Lessons for test and treat in an anti-retroviral programme post decentralisation in Uganda; A retrospective analysis of outcomes in public healthcare facilities within the Lablite project

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Abstract

Background: We describe the decentralisation of antiretroviral therapy (ART) alongside Option B+ roll-out in public healthcare facilities in the Lablite project in Uganda. Lessons learned will inform programs now implementing Universal Test and Treat (UTT).

Methods: Routine data were extracted from ART registers between October 2012 and March 2015, retrospectively for all adults and children initiating ART at 2 primary care (PC) facilities (spokes) and their corresponding district hospitals (hubs) in Northern and Central Uganda. We describe ART initiation over time, and retention and use COX models to explore risk factors for attrition due to mortality and loss to follow-up. Results from tracing of patients lost to follow-up were used to correct retention estimates.

Results: Of 2100 ART initiations, 1125 were in the North, including 944(84%) at the hospital and 181(16%) in PC; children comprised 95(10%) of initiations at the hubs and 14(8%) at the spokes. Corresponding numbers were 642(66%) at the hub and 333(34%) in spokes in the Central region (77(12%) and 22(7%) respectively in children). Children <3 years comprised the minority of initiations (in children) at all sites. Twenty-three percent of adult ART initiations in the North hub were Option B+ compared with 45% at the spokes (25% and 65% respectively in Central).

Proportions retained in care in the North hub at 6 and 12 months were 92% (95% CI 90-93), 89%(87-91). Corresponding corrected estimates in North spokes were 87%(78,93) and 82%(72,89). In the Central hub corrected estimates were 84%(80,87) and 78%(74,82), respectively and 89% (77.9,95.1) and 83% (64.1, 92.9) in spokes. Among adults newly initiating ART, being older was independently associated with a lower risk of attrition (aHR=0.93 per 5 years (95% CI 0.88, 0.97)), Other independent risk factors included: initiating with Tenofovir-based regimen versus zidovudine 0.60 (0.46, 0.77); year of ART initiation (2013 aHR= 1.55 (95% CI 1.21, 1.97), ≥ 2014 aHR= 1.41 (1.06, 1.87) versus 2012; hub versus spoke (aHR= 0.35 (95% CI 0.29, 0.43)); and Central versus North (aHR= 2.28 (1.86, 2.81)).Independently, patient type was associated with retention;

Conclusion: Post ART decentralisation, people living with HIV were willing to initiate ART in rural primary care facilities. Retention on ART was variable across facilities, attrition was higher among some groups including younger adults and women initiating ART during pregnancy/breastfeeding. Interventions to support these groups are required to optimise benefits of expanded access to HIV services under UTT.

Key words: Antiretroviral therapy, Human Immunodeficiency Virus, Decentralisation, Retention, Attrition, sub-Saharan Africa

Background

In 2017 the number of adults living with HIV in Uganda was estimated at 1.3 million (5.9%) (1, 2). To reach universal access to antiretroviral therapy (ART) decentralization of HIV treatment from hospitals to primary care (PC) facilities is necessary. Several studies have also shown that decentralisation of ART services to PC improves access to care and improves retention among children and adults (3-6).

From 2012 many sub-Saharan African countries transitioned from a CD4 cell count threshold of 350 to 500 cells/mm3 and adopted Option B+, where all pregnant and breastfeeding women are eligible for ART regardless of CD4 cell count or WHO stage, in accordance with WHO recommendations to eliminate mother to child transmission (7-9). Decentralisation of ART provision to lower level PC health facilities was scaled-up from November 2012 in Uganda, alongside the introduction of Option B+. Implementation of these strategies occurred in phases starting in regions with the highest HIV prevalence. In 2013, under the national ART guidelines all patients identified with HIV infection and CD4<500 cells were eligible for ART, up from CD4<350 cells in 2010. From March 2014, the Ministry of Health (MOH) in Uganda effected a change in guidelines indicating a regimen of Tenofovir, Lamivudine, Efavirenz (TDF/3TC/EFV) for first line following WHO recommendations. Currently ART is to be provided free of charge through the Universal Test and Treat (UTT) approach for all HIV-positive individuals in Uganda following this recommendation from WHO (10). Whilst efforts to scale-up had increased ART coverage to 72% by end of 2017 (2, 11) and the proportion of pregnant women starting ART has reached 97% (12), a number of individuals living with HIV still do not have access to ART. Challenges for programmes remain around retention in care and ART use during postnatal care (7, 13-15). In Uganda, loss to follow-up rates by 6 months for Option B+ women varied between 10% and 30% in the period 2010-2016 (15-17), with similarly high attrition in other African settings (18). Lessons learned through decentralization and Option B+ will inform optimal strategies for UTT, for example indicators of quality of HIV care including routine counselling and testing, and subsequent initiation of ART.

The Lablite project worked with Ministries of Health (MOH) in Malawi, Zimbabwe and Uganda to evaluate ART rollout in non-research sites in the three countries. In Uganda, Lablite was present in two districts, Agago in the North and Kalungu in Central/SW Uganda; districts which differed in terms of their catchment populations and settings. Both sites comprised a district hospital (hub) and 2 PC facilities in the surrounding area (spokes) (9). We used the staff at the hub to train, mentor and support the spokes, and to build confidence of lower healthcare staff to initiate and monitor ART. Subsequently patient referrals upwards or downwards were based on level of expertise and service need.

We aimed to document outcomes, treatment changes, retention and risk factors for attrition due to loss to follow-up and mortality among children and adults newly initiated on ART between 2012 and 2015. We summarise key lessons learned following ART decentralisation post Option B+ and implementation of changes in ART guidelines in Uganda and consider the implications for optimising UTT implementation.

Methods

Study setting, design and population

Between October 2012 and March 2015 in Uganda, MOH implemented Option B+ and decentralisation of ART services to PC. In the Lablite project we retrospectively collected routine patient-level data for children and adults enrolled in HIV care in 2 geographical regions including the district hospital (hub) and 2 corresponding PC health facilities (spokes). Through Lablite, working with MOH, we implemented an HIV care task shifting model from hospital- based physician to primary care nurse in November 2012 as MOH rolled out option B+ in PC health facilities. Sites were chosen in consultation with MOH. : Agago district in the North is a post-conflict area, which is difficult to reach; it has an HIV prevalence of 8.2% and a catchment of 285,300. Kalongo hospital

(hub) has provided ART since 2005, is owned by the Uganda Roman Catholic church and, through Lablite, was linked to 2 PC health facilities (spokes) , Paimol and Lira Kato health centres in the district (Figure 1). Prior to decentralisation of ART services, Paimol and Lira Kato had no ART outreach programs and patients had to travel approximately 56km round-trip to Kalongo hospital (or 76km to Patongo hospital) for ART (19). Option B+ in these PC facilities started in April 2013, followed by general ART provision from May 2013. Post ART decentralisation Paimol and Lira Kato provided ART to catchments of 23,940 and 19,215 respectively. The hub or nearby hospitals in the North provided CD4 cell count testing facilities for samples taken at the PC facilities so patients did not have to travel, but technical challenges remained with the CD4 testing machine at the hospital, resulting in testing not always being available. From June 2014, the North (Kalongo) hospital implemented the increased CD4 threshold for ART initiation, and subsequently changed first line treatment to Tenofovir, Lamivudine, Efavirenz (TDF/3TC/EFV) from July 2014. The MOH implemented these changes in ART national guidelines in a tiered approach (at higher level facilities first) with training from hospital to PC. ART initiation and/or regimen provision depended on guidelines and the drug supply chain of implementing partners. The MOH provided on-site training to all HIV care health facility staff, with the Lablite team, through a hub–spoke mentorship training module on new drug regimen dosing, side-effects and supply chain management prior to implementation of changes, resulting in varying implementation dates for health facilities (Table 1)(9).

Table 1

Dates by facility for implementation of Option B+, decentralisation and changes in treatment guidelines for patients newly initiated on ART in 2 district hospitals (hubs) and corresponding primary health care units (spokes) between 2013-2015

	Central hub (Bukulula)	Central spoke (Lukaya)	Central spoke (Kiragga)	North hub (Kalongo)	North spoke (Paimol)	North spoke (Lira Kato)
Option B+	October Q4 2012	October Q4 2012	Q4 2012	October Q4 2012	April Q2 2013	April Q2 2013
General ART provision	2005	March Q1 2013	March Q2 2013	2005	April Q2 2013	April Q2 2013
Change in CD4 threshold from 350 to 500	Q2 2014	Q2 2014	Q2 2014	March/April Q2 2014	August Q3 2014	September Q3 2014
Regimen change to first line TDF/3TC/ EFV	June Q2 2014	July Q2 2014	August Q2 2014	July Q3 2013*	September Q4 2013	September Q4 2013

Q1 –first quarter, Q2 – second quarter, Q3 – third quarter, Q4 – fourth quarter.
Tenofovir, Lamivudine and Efavirenz (TDF/3TC/EFV) first line antiretroviral therapy

Kalungu (Central) district has an HIV prevalence of 12.5% (19) and a catchment of ~ 44,300; the district includes truck driver stops along a national highway and fishing villages. ART has been available through the health services in a Health Centre, designated as the equivalent of a District hospital (Bukulula) since 2005. During the Lablite project the Bukulula facility (hub) was linked to 2 PC facilities as spokes, Lukaya and Kiragga (Figure 1).

Figure 1: Map of health facilities within the Lablite project in Uganda

Prior to decentralisation Bukulula provided outreach ART to Lukaya one of the PC facilities (whereby staff from Bukulula visited Lukaya 1 day/week to provide ART consultations) whilst another private provider serviced Kiragga PC health centre. Option B+ provision at the PC facilities started in October 2012 (Table 1). MOH, working with Lablite, started general ART provision at PC facilities in April 2013, with Lukaya and Kiragga providing ART to catchments of ~5,600 and ~9000 individuals, respectively. Changes in CD4 thresholds for ART initiation were implemented from the second quarter of 2014. Bukulula implemented a regimen change to first line TDF/3TC/EFV in May 2014, following MOH training, with the change in PC occurring approximately 3-months later. Samples were collected at the PC facilities and sent to the Bukulula hub for CD4 cell count testing.

Data collection

Data clerks extracted and entered data into a bespoke database from facility ART registers between October 2012 and March 2015 for all adults and children newly initiating ART. We captured ART register data on sex, age, WHO stage, weight, and CD4 cell count at ART initiation and monthly follow-up data for ART use, treatment changes (including interruption), transfers out of the facility, information on pregnancy and breastfeeding and Tuberculosis status. Assessment for WHO disease stage and CD4 cell count were scheduled at 6-monthly visits. In a few cases a 2-monthly supply of ART was given at the physician's discretion if the patient had a history of good adherence. Individuals on ART could send someone else to pick-up their drugs; this was more common in the North due to the long distances covered by clients to reach ART facilities (20). In 2014, the MOH introduced an open Medical Record System electronic database tool at the Bukulula hub in Central. Alongside the paper ART registers, data clerks entered patient data into the electronic tool retrospectively. In Lablite, this resulted in delays in updating the ART register. At Kalongo hospital in the North, a data clerk extracted data from a pre-existing electronic data system. For all the PC facilities, data clerks collected information from the paper ART registers. We checked data for consistency, raised queries and made changes as necessary with support from health workers and the district data clerks. We obtained additional information from patient cards in response to queries or if data were missing from the ART register.

All men were classified as needing ART for their own health. Women were subdivided into Option B+ clients and those starting ART for their own need. All women started ART at a CD4 below the threshold for initiation by date (Table 1) and/or were WHO stage 3/4 disease were classified as starting ART for their own need. Other women were classifies as follows. At the Central hub and spokes, we differentiated Option B+ patients from other female patients by the presence of an antenatal care number or expected delivery date for pregnancy or Early Infant Diagnosis number for breastfeeding in the ART register (Table 2).

Table 2

Reasons for initiating ART at the Hub and Primary care health facilities among children, adult men, B+ women and women

	Type of patient	Reason for initiating ART	Central hub n(%)	Central spokes n (%)	North hub n(%)	North spokes n(%)	Total
Group 1	Number of Children newly initiated on ART n (row %)	<15 years	77 (37.0)	22 (10.6)	95 (45.7)	14 (6.7%)	208 (100%)
	Number of Adults newly initiated on ART n (row %)	≥15 years	565 (29.9)	311 (16.4%)	849 (44.9)	167 (8.8%)	1892 (100%)
Group 2	Men in Need of ART (1) (% of all adults at facility)	CD4<350/500 or WHO 3/4	146 (25.8)	28 (9.0%)	145 (17.1)	29 (17.4%)	348 (16.6)
	Men in Need of ART¥ (2) (% of all adults at facility)	Unknown CD4 or WHO Stage	15 (2.7)	4 (1.3%)	137 (16.1)	8 (4.8%)	164 (7.8)
Group 3	B+ women (% of all adults at facility)	Pregnant or breastfeeding	143 (25.3)	202 (65.0%)	193 (22.7)	75 (44.9%)	613 (29.2)
Group 4	Women in need of ART† (1) (% of all adults at facility)	CD4<350/500 or WHO 3/4	220 (38.9)	59 (19.0%)	147 (17.3)	39 (23.4%)	465 (22.1)
	Women in need of ART¥ (2) (% of all adults at facility)	Unknown CD4 or WHO Stage	41 (7.3)	18 (5.8%)	227 (26.7)	16 (9.6%)	302 (14.4)

†women in need of ART for their own health CD4<350/500 or WHO stage 3 or 4; B+ women or presence of an antenatal care number or expected delivery date for pregnancy or Early Infant Diagnosis number for breastfeeding in the ART register

¥ If (WHO disease staging 1/2 and unknown CD4) or (CD4>threshold and unknown stage) or (unknown stage and unknown CD4)

We believed these fields were poorly completed (particularly early on), hence in addition, before June 2014 (when regimen changes were implemented at the Central hub), all women who initiated

on TDF/3TC/EFV (with CD4 unknown or ≥350 were assumed to be Option B+ women; similar assumptions were made for women starting ART at the Central spokes before July 2014 (with CD4 cut-off raised to ≥500 for initiations in June 2014). Once TDF/3TC/EFV was being used as the first-line regimen at a site, we were unable to use regimen to distinguish Option B+ women from other women; we used pregnancy date, EID/ANC number and WHO stage/CD4 where available and otherwise assumed women were starting ART for need. In the North patient source (captured in the electronic data at the hub) was used to classify Option B+ women: women who were recorded as entering the HIV programme for "PMTCT" and started ART within 1 month of entry were assumed to have started Option B+; this did not allow us to capture women starting Option B+ during breastfeeding. At the North spokes information on the paper ART registers (including regimen, WHO stage, CD4 and date of initiation) was used similarly to in the Central spokes. In the North WHO staging was often not completed due to lack of understanding (particularly at the hub); although improvements were made over time, health system challenges still existed with limited human resources and high turnover of staff.

Health workers recorded data on mortality if available from registers, usually informed by peer clients. There were systems in place through a non-governmental organisation to trace all clients lost to follow-up in the North hub. We actively tried to trace a sample of all adult patients lost to follow-up at the remaining 5 facilities through either community contacts, peer clients or phone calls where phone contacts were available, and clients had consented. At most, three tracing attempts were made. Tracing outcomes included: death, transfer to another ART facility or dropped out of care (i.e. genuinely lost from follow-up).

Statistical analysis

Data on individuals newly initiating ART during the study period were included; participants who transferred-in to facilities already on treatment were excluded. Descriptive analyses of patient profiles included socio-demographic variables using proportions and medians (IQR). We present data on children <3years and 3-14 years and adults (≥15 years), as guidelines have used these categories for treatment regimens and ART initiation. Adult groups were identified as follows; B+ women, non-B+ women and men. We explored associations between groups and baseline characteristics using chi-square tests for categorical variables and rank sum tests for continuous variables.

Attrition was defined as death or loss to follow-up (not seen for more than 3 months since last ART supply). Crude rates for attrition and 95% confidence intervals around the rates are provided. We used Kaplan Meier methods to estimate retention (1- attrition) in care differentiated by service provision (spoke versus hub). Differences in retention between groups (type of health facility) were assessed using log rank tests. A naive analysis using passively recorded deaths from routine clinic data and loss-to-follow-up as defined above was conducted initially. Adjusted estimates were obtained based on tracing outcomes; a weight of 1 was assigned to all patients whose outcomes were known prior to tracing; a weight of 0 was assigned to all patients with unknown outcome (either lost to follow-up and not traced or lost to follow-up) and a weight equal to the ratio of all patients lost to follow-up over those lost and sampled with tracing outcomes ascertained to patients traced with vital status (21). Weights were calculated separately by region and facility-level (hub/spoke). Although tracing was attempted at both Central spokes we only received information from one: because the patient characteristics were different at the two spokes, we only made adjustment to estimates from the one spoke with tracing information.

We investigated risk factors for attrition in separate COX regression analyses for children and adults newly initiated on ART. We used backwards model selection where we start with all factors of interest, irrespective of univariable analysis. We present univariable and multivariable COX regression models including hazard ratios and 95% confidence intervals, and p-values. We considered age, sex, year of ART initiation (2013), starting regime and patient type (B+ women, adult men and adult women in need of ART), region and type of facility (note CD4 cell count was

more likely to be missing among B+ women since it was not required for eligibility) as potential predictors. Analyses were performed using STATA version 15.1.

Results

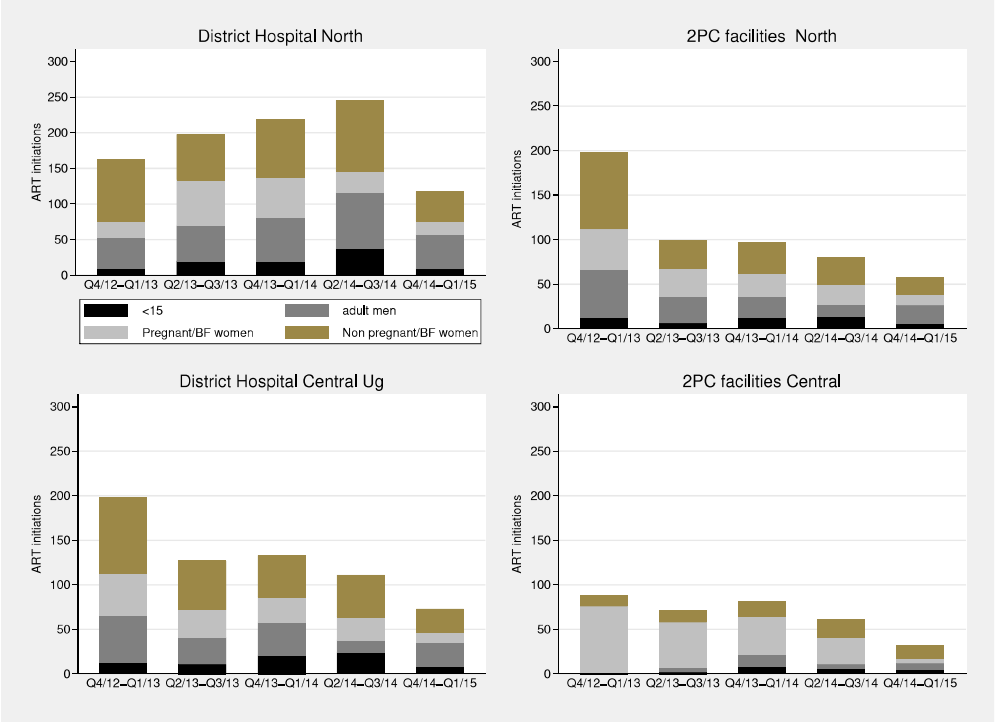
Baseline characteristics of participants in the 2 hubs and corresponding spokes are presented in Table 3.

	Central				**North**			
Characteristic	**Hub**	**% of total or of sub-group**	**spokes**	**% of total or of sub-group**	**Hub**	**% of total or of sub-group**	**spokes**	**% of total or sub-group**
Children								
Numbers enrolled	**77**	**77%**	**22**	**22%**	**95**	**10%**	**14**	**8%**
Age								
<3 years	16	67	8	33	32	89	4	11
3-14 years	61	81	14	19	63	86	10	14
Adult Males								
Numbers enrolled	**161**	**83**	**32**	**17**	**282**	**88**	**37**	**12**
Age (years)	37		40		35			35
Median	(29-46)		(31-51)		(30-41)			(30-45)
(IQR)								
WHO stage								
Stage 1/2	129	80	19	60	107	38	15	41
Stage 3/4	31	19	11	34	11	4	22	59
Missing	1	1	2	6	164	58	0	0
CD4								
Number with CD4 cell counts	148	92	24	75	179	63	20	54
Median	245		222		287		274	
(IQR)	(135-338)		(153-288)		(181-440)		(179-380)	
B+ adult females								
Numbers enrolled	**143**	**41**	**202**	**59**	**193**	**72**	**75**	**28**
Age (years)	27		25		26		27	
Median (IQR)	(22-32)		(22-29)		(21-31)		(21-30)	
WHO stage								
Stage 1/2	142	99	199	98	161	83	75	100

Stage 3/4	0	0	0	0	0	0	0	0
Missing	1	1	3	2	32	17	0	0
CD4								
Number with CD4 cell counts	85	59	69	34	67	35	7	9
Median	546 (440-777)		508 (426-733)		614 (485-733)		659	
(IQR)							(440-755)	
Women in need of ART								
Numbers enrolled	**261**	**77**	**77**	**23**	**374**	**87**	**55**	**13**
Median Age (years)	30		29		33		30	
(IQR)	(24-40)		(24-36)		(26-42)		(24-40)	
WHO stage								
Stage 1/2	231	88	61	79	106	28	30	55
Stage 3/4	29	11	13	17	12	3	24	44
Missing	1	1	3	4	256	69	1	2
Number with CD4 cell counts	231	89	58	75	203	54	25	45
Median (IQR)	266 (172-332)		242 (191-333)		322 (230-450)			290 (137-356)

There were 2100 ART initiations at the 2 hubs and 4 spokes. Of these, 1892 (90%) were in adults and 208 (10%) in children. In Northern Uganda, there were 1125 ART initiations, including 944 (84%) at the hub and 181 (16%) in spokes. At the North hub 95 (10%) of all initiations were in children; in comparison 14 (8%) of all initiations across both spokes were in children (Figure 2).

Figure 2: Numbers of patients newly initiated on ART at the hospital and Primary care health facilities



In Central Uganda, there were 975 ART initiations, 642 (66%) at the hub and 333 (34%) at the spokes. At the Central hub 77 (12%) of all initiations were in children compared with 22 (6%) at the 2 spokes. Figure 2 shows changes in uptake of ART post B+ and the decentralisation of ART from hub to spokes in 6-monthly periods. The proportion of ART initiations in children 0-14 years (of all ART initiations) increased from 6% at 0- 6 months post B+ to 9% at 6-12 months, 8% at 12-18 months and 14% at 18 -24 months in North. Similarly, in Central ART initiations in children increased from 5% at 0-6 months to 7% at 6-12 months, 14% at 12-18 months and 17% at 18-24 months. We observed a decline in ART initiations at both hubs following decentralisation from the second quarter of 2014 in the North and second quarter of 2013 in Central. At the spokes there was a steady increase in patient numbers enrolled over time, including patients in need of ART in the year of ART.

Pre-ART decentralisation characteristics

The median age (IQR) at ART initiation in children <15 years was 4.1 (1.7, 7.6) in the North versus 4.9 (2, 7) in Central. As shown in(Table 3) overall there were no significant differences in the proportion of children < 3 years versus 3-15 years between hub and spokes (p = 0.5). Within region there were no significant differences in ages of children initiating ART between hub and spokes: 4.6 (1.7, 7.9) versus 4.0 (1.6, 7) (p=0.4) in the North and 4.9 (2, 7) versus 3.0 (1.4, 8)(p=0.4) in Central respectively. Of all ART initiations in children <15 years, children <3 years were in the minority at all sites, 33% in North and 26% in Central.

The median age among adults ≥15 years newly initiating ART in the North was 31 (25, 39) versus 29 (24, 37) in the Central region. Within region, there were differences in the ages of adults initiating ART between hub and spokes; 31 (26, 39) versus 29 (24, 36) (p=0.001) in the North and 30 (24, 40) versus 26 (23, 32) (p<0.001) in Central. Overall B+ patients were younger than patients in need of ART: in the North median age was 26 (21, 30) among Option B+ women versus 34 (27, 50) in patients

in need of ART (p<0.001); and in Central 25 (22, 30) among Option B+ women versus 32 (25, 42) in patients in need of ART (p<0.001).

Reasons for initiating ART

Men or women in need of treatment either had CD4 < 350/500 or WHO disease stage 3 or 4, or had tuberculosis. Three groups of patients considered were; adult men (all in need of ART for their own health), Option B+ women and women in need of ART for their own health. Approximately one fifth (23%) of adult ART initiations in the North hub were Option B+ compared with 45% at the spokes (p<0.001), with higher proportions of men in need (33% in hub versus 22% in spokes) and women in need of ART at the hub (44% in hub versus 33% in spokes) (Table 2). In Central 25% of adult initiations were Option B+ at the hub compared with 65% at the spokes (p<0.001); a higher proportion of men in need of ART initiated at the hub than in spokes (29% versus 10%, p<0.001) and, similarly of women in need of ART (46% versus 25% at the hub and spokes respectively).

The WHO staging was frequently missing in the North, particularly at the hub Table 3. A high proportion of adult men initiating ART ~55%, females initiating ART for their own health (69%) and Option B+ women (17%) at the hub had no staging information. Corresponding proportions at the spokes in the North were only in B+ woman.

The WHO staging at the hub and spokes was similar in the Central: 89% and 90% respectively were WHO stage 1/2, 11% and 8% were WHO stage 3/4 and there were very few patients with missing staging.

Overall two thirds of adult patients initiating ART had a baseline CD4 cell count, with median (IQR) 315 (207, 462) cells per µl. Option B+ simplified ART initiation among pregnant women as they did not require CD4 cell count testing. Baseline CD4 cell counts were similar within region. In the North CD4 testing was done intermittently at both hub and spokes, and baseline CD4 was similar in men and women in need of ART; 179/282 (63%) adult men had a CD4 count at the hub, with median (IQR)) 287 (181, 440) compared with 20/37 (54%) men with median 274 (179, 380) in spokes; corresponding estimates among women in need of ART were 10/27 (37%) with median 289 (131, 324) and 25/55 (45%) with median 290 (137, 356) at hub and spokes respectively. In Central, median CD4 cell counts were similar among men and women in need of ART; median (IQR) CD4 cell count among 148/161 (91%) adult men in need of ART was 245 (135, 338) at the hub compared with median CD4 count in 24/32 (75%) of men in spokes of 222 (153, 288) in spokes. Median CD4 for 231/261 (89%) women in need of ART was 266 (172, 332) at the hub and for 58/77 (75%) women was 242 (191, 333) in spokes. The majority of women initiating ART for Option B+ did not have a CD4 count (in the North 65% at the hub, 91% in spokes; in Central 41% at the hub, 66% at the spokes); among all Option B+ women with pre-ART CD4, median (IQR) was 562 (445-744).

First line and Second line ART in children

The majority (71%) of children <15 years were started on AZT/3TC/NVP, 10% on ABC/3TC/EFV, 7% on ABC/3TC/NVP, 4% on AZT/3TC/EFV, 3% on TDF/3TC/EFV and 3% on d4T/3TC/NVP and ~1% on other regimens. From Q4/13-Q1/14 there was a shift from AZT to regimens with ABC in the Central but in the North AZT/3TC/NVP (Table 4) was maintained.

Table 4

Initial ART regimens in patients newly initiated on ART before (2014) and after 2014 following decentralisation and changes in treatment guidelines

First line ART in Children < 15 years	Before 2014				From 2014			
	Central Hub	Central spokes	North Hub	North spokes	Central Hub	Central spokes	North Hub	North spokes
TDF/3TC/EFV or NVP	1 (3)	-	2 (5)	-	2 (4)	1 (6)	4 (8)	-
AZT/3TC/EFV or NVP	25 (80.7)	2 (50)	37(94.8)	3(100)	20 (43.4)	8 (44)	51 (91.1)	10 (91)
D4T/3TC/EFV or NVP	5 (16)	1 (25)	-	-	-	-	-	-
ABC/3TC/EFV or NVP	-	1 (25)	-	1 (11)	23 (49.9)	9 (50)	-	1 (9)
ABC-3TC-LPV	-	-	-	-	1 (2)	-	-	-
First line ART in Adults non-B+ patients	Central Hub	Central spokes	North Hub	North spokes	Central Hub	Central spokes	North Hub	North spokes
TDF/3TC/EFV or NVP	70 (26.4)	28 (54.9)	316 (96)	14 (77.8)	131 (83.4)	48 (82.3)	324 (98.3)	52 (70.3)
AZT/3TC/EFV or NVP	194 (73.1)	22 (43.1)	9 (3)	4 (22.2)	26 (16.5)	10 (17.2)	4 (1)	22 (29.7)
D4T/3TC/EFV or NVP	-	-	-	-	-		-	
ABC/3TC/EFV or NVP	1 (1)	-	-	-	-		-	
ABC-3TC-LPV	-	-	-	-	-		-	
AZT-3TC-ATV-r	-	1 (2)	-	-	-		-	
First line ART in Adults B+ women	Central Hub	Central spokes	North Hub	North spokes	Central Hub	Central spokes	North Hub	North spokes
TDF/3TC/EFV or NVP	88 (99)	146 (100)	116 (99)	50 (100)	53 (98.2)	56 (100)	75 (99)	25 (100)
AZT/3TC/EFV or NVP	1 (1)		1 (1)		1 (1.9)		1 (1)	
D4T/3TC/EFV or NVP	-	-	-	-	-	-	-	-
ABC/3TC/EFV or NVP	-	-	-	-	-	-	-	-
ABC-3TC-LPV	-	-	-	-	-	-	-	-
AZT-3TC-ATV-r	-	-	-	-	-	-	-	-

First line and Second line ART in adults

Overall the majority of adults newly initiated on ART started a TDF based regimen (Table 4). In the North prior to 2014, 96% of adult men and women in need of ART at the hub-initiated ART with a TDF-based regimen versus 78% in spokes (based on only 18 patients); the remaining patients initiated an AZT-based regimen. Prescribing practice remained similar after 2014.

Use of AZT-based ART was higher in the Central region prior to 2014, with only 26% of non-Option B+ patients at the hub and 54% in spokes initiating with a TDF-based regimen. From 2014 in Central 83% initiated with a TDF-based regimen at the hub and 82 % in spokes, with a shift from AZT to TDF.

All but 4 Option B+ women started a TDF-based regimen.

Treatment, attrition and retention on ART in children

Median (IQR) follow-up of 109 children in the North was 11 months IQR (7, 17) months and 12% (3 deaths and 10 losses to follow-up) either died or were lost during follow-up. Of the 99 children who started ART in Central, median (IQR) follow-up was 6 (3-12) months and 25% (1 death and 25 losses to follow-up) died or were lost during follow-up.

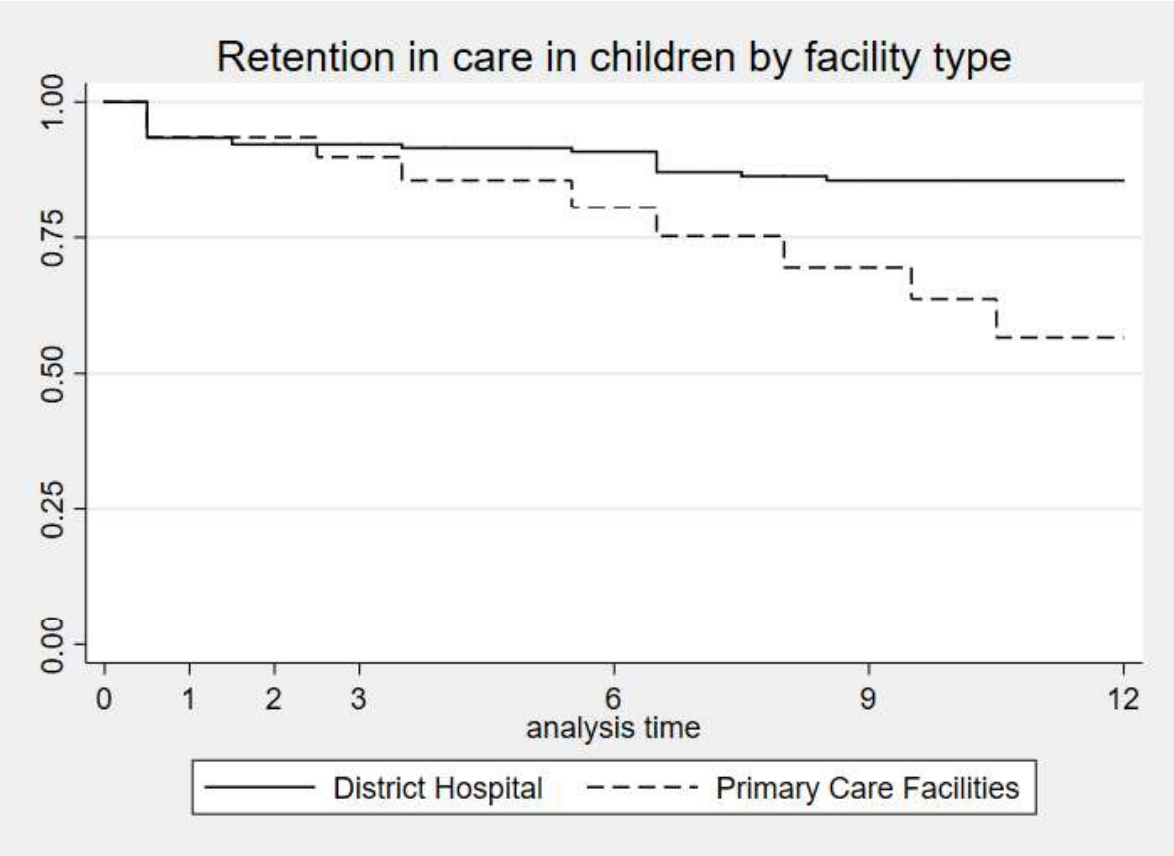
In the North median follow-up at the hub and spokes were 11 (8, 18) months and 6 (2, 12) months respectively compared with 9 (4, 12) months and 4 (0-12) months in Central respectively. Over the follow-up period there was one drug substitution among children in the North and 11 (11%) drug substitutions in the Central (10 at the hub) Over the 12 months follow-up, 1 switch to second line ART occurred in Central.

The overall attrition rate in children was higher in the Central at 3.0/100 person years (95% CI (2.03, 4.45)) vs 1.0/100 person years (95%CI (0.60, 1.77)) than in the North (p=0.002). Overall attrition rates were lower in the hub than in spokes (1.4/100 person years 95% CI (0.94, 2.03) versus 5.6/100 person years 95% CI (3.19, 9.90) (p=0.001). Overall attrition rates were also lower in older children starting ART aged 3-15 years than in children <3 years (1.2/100 person years 95% CI (0.79, 1.94) versus 3.4/100 person years 95% CI (2.17, 5.36) < 3 years (p=0.001)). The age effect was observed in both regions although only reached statistical significance in the Central region: in the North attrition rates were 0.7/100 person years (95% CI 0.31, 1.52) in children 3-15 years versus 1.8/100 person years (95% CI 0.87, 3.82) in children < 3 years (p = 0.1); corresponding rates in Central were 2.0/100 person years (95% CI 1.14, 3.40) and 7.0/100 person years (95% CI 3.95, 12.25) (p = 0.01);

Although data suggested higher attrition in spokes, with limited data in the North, the difference in attrition rates between hub and spokes was non-significant: 0.9/100 person years (95% CI 0.46, 1.60) versus 3.0/100 (95% CI 0.95, 9.16) person years respectively (p = 0.1). In the Central; attrition rates were 2.2/100 person years (95% CI 1.36, 3.62) in the hub versus 8.0/100 person years in spokes (95% CI 4.18, 15.44) (p = 0.01)

Overall retention was 92% (95% CI 86, 97) and 89% (95% CI 81, 94) at 6 and 12 months, respectively in the North compared with 85% (95% CI 75, 91) and 75% (95% CI 63, 83) at 6, and 12 months, respectively in Central (Figure 3).

Figure 3:

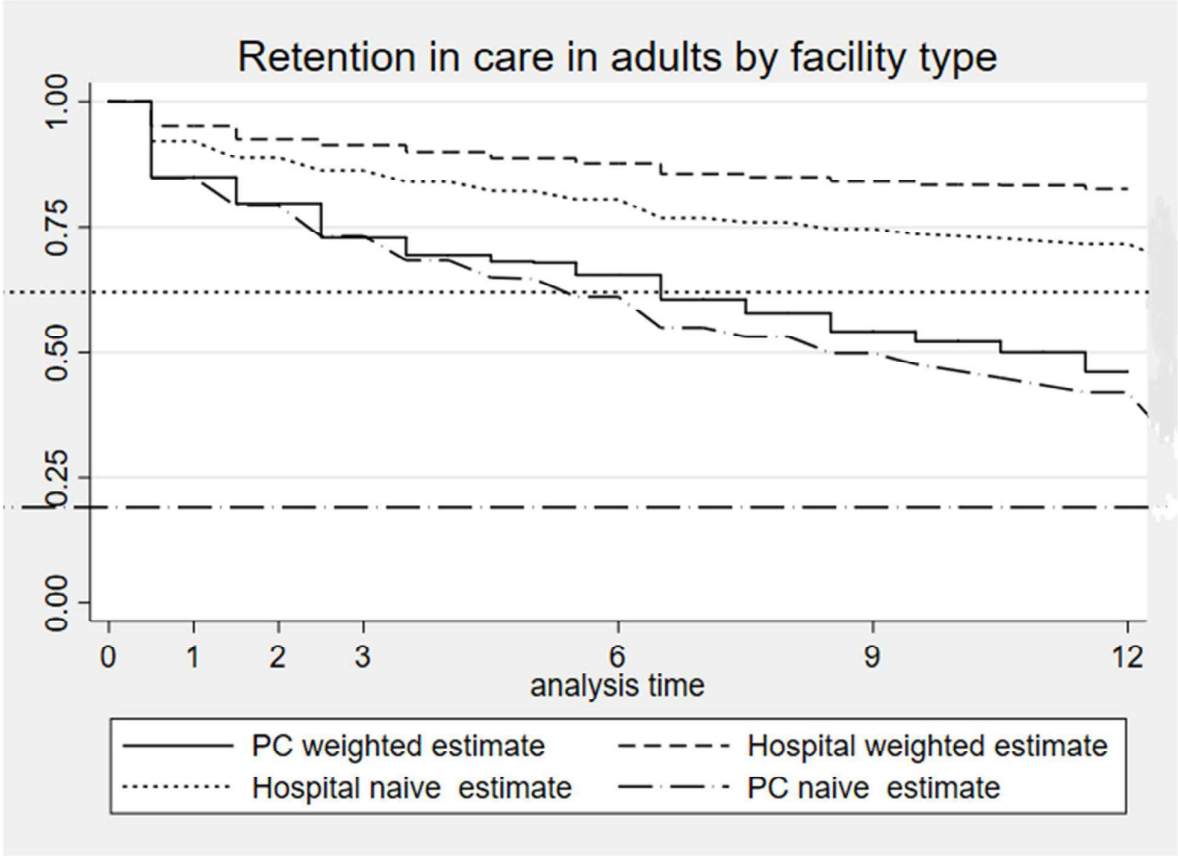


Treatment, attrition and retention in care in adults

Median follow-up in North among 1016 adults newly initiated on ART was 11 (5-19) months and 168/1016 (16%) either died (26) or were lost (142) during follow-up. Of 876 adults initiated on ART in Central, median follow-up was 6 (2-12) months and 392/876 (45%) either died (11) or were lost to follow-up (381). ART substitution rates among adults were low (0.75 per 100 person years in North over the first 12 months versus 2.71 per 100 person years in Central (p<0.001). There were 27 (3.2%) first line substitutions recorded at the hub in the North (17/27 from NVP to EFV) compared with 7 (4.2%) substitutions in spokes (4 of 7 from NVP to EFV) (difference in proportion of substitutions between hub and spokes, p=0.5). There were 39 (6.9%) substitutions at the hub in Central, 16/39 were from AZT-3TC-NVP to AZT-3TC-EFV and 15/39 from AZT-3TC-NVP (9) or TF-3TC-EF (6) to TDF-3TC-NVP, compared with 4 (1.3%) substitutions in spokes (3 of 4either AZT-3TC-NVP (2) or TF-3TC-NVP (1) to TDF-3TC-EFV) (difference in proportion of substitutions between hub and spokes, p<0.001). The proportion of patients who switched to second line was low (<2%): 12 (1.4%) switches to second line in the hub in the North compared to 11 (1.9%) in the Central hub. Second line regimens included LPV/r or ATV/r. We only found 2 switches at the Central spokes and none in spokes in the North.

Overall crude attrition rates were lower in the hubs at 1.7/100 person years (95% CI 1.54, 1.94) compared with spokes at 8.5/100 person years (95% CI 7.51, 9.53). Overall crude attrition rates in adults were higher in the Central than in the North: 5.1/100 person years (4.58, 5.58) vs 1.4/100 person years (1.20, 1.62) in the North(p<0.001). In a naïve analysis at 12 months estimated retention in care was 83% (95% CI: 80-85) in the North compared with 57% (95% CI: 53- 61) in Central (Figure 4).

Figure 4



In a naïve analysis at 6 months, overall retention in care at the hub was 86% (95% CI 84 - 87) and 62% (95%CI 57 -66) in spokes. In a naïve analysis at 12 months, overall retention in care at the hub was 80% (95% CI 78 – 82) and 43% (95%CI 38 -48) in spokes. Proportions retained in care at the hub in the North at 6, and 12 months were 92% (95% CI 90-93), 89% (95% CI 87-91) respectively compared with 76% (95% CI 73-80) and 65% (95% CI 61-69) at the Central hub. In a naïve analysis at 6 months, retention in care at the spokes was 58% (95% CI 49 - 65) in the North and 64% (95%CI 58 - 69) in Central. At 6 months post-decentralisation estimated retention at the hub among Option B+ women was 89% (95% CI 84- 93) in North and 69% (95%CI 61-76) in Central. Option B+ retention in the spokes at 6-months was lower than at the hubs at 53% (95% CI 41- 64) in the North and 59% (95% CI 52 - 66) in Central. Estimated retention among adult men at 6 months was 65% (95%CI 44 - 79) and 62% (95%CI 40 - 77) in the North and Central respectively; and corresponding proportions among women in need of ART was 63% (95%CI 47 - 76) and 77% (95%CI 65 - 86) respectively.

Tracing outcomes in adults

Tracing was implemented routinely in the North hub but not at the North spokes. Of the 207 patients lost to follow-up in the Central hub, 127 were successfully traced and outcomes ascertained (1 died, 29 self-transferred to another ART facility, 97 dropped out of care)(Table 5).

Table 5: Tracing and outcomes for adults in care at the Central health facilities and North spokes

					Tracing outcomes			
Health facility	All patients	Patients lost to follow-up	Patients lost to follow-up; tracing attempted	Patients traced with vital status ascertained	Death	Self-transferred to alternative health facility	Dropped out of care (1 attempt to trace)	Dropped out of care (>1 attempt to trace)
Central hub	642	207	207	127	1	29	39	58
Central spoke Kiragga†	98	45	45	14	0	6	3	5
North¥ Spokes Lira Kato Paimol	 99 82	 41 37	 41 37	 8 7	 0 0	 0 0	 8 7	 0 0

†Tracing information available for 1 Central spoke

¥Tracing was not done for patients in North hub because mechanism was in place for tracing lost patients

Patients whose outcome was ascertained through tracing at the Central hub were similar in age (p = 0.2) and CD4 cell count (p = 0.6) to those for whom outcomes could not be ascertained. Corrected estimates for retention, incorporating tracing outcomes (probability weight of 207/127), at the Central hubwere 84% (95% CI 80, 87) at 6 months and 78% (95% CI 74, 82) at 12 months. In Central spokes corrected estimates at 6 and 12 months 89% (95% CI 77.9, 95.1) and 83% (95% CI 64.1, 92.9) with (probability weight of 45/14 used for the first spoke with no correction made at the second spoke where tracing information was not available).At the spokes in the North, proportions in care at 6 and 12 months in naïve analysis were 58% (95% CI 49-65), 46% (95% CI 37-54) and corrected estimates (with probability weights 37/7 at the first spoke and 41/8 at the second spoke) were 87% (95% CI 78.1, 92.8) and 82% (95% CI 71.6, 89.2). In the Central stigma and undocumented transfers were more frequently cited as reasons for drop-out whereas in the North anecdotal reasons for dropping out of care was given as male involvement (where guidelines encourage pregnant women to come with their partners during the first ANC attendance) and stigma.

Risk factors for attrition from care after ART initiation in children and adults

Table 6 shows the univariable and multivariable results of the Cox proportional hazards model. In the children being older 3-15 years versus <3 years was independently associated with a lower risk of attrition (aHR=0.49 (95% CI 0.25, 0.95)), as was initiation after 2013 when the first-line regimen change was implemented (aHR= 0.37 (95% CI 0.17, 0.83)), there was a lower risk of attrition in hubs (aHR= 0.30 (95% CI 0.15, 0.63)) compared to the spokes, and a higher risk in Central region compared to North aHR= 2.65 (95% CI 1.33, 5.29). Among the adult men and women newly initiating ART, being older was independently associated with a lower risk of attrition (aHR=0.93 per 5 years (95% CI 0.88, 0.97)), Other independent risk factors included: year of ART initiation (2013 aHR= 1.55 (95% CI 1.21, 1.97), ≥ 2014 aHR= 1.41 (95%CI 1.06, 1.87), versus 2012); a lower risk in hubs versus spokes (aHR= 0.35 (95% CI 0.29, 0.43)); a lower risk on a tenofovir based regimen versus zidovudine 0.60 (0.46, 0.77); and a higher risk of attrition in Central compared to North (aHR= 2.28 (95% CI 1.86, 2.81)). After adjustment for age, year of ART initiation, drug regimen, type of facility and region; a lower risk in adult men aHR=0.80 (95% CI 0.60, 1.06), and women initiated on ART for their own health aHR=0.76 (0.60, 0.96) than Option B+ women (p=0.07). We further assessed factors using weighted data in adults (correcting for loss to follow-up and results were qualitatively similar (data not shown).

Table 6: Hazard ratios from Cox proportional Model for attrition (loss to follow-up and mortality) on ART in children and adults starting ART in Hub/ spokes facilities post-ART decentralisation

	Children					**Adults**			
	Univariable analysis Crude HR (95% CI)	p- value	Adjusted HR[1] (95% CI)	p- value		Univariable analysis Crude HR	p- value	Adjusted HR*	p- value
Factor									
Age 3-15 years versus <3 years	0.34 (0.17, 0.68)	0.003	0.49 (0.25, 0.95)	0.04	**Age** Per 5-year increase	0.89 (0.85, 0.93)	<0.001	0.93 (0.89, 0.95)	0.003
Sex Male vs female	0.70 (0.36, 1.36)	0.3			**Gender** Sex Male vs female	0.66 (0.54, 0.81)	<0.001		
Hub vs spokes	0.27 (0.14, 0.55)	<0.001	0.30 (0.15, 0.63)	0.001	**Health facility type** Hub vs spokes	0.25 (0.21, 0.30)	<0.001	0.35 (0.29, 0.43)	<0.001
Central versus Northern region	2.87 (1.46, 5.64)	0.002	2.65 (1.33, 5.29)	0.01	**Region** Central versus Northern region	3.30 (2.76, 3.96)	<0.001	2.28 (1.86, 2.81)	<0.001
Initiated after 2013	0.34 (0.16, 0.73)	0.01	0.37 (0.17, 0.83)	0.02	**Year of ART Initiation** 2012 2013 ≥ 2014	1 1.26 (1.00, 1.59) 0.82 (0.63, 1.07)	<0.001	1 1.55 (1.21, 1.97) 1.42 (1.06, 1.89)	0.003
Drug[1] regimen Abacavir versus other (zidovudine, based regimen)	0.46 (0.11, 1.95)	0.3			**Drug[2] regimen** Tenofovir based regimen versus zidovudine based regimen)	0.60 (0.50, 0.73)	<0.001	0.60 (0.46, 0.77)	<0.001
					Patient type B+ women Men	1		1	0.07

					Women in need of ART	0.58 (0.46, 0.72) 0.64 (0.54, 0.77)	<0.001	0.80 (0.60, 1.06) 0.76 (0.60, 0.96)	

*Gender not adjusted due to collinearity with patient type

[1]Define children Abacavir based regimen (ABC-3TC-EV (Abacavir, Lamivudine, Efavirenz) or ABC-3TC-NV (Abacavir, Lamivudine, Nevirapine) and (1 on ABC-3TC-LPV) versus AZT based (AZT-3TC-NV (Zidovudine, Lamivudine, Nevirapine) or few on TF-3TC-EF/NV)

[2] Adults Tenofovir based regimen (TF-3TC-EF (Tenofovir, Lamivudine, Efavirenz) or TF-3TC-NV (Tenofovir, Lamivudine, Nevirapine) versus AZT Zidovudine based (AZT-3TC-EF (Zidovudine, Lamivudine, Efavirenz) or AZT-3TC-NV (Zidovudine, Lamivudine, Nevirapine) and 1 on AZT-3TC-ATV-r)

Discussion

We evaluated the roll out of ART in public healthcare facilities in 2 district hubs (hubs) and 2 linked spokes in two districts within the Lablite implementation project in Uganda. After decentralisation we observed an increase in patients enrolled at the spokes in each region over time.

Estimated retention at 6 months in children was better >80% at the hubs compared to spokes and fewer numbers of children were seen in spokes. We observed similar retention rates in adult general ART, to previous study in Tanzania that reported 81% retention at 12 months in public health facilities (22). At 6 months post-decentralisation estimated retention among Option B+ women was 69% in Central and 89% in North, compared with 91% in Zimbabwe and 79% in Malawi respectively (9). We found that spokes newly initiating ART had significantly lower retention for women initiating through Option B+. Possible explanations for the difference in retention included undocumented or silent transfers which were also linked to stigma and disclosure. Research in similar settings has shown that lower retention rates in Option B+ women compared with adults could be linked to resistance to start ART and disclosure (23, 24). In an analysis of African regions of the International epidemiologic Databases to Evaluate AIDS (IeDEA) higher retention at 12 months was associated with CD4 cell count<350 (25). The latter comprised of adults who had initiated ART for their own health with CD4 cell count<350. Of note even within UTT, pregnant women lost early in care are at higher risk for mother to child transmission. Recent findings show that even within a test and treat program many pregnant women did not remain in care therefore facilitating strategies to improve retention remains important (26).

Retention on ART was very variable across facilities; although it appeared significantly better in the hubs compared to spokes, we had limited information on losses to follow-up in spokes through tracing. There were undocumented efforts to improve retention such as peer mentors at the Central hub and this may have improved retention at the hub and slowly translate into improvements in spokes. The North particularly included the hard to reach population and vulnerable due to conflict, but mechanisms in place to support the losses were successful. Although spokes received monitoring and training support from the district hubs, support was sporadic due to staffing and logistical constraints. Mechanisms to adapt to increasing number of patients in spokes, including data collection and monitoring could have compromised services and quality of care. We found that loss to follow-up consisted of substantial undocumented transfers through tracing for at least one third of patients, as has been observed in other ART programmes in Uganda and East Africa (27, 28). Similar to studies in Ethiopia, Lesotho and Malawi attrition from treatment sites was mainly due to loss to follow-up (9, 29, 30).

Importantly, in ART programmes that have been in existence for a longer time, poor retention could be due to undocumented transfers (14, 15, 31, 32). Of note at least 50% of losses to follow-up comprised of silent transfers and could lead to considerable underestimation of retention. In a meta-analysis by Zurcher et al. (2017), proportions of patients successfully traced (of those lost to follow-up) ranged from 20-100%, with 34% of those successfully traced having died and 23.9% having transferred their care; the latter tended to be common in facilities that had provided ART for longer. In our study, both the Central and North hubs had provided ART since 2005. At the Central hub we found 29% of those traced had genuinely transferred care.

Regional differences in retention between North and Central could have been partly due to differences in study setting. Observed differences could be due to more comprehensive follow-up in the North hub (with routine tracing of patients lost to follow-up) compared to the Central hub, where any routine tracing was largely restricted to PMTCT clients. The Central catchment population at spokes comprised of the most at risk population including truck drivers, fisherfolk, commercial sex workers with a high population HIV prevalence at 18%. Retention at the North hub was comparable to retention seen in Malawi and Ethiopia (4, 8). Some of the differences across

countries may be due to varying definitions of loss to follow-up and more comprehensive follow-up on the Uganda ART registers than in Malawi for example (where follow-ups are not recorded on the ART register). In a large cohort of children on ART in Malawi the estimate of loss to follow-up among paediatric HIV patients was 23% at 1 year on treatment (33). Whereas these findings are comparable to our proportions in children, knowledge of paediatric treatment outcomes after ART decentralisation in sub-Saharan Africa remains low (6, 34). This study not only highlights social-demographic features of health care but examines potential effect of programme characteristics that may affect retention.

Transitions to second line treatments up to 2 years was comparable to other countries such as Malawi and Ethiopia (8, 29) and remained low (<10%) similar to another research setting in Uganda Data from 16 African countries across Africa documented a rate of 7.9% switches to second line after 5 years. A large successful (close to achieving 90-90-90 target) ART program in Rwanda reported that approximately 4% of all ART patients ≥15 years had switched to second line treatment over a decade (2007-2016) (35). (36). As ART becomes available to all HIV-infected individuals, viral suppression remains the key measure of treatment success. The goal of monitoring ART to maximise first line treatment options remains important. From 2015, viral load monitoring had started under the national drug surveillance and monitoring programme and was only collected in a few patients at the time.

Our findings on younger age as a risk factor for attrition reinforce findings from many other studies in sub-Saharan Africa (16, 22, 37). Whilst CD4 cell count was also a risk factor in the latter studies, this is not shown in our study as a large number 99% of Option B+ patients in spokes in the North had no CD4 cell count measurements done and 66% in Central. A higher attrition rate observed in B+ women (with CD4 cell count >350 and later >500) is indicative of the impact of CD4 cell count. . A higher proportion of newly initiated adult men and women in need of ART had CD4 cell counts done at the hub 55% than in spokes at 26%. Suboptimal retention is associated with poor viral suppression, increased switching and subsequent mortality. A study in Zimbabwe showed that POC testing for women and CD4 count specific counselling was associated with retention (38, 39). It is plausible that knowledge of CD4 cell count or viral load may enhance patient adherence to ART and knowledge of patient health status may sustain patients in care and improve health outcomes. Associations of retention with initial drug regimen support findings by Asiimwe et al, initiating ART with a Tenofovir based regimen was associated with better retention than a Zidovudine based regimen (16).

One limitation of our study lies in the definition of losses to follow-up, patients were classified as dropped if they did not return to the clinic for 3 months after their last scheduled visit but some had prior gaps in care. Few patients were identified through tracing attempts partly due to lack of contact information If we had used strict definitions for loss to follow-up such as first gap in care, retention rates would be lower than estimated from other studies such as INSPIRE (13). Adopting standardised definitions that translate into health outcomes suggested by Rollins (INSPIRE) would inform national HIV programmes (13). Challenges existed in collecting and defining patient profile, ART regimen provision across different data collecting systems. The mission hub in the North used a different electronic system for data capture from the MOH system to the one introduced at the Central hub during the study. Health system challenges such as high staff turnover in the North spokes delayed update of ART registers. The investment and efforts needed to support the spokes to sustain and retain patients on treatment plus high turnover remains a challenge as in other studies (13).

Lessons for universal test and treat

In our study, most attrition was due to high rate of loss to follow-up and efforts to trace individuals revealed undocumented transfers. Outcomes were sporadically recorded on paper and mechanisms

to trace patients lost to follow-up were lacking. The limited function of reporting systems for death or tools to measure retention made it difficult to assess outcomes in health facilities without support from implementing partners. Efforts to improve and sustain data collection systems using hub-spoke mentoring approach to support task-shifting could still be implemented. The latter approach might require more investment in human and financial resources for monitoring.

Conclusion

Our findings show that adopting a hub-spoke mentoring approach in providing knowledge through training health workers improved access, innovations among younger adults and pregnant or breastfeeding women would be valuable for scaling-up ART programmes. However, the approach may require investment in improving primary care health facilities, functional monitoring systems and human resource interventions. Further studies assessing the longer term impact of decentralisation to inform programs and policies for universal access to test and treat are warranted.

Declarations

Ethical review statement: The JCRC (in full) ethics and research committee provided ethical approval for this study. We used routinely collected data from health facilities and de-identified participant information for the analysis. The need to obtain informed consent from our study subjects was waived.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: None declared

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Authors contributions: SKM contributed substantially towards the supervision of data collection; analysis and interpretation of the data; writing manuscript. GA, IM, DS contributed to the proposal writing; participated in data collection and contributed towards interpretation and analysis of the results; JS, CK, EK, DF and DMG contributed towards the study design; proposal writing; interpretation of the results; writing the manuscript.

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