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Supplementary appendix 3

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Supplementary appendix

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Table S1: Key investigations performed to diagnose HIV-related CNS infection

	Tanzania	Malawi	Cameroon
CT brain scan performed, % (n/N)			
CNS cases	8 (7/90)	0 (0/76)	53 (48/90)
Non-CNS cases	7 (3/41)	0 (0/25)	78 (7/9)
Total	8 (10/131)	0 (0/101)	56 (55/99)
LP performed, % (n/N)			
CNS cases	99 (98/99)	100 (79/79)	61 (55/90)*
Non-CNS cases	98 (50/51)	100 (27/27)	78 (7/9)
Total	99 (148/150)	100 (106/106)	63 (62/99)

Abbreviations: CT: Computerised tomography; CNS: Central nervous system; LP: Lumbar puncture

*Note that lumbar puncture would not commonly be performed in the presence of radiological features suggestive of cerebral toxoplasmosis and other contraindications e.g., space-occupying lesions.

Table S2: Baseline characteristics for Cryptococcal meningitis cases

	Tanzania N=59	Malawi N=53	Cameroon N=36
Sex, male, % (n/N)	41 (24/59)	58 (31/53)	56 (20/36)
Age (year), median (IQR)	39 (29-47)	38 (32-44)	40 (36-44)
CD4 count (cells/ μ L), median (IQR)	39 (10-108) ^a	27 (7-71) ^b	45 (28-66) ^c
AHD; CD4<200 cells/ μ L, % (n/N)	92 (36/39)	88 (44/50)	100 (25/25)
Altered mental status, % (n/N)	75 (44/59)	62 (33/53)	61 (22/36)
Critically unwell, % (n/N)	90 (53/59)	85 (45/53)	89 (32/36)

^a Missing CD4 data for 20 records.

^b Missing CD4 data for 3 records.

^c Missing CD4 data for 11 records.

Table S3: Baseline characteristics CNS infection cases

	Cryptococcal meningitis N= 148	Tuberculous meningitis N= 47	Bacterial meningitis N= 26	Cerebral Toxoplasmosis N= 39
Sex, male, % (n/N)	51 (75/148)	55 (26/47)	50 (13/26)	44 (17/39)
Age (year), median (IQR)	39 (32-44)	40 (35-42)	38 (33-45)	42 (38-45)
Weight (kg), median (IQR)	55 (50-64) ^a	52 (48-61) ^c	57 (50-65) ⁱ	79 (73-86) ^l
CD4 count (cells/ μ L), median (IQR)	37 (11-80) ^b	104 (46-172) ^f	148 (73-255) ^j	87 (35-143) ^m
AHD: CD4<200 cells/ μ L, % (n/N)	92 (105/114)	88 (28/32)	60 (12/20)	88 (22/25)
Critically unwell AHD, any danger signs, % (n/N) (of those with AHD)	85 (89/105)	89 (25/28)	92 (11/12)	86 (19/22)
VL (copies/mL-%), median (IQR)	135000 (8052-507000) ^c	621866 (41648-3484105) ^e	38260 (7430-127000) ^k	309683 (28445-742594) ⁿ
Reported ART exposure, % (n/N)	67 (99/147)	70 (33/47)	58 (15/26)	51 (20/39)
Time on ART (months), median (IQR) (of those exposed to ART)	21 (3-68) ^d	7 (1-49) ^h	45 (9-90)	56 (16-80) ^o
Altered mental status, % (n/N)	67 (99/148)	77 (36/47)	81 (21/26)	62 (24/39)
Critically unwell, % (n/N)	88 (130/148)	91 (43/47)	88 (23/26)	85 (33/39)
ECOG score \geq 4, % (n/N)	56 (80/143)	73 (33/45)	65 (17/26)	72 (28/39)
Anaemia Hb<7 g/dL, % (n/N)	3 (4/143)	11 (5/45)	4 (1/25)	0 (0/39)
eGFR >89 ml/min, % (n/N)	73 (106/145)	51 (23/45)	63 (15/24)	51 (20/39)
eGFR 60-89 ml/min, % (n/N)	20 (29/145)	29 (13/45)	29 (7/24)	38 (15/39)
eGFR 45-59 ml/min, % (n/N)	5 (7/145)	13 (6/45)	0 (0/24)	5 (2/39)
eGFR 30-44 ml/min, % (n/N)	1 (1/145)	0 (0/45)	0 (0/24)	3 (1/39)
eGFR <30 ml/min, % (n/N)	1 (2/145)	7 (3/45)	8 (2/24)	3 (1/39)

Notes: 6% (15/269) participants had a coinfection with a second central nervous system infection. These participants are represented in both columns for their CNS infection type.

^a 14 participants with ccm missing weight ^b 34 participants with ccm missing CD4 ^c 85 participants with ccm missing viral load ^d 12 participants with ccm missing time on ART

^e 14 participants with tbm missing weight ^f 15 participants with tbm missing CD4 ^g 36 participants with tbm missing viral load ^h 7 participants with tbm missing time on ART

ⁱ 7 participants with bac missing weight ^j 6 participants with bac missing CD4 ^k 12 participants with bac missing viral load

^l 73 participants with toxo missing weight ^m 14 participants with toxo missing CD4 ⁿ 13 participants with toxo missing viral load ^o 2 participants with toxo missing time on ART

^p 35 participants with CNS infection missing weight ^q 67 participants with CNS infection missing CD4 ^r 151 participants with CNS infection missing viral load ^s 121 participants with CNS infection missing time on ART.

eGFR: estimated Glomerular Filtration Rate, classified as normal (>89 ml/min), mild (60-89 ml/min), mild-moderate (34-59ml/min), moderate-severe (30-44 ml/min) and severe (15-29 & <15 ml/min).

Critically unwell cases were defined as possessing one or more of the following criteria: abnormal mental status, focal neurology, respiratory rate >20 breaths/min, heart rate >120 beats/min, systolic blood pressure <90 mmHg, temperature >39°C or Eastern Cooperative Oncology Group score >3.

Table S4: Induction treatment for cryptococcal meningitis administered

Treatment of Cryptococcal meningitis cases	Tanzania % (n) N=59	Malawi % (n) N=53	Cameroon % (n) N=36	Total % (n) N=148
1-week AmB + 5-FC	61 (36/59)	77 (41/53)	0 (0/36)	52 (77/148)
1-week Liposomal AmB + 5-FC	0 (0/59)	21 (11/53)	0 (0/36)	7 (11/148)
2 weeks FLU + 5-FC	19 (11/59)	0 (0/53)	100 (36/36)	32 (47/148)
Other*	17 (10/59)	0 (0/53)	0 (0/36)	7 (10/148)
Missing	3 (2/59)	2 (1/53)	0 (0/36)	2 (3/148)

*2 weeks AMB + Fluconazole (n=3), 2 weeks AmB + 5FC (n=2), unknown (n=5).

Table S5: Length of hospitalisation

	Time spent in hospital (days), median (IQR), n N=269			
	Tanzania	Malawi	Cameroon	Total
CNS Cases-All	13 (7-18) n=92	8 (6-12) n=80	15 (8-22) n=89	11 (7-17) n=261
Cryptococcal meningitis	14 (9-18) n=55	8 (7-11) n=53	18 (14-26) n=35	12 (8-18) n=143
Tuberculous meningitis	10 (7-18) n=28	18 (4-44) n=7	10 (7-23) n=11	10 (7-19) n=46
Bacterial meningitis	13 (6-19) n=4	8 (3-13) n=15	19 (12-22) n=6	11 (6-15) n=25
Cerebral toxoplasmosis	Not applicable	Not applicable	11 (8-19) n=39	11 (8-19) n=39

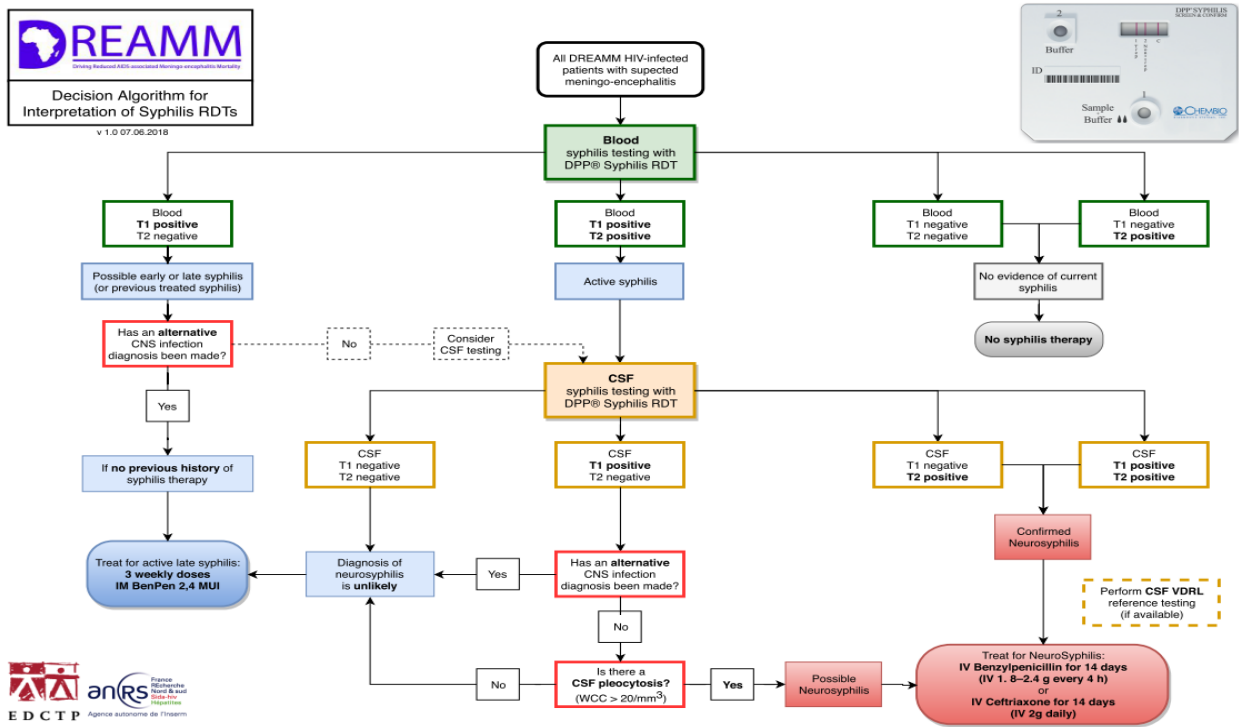


Figure S1: Syphilis algorithm from the DREAMM Educational Module on neurosyphilis.

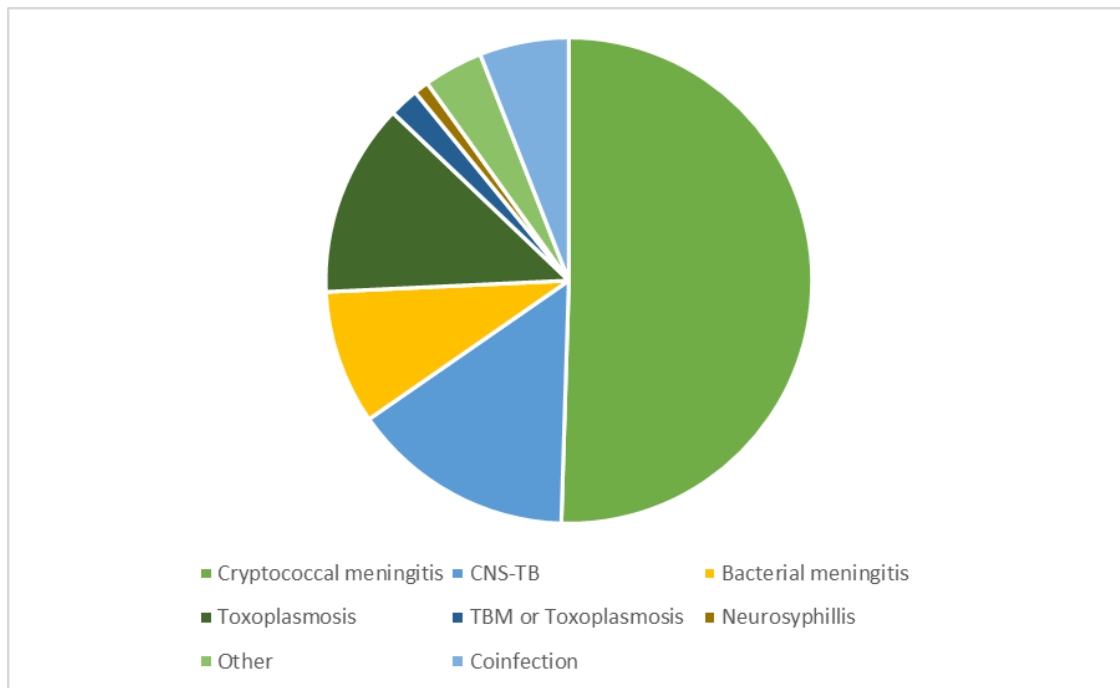


Figure S2: CNS infection type