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Supplementary appendix 3

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Appendix 3

Contents

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Supplementary Materials

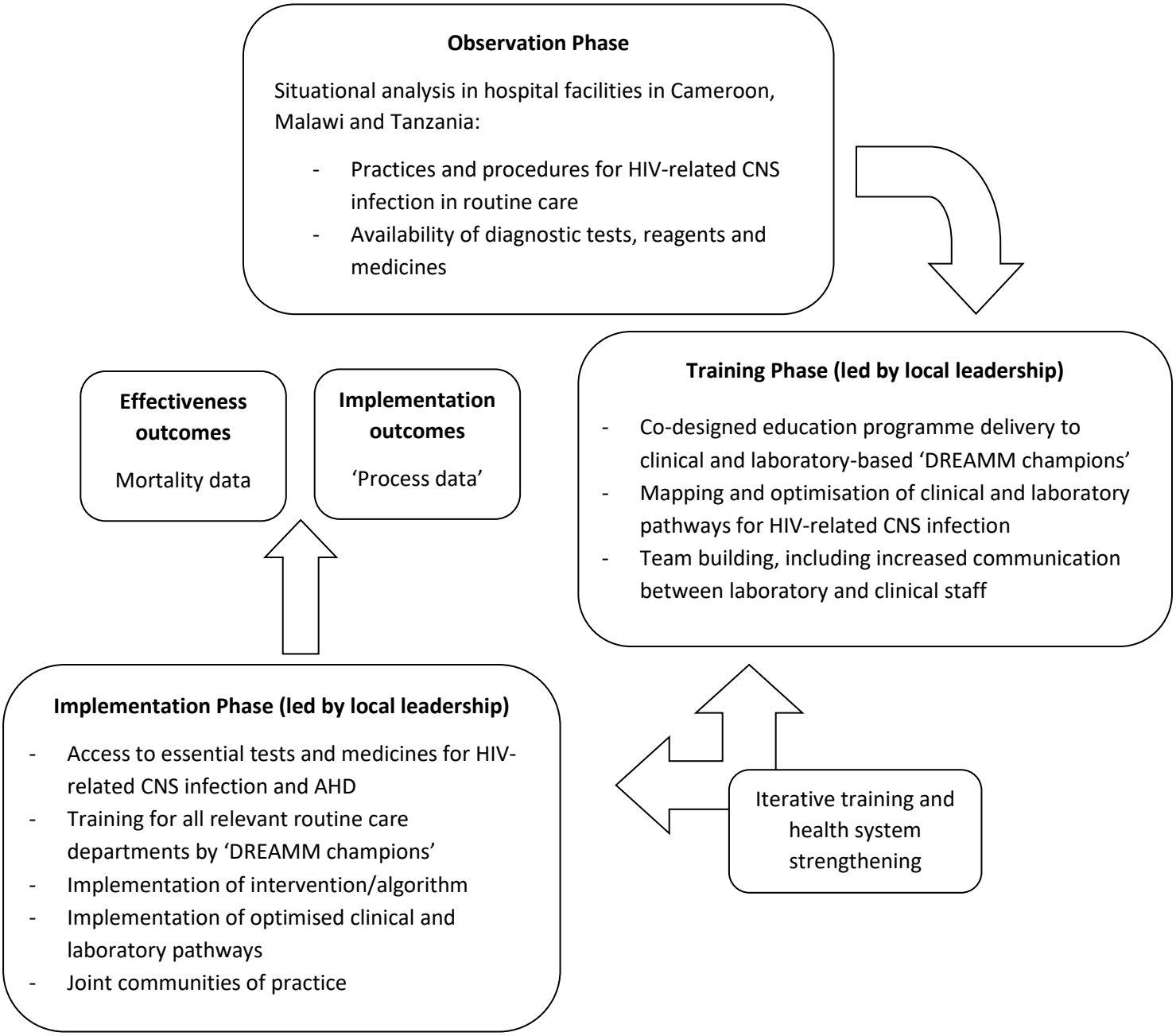

Figure 1. DREAMM Methodology

Barriers to the delivery of quality care for people living with HIV presenting to public hospitals with suspected CNS infection in African LMICs include:

- Lack of universal health care (UHC)
- Poor retention into care +/- ART non-adherence or failure
- Late presentation to care
- Lack of leadership and/or team-building skills for healthcare staff
- Little or no access to RDTs including CrAg LFAs and urinary LAM
- No or limited access to life-saving medicines for cryptococcal meningitis including flucytosine and amphotericin B
- Lack of training tailored to frontline HCWs and laboratory technicians on the prevention, diagnosis and management of HIV-related CNS infection
- Overstretched out-patient and hospital services
- Breakdown of laboratory testing due to un-serviced equipment; lack or inconsistent supply of laboratory reagents, and, poor training of laboratory technicians
- Poor communication between clinical HCWs and laboratory technicians
- Weak laboratory reporting systems causing delayed test turnaround times
- Overall weak and uncoordinated health systems including poor patient and laboratory pathways for people living with HIV with AHD and suspected HIV-related CNS infection

Abbreviations: CNS: Central Nervous System; RDTs: Rapid diagnostic tests; CrAg LFA: Cryptococcal antigen lateral flow assay; LAM: Lipoarabinomannan; HCW: Healthcare workers.

Figure 2. Amalgamated findings from observation phase situational analyses performed in four secondary and tertiary level hospitals in Tanzania, Malawi and Cameroon

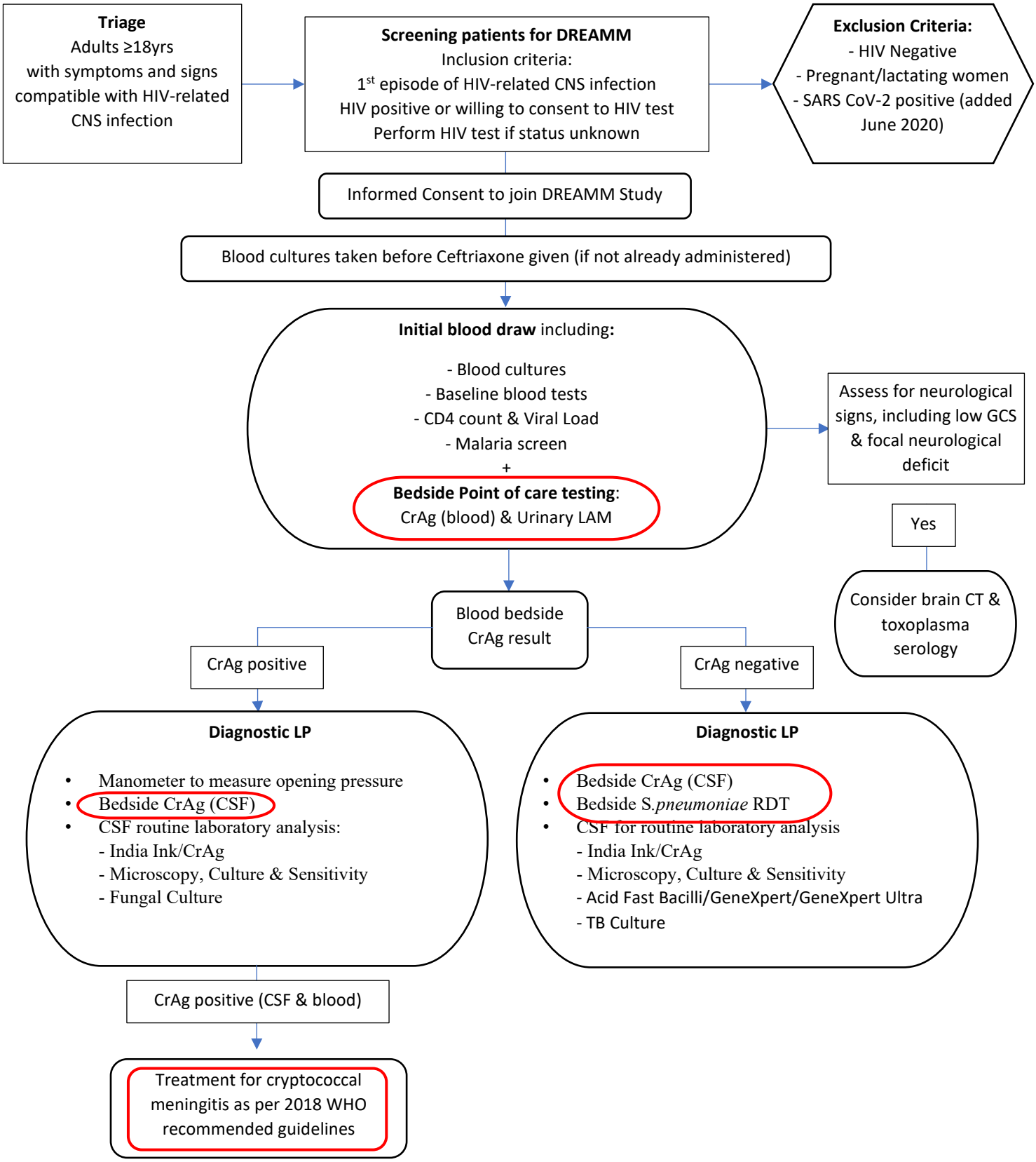

Figure 3. Overview of abridged DREAMM algorithm highlighting key features (Bedside point of care testing and implementation of WHO cryptococcal meningitis guidelines). CNS: Central nervous system; CrAg: Cryptococcal antigen; LAM: Lipoarabinomannan; GCS: Glasgow Coma Score; CT: Computerised tomography; CSF: Cerebral spinal fluid; RDT: Rapid diagnostic test; WHO: World Health Organisation; TB: tuberculosis.

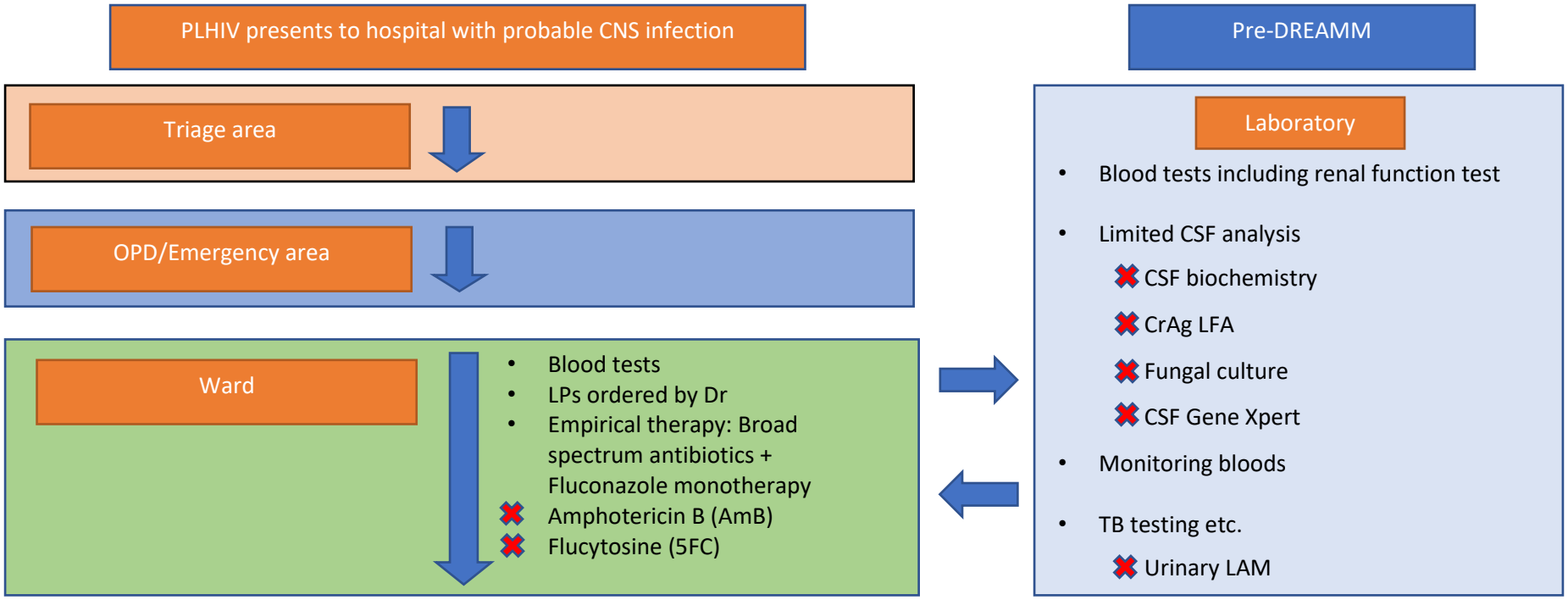

Figure 4. Summary of routine care patient and laboratory pathways for HIV-related CNS infection in a secondary level hospital in Dar es Salaam, Tanzania in 2017, prior to the DREAMM intervention. Red crosses denote a lack of access.

LP: Lumbar puncture; CSF: Cerebrospinal fluid; CrAg LFA: Cryptococcal antigen lateral flow assay; LAM: Lipoarabinomannan; PLHIV: People living with HIV; CNS: Central nervous system

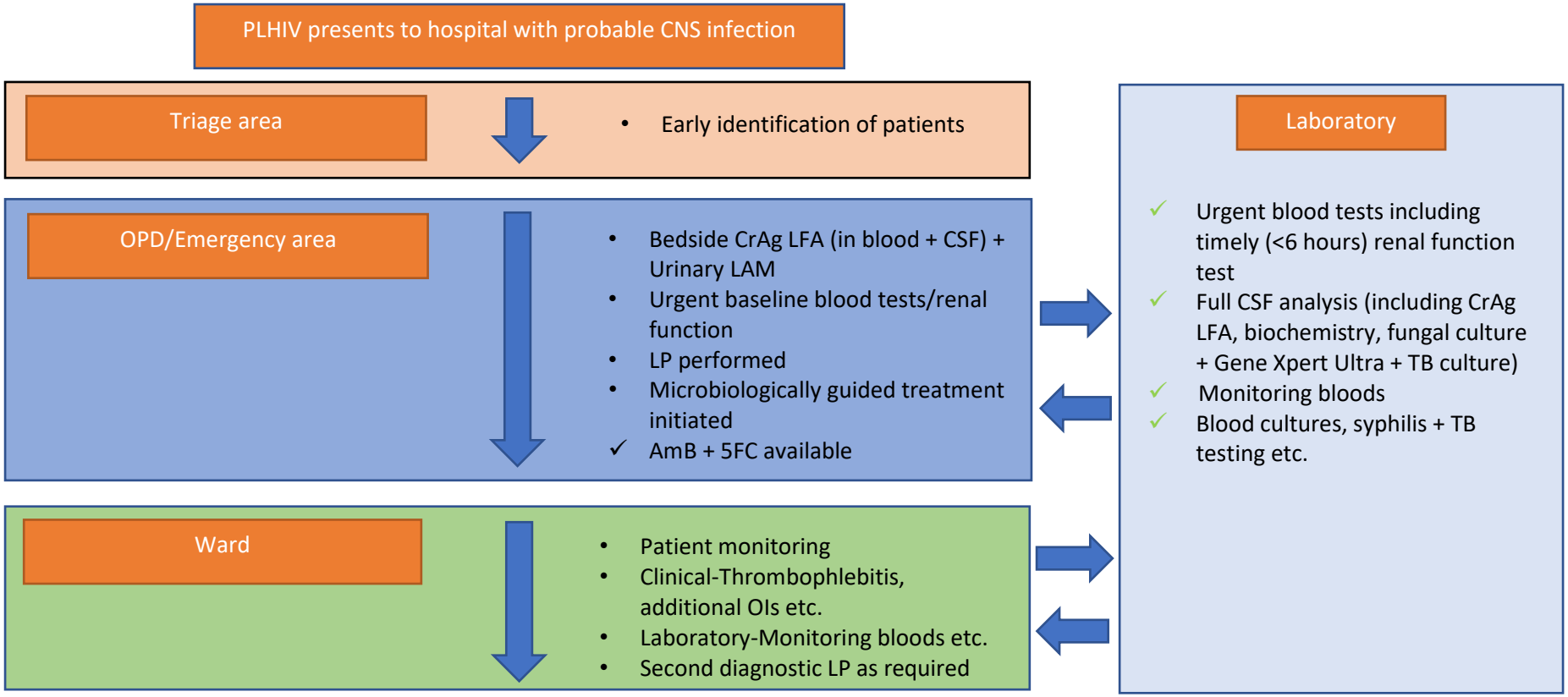

Figure 5. Patient and laboratory pathways for HIV-related CNS infection following the implementation of DREAMM in 2017 in a secondary level hospital in Dar es Salaam, Tanzania*

CrAg LFA: Cryptococcal antigen lateral flow assay; LAM: Lipoarabinomannan; OI: Opportunistic infection; LP: Lumbar puncture

*New, optimised and locally adapted patient and laboratory pathways for HIV-related CNS infection were devised and implemented in the final, implementation phase of the project. To reduce the time from patient presentation to hospital and diagnostic procedures and targeted, microbiologically driven treatment, people living with HIV with symptoms and signs of HIV-related CNS infection were identified in the triage area by newly trained nursing staff and lay people using a visual aide. A 'soft block' in terms of health systems engineering was overcome in that lumbar punctures (LPs), which were previously only performed in the ward, could now be performed in the emergency/outpatient (OPD) area. Bedside rapid diagnostic tests (RDTs), routine blood tests, and, where possible, safe, administration of targeted treatment were all performed in a new, dedicated 'meningitis room' located in the OPD/emergency area. Health system engineering 'hard blocks' in the laboratory (lack of CrAg tests, reagents to perform CSF biochemistry, Gene Xpert platforms issues processing CSF samples etc.) were also overcome and training in new procedures (performing RDTs, CSF biochemistry, fungal culture, Gene Xpert Ultra testing of CSF etc.) delivered to laboratory technicians.

Table 1. Baseline characteristics, Implementation phase by CNS-infection status, by country

Characteristic	CNS-infection cases			Non-CNS-infection cases		
	Tanzania N=99	**Malawi N=80**	**Cameroon N=90**	**Tanzania N=51**	**Malawi N=27**	**Cameroon N=9**
Male, % (n/N)	37.4 (37/99)	62.5 (50/80)	46.7 (42/90)	29.4 (15/51)	66.7 (18/27)	33.3 (3/9)
Age (year), median (IQR)	39 (30-46)	39 (33-43)	41 (36-45)	38 (30-45)	37 (30-47)	45 (34-58)
Weight (kg), median (IQR)[1]	51.3 (48-64)	55 (50-62)	60 (55-67)	58 (50-70)	51 (46-56)	-
CD4 count (cells/µL), median (IQR)[2]	63 (22-138.5)	62 (15-151)	60 (35-110)	265 (47-438)	317 (205-468)	223 (101-598)
AHD; CD4<200 cells/µL, % (n/N)	85.3 (58/68)	81.3 (61/75)	89.8 (53/59)	46.7 (14/30)	22.7 (5/22)	50.0 (3/6)
Critically unwell* with AHD, % (n/N) (of those with AHD)	91.4 (53/58)	85.3 (52/61)	84.9 (45/53)	100.0 (14/14)	100.0 (5/5)	100.0 (3/3)
VL (copies/mL-%), median (IQR)[3]	67241 (59796-97545)	103000 (824-399000)	236052 (15477-750155)	-	167 (40-12500)	216 (46-145063)
ART exposed, % (n/N)	68.4 (67/98)	63.8 (51/80)	61.1 (55/90)	76.5 (39/51)	92.6 (25/27)	77.8 (7/9)
Time on ART (months), median (IQR) (of those exposed to ART)[4]	7.9 (.6-30.6)	26.0 (6.3-109.7)	55.5 (11.9-93.3)	33.0 (15.0-65.3)	32.3 (6.3-109.7)	31.4(28.0-63.8)
Reported adherent, % (n/N) (of those exposed to ART)	49.3 (33/67)	75.5 (37/49)	25.5 (14/55)	71.9 (23/32)	80.0 (20/25)	42.9 (3/7)
Abnormal mental status, % (n/N)	78.8 (78/99)	72.5 (58/80)	61.1 (55/90)	88.2 (45/51)	85.2 (22/27)	100.0 (9/9)
Critically unwell*, % (n/N)	92.9 (92/99)	88.8 (71/80)	84.4 (76/90)	98.0 (50/51)	96.3 (26/27)	100.0 (9/9)
ECOG score≥4, % (n/N)	78.4 (76/97)	35.9 (28/78)	70.8 (63/89)	75/0 (36/48)	29.6 (8/27)	55.6 (5/9)
Anaemia Hb<7 g/dL, % (n/N)	8.2 (8/97)	2.7 (2/75)	2.2 (2/89)	14.0 (7/50)	4.0 (1/25)	0.0 (0/9)

*Critically unwell defined as abnormal mental status or focal neurology or respiratory rate> 20 or heart rate>120 or blood pressure<90 or temperature>39 or ECOG score>3.
[1]Data were missing for weight in CNS cases; Tanzania (n=7), Malawi (n=5) Cameroon (n=61) and non CNS cases; Tanzania (n=8), Malawi (n=1) Cameroon (n=9). [2]Data were missing for CD4 in CNS cases; Tanzania (n=31), Malawi (n=5) Cameroon (n=31) and non-CNS cases; Tanzania (n=21), Malawi (n=5) Cameroon (n=3). [3]Data were missing for viral load in CNS cases; Tanzania (n=96), Malawi (n=27) Cameroon (n=28) and non-CNS cases; Tanzania (n=51), Malawi (n=9) Cameroon (n=7). [4]Data were missing for time on ART in CNS cases; Tanzania (n=17), Malawi (n=2) Cameroon (n=6) and non-CNS cases; Tanzania (n=17), Malawi (n=1) Cameroon (n=1).

Table 2. Implementation phase 'Process data'*

Characteristic	Total N=356
Diagnostics	
LP ordered, n (%)	89.6 (319/356)
LP performed, n (%)	89.0 (316/355)
Time (hours) from enrolment to LP, median (IQR)	1.0 (0.4, 1.5) n=307
CT ordered, n (%)	26.0 (90/346)
CT performed, n (%)	19.73 (65/330)
Time (hours) from enrolment to CT, median (IQR)**	-24.4 (-47.4, 2.0) n=50
Time (hours) from enrolment to treatment	
All cases, N=356	5.0 (2.0, 22.7) n=271
CNS cases, N=269	5.0 (2.0, 22.4) n=249
Cryptococcal meningitis cases, N=148	4.3 (2.3, 17.0) n=142
Tuberculous meningitis cases, N=52	27.2 (16.3, 74.9) n=48
Bacterial meningitis cases, N=26	1.3 (0.5, 8.4) n=23
Cerebral Toxoplasmosis cases, N=44	5.3 (1.8, 15.0) n=42

* 'Process data' were underpinned by the implementation of the DREAMM intervention and implementation strategies outlined in the Methods section (5) The DREAMM intervention, and, 6) The DREAMM implementation strategies).

** CT brain was often available prior to hospital admission for the DREAMM site in Cameroon reflecting differences in access to investigations and the role of private radiology facilities in health systems in DREAMM sites in this particular context.

Table 3. Process data, Implementation phase by country, CCM and TBM cases

	CCM				TBM			
Characteristic	**Tanzania N=59**	**Malawi N=53**	**Cameroon N=36**	**Total N=148**	**Tanzania N=33**	**Malawi N=7**	**Cameroon N=12**	**Total N=52**
Diagnostic LP performed, % (n/N)	98.3% (58/59)	98.1% (52/53)	94.4% (34/36)	98.3% (144/148)	97.0% (32/33)	100.0% (7/7)	91.7% (11/12)	96.2% (51/53)
Time from study inclusion to LP (hours), median (IQR)	1.0 (0.6,1.4) *missing=3*	0.3 (0.08, 1.0) *missing=3*	1.0 (0.8, 1.6) *missing=2*	0.9 (0.3, 1.4) *missing=8*	1.0 (0.8, 1.5) *missing=1*	0.6 (0.2, 1.2) *missing=0*	1.3 (0.5, 1.8) *missing=1*	1.0 (0.5, 1.6) *missing=2*
At least one therapeutic LP, % (n/N)	59.3% (35/59)	32.1% (17/53)	66.7% (24/36)	51.4% (76/148)	-	-	-	-
Time (hours) to targeted treatment, median (IQR)	6.8 (3.8, 22.7) *missing=3*	2.1 (1.2, 5.1) *missing=3*	4 (2.3, 5.5) *missing=1*	4.1 (2.3, 17.0) *missing=7*	27.3 (22.7, 82.0) *missing=2*	15.2 (1.0, 95.0) *missing=1*	26.0 (15.0, 41.0) *missing=1*	27.2 (16.3, 74.9) *missing=4*

NB: The diagnosis of cryptococcal meningitis (CCM) can be rapid, within hours, due to excellent diagnostics, as compared to tuberculous meningitis (TBM) where achieving a diagnosis not uncommonly requires a 2nd LP at 24-48 hours from admission

Table 4. Mortality data, implementation versus observation, overall and for both Lilongwe & Zomba DREAMM sites in Malawi (unadjusted by study site)

Mortality data	Observation n/N(%)	Implementation n/N(%)	Unadjusted Risk Difference (95% CI)	p-value
2-week mortality	63/129 (48.8%)	72/301 (23.9%)	-0.27 (-0.36, -0.17)	<0.001
10-week mortality	71/129 (55.0%)	117/300 (39.0%)	-0.18 (-0.28, -0.08)	<0.001
Malawi				
2-week mortality	11/35 (31.4%)	24/105 (22.9%)	-0.07 (-0.25, 0.10)	0.42
10-week mortality	13/35 (37.1%)	40/105 (38.1%)	0.02 (-0.16, 0.21)	0.83

All cases, excluding loss to follow up

Table 5. Mortality data, implementation versus observation -CNS cases only in implementation phase-

Mortality data	Observation n/N(%)	Implementation n/N(%)	Risk Difference[1] (%) (95% CI)	p-value	Risk Difference[2] (%) (95% CI)	p-value
2-week mortality	63/129 (48.8%)	58/242 (24.0%)	-24 (-34, -13)	<0.001	-23 (-34, -13)	<0.001
10-week mortality	71/129 (55.0%)	98/241 (40.7%)	-13 (-23, -2)	0.02	-12 (-23, -1)	0.03
Tanzania						
2-week mortality	38/67 (56.7%)	28/96 (29.2%)	-28 (42, -13)	<0.001	-26 (-41, -11)	0.001
10-week mortality	43/67 (64.2%)	46/95 (48.4%)	-16 (-31, -0.1)	0.04	-15 (-30, -0.1)	0.05
Lilongwe*						
2-week mortality	11/35 (31.4%)	12/57 (21.1%)	-10 (-29, -8)	0.28	-8 (27, 11)	0.42
10-week mortality	13/35 (37.1%)	23/57 (40.4%)	-3 (-17, 24)	0.76	4 (-18, 25)	0.74
Cameroon						
2-week mortality	14/27 (51.9%)	18/89 (20.2%)	-32 (-52, -11)	0.003	-31 (-52, -11)	0.003
10-week mortality	15/27 (55.6%)	29/89 (32.6%)	-23 (-44, -2)	0.03	-23 (-44, -2)	0.03

All cases at observation, CNS cases at implementation, excluding Zomba and loss to follow up. [1] Adjusted for site [2] Adjusted for site, age, sex, ART exposure. *Note. Zomba is excluded from this analysis as no observation data was collected.

Table 6. Sensitivity Analysis: Mortality data, implementation versus observation

Mortality data	Observation n(%)	Implementation n(%)	Risk Difference[1] (%) (95% CI)	p-value	RD[2] (%) (95% CI)	p-value
2-week mortality	73/139 (52.2%)	69/272 (25.4%)	-25 (-35, -15)	<0.001	-25 (-35, -15)	<0.001
10-week mortality	81/139 (58.3%)	110/272 (40.4%)	-15 (-25, -0.05)	0.004	-14 (-24, -4)	0.005
Tanzania						
2-week mortality	47/76 (61.8%)	32/102 (31.4%)	-30 (-45, -16)	<0.001	-29 (-43, -15)	<0.001
10-week mortality	52/76 (68.4%)	51/102 (50.0%)	-18 (-33, -4)	0.01	-17 (-32, -3)	0.02
Lilongwe*						
2-week mortality	11/35 (31.4%)	16/71 (22.5%)	-9 (-27, 9)	0.34	-10 (-28, -9)	0.31
10-week mortality	13/35 (37.1%)	27/71 (38.0%)	-0.5 (-20, 19)	0.96	-2 (-21, 17)	0.86
Cameroon						
2-week mortality	15/28 (53.6%)	21/99 (21.2%)	-32 (-53, -12)	0.002	-33 (-53, -13)	0.001
10-week mortality	16/28 (57.1%)	32/99 (32.3%)	-25 (-45, -4)	0.02	-25 (-45, -4)	0.02

All cases excluding Zomba, loss to follow up = died [1] Adjusted for site [2] Adjusted for age, sex, ART exposure
**note Zomba is excluded from this analysis as no observation data was collected

Table 7. Time to death analysis, observation versus implementation, all cases in observation and CNS cases only in implementation

	Died within 10 weeks n/N (%)	Time from enrolment to death Mean days (SD)	HR* (95% CI)	p-value	HR** (95% CI)	p-value
Overall						
Observation	71/129 (55.0%)	7.9 (13.9)	1.00	0.001	1.00	0.004
Implementation	98/241 (40.7%)	17.0 (18.0)	0.60 (0.44, 0.82)		0.63 (0.45, 0.86)	
Tanzania						
Observation	43/67 (64.2%)	6.8 (12.2)	1.00	0.01	1.00	0.007
Implementation	46/95 (48.4%)	17.4 (19.5)	0.57 (0.37, 0.86)		0.56 (0.36, 0.85)	
Lilongwe						
Observation	13/35 (37.1%)	11.7 (17.1)	1.00	0.90	1.00	0.70
Implementation	23/57 (40.4%)	19.2 (20.8)	1.04 (0.53, 2.06)		0.87 (0.42, 1.79)	
Cameroon						
Observation	15/27 (55.6%)	7.6 (15.9)	1.00	0.006	1.00	0.11
Implementation	29/89 (32.6%)	14.8 (12.8)	0.42 (0.22, 0.78)		0.58 (0.29, 1.14)	

All cases in observation and CNS cases only in implementation, excluding Zomba and loss to follow up
*Adjusted for site **Adjusted for site, age, sex, mental status, ART exposure