Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2022, Vol. 42(9) 918–925


Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/03331024221088994
journals.sagepub.com/home/cep
SAGE

Burden of headache in a HIV-positive population of sub-Saharan Africa

Massimo Leone[1], Luca Giani[2], Monica Phaka[3], Derya Uluduz[4], Şaşmaz Tayyar[5], Maureen Kamponda[3], Victor Tamba Tolno[3], Giovanni Guidotti[6], Maria Cristina Marazzi[7] and Timothy J Steiner[8,9]

Abstract

Background: About 26 million people are living with HIV in sub-Saharan Africa. The DREAM programme in sub-Saharan Africa provides free healthcare for HIV/AIDS and a range of chronic non-communicable diseases. HIV is a risk factor for neurological non-communicable diseases including stroke and epilepsy, which themselves are associated with headache, and HIV may be a direct risk factor for headache. We investigated the prevalence and burden of headache in a HIV+ population in sub-Saharan Africa.

Methods: At the DREAM Centre in Blantyre, Malawi, a low-income country with a population of 19 million and 9.2% HIV prevalence, a structured questionnaire was administered by a trained lay interviewer to consecutively attending HIV+ patients aged 6–65 years. All were monitored with regular viral load detection.

Results: Of 513 eligible patients invited, 498 were included (mean age 34.1 ± 12.8 years; 72% females; 15 declined). All were on antiretroviral treatment, with viral load undetectable in 83.9%. The 1-year prevalence of headache was 80.3% (females 83.6%, males 71.9%); 3.8% had ≥15 headache days/month, 1.4% had probable medication-overuse headache. Mean overall headache frequency was 4.4 ± 5.4 days/month. Those reporting headache lost means of 2.3% of paid workdays and 3.3% of household workdays because of headache. Only one third had sought advice for their headache.

Conclusions: Headache is very prevalent among HIV+ patients in Malawi, imposing additional burden and costs on individuals and the community. Management of headache disorders should be implemented in HIV centres, as it is for other chronic non-communicable diseases.

Keywords

Headache, HIV, disease burden, epidemiology, sub-Saharan Africa, Global Campaign against Headache

Date received: 3 November 2021; revised: 14 February 2022; accepted: 16 February 2022

Introduction

Headache disorders are major contributors worldwide to the global burden of disease: collectively, they are the third cause of years lived with disability (YLDs) (1).

According to recent population-based studies within the Global Campaign against Headache, which used a standardized protocol and questionnaire (2,3), headache prevalence and attributed burden in countries of sub-Saharan Africa (SSA) are similar to those found elsewhere (4,5). Populations and life expectancy in SSA are rapidly increasing, and non-communicable diseases (NCDs) in this part of the world make an ever-growing contribution to the total burden of disease (6).

[1]Neuroalgology Unit, Foundation IRCCS Carlo Besta Neurological Institute, Milan, Italy
[2]Neurorehabilitation Department, IRCCS Istituti Clinici Scientifici Maugeri di Milano, Milan, Italy
[3]DREAM Program, Health Department, Blantyre, Malawi
[4]Neurology Department, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey
[5]Public Health Department, Mersin University School of Medicine, Mersin, Turkey
[6]Health Department, Azienda Sanitaria Locale (ASL) Roma 1, Regione Lazio, Rome, Italy
[7]Department of Human Sciences, LUMSA University, Rome, Italy
[8]Division of Neuromedicine and Movement Science, Norwegian University of Science and Technology, Trondheim, Norway
[9]Department of Brain Sciences, Imperial College London, London, UK

Corresponding author:
Massimo Leone, Fondazione IRCCS Istituto Neurologico Carlo Besta, UO Neuroalgologia, Via Celoria 11, 20133 Milan, Italy.
Email: massimo.leone@istituto-besta.it

At the same time, illness due to human immunodeficiency virus (HIV) is highly prevalent in SSA, increasingly so in the last decade (7).

Before the widespread availability of antiretroviral drugs, neurological complications among HIV+ patients in SSA were common, arising mainly from opportunistic infections encouraged by immunodeficiency (low CD4 count). Now, much improved access to antiretroviral treatment (ART) has greatly increased the number (to many millions) of patients living with HIV but with undetectable viral loads and extended life expectancy. However, persistence of the virus even in very small amounts in the brains of HIV+ patients increases the risks of brain dysfunction and of neurological diseases such as stroke and epilepsy (8,9). Since they are themselves brain disorders, primary headaches may also be influenced by the persistence of undetectable levels of HIV (8–12). There are few data on this. A recent study conducted in a HIV-positive (HIV+) rural population of Uganda found a headache prevalence of only 28% (13), but the sample size was small (N = 333) and case ascertainment depended on the single screening question, "Do you have headaches?".

The aim of the present study was to make better estimates of the prevalence and attributable burden of headache in a HIV+ population in SSA. The purpose was to establish whether such populations merited special studies of headache. The opportunity arose through an ongoing collaboration with the Disease Relief through Excellent and Advanced Means (DREAM) programme, active in 10 SSA countries to provide health care for HIV/AIDS and a range of NCDs such as arterial hypertension and diabetes (14). DREAM has operated in Malawi since 2005.

Malawi is a low-income SSA country with a population of 19 million, of whom 83% live in rural areas (15) and 88% are younger than 45 years (16). HIV/AIDS is common here, but prevalence has fallen from 14.4% to 9.7% with increased access to ART – from 3.1% in 2005 to 84% in 2019 (17). Life expectancy among the general population has increased by 18 years, to 63, between 2000 and 2016 (18). The country has very few neurologists, and only 0.04 doctors per 1000 inhabitants (the European mean is 4 per 1000). Most medical activities are, therefore, usually performed by clinical officers, medical officers, health officers or, sometimes, nurses (19).

Methods

Ethics

The study was planned and conducted in accordance with the Helsinki Declaration and approved by the Ethics Committees of the IRCCS Neurological Institute "Carlo Besta", Milan, Italy and of the National Health Sciences Research Committee, Ministry of Health, Lilongwe, Malawi. Written informed consent was obtained from all participants before enrolment. Personal data were anonymized before analysis.

Data availability

Raw anonymized data are available for legitimate purposes upon request at: https://doi.org/10.5281/zenodo.4656712.

Study design and procedures

This was a cross-sectional questionnaire-based survey of consecutively presenting HIV+ patients aged 6–65 years attending a HIV centre and who had been followed for at least 1 year under ART. Patients were enrolled during routine visits to the centre.

Survey site

The study was conducted at the DREAM centre in Blantyre, the second largest city of Malawi.

Selection and training of interviewer

The interviewer was a professional journalist experienced in health-related surveys who attended online training including clinical aspects of headache disorders and the theoretical and practical aspects of the study design and purpose. She was supervised by a local physician (VT) and received remote assistance from headache specialists in Italy (ML, LG).

Enquiry

Questions addressed 1-year prevalence of headache, of headache on ≥15 days/month (H15+) and of probable medication-overuse headache (3) (pMOH: see below), and point (1-day) prevalence of any headache ("headache yesterday"), along with attributable burden (focusing on symptom burden and lost productive time). The questionnaire was the Headache-Attributed Restriction, Disability, Social Handicap and Impaired Participation (HARDSHIP) questionnaire (3), but with enquiry reduced to a minimum for our purpose in order to encourage participation. Accordingly, we included only six modules of the full (modular) questionnaire (3). These were translated into Chichewa, the local language, in accordance with *Lifting The Burden*'s translation protocol for lay documents (20). Interviews were conducted in this language.

Personal and demographic enquiry and a neutral headache screening question ("Have you had a headache during the last 12 months?") were addressed to all

participants. These were followed in those screening positively by questions into characteristics of headache and symptom burden, lost productive time due to headache and use of symptomatic medication. More specifically, we enquired into days with headache in the last 30 days (frequency), usual duration of attacks (in minutes, hours or days, or "never goes away") and usual intensity of headache (recorded on a verbal rating scale as "not bad", "quite bad", "very bad"). Lost productive time was quantified using the 30-day version of the Headache-Attributed Lost Time (HALT-30) index (21) incorporated as one of the modules in HARDSHIP. This asked participants on how many days in the preceding 30 days they could do none or less than half of their usual paid work (schoolwork in the case of those at school) or of their usual household work because of headache. Finally, a set of questions asked about headache on the day before the visit ("headache yesterday"). Participants reporting headache yesterday were asked about its intensity, duration, how it had affected their ability to accomplish their normal activities ("could do everything as normal", "could do more than half of normal", "could do less than half of normal", "could do nothing at all"), and whether they had taken medication for it.

We abbreviated the diagnostic module of HARDSHIP, since we did not aim to collect all clinical details (for example, quality and lateralization of pain, and accompanying symptoms) needed to apply international diagnostic criteria for episodic headache types (migraine or tension-type headache) (22). However, H15+ was identified by reported frequency (15 days or more) in the preceding month. Participants who also reported acute medication intake on >12 days in the month were considered to have pMOH.

Information about ART and viral load was obtained from the DREAM database of patients.

Data entry and management

Responses to the enquiry were collected on paper sheets during face-to-face interviews. Data were then entered by the interviewer in anonymized form into a secure online database through a Microsoft Access-based interface designed to limit missing or inconsistent insertions. Four authors (LG, ML, TJS, TS) scrutinized the entries for completeness and inconsistencies. Errors were resolved by reviewing the response sheets or re-questioning the participant.

Statistics and analysis

We aimed to enroll 500 subjects, which we considered achievable within 3 months with the resources available.

We recorded gender as male or female. We recorded age in years as reported and analyzed it both as a continuous variable and categorized (<18, 18–27, 28–37, 38–47, 48–57, ≥58 years).

Usual attack duration (whether treated or not, as a measure of burden) was recorded in minutes when <1 hour, hours when ≥1 and <24, or days when ≥24 hours, then transformed into hours and analyzed both as a continuous variable and categorized (<4 hours, 4–72 hours, >72 hours). Participants reporting unremitting headache ("never goes away") were excluded from this analysis. We assumed attack frequency per month was equal to reported days with headache per month when attack duration was reported as ≤24 hours. When duration was >24 hours, we assumed this was factored into reported days with headache and, accordingly, applied a correction, estimating attack frequency by dividing days with headache per month by duration in days. We estimated mean proportion of time in ictal state as ([attack frequency/month * duration in hours]/30 * 24) * 100%.

Duration of headache yesterday was similarly recorded in minutes or hours (24 hours when reported for the entire day), and analyzed in hours.

Headache intensity, whether usual or of headache yesterday, was coded numerically, with "not bad" equated to mild = 1, "quite bad" to moderate = 2 and "very bad" to severe = 3. These data were treated as continuous.

Data analysis was performed using Microsoft Excel 2010 and SPSS 25.0. Continuous data were summarized as means ± SDs. Proportions were calculated as percentages with 95% confidence intervals (CIs). We used Student's t, Kruskal-Wallis and chi-squared tests to compare distributions and proportions. Missing data were excluded from the analyses by pairwise deletion. We regarded $p < 0.05$ as significant.

Results

Interviews were conducted from October to December 2019.

We proposed the study to 515 patients, of whom 15 (2.9%) declined to participate. Of the 500 interviewed, 498 met the entry criteria and were included in the analysis (two excluded because of age >65 years).

Demographic characteristics of the study sample

These are displayed in Table 1. Females (n = 359/498, 72.1%) exceeded males (n = 139/498, 27.9%), the ratio of 2.6:1 reflecting the F:M ratio in the HIV+ population in SSA (17) rather than that in the general population of Malawi (1.02) (23). Mean age was 34.1 ± 12.8 years (median 37, range 11–63 [although the study was

open to those aged 6 years or older, none were younger than 11]) (Table 1).

Headache prevalence

The overall 1-year prevalence of any headache was 80.3% (n = 400/498; 71.9% among males, 83.6% among females; p = 0.008) (Table 2). Most headache (n = 381/400; 95.25%) was episodic but 19 participants (4.75%; 2 males [1.4%], 17 females [4.7%]; p = 0.1) reported H15+, seven of these (all female) having pMOH. About 80% (n = 323/400) of those reporting headache in the last year also reported headache in the last month (Table 2). Headache yesterday was reported by 82 participants (16.5%; males 14 [10.1%], females 68 [18.9%]; p = 0.02).

Prevalence of any headache last year, of H15+ and of pMOH, did not differ significantly between the age categories (p = 0.08, p = 0.07 and p = 0.6 respectively), although no cases of H15+ were reported by those aged <18 years. However, headache yesterday was reported increasingly with age, and significantly more by those aged ≥18 years than by those aged <18 (p = 0.013).

Table 1. Demographic characteristics of the sample (N = 498) and those reporting headache (N = 400).

Characteristic	Overall n (%)	Those reporting headache n (%)	
		All	Aged ≥18 years
Total	498	400	329
Gender			
Male	139 (27.9)	100 (25.0)	62 (18.8)
Female	359 (72.1)	300 (75.0)	267 (81.2)
Age (years)			
<18	97 (19.5)	71 (17.8)	–
18–27	60 (12.0)	51 (12.8)	51 (15.5)
28–37	106 (21.3)	94 (23.5)	94 (28.6)
38–47	166 (33.3)	129 (32.3)	129 (39.2)
48–57	58 (11.6)	47 (11.8)	47 (14.3)
>58	11 (2.2)	8 (2.0)	8 (2.4)

Symptom burden

The overall mean number of headache days per month among the 400 participants with headache was 4.4 ± 5.4. Headache frequency was, of course, much higher among those with H15+ (22.4 ± 4.7 days/month) and those with pMOH (21.1 ± 5.6 days/month) than in those with episodic headache (3.5 ± 3.6 days/month).

Headache intensity was rated mild by 39.0% (n = 156/400) of participants with headache, moderate

Table 2. Prevalence of headache overall and by gender and age (N = 498).

	N	Headache last year	Headache last month	Headache yesterday	Headache on ≥15 days/ month	Probable medication-overuse headache
		n (% [95% confidence intervals])				
All (N = 498)	498	400 (80.3 [76.6–83.6])	323 (64.9 [60.6–68.9])	82 (16.5 [13.5–20.0])	19 (3.8 [2.5–5.9])	7 (1.4 [0.7–2.9])
Gender						
Male	139	100 (71.9 [64.0–78.7])	75 (54.0 [45.7–62.0])	14 (10.1 [6.1–16.2])	2 (1.4 [0.3–5.1])	0 (0.0 [0–2.7])
Female	359	300 (83.6 [79.4–87.0])	248 (69.1 [64.5–74.0])	68 (18.9 [15.2–23.3])	17 (4.7 [3.0–7.5])	7 (1.9 [0.9–4.0])
Age (years)						
<18	97	71 (73.2 [63.6–81.0])	63 (64.9 [55.0–73.7])	8 (8.2 [4.2–15.4])	0 (0.0 [0–3.8])	0 (0.0 [0–3.8])
18–27	60	51 (85.0 [73.9–91.9])	38 (63.3 [50.7–74.4])	6 (10.0 [4.7–20.1])	3 (5.0 [1.4–13.7])	2 (3.3 [0.6–11.4])
28–37	106	94 (88.7 [81.2–93.4])	76 (71.7 [62.5–79.4])	17 (16.0 [10.3–24.2])	2 (1.9 [0.3–6.6])	1 (0.9 [0.1–5.2])
38–47	166	129 (77.7 [70.8–83.4])	101 (60.8 [53.3–67.9)	34 (20.5 [15.0–27.3)	9 (5.4 [2.9–10.0])	3 (1.8 [0.5–5.2])
48–57	58	47 (81.0 [69.1–89.1])	41 (70.7 [58.0–80.8])	14 (24.1 [3.7–18.6])	5 (8.6 [3.7–18.4])	1 (1.7 [0.1–9.1])
over 58	11	8 (72.7 [43.4–90.3])	4 (36.4 [15.2–64.6])	3 (27.3 [9.7–56.6])	0 (0.0 [0–25.9])	0 (0.0 [0–25.9])
all ≥18	401	329 (82.0 [78.0–85.5])	260 (64.8 [60.0–69.4])	74 (18.5 [15.0–22.5])	19 (4.7 [3.1–7.3])	7 (1.7 [0.8–3.6])

by 52.3% (n = 209/400) and severe by 8.8% (n = 35/400). Mean headache intensity was 1.7 ± 0.6, lower in those with episodic headache (1.7 ± 0.6) than in those with H15+ (2.3 ± 0.7; $p < 0.0001$). Most participants with pMOH (n = 5/7) reported "very bad" headache (mean intensity 2.7 ± 0.5).

With two participants (0.5%) complaining of continuous headache excluded (N = 398), mean headache duration was 9.3 ± 20.6 hours (median 2 hours, indicating a highly skewed distribution). Almost two thirds of participants (n = 262/398; 65.8%) reported usual headache durations of <4 hours, about one third (n = 130/398; 32.7%) reported 4–72 hours and only six (1.5%) reported longer durations.

The proportion of time in ictal state (taking account of the 24 with attack duration >24 hours) was (4.3*9.3/30*24)*100 = 5.6%.

Matching intensity (moderate or severe) and duration of attacks (4-72 hours), 104 of the 498 participants (20.1%) might have had migraine (20). Another 133 (26.7%) had moderate-to-severe headaches of <4 hours.

Analgesic consumption

Analgesics were commonly used. Over three quarters (n = 310/400; 77.5%) of those with headache reported analgesic use, well over half (n = 230/400; 57.5%) within the preceding month. Seven participants, all with H15+, reported frequent use (>12 days/month), always of paracetamol. Triptans were not available in Malawi.

Lost productivity burden

In those of working age (18–65 years; n = 401), 329 (82.0%) reported headache in the preceding year, with 99 of these (30.1%) losing one or more days of productive time in the preceding month because of headache (15 [4.6%] from paid work, 49 [14.9%] from household work and 35 [10.6%] from both). Mean paid workdays lost were 0.6 ± 2.1. This represented 2.7% of days lost per person with headache (assuming 22 workdays/month) and 2.2% (2.7% * 82.0%) per adult (18–65 years old) in the sample. Mean household workdays lost were 1.2 ± 3.0, representing 3.9% of 30 days/month per person with headache and 3.2% (3.9% * 82.0%) per adult in the sample.

Participants with H15+ (n = 19) accounted for 32.2% of all days of paid or household work lost. Those with pMOH (n = 7) were responsible, proportionately, for the greatest losses: means of 5.4 ± 7.7 workdays (i.e., 24.5% [5.4/22]; 0.4% [24.5% * (7/401)] per adult in the sample) and 7.6 ± 5.3 household workdays (i.e., 25.3% [7.6/30]; 0.4% [25.3% * (7/401)] per adult in the sample). Overall, those with pMOH accounted for 15.7% of all days lost (i.e., each person with pMOH was responsible for 2.2% of total days lost).

Headache yesterday

With mean headache days/month = 4.4 (see above), average probability of headache on any particular day for the 80.3% (n = 400/498) of participants with headache was 0.15 (4.4/30). Thus, predicted 1-day prevalence in the sample was 11.7% (0.15*80.3%). In fact, headache yesterday was reported by 82 (16.5% of the sample).

Two thirds of those with headache yesterday nonetheless were able to do all (n = 43/82; 52.4%) or more than half (n = 12/82; 14.6%) of their planned activities. But, because of headache yesterday, 20 participants (24.4% of those affected; 4.0% of the sample) had been able to carry out none of these activities and an additional seven (8.5%; 1.4% of the sample) less than half.

Thus, assuming yesterday was a typical day, our findings indicate that one in six (16.5%) of HIV+ people have headache on any particular day and more than one in 20 (4.0 + 1.4%) are severely functionally impaired by it.

Antiretroviral treatment

Lamivudine (3TC) was used in 100% of patients, tenofovir (TDF) in 89%, efavirenz (EFV) in 41% and dolutegravir (DTG) in 37%. Ritonavir (RTV), atazanavir (ATV), nevirapine (NVP), zidovudine (AZT), abacavir (ABC), lopinavir (LPV) and darunavir (DRV) were less used (12% of patients or fewer). Most patients (87.8%) were on triple therapy, most commonly 3TC + TDF + EFV (n = 201 [40.4%]), 3TC + DTG + TDF (n = 181 [36.3%]), 3TC + AZT + NVP (n = 33 [6.6%]), or 3TC + NVP + TDF (n = 16 [3.2%]). Four agents were used in 11.8%, usually 3TC + TDF + RTV + ATV (n = 42 [8.4%]) or 3TC + ATV + AZT + RTV (n = 9 [1.8%]). Only 0.4% were on five agents.

Viral load

Viral load was undetectable in 83.9% (n = 418/498) of participants, <10,000 copies/ml in 10.2% (n = 51), 10–50,000 copies/ml in 4.8% (n = 24) and >50,000 copies/ml in 1.0% (n = 5). All groups had similar 1-year prevalence of headache ($p = 0.16$ [Kruskal-Wallis test]) with no differences found in frequency ($p = 0.738$), intensity ($p = 0.094$) or attack duration ($p = 0.224$). However, numbers were small in the last three groups.

Discussion

In this study we observed a high 1-year headache prevalence (80.3%) and high attributable burden among HIV+ patients.

It was not a definitive study, with relatively small numbers. While it offers a number of insights into the topic of comorbidity between headache and HIV, it was designed to consider only this, not causation. We do not know whether the headaches reported by participants represented pre-existing disorders, or were related to HIV infection and/or to antiretroviral drugs. Comparison with data from the general population of Malawi would be informative, but unfortunately there are none.

The literature does provide some other help, however. In a small study of a HIV+ population (N = 119), none receiving antiretroviral drugs, 87% reported headache in the preceding 12 months (24). This was not only higher than but outside the 95% CI of our finding (80.3% [76.6–83.7%]) among participants who were all on ART. Significance is added by the considerably higher proportion of females in our study (72% compared with only 37%) (24), who are more predisposed to headache, countering the proposal that antiretroviral drugs might be a material cause of headache in HIV+ populations. Studies looking directly at headache as a reported adverse effect of antiretroviral drugs also offer little support to this proposal, with reporting rates among patients taking one or more of lamivudine, tenofovir, efavirenz, dolutegravir and ritonavir/lopinavir (the drugs used in our population) ranging from 1% to 18% (25–32).

HIV is a recognized risk factor for epilepsy and stroke (8,9), both pathologies sharing certain common mechanisms with some types of headache (10,12). HIV may also directly increase the risk of headache (33), but further studies are needed to confirm this. We can discount opportunistic infections of the brain (toxoplasmosis, herpes zoster, tuberculosis, Cryptococcus meningitis etc), which occur in seriously immunosuppressed HIV+ patients in AIDS stage 3 and 4 and cause headache along with other neurological symptoms. These are complications encountered in untreated patients or when there is a failure of ART, while the great majority of our patients were well, with undetectable viral loads.

In a recent study conducted on a HIV+ sample in Uganda (N = 333), referred to earlier, headache, defined as "yes" in answer to the question "Do you have headaches?" was reported by only 28% of participants (13). This questionably low value – compared to ours and to those from general population studies from Ethiopia (34) and Zambia (35), nearby SSA countries – had seven likely contributory explanations. First, the screening question in the Ugandan study was imprecise, providing no time frame. Second, it was embedded in a broader health questionnaire, which tends to reduce case ascertainment (2). Third, the sample was again unusual in its low proportion of females (51%) given that HIV is more prevalent among females in SSA (17). Fourth, the sample size of N = 333 was small (2). Fifth, the Ugandan study was in a rural population while ours was in an urban setting. Sixth, the Ugandan study did not report viral load (13). Viral load is the most reliable measure in the follow-up of HIV+ patients, being indicative not only of efficacy of and resistance to ART but also of adherence and retention within follow-up, the last reflecting patients' behaviours that might affect their propensity to headache. Last, to enter our study, we required that patients had already been followed in the centre for at least one year. Differences in follow-up duration between studies may influence readiness to report symptoms. Additionally, any effect HIV might have on headache would, presumably, take time to develop. Taken together, these differences make it difficult to compare the two studies.

Although there are no other data from Malawi, the studies in the nearby countries of Ethiopia (34) and Zambia (35) offer some comparisons. These found the 1-year prevalence of any headache in the general populations of these countries (adjusted as appropriate for age, gender and/or habitation [urban versus rural]) to be 43.1% and 61.6% respectively, both lower than (and outside the 95% CI of) the 80.3% [76.6–83.7%] observed in our HIV+ sample. The relatively high proportion of females in our study (72.1% compared to 55.3% in Ethiopia and 60.3% in Zambia) might in part explain this, but was not able to do so fully since males in our study also had a high prevalence of headache (71.9%). It should be borne in mind that the studies in Ethiopia and Zambia were both limited to participants aged 18–65 years, and that we could not, in our study, adjust for age, gender or habitation because we had no reliable data for the overall HIV+ population.

Despite the higher prevalence, paid workdays lost due to headache (among the working-age population) were only a little higher in our study, at 2.2%, than those observed in the general populations of Zambia (1.9%) (4) and Ethiopia (1.6%) (5). The latter studies reported higher mean headache intensities: on a 3-point scale (0–3), ours was 1.7 whereas the Ethiopia study reported 2.4 for tension type headache and 2.6 for migraine (34) and the Zambia study reported 1.9 and 2.7 for each of these (35). Reporting of headache intensity is inexact, and culturally influenced, while the 3-point scale lacks sensitivity. Additionally, headache intensity is influenced by analgesics, used by 77.5% of our sample, 57.5% in the last month. Unfortunately,

similar data were not reported in the other studies. Headache frequency is a major determinant of lost productive time. Mean headache days per month were 4.4 in our study, very similar to 4.6 in the Ethiopia study (5) but lower than 10.3 in the Zambia study (4), greatly inflated by the very high prevalence of H15+ (11.5% adjusted) (4). In our study this value was 3.8%, in Ethiopia 3.2% (34).

Many non-disease-related factors influence lost paid workdays, culture and economic necessity being important among them. Malawi is a low-income country: loss of pay has severe consequences. We did not collect data on occupation or type of employment.

The main limitations of our study were in the relatively small sample size (N = 498) (2) and the lack of diagnostic details. For these reasons, we do not wish to emphasize the differences between our HIV+ sample and the two general population samples. Our study should be regarded as a starting point in addressing the question: is there merit in assessing headache prevalence and attributed burden specifically in HIV+ populations? Our findings – that both are high – strongly indicates that there is.

Conclusions

Our study showed high headache prevalence and attributable burden among HIV+ patients in Malawi, disclosing a large unmet need for headache care.

Crucially, the burden of headache weighs no less heavily, and should not be less regarded, in the presence of HIV infection. HIV centres have been proposed as best able to unify treatment of both HIV/AIDS and NCDs (36), a process that would be in line with the World Health Organization's call and proposals for universal health coverage founded on "a strong and resilient people-centred health system with primary care as its foundation" (37) as well as WHO's Intersectoral Global Action Plan 2022-2031 on epilepsy and other neurological disorders (38). A step forward is to develop headache care at HIV centres, and the DREAM centre in Blantyre has embarked upon this (39).

Public Health Relevance

- People living with HIV in sub-Saharan Africa have a high prevalence of headache.
- Headache imposes additional burden and costs.
- Introducing headache care in HIV centres would meet a large need and could improve living conditions of individuals and their communities.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by *Lifting The Burden* and Fondazione Italiana Cefalee (FICEF).

ORCID iDs

Massimo Leone https://orcid.org/0000-0001-7475-4049
Luca Giani https://orcid.org/0000-0002-9565-5610

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1204–1222.
2. Stovner LJ, al Jumah M, Birbeck GL, et al. The methodology of population surveys of headache prevalence, burden and cost: Principles and recommendations from the Global Campaign against Headache. *J Headache Pain* 2014; 15: 1–30.
3. Steiner TJ, Gururaj G, Andrée C, et al. Diagnosis, prevalence estimation and burden measurement in population surveys of headache: presenting the HARDSHIP questionnaire. *J Headache Pain* 2014; 15: 3.
4. Mbewe E, Zairemthiama P, Paul R, et al. The burden of primary headache disorders in Zambia: national estimates from a population-based door-to-door survey. *J Headache Pain* 2015; 16: 513.
5. Zebenigus M, Tekle-Haimanot R, Worku DK, et al. The burden of headache disorders in Ethiopia: national estimates from a population-based door-to-door survey. *J Headache Pain* 2017; 18: 58.
6. Gouda HN, Charlson F, Sorsdahl K, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: results from the Global Burden of Disease Study 2017. *Lancet Global Health* 2019; 7: e1375–e1387.
7. World Health Organization. HIV/AIDS, https://www.who.int/news-room/fact-sheets/detail/hiv-aids (2021, accessed 16 March 2022).
8. Benjamin LA, Corbett EL, Connor MD, et al. HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: A case-control study. *Neurology* 2016; 86: 324–33.
9. Mateen FJ, Shinohara RT, Carone M, et al. Neurologic disorders incidence in HIV+ vs HIV− men: Multicenter

AIDS Cohort Study, 1996–2011. *Neurology* 2012; 79: 1873–80.
10. Bigal ME, Lipton RB, Cohen J, et al. Epilepsy and migraine. *Epilepsy & Behavior* 2003; 4: 13–24.
11. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. *J Headache Pain* 2020; 21: 23.
12. Ramzan M. Chapter 42 Stroke, migraine, and headache. *Handb Clin Neurol* 2008; 93: 841–849.
13. Sohail S, Nakigozi G, Anok A, et al. Headache prevalence and its functional impact among HIV-infected adults in rural Rakai District, Uganda. *J Neurovirol* 2019; 25: 248–253.
14. Dream – Sant'Egidio. Home, https://www.dream-health.org/ (accessed 16 March 2022).
15. World Bank. Malawi - Data, https://data.worldbank.org/country/malawi (accessed 16 March 2022).
16. PopulationPyramid.net. Population of World 2019, https://www.populationpyramid.net/malawi/2019/ (accessed 19 May 2021).
17. UNAIDS. AIDSinfo, http://aidsinfo.unaids.org/ (accessed 16 March 2022).
18. World Bank. Life expectancy at birth, total (years) - Malawi Data, https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=MW (2019, accessed 16 March 2022).
19. World Health Organization. *Atlas: Country Resources for Neurological Disorders, 2nd ed*. Geneva: World Health Organization, 2017.
20. Peters M, Bertolote JM, Houchin C, et al. Translation protocol for lay documents. *J Headache Pain* 2007; 8: S43–S44.
21. Steiner TJ, Lipton RB, *Lifting The Burden*: The Global Campaign against Headache. The Headache-Attributed Lost Time (HALT) Indices: measures of burden for clinical management and population-based research. *J Headache Pain* 2018; 19: 12.
22. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
23. World Bank. Population, female (% of total population) – Malawi Data, https://data.worldbank.org/indicator/SP.POP.TOTL.FE.ZS?locations=MW (2019, accessed 16 March 2022).
24. Sampaio Rocha-Filho PA, Torres RCS, Ramos Montarroyos U. HIV and headache: a cross-sectional study. *Headache* 2017; 57: 1545–1550.
25. Avihingsanon A, Maek-A-Nantawat W, Gatechompol S et al. Efficacy and safety of a once-daily single-tablet regimen of tenofovir, lamivudine, and efavirenz assessed at 144 weeks among antiretroviral-naive and experienced HIV-1-infected Thai adults. *Int J Infect Dis* 2017; 61: 89–96.
26. Orkin C, DeJesus E, Sax PE et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV* 2020; 7: e389–e400.
27. Wohl DA, Yazdanpanah Y, Baumgarten A et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; 6: e355–e363.
28. Hoffmann C and Llibre JM. Neuropsychiatric adverse events with dolutegravir and other integrase strand transfer inhibitors. *AIDS Rev* 2019; 21: 4–10.
29. Yagura H, Watanabe D, Kushida H et al. Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse events in Japanese individuals infected with HIV-1. *BMC Infect Dis* 2017; 17: 622.
30. Flamm JA, Brinson C, Clarke A et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV* 2020; 7: e389–e400.
31. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs* 2003; 63: 769–802.
32. Molina JM, Squires K, Sax PE et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV* 2018; 5: e211–e220.
33. Kirkland KE, Kirkland K, Many WJ, et al. Headache among patients with HIV disease: prevalence, characteristics, and associations. *Headache* 2012; 52: 455–66.
34. Zebenigus M, Tekle-Haimanot R, Worku DK, et al. The prevalence of primary headache disorders in Ethiopia. *J Headache Pain* 2016; 17: 110.
35. Mbewe E, Zairemthiama P, Yeh H-H, et al. The epidemiology of primary headache disorders in Zambia: a population-based door-to-door survey. *J Headache Pain* 2015; 16: 515.
36. United Nations 66/2. Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, https://www.who.int/nmh/events/un_ncd_summit2011/political_declaration_en.pdf (2012, accessed 16 March 2022).
37. World Health Organization. Universal Health Coverage, https://www.who.int/health-topics/universal-health-coverage#tab=tab_1 (2019, accessed 16 March 2022).
38. World Health Organization. Draft Intersectoral global action plan on epilepsy and other neurological disorders 2022-2031, https://www.who.int/news/item/12-01-2022-draft-intersectoral-global-action-plan-on-epilepsy-and-other-neurological-disorders-2022-2031 (2021, accessed 16 March 2022)
39. Leone M, Palombi L, Guidotti G. et al. What headache services in sub-Saharan Africa? The DREAM program as possible model. *Cephalalgia* 2019; 39: 1339–1340.