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Adoption of new HIV treatment guidelines and drug substitutions within first-line as a measure of quality of care in rural Lesotho: health centers and hospitals compared

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Abstract

OBJECTIVE In 2007, Lesotho launched new national antiretroviral treatment (ART) guidelines, prioritising tenofovir and zidovudine over stavudine as a backbone together with lamivudine. We compared the rate of adoption of these new guidelines and substitution of first-line drugs by health centers (HC) and hospitals in two catchment areas in rural Lesotho.

METHODS Retrospective cohort analysis. Patients aged ≥16 years were stratified into a HC- and a hospital-group. Main outcome variables: Type of backbone at ART-initiation (i), substitutions within first line (ii) and type of backbone among patients retained by December 2010 (iii). A multiple logistic regression model including HC *vs.* hospital, patient characteristics (sex, age, WHO-stage, baseline CD4-count, concurrent pregnancy, concurrent tuberculosis treatment) and year of ART-start, was used.

RESULTS Of 3936 adult patients initiated on ART between 2007 and 2010, 1971 started at hospitals and 1965 at HCs. Hospitals were more likely to follow the new guidelines as measured by prescription of backbones without stavudine (Odds-ratio 1.55; 95%CI: 1.32–1.81) and had a higher rate of drug substitutions while on first-line ART (2.39; 1.83–3.13). By December 2010, patients followed at health centres were more likely to still receive stavudine (2.28; 1.83–2.84).

CONCLUSIONS Health centers took longer to adopt the new guidelines and substituted drugs less frequently. Decentralised ART-programmes need close support, supervision and mentoring to absorb new guidelines and to adhere to them.

keywords HIV, antiretroviral therapy, decentralization, task shifting, quality of care

Introduction

Early on during the global effort to increase access to antiretroviral treatment (ART), the challenge of the lack of sufficient health workforce in some African countries was recognised (Kober & Van Damme 2004). To tackle this health workforce shortage, WHO proposed in 2007 to shift the task of providing ART from physicians to non-physician clinicians, mainly nurses and clinical officers (World Health Organisation & HIV/AIDS Programme 2007). Published data from pilot-programmes in Lesotho, Rwanda, Malawi, Swaziland, Zambia, Kenya, Uganda and South Africa, using a nurse-based approach are encouraging (Bedelu *et al.* 2007; van Griensven *et al.* 2008; Chang *et al.* 2009; Cohen *et al.* 2009; Massaquoi *et al.* 2009; Shumbusho *et al.* 2009; Humphreys *et al.* 2010; Selke *et al.* 2010). However, most of them examined nurse-based follow-up but not nurse-based initiation of ART. In a systematic review, Callaghan *et al.* (2010) concluded that task shifting offers high-quality, cost-effective care to more patients than a physician-centered model. A randomised-controlled trial (Sanne *et al.* 2010) from South Africa showed that nurse-based ART-monitoring is not inferior to physician-based care in terms of main outcomes (mortality, retention, ART-interruption owing to drug toxicity). On the basis of the increasing evidence in favour of task shifting for ART, many countries with shortages in their health workforce started to implement nurse-based models and achieved rapid scale-up of treatment coverage (UNAIDS 2010).

However, relatively little is known about the capacity of decentralised nurse-based care to adopt changes in

national policy and guidelines. Maintenance of adequate training and ongoing support are recognised as a particular challenge in nurse-based ART-programmes (Callaghan *et al.* 2010). In 2009, WHO published new ART treatment guidelines recommending earlier start of ART and phasing out of stavudine (D4T) use (World Health Organization 2009). Publication of practice guidelines does not guarantee their use in clinical practice. Routine evaluation of adherence to guidelines has thus been recommended as a measure of quality of care (Suarez-Lozano *et al.* 2009). In several low-income countries guidelines are changing or have changed already. More drugs are now available to individualise first-line ART-regimens. Choosing the right regimen and substituting drugs in case of side effects or drug interactions has become possible but it has made delivery of ART more complex than it was a few years ago. ART-nurses have, for example, to learn to interpret laboratory parameters, such as serum creatinine. This poses a particular challenge to decentralised nurse-based programmes, where the providers of ART often do not have the opportunity to access new information or to get advice from specialists. Data on adherence to guidelines in decentralised nurse-based programmes where national guidelines have changed, and where new first-line options are available are therefore useful to assess the quality of care in such settings.

With an estimated adult prevalence of 23.6%, Lesotho has the third-highest HIV rate in the world and is simultaneously severely hit by the health workforce shortage (Ministry of Health and Social Welfare & National AIDS Commission 2009; UNAIDS 2010; World Health Organization 2010). From 2007 on, ART-services were fully decentralised to nurse-led health centers and already in the then published national ART-guidelines either tenofovir (TDF) with lamivudine (3TC) or zidovudine (AZT) with lamivudine became the preferred nucleoside reverse transcriptase inhibitors (NRTI) backbones. Stavudine backbones became the alternative first-line regimen in case of contraindications to zidovudine and TDF (Ministry of Health and Social Welfare of Lesotho, M.O.H.S.W. 2007). In Lesotho, task shifting to nurses included initiation and follow-up of ART. The decentralisation of ART to health centers led to a significant increase in ART-coverage in Lesotho with over 50% coverage by the end of 2009 (National AIDS Commission 2010).

This study aims to compare nurse-based ART at health centers to ART at hospitals in terms of adherence to treatment guidelines after the introduction of the 2007 guidelines and number of drug substitutions because of side effects, pregnancy or concomitant anti-tuberculosis (TB) treatment. Data originate from two rural catchment areas of Lesotho, where decentralisation of ART started in 2007 and was completed by 2008.

Methods

Objective and design

The primary objective of this retrospective cohort analysis was to compare health centers to hospitals in terms of adoption and adherence to new treatment guidelines, using as a proxy the type of first-line regimen (i), the number of substitutions within first-line regimen (ii) and the type of first-line regimen among retained patients by December 2010 (iii) in two rural catchment areas of Lesotho between 2007 and 2010. As a secondary objective health centers and hospitals were compared on type of non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz *vs.* nevirapine) for patients on concomitant TB.

Setting

The study includes data from two hospital catchment areas in rural Lesotho. Seboche catchment area, located in northern Lesotho, district Botha-Bothe, has an estimated population of 55 000 inhabitants. It is served by one hospital and five health centers. Paray catchment area belongs to the mountainous district Thaba-Tseka, central Lesotho, with about 77 000 inhabitants. It is served by one hospital and seven health centers. Both hospitals are run under the Christian Health Association of Lesotho. The hospitals supervise the health centers within their catchment areas and serve as their referral facility. Both catchment areas benefit from various health projects supported by SolidarMed, a Swiss non-governmental organisation. The SolidarMed ART-project started in 2005 and assists in the implementation of the national ART-programme. The two hospitals started providing ART in 2005. From 2007 on, Lesotho started to implement a nurse-based model to decentralise and scale-up provision of ART. In the two catchment areas, decentralisation from the hospital to its nurse-led health centers was completed by 2008.

The health centers are usually served by one nurse-clinician, one nurse-assistant and several lay counsellors. Most nurse-clinicians went through the standardised Integrated Management of Adult and Adolescent Illness training (IMAAI) before being sent to a health center. The Ministry of Health and Social Welfare of Lesotho, as well as various implementing partners, provide regular short-trainings on HIV-related issues, especially in case of changes in guidelines or policies. However, in daily practice, the nurse-clinician is often absent from the health

center because of meetings or workshops, and during this time, he/she is replaced by the nurse-assistant. Not all nurse-assistants have had IMAAI or specific ART-training. At the time the study was conducted, nurses rotated from the hospital to the health center annually.

The hospitals have three to five physicians. Similar to health centers, most ART-patients at the hospital are seen by nurses. However, at the hospital the ART-department is headed by a physician who supervises the nurses and assists them in case of patients with particular complaints or complications.

Hospitals, as well as health centers, order their drugs at district level and they are delivered on a monthly basis. The drug supply system as well as the accessibility of the different types of antiretroviral drugs are the same for the health centers and hospitals. The overall availability of antiretroviral drugs in Lesotho has been very good over the last years, and no severe stock-outs have been reported within the two catchment areas of the study-cohorts.

In 2007, the Ministry of Health and Social Welfare published revised national ART-guidelines (Ministry of Health and Social Welfare of Lesotho, 2007). Tenofovir or zidovudine in combination with lamivudine and efavirenz became the first-line regimens of first intention. Nevirapine and stavudine became alternative drugs to be used in case of contra-indications or side effects to the recommended first-line regimens. This was a significant change, as in the previous guidelines from 2004, the recommended first-line regimen had stavudine as a backbone, Tenofovir was not yet available, and nevirapine was the recommended NNRTI (Ministry of Health and Social Welfare of Lesotho 2004). However, the 2007 guidelines stated that for

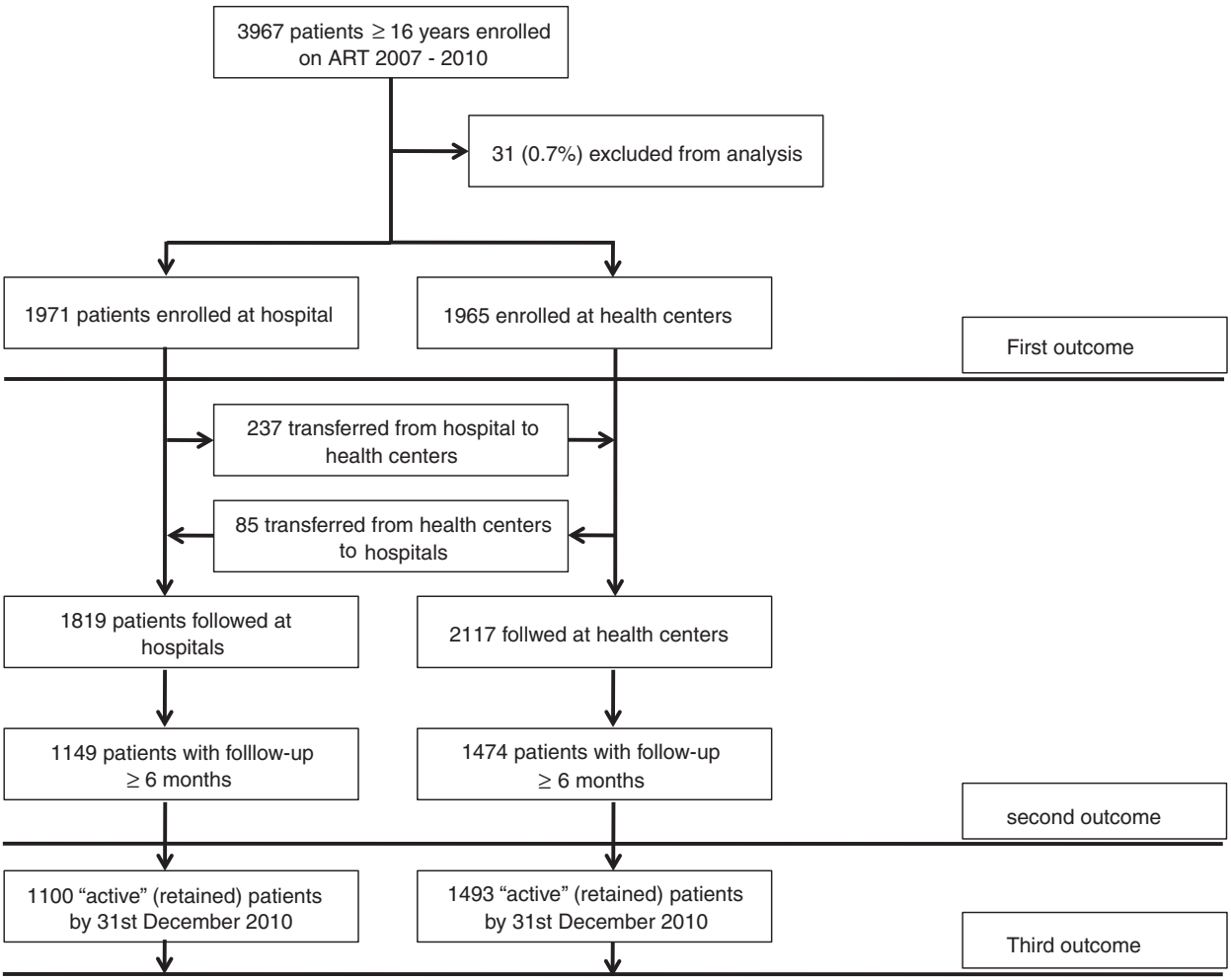

Figure 1 Patient-flow and moment of analysis for each outcome.

patients who were already on stavudine, only those who experienced side effects should be substituted. The others should remain on the stavudine regimen.

The national 2007 guidelines define which first-line regimen has to be chosen based on laboratory baseline values (haemoglobin, liver-function tests and creatinine) and clinical conditions, such as pregnancy (avoidance of TDF and EFV) or concurrent tuberculosis therapy (avoidance of nevirapine if ≥3 years of age). Depending on the type of regimen, the guidelines specify different laboratory monitoring schedules, such as for example 6 monthly serum creatinine measurement in case of TDF or monthly haemoglobin at the beginning of a zidovudine-containing regimen. They also define laboratory thresholds and clinical conditions when drugs should be substituted as for example in case of anaemia under zidovudine or severe skin rash under nevirapine. Nurses at health centers can choose and substitute the first-line drugs autonomously, following the national guidelines. No advice from a physician is needed.

Laboratory examinations have not been decentralised to health center level. Blood samples, as well as sputum smears for tuberculosis, are transported from the health centers by motorbike riders on a weekly basis and analysed at the referral hospital. Nurses receive the laboratory results 3–7 days later. Table 1 provides an overview comparing resources for ART-provision that are available at the two hospitals and the health centers.

Inclusion criteria

All patients aged ≥16 years, initiated on ART at one of the 14 facilities within the two catchment areas between 1st January 2007 and 31st December 2010 were eligible. Patients where information about prescribed regimen was incomplete or who were put on an ART-regimen other than one of the six-first-line regimens recommended by the national guidelines were excluded from analysis.

Data collection

Data originate from the national ART-patient cards. Each patient ever initiated on ART in Lesotho receives such a card where basic clinical, laboratory and therapeutic information is noted at every visit. When enrolled on ART, each patient in Lesotho receives a national unique ART-number that shows at which facility ART was started. In case of transfer, the patient-card remains at the original facility and is labelled as 'transfer out'. The facility where the patient was transferred to opens a new patient-card that is labelled as 'transfer in'. However, the patient keeps his/her original unique national number. This allows to track individual patients in case of transfer. Since 2005, SolidarMed-employed data-managers visit the facilities in the two catchment areas on a monthly basis to enter the patient-data into an ACCESS database. A data-coordinator performs regular quality-checks, and twice a year the database is analysed for project monitoring reasons. Before the analysis of the data for this study, key-variables of each patient, such as baseline characteristics, were again counter checked with the original paper-based ART-card to ensure accuracy of processed data.

Processed variables and statistical analysis

Analysis looked at three primary outcome variables: Type of nucleoside backbone within the first-line regimen prescribed at initiation (i), number of substitutions within first-line regimen (ii) and type of backbone within first-line regimen at the last visit among patients who were still retained by December 2010 (iii). Type of facility where patients were initiated on ART or followed on ART was the main predictor variable (health center *vs.* hospital). Covariates were the year of initiation (2007–2010), patient baseline characteristics (sex, age-groups, clinical WHO-

Table 1 Resources available for ART-services at the two hospitals and the 12 health centers involved in the study

	Seboche Hospital	Paray Hospital	Health Centers
Number of physicians	4	4	0
Number of nurse-clinicians providing ART	3	2	1
Number of nurse-assistants providing ART	2	3	1
Number of Lay-counsellors	5	7	2
Number of patients enrolled on ART 1st January 2007 to 31st October 2010	970	1001	171 (161–214)*
CD4-testing on site	Yes	Yes	No
Haemoglobin-testing on site	Yes	Yes	4 out of 12
Biochemistry on site	Yes	Yes	No
Viral Load testing on site	No	No	No
TB-services available	Yes	Yes	Yes
Sputum microscopy on site	Yes	Yes	No
X-Ray on site	Yes	Yes	No

ART, antiretroviral treatment; TB, tuberculosis.
*Median and interquartile range of the number of patients started on ART per health center.

stage at initiation, baseline CD4-count categories, concurrent tuberculosis treatment at initiation, concurrent pregnancy at initiation), new TB therapy while already on ART and new pregnancy while already on ART.

Analysis for outcome 1 includes all patients who were eligible. Outcome 2 only includes patients with a documented follow-up of at least 6 months. Outcome 3 includes patients who were still alive and on ART by 31st December 2010, defined as the last documented follow-up visit being 30 September 2010 or later (Figure 1).

For analysis of all outcome variables the cohort was divided into health centers *vs.* hospitals. Patients who were transferred from the hospital to the health center while already being on ART, are stratified to the hospital-group for the first outcome (type of initial first-line regimen prescribed) and to the health center group for the other two outcomes (number of substitutions and type of regimen by December 2010). Significance of differences in baseline characteristics between the two groups was assessed through Pearson chi-square test in case of categorical and Mann–Whitney *U*-test in case of continuous variables. Analysis of the three main outcome variables was performed with a multiple logistic regression model allowing for all covariates mentioned previously. For the second and third outcome, TB therapy and pregnancy while already taking ART, replaced TB therapy and pregnancy at initiation of ART as covariates. For the secondary outcome, type of NNRTI among patients on concomitant TB treatment, univariate logistic regression with type of facility (health center *vs.* hospital) as predictor and type of NNRTI as outcome was used. Analyses were run on STATA 10.1®.

Ethical considerations

The retrospective analysis of the two cohorts was approved by the Ethical Committee of the Ministry of Health and Social Welfare of Lesotho. The monthly data-entry is performed confidentially. The database contains no patient names and is stored on a password-protected computer.

Results

Participation and baseline characteristics

Between 1st January 2007 and 31st December 2010, 3967 patients aged ≥16 years were initiated on ART. Thirty-one (0.73%) were excluded from analysis, as the database did not clearly define the type of initial ART-regimen (30) or the initial regimen was different from the six recommended standard first-line regimens (1). Table 2 displays the

Table 2 Baseline characteristics of patients included in the study

	Whole cohort (n = 3936)	Health centers (n = 1965)	Hospitals (n = 1971)	P-value
Female patients (%)	2538 (64.5)	1273 (64.8)	1265 (64.2)	0.693
Age-groups (%)				
16–25 years	253 (6.4)	143 (7.3)	110 (5.6)	<0.001
25–49 years	2883 (73.4)	1363 (69.4)	1520 (77.1)	
>49 years	800 (20.3)	459 (23.4)	341 (17.3)	
WHO-stage at initiation (%)				
Stage 1	847 (21.5)	479 (24.4)	368 (18.7)	<0.001
Stage 2	1381 (35.1)	819 (41.7)	562 (28.5)	
Stage 3	1413 (35.9)	577 (29.4)	836 (42.4)	
Stage 4	295 (7.5)	90 (4.6)	205 (10.4)	
CD4-count at baseline (cells/μl) (%)				
<50	447 (11.4)	148 (7.5)	299 (15.2)	<0.001
50–99	499 (12.7)	184 (9.4)	315 (15.9)	
100–199	1068 (27.1)	525 (26.7)	543 (27.6)	
>200	1729 (43.9)	1035 (52.7)	694 (35.2)	
Missing	193 (4.9)	73 (3.7)	120 (6.1)	
Median weight at initiation (KG) (iqr)	56 (50–63)	56 (50–63)	56 (49–63)	0.002
Anti-tuberculosis therapy at initiation (%)	312 (7.9)	69 (3.5)	243 (12.3)	<0.001
Pregnant at initiation (%)	171 (4.3)	76 (3.9)	95 (4.8)	0.197

Baseline characteristics at initiation of antiretroviral treatment in the health center and the hospital subcohort. Iqr, interquartile range.

baseline characteristics of the 3936 patients included in analysis. Patients initiated at health centers were on average older and started ART at a less advanced stage of the disease. There were fewer patients started on ART while on TB treatment at health centers. Of the 3936 patients, 1965 (49.9%) were initiated on ART at a health center. During follow-up, 237 patients were transferred from one of the hospitals to a health center and 85 from one of the health centers to a hospital, resulting in 2117 (53.4%) who were followed up at health centers. Figure 1 shows the patient-flow and the points of analysis for each of the three primary outcomes.

Type of first-line regimen prescribed at initiation of ART per year of initiation

Table 3 shows the NRTI-component chosen for first-line regimen. The health centers took longer to implement the new guidelines and to make TDF the dominant first-line NRTI-backbone. Stavudine continued to be prescribed more frequently at the health centres throughout the study period.

Number of substitutions within first-line regimen

Overall, 2623 patients have a documented follow-up ≥6 months, 1474 in the health centers 1149 in the hospitals (see Figure 1). Among these, 384 (15%) had at least once a drug substitution within first-line regimen, 55 (2%) had two and 6 (0.2%) three substitutions. Median time to first, second and third substitution were 229 (inter-quartile range: 76–474), 354 (161–635) and 472 (111–529) days after ART-start, respectively with no significant differences between the physician-assisted and the nurse-based model. At the health centers, 131 (8%) had one and 11 (0.8%) had two substitutions as compared to 253 (22%) and 44 (4%) respectively at the hospitals. Reasons for changing were side effects (329), newly diagnosed tuberculosis (30) and pregnancy (25).

Table 4 shows unadjusted and adjusted Odds-ratios of predictors for being substituted at least once within first-line regimen among the patients followed for at least 6 months. Female sex, pregnancy, newly diagnosed tuberculosis, a D4T- or an AZT backbone and ART-start before 2010 were associated with drug substitution within first

Table 3 Initial Nucleoside Reverse Transcriptase Inhibitor in the first-line ART-regimen

NRTI-component of initial ART-regimen	Health centers (n = 1965)		Hospitals (n = 1971)		TDF or AZT backbone (hospital *vs.* HC) adjusted OR (95% CI)	Adjusted P-value
	n	% (95%CI)	n	% (95%CI)		
2007						
d4T	15	68 (45; 86)	218	44 (39; 48)	4.10 (1.5; 11.4)	0.008
AZT	7	32 (14; 55)	280	56 (52; 61)		
TDF	0	0	0	0		
2008						
d4T	168	45 (40; 51)	141	27 (24; 32)	2.05 (1.52; 2.78)	<0.001
AZT	119	32 (27; 37)	140	28 (24; 32)		
TDF	84	23 (18; 27)	232	45 (41; 49)		
2009						
d4T	315	33 (30; 36)	69	14 (11; 18)	3.04 (2.24; 4.12)	<0.001
AZT	328	34 (31; 37)	148	30 (26; 35)		
TDF	316	33 (30; 36)	269	55 (51; 60)		
2010						
d4T	79	13 (10; 16)	33	7 (5; 10)	2.15 (1.34; 3.44)	0.002
AZT	213	35 (31; 39)	153	32 (28; 37)		
TDF	321	52 (48; 56)	288	61 (56; 65)		
Total (2007–2010)						
d4T	577	29 (27; 31)	461	23 (22; 25)	1.55 (1.32; 1.81)	<0.001
AZT	667	34 (32; 36)	721	37 (35; 39)		
TDF	721	37 (35; 39)	789	40 (38; 32)		

NRTI-component within the initial first-line regimen prescribed over the years. D4T, Stavudine; AZT, Zidovudine; TDF, Tenofovir. Odds-ratios relate to the likelihood of receiving AZT or TDF as NRTI-backbone (not D4T) at hospitals as compared to health centers. Odds-ratios and P-values derive from a multiple logistic regression model allowing for all baseline variables listed in Table 2: age-groups, gender, WHO-stage at initiation, CD4-count categories at baseline, pregnant while starting ART, on anti-tuberculosis treatment while starting ART. OR, Odds-ratio; 95%CI, 95% confidence-intervals; NRTI, nucleosid reverse transcriptase inhibitor; ART, antiretroviral treatment.

Table 4 Predictor variables for being substituted at least once within first-line regimen

Predictor variable	Unadjusted OR (95%CI)	Unadjusted *P*-value	Adjusted OR (95%CI)	Adjusted *P*-value
Hospital (vs. HC)	2.89 (2.31; 3.63)	<0.001	2.39 (1.83; 3.13)	<0.001
Female sex	1.51 (1.18; 1.93)	0.001	1.41 (1.07; 1.87)	0.016
Age				
16–24 years	1		1	
25–49 years	0.98 (0.62; 1.55)	0.926	0.90 (0.53; 1.54)	0.711
≥50 years	0.86 (0.52; 1.43)	0.568	1.02 (0.57; 1.83)	0.943
Pregnant while on ART	4.03 (2.41; 6.76)	<0.001	2.93 (1.62; 5.28)	<0.001
New TB-treatment while on ART	11.08 (6.05; 20.29)	<0.001	7.73 (3.64; 16.4)	<0.001
NRTI-backbone				
TDF	1		1	
AZT	2.41 (1.77; 3.29)	<0.001	1.77 (1.23; 2.54)	<0.001
D4T	3.89 (2.86; 5.28)	<0.001	3.13 (2.19; 4.48)	<0.001
Year of ART-initiation				
2010	1		1	
2009	4.37 (2.01; 9.50)	<0.001	3.67 (1.67; 8.08)	0.001
2008	13.07 (6.06; 28.17)	<0.001	8.34 (3.82; 18.21)	<0.001
2007	31.05 (14.33; 67.27)	<0.001	13.4 (6.00; 29.94)	<0.001
WHO-Stage at initiation				
Stage 1	1		1	
Stage 2	1.05 (0.77; 1.43)	0.771	1.06 (0.75; 1.49)	0.748
Stage 3	1.41 (1.04; 1.91)	0.027	1.21 (0.85; 1.72)	0.286
Stage 4	1.47 (0.92; 2.35)	0.103	1.14 (0.66; 1.97)	0.627
Baseline CD4-count				
0–49	1		1	
50–99	0.86 (0.56; 1.33)	0.493	0.85 (0.52; 1.38)	0.518
100–199	0.81 (0.56; 1.18)	0.275	0.92 (0.60; 1.40)	0.689
>200	0.61 (0.43; 0.88)	0.008	0.90 (0.59; 1.37)	0.634

Unadjusted and adjusted Odds-ratios of different predictor variables to be substituted at least once within first-line regimen among patients with a follow-up of at least 6 months. Odds-ratios and *P*-values derive from a multiple logistic regression model allowing for all predictor variables listed in the table. HC, health center; OR, odds ratio. 95%CI, 95% confidence interval; TB, tuberculosis.
TDF, tenofovir; AZT, zidovudine; d4T, stavudine; NNRT, nucleoside reverse transcriptase inhibitor; ART, antiretroviral treatment.

line. After allowing for all covariates, patients at hospitals were still more likely to be substituted within first line as compared to health centers [OR, 2.39 (95%CI, 1.83; 3.13)].

Type of NRTI by the end of 2010

Of the 3936 patients enrolled into the study, 2593 (65.9%) were still accessing services within the catchment areas by December 2010, defined as the last appointed visit-date being 30 September 2010 or later. Of these, 2587 (99.8%) received still a first-line regimen. Figure 2 shows the regimen-backbone among patients retained by the end of 2010 at their last visit, stratified by the year when ART was initiated. After allowing for all covariates, patients followed by the nurse-based model were more likely to remain on a regimen with a stavudine backbone [OR, 2.28 (95%CI, 1.83; 2.84)].

Type of NNRTI while on tuberculosis therapy

Overall, 370 were on concommittant tuberculosis treatment, 272 (74%) at the hospitals and 98 (26%) at the health centers. At the hospitals, 260 (96%) were on a regimen with efavirenz as NNRTI as compared to 87 (87%) at the health centers. Patients on tuberculosis therapy at hospitals were more likely to receive the recommended NNRTI (efavirenz) as compared to patients followed at health centers (OR, 3.3; 95%CI, 1.5; 7.5).

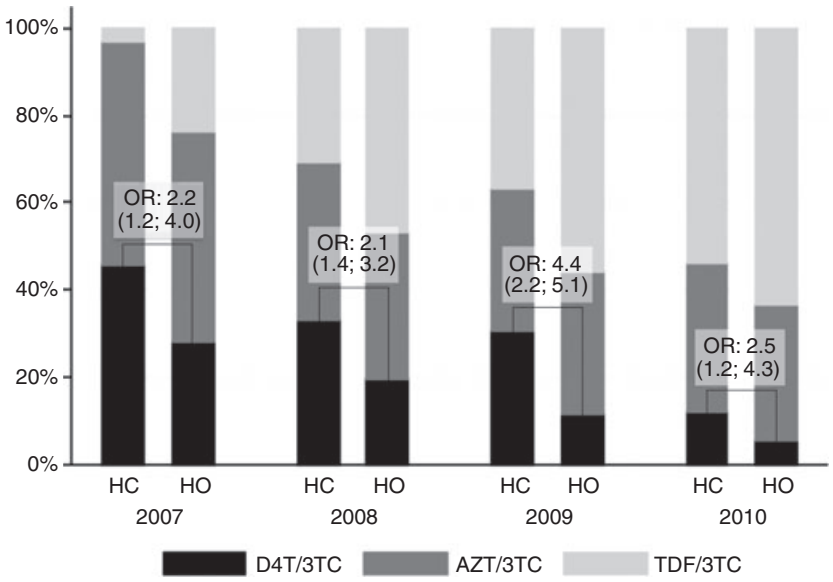

Figure 2 Type of nucleoside reverse transcriptase inhibitors (NRTI) at last consultation among patients retained by December 2010. NRTI-component at last visit among patients who were still on a standard first-line regimen and still seeking service within the catchment areas by December 2010. The odds-ratios are related to the likelihood of receiving a first-line regimen that does not contain stavudine at hospitals as compared to health centers. Adjusted odds-ratios derive from a multiple logistic regression model allowing for gender, age-groups, initial WHO-stage, baseline CD4-count, development of tuberculosis (TB) while on antiretroviral treatment (ART) and new pregnancy while on ART. OR, odds-ratio. Figures in brackets are the 95% confidence interval of the odds-ratios. HO, Hospitals; HC, Health centers. 3TC, lamivudine, D4T, stavudine, AZT, zidovudine, TDF, tenofovir.

Discussion

This retrospective cohort analysis comparing health centers and hospitals in rural Lesotho used adoption of and adherence to new national guidelines and rate of substitution within first-line ART-regimens as a proxy for quality of care. It stratified patients according to the type of the facility where they received ART: health centers and hospitals. The health centers took longer to implement the national ART-guidelines from 2007 that recommend favouring TDF and zidovudine as backbone instead of stavudine. The difference remained significant after allowing for multiple possible confounders. Health centers had a significantly lower number of substitutions within first-line ART-regimen and among patients retained by December 2010, the proportion still taking stavudine was significantly higher than at hospitals. Moreover, health centers prescribed to patients with concomitant TB treatment significantly more often a nevirapine-containing regimen, even though the guidelines strongly recommend an efavirenz base because of drug interactions. These results indicate that the health centers take longer to absorb new guidelines, substitute less frequently for side effects and may more often divert from the recommendations of national guidelines.

This study has three important limitations. First, it is a retrospective analysis, patients have not been randomly assigned to health centers or hospitals. This results in two cohorts with quite different baseline characteristics (Table 2) that may interfere with the assessed outcome variables. Analyses run, are adjusted for all baseline characteristics and the results remained significant. However, there might be other confounders that have not been assessed. In particular, the following information that has to guide the choice of first-line regimen according to the Lesotho guidelines has not been taken into consideration: serum creatinine, haemoglobin, liver-function tests and pre-existing neuropathy. Second, we have no data indicating whether the substitutions at the hospitals were justified and no data whether patients followed at the health centers more frequently suffered from unrecognised side effects. Third, the fact that laboratory tests were not available on site in the health centers may have influenced the outcomes. The national guidelines request a baseline haemoglobin or creatinine value for regimens that contain zidovudine or Tenofovir, respectively. However, as shown in Table 2, for 96.3% of health center patients a baseline CD4-count was recorded. As the bloodsamples for creatinine and haemoglobin follow exactly the same transport procedure as of the CD4-counts, one may assume, that the

procedure to get these laboratory tests at baseline was not a major obstacle. However, it may still have had an impact on the willingness of the nurses to prescribe the new first-line drugs because they required more laboratory monitoring on follow-up.

Observational studies assessing decentralised, nurse-based ART-programmes in Sub-Saharan Africa uniformly report improvement in access, good key-outcomes and good compliance with the ART-guidelines (Bedelu *et al.* 2007; van Griensven *et al.* 2008; Chang *et al.* 2009; Cohen *et al.* 2009; Morris *et al.* 2009; Shumbusho *et al.* 2009; Humphreys *et al.* 2010). However, decentralised nurse-based ART may be challenged by changes in policies and guidelines – unless there is intensive training and mentoring. It is likely, that on a large scale this supervision cannot be provided and the quality of decentralised nurse-based ART may suffer if no regular clinical mentoring is provided – in particular during the time when new guidelines are implemented.

The reported frequency of drug substitution for toxicity in other cohorts from Sub-Saharan Africa is comparable to the one of the hospital-group in this study, whereas the number of substitutions at health centers is far below the one reported in the literature (Boulle *et al.* 2007; Forna *et al.* 2007; Braitstein *et al.* 2010). This suggests that in the health center model side effects and other reasons for substituting drugs within first-line ART may have been overlooked. Qualitative studies are needed to determine the reasons for health centers sticking longer to stavudine-based regimens and substituting less frequently drugs for side effects. Preferring an old drug one knows may be one reason and some of the nurses may have been particularly reluctant to prescribe Tenofovir, as they did not feel comfortable calculating the renal creatinine clearance as requested in the national guidelines. Uncertainty about side effects and interpretation of laboratory results may be a reason for substituting less frequently.

The results of our study do not question the public health approach for decentralised ART-delivery in resource-limited settings. The demonstrated benefits of nurse-based decentralised ART that allowed a massive scale-up in many high-prevalence countries clearly outweigh the problems observed in this study. However, the study indicates two particular challenges for decentralised nurse-based programmes. First, nurse-based facilities need particular attention when new guidelines are introduced. Second, nurses may need particular training in recognising side effects and substituting drugs within the first-line regimen. As recommended by WHO, a regular on-the-job clinical mentoring of nurses by higher cadres experienced in HIV-management may be a good and practical approach to these challenges (World Health Organization 2008).

In decentralised ART-programmes where the task of providing ART has been shifted to nurses, particular attention is needed to update nurses on new guidelines and to mentor them about side effects of ART, drug interactions and possibilities of drug substitution within first-line regimen.

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References

Bedelu M, Ford N, Hilderbrand K & Reuter H (2007) Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. *Journal of Infectious Diseases* **196** (Suppl. 3), S464–S468.

Boulle A, Orrel C, Kaplan R *et al.* (2007) Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. *Antiviral Therapy* **12**, 753–760.

Braitstein P, Ayuo P, Mwangi A *et al.* (2010) Sustainability of first-line antiretroviral regimens: findings from a large HIV treatment program in western Kenya. *Journal of Acquired Immune Deficiency Syndromes (1999)* **53**, 254–259.

Callaghan M, Ford N & Schneider H (2010) A systematic review of task shifting for HIV treatment and care in Africa. *Human Resources for Health* **8**, 8.

Chang LW, Alamo S, Guma S *et al.* (2009) Two-year virologic outcomes of an alternative AIDS care model: evaluation of a peer health worker and nurse-staffed community-based program in Uganda. *Journal of Acquired Immune Deficiency Syndromes (1999)* **50**, 276–282.

Cohen R, Lynch S, Bygrave H *et al.* (2009) Antiretroviral treatment outcomes from a nurse-driven, community-supported HIV/AIDS treatment programme in rural Lesotho: observational cohort assessment at two years. *Journal of the International AIDS Society* **12**, 23.

Forna F, Liechty CA, Solberg P *et al.* (2007) Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda. *Journal of Acquired Immune Deficiency Syndromes (1999)* **44**, 456–462.

Humphreys CP, Wright J, Walley J *et al.* (2010) Nurse led, primary care based antiretroviral treatment versus hospital care: a controlled prospective study in Swaziland. *BMC Health Services Research* **10**, 229.

Kober K & Van Damme W (2004) Scaling up access to antiretroviral treatment in southern Africa: who will do the job? *Lancet* **364**, 103–107.

Massaquoi M, Zachariah R, Manzi M *et al.* (2009) Patient retention and attrition on antiretroviral treatment at district level in rural Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene* **103**, 594–600.

Ministry of Health and Social Welfare & National AIDS Commission (2009) National HIV and AIDS Estimates for Lesotho 2009. http://www.nas.org.ls/documents/default.php (accessed September 5, 2010).

Ministry of Health and Social Welfare of Lesotho (2004) *National Anti-retroviral Treatment Guidelines 2004*. Ministry of Health and Social Welfare of Lesotho, Maseru, Lesotho.

Ministry of Health and Social Welfare of Lesotho, M.O.H.S.W. (2007) *National Antiretroviral Treatment Guidelines 2007*. Ministry of Health and Social Welfare of Lesotho, Maseru, Lesotho.

Morris MB, Chapula BT, Chi BH *et al.* (2009) Use of task-shifting to rapidly scale-up HIV treatment services: experiences from Lusaka, Zambia. *BMC Health Services Research* **9**, 5.

National AIDS Commission (2010) *Annual Report on the National Response to HIV and AIDS – Reporting Period January to December 2009*. National AIDS Commission, Maseru, Lesotho.

Sanne I, Orrell C, Fox MP *et al.* (2010) Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet* **376**, 33–40.

Selke HM, Kimaiyo S, Sidle JE *et al.* (2010) Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. *Journal of Acquired Immune Deficiency Syndromes (1999)* **55**, 483–490.

Shumbusho F, van Griensven J, Lowrance D *et al.* (2009) Task shifting for scale-up of HIV care: evaluation of Nurse-Centered Antiretroviral Treatment at Rural Health Centers in Rwanda. *PLoS Medicine* **6**, e1000163.

Suarez-Lozano I, Viciana P, Lacalle JR *et al.* (2009) The relationship between antiretroviral prescription patterns and treatment guidelines in treatment-naïve HIV-1-infected patients. *HIV Medicine* **10**, 573–579.

UNAIDS (2010) Global Report, ISBN 978-92-9173-871-7. Available at http://www.unaids.org.

van Griensven J, De Naeyer L, Uwera J, Asiimwe A, Gazille C & Reid T (2008) Success with antiretroviral treatment for children in Kigali, Rwanda: experience with health center/nurse-based care. *BMC Pediatrics* **8**, 39.

World Health Organisation & HIV/AIDS Programme (2007) *Task Shifting to Tackle Health Worker Shortages*. World Health Organisation & HIV/AIDS Programme. Available at: http://www.who.int.

World Health Organization (2008) *Task Shifting – Global Recommendations and Guidelines*. World Health Organization. Available at: http://www.who.int.

World Health Organization (2009) Rapid advice – antiretroviral therapy for HIV infection in adults and adolescents. World Health Organization. Available at: http://www.who.int.

World Health Organization (2010) World Health Statistics 2010, ISBN 978 92 4 156398 7. Available at: http://www.who.int/whosis/whostat/2010/en/index.html.

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