Responding to HIV in Malawi: towards a continuum of care

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During the last decade ART services in eastern and southern Africa expanded tremendously. In parallel, strategies, approaches, initiatives, policies and guidelines were developed at global, regional and national level. Malawi, in a microcosm, shows these developments like the Great in the Small.

**Chapter 1** sets the scene by briefly describing the spread of HIV in sub Saharan Africa and Malawi at the outset of the research. I outline the barriers to a successful response and the devastating effects of HIV on people’s lives. The Chapter introduces the public health approach and operations research as key tools to stem the epidemic in Malawi, leading to the aim and the objectives of this thesis that were developed and achieved at Lighthouse Trust, a major HIV service provider in Lilongwe, Malawi, between 2002 and 2010.

Of note, the systems set up during the research were as important as the findings themselves. The research process influenced how the Lighthouse Trust operated later on. Though the studies targeted different patient groups with HIV infection that entered services at different points, all the studies aimed at improving access to and retention in HIV care- elements that are essential to the further progress in the response to HIV.

Ensuring good adherence is critical to the success of anti-retroviral treatment (ART). However, in resource-poor contexts, where paediatric HIV burden is high there has been limited progress in developing or adapting tools to support adherence for HIV-infected children on ART and their caregivers. In **Chapter 2** we present formative research to assess children’s adherence and to explore the knowledge, perceptions and attitudes of caregivers towards children’s treatment.

All children who started ART between September 2002 and January 2004 (when ART was at cost in Malawi) were observed for at least 6 months on ART. Their adherence was assessed quantitatively by asking caregivers of children about missed ART doses during the previous 3 days at monthly visits. Attendance to clinic appointments was also monitored. In June and July 2004, four focus group discussions, each with 6 to 8 caregivers, and 5 critical incident narratives were conducted to provide complementary contextual data on caregivers’ experiences on the challenges to and opportunities of paediatric ART adherence.

We followed prospectively 47 children who started ART between 8 months and 12 years of age over a median time on ART of 33 weeks (2-91 weeks). 72% (34/47) never missed a single dose according to caregivers’ report and 82% (327/401) of clinic visits were either as scheduled, or before or within 1 week after the scheduled appointment. Caregivers were generally knowledgeable about ART and motivated to support children to adhere to treatment despite facing multiple challenges. Caregivers were particularly motivated by seeing children begin to get better; but faced challenges in meeting the costs of medicine and transport, waiting times in clinic, stock outs and remembering to support children to adhere in the face of multiple responsibilities.

In the era of rapid scale-up of treatment for children there is need for holistic support strategies that focus on the child, the caregiver and the health worker and which are situated within the reality of fragile health
systems. The findings highlighted the need for cost-free and less complex paediatric ART regimes and culturally appropriate tools to support children's adherence.

In June 2004, Lighthouse was the first clinic to provide free ART in the public sector, but few children accessed the services. Chapter 3 describes the introduction of provider-initiated HIV testing and counselling (PITC) and an ART clinic at the paediatric department at KCH in Quarter 4 (Q4) 2004. We analysed prospectively collected, aggregated data of quarterly reports from Q1 2003 to Q4 2006 from HTC centre registers, ART registers and clinic registrations at the ART clinics of both Lighthouse and the paediatric department. By comparing data of both facilities before (Q1 2003 to Q3 2004), and after the introduction of the services at the paediatric department (Q4 2004 to Q4 2006), we assessed the effect of this intervention on the uptake of HIV services for children at KCH. Overall, 3971 children were tested for HIV, 2428 HIV-infected children were registered for care and 1218 started ART. Between the two periods, the median (interquartile range, IQR) number of children being tested, registered and starting ART per quarter rose from 101 (53-109) to 358 (318-440), 56 (50-82) to 226 (192-234) and 18 (8-23) to 139 (115-150), respectively. The median proportion of tested clients per quarter that were children rose from 3.8% (2.7-4.3) to 9.6% (8.8 to 10.0) (p = 0.0009) and the proportion of ART starters that were children rose from 6.9% (4.9-9.3) to 21.1% (19.2-24.2) (p = 0.0036). The proportion of registered children and adults starting ART each quarter increased similarly, from 26% to 53%, and 20% to 52%, respectively.

In Chapter 4 we examined anthropometric status and response to ART in children treated at Lighthouse Trust as malnutrition is common in HIV-infected children in Africa and an indication ART. All children aged <15 years who started ART between January 2001 and December 2006 were included and followed until March 2008. Weight and height were measured at regular intervals from 1 year before to 2 years after the start of ART. Sex- and age-standardized z-scores were calculated for weight-for-age (WAZ) and height-for-age (HAZ). Predictors of growth were identified in multivariable mixed-effect models. A total of 497 children started ART and were followed for 972 person-years. Median age (IQR) was 8 years (4-11 years). Most children were underweight (52% of children), stunted (69%), in advanced clinical stages (94% in WHO stages 3 or 4) and had severe immunodeficiency (77%). After starting ART, median (IQR) WAZ and HAZ increased from -2.1 (-2.7 to -1.3) and -2.6 (-3.6 to -1.8) to -1.4 (-2.1 to -0.8) and -1.8 (-2.4 to -1.1) at 24 months, respectively (P < 0.001). In multivariable models, baseline WAZ and HAZ scores were the most important determinants of growth trajectories on ART.

We concluded that despite a sustained growth response to ART among children remaining on therapy, normal values were not reached. Interventions leading to earlier HIV diagnosis and initiation of treatment could improve growth response.
Chapter 5 had the objectives to a) determine true outcomes of patients lost to follow-up (LTFU) and b) identify risk factors associated with successful tracing and deaths of patients LTFU from ART at Lighthouse Trust. Patients who were more than 2 weeks late according to their last ART supply and who provided a phone number or address in Lilongwe were eligible for tracing. Their outcomes were updated and risk factors for successful tracing and death were examined.

Of 1800 patients LTFU with consent for tracing, 724 (40%) were eligible and tracing was successful in 534 (74%): 285 (53%) were found to be alive and on ART; 32 (6%) had stopped ART; and 217 (41%) had died. Having a phone contact doubled tracing success (adjusted odds ratio, aOR = 2.1, 95% CI 1.4-3.0) and odds of identifying deaths [aOR = 1.8 (1.2-2.7)] in patients successfully traced. Mortality was higher when ART was fee-based at initiation (aOR = 2.3, 95% CI 1.1-4.7) and declined with follow-up time on ART. Limiting the analysis to patients living in Lilongwe did not change the main findings.

We concluded that ascertainment of contact information is a prerequisite for tracing, which can reveal outcomes of a large proportion of patients LTFU. Having a phone contact number is critical for successful tracing, but further research should focus on understanding whether phone tracing is associated with any differential reporting of mortality or LTFU.

Chapter 6 aimed to analyse mortality, LTFU and retention on ART in the first year of ART across all age groups in the Malawi national ART programme in a cohort including all patients who started ART in Malawi's public sector clinics between 2004 and 2007.

ART registers were photographed, information entered into a database and merged with data from clinics with electronic records. Rates per 100 patient-years and cumulative incidence of retention were calculated. Subhazard ratios (sHRs) of outcomes adjusted for patient and clinic-level characteristics were calculated in multivariable analysis, applying competing risk models.

A total of 117,945 patients contributed 85,246 person-years: 1.0% were infants below 2 years, 7.4% children 2-14, 7.5% young people 15-24, and 84.2% adults 25 years and above. Sixty percent of patients were female: women outnumbered men from age 14 to 35 years. Mortality and LTFU were higher in men from age 20 years. Infants and young people had the highest rates per 100 person-years for mortality (23.0 and 19.4) and LTFU (24.7 and 19.3), and the highest adjusted relative risks compared to age group 25-34 years: sHRs were 1.37 (95% confidence interval (CI) 1.17-1.60) and 1.17 (95% CI 1.10-1.25) for death and 1.37 (95% CI 1.18-1.59) and 1.27 (95% CI 1.19-1.35) for LTFU, respectively.

In this country-wide study patients aged 0-1 and 15-24 years had the highest risk of death and LTFU, and from age 20 men were at higher risk than women. Interventions to improve outcomes in these patient groups are required.

In Chapter 7 we described the results of measures to improve uptake of ART among eligible pregnant women. Between October 2006 and December 2009, interventions implemented at ANC and ART facilities in urban Lilongwe aimed to better link services for women with CD4 counts <250/μl. A monitoring system followed
women referred for ART to examine trends and improve practices in referral completion, on-time ART initiation and ART retention.

Six hundred and twelve women were ART eligible: 604 (99%) received their CD4 result, 344 (56%) reached the clinic, 286 (47%) started ART while pregnant and 261 (43%) were either alive on ART or transferred out after 6 months. Between 2006 and 2009, the median (IQR) time between CD4 blood draw and ART initiation fell from 41 days (17-349) to 15 days (7-42) (P=0.183); the proportion of eligible individuals starting ART while pregnant and retained for 6 months improved from 17% to 65% (P<0.001). Delays generally shortened within the continuum of care from 2006 to 2009; however, time from CD4 blood draw to ART referral increased from 7 to 14 days.

We concluded that referrals between facilities and delays through CD4 count measurements create bottlenecks in patient care. Retention improved over time, but delays within the linkage process remained. ART initiation at ANC plus use of point-of-care CD4 tests may further enhance ART uptake.

In Chapter 8 we compared ART prescribing between nurses and clinical officers during routine clinic visits at Lighthouse Trust clinics to inform policy in paediatric ART management. Caregivers of children on first-line ART provided information about visit dates, pill counts, ART dosage and formulation to a nurse and, subsequently, to a clinical officer. Nurses and clinical officers independently calculated adherence, dosage based on body weight, and set next appointment date. Clinical officers, but not nurses, accessed an electronic data system that made the calculations for them based on information from prior visits, actual and expected pill consumption, and standard drug supplies. Nurses calculated with pen and paper. For numerical variables, we used Bland-Altman graphs to plot differences of each nurse clinical officer pair against the mean, showed the 95% limits of agreement (LoA), and the mean difference across all reviews. Kappa statistics assessed agreement for categorical variables.

A total of 704 matched nurse clinical officer reviews of 367 children attending the ART clinics between March and July 2010 were analyzed. Eight nurses and 18 clinical officers were involved; two nurses and five clinical officers managed 100 visits or more. Overall, there was a good agreement between the two cadres. Differences between nurses and clinical officers were within narrow LoA and mean differences showed little deviation from zero, indicating little skewing towards one cadre. LoA of adherence and morning and evening ART dosages varied from -24% to 24%, -0.4 to 0.4 and -0.41 to 0.40 tablets, respectively, with mean differences (95% CI) of 0.003 (-0.9, 0.91), -0.005 (-0.02, 0.01) and -0.009 (-0.02, 0.01). Next appointment calculations differed more between cadres with LoA from -40 to 42 days [mean difference: 0.96 days (95%CI: -0.6 to 2.5)], but agreement in the ART formulation prescribed was very good (kappa 0.93).

Nurses’ ART prescribing practices and calculations of adherence and next appointments were similar to clinical officers, although clinical officers used an electronic system. Our findings support the decision of Malawi’s health officials to utilize nurses to manage paediatric ART patients.

Chapter 9 revised the drivers for the successful ART scale up in Malawi and reflected on the role of operations research in this context. A brief outline of the changing epidemiology of HIV and key interventions led to a
framework that helped illustrating how the various studies presented in Chapters 2 to 8 contributed to increasing access to and retention of PLHIV in care. The Chapter highlights the studies’ implications for Malawi’s national programme, lessons learned and limitations of our research.

To conclude, over the research period the focus of the HIV response shifted from an emergency and rapid scale up mode to retaining patients on ART, emphasizing the chronic aspect of HIV care. We also understand now that early and widespread use of ART prevents transmission. Expanding access and achieving high retention make “treatment as prevention” work on the large scale - interventions that appeared fragmented in the past, focussing on either prevention or treatment, act synergistically. Malawi’s HIV programme applies this concept with universal treatment for PLHIV who are children < 2 years, pregnant women and patients with TB and Hepatitis B and starts to reverse its HIV epidemic. Retention doesn’t mean only retaining people on ART. We need to retain PLHIV across an entire test-treat-retain continuum. The studies presented here have contributed to our understanding of the gaps and opportunities within this continuum.

The public health approach for ART is the appropriate strategy to tackle HIV in Malawi. Operations research, as an essential part of it, acts as reality check and compass when implementing new policies and guidelines. “Having effective regimens is not enough all by itself, however; effective delivery of programmes are even more important” [(1) citing (2)]- operations research needs to inform service delivery and can be even complementary. The lessons learned and systems set up in responding to HIV might be beneficial in controlling other communicable and non communicable diseases in Malawi.

The continuum of care is an ideal. In reality, gaps in HIV services are wide open. LTFU remains high and often we do not know the scope of the problem, the causes and how to improve our services. What is the long term retention of patients who started on ART? What are the outcomes of patients who started under the “test and treat approach”: pregnant women and children < 2 years? How can we improve access and retention of HIV exposed infants? What happens to infants, children and pregnant women who are LTFU?

Responding to HIV is a global effort. Malawi, a country with few resources, can’t fight HIV in isolation. It requires funds for ART, for human resources to implement the guidance proposed by international policy makers, and for operations research that is embedded in the routine services. The exchange of views and research findings with others boosts the morale of the people who do the job on the ground. The feeling of being part of that global community motivates to take on the tasks ahead, to “turn the tide together”.
