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Headache prevalence and its functional impact among HIV-infected adults in rural Rakai District, Uganda

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Abstract

Headache is common, but its prevalence and impact in sub-Saharan Africa and especially in HIV+ individuals is relatively unknown. We sought to determine the prevalence and functional impact of headache among HIV-infected (HIV+) adults in a cross-sectional observational cohort study in rural Rakai District, Uganda. Participants completed a sociodemographic survey, depression screen, functional status assessments, and answered the headache screening question, “Do you get headaches?” Participants responding affirmatively were assessed with the ID Migraine tool for diagnosis of migraine and Headache Impact Test-6 to determine functional impact of headache. Characteristics of participants with and without headaches and with and without functional impairment were compared using t-tests for continuous variables, chi-square tests for categorical variables, and multivariate logistic regression. Of 333 participants, 51% were males, mean age was 37 (SD 9) years, 94% were on antiretroviral therapy (ART) and mean CD4 count was 403 (SD 198) cells/μL. Headache prevalence was 28%. Among those reporting headache, 19% met criteria for migraine, 55% reported functional impairment, and 37% reported substantial or severe impact

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Conflicts of Interest:

Mr. Sohail reports no conflicts of interest.
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of headache. In multivariate analyses, female sex (odds ratio (OR) 2.58) and depression (OR 2.49) were associated with increased odds while ART (OR 0.33) decreased odds of headache. Participants with substantial/severe functional impact were more likely to meet criteria for depression (32% vs 9%). In conclusion, headache prevalence in HIV+ rural Ugandans was lower than global averages but still affected more than one-quarter of participants and was associated with significant functional impairment.

Keywords

headache; migraine; epidemiology; HIV; Africa

Headache is one of the most common health problems globally. According to the 2015 Global Burden of Disease Study, headache (grouping together migraine, tension-type headache, and medication overuse headache) affects approximately half of the world's population between 15 and 64 years of age and is the most prevalent neurological disorder worldwide (Global Burden of Disease Injury Incidence Prevalence Collaborators 2016). However, very little is known about headache disorders in Sub-Saharan Africa (SSA) with the majority of available evidence from this region focusing on headache in human immunodeficiency virus (HIV) uninfected (HIV-) adults.

Assessing the burden of headache in SSA is complicated by the HIV epidemic. Approximately 70% of global HIV infections are in SSA (Kharsany and Karim 2016), and headache may be more common among HIV-infected (HIV+) than HIV- individuals (Mirsattari, Power et al. 1999). While primary headache disorders may be the most common type of headache among HIV+ individuals on ART (Mirsattari, Power et al. 1999), secondary etiologies, including central nervous system (CNS) opportunistic infections (Kirkland, Kirkland et al. 2012) and use of particular antiretroviral drugs such as zidovudine (Max and Sherer 2000), may lead to increased headache prevalence and complicate assessment. Still, evidence from the developed world suggests headache is the most common form of pain reported among HIV+ individuals (Norval 2004) and an important factor influencing quality of life (Evers, Wibbeke et al. 2000).

Few systematic studies of headaches among HIV+ outpatients have been performed in SSA, including Uganda, which has a national HIV prevalence of 7.3% (World Health Organization 2017). Given reports that headache is the most common cause of pain in Western HIV+ populations and related to poorer quality of life, we hypothesized that it may be a significant but under-recognized health condition among HIV+ populations in SSA as well. Therefore, we investigated the prevalence of headache in HIV+ individuals in rural Rakai District, Uganda using previously validated surveys to determine the point prevalence and functional impact of headache.

METHODS

Study Participants:

Study participants were drawn from the Rakai Community Cohort Study, an open, community-based cohort of adults residing in 50 communities in Rakai District which are

representative of rural Uganda. Eligible consenting participants were 20 years or older and HIV+. Exclusion criteria included severe systemic illness, a known history of CNS opportunistic infections, inability to provide informed consent, and physical disability resulting in inability to travel to the main Rakai Health Sciences Program clinic.

Study Procedures:

Participants were enrolled in this cross-sectional observational cohort study between June 2015 and June 2017. Each participant completed a socio-demographic and behavioral interview, depression scale (Center for Epidemiologic Studies – Depression (CES-D) (Radloff 1977)), and functional status assessments (Patient Assessment of Own Functioning Inventory (PAOFI) (Chelune and Lehman 1986) and Karnofsky Performance Status (Karnofsky and Burchenal 1949)). Headache prevalence was assessed using a single question: “Do you have headaches?” Participants who responded affirmatively to this question were further assessed using the ID-Migraine screening tool (Lipton, Dodick et al. 2003), which has been shown to be highly sensitive and specific in the diagnosis of a migraine, and Headache Impact Test-6 (HIT-6; range 36–78) (Kosinski, Bayliss et al. 2003), which was developed to assess the functional impact of headaches and has been validated in 27 countries (Gandek, Alacoque et al. 2003). All survey instruments were translated into and administered in Luganda, the local language. Participants also underwent a peripheral blood draw for confirmation of HIV status and determination of CD4 cell count.

Standard Protocol Approvals, Registration and Patient Consents:

Written informed consent for study participation was obtained from all participants. This study was approved by the Western Institutional Review Board, the Uganda Virus Research Institute Research and Ethics Committee, and the Uganda National Council for Science and Technology.

Statistical Analysis:

Headache prevalence was defined as a “yes” answer to the question, “Do you have headaches?” A diagnosis of migraine was made using the ID Migraine screening tool and defined as positive for migraine if the patient answered “yes” on any two of the three questions (Lipton, Dodick et al. 2003). The functional impact of headache was determined using the HIT-6 questionnaire in which the response to each question is given a numeric score and summed to provide an overall headache severity level. Results were then categorized using the standard HIT-6 classification (range 36–78): little or no impact (36–49), some impact (50–55), substantial impact (56–59), or severe impact (60–78) (Kosinski, Bayliss et al. 2003). Depression was defined as a CES-D score ≥ 16 .

Comparative analyses between participant groups were performed using chi-square tests for categorical variables and t-tests for continuous variables. Logistic regression was performed to determine significant independent predictors of headaches and headache severity. All analyses were completed using Stata version 14 (StataCorp, College Station, TX).

RESULTS

Of the 333 HIV+ participants enrolled, 170 (51%) were males, the mean (standard deviation [SD]) age was 37 (9) years, and the mean education level was 6 ($\pm$ 3) years (Table 1). Nearly all (94%; n=312) were on antiretroviral therapy (ART), and mean CD4 count was 403 ($\pm$ 198) cells/ μ L. Eight percent met criteria for depression. Average body mass index (BMI) was 23 ($\pm$ 3) with 4% of participants being obese, 16% overweight, and 5% underweight.

Overall, 93 (28%) of participants reported headaches. Of those, 91 participants (98%) completed the additional headache screening tools. Approximately one-fifth of participants with headache met criteria for migraine (n=17; 19%); the remaining headaches were not further classified. Among all participants with headache, nausea was the most commonly reported symptom (35%, n=32) on the ID Migraine screen, followed by headaches that limited activities (22%; n=20), and photophobia (14%; n=13).

HIT-6 mean score among all participants with headache was 51 ($\pm$ 8). Based on total HIT-6 scores, more than half (55%) of participants with headache reported functional impact on their lives with 28% reporting some impairment, 12% reporting substantial impact, and 15% reporting severe impact. Severe pain was the most commonly reported symptom on the HIT-6 with 89% (n=81) of participants reporting this symptom at least rarely (Table 2). Of symptoms reported to occur very often or always, severe pain was also the most commonly reported symptom (very often in 13%, always in 5%). Approximately 80% reported their activities were limited or they wished to lie down after a headache at least rarely. Two-thirds reported they felt tired, fed up and had their concentration limited by headache at least rarely.

Female sex was strongly associated with headache prevalence ($p < 0.001$), while use of ART ($p=0.04$) and alcohol ($p=0.04$) were associated with decreased headache prevalence (Table 3). There was a trend toward a higher BMI among those with headache, but this did not reach statistical significance ($p=0.06$). There were no associations between headache and age, current or nadir CD4 count, or use of tobacco, narcotics or traditional medications. Fatigue occurred in 18% of participants with headaches versus 8% without headaches ($p=0.006$) while depression was found in 15% of those with headaches compared to 6% of those without headaches ($p=0.007$). Headache was associated with poorer functional status as measured by the PAOFI (148 vs 155, $p < 0.001$) and Karnofsky performance status (95 vs 96, $p=0.04$). In multivariate logistic regression analyses including sex, ART use, CD4 count, BMI, alcohol use and depression, female sex (OR 2.58 [1.46, 4.56], $p = 0.001$) and depression (OR 2.49 [1.09, 5.69], $p = 0.03$) remained associated with increased odds of headache while ART had a protective effect (OR 0.33 [0.13, 0.86], $p=0.02$) (Table 4).

There were no significant demographic differences between those who reported no, little or some impact of headache on their functional status compared to those reporting substantial or severe impact (Table 3). However, those reporting substantial or severe functional impact were more likely to meet criteria for depression (32% vs 9%, $p=0.007$). There were no demographic or functional status differences between those with migraine compared to those with other types of headache (data not shown).

DISCUSSION

This is the first systematic study of headache among HIV+ outpatients in SSA and one of the few studies of headache conducted in this region. Overall headache prevalence was 28% with 5% of all participants meeting criteria for migraine. Both headache and migraine prevalence were lower in this study than most prior population-based studies, such as the Global Burden of Disease studies (Global Burden of Disease Study 2015, Global Burden of Disease Injury Incidence Prevalence Collaborators 2016). In addition, headache prevalence was lower than other studies from SSA, including studies from Nigeria and Zambia that found headache prevalence to be 66% and 72%, respectively (Ezeala-Adikaibe, Onyekonwu et al. 2014, Mbewe, Zairenthiama et al. 2015). However, these findings are similar to previous studies reporting headache prevalence of 22% in Ethiopia (Mengistu and Alemayehu 2013) and 23% in Tanzania (Dent, Spiss et al. 2004). Of note, none of these studies were conducted in HIV+ individuals, and headache prevalence has previously been reported to be higher in persons living with HIV (Mirsattari, Power et al. 1999). However, comparison of these studies is difficult due to methodological differences such as use of differing headache assessment tools and study population characteristics. This study investigated relatively healthy HIV+ outpatients who volunteered to participate in a clinical research study and, thus, are likely not representative of the HIV+ population of rural Uganda as a whole.

Other factors may also contribute to the lower headache prevalence observed in this population. For example, Mengistu et al. hypothesized that the low headache prevalence observed in their Ethiopian study may be attributable to greater tolerance to pain among rural populations where headache, even if persistent and recurrent, may be perceived as a trivial problem in the setting of more challenging health and economic issues (Mengistu and Alemayehu 2013) thus leading to underreporting of headache prevalence or severity. Several other African studies have noted higher headache prevalence in urban than rural populations (Woldeamanuel, Andreou et al. 2014, Mbewe, Zairenthiama et al. 2015). The current study was also from a rural area which may partially explain the lower headache prevalence.

While 19% of participants with headaches met criteria for migraine in this study, overall migraine prevalence was 5%, which is substantially lower than the estimated migraine prevalence of ~10–15% in the global adult population (Global Burden of Disease Study 2015, Global Burden of Disease Injury Incidence Prevalence Collaborators 2016). The prevalence of migraine in the United States is around 6% for men and 18% for women (Migraine Research Foundation) while in this study was 2% in men and 8% in women. These rates are lower than previously reported studies from other SSA countries, including Nigeria (16.7%) (Ezeala-Adikaibe, Stella et al. 2012), but are similar to a systematic review of headache studies from Africa which noted an overall migraine prevalence of 5.6% (Woldeamanuel, Andreou et al. 2014).

Prior estimates of migraine prevalence among HIV+ populations have varied widely. Recent studies from the University of Mississippi (Kirkland, Kirkland et al. 2012) and Brazil (Sampaio Rocha-Filho, Torres et al. 2017) have found migraine prevalence to be higher than global averages with a 46% and 44.5% prevalence respectively among HIV+ cohorts with

well-controlled HIV infection. These rates are much higher than what were found in this study and may reflect differing methodologies employed or the differing ethnicities, socioeconomic statuses and cultural factors of the cohorts studied.

Many of the risk factors for headache identified in this study are similar to those reported in prior studies, including female sex (Woldeamanuel, Andreou et al. 2014) and higher BMI (Chai, Scher et al. 2014). The latter suggests headache may become more common as obesity rates rise in SSA. However, while prior studies have identified tobacco and alcohol use (Taylor 2015) (Dueland 2015), as well as lower CD4 counts (Kirkland, Kirkland et al. 2012) as risk factors for the presence of headache, these associations were not observed in this study. In fact, in univariate analyses, alcohol use was associated with lower prevalence of headache, but this was not statistically significant in multivariate analyses and likely reflects the higher rates of alcohol use among men than women in this cohort. Prior studies have shown ART use to be protective against headaches (Evers, Brilla et al. 1998), a finding which was replicated in this study. This might further explain why the studies in San Francisco and Brazil, which included primarily ART-naïve participants, found much higher rates of headache and migraine.

Headache was associated with impaired functional status and significant headache-associated disability in this cohort, similar to other studies in Africa (Woldeamanuel, Andreou et al. 2014, Morgan, Eguia et al. 2015, Zebenigus, Tekle-Haimanot et al. 2017) and in HIV+ cohorts (Kirkland, Kirkland et al. 2012, Sampaio Rocha-Filho, Torres et al. 2017). A study in Zambia reported headaches led to lost working days which they estimated accounted for a loss in the national gross domestic product of nearly 2% (Mbewe, Zairenthiama et al. 2015). Further investigations are warranted to assess the full societal burden of headache in Uganda and other regions of SSA.

This study represents the first systematic study of headaches in a rural HIV+ population in SSA but has several limitations. This study cohort consisted of outpatients, the majority of whom were on ART and not severely immunocompromised. Therefore, the study population may not be representative of the HIV+ population in this region. Well-validated and widely accepted questionnaires were employed for this study, but these tools had not previously been used in Uganda so their specific reliability in this context is unknown. Finally, the major limitation of this study was the lack of diagnostic precision in evaluating particular headache disorders other than migraine. Given the resource limitations of the study setting, no neurologists were available to assess individual participants, and neuroimaging studies and lumbar punctures were also not routinely available. Therefore, secondary causes of headaches cannot be entirely excluded and International Headache Society diagnostic criteria for primary headache disorders could not be applied.

CONCLUSION

This study provides an estimate of the prevalence and burden of headache among HIV+ individuals in rural Uganda. While headache was less prevalent than in many previous studies from other regions, it remained common in this population, affecting more than one-quarter of study participants and was associated with significant functional impairment even

when on effective ART. This study also highlights the challenges associated with assessing headache in rural HIV+ cohorts with limited neurologic resources to exclude secondary causes of headache and fully classify primary headache disorders. In addition, the discrepant results of this study, which found a lower headache and migraine prevalence than many earlier studies of HIV+ cohorts from other regions, highlight the necessity of further evaluation of headache in HIV+ cohorts on newer ART regimens with well-controlled chronic HIV infection to determine whether headache is still more prevalent amongst HIV+ individuals in the current ART era. Further studies are also warranted to evaluate the societal impact of headache in SSA and to improve the diagnosis and management of headache disorders amongst this population in order to alleviate the morbidity associated with headache.

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Table 1.

Demographic characteristics of the study population.

	n=333
Male [n (%)]	170 (51%)
Age (years) [mean (SD)]	37 (9)
Education (years) [mean (SD)]	6 (3)
Antiretroviral use [n (%)]	312 (94%)
CD4 nadir [n (%)]	
< 200 cells	26 (13%)
350–500 cells	57 (28%)
Current CD4 [mean (SD)]	403 (198)
BMI [mean (SD)]	23 (3)
Tobacco use [n (%)]	38 (11%)
Traditional medication use [n (%)]	3 (1%)
Narcotic use [n (%)]	3 (1%)
Alcohol use [n (%)]	144 (43%)
Functional Status	
Fatigue [n (%)]	36 (11%)
PAOFI Total Score [mean (SD)]	153 (14)
Karnofsky Score [mean (SD)]	96 (7)
Depression [n (%)]	28 (8%)
CES-D Score [mean (SD)]	4 (7)

Table 2.

Frequency of symptoms reported on the Headache Impact Test-6 (HIT-6) questionnaire amongst participants with headaches (n=91).

	Severe pain	Activities limited	Lie down	Tired	Fed Up	Concentration Limited
Never	10 (11%)	20 (22%)	20 (22%)	31 (34%)	28 (31%)	31 (34%)
Rarely	28 (31%)	35 (38%)	23 (25%)	30 (33%)	33 (36%)	30 (33%)
Sometimes	36 (40%)	30 (33%)	37 (41%)	24 (26%)	22 (24%)	24 (26%)
Very often	12 (13%)	4 (4%)	8 (9%)	5 (5%)	7 (8%)	4 (4%)
Always	5 (5%)	2 (2%)	3 (3%)	1 (1%)	1 (1%)	2 (2%)

Table 3.

Comparison of demographic and clinical factors and measures of functional status among participants with and without headaches and among those participants with headaches who reported substantial or severe functional impact to those participants with headache reporting less severe functional impact of headaches.

	Headache (n = 93)	No Headache (n = 240)	p	Substantial/ Severe Impact (n = 25)	No, Little or Some Impact (n = 66)	p
Female [n (%)]	63 (68%)	100 (42%)	< 0.001	19 (76%)	43 (65%)	0.32
Age (years) [mean (SD)]	38 (10)	37 (8)	0.87	39 (12)	37 (9)	0.37
ART use [n (%)]	83 (89%)	229 (95%)	0.04	21 (84%)	60 (91%)	0.35
CD4 nadir < 200 [n (%)]	7 (17%)	19 (12%)	0.31	2 (20%)	5 (16%)	0.93
Current CD4 [mean (SD)]	428 (187)	394 (202)	0.17	409 (183)	435 (191)	0.56
BMI [mean (SD)]	23.4 (4)	22.5 (3)	0.06	25 (6)	23 (3)	0.24
Traditional medication use [n (%)]	0 (0%)	3 (1%)	0.28	0 (0%)	0 (0%)	1
Alcohol use [n (%)]	32 (34%)	112 (47%)	0.04	7 (28%)	25 (38%)	0.38
Functional Status						
Fatigue [n (%)]	17 (18%)	19 (8%)	0.006	5 (20%)	12 (18%)	0.84
Depression [n (%)]	14 (15%)	14 (6%)	0.007	8 (32%)	6 (9%)	0.007
CES-D score [mean (SD)]	7 (8)	4 (7)	0.002	11 (12%)	5 (6%)	0.02
PAOFI Total Score [mean (SD)]	148 (17)	155 (13)	<0.001	145 (15)	149 (17)	0.27
Karnofsky Score [mean (SD)]	95 (7)	96 (7)	0.04	94 (6)	95 (7)	0.52

Table 4.

Logistic regression analyses of demographic and clinical factors associated with increased odds of headache. All factors with $p < 0.20$ in univariate analyses were included in the multivariate analysis.

	<i>Univariate Regression</i>			<i>Multivariate Regression</i>	
	OR (95% CI)	p		OR (95% CI)	p
Female Sex	2.94 (1.77, 4.87)	< 0.001		2.58 (1.46, 4.56)	0.001
ART Use	0.40 (0.16, 0.97)	0.04		0.33 (0.13, 0.86)	0.02
CD4 Count	1.00 (1.00, 1.00)	0.17		1.00 (1.00, 1.00)	0.27
BMI	1.83 (1.00, 1.14)	0.04		1.03 (0.96, 1.11)	0.41
Alcohol Use	0.60 (0.36, 0.99)	0.04		0.90 (0.52, 1.56)	0.70
Depression	2.90 (1.31, 6.26)	0.009		2.49 (1.09, 5.69)	0.03