

The Treatment and Characterization of Burkitt Lymphoma in Africa

Report of the Multi-Center Study by the INCTR African BL Strategy Group

Paris Meeting
May 2011



Protocol Objectives

- To characterize the presentation features of BL
- To assess response, EFS, and OS in patients treated according to a uniform protocol
- To compare presentation features and outcomes of HIV pos vs HIV neg patients
- To assess the efficacy of a salvage regimen (Second Line Treatment)

Treatment Protocol

- First Line Treatment (COM + IT therapy) for newly diagnosed, previously untreated patients
 - 3 cycles of therapy for “low risk” patients
 - 6 cycles of therapy for “high risk” patients
- Second-Line Treatment (IFOS/MESNA, etoposide, ara-c + IT therapy)
 - Patients who fail to respond to First-Line Treatment
 - Patients who relapse early (within 3 months) after completion of First-Line Treatment

Patient Characteristics

Aug 2004 – Dec 2009

Sex	Males	231
	Females	126
Age	Median	7 years
	Range	2 – 59 years
Total enrolled		357
HIV Status	Positive	15 (4.6% of those tested)

Presentation Sites of Disease – All Patients

<i>Site of Disease</i>	<i>(%)</i>
Jaw	60.5
Abdomen/Pelvis	55.4
Orbit	20.7
Lymph nodes	20.4
Bone marrow	14.4
CNS	6.7
Other	7.3

Comparison of HIV+/- Patients

<i>Site of Disease</i>	HIV neg. (%)	HIV pos. (%)
Jaw	61.7	53.3
Abdomen/pelvis	57.2	46.7
Orbit	21.5	13.3
Lymph nodes	19.9	33.3
Bone marrow	15.8	0
CNS	7.4	0
Other sites	7.3	6.7

BM & CSF was not evaluated in many HIV + patients

Comparison of HIV+/- Patients

	HIV neg.	HIV pos
Males/Females	203/108 (1.9:1)	8/7 (1.1:1)
Age range	2 – 28 years	2 – 59 years
Median age	7 years	6 years
Average age	7.3 years	16 years

HIV +: 7 males \leq 7 yrs; 1 male = 48 yrs; 4 females \leq 10 yrs, 3 females \geq 40 yrs

Staging for African BL: Magrath Stage/Risk Group

Stage Definition (Magrath et al)

A A single extraabdominal tumor

B Multiple extraabdominal tumors

C Abdominal tumor with or without facial tumors

D Abdominal tumor with tumor at other sites (except face alone)

Risk Protocol Definition

Low A single extraabdominal tumor < 10 cm

High All patients not meeting definition for LR

Stage (Magrath et al)

<i>Stage</i>	Number (%)
A	20 (5.6)
UA	27 (7.6)
B	112 (31.3)
C	59 (16.5)
UC	77 (21.6)
D	62 (17.3)

It was not possible to state with certainty that patients listed as "UA" or "UC" met the definition for stage A or C because of the high % of patients who did not have BM/CSF exams

Presentation Features: Comments

- Majority of patients had multiple sites of disease (91%)
- Patients with “single” sites of disease had large extraabdominal tumors (>10 cm) or intraabdominal masses – only 6 met the definition of “low risk”
- Patients with known BM and/or CNS involvement were included
- Patients who did *not* have a diagnostic BM (47%) or CSF exam (52%) prior to treatment were also included

Presentation Features: Comments

- Difficult to utilize “classical” staging systems used for lymphomas (i.e., St Jude) because large numbers of patients did not have BM (47%) or CSF evaluated (52%).
- 356 of the 357 patients were treated according to the High Risk Arm even though 6 patients were Low Risk per the protocol definitions.

Response to First-Line Treatment

Response	Total	%
CR	271	75.9
PR	46	12.9
NR	10	2.8
NE	30	8.4

NE: 24 early deaths (tumor lysis, 10, infection, 7, disease, 4, 3, unknown, but refused rx) and 6, lost to follow up.

Failures to First Line Treatment

- Relapses: 67 (24.7% of CRs)
- PR/NR: 56
- Treatment
 - Second Line treatment only: 54
 - Repeat First Line treatment only: 16
 - Both regimens: 18
 - No treatment: 35

Second Line Treatment

	No. of Patients
Reason Second Line Given	
PR/NR to First Line Rx	35
Relapse after First Line Rx	37
Response to Second Line	
CR	27
PR/NR	42
NE	3

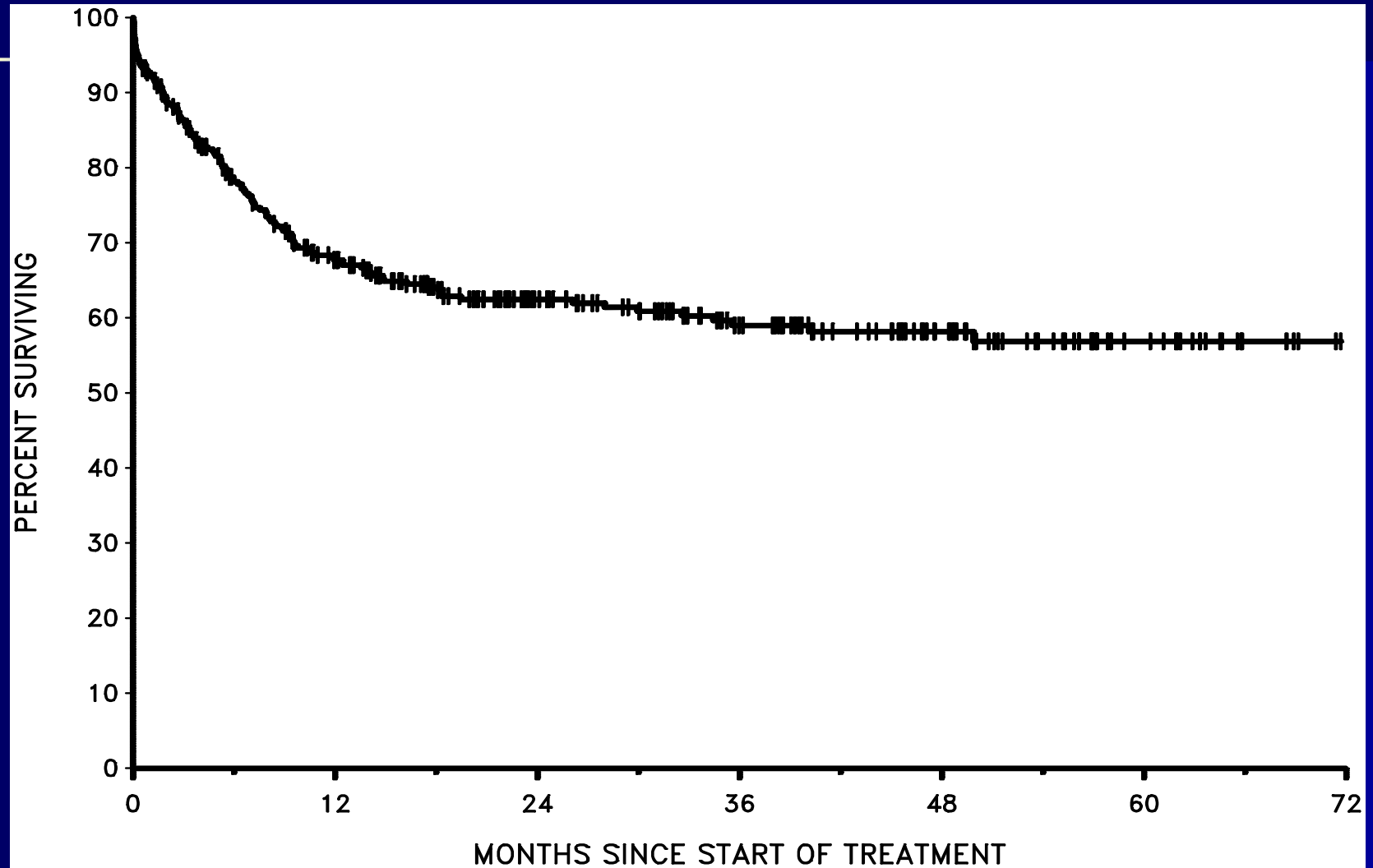
Second Line Treatment - Outcome

- Median survival time 5.1 months (note: one patient alive at 64 months).
- Estimated survival from the time of the start of Second-Line Treatment:
 - 44% at 6 months
 - 34% at 12 months

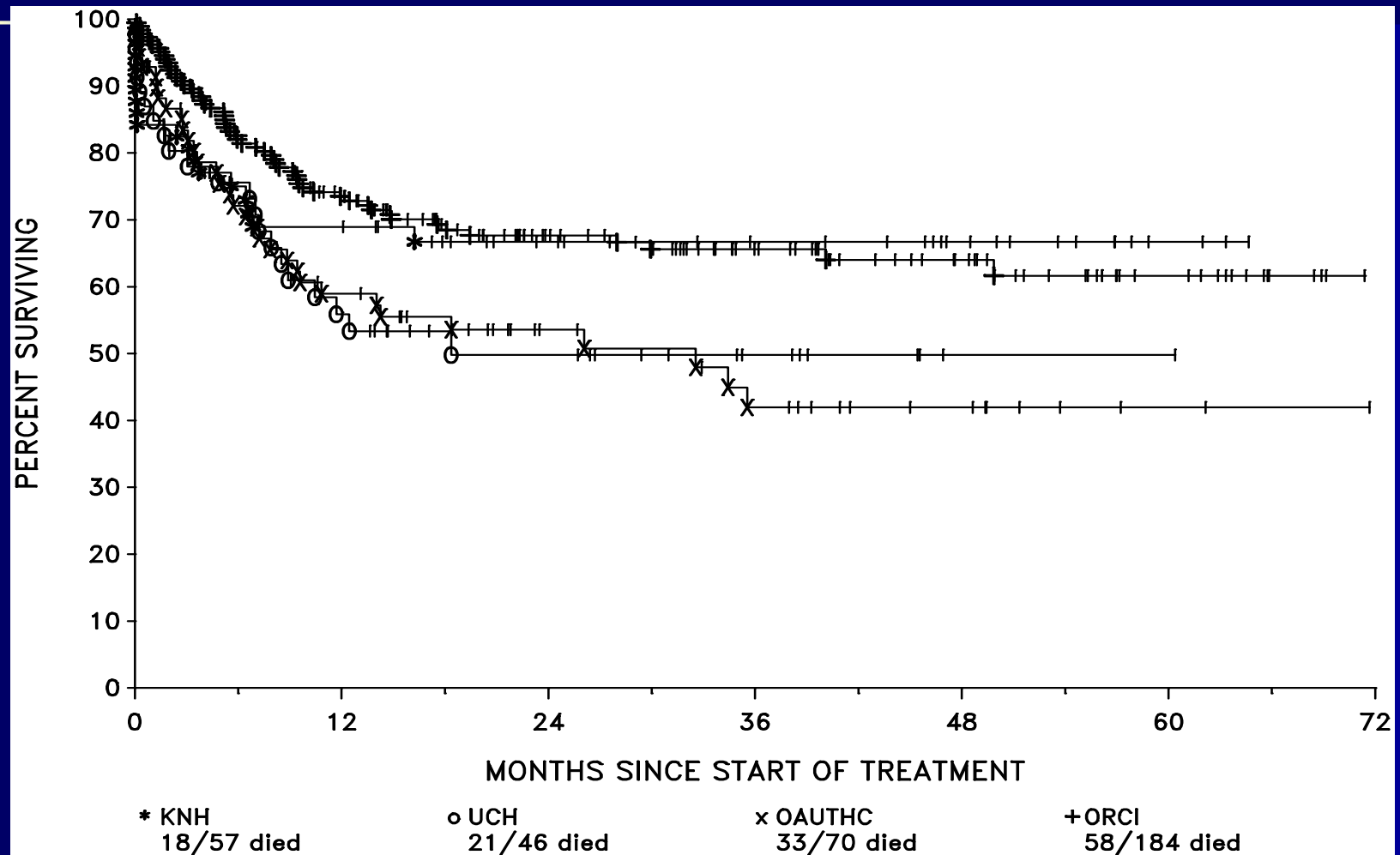
Event Free and Overall Survival – All Patients

- Event Free Survival
 - Events defined as: induction deaths, remission deaths, first relapse, progressive disease, second cancer
 - 54% at 1 year
 - 52% at 2 years
- Overall Survival
 - 68% at 1 year
 - 62% at 2 years

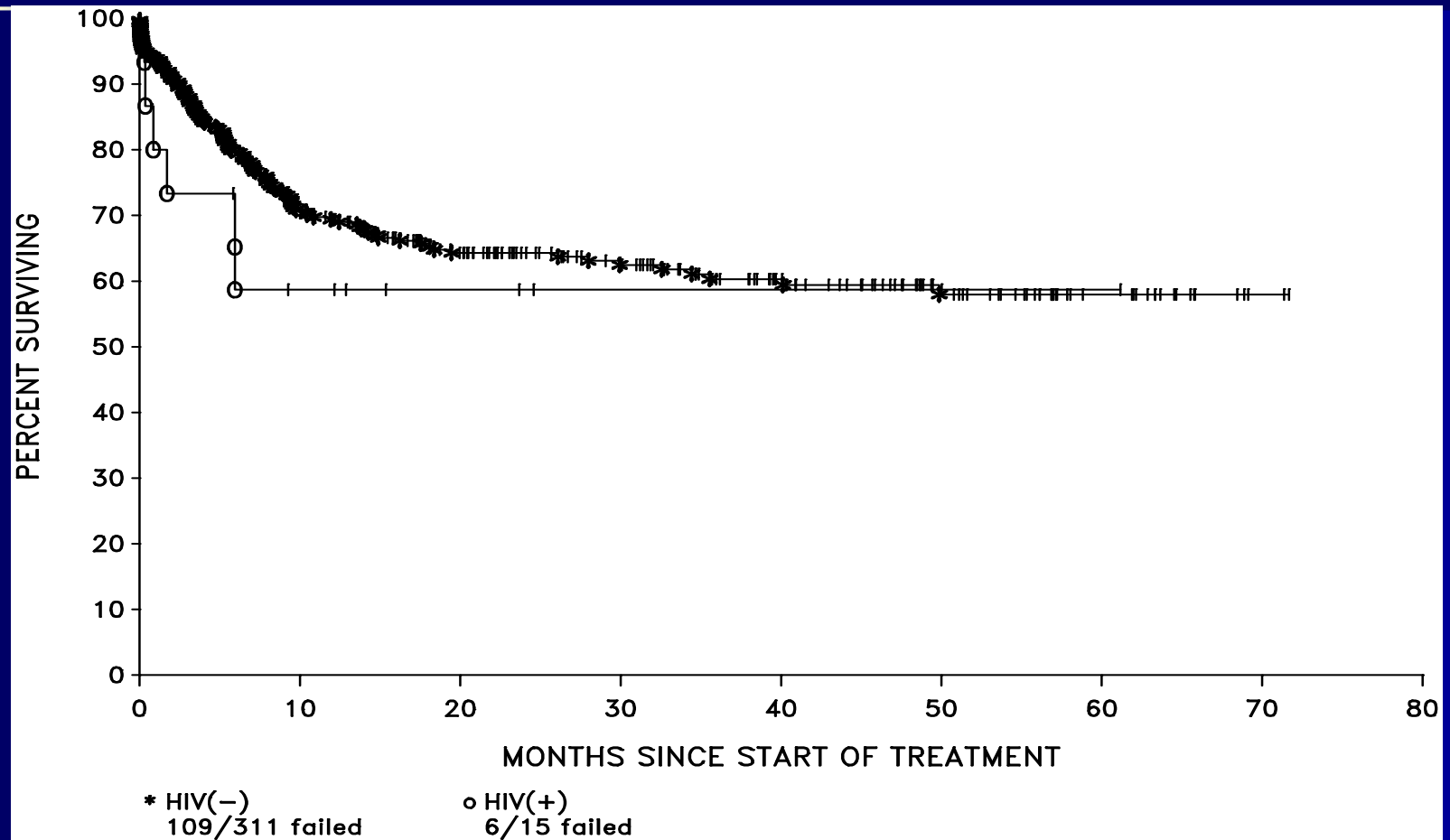
Survival – All Patients



Comparison of Survival



Comparison of Survival: HIV+/-



Challenges Encountered

- Families incur the majority of costs associated with treatment including transportation
 - Reasons for therapy abandonment/refusal of treatment at relapse
 - Results in decreased follow up, particularly when they experience “problems” - fever, signs of disease recurrence

Challenges Encountered

- Continuing decrease in patient accrual at 3 institutions (KNH, UCH, ORCI)
 - ? Publication of “national guidelines” for the treatment of BL in Tanzania
 - ? Internal politics – two competing protocols for the treatment of BL in the same institution
 - ? Frequent or prolonged absences of PIs
 - ? Decreased interest over time

Challenges Encountered

- Problems in the provision of basic care and the management of BL patients persist
 - Failure or inability to perform required tests such as BM, CSF, blood chemistries, including LDH
 - Inability to follow protocol eligibility criteria and guidelines for treatment modifications
 - Inability to properly monitor patients with high tumor burdens on general pediatric wards
 - Delays in initiating therapy after dx is made
 - Delays in initiating therapy for relapse or PR

Challenges Encountered

- Preventable deaths occur
 - Tests necessary to monitor patients before and during therapy are not performed either due to costs for patients or broken equipment
 - Malaria deaths occur after treatment completed
 - Deaths due to contagious diseases such as measles occur when children are kept in the hospital after treatment is completed to ensure that their families pay the “hospital bills”!

Challenges Encountered

- Inaccurate Diagnoses
 - Majority of diagnoses are made by FNA
 - Immunophenotyping is not performed
 - When a clinical presentation doesn't correspond to the diagnosis made, this doesn't prompt an immediate request for consultation (iPath)
 - Some late relapses may be attributed to an inaccurate initial diagnosis – results in incorrect treatment and wastage of resources
 - Misinterpretation of cytospins resulting in "overcall" of CNS disease

Challenges Encountered

- Drug Procurement and Inventory
 - CIPLA will now only fill orders that meet a certain value/quantity ("batch" size)
 - This results in local purchases of their products (more costly – sometimes 2 to 3 times the price)
 - Failure to pick up drug shipments at the airport!
 - Failure to regularly monitor inventory for quantities – particularly those due to expire
 - Running out of study drugs
 - Thinking that drug supplies have run out, when they are actually available

Is There Any Good News?



Progress

- 63.8% completed First Line Treatment (FL)
- Reasons for failure to complete FL
 - Change to Second Line (11.7%)
 - Deaths (10.9%)
 - Stopped treatment, but alive in CR (5.9%)
 - Abandoned rx and lost to follow up (3.9%)
 - Refused/not offered rx at PR/NR, relapse (2.8%)
 - Couldn't afford Second Line treatment (0.5%)
 - Medical decision to stop therapy (0.3%)

Progress

- INCTR is able to provide chemotherapy and antibiotics thanks to generous donors
- Patient follow up continues to improve resulting in visits made to patients living in remote areas resulting in a decrease in unknown outcomes
- New data entry system was implemented in 2010
 - Data is entered “off-line”
 - Requires minimal “internet connection time” to upload data to central database
 - System upgrades transparent to the user
 - Data is securely stored and virus protected

Progress

- On-site and off-site data monitoring continues
- Training and education via iPath is available, valuable in reviewing/confirming diagnoses
- St Mary's Hospital Lacor started accruing patients in 2010
- Bugando Medical Centre, Mwanza will start the study soon
- Data analyzed, publication drafted

Summary

- 130 patients have died (24, induction, 23 remission and 83 with disease)
- Relapse patients or PRs to First-Line could be salvaged with Second Line Treatment or Repeat First Line Treatment (late relapse)
- Patient accrual continues
 - 108 patients since January, 2010 (total: 465)
 - St Mary's Hospital Lacor in Uganda has accrued 61 eligible patients since starting the study in March 2010

Conclusions

- There is a need to further improve diagnostic capabilities & supportive care
- It is possible to cure patients, even in the setting of relapse or PR with this protocol
- Differences exist among the centers with respect to OS (60% to 74% at 1 year)
- There was no difference in OS between HIV+/- patients
- OS for all centers is 68% at 12 months

Rapid Response



3.5
weeks



Total cost
of chemo
~ \$200



INCTR African BL Treatment Project

Acknowledgements

- **KNH, Nairobi**
 - **Dr Jessie Githang'a**
 - **Dr Jamilla Rajab**
 - **Mr Oliver Oruko**
- **OAUTHC, Ile-Ife**
 - **Dr Muheez Durosinmi**
 - **Dr OO Adeodu**
 - **Dr L Salawu**
 - **Mr Lukman Bashir**
- **NCI, Bethesda, MD USA**
 - **Dr David Venzon**
- **UHC, Ibadan**
 - **Dr Yetunde Aken'Ova**
 - **Dr Biobele Brown**
 - **Mrs Tosin Olajedo**
- **ORCI, Dar es Salaam**
 - **Dr Twalib Ngoma**
 - **Dr Jane Kaijage**
 - **Mr Seif Mkamba**

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Falcon, Udo Bode, Ian Magrath