*$P < .0001$.
ARV = antiretroviral; HIV = human immunodeficiency virus; SD = standard deviation.

Table 1 presents the demographic data between the primary headache and non-headache patients. The patients with and without headache did not differ on most demographic variables (age, years of education, gender, race), duration of HIV, or number of prescribed ARVs. Most notably, the patients with headache had significantly lower CD4 counts than did those without headache (M = 326.70 [222.85] vs 585.51 [228.48], $P < .0001$).

Primary Headache Diagnoses.—Two headache researchers (1st and 4th authors) reviewed each patient's SHID-R responses for concordance with

Table 2.—Headache Characteristics by Diagnosis, Excluding Chronic and Probable TTH (n = 100)

	EM Without Aura n (%)	EM With Aura n (%)	Probable Migraine n (%)	Chronic Migraine n (%)	Episodic TTH n (%)
Number diagnosed†	14 (13.59)	8 (7.77)	11 (10.68)	55 (53.40)	12 (11.65)
Symptom					
Pain location					
Frontal	10 (71.43)	3 (37.50)	7 (63.64)	39 (70.91)	4 (33.33)
Temporal	6 (42.86)	6 (75.00)	3 (27.27)	32 (58.18)	7 (58.33)
Supraorbital	1 (7.14)	1 (12.50)	3 (27.27)	15 (27.27)	1 (8.33)
Orbital	1 (7.14)	1 (12.50)	0 (0.00)	1 (1.82)	3 (25.00)
Occipital	0 (0.00)	1 (12.50)	0 (0.00)	2 (3.64)	2 (16.67)
Pain distribution					
Unilateral	6 (42.86)	3 (37.50)	8 (72.73)	14 (25.45)	3 (25.00)
Bilateral	8 (57.14)	5 (62.50)	3 (27.27)	41 (74.55)	9 (75.00)
Pain features					
Pulsating	6 (42.86)	7 (87.50)	3 (27.27)	33 (60.00)	2 (16.67)
Pressing/tightening	8 (57.14)	1 (12.50)	8 (72.73)	22 (40.00)	10 (83.33)
Severe pain (>5/10)	13 (92.86)	7 (87.50)	11 (100.00)	55 (100.00)	5 (41.67)
Aggravated by activity	13 (92.86)	8 (100.00)	6 (54.55)	52 (94.55)	2 (16.67)
Phonophobia	14 (100.00)	8 (100.00)	6 (54.55)	54 (98.18)	2 (16.67)
Photophobia	12 (85.71)	8 (100.00)	5 (45.45)	54 (98.18)	1 (8.33)
Nausea	6 (42.86)	5 (62.50)	4 (36.36)	17 (30.91)	0 (0.00)
Vomiting	2 (14.29)	4 (50.00)	2 (18.18)	6 (10.91)	0 (0.00)
Onset in relation to HIV					
Before HIV	2 (14.29)	1 (12.50)	3 (27.27)	3 (5.45)	9 (75.00)
After HIV	12 (85.71)	7 (87.50)	8 (72.73)	52 (94.55)	3 (25.00)

†Percentages within this row refer to percentages of the entire headache sample (n = 103). All other percentages are in reference to that particular diagnosis/column. Table excludes 1 patient with chronic TTH, 1 with probable chronic TTH, and 1 with probable episodic TTH.

EM = episodic migraine; HIV = human immunodeficiency virus; ICHD = International Classification of Headache Disorders; TTH = tension-type headache.

ICHD-II criteria to establish primary headache diagnoses: interrater agreement was 99.03% (102/103 primary headache diagnoses). The one discrepant diagnosis was resolved through discussion. Table 2 presents the primary headache semiologies and symptoms of the 100 patients without documented secondary causes (excluding 1 patient with chronic TTH, 1 with probable chronic TTH, and 1 with probable episodic TTH). The overwhelming majority (88/103; 85.44%) reported symptoms consistent with migrainous subforms, and over half the patients with headache (55/103; 53.40%) met ICHD-II appendix criteria for chronic migraine. Most patients with symptoms of chronic migraine reported taking headache-related medications multiple times per week but did not merit a diagnosis of medication overuse headache (MOH) because they denied that their headache developed or worsened during medication use (as is required for a diagnosis of MOH per ICHD-II revised appendix code 8.2, Criterion C[21]). Of those with episodic migraine, 36.36% (8/22) reported aura symptoms. In virtually all cases of both episodic and chronic migraine, severe pain intensity, aggravation by activity, and photophobia/phonophobia were present. However, many patients also reported 1 or 2 atypical migraine features such as bilateral pain distribution, non-pulsating pain quality, and absence of nausea and/or vomiting. Patients categorized as "probable migraine" met all requisite diagnostic criteria except either criterion B (4- to 72-hour pain duration) or criterion D (nausea/vomiting or photophobia and phonophobia) of the ICHD-II.

Table 3.—Correlations Between Headache and HIV Disease Variables (n = 103 With Primary Headache Diagnoses)

	CD4	HIV Duration	MIDAS	HIT-6	Severity	Frequency
CD4	–	0.08	–0.41**	–0.41**	–0.33*	–0.32*
HIV duration		–	–0.10	–0.04	–0.01	–0.15
MIDAS			–	0.80**	0.58**	0.79**
HIT-6				–	0.69**	0.75**
Severity					–	0.53**
Frequency						–

*P = .001; **P < .0001.
HIT-6 = Headache Impact Test; HIV = human immunodeficiency virus; MIDAS = Migraine Disability Assessment Questionnaire.

TTH semiologies constituted 14.56% (15/103) of headache diagnoses, the majority of which (11/15) were consistent with frequent episodic TTH (ICHD-II code 2.2). In contrast to the migrainous subforms, most patients with episodic TTH reported that their headaches predated their HIV diagnosis. One patient reported symptoms consistent with chronic TTH, 1 with probable chronic TTH, and 1 with probable episodic TTH. No patients reported symptoms consistent with cluster headache.

Relationships Between Headache and HIV Variables.—As an initial means of quantifying relationships between headache and HIV disease variables, Pearson correlations were conducted between relevant variables of interest among all patients with primary headache semiologies (see Table 3). Highly significant negative (inverse) relationships were found between CD4 counts and headache severity, headache frequency, and headache-related disability (MIDAS and HIT-6), indicating that as HIV progresses (as CD4 counts decline), headaches become more severe, more frequent, and more disabling. Specifically, CD4 count alone explained 16.4-17.0% of variance in MIDAS and HIT-6 scores and 10.1-10.7% in ratings of headache severity and frequency. Conversely, duration of HIV was not significantly associated with any headache variables.

Univariate ANOVAs were used to assess differences in clinical variables of interest among patients with chronic migraine, episodic migraine, and episodic TTH (including probable diagnoses). Groups were compared on CD4 counts, number of prescribed ARVs, number of comorbid diagnoses, duration of HIV, and the 2 measures of headache-related disability. Of these variables, only CD4 count ($F\ [2,98] = 6.97$, $P = .001$, partial $\eta^2 = 0.12$) and headache-related disability (MIDAS: $F\ [2,98] = 70.89$, $P < .001$, partial $\eta^2 = 0.56$; HIT-6: $F\ [2,98] = 61.91$, $P < .001$, partial $\eta^2 = 0.59$) differed significantly between groups. Tukey HSD post hoc analyses confirmed that patients with chronic migraine had significantly lower CD4 counts than those with episodic TTH ($P = .001$) and that episodic migraineurs had lower CD4 counts than those with episodic TTH that approached significance ($P = .05$), both indicative of an association between the severity of HIV and the type of headache experienced. Thirteen chronic migraineurs, 7 episodic migraineurs, and 2 patients with episodic frequent TTH had AIDS. Chronic migraine patients also had significantly higher headache-related disability than both episodic migraineurs and patients with episodic TTH on both the MIDAS and HIT-6 (all P values < .001); episodic migraineurs reported significantly higher headache-related disability on both measures than patients with episodic TTH (all P values ≤ .001). Table 4 presents group mean values on the HIV and headache-related disability variables.

DISCUSSION/CONCLUSIONS

Despite its high prevalence, headache remains understudied among patients with HIV disease, and few attempts have been made to characterize headache symptoms and typologies among these patients.

Table 4.—HIV Variables and Headache-Related Disability Among Primary Headache Subtypes (n = 101 With Chronic Migraine, Episodic Migraine, or Episodic TTH, Including Probable Headache Diagnoses)

	Chronic Migraine (n = 55)	Episodic Migraine (n = 33)	Episodic TTH (n = 13)
HIV variables			
CD4 count	272.27[a] (130.04)	349.06† (244.08)	512.77[b]† (365.52)
Number of prescribed ARVs	3.65 (0.87)	3.24 (1.37)	2.92 (1.38)
Number of comorbid diagnoses	3.00 (1.23)	2.52 (1.44)	2.08 (1.85)
Duration of HIV (months)	96.75 (63.27)	118.76 (82.27)	94.15 (82.79)
Headache-related disability			
MIDAS	191.05[a] (57.41)	81.82[b] (77.94)	7.77[c] (18.36)
HIT-6	74.87[a] (3.76)	65.12[b] (10.07)	50.54[c] (7.60)

†Mean CD4 count differences between the episodic migraine and episodic TTH groups approached significance ($P = .05$).
Means with different superscripts differ significantly at $P \leq .001$.
ARV = antiretroviral; HIT-6 = Headache Impact Test; HIV = human immunodeficiency virus; MIDAS = Migraine Disability Assessment Questionnaire; TTH = tension-type headache.

Existing studies have obtained divergent findings regarding the prevalence of primary and secondary headache disorders among this population, and virtually all of these studies occurred before the widespread proliferation of HAART. The main objectives of the present study were to characterize headache symptoms and typologies in the era of HAART and to assess relations between HIV disease variables and headache among patients with HIV disease.

Approximately half (53.5%) of the participants in the present study suffered from problematic headaches, confirming similarly high prevalence rates obtained from earlier studies (Evers et al, Mirsattari et al, Graham and Wippold, Singer et al).[2-4,9] However, documented secondary causes resulting from opportunistic encephalic infections were rare (2.80%). Endorsement of headache symptoms consistent with a dull, bilateral ache that might be directly attributable to the HIV infection itself was also uncommon and reported only among patients with longstanding disease; virtually all of these patients reported numerous other features that were diagnostically consistent with migraine.

Most previous studies reporting much higher rates of secondary headache causes among patients with HIV were conducted prior to the advent of HAART,[11,15] and thus, high rates of secondary causes were likely attributable to lack of adequate treatment. For instance, only 19% of patients in Lipton et al[11] were taking azidothymidine, which at that time had just received Food and Drug Administration approval as the first ARV medication for HIV disease in the United States. By comparison, in the present study, nearly all patients (88%) were on HAART combination regimens of 3 or more ARVs. Beyond the benefits of ARVs, patients in the earlier studies were obtained from headache inpatient clinics[15] and emergency room settings.[11] In the present study, all of the patients were recruited during routine HIV follow-up appointments and were thus not likely affected by potential selection bias or under acute distress. These differences in treatment regimens and patient samples likely account for observed differences in rates of identifiable secondary causes of headache. Our findings regarding secondary causes are strengthened by results from more recent studies that have also observed high frequencies of primary vs secondary headache disorders among patients with HIV disease.[2,3]

Regarding our attempt to characterize the "typical" headache pattern, in general, headaches among HIV patients were frequent and severe, aggravated by activity, and accompanied by photophobia and phonophobia. Concordantly, the large majority of primary headache semiologies were diagnostically consistent with migraine vs TTH. Most notable is the preponderance of patients who met ICHD-II revised

appendix criteria for chronic migraine, which at the time of the earlier studies was not a diagnostic entity. Despite the high prevalence of migraine, many patients meeting criteria reported 1 or 2 atypical features such as bilateral location or non-pulsating quality. These 2 characteristics have been reported with some consistency previously[2,10] and thus appear relatively common to headache presentations that occur among patients with HIV disease. Pain site and the presence of nausea and vomiting varied throughout the sample, perhaps as a function of the wide distribution of HIV severity.

Our findings that migraine (and particularly chronic migraine) is the most common form of primary headache among individuals with HIV is consistent with the results obtained by Mirsattari et al,[3] who likewise confirmed that the majority of HIV patients with primary headache show a migrainous typology (76% % vs 85% in the present study). They contrast with those of Evers and colleagues,[2] who instead found TTH semiologies more common than migraine. Methodological differences likely account for these discrepant results in that the present study includes a far greater proportion of patients on ARVs (93.5% vs 65%) and recruited patients during routine examinations only instead of those presenting specifically for other nonspecific complaints or opportunistic infections.

Significant relations were observed between CD4 counts and the presence of headache, the frequency and severity of headache, and the type of headache itself. Patients with more advanced disease were more likely to have headaches, more frequent, severe, and disabling headaches, and more migrainous vs TTH presentations. These relations were highly significant after controlling for multiple comparisons and corroborated by large effect sizes. Importantly, these differences were not attributable to differences in duration of HIV or number of prescribed ARVs. From this perspective, the progression of HIV as measured by CD4 counts is clearly of central importance in predicting headache symptoms. The unexpected lack of a relationship with HIV duration is likely a function of the current context of HIV disease care in which patients are now living with HIV years longer than prior to HAART.[17] Given that participants were involved in regular medical follow-ups specifically for HIV/AIDS and that nearly all were on HAART regimens, the present sample likely represents a profile of aggressive treatment that may not be reflective of individuals who do not receive regular medical care.

Nevertheless, these findings speak to the importance of regular monitoring of CD4 levels in clinical settings and indicate that physicians should be attentive to headache symptoms among patients with more advanced disease. Because compliance with HAART is critical to disease progression, emphasizing chronicity and adjustment over terminality may allow for improved patient education and medication compliance, in turn improving headache outcomes. Indeed, the most successful self-managing HIV patients are knowledgeable about HIV and its treatment, motivated to change behaviors to ensure treatment compliance, and communicate effectively with treatment providers and social support networks.[30,31] As was evidenced anecdotally in this study, many healthy participants knew their most recent CD4 count reading and understood that their overall health is greatly affected by the rise and fall of that number. Conversely, patients who reported frequent problematic headache often did not fit this profile as they exhibited a relatively poorer knowledge of the HIV disease process and the importance of HAART compliance through conversations with researchers. Although the present study did not investigate HAART compliance per se, the patient subgroupings and response styles are consistent with the notion that those HIV patients whose illness is well-controlled have much better HIV and headache outcomes than do their sicker counterparts.

Compared with prior studies on headache in HIV patients, this study is unique for several reasons. The patient sample was large and diverse both ethnically (79% non-Caucasian) and in terms of HIV disease severity, with a substantial proportion of patients in each category of HIV immunological staging. In contrast to earlier studies, diagnoses were made in strict accordance with the most recent ICHD-II[10] and revised appendix criteria.[21] To our knowledge, this is the first study to assess headache diagnoses using the most recent diagnostic criteria.

Perhaps most notably, because most of the few existing studies were conducted prior to the peak of HAART success, the present study likely affords a more accurate characterization of the current HIV/AIDS population in an era wherein almost all patients are on multiple ARV medications. The observation that patients in our study had a longer duration of HIV yet higher CD4 counts than patients in several previous studies attests indirectly to the success of HAART in reducing disease progression and opportunistic infections and indicates that the present HIV population and its headache features are considerably different from those in the pre-HAART studies (both in terms of the high prevalence of migrainous presentations and the low frequency of identified secondary causes).

One limitation of the present study lies in the extent to which these findings may generalize to Hispanic patients, who constituted only 3.5% of the study sample yet are also disproportionately affected by HIV disease in comparison with Caucasian Americans.[1] A limitation of the present study is the absence of neuroimaging procedures or lumbar punctures for definitive exclusion of secondary causes. As such, we cannot entirely exclude the possibility that some patients with primary headache semiologies might have had unidentified causes from HIV-related pathophysiology. These procedures were not employed primarily because patient physical and medical histories were not suggestive of secondary causes and in light of data indicating that neuroimaging procedures have low yield in typical primary headache presentations (Mirsattari et al), but also because the goal of this study was to define the characteristic symptoms of headache among these patients. Our conclusions about secondary causes were informed by review of patient medical histories, patient self-report of past or current encephalic infections, and the characteristics of reported headache symptoms. Patients were recruited in the context of routine and frequent follow-up appointments from their regular HIV provider; the information obtained from medical records was thus quite extensive, and many patients had histories of more extensive testing for HIV-related pathophysiology.

Though our findings confirm previous suggestions that neuroimaging for detection of secondary causes is likely unwarranted in HIV patients with typical primary headache symptoms, CD4 counts above 200, and an absence of focal neurological deficits,[3,4] replication with neuroimaging designs is nevertheless warranted to inform more definitive statements about the need for neuroimaging in this population. Future studies could model the methodology of the current study while adding confirmatory testing for HIV-related pathophysiology and including a higher proportion of Hispanic patients. Replication of the present findings would indeed challenge the need for extensive diagnostic workups in response to headache symptoms conforming to primary headache semiologies, likely reducing costs to both patients and society as a whole. Further research should focus also on longitudinal designs in which the characteristics and severity of both preexisting and de novo headaches are followed over time and in relation to ARV compliance specifically, and in which headache typologies of patients with HIV disease are compared with patients with other chronic immune diseases.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Kale E. Kirkland, Todd A. Smitherman

(b) Acquisition of Data
Kale E. Kirkland, Karl Kirkland, W. J. Many Jr

(c) Analysis and Interpretation of Data
Kale E. Kirkland, Todd A. Smitherman

Category 2

(a) Drafting the Manuscript
Kale E. Kirkland, Todd A. Smitherman

(b) Revising It for Intellectual Content
Kale E. Kirkland, Todd A. Smitherman, Karl Kirkland, W. J. Many Jr

Category 3

(a) Final Approval of the Completed Manuscript
Kale E. Kirkland, Todd A. Smitherman, Karl Kirkland, W. J. Many Jr

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