# Reduction in mortality from HIV-related CNS infections in routine care in Africa (DREAMM): a before-and-after, implementation study

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## Summary

**Background** Four decades into the HIV epidemic, CNS infection remains a leading cause of preventable HIV-related deaths in routine care. The Driving Reduced AIDS-associated Meningo-encephalitis Mortality (DREAMM) project aimed to develop, implement, and evaluate pragmatic implementation interventions and strategies to reduce mortality from HIV-related CNS infection.

**Methods** DREAMM took place in five public hospitals in Cameroon, Malawi, and Tanzania. The main intervention was a stepwise algorithm for HIV-related CNS infections including bedside rapid diagnostic testing and implementation of WHO cryptococcal meningitis guidelines. A health system strengthening approach for hospitals was adopted to deliver quality care through a co-designed education programme, optimised clinical and laboratory pathways, and communities of practice. DREAMM was led and driven by local leadership and divided into three phases: observation (including situational analyses of routine care), training, and implementation. Consecutive adults (aged ≥18 years) living with HIV presenting with a first episode of suspected CNS infection were eligible for recruitment. The primary endpoint was the comparison of 2-week all-cause mortality between observation and implementation phases. This study completed follow-up in September, 2021. The project was registered on ClinicalTrials.gov, NCT03226379.

**Findings** From November, 2016 to April, 2019, 139 eligible participants were enrolled in the observation phase. From Jan 9, 2018, to March 25, 2021, 362 participants were enrolled into the implementation phase. 216 (76%) of 286 participants had advanced HIV disease (209 participants had missing CD4 cell count), and 340 (69%) of 494 participants had exposure to antiretroviral therapy (ART; one participant had missing ART data). In the implementation phase 269 (76%) of 356 participants had a probable CNS infection, 203 (76%) of whom received a confirmed microbiological or radiological diagnosis of CNS infection using existing diagnostic tests and medicines. 63 (49%) of 129 participants died at 2 weeks in the observation phase compared with 63 (24%) of 266 in the implementation phase; and all-cause mortality was lower in the implementation phase when adjusted for site, sex, age, ART exposure (adjusted risk difference –23%, 95% CI –33 to –13; p<0·001). At 10 weeks, 71 (55%) died in the observation phase compared with 103 (39%) in the implementation phase (–13%, –24 to –3; p=0·01).

**Interpretation** DREAMM substantially reduced mortality from HIV-associated CNS infection in resource-limited settings in Africa. DREAMM scale-up is urgently required to reduce deaths in public hospitals and help meet Sustainable Development Goals.

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## Introduction

The precise burden of CNS infections in low-income and middle-income countries (LMICs) in Africa remains unknown, but these opportunistic infections might contribute up to a third of HIV-related deaths.[1] Cryptococcal meningitis remains a leading cause of HIV-related CNS infection, contributing up to 20% of HIV-related mortality despite antiretroviral therapy (ART) roll-out; tuberculous and bacterial meningitis, and cerebral toxoplasmosis are also common causes of HIV-related death.[1] Incidence of cryptococcal meningitis is likely to remain high in African LMICs as substantial numbers of people living with HIV continue to present or re-present to care with advanced HIV disease, and

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For the French translation of the abstract see Online for appendix 1

For the Portuguese translation of the abstract see Online for appendix 2

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See **Online** for appendix 3

## Research in context

### Evidence before this study

To meet UN Sustainable Development Goals and for humanitarian reasons there is an urgent need to reduce mortality caused by HIV-associated CNS infections in low-income and middle-income countries (LMICs) in Africa within routine care services. CNS infections are a leading cause of HIV-related deaths, with cryptococcal meningitis alone accounting for up to 20%, despite antiretroviral therapy roll-out. The exact burden of HIV-related CNS infections is unknown, because many cases in routine care are undiagnosed, but they might contribute up to a third of HIV-related deaths. The gap between knowledge and action for HIV-related CNS infection and advanced HIV disease more broadly remains large in resource-limited settings and is a key driver of HIV-related mortality. Between Jan 1, 2004, and Jan 31, 2023, PubMed, Cochrane Library, and Embase were all searched using the terms "HIV", "AIDS", "LMICs", "HIV-related CNS Infections", "cryptococcal meningitis", "tuberculous meningitis", "bacterial meningitis", "cerebral toxoplasmosis", "implementation interventions", and "implementation strategies", and appropriate variations of each of these terms. Only English language papers were considered. 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.

### Added value of this study

The Driving Reduced AIDS-associated Meningo-encephalitis Mortality (DREAMM) project is, to our knowledge, the first study that aimed to develop, implement, and evaluate pragmatic implementation interventions and strategies to reduce mortality from HIV-related CNS infection in public hospitals within routine care services. The study was conducted in five public hospitals in Cameroon, Malawi, and Tanzania and divided into three phases: observation, training, and implementation. The main intervention was the implementation of a stepwise algorithm for HIV-related CNS infection. The four main causes of HIV-related CNS infection (cryptococcal meningitis, tuberculous and bacterial meningitis, and cerebral toxoplasmosis) were targeted. Two implementation strategies were devised iteratively during the observation and training phases: empowerment of local leadership to design and implement all interventions and a health system strengthening approach for hospitals was adopted to deliver quality care. The Health system strengthening approach included an open access, co-designed education programme for front-line health-care workers and laboratory technicians, optimised clinical and laboratory pathways, and joint laboratory and clinical communities of practice. Our results suggest that DREAMM implementation interventions and strategies can substantially reduce all-cause 2-week mortality among people living with HIV presenting to public hospitals with suspected HIV-related CNS infection.

### Implications of all the available evidence

Health system deficiencies and failure of translation of proven interventions into routine care are important drivers of preventable HIV-related deaths. Addressing drivers of preventable mortality is a humanitarian imperative. Scale-up of the DREAMM implementation interventions and strategies has potential to substantially reduce HIV-related mortality in routine care and help meet Sustainable Development Goals. Additional implementation studies are needed to further reduce mortality after discharge and address excessive mortality in ambulatory care settings.

over half of patients with cryptococcal meningitis are either non-adherent ART or on a failing regimen.[2,3]

Many people living with HIV with CNS infection are undiagnosed or receive ineffective treatment in routine care, despite advances in diagnostic tests, clinical treatment trials, and updated WHO guidelines.[2,4,5] Lack of access to tests for advanced HIV disease and WHO-listed essential medicines, including amphotericin B and flucytosine for cryptococcal meningitis, is a barrier to saving lives from HIV-related CNS infection despite programmatic advances.[6,7,8] Even where medicines are available, outcomes from routine care studies compared with those from clinical trials remain suboptimal.[2,9,10] A systematic review and meta-analysis found that in African LMICs routine care of cryptococcal meningitis, tuberculous meningitis, and pneumococcal meningitis was associated with short term mortality of 44%, 46%, and 54%, respectively;[11] the pooled short-term mortality from cryptococcal meningitis was twice that in clinical trials. Additional key barriers to reducing HIV-related CNS infection deaths include weak health systems[12] and health-seeking behaviour (eg, late presentation, ART non-adherence, and refusal of lumbar puncture).[6,12,13] Delays in diagnosis and subsequent initiation of treatment are important contributing factors to CNS infection mortality.[14,15]

An urgent need exists both to prevent and to treat HIV-related CNS infection in routine care settings for humanitarian reasons and to meet UNAIDS targets and Sustainable Development Goals (SDGs).[16] The gap between knowledge and action remains substantial not only for the management of CNS infections, but advanced HIV disease more broadly.[17,18] Implementation science is a powerful tool in global health to bridge the gap between clinical trial outcomes and successful implementation of evidence-based interventions.[17,18] Implementation strategies for HIV-related CNS infection that focus on health system strengthening have high potential to reduce deaths. Indeed, delivery of cryptococcal meningitis care is complex and requires

a robust health system to deliver the latest advances from clinical trials.[12,19] To date, strategies for delivery of quality care in public hospitals in African LMICs have largely been overlooked.[20,21]

The Driving Reduced AIDS-associated Meningoencephalitis Mortality (DREAMM) implementation science project aimed to develop, implement, and evaluate pragmatic implementation interventions and strategies to reduce mortality from HIV-related CNS infection in public hospitals in Cameroon, Malawi, and Tanzania within routine care.

## Methods

### DREAMM project design and oversight

DREAMM was a multi-centre hybrid type 2 implementation science project[22] with a before-and-after design. The project was divided into three sequential phases: observation, training, and implementation.

The study adopted a combination of mixed methods (social science, education, and health economics), health system engineering and clinical trial protocols (appendix p 3). Standard operating procedures from cryptococcal meningitis clinical trials were adapted for use in routine care settings, and 2-week and 10-week clinical outcomes used in trials of HIV-related CNS infection were adopted. Social science theories of system and behavioural change, including rapid community appraisal and health system engineering, are key tenets of the DREAMM approach.[23–26] In particular, we used similar tenets to SEED-SCALE with an emphasis on communities of hospital staff and their leaders driving bottom-up change based on humanitarian and justice-led principles using, where possible, existing resources.[25] External input was provided as needed by world-leading experts in education, social science, laboratory science, health economics, trials of meningitis in resource limited settings, and health system strengthening.

Local ethical and national regulatory approvals were obtained and from St George's Research Ethics Committee (SGREC16.0010), UK; the Ministry of Health, Community Development, Gender, Elderly and Children (NIMR/HQ/R.8c/Vol.I/1090), Tanzania; the Office of Human Research Ethics (16/7/1635), Malawi; and Comité National d'Ethique pour la Recherche en Santé Humaine (0977/A/MINSANTE/SESP/SG/DROS/), Cameroon. All participants provided written informed consent. If a participant had an altered mental status (defined as the presence of one or more of the following: a Glasgow Coma Score <15 [low level of consciousness], a recent seizure, or a change in behaviour), written informed consent was obtained from the next of kin; if a participant recovered the capacity to provide consent, written informed consent was obtained from that 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.

### DREAMM observation phase

The observation phase aimed to identify barriers and facilitators for HIV-related CNS infection care delivery in African LMICs. Situational analyses including documentation of existing practices and procedures and 2-week and 10-week outcomes were recorded in Amana Hospital and Mwananyamala Hospital (Dar es Salaam, Tanzania), Kamuzu Central Hospital (Lilongwe, Malawi), and Hôpital Central de Yaoundé (Yaoundé, Cameroon). DREAMM observation took place prospectively over the following periods: from November, 2016, to February, 2017, in Tanzania, March to May, 2017, in Malawi, and December, 2018, to April, 2019, in Cameroon. Common barriers for delivery of quality care for suspected HIV-related CNS infection are in appendix 3 (p 4).

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

### DREAMM sites

Geographically distinct tertiary and secondary level public health hospital sites with local experts in research or implementation were chosen to lead the project and identify generalisable implementation interventions and strategies for HIV-related CNS infection. Clinical care for HIV-related CNS infection was centralised in acute-care hospital settings due to the need for expert clinical care, intensive monitoring, and commodity storage requirements.

DREAMM interventions and strategies were implemented sequentially from January, 2018, to March, 2021, in the following sites: Amana (January, 2018, to August, 2019) and Mwanayamala (October, 2018, to August, 2019) Hospitals (Dar es Salaam, Tanzania), Kamuzu Central Hospital (March, 2018, to December, 2018; Lilongwe, Malawi), Hôpital Central Yaoundé (September, 2019, to March, 2021; Yaoundé, Cameroon), and Zomba Central Hospital (August, 2020, to March, 2021; Zomba, Malawi). The median implementation phase recruitment duration was 10 months (range 0 months).

### Participants

A syndromic approach to HIV-related CNS infection was adopted. Because the aim was for devised implementation interventions and strategies to become standard of care, exclusion criteria were minimal.

Consecutive adults living with HIV aged 18 years or older presenting 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, 2020, individuals diagnosed with SARS-CoV-2 infection were excluded. Advanced HIV disease in adults is defined here as a CD4 count less than 200 cells per μL. Critically unwell patients were defined as possessing

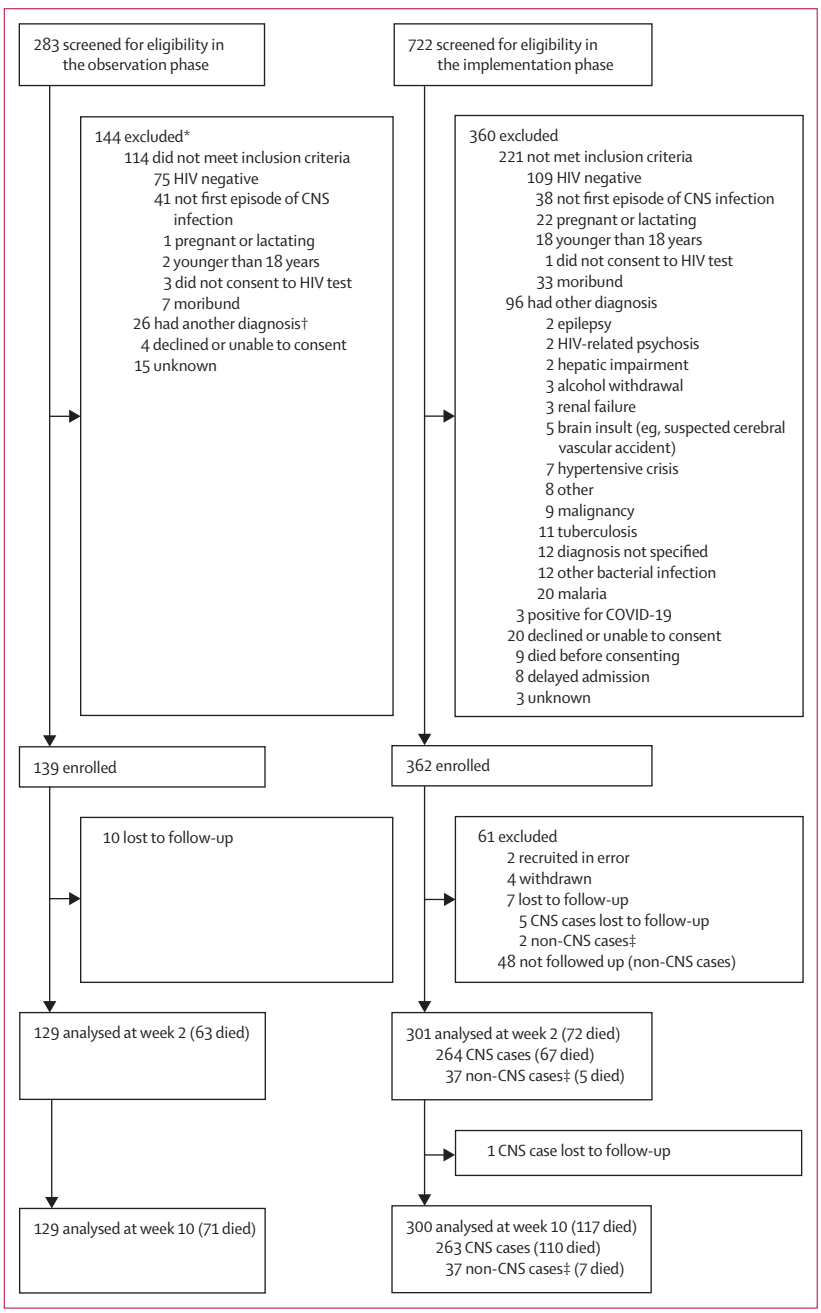


***Figure 1:*** **Study profile**
DREAMM=Driving Reduced AIDS-associated Meningo-encephalitis Mortality project. *Number of reasons exceeds the number excluded because some participants had more than one reason for exclusion. †Includes diagnoses such as cerebral malaria and hypertensive crisis evident on screening. ‡Non-CNS cases were cases that presented with suspected HIV-related CNS but in whom, following investigation including with the DREAMM algorithm, a CNS infection was disproved.

one or more of the following criteria: altered mental status, focal neurology, 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 of more than 39°C, or Eastern Cooperative Oncology Group score of more than 3.

Initially the focus of DREAMM was the outcome of HIV-related CNS infection after implementation strategies tailored to CNS infection, and non-CNS cases were not followed up once CNS infection was disproved. Therefore non-CNS cases from Tanzania do not have follow-up data. These participants were removed from the denominator for the mortality analysis. The DREAMM protocol was subsequently amended to include follow-up of participants with non-CNS disease from Cameroon and Malawi to aid the mortality comparison.

### The DREAMM intervention

The main intervention was the implementation of a step-wise algorithm for HIV-related CNS infection (appendix 3 p 5).[27] The four main causes of HIV-related CNS infection (cryptococcal meningitis, tuberculous and bacterial meningitis, and cerebral toxoplasmosis) were targeted. Malaria was excluded. Key DREAMM algorithm features included bedside rapid diagnostic testing by clinical staff, done in parallel with laboratory testing, which included standard microbiological techniques such as cerebrospinal fluid culture. All participants received cryptococcal antigen (CrAg) lateral flow assay in blood and cerebrospinal fluid and urinary lipoarabinomannan testing.[28] A second important algorithmic feature was the implementation of 2018 WHO cryptococcal meningitis guidelines.[4,29] In line with national guidance, 1 week of amphotericin B deoxycholate (1 mg/kg per day) plus oral flucytosine (100 mg/kg per day) followed by 1 week of high-dose fluconazole (1200 mg daily) was implemented as first-line therapy for cryptococcal meningitis in Malawi and Tanzania. Due to ease of administration and monitoring, the alternative oral regimen of 2 weeks of high-dose fluconazole (1200 mg daily) plus flucytosine (100 mg/kg per day) was chosen in Cameroon.

### DREAMM implementation strategies

Two implementation strategies were devised iteratively during the observation and training phases: empowerment of local leadership to design and implement all interventions, and delivery of quality care for HIV-related CNS infection in resource-limited settings. A triad of research or implementation leads, hospital directors, and local ministries of health underpinned the implementation of the DREAMM intervention. A health system strengthening approach for hospitals was adopted to engineer delivery of quality care through an open access, co-designed education programme for front-line healthcare workers and laboratory technicians, optimised clinical and laboratory pathways to rapidly diagnose patients and administer targeted treatment, and joint laboratory and clinical communities of practice.

Training on the DREAMM algorithm, and the main causes of HIV-related CNS infection, alongside mapping of existing clinical and laboratory pathways was done during the training phase. Following a needs assessment,

participatory approaches to learning through the development of workshops, as well as visual aids were prioritised.[30,31] The DREAMM education programme used a train the trainer methodology.[32,33]

During DREAMM implementation, essential medicines including amphotericin B and flucytosine, diagnostic tests, and medical equipment (eg, manometers for the management of raised intracranial pressure) for HIV-related CNS infection were provided free of charge.[6] Optimised clinical and laboratory pathways and the DREAMM algorithm were implemented.

### Outcomes

The primary endpoint was the comparison of 2-week all-cause mortality between observation and implementation phases. 2-week mortality is more likely due to CNS mortality and the majority of DREAMM interventions and strategies occurred during hospital admission.[2] 10-week all-cause mortality is a key secondary outcome and gives a longer-term effect estimate. All deaths and readmissions were reported within 48 h of occurrence to the Project Management Group (SM, CKa, CKo, SN, SJK, TB-C, and AL).

### Process evaluation objectives and outcomes

Process data were collected to document quality improvements in the delivery of care, the rapidity of diagnosis and administration of targeted treatment according to the cause of CNS infection being key for improved outcomes. Unless contraindicated (eg, in cases of cerebral toxoplasmosis) lumbar puncture is the gold standard investigation for HIV-related CNS infection. Thus, during DREAMM implementation, time from enrolment to relevant diagnostic procedure (eg, lumbar puncture, brain imaging), and targeted treatment, was documented. Additionally, the accuracy of point-of-care tests by clinical staff as an approach to rapidly diagnose CNS infection, in parallel to routine laboratory-based testing, was evaluated by documenting concordance of bedside and routine laboratory point-of-care test results. All discordant results were reported in real-time and decisions impacting clinical care expedited.

### Statistical analysis

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 mortality between these phases. Mortality at 2 weeks from HIV-related CNS infection in routine care in African LMICs has been estimated to be more than 50%. Including 121 participants in both the observation and implementation phases would give 90% power, at the 5% significance level, to detect a reduction in 2-week mortality from 50% to 30%. Additional participants were recruited to describe the epidemiology of HIV-related CNS infection.

The descriptive analysis included all participants enrolled into the study. For the implementation phase, during which standardised investigations were done, baseline characteristics were also compared between clinically confirmed CNS-infection cases versus non-CNS infection cases with $\chi^2$ tests for categorical variables and *t* tests for continuous variables. Missing data were not imputed.

For the implementation phase, process data were summarised as number and percentage for categorical variables and median and IQR for continuous variables, which was presented by CNS-infection cause for cryptococcal and tuberculous meningitis.

For the comparison of outcome measures between the observation and implementation phases, only participants from sites with data from both phases were included. A separate analysis was done, not adjusting for site, to include data collected from the last site in Zomba, Malawi. The observation phase was not done here because of ethical considerations (commodities for advanced HIV disease including amphotericin B and flucytosine were available in Malawi through The Global Fund to Fight AIDS, Tuberculosis and Malaria from 2019 onwards, when the site was launched, and in view of promising preliminary results from DREAMM). Participants lost

| | Observation phase (N=139) | Implementation phase (N=356)* |
|---|---|---|
| Sex | | |
| Female | 69/139 (50%) | 191/356 (54%) |
| Male | 70/139 (50%) | 165/356 (46%) |
| Age, years | 38 (32–45) | 39 (33–45) |
| Weight, kg† | 53 (48–58) | 55 (50–65) |
| CD4 count, cells per μL‡ | 53·5 (20–144) | 75·5 (28–207) |
| Advanced HIV disease§ | 22/26 (85%) | 194/260 (75%) |
| Critically unwell¶ with advanced HIV disease | .. | 172/194 (89%) |
| Viral load, RNA copies per mL‖ | 45 759 (176–180 650) | 102 993 (839–520 859) |
| ART exposed | 96/139 (69%) | 244/355 (69%) |
| Time on ART, of those exposed to ART, months** | 20·0 (3·0–55·5) | 26·6 (4·1–67·3) |
| Reported adherent to ART, of those exposed to ART | 55/96 (57%) | 131/244 (54%) |
| Altered mental status | 102/132 (77%) | 268/356 (75%) |
| Critically unwell¶ | .. | 324/356 (91%) |
| ECOG score ≥4 | .. | 216/348 (62%) |
| Anaemia haemoglobin <7 g/dL | 18/87 (21%) | 20/345 (6%) |
| eGFR, mL/min†† | .. | 98 (73·5–132·2) |

Data are n/N (%) or median (IQR). ART=antiretroviral therapy. ECOG=Eastern Cooperative Oncology Group. eGFR=estimated glomerular rate. *362 were enrolled but two were recruited in error and four withdrew. †Data missing for 109 participants at observation and 91 at implementation. ‡Data missing for 113 participants at observation and 96 at implementation. §Defined as CD4 count of more than 200 cells per μL. ¶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 mmHg, temperature higher than 39°C, or ECOG score of more than 3. ‖Data missing for 131 participants at observation and 213 at implementation. **Data missing for 28 participants at observation and 44 at implementation. ††No data collected in the observation phase, creatinine results missing for 16 participants in implementation phase.

***Table 1:*** **Baseline characteristics of all cases in the observation and implementation phases**

| | CNS-infection cases (N=269) | Non-CNS-infection cases (N=87) | p value* |
|---|---|---|---|
| Sex | | | |
| Female | 140/269 (52%) | 51/87 (49%) | .. |
| Male | 129/269 (48%) | 36/87 (41%) | 0·29 |
| Age, years | 40 (35–45) | 38 (30–47) | 0·75 |
| Weight, kg† | 55 (50–65) | 54 (49–65) | 0·88 |
| CD4 count, cells per µL‡ | 61 (25–137) | 282 (101–468) | <0·001 |
| Advanced HIV disease§ | 172/202 (85%) | 22/58 (38%) | <0·001 |
| Critically unwell* with advanced HIV disease | 150/172 (87%) | 22/22 (100%) | 0·08 |
| Viral load, RNA copies per mL¶ | 135 219 (8052–621 866) | 216 (40–32 100) | <0·001 |
| ART exposed | 173/268 (65%) | 71/87 (82%) | 0·003 |
| Time on ART, of those exposed to ART, months‖ | 21·1 (3·4–66·7) | 32·3 (12·6–79·1) | 0·16 |
| Reported adherent to ART, of those exposed to ART | 84/160 (53%) | 46/64 (72%) | 0·008 |
| Altered mental status | 191/269 (71%) | 77/87 (89%) | 0·001 |
| Critically unwell** | 239/269 (89%) | 85/87 (98%) | 0·01 |
| ECOG score ≥4 | 167/264 (63%) | 49/84 (58%) | 0·42 |
| Anaemia haemoglobin <7 g/dL | 12/261 (5%) | 8/84 (10%) | 0·09 |

Data are n/N (%) or median (IQR). ART=antiretroviral therapy. ECOG=Eastern Cooperative Oncology Group. *$\chi^2$ test for binary variables, t-test for continuous variables, and Wilcoxon rank-sum test for comparing viral load. †Data missing for 73 CNS infection cases and 18 non-CNS infection cases. ‡Data missing for 67 CNS infection cases and 29 non-CNS infection cases. §Defined as CD4 count of more than 200 cells per µL. ¶Data missing for 151 CNS infection cases and 62 non-CNS infection cases. ||Data missing for 25 CNS infection cases and 19 non-CNS infection cases. **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 mmHg, temperature higher than 39°C, or ECOG score of more than 3.

***Table 2:*** **Baseline characteristics of all cases in the implementation phase by CNS infection status**

to follow-up were excluded from the analysis but included in sensitivity analyses.

The proportion of participants who died from any cause by 2 weeks and 10 weeks in the observation and implementation phases, overall and by country, are presented.

Multivariable generalised linear models, with phase (observation and implementation) as the main predictor, with an identity-link function and binomial distribution of deaths, were used to calculate the risk difference (RD) and 95% CIs in the proportion of participants who died at 2 and 10 weeks between the two phases.

Time from study inclusion to death was analysed as time-to-event outcomes and was summarised by the number (%) of participants who died and mean (SD) time to death. Kaplan-Meier plots were created, and Cox regression models used to derive hazard ratios and two-sided 95% CIs. Participants were censored at 10 weeks and participants lost to follow-up censored on the last date that they were known to be alive. The analysis was done overall and by country.

An analysis adjusting only for site, and an adjusted analysis, adjusting for age, sex, ART exposure, and in the Cox regression model only, altered mental status (because the risk difference model would not converge with altered mental status included), was done. CD4 cell count and bodyweight were prespecified confounders; however, due to a large amount of missing data in the observation phase they were not included in the models. The main conclusions are drawn from the adjusted analysis.

As a sensitivity analysis, the RD and 95% CI for 2-week and 10-week mortality comparing all cases in the observation phase with the implementation phase, both overall and by country, assuming all lost to follow-up participants had died, was also done.

Further exploratory subgroup analyses of two key outcomes (2-week and 10-week all-cause mortality) were done to explore the outcomes in different groups of participants. The subgroups were formed with the same covariables used in the adjusted analyses. The subgroup analyses were by country, ART exposure, and restricted to participants with clinically confirmed CNS infection.

All analyses were done with Stata (version 17). The project was registered on 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

139 (observation phase) and 362 (implementation phase) people living with HIV with suspected CNS infection were enrolled by trained routine care staff supervised by research or implementation support staff using a syndromic approach, respectively (figure 1). An example of hospital flow of participants before implementation and after implementation of DREAMM in the first DREAMM site is in appendix 3 (pp 6–7). 356 participants (of 362 enrolled, two participants were enrolled in error and four withdrew) were analysed at baseline in the implementation phase (figure 1).

During the DREAMM implementation phase, CNS infection was ruled out in 87 (24%) of 356 participants following investigation (termed non-CNS cases), and alternative diagnoses (eg, renal failure, non-CNS disseminated tuberculosis, and sepsis) were established. 269 (76%) of 356 participants had a probable or confirmed (based on positive microbiological testing) CNS infection after investigation.

Key baseline characteristics were similar between the DREAMM observation and implementation phases (table 1; appendix 3 p 8). Most participants were severely immunosuppressed, ART experienced, had altered mental status, and met criteria for critically unwell advanced HIV disease. A high proportion of data for CD4 and viral load were missing (table 1). Implementation phase baseline immunological characteristics differed between CNS and non-CNS cases (table 2).

| | Observation phase, n/N (%) | Implementation phase, n/N (%) | Adjusted for site | | Adjusted for site age, sex, and ART exposure | |
|---|---|---|---|---|---|---|
| | | | Risk difference, % (95% CI) | p value | Risk difference, % (95% CI) | p value |
| **Overall mortality** | | | | | | |
| 2-week mortality | 63/129 (49%) | 63/266 (24%) | –23% (–34 to –13) | <0·001 | –23% (–33 to –13) | <0·001 |
| 10-week mortality | 71/129 (55%) | 103/265 (39%) | –14% (–24 to –3) | 0·01 | –13% (–24 to –3) | 0·01 |
| **Tanzania*** | | | | | | |
| 2-week mortality | 38/67 (57%) | 29/99 (29%) | –27% (–42 to –13) | <0·001 | –26% (–41 to –11) | 0·001 |
| 10-week mortality | 43/67 (64%) | 47/98 (48%) | –16% (–31 to –1) | 0·04 | –16% (–31 to –1) | 0·04 |
| **Malawi (Lilongwe only†)** | | | | | | |
| 2-week mortality | 11/35 (31%) | 15/70 (21%) | –10% (–28 to 8) | 0·28 | –11% (–29 to 7) | 0·24 |
| 10-week mortality | 13/35 (37%) | 26/70 (37%) | 0% (–20 to 20) | 1·00 | –2% (–21 to 18) | 0·87 |
| **Cameroon** | | | | | | |
| 2-week mortality | 14/27 (52%) | 19/97 (20%) | –32% (–53 to –12) | 0·002 | –32% (–53 to –12) | 0·002 |
| 10-week mortality | 15/27 (56%) | 30/97 (31%) | –25% (–46 to –4) | 0·02 | –25% (–46 to –4) | 0·02 |

All patients, excluding Zomba (n=36) and patients lost to follow-up. ART=antiretroviral therapy. *Outcome data for the non-CNS infection cases (n=48) from Tanzania are unavailable. †Data from Zomba are excluded from this analysis because no observation data were collected for this site.

***Table 3:*** **Overall mortality and mortality by country in the implementation and observation phases**

The SARS-CoV-2 pandemic impacted recruitment in Zomba, Malawi, and Yaoundé, Cameroon; however, there was no evidence that the pandemic affected the baseline characteristics of recruited participants.

During the observation phase, few investigations were done within routine care. Diagnostic lumbar punctures were done in 41 (30%) of 139 participants and CT brain scans were done in 15 (11%). Cerebrospinal fluid results following lumbar puncture were available in 34 (24%) of 139 participants to inform targeted therapy. During the observation phase, treatment was largely empirical including broad-spectrum antibiotics (eg, ceftriaxone in 119 [97%] of 123 and fluconazole in 93 [91%] of 102).

After implementation of DREAMM, lumbar punctures were done in 316 (89%) of 355 participants (appendix 3 p 9). Of note, lumbar puncture might be contraindicated in patients with suspected cerebral toxoplasmosis, which is diagnosed by CT brain scan and serological testing. Diagnostic lumbar punctures were done within 90 min of enrolment for over 75% of participants with cryptococcal and tuberculous meningitis (appendix 3 p 10). Furthermore, targeted treatment according to the cause of CNS infection was administered a median 5·0 h (IQR 2·0–22·7) from enrolment, a key aim of the optimised clinical and laboratory pathways at each site (appendix 3 p 9). Treatment for tuberculous meningitis was administered at a median of 27·2 h (16·3–74·9) reflecting less sensitive diagnostic tests for tuberculous meningitis, and the practice of performing a second lumbar puncture at 24–48 h to help establish a diagnosis (appendix 3 p 10). A microbiological or radiological diagnosis for CNS cases was obtained in 203 (76%) of 269 cases.

Although bedside point-of-care testing guided rapid appropriate therapeutic decisions within the DREAMM algorithm, a preliminary analysis of the concordance of CrAg, urinary lipoarabinomannan, and *Streptococcus pneumoniae* testing between the bedside and laboratory fell short of 100% concordance, even for the best performing CrAg test.[34]

Adjusting for site, age, sex, and ART exposure, all-cause mortality was lower in the implementation than in the observation phase at 2 weeks and 10 weeks (table 3). These results do not include participants in Zomba because the observation phase did not take place at this site. The same mortality analysis, unadjusted for study site and including data from Zomba, showed similar results (appendix 3 p 11). By country, a similar trend in mortality was observed in Cameroon and Tanzania; however, in Malawi no difference in mortality was seen (table 3).

After restricting the implementation phase to participants with CNS infection only (the initial population of interest and to which DREAMM interventions and strategies were tailored), the RD for 2-week all-cause mortality (respective adjusted RD –23%, 95% CI –34 to 13; p<0·001) and 10-week all-cause mortality (–12%, –23 to –1; p=0·03) again showed similar reductions in mortality after DREAMM implementation (appendix 3 p 11).

Assuming that all participants lost to follow-up died before 2 weeks, the adjusted RD for mortality at 2 weeks was –25% (95% CI –35 to –15), and at 10 weeks was –14% (–24 to –4; appendix 3 p 11).

In the observation phase, median time to death was 3 days (IQR 2–7) and in the implementation phase was 9 days (4–22; figure 2; table 4). When implementation data were restricted to CNS infection cases only, results were similar (appendix 3 p 12). All-cause mortality at 10 weeks in the implementation phase was 40% lower than in the observation phase (adjusted HR 0·60, 95% CI 0·44–0·82; p=0·002; table 4). A similar trend was seen by

country in Cameroon and Tanzania; however, in Malawi no difference in mortality rate was seen (table 4).

## Discussion

DREAMM implementation interventions and strategies substantially reduced all-cause 2-week mortality from 49% to 24% among people living with HIV presenting to public hospitals in Africa with suspected HIV-related CNS infection. Health system engineering combined with a multidisciplinary approach driven by local leadership proved a powerful means for enacting quality care. DREAMM effectively translated results of recent clinical trials closing the substantial gap between clinical trial and routine care outcomes.[2,9,10]

We believe our results are generalisable considering the substantial reductions in mortality demonstrated in public hospitals in geographically disparate regions of Africa with diverse health systems. Although programme activities are commonly measured, our consortium developed and delivered a novel methodology that can be used by local health leaders and front-line health-care workers to demonstrably reduce mortality from HIV-related CNS infection in routine care settings. It would not have been feasible for routine health-care workers to monitor activity beyond the clinically impactful process and mortality data collected. Such data from routine care settings are sparse but crucial to provide accurate surveillance data and inform HIV programmes.

A potential limitation of our study was that the cause of hospital admission in the observation phase was most often unknown, leading to empirical treatment and poor outcomes. However, observation and implementation baseline characteristics were comparable, except for baseline haemoglobin, which most probably reflects a bias in haemoglobin testing in the observation phase, favouring those who appeared anaemic. Our observation and implementation phase cohorts were significantly more unwell (eg, presence of altered mental status in participants with CNS infection, which is a poor prognostic marker) than clinical trial participants recruited in recent cryptococcal meningitis trials.[2,5] Although the SARS-CoV-2 pandemic adversely impacted recruitment, there was no evidence it impacted the severity of the clinical status of screened or enrolled participants as evidenced by the high proportion of participants in the implementation phase with altered mental status and those deemed critically unwell at presentation.

Another potential limitation was that participants in whom a diagnosis of CNS infection was disproved in Tanzania were not followed up at study outset. Lastly,

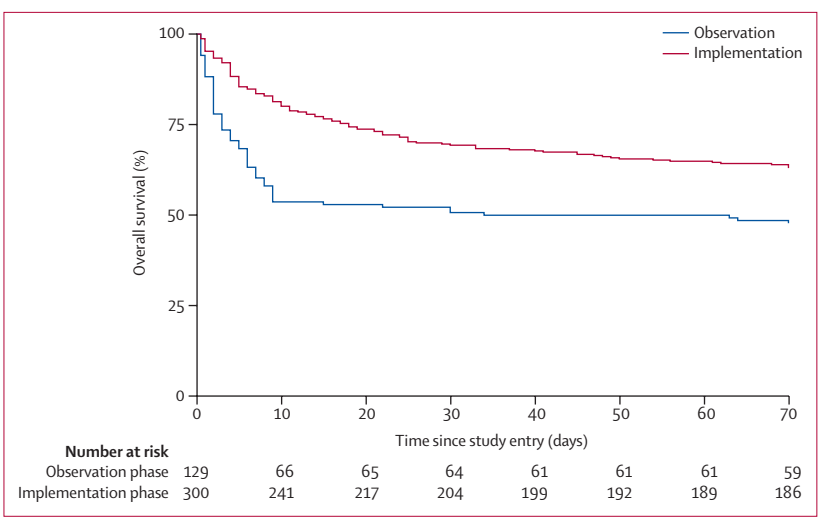


*Figure 2:* **Kaplan Meier survival curve for the observation and implementation phases, overall, excluding cases lost to follow-up**

| | Died within 10 weeks, n/N (%) | Adjusted for site | | Adjusted for site age, sex, mental status, and ART exposure | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| **Overall** | | | | | |
| Observation phase | 71/129 (55%) | 1 (ref) | .. | 1 (ref) | .. |
| Implementation phase | 103/265 (39%) | 0·58 (0·43–0·79) | 0·001 | 0·60 (0·44–0·82) | 0·002 |
| **Tanzania** | | | | | |
| Observation phase | 43/67 (64%) | 1 (ref) | .. | 1 (ref) | .. |
| Implementation phase | 47/98 (48%) | 0·56 (0·37–0·85) | 0·006 | 0·55 (0·36–0·84) | 0·006 |
| **Malawi (Lilongwe only)** | | | | | |
| Observation phase | 13/35 (37%) | 1 (ref) | .. | 1 (ref) | .. |
| Implementation phase | 26/70 (37%) | 0·96 (0·49–1·86) | 0·89 | 0·85 (0·42–1·71) | 0·64 |
| **Cameroon** | | | | | |
| Observation phase | 15/27 (56%) | 1 (ref) | .. | 1 (ref) | .. |
| Implementation phase | 30/97 (31%) | 0·40 (0·21–0·74) | 0·003 | 0·51 (0·26–1·00) | 0·05 |

All patients, excluding Zomba and patients lost to follow-up. ART=antiretroviral therapy.

*Table 4:* **Time-to-death analysis in the observation and implementation phases, all cases**

due to observation phase methodology in which standard of care practices and procedures were merely documented, there were insufficient data to adjust for CD4, viral load, and weight. Missing CD4 and viral load data reflected routine care health-system issues and could be confounding. However, the time between observation and implementation phase was short, and the mortality reduction was substantial and observed consistently in all sites, so we believe it is unlikely that such a marked change in mortality observed in different contexts is a result of underlying temporal changes. Additionally, mortality is not a subjective outcome, making it less prone to bias. No statistically significant mortality difference was noted in Malawi. We hypothesise that the reason for this is lack of power and the Lilongwe site having external research and service support before the implementation phase. As a result, key elements of the DREAMM intervention (eg, access to CrAg tests, antifungal medicines, and trained research staff) were present during the observation phase in this site. After the implementation of the DREAMM intervention and strategies in Lilongwe, routine care health-care workers and laboratory technicians were able to match the performance of their expert implementation or research colleagues in delivering quality care for HIV-related CNS infection. Matching the standard of care within research or implementation projects is key for the sustainability of effective models of care in public hospitals.

Efforts to improve access to tests and medicines for HIV-related CNS infection and opportunistic infections across LMICs including in French and Portuguese-speaking Africa need to be intensified. Since 2019, Unitaid and The Clinton Health Access Initiative have rolled out advanced HIV disease commodities including CrAg tests, liposomal amphotericin B, and flucytosine in eight African LMICs including Malawi and Tanzania.[8] As part of the work of Cryptococcal Meningitis Action Group, members of our consortium are co-leading work with civil society, Ministries of Health, supply chain experts, global health partners, and African health leaders from high cryptococcal disease burden countries to facilitate the Global Fund New Funding Model cycle and the US President's Emergency Plan for AIDS Relief 2023 Country Operational Plan applications to ensure that poor access to advanced HIV disease commodities is not a driver of preventable mortality.

The DREAMM model of care for adults with advanced HIV disease presenting to care with suspected CNS infection is ready for scale-up. Of note, the DREAMM algorithm does not include the management of CNS infection relapse cases. Our aim was to show that rapid diagnosis and targeted treatment according to latest WHO guidance would reduce mortality because the first episodes of HIV-related CNS infection and the outcome of relapsed CNS cases is likely to be different. Furthermore, CrAg testing (the first step of the DREAMM algorithm) is not helpful in diagnosing cryptococcal meningitis relapse because an individual can test positive for months after a first episode. Additionally, the clinical management of relapse cases is different to the management of first presentations of CNS infection and separate management approaches are needed.

We plan to assess acceptability, feasibility, and sustainability of DREAMM scale-up. The overall intervention cost is likely to be low because it is mainly driven by the time of local leadership to train and mentor frontline health-care workers and laboratory technicians over time and the cost of existing technologies. DREAMM epidemiological data including mortality according to HIV-related CNS infection causes will be published shortly. Additional work with frontline health-care workers, local leaders, and civil society is planned to optimise prehospitalisation and post-discharge care to reduce mortality further.

Laboratory assistance and oversight are needed to ensure robust health systems for accurate use of bedside point-of-care tests by clinical staff. DREAMM point-of-care pathways incorporated laboratory oversight for quality assurance mechanisms such as testing of controls, monitoring of storage conditions, training of clinical staff to perform point-of-care tests, and correctly interpreting results, and trouble-shooting discordant results. Additionally, there is often diagnostic uncertainty between diagnoses of bacterial and tuberculous meningitis, and laboratory results (including evolution of cerebrospinal fluid white cell count, protein, and glucose parameters on empirical broad-spectrum antibiotic therapy) are often essential in determining the correct therapeutic approach.

DREAMM has the potential to fill a notable global health gap in delivering locally led quality care in public hospitals to harmonise clinical trial and routine care outcomes. DREAMM scale-up, alongside implementation of CrAg screening programmes, is necessary to substantially reduce routine care HIV-related CNS deaths and help meet SDGs. Indeed, weak and neglected health systems are drivers of preventable mortality. In addition, most global health stakeholders focus on ambulatory care settings to deliver a public health approach to ending the HIV epidemic. In our experience, public hospitals in African LMICs are often neglected, lacking access to essential tests and medicines and the training and viable health systems needed to deliver quality care. Public hospitals are therefore in urgent need of health system strengthening including through implementation of DREAMM and other proven models of care. Our work has shown that African-led health-system strengthening in resource-limited settings is practicable and feasible. In our view, lack of public hospital strengthening, and optimised pre-hospital and post-hospital care, are key barriers to global health community efforts to end unacceptable HIV-related deaths.

For more on the **Cryptococcal Meningitis Action Group** see https://endaidsaction.group/

### Contributors

AL conceptualised and designed the study in close collaboration with all authors. A-MR led the education aspects of the project. SF led the social science aspects of the project. RR led the health economics aspects of the project. AS-L led the laboratory science aspects of the project. SM, CKa, SSL, CKo, SN, and SP led the enrolment of participants and collected data. SFM, SJ, and JB wrote the analysis plan. EB and senior statistician JB accessed, verified, and analysed the data for the final analysis. AL wrote the first draft of the manuscript. 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.

### Declaration of interests

AL, DSL, and JB all received support for this project from European and Developing Countries Clinical Trials Partnership (EDCTP), paid to their institutions. AL has received grants from EDCTP, the National Institute for Health and Care Research, and the National Institutes of Health, and consultancy fees from Unitaid to advise on the Unitaid-CHAI Advanced HIV Disease programme, all paid to St George's University of London; AL is also the Chair and Lead of the End AIDS Action Group, which encompasses the work of the Cryptococcal Meningitis Action gorup, an unfunded role. RR received a grant from The National Institute of Allergy and Infectious Diseases, paid to their institution. OL receives consulting fees and payments or honoraria of less than US$1000 per year from Gilead Sciences; and is part of the advisory board for Mundipharma. THa received an investigator award from Gilead Sciences and has received payments or honoraria from Gilead Sciences and Pfizer for speaking fees. All other authors declare no competing interests.

### Data sharing

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

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