Causes of HIV-related CNS infection in Cameroon, Malawi, and Tanzania: epidemiological findings from the DREAMM HIV-related CNS implementation study

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Summary

Background **CNS infections cause approximately a third of HIV-related deaths. The Driving Reduced AIDS-Associated Meningo-encephalitis Mortality DREAMM study aimed to prospectively diagnose the aetiology of HIV-related CNS infection in five public hospitals in Cameroon, Malawi, and Tanzania.**

Methods **DREAMM was a multicentre, hybrid type-2 implementation science project. Adults (aged ≥18 years) presenting with a first episode of suspected CNS infection, who were HIV seropositive or willing to have an HIV test, were eligible for recruitment. Following implementation of the DREAMM model of care, we measured the prevalence of cryptococcal meningitis, tuberculous meningitis, bacterial meningitis, and cerebral toxoplasmosis and did a χ^2 test to assess whether prevalence differed between countries. We also reported disease-specific mortality and *Toxoplasma gondii* seroprevalence.**

Findings **Of 356 participants with suspected CNS infection analysed at baseline, 269 (76%) were diagnosed as having a CNS infection. Of these, 202 (75%) had a confirmed diagnosis. Between Cameroon, Malawi, and Tanzania, the prevalence of the four main types of CNS infection differed (cryptococcal meningitis p=0·0014, bacterial meningitis p=0·0043, CNS tuberculosis p<0·0001, and toxoplasmosis p<0·0001). Cryptococcal meningitis (148 [55%] of 269) was the leading cause overall. The next most common causes were CNS tuberculosis in Tanzania (29 [29%] of 99) and bacterial meningitis in Malawi (15 [19%] of 80). In Cameroon, cerebral toxoplasmosis (39 [43%] of 90) was the leading cause followed by cryptococcal meningitis (36 [40%] of 90). For cryptococcal meningitis, all-cause 2-week mortality was 23% (34 of 147) and all-cause 10-week mortality was 45% (66 of 146).**

Interpretation **Within the study population, the aetiology of HIV-related CNS infection varied substantially between Malawi, Cameroon, and Tanzania. Additional prospective epidemiological data are needed to inform HIV programmes. 2-week cryptococcal meningitis mortality outcomes were similar to those of clinical trials. However, new interventions are urgently needed to sustain mortality reductions following hospital discharge.**

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Introduction

HIV-related CNS infections are the second most common cause of adult HIV-related deaths after tuberculosis, causing approximately a third of HIV-related deaths.[1,2] Most cases occur in people with advanced HIV disease,[1] defined in adults by WHO as a CD4 count of less than 200 cells per µL. In low-income and middle-income countries (LMICs), antiretroviral therapy (ART) non-adherence and failure are key drivers of CNS infections, leading to largely unchanged incidence despite ART roll-out.[3,4]

Cryptococcal meningitis is widely reported as the leading cause of adult HIV-related CNS infection in African LMICs.[1] Additional common causes include tuberculous meningitis, bacterial meningitis, and cerebral toxoplasmosis.[1] However, the epidemiology of HIV-related CNS infection according to aetiology within African LMIC settings is poorly described. Additionally, outcomes within routine care services are rarely collected or published. A systematic review and meta-analysis of the available data found that the routine care of cryptococcal meningitis, tuberculous meningitis, and pneumococcal meningitis (the most common cause of HIV-related bacterial meningitis) in African LMICs was associated with 2-week mortality of 44% (95% CI 39–49), 46% (33–59), and 54% (44–64), respectively.[5] Mortality

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See **Online** for appendix 3

Research in context

Evidence before this study

HIV-related CNS infections cause up to a third of HIV-related deaths, which have plateaued in recent years. There is an urgent need to reduce mortality caused by HIV-associated CNS infections in African low-income and middle-income countries (LMICs) and bridge the gap between clinical trial and routine-care outcomes. To achieve this goal, the epidemiology of HIV-related CNS infections needs to be understood as many cases remain undiagnosed within routine-care services. In the efforts to end AIDS deaths, epidemiological data are essential to inform HIV programmes and ensure accurate composition and quantification of packages of care for HIV-related CNS infections according to aetiology. For example, it is not currently known whether packages of care for HIV-related CNS infection need to be adapted regionally. The DREAMM project developed, implemented, and assessed pragmatic interventions and strategies that substantially reduced mortality from adult HIV-related CNS infection in Cameroon, Malawi, and Tanzania. A key project aim was to prospectively determine the aetiology of HIV-related CNS infections. We searched PubMed, Cochrane Library and Embase for studies published between Jan 1, 2004, and Nov 1, 2023, using the following terms: "HIV", "AIDS", "LMICs", "HIV-related CNS Infections", "cryptococcal meningitis", "tuberculous meningitis", "bacterial meningitis", "cerebral toxoplasmosis", "implementation interventions", implementation strategies", and appropriate variations of each. No studies were found that translated research evidence into routine practices and procedures to reduce deaths from HIV-related CNS infection in adults in African LMICs. Prospective, multicentre studies of the epidemiology of adult HIV-related CNS infection in this context were similarly lacking.

Added value of this study

The Driving Reduced AIDS-Associated Meningo-encephalitis Mortality (DREAMM) epidemiological results have underscored potential geographical variation in the aetiology of HIV-related CNS infection in five public hospitals in Cameroon, Malawi, and Tanzania. Such epidemiological data are important to enable ministries of health, implementing partners, and global funders to accurately quantify need for tests, services, and medicines for HIV-related CNS infection and potentially adapt these regionally to save lives. Additionally, DREAMM aetiology-specific CNS mortality data presented here have shown that short-term mortality outcomes for cryptococcal meningitis, a leading cause of HIV-related CNS infection and deaths, similar to those of clinical trials within resource-limited settings, are achievable within routine-care services in African LMICs. However, new interventions are urgently needed to sustain mortality reductions following hospital discharge in line with data showing substantial post-hospitalisation mortality for people living with HIV.

Implications of all the available evidence

The study's findings from five public hospitals point to potential regional variation in the aetiology of HIV-related CNS infections. However, additional epidemiological data are required to unequivocally describe national and regional prevalences of HIV-related CNS infection according to aetiology in African LMICs. The project also underlined the effect of in-hospital interventions on short-term mortality, emphasising the need for tailored diagnostic and treatment approaches. Algorithms and implementation strategies, in addition to post-discharge interventions, are crucial to inform care, reduce mortality, and shape health-care policies in resource-limited settings. Specifically, the DREAMM project's intervention and strategies synergise with advanced-HIV programmes, offering streamlined diagnostic and treatment approaches. Integration into broader health-care systems has the potential to ensure sustained impact, enhancing overall HIV care strategies and global efforts to end HIV-related deaths. This study has shed light on important gaps in the provision of care for HIV-related CNS infection within routine care, while providing evidence of the impact of in-hospital interventions and implementation strategies to provide rapid, targeted therapy according to CNS-infection aetiology, thus reducing mortality. The DREAMM project highlights the need for strengthened, locally led health systems, including HIV-related CNS infection packages of care targeting the full range of aetiologies and improved access to essential tests and medicines. Unanswered questions centre on optimal post-discharge care and the potential effect of regional differences in the aetiology of HIV-related CNS infection. Future research into HIV-related CNS infection must add to the epidemiological data presented here and explore long-term outcomes and effective strategies for diverse health-care contexts.

data for cerebral toxoplasmosis are also lacking; however, cerebral toxoplasmosis caused 10% of both hospital admissions and deaths in a multicentre cohort of people living with HIV admitted to hospital over a 6-month period in west Africa and was associated with inpatient mortality of 29% in a small cross-sectional study from Cameroon.[6,7]

For more on **DREAMM** see https://www.dreamm.net

To meet the Sustainable Development Goals (SDGs), and for humanitarian reasons, persistently high mortality from HIV-related CNS infection must be urgently addressed.[8] Despite advances in diagnostic tests, clinical trials, policy, and advanced-HIV disease programmes,[3,9,10] notable gaps in the provision of care for HIV-related CNS infection within routine care services persist. Driving Reduced AIDS-Associated Meningo-encephalitis Mortality (DREAMM) was a multicentre, hybrid type-2 implementation science project[11] that developed, implemented, and assessed pragmatic interventions and strategies to reduce mortality from HIV-related CNS infection in five secondary and tertiary public hospitals in Cameroon, Malawi, and Tanzania. These new strategies substantially reduced HIV-related CNS infection mortality within routine care services.[12]

DREAMM was divided into three sequential phases: observation, training, and implementation. Observation-phase findings provided a situational analysis of practices and procedures for adult HIV-related CNS infection within routine care services.[12] A key finding of the observation phase was that proven diagnoses of HIV-related CNS infection were rarely made, leading to largely empirical treatment, resulting in poor outcomes.[12] Measures to strengthen health systems and provision of specific packages of care to rapidly diagnose and manage HIV-related CNS infection according to aetiology are therefore urgently required. To inform the quality of HIV programmes and composition of packages of care for HIV-related CNS infection and assess whether these vary regionally, epidemiological data on the aetiology of CNS infection and disease-specific mortality data are required. Within African LMICs, as highlighted by WHO, such data, including the prevalence of cerebral toxoplasmosis, are largely unavailable.[13]

Here we present epidemiological data on the cause of CNS infection and disease-specific HIV-related CNS infection mortality during the DREAMM implementation phase in Malawi, Cameroon, and Tanzania. We focused on this phase because, during the observation phase, many diagnostic tests were largely unavailable.

Methods

Participants

Between Jan 9, 2018, and March 25, 2021, consecutive adults (aged ≥18 years) living with HIV presenting to one of the five participating hospitals with a first episode of suspected CNS infection were eligible for recruitment. Additional inclusion criteria were being HIV seropositive or willing to have an HIV test, and willingness to participate in the study. Exclusion criteria were suspected relapse of HIV-related CNS infection, being HIV seronegative, pregnancy or lactation, and confirmed diagnosis of primary CNS lymphoma or cerebral malaria. From June 25, 2020, individuals diagnosed with SARS-CoV-2 infection were excluded.

Local ethics and national regulatory approvals were obtained from St George's Research Ethics Committee (SGREC16.0010); the Ministry of Health, Community Development Gender, Elderly & Children Tanzania (NIMR/HQ/R.8c/Vol.I/1090) in Tanzania; the Office of Human Research Ethics and the National Health Sciences Research Committee (16/7/1635) in Malawi; and Comité National d'Ethique pour la Recherche en Santé Humaine (0977/A/MINSANTE/SESP/SG/DROS/) in Cameroon. All participants provided written informed consent. If a participant had altered mental status, written informed consent was obtained from the next of kin; if capacity to provide consent recovered, written informed consent was obtained directly from the participant. The development and delivery of the project was overseen by an independent Data Safety Monitoring Board and a Project Safety and Advisory Committee, including patient advocates and civil society representatives.

Overview of procedures

As part of the syndromic approach to the diagnosis of HIV-related CNS infection adopted, routine care staff were trained on the symptoms and signs of the four main causes of HIV-related CNS infection (cryptococcal meningitis, bacterial meningitis, tuberculous meningitis, and cerebral toxoplasmosis) as well as neurosyphilis. Diagnosis and management of the primary CNS infection was made according to the stepwise DREAMM algorithm described elsewhere.[12] Two key features of the algorithm were bedside rapid diagnostic tests (RDTs) in parallel with full laboratory testing.[12] Unless clinically contraindicated (eg, due to raised intracranial pressure in cases of suspected cerebral toxoplasmosis), all participants received a full CSF analysis including white cell count, protein, glucose, and culture examinations. Within public hospitals in African LMICs, brain biopsy and polymerase chain technologies beyond GeneXpert testing are largely unavailable, and access to neuroimaging is often very limited within routine-care services. Key investigations for HIV-related CNS infection performed (lumbar puncture and brain imaging) according to clinical presentation have been described elsewhere.[12]

For more on **DREAMM clinical training** see https://figshare.com/projects/DREAMM_Clinical_Training/127199

Ongoing mentorship and laboratory-capacity building occurred within weekly joint laboratory and clinical communities of practice that were attended by routine-care laboratory and clinical staff, the site principal investigators (PIs) and their research or implementation teams, and the international experts.[12] A virtual ward round of each participant took place during these communities of practice.[12] Clinical presentations, results of bedside RDTs and laboratory tests, working diagnoses, differential diagnoses, and treatments administered were reviewed extensively.

In addition to the weekly virtual ward rounds, all final diagnoses of primary CNS infection and non-CNS infection were assessed for accuracy and consistency through case record form review by international experts in consultation with the site PIs and their respective teams. In rare cases of persistent diagnostic uncertainty, additional reviews were requested from independent experts.

Diagnostic procedures for individual infections

Unless contraindicated, all DREAMM participants received a bedside cryptococcal antigen lateral flow assay (CrAg LFA) in blood and CSF, and urinary lipoarabinomannan to detect tuberculosis.

Cryptococcal meningitis was diagnosed by a positive CrAg in blood and CSF. Additionally, fungal cultures were performed following routine laboratory-capacity building as part of the DREAMM intervention. Concordance of bedside RDTs with laboratory testing was verified and any discordant cases reviewed by the site

PI and Chief Investigator within 24 h. If the CrAg LFA tests were negative, then we also did a *Streptococcus pneumoniae* RDT in CSF. If the level of consciousness was low, or focal neurological deficits were identified, or any other clinical suspicion of cerebral toxoplasmosis or space-occupying lesions was present, we did neuroimaging.[12] Following investigation, if we found no evidence of CNS infection and an alternative diagnosis (eg, renal failure, disseminated tuberculosis, or urinary sepsis) that can resemble a presentation with CNS infection was identified or suspected, then the participant was classified as a non-CNS case.

Bacterial meningitis was diagnosed microbiologically on the basis of one or more tests being positive in CSF: *S pneumoniae* RDT, gram stain, or CSF bacterial culture. Probable cases were diagnosed and managed by the site PIs and discussed during the weekly communities of practice.

Confirmed cases of tuberculous meningitis[14] met one or more of the following criteria: acid-fast bacilli seen in the CSF, *Mycobacterium tuberculosis* cultured from the CSF, or a CSF-positive commercial nucleic acid amplification test. We did both GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA) testing in parallel in both CSF and urine samples. CNS tuberculosis was defined as including cases of tuberculous meningitis and tuberculoma. We did urinary lipoarabinomannan testing in all participants, in line with the latest WHO recommendations on advanced HIV disease.[15] In cases of diagnostic uncertainty, we did a second lumbar puncture (with repeat CSF white cell count, protein, glucose, large-volume CSF-tuberculosis culture, and commercial nucleic acid amplification) within 48 h, in line with recommended practices for tuberculous meningitis diagnosis.[16] Probable and likely cases were

	CNS infection				Without CNS infection			
	Tanzania (n=99)	Malawi (n=80)	Cameroon (n=90)	Total (n=269)	Tanzania (n=51)	Malawi (n=27)	Cameroon (n=9)	Total (n=87)
Sex								
Female	62/99 (63%)	30/80 (38%)	48/90 (53%)	140/269 (52%)	36/51 (71%)	9/27 (33%)	6/9 (67%)	51/187 (59%)
Male	37/99 (37%)	50/80 (63%)	42/90 (47%)	129/269 (48%)	15/51 (29%)	18/27 (67%)	3/9 (33%)	36/87 (41%)
Age, years	39 (30–46; n=99)	39 (33–43; n=80)	41 (36–45; n=90)	40 (35–45; n=269)	38 (30–45; n=51)	37 (30–47; n=27)	45 (34–58; n=9)	38 (30–47; n=87)
Bodyweight, kg	51 (48–64; n=92)	55 (50–62; n=75)	60 (55–67; n=29)	55 (50–65; n=196)	58 (50–70; n=43)	51 (46–56; n=26)	..*	55 (50–65; n=69)
CD4 count, cells per µL	63 (22–139; n=68)	63 (17–151; n=75)	60 (35–110; n=59)	61 (25–137; n=202)	265 (47–438; n=30)	338 (205–468; n=22)	223 (101–598; n=6)	282 (101–468; n=58)
Advanced HIV disease (CD4 <200 cells per µL)	58/68 (85%)	61/75 (81%)	53/59 (90%)	172/202 (85%)	14/30 (47%)	5/22 (23%)	3/6 (50%)	22/58 (38%)
Critically unwell† with advanced HIV disease	53/58 (91%)	52/61 (85%)	45/53 (85%)	150/172 (87%)	14/14 (100%)	5/5 (100%)	3/3 (100%)	22/22 (100%)
Viral load, copies per mL	67 241 (59 796–97 545; n=3)	103 000 (824–399 000; n=53)	236 052 (15 477–750 155; n=62)	135 419 (8052–621 866; n=118)	..*	167 (40–12 500; n=18)	216 (46–145 063; n=7)	216 (40–32 100; n=25)
ART exposed	67/98 (68%)	51/80 (64%)	55/90 (61%)	173/268 (65%)	39/51 (76%)	25/27 (93%)	7/9 (78%)	71/87 (82%)
Time on ART, months	8 (1–31; n=82)	25 (4–54; n=78)	56 (12–93; n=84)	21 (3–67; n=244)	33 (15–65; n=34)	32 (6–110; n=26)	31 (28–64; n=8)	32 (13–79; n=68)
Altered mental status	78/99 (79%)	58/80 (73%)	55/90 (61%)	191/269 (71%)	45/51 (88%)	22/27 (81%)	9/9 (100%)	76/87 (87%)
Critically unwell†	92/99 (93%)	71/80 (89%)	76/90 (84%)	239/269 (89%)	50/51 (98%)	26/27 (96%)	9/9 (100%)	85/87 (98%)
ECOG score ≥4	76/97 (78%)	28/78 (36%)	63/89 (71%)	167/264 (63%)	36/48 (75%)	8/27 (30%)	5/9 (56%)	49/84 (58%)
Anaemia, haemoglobin <70 g/L	8/97 (8%)	2/75 (3%)	2/89 (2%)	12/261 (5%)	7/50 (14%)	1/25 (4%)	0/9 (0%)	8/84 (10%)
eGFR								
Normal, >89 mL/min	54/97 (56%)	61/75 (81%)	50/90 (56%)	165/262 (63%)	19/50 (38%)	14/22 (64%)	5/9 (56%)	38/81 (47%)
Mild, 60–89 mL/min	31/97 (32%)	8/75 (11%)	31/90 (34%)	70/262 (27%)	17/50 (34%)	0/22 (0%)	3/9 (33%)	20/81 (25%)
Moderate, 45–59 mL/min	8/97 (8%)	3/75 (4%)	4/90 (4%)	15/262 (6%)	6/50 (12%)	5/22 (23%)	0/9 (0%)	11/81 (14%)
Moderate–severe, 30–44 mL/min	1/97 (1%)	0/75 (0%)	1/90 (1%)	2/262 (1%)	1/50 (2%)	1/22 (5%)	1/9 (11%)	3/81 (4%)
Severe, <30 mL/min	3/97 (3%)	3/75 (4%)	4/90 (4%)	10/262 (4%)	7/50 (14%)	2/22 (9%)	0/9 (0%)	9/81 (11%)

Data are n/N (%) or median (IQR; n with available data). ECOG scale indicates increasing levels of disability, with 0 indicating fully active, 1 being restricted in strenuous activity, 2 being restricted in work activity but ambulatory and capable of self-care, 3 being capable of limited self-care, 4 being completely disabled, and 5 being dead. ART=antiretroviral therapy. ECOG=Eastern Cooperative Oncology Group. eGFR=estimated glomerular filtration rate. *Data missing for all participants. †Defined as the presence of altered mental status or focal neurology or respiratory rate of more than 20 breaths per min, heart rate of more than 120 beats per min, systolic blood pressure of less than 90 mm Hg, temperature higher than 39°C or ECOG score of more than 3.

Table 1: **Baseline characteristics**

identified by the site PIs in consultation with international experts, including during the weekly communities of practice. Despite investigation, diagnostic uncertainty persisted in certain cases and, where cerebral toxoplasmosis was included in the differential diagnosis, these cases were defined as CNS-tuberculosis or cerebral toxoplasmosis and treated for both pathogens. Disseminated tuberculous cases had no evidence of meningeal inflammation in CSF but, as this was not routine practice within the sites, and also due to limitations in availability of neuroimaging, it was not feasible to scan all participants with suspected tuberculous to exclude subclinical tuberculomas, which are common in miliary tuberculous.[17,18]

Cerebral toxoplasmosis was diagnosed according to clinical history (including presence of seizures or focal neurology), compatible radiological findings on contrast brain CT or MRI, and positive *Toxoplasma gondii* serology. To help identify the seroprevalence of *T gondii*, we did serological testing in all participants. In the absence of a diagnosis of cerebral toxoplasmosis, positive *T gondii* serology usually denotes latent infection.

We tested for neurosyphilis when RDTs for syphilis (DPP, Chembio, Biosynex, Illkirch-Graffenstaden, France) were positive in blood according to an algorithm (appendix 3 p 5). Positive syphilis RDTs in CSF were confirmed, where possible, with a reactive CSF Venereal Disease Research Laboratory assay. Presumptive neurosyphilis was identified during the communities of practice.[19]

Statistical analysis

The sample size was driven by the all-cause mortality comparison, reported elsewhere,[12] between the observation and implementation phases: the total planned recruitment for the mortality comparison was 125 participants for the DREAMM observation phase and 140 participants for the DREAMM implementation phase to ensure sufficient power to compare all-cause mortality between these phases. To describe the epidemiology of HIV-related CNS infection aetiology using an estimate of 60% prevalence for cryptococcal meningitis, 145 participants were required to be enrolled within the implementation phase for 8% precision on a 95% CI.

We calculated the prevalence of cryptococcal, tuberculous, and bacterial meningitis and cerebral toxoplasmosis, defined as the number of participants diagnosed divided by the total number of participants with a CNS infection diagnosis, and expressed as a proportion. We presented these estimates overall and by site.

We summarised demographic and clinical characteristics by country, CNS infection type, and by CNS infection cases (participants with a probable or confirmed HIV-related CNS infection) and non-CNS infection cases (where an HIV-related CNS infection was disproved). To compare characteristics between CNS infection cases and non-CNS infection cases, we used a χ^2 test for categorical variables and a *t* test for continuous variables.

The percentage of CNS infection cases with each CNS infection type are presented along with the percentage that were microbiologically or radiologically confirmed. We used a χ^2 test to compare proportions across countries.

For the non-CNS infection cases, we categorised the causes of admission and the percentages of each cause were presented by country along with the 2-week and 10-week all-cause mortality.

We calculated the percentage and exact (Clopper–Pearson) 95% CIs of all-cause mortality at 2 weeks, 10 weeks, and 6 months (obtained by telephone follow-up) for the CNS infection cases, overall, by country, CNS infection type, and cryptococcal meningitis treatment type. All analyses were performed using Stata (version 17).

The DREAMM study is registered with ClinicalTrials.gov, NCT03226379.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 356 participants with suspected CNS infection analysed during the implementation phase, 269 (76%) were confirmed to have CNS infection and 87 (24%) had no CNS infection. Overall, participants with CNS infection had a lower CD4 count (median CD4 count 61 cells per µL [IQR 25–137] *vs* 282 cells per µL [101–468]; p<0·0001), higher viral load (median 135 419 copies per mL [8052–621 866] *vs* 216 copies per mL [40–32 100]; p<0·0001), and less ART experience (173 [65%] of 268 *vs* 71 [82%] of 87; p=0·0029) than those with no CNS

	Tanzania (n=51)	Malawi (n=27)	Cameroon (n=9)	Total n=87)
Tuberculosis	9/35 (26%)	7/25 (28%)	2/9 (22%)	18/69 (26%)
Renal impairment	6/35 (17%)	5/25 (20%)	0/9 (0%)	11/69 (16%)
Sepsis	4/35 (11%)	7/25 (28%)	0/9 (0%)	11/69 (16%)
Other bacterial Infection*	6/35 (17%)	1/25 (4%)	1/9 (11%)	8/69 (12%)
Cerebral malaria	5/35 (14%)	0/25 (0%)	1/9 (11%)	6/69 (9%)
Epilepsy	3/35 (9%)	3/25 (12%)	0/9 (0%)	6/69 (9%)
Brain insult†	1/35 (3%)	3/25 (12%)	1/9 (11%)	5/69 (7%)
Other‡	4/35 (11%)	7/25 (28%)	5/9 (56%)	16/69 (23%)
2-week mortality	1/3 (33%)§	3/26 (12%)¶	1/8 (13%)‖	5/37 (14%)§¶‖
10-week mortality	1/3 (33%)§	5/26 (19%)¶	1/8 (13%)‖	7/37 (19%)§¶‖

Data are n/N (%). Some participants had more than one additional diagnosis, therefore the number of diagnoses is greater than the number of participants. *Pneumonia (n=3), syphilis (n=3), urinary tract infection (n=1), and non-specified bacterial infection (n=1). †Cerebrovascular accident (n=3), acquired brain injury (n=1), and meningeal haemorrhage (n=1). ‡Alcohol related (n=4), CNS lymphoma (n=3), psychosis (n=2), bleeding disorder (n=1), cardiomyopathy (n=1), diabetes (n=1), malaria (n=1), malignancy (n=1), migraine (n=1), and vasculitis (n=1). Unknown causes numbered 16 in Tanzania, two in Malawi, and none in Cameroon. §48 non-CNS cases in Tanzania were not followed up. ¶One participant from Malawi was lost to follow-up before 2 weeks. ‖One participant from Cameroon was lost to follow-up before 2 weeks.

Table 2: **Causes of hospital admission and 2-week and 10-week mortality for non-CNS cases**

	Tanzania (n=99)	Malawi (n=80)	Cameroon (n=90)	Total (n=269)	Microbiologically or radiologically proven diagnoses (n=202)
Cryptococcal meningitis	59 (60%; 49–69)	53 (66%; 55–76)	36 (40%; 30–51)	148 (55%; 49–61)	144/148 (97%)*
CNS tuberculosis†	29 (29%; 21–39)	7 (9%; 3–17)	11 (12%; 6–21)	47 (17%; 13–23)	17/47 (36%)‡
Bacterial meningitis	5 (5%; 2–11)	15 (19%; 11–29)	6 (7%; 2–14)	26 (10%; 6–14)	11/26 (42%)§
Cerebral toxoplasmosis	0	0	39 (43%; 33–54)	39 (14%; 11–19)	38/39 (97%)
CNS tuberculosis or cerebral toxoplasmosis	4 (4%; 1–10)	0	1 (1%; <1–6)	5 (2%; 1–4)	NA
Neurosyphilis	3 (3%; 1–9)	5 (6%; 2–14)	0	8 (3%; 1–6)	7/8 (88%)
Other	5 (5%; 2–11)	3 (4%; 1–11)	3 (3%; 1–90)	11 (4%; 2–7)¶	0

Data are n (%; 95% CI) or n/N (%). 15 (6%) of 269 participants had a co-infection with a second CNS infection. These participants are represented twice in the table; therefore, the sum of numerators in each row will be more than the denominator. CrAg LFA=cryptococcal antigen lateral flow assay. NA=not applicable. RDT=rapid diagnostic test. *Four participants were CrAg LFA positive in blood but not in CSF and according to independent expert review were thought to have cryptococcal meningitis. †CNS tuberculosis was defined as cases of tuberculous meningitis and tuberculoma. ‡Nine (19%) of 47 participants were GeneXpert positive in CSF and 14 (30%) were GeneXpert Ultra positive in CSF (six participants had a positive test on both assays). §Ten (40%) of 25 were *Streptococcus pneumoniae* RDT positive and 11 (42%) of 26 were *S pneumoniae* RDT positive or culture positive. Bacterial meningitis cases were *S pneumoniae* RDT or culture positive in Cameroon (one [20%] of five), Malawi (nine [60%] of 15), and Tanzania (one [17%] of six). ¶Three viral, one varicella zoster encephalitis, and seven unknown.

Table 3: **CNS infection type**

	Tanzania		Malawi		Cameroon		Total	
	2-week mortality	10-week mortality	2-week mortality	10-week mortality	2-week mortality	10-week mortality	2-week mortality	10-week mortality
1 week amphotericin B deoxycholate plus flucytosine	8/36 (22%; 10–39)	17/36 (47%; 30–65)	9/41 (22%; 12–38)	18/41 (44%; 29–60)	0/0	0/0	17/77 (22%; 14–33)	35/77 (45%; 35–57)
1 week liposomal amphotericin B deoxycholate plus 5-fluorocytosine	0/0	0/0	3/11 (27%; 8–63)	6/11 (55%; 24–82)	0/0	0/0	3/11 (27%; 8–63)	6/11 (55%; 24–82)
2 weeks fluconazole plus flucytosine	3/10 (30%; 6–65)*	5/10 (50%; 19–81)*	0/0	0/0	7/36 (19%; 9–36)	13/36 (36%; 22–53)	10/46 (22%; 12–36)	18/46 (39%; 26–54)

Data are n/N (%; 95% CI). *One participant in Tanzania, fluconazole 1200 mg plus flucytosine 25 mg group, was lost to follow-up before 2 weeks.

Table 4: **Cryptococcal meningitis mortality**

	Tanzania	Malawi*	Cameroon	Total
CNS cases	44/81 (54%)	8/58 (14%)	87/89 (98%)	139/228 (61%)
Non-CNS cases	24/38 (63%)	2/13 (15%)	9/9 (100%)	35/60 (58%)
Total	68/119 (57%)	10/71 (14%)	96/98 (98%)	174/288 (60%)

Data are n/N (%). *Data for Zomba, Malawi are unavailable.

Table 5: Toxoplasma gondii **seroprevalence**

infection (table 1). Due to health-system challenges relating to CD4 counts and viral loads beyond the scope of the DREAMM project, CD4 count results were available in 260 (73%) of 356 participants, and viral load results available in 143 (40%) participants. The main diagnoses, among those known, within the non-CNS-infection group were tuberculosis (18 [26%] of 69), renal impairment (11 [16%]), and sepsis (11 [16%]; table 2).

Following implementation of the new DREAMM clinical and laboratory pathways for the main causes of CNS infection (cryptococcal meningitis, bacterial meningitis, cerebral toxoplasmosis, and tuberculosis meningitis) and neurosyphilis, 202 (75%) of 269 patients had a microbiologically or radiologically confirmed diagnosis (table 3). Between Cameroon, Malawi, and Tanzania, the prevalence of the four main types of CNS infection differed (cryptococcal meningitis [p=0·0014], bacterial meningitis [p=0·0043], CNS tuberculosis [p<0·0001], and toxoplasmosis [p<0·0001]). Overall, most participants with CNS infection had cryptococcal meningitis (55% [95% CI 49–61]; 148 of 269), which was the leading cause of HIV-related CNS infection in Malawi (66% [55–76]; 53 of 80) and Tanzania (60% [49–69]; 59 of 99; table 3; appendix 3 p 5). The second most common HIV-related CNS infection diagnoses were CNS tuberculosis in Tanzania (29% [21–39]; 29 of 99) and bacterial meningitis in Malawi (19% [11–29]; 15 of 80). In Cameroon, cerebral toxoplasmosis was the leading cause of HIV-related CNS infection (43% [33–54]; 39 of 90), followed by cryptococcal meningitis (40% [30–51]; 36 of 90; table 3). Additionally, neurosyphilis was identified in 3% (1–6; eight of 269) of participants (table 3).

172 (85%) of 202 participants with confirmed CNS infection had advanced HIV disease, 191 (71%) of 269 had altered mental status (a poor prognostic marker),

	Tanzania			Malawi			Cameroon			Total		
	2-week mortality	10-week mortality	6-month mortality	2-week mortality	10-week mortality	6-month mortality	2-week mortality	10-week mortality	6-month mortality	2-week mortality	10-week mortality	6-month mortality
All CNS cases	28/96 (29%; 20–39)*†‡	46/95 (48%; 38–59)*†‡§	52/93 (56%; 45–66)	21/79 (27%; 17–38)¶	35/79 (44%; 33–56)¶	38/60 (63%; 50–75)	18/89 (20%; 12–30)‖	29/89 (33%; 23–43)‖	32/89 (36%; 26–47)	67/264 (25%; 20–31)*†‡¶‖	110/263 (42%; 36–48)*†‡§¶‖	122/242 (50%; 44–57)
Cryptococcal meningitis	14/58 (24%; 14–37)*	28/57 (49%; 36–63)*§	33/56 (59%; 45–72)	13/53 (25%; 14–38)	25/53 (47%; 33–61)	26/38 (68%; 51–82)	7/36 (19%; 8–36)	13/36 (36%; 21–54)	13/36 (36%; 21–54)	34/147 (23%; 17–31)*	66/146 (45%; 37–54)*§	72/130 (55%; 46–64)
Tuberculous meningitis	9/28 (32%; 16–52)†	12/28 (43%; 24–63)†	14/27 (52%; 32–71)	0/6¶	1/6 (17%; 4–64)¶	1/5 (20%; 1–72)	4/11 (36%; 11–69)	5/11 (45%; 17–77)	7/11 (64%; 31–89)	13/45 (29%; 16–44)†¶	18/45 (40%; 26–56)†¶	22/43 (51%; 35–67)
Bacterial meningitis	2/4 (50%; 7–93)‡	2/4 (50%; 7–93)‡	2/4 (50%; 7–93)	6/15 (40%; 16–68)	7/15 (47%; 21–73)	9/12 (75%; 43–95)	2/6 (33%; 4–78)	2/6 (33%; 4–78)	2/6 (33%; 4–78)	10/25 (40%; 21–61)‡	11/25 (44%; 24–65)‡	13/22 (59%; 36–79)
Cerebral toxoplasmosis	0/0	0/0	0/0	0/0	0/0	0/0	4/38 (11%; 5–25)‖	8/38 (21%; 10–37)‖	9/38 (24%; 11–40)	4/38 (11%; 5–25)‖	8/38 (21%; 10–37)‖	9/38 (24%; 11–40)

Data are n/N (%; 95% CI). *One participant in Tanzania with cryptococcal meningitis was lost to follow-up before 2 weeks. †One participant in Tanzania with tuberculous meningitis was lost to follow-up before 2 weeks. ‡One participant in Tanzania with bacterial meningitis was lost to follow-up before 2 weeks. §One participant in Tanzania with cryptococcal meningitis was lost to follow-up between 2 weeks and 10 weeks. ¶One participant in Malawi with tuberculous meningitis was lost to follow-up before 2 weeks. ||One participant in Cameroon with cerebral toxoplasmosis was lost to follow-up before 2 weeks.

Table 6: **Mortality by CNS infection type**

239 (89%) of 269 had at least one marker for classification as critically unwell,[20,21] and 167 (63%) of 264 were bedbound. 97 (37%) of 262 participants had a baseline estimated glomerular filtration rate (eGFR) below 90 mL/min (table 1). 52 (19%) of 269 participants with HIV-related CNS infection tested urinary lipoarabinomannan positive.

Cryptococcal meningitis baseline characteristics by country are shown in appendix 3 (p 2), as are baseline characteristics according to CNS infection status (appendix 3 p 3). 99 (67%) of 148 participants with cryptococcal meningitis had altered mental status and the median CD4 count was 37 (IQR 11–80). 39 (27%) of 145 participants had a baseline eGFR below 90 mL/min (appendix 3 p 3). Administered cryptococcal meningitis treatment strategies are described in appendix 3 (p 4) per country according to national guidelines at the time of the project. Mortality from cryptococcal meningitis according to treatment strategy administered within routine care services is presented in table 4. On the basis of post-mortem data[22] and expert review, a small subset of participants with symptoms and signs compatible with meningitis who were CrAg positive in blood, but CSF CrAg negative, were treated for cryptococcal meningitis.

Of participants with CNS tuberculosis, of those who received molecular testing, nine (24%) of 38 tested positive on CSF GeneXpert and 14 (40%) of 35 on GeneXpert Ultra. Four (12%) of 33 tuberculous meningitis cases were positive on urine GeneXpert and seven (28%) of 25 on urine GeneXpert Ultra testing. 24 (52%) of 46 participants were urinary lipoarabinomannan positive. In five (2%) of 269 participants, a diagnosis remained unclear following investigation and treatment for both CNS tuberculosis and cerebral toxoplasmosis was administered (table 3). In participants with bacterial meningitis, 11 (42%) of 26 were *S pneumoniae* RDT or culture positive (table 3).

Using the DREAMM algorithmic approach, 15 (6%) of 269 participants had a co-infection with a second CNS infection. Of 148 cryptococcal meningitis cases, 11 (7%) had a second CNS infection including tuberculous meningitis (n=4), bacterial meningitis (n=1), cerebral toxoplasmosis (n=3), and neurosyphilis (n=3). Similarly, of 47 participants with tuberculous meningitis, six (13%) had a second CNS infection including cryptococcal meningitis (n=4), bacterial meningitis (n=1), and neurosyphilis (n=1; table 3). Of note, five (63%) of eight neurosyphilis cases were CNS co-infections.

31 (9%) of 329 participants tested had primary or secondary syphilis, including 23 (9%) of 269 CNS infection cases and eight (10%) of 87 non-CNS cases. Overall, *T gondii* seroprevalence in this cohort of adults with suspected CNS infection at presentation was 60% (174 of 288), with seroprevalence of 98% (96 of 98) in Cameroon, 14% (ten of 71) in Malawi, and 57% (68 of 119) in Tanzania (table 5).

Disease-specific CNS infection mortality is presented in table 6. Overall, all-cause 2-week mortality for any CNS infection type was 25% (67 of 264) and 10-week mortality was 42% (110 of 263; table 6). For all-cause cryptococcal meningitis, 2-week mortality was 23% (34 of 147) and 10-week mortality was 45% (66 of 146; table 6). Overall, 6-month mortality in participants with CNS infection was 50% (122 of 242; table 6). 6-month cryptococcal meningitis mortality was 55% (72 of 130) compared with 6-month mortality of 24% (nine of 38) for cerebral toxoplasmosis. Overall, the median length of hospitalisation was 11 days (IQR 7–17). The median

length of hospitalisation for cryptococcal meningitis was 12 days (8–18) and this finding was similar across the different aetiologies (appendix 3 p 4).

Discussion

To our knowledge, prospective epidemiological data on the aetiology of HIV-related CNS infection in multiple African LMICs within routine-care services have not been reported elsewhere. The epidemiological data presented here are essential to enable ministries of health, implementing partners, and global funders to accurately quantify need for tests, services (eg, brain imaging), and medicines for HIV-related CNS infection according to aetiology and potentially adapt these regionally to save lives.

Within the DREAMM implementation cohort of adults with suspected CNS infection, the aetiology of HIV-related CNS infection varied substantially between Malawi, Cameroon, and Tanzania. However, additional epidemiological data are needed to unequivocally describe national and regional prevalences of HIV-related CNS infection according to aetiology in African LMICs. The DREAMM approach was holistic, pragmatic, and stepwise, targeting diverse aetiologies of HIV-related CNS infection and adapted to resource-limited contexts where availability of diagnostics and medicines within routine-care services is often limited. In our study, access to diagnostics and essential medicines and training on the most common causes of HIV-related CNS infection and neurosyphilis were made available within the project. In line with the published literature, cryptococcal meningitis was the leading cause of HIV-related CNS infection overall. However, in Cameroon, cerebral toxoplasmosis was the most common aetiology, followed by cryptococcal meningitis. The high seroprevalence of *T gondii* in Cameroon (98%) compared with Malawi (14%) and Tanzania (57%) within this cohort with suspected HIV-related CNS infection supports our findings. In Malawi, severe bacterial meningitis was the second most common cause of HIV-related CNS infection, with most cases being due to *S pneumoniae*. Neurosyphilis, a rarer but important cause of treatable HIV-related CNS infection with high morbidity, was most commonly diagnosed as a co-infection.

Following implementation of DREAMM, 202 (75%) of 269 HIV-related CNS cases had a microbiologically or radiologically confirmed CNS diagnosis. The holistic and pragmatic approach to the diagnosis and treatment of HIV-related CNS infection that took into account resource-limited contexts by adopting a stepwise algorithm was also key in identifying common and treatable additional diagnoses (eg, tuberculosis, sepsis, and syphilis). The DREAMM methodology also enabled the prompt diagnosis and treatment of additional CNS infection co-infections in 15 (6%) of 269 cases that would probably have been missed using commonly adopted siloed approaches to diagnosis and management, further reducing morbidity and mortality. Additionally, 31 (9%) of 329 participants were diagnosed with primary or secondary syphilis. Furthermore, in our experience, the DREAMM intervention and implementation strategies, which included locally led improvements in delivery of quality care, had knock-on effects on the hospital care provided for other causes of serious illness. Indeed, in 87 (24%) of 356 people living with HIV presenting to public hospitals with suspected CNS infection, a diagnosis of CNS infection was disproved after investigation. Alternative diagnoses (eg, disseminated tuberculosis, sepsis, renal failure, and cerebral lymphoma) that can all present with similar syndromes to CNS infection (eg, confusion with renal failure or urinary sepsis) were expedited by routine-care staff enabling appropriate referrals (eg, to oncology services or dialysis where available), thus helping improve the standard of routine care overall within public hospitals.

Short-term cryptococcal meningitis mortality was similar to findings from cryptococcal meningitis trials, helping bridge the gap between clinical trial and routine-care outcomes. Indeed, 2-week all-cause mortality in the DREAMM cohort of 148 participants with cryptococcal meningitis from Cameroon, Malawi, and Tanzania was 23%, similar to clinical trial outcomes within resource-limited settings and in line with inpatient all-cause mortality data for cryptococcal meningitis from those receiving flucytosine-containing regimens within a South African flucytosine-access programme.[3,9,23] Such mortality data from African LMICs outside South Africa are sparse, but are key to informing the delivery of quality care within advanced HIV disease programmes and ongoing efforts by global health stakeholders to end AIDS deaths by 2030. Several flucytosine-containing regimens, all recommended within the 2018 WHO cryptococcal disease guidance,[10] since updated to include the Ambition trial regimen,[24] were administered. This practice reflected differences in national guidelines, often reduced access to essential medicines within routine-care services, and the availability of adequate monitoring facilities for safe amphotericin B administration. For example, in Cameroon, because of reduced availability of monitoring, the purely oral regimen of 2 weeks of fluconazole and flucytosine was used, in line with national guidelines.

The proportion of cryptococcal meningitis participants enrolled with altered mental status (99 [67%] of 148), a poor prognostic marker, was substantially higher than in recent cryptococcal meningitis trials as was the proportion who were critically unwell (130 [88%]), which likely would have precluded enrolment into a clinical trial.[3,9,20,21] This finding, together with the need for optimised post-hospital care,[25] helps explain the continued mortality beyond 2 weeks. Indeed, 10-week and 6-month outcomes were substantially poorer than in clinical trials in resource-limited settings. Of note, discharge care reverted to in-country standard of care following hospitalisation

with DREAMM methodology focused on in-hospital interventions and strategies to reduce mortality. Therefore, in line with analyses of post-hospital mortality data,[25] although short-term mortality was substantially reduced, there is an urgent need to optimise post-hospital care for people living with HIV recovering from HIV-related CNS infection.

Over a third of participants had renal impairment (eGFR <90 mL/min) at baseline, highlighting the importance of laboratory capacity building beyond microbiological services to provide accurate and timely renal-function testing, along with WHO-recommended ancillary treatments (eg, pre-hydration before starting antifungal therapy for cryptococcal meningitis).[24] Additionally, in line with data on routine care for cryptococcal meningitis from South Africa, the median length of hospitalisation was 11 days.[23] This finding highlights that, when essential tests and medicines are made available, alongside public hospital strengthening to deliver quality care in line with recent WHO-recommended guidance, hospital stays for HIV-related CNS infection are substantial.[23] For many critically unwell people living with HIV, life-saving care, such as that required for the initial diagnosis and management of HIV-related CNS infection, cannot be effectively and safely delivered in routine ambulatory-care settings. Indeed, the delivery of quality in-hospital care was a cornerstone in the successful translation of trial results into routine-care services within DREAMM in terms of short-term mortality outcomes. In addition to measures to strengthen public hospitals, outpatient interventions to prevent the development of meningitis, such as cryptococcal antigen screening, vaccination programmes (including against *S pneumoniae* infection), and public health advice, remain crucial to reducing mortality overall.

The study's strengths lie in its wide geographical coverage, holistic and pragmatic approach tailored to resource-limited settings, and the resulting substantial HIV-related CNS infection mortality reductions and data-driven policy implications. However, the study has some limitations and potential biases. First, in line with the project's aims, the epidemiological data presented here focuses on public hospitals and might not be representative of findings from private facilities. Furthermore, additional epidemiological data from across African LMICs are required to further assess the generalisability of our epidemiological findings and unequivocally describe the national and regional epidemiology of HIV-related CNS infection. Second, variations in diagnostic capabilities across sites could introduce bias. However, the fact that access to tests and medicines was provided during the implementation phase of the study and that most of the DREAMM cohort received a confirmed diagnosis leading to substantially reduced mortality argues against this. Additionally, following DREAMM implementation, the principles underlying the management of HIV-related CNS infection and intensive external review of diagnoses and management were uniform across sites. Although small numbers of diagnoses with very atypical presentations might have been missed, our epidemiological findings are unlikely to be explained by this possibility or differences in access to diagnostic tests. Third, cases classified as disseminated tuberculosis had no evidence of meningeal inflammation in CSF but, because of insufficient resources, did not receive routine neuroimaging to exclude subclinical tuberculomas, which are common in miliary tuberculosis. Our study might therefore have underestimated the prevalence of CNS tuberculosis. Finally, the DREAMM intervention and implementation strategies focused on in-hospital practices and procedures in the hours and days following hospitalisation, therefore post-discharge care lacked detailed exploration, limiting insights into longer-term outcomes.

The DREAMM project's findings provide evidence for the clinical and public health benefits of tailored packages of care for HIV-related CNS infections targeting the full range of aetiologies in LMICs. The improvements in diagnostic accuracy and mortality rates underscore the potential of the DREAMM model to be scaled up and adapted to other resource-limited settings, contributing to global efforts to reduce HIV-related deaths and achieve the SDGs. Algorithms and implementation strategies,[12] in addition to post-discharge interventions, are crucial to inform care, reduce mortality, and shape health-care policies in resource-limited settings. Specifically, the DREAMM project's intervention and implementation strategies synergise with advanced-HIV programmes, offering streamlined diagnostic and treatment approaches. Integration into broader health-care systems has potential to ensure sustained impact, enhancing overall HIV care strategies and global efforts to end HIV-related deaths.

In conclusion, the DREAMM project has shed light on important gaps in the provision of care for HIV-related CNS infection within routine care, while providing evidence of the effect of in-hospital interventions and implementation strategies to provide rapid, targeted therapy according to CNS infection aetiology and thus reduce mortality. To meet the SDGs and for humanitarian reasons, DREAMM highlights the imperative need for strengthened, locally led health systems, including HIV-related CNS infection packages of care targeting the full range of aetiologies and improved access to essential tests and medicines. Urgent investment in public hospitals, including in data systems, is needed to roll out models of care including DREAMM to provide quality care, as well as accurate surveillance data on the aetiology of HIV-related CNS infection. Unanswered questions centre on optimal post-discharge care and the effect of potential regional differences in the aetiology of HIV-related CNS infection. Future research on HIV-related

CNS infection needs to add to the epidemiological data presented here and explore long-term outcomes and effective strategies for diverse health-care contexts.

Contributors

AL conceptualised and co-designed the study in close collaboration with all authors. SM, CKa, SLK, CKo, SN, and SP led the enrolment of participants and collected data. ASL led the DREAMM laboratory training programme. SFM, SJ, and JB wrote the analysis plan. EB and senior statistician JB accessed, verified, and analysed the data for the final analysis. AL led the writing of the first draft of the manuscript with EB and RG. All authors contributed to manuscript writing, reviewing, and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

See Online for appendix 4

The authors of this paper have submitted an equitable partnership declaration (appendix 4). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health*'s broader goal to decolonise global health.

Declaration of interests

We declare no competing interests.

Data sharing

All data used for this study are available upon successful application to the study team.

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