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The DREAMM Project: Epidemiology of CNS Infection

By The DREAMM Consortium
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Background

- Up to a **third of HIV-related deaths** are due to central nervous system (CNS) infection.
- **Cryptococcal meningitis** is a leading cause of HIV-related meningoencephalitis in African LMICs contributing to 15-20% HIV-related deaths[1]. Mortality at 1-year in resource limited settings (RLS) is commonly ≥70%[2, 3].
- Additional leading causes of HIV-related CNS infection include **tuberculous meningitis**, **bacterial meningitis** and **cerebral toxoplasmosis**.
- A confirmed diagnosis of CNS infection is often not made in RLS and empirical treatments are commonly prescribed.
- Prospective regional **epidemiological data is lacking** and needed to inform Ministries of Health, global funders and implementing partners on tests and medicines needed.

DREAMM Project Aims:

1. Prospectively describe the epidemiology of HIV-related CNS infection in three geographically distinct countries.
2. Reduce HIV-related CNS infection mortality in hospital RLS.
3. Devise a model of care for PLHIV presenting with probable CNS infection.

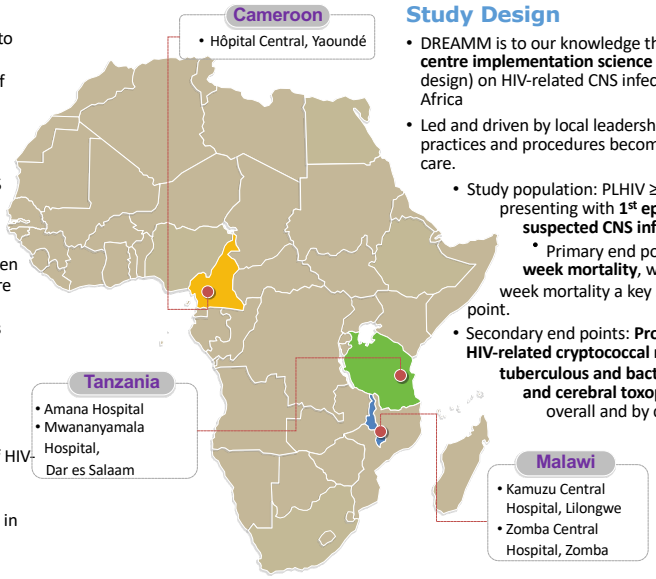
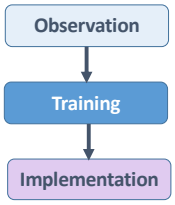


Figure 1. 5 Ministry of Health-supported hospital DREAMM sites

Study Design

- DREAMM is to our knowledge the first **multi-centre implementation science project** (hybrid II design) on HIV-related CNS infection in RLS in Africa
- Led and driven by local leadership such that practices and procedures become standard of care.
- Study population: PLHIV ≥ 18 years presenting with **1st episode of suspected CNS infection**.
- Primary end point: **All-cause 2-week mortality**, with all-cause 10-week mortality a key secondary end point.
- Secondary end points: **Proportion with HIV-related cryptococcal meningitis, tuberculous and bacterial meningitis, and cerebral toxoplasmosis**, overall and by country.

- Three DREAMM Phases:



Implementation included:

DREAMM Intervention

Algorithm for management of HIV-related CNS infection, with bedside rapid diagnostic tests (RDTs) and WHO recommended treatment for cryptococcal meningitis.

Implementation Strategies

1) Empowerment of local leadership to design and deliver all interventions and strategies
2) Quality improvement in healthcare delivery through:
   - Co-designed education programme
   - Health system engineering
   - Joint communities of practice

Overall Epidemiological Results

- 139 participants recruited in observation phase, 356 in implementation.
- In the observation phase, 10.1% (14/139) had microbiologically confirmed CNS infection, and most were treated empirically.
- Following implementation of DREAMM 75% (269/356) had a probable or confirmed CNS infection, and 77.3% (174/225) were microbiologically confirmed.
- Here we present implementation phase baseline characteristics, cause of HIV-related CNS infection and related mortality for CNS cases, overall and by country.

Baseline Characteristics

Baseline characteristics	Cryptococcal meningitis N= 148	Tuberculous meningitis N= 47	Bacterial meningitis N= 26	Cerebral Toxoplasmosis N= 39	All CNS Infection cases N=269
Sex, male, % (n/N)	50.7 (75/148)	55.3 (26/47)	50.0 (13/26)	43.6 (17/39)	48.0 (129/269)
Age (year), median (IQR)	39 (32-44)	40 (35-42)	38 (33-45)	42 (38-45)	40 (35-45)
CD4 count (cells/μL), median (IQR)	37 (11-81)	104 (46-172)	148 (73-255)	87 (35-143)	61 (25-137)
AHD; CD4<200 cells/μL, % (n/N)	92.1 (105/114)	87.5 (28/32)	60.0 (12/20)	88.0 (22/25)	85.2 (172/202)
Viral Load (copies/mL-%), median (IQR)	135000 (8052-507000)	621866 (41648-3484105)	38260 (7430-127000)	309683 (28445-742594)	135419 (8052-621866)
Reported ART exposure, % (n/N)	67.4 (99/147)	70.2 (33/47)	57.7 (15/26)	51.3 (20/39)	64.6 (173/268)
Reported non-adherent, n(%) (of those exposed to ART)	59.1 (55/93)	51.7 (15/29)	53.9 (7/13)	20.0 (4/20)	52.5 (84/160)

Table 1. Baseline Characteristics by CNS Type
Large amounts of missing data for CD4 count (67 missing) and Viral Load (154 missing). Where available, most participants had high detectable viral loads and low CD4 counts <200 cells/μl.

- HIV-related CNS cases were severely immunodepressed, median CD4 61 (IQR 25-137).
- 65% (173/268) had prior ART exposure, median time ART 21 months (IQR 3-67).
- 71% (191/269) had abnormal mental status, 89% (239/269) were critically unwell at presentation.

Cause of HIV-related CNS Infection Overall

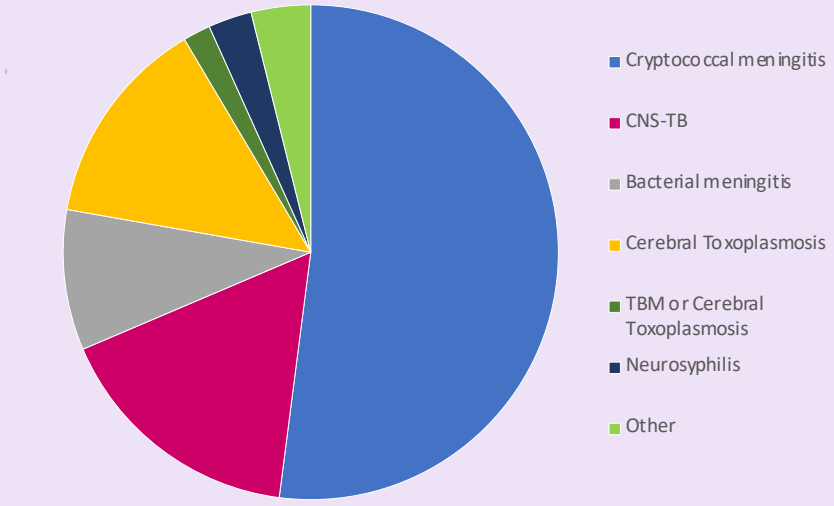


Figure 2. CNS Infection Type

- HIV-related CNS infection cause varied. In both Malawi (66.3%, 53/80) and Tanzania (59.6% 59/99) cryptococcal meningitis was the commonest CNS infection.
- In Cameroon the leading cause of infection was cerebral toxoplasmosis (43.3% 39/90), followed by cryptococcal meningitis (40.0% 36/90).
- CNS TB and *S.pneumoniae* meningitis were the second commonest causes in Tanzania and Malawi respectively.

HIV-related CNS Infection Mortality

	2-week mortality % (95%CI) (n/N)	10-week mortality % (95%CI) (n/N)
CNS Cases-All	25 (20-31) (67/264)	42 (36-48) (110/263)
Cryptococcal meningitis	23 (17-31) (34/147)	45 (37-54) (66/146)
Tuberculous meningitis	29 (16-44) (13/45)	40 (26-56) (18/45)
Bacterial meningitis	40 (21-61) (10/25)	44 (24-65) (11/25)
Cerebral toxoplasmosis	11 (5-25) (4/38)	21 (10-37) (8/38)

Table 2. Mortality by CNS Infection Type

- Overall, DREAMM 2-week all-cause mortality from CNS infection was 25 % (95% CI 20-31), comparing favourably to existing routine care data[4].
- 23% (34/147) 2-week cryptococcal meningitis mortality compares favourably to GERMS-SA data[5] from South Africa's flucytosine access programme (24% in-patient mortality).
- Further work to prevent mortality post-discharge/after 2-weeks is planned.

Conclusion

- Following DREAMM implementation a confirmed diagnosis was made in over 75% HIV CNS infection cases using existing technologies, compared to only 10% in the observation phase.
- The epidemiology of CNS infection appears to vary regionally: cryptococcal meningitis the leading cause in Tanzania and Malawi, and cerebral toxoplasmosis in Cameroon.
- When used by frontline HCWs and laboratory technicians, the DREAMM intervention appears effective at confirming CNS infection using existing technologies, leading to targeted treatment and improved 2-week mortality[6].
- Work to reduce post-discharge mortality is urgently required and planned.

[1]Jarvis, Joseph N., *et al. BMC infectious diseases* 10.1 (2010): 1-6. [2]Gaskell, Katherine M *et al. PloS one* vol. 9,11 e110285. 6 Nov. 2014, doi:10.1371/journal.pone.0110285 [3]Zhao, Hua-Zhen *et al. BMC infectious diseases* vol. 18,1 643. 12 Dec. 2018, doi:10.1186/s12879-018-3460-7 [4]Tenforde MW, Gertz AM, Lawrence DS, *et al.* Mortality from HIV-associated meningitis in sub-Saharan Africa: a systematic review and meta-analysis. *Journal of the International AIDS Society* 2020;**23**. doi:10.1002/jia2.25416. [5] Cryptococcal meningitis in-hospital outcomes in a South African 5-FC access programme, IAS 2021, July 18-21 2021. [6]Meningitis package of care in 3 African countries (DREAMM), IAS 2021, July 18-21 2021.

CNS: Central Nervous System; RLS: Resource Limited Setting; LMICs: Low-and Middle-income countries; PLHIV: People living with HIV; ART: Antiretroviral therapy; RDT: Rapid Diagnostic Test; HCW: Healthcare worker

PRESENTED AT CROI 2022