Twelve-Month Outcomes of Community-Based Differentiated Models of Multimonth Dispensing of ART Among Stable HIV-Infected Adults in Lesotho: A Cluster-Randomized Noninferiority Trial

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Background: Lesotho adopted the test-and-treat approach for HIV treatment in June 2016, which increased antiretroviral treatment (ART) clinic volume. We evaluated community-based vs. facility-based differentiated models of multimonth dispensing of ART among stable HIV-infected adults in Lesotho.

Methods: Thirty facilities were randomized to 3 arms, facility 3-monthly ART (3MF) (control), community ART groups (3MC), and 6-monthly community distribution points (6MCD). We estimated risk differences (RDs) between arms using population-averaged generalized estimating equations, controlling for baseline imbalances and specifying for clustering. The primary outcome was retention in ART care by intention-to-treat and virologic suppression as a secondary outcome (ClinicalTrials.gov: NCT03438370).

Results: A total of 5,336 participants were enrolled, with 1898, 1558, and 1880 in 3MF, 3MC, and 6MCD, respectively. Retention in ART care was not different across arms and achieved the prespecified noninferiority limit (−3.25%) between 3MC vs. 3MF (control); 6MCD vs. 3MF; and 6MCD vs. 3MC, adjusted RD = −0.1% [95% confidence interval (CI): −1.6% to 1.5%], adjusted RD = −1.3% (95% CI: −3.0% to 0.5%), and adjusted RD = −1.2% (95% CI: −2.9% to 0.5%), respectively. After 12 months, 98.6% (n = 1503), 98.1% (n = 1126), and 98.3% (n = 1285) were virally load (VL) suppressed in 3MF, 3MC, and 6MCD, respectively. There were no differences in VL between 3MC vs. control and 6MCD vs. control, risk ratio (RR) = 1.00 (95% CI: 0.98 to 1.01) and RR = 1.00 (95% CI: 0.98 to 1.01), respectively.

Conclusions: There were no differences in retention and VL suppression for stable HIV-infected participants receiving multimonth dispensing of ART within community-based differentiated models when compared with the facility-based standard-of-care model.

Key Words: HIV, differentiated models of care, community ART groups, Lesotho, antiretroviral treatment

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INTRODUCTION

Background

In June 2016, Lesotho adopted the WHO Test-and-Treat approach requiring immediate initiation of antiretroviral treatment (ART) for all PLHIV.[1] ART is lifelong treatment and requires patient adherence to medication and retention in care. Barriers to ART adherence and retention are long distance to health facilities, long waiting times, travel costs, facility congestion, poor social support, and patient autonomy.[2–8] Many PLHIV in sub-Saharan Africa undergo frequent visits

for ART pick ups every 1–2 months, congesting already burdened health systems, resulting in poor adherence and/or detachment from care for the patient. Scaling up of ART services requires adequate supply of ART of at least 3 months,[9] thus minimizing frequent medication pick ups.

Lesotho currently recommends 3–6-month dispensing of ARV drugs for patients with viral load <1000 copies/mL.[10] However, because of logistical and other structural challenges (storage space, adequate supplies, and standing country policies), multimonth dispensing (MMD) in Lesotho was only introduced at 3-monthly intervals in facilities only for stable ART patients.[10] Community-based models of care are postulated to further strengthen adherence, retention, and viral suppression.[11] Community ART Groups (CAGs) have been successfully implemented elsewhere in Southern Africa, and introducing MMD into them can have the same intended outcomes as facility-based interventions, while additionally decongesting and decentralizing facilities.[12] We evaluated implementation of community-based vs. facility-based differentiated models of MMD of ART among stable HIV-infected adults in Lesotho.

METHODS

Study Design

A detailed description of the study protocol is described elsewhere.[13] Briefly, this was a cluster-randomized noninferiority trial with 3 differentiated models of multimonth scripting and dispensing (MMSD) undertaken in 30 facilities (clusters), in Lesotho. The selection criteria (Fig. 1) were as follows: (1) had at least 430 patients currently on ART to fulfill the facility sample size requirement, (2) were either already implementing CAGs or implementation of CAGs was deemed feasible, (3) had adequate supply chain procedures for MMSD, and (4) routine data collection procedures were in place. Each study arm had 10 facility clusters. The clusters were stratified into urban and rural, according to the geographic location, and randomized to: (1) control—3-monthly dispensing of ART at health facilities (3MF); (2) intervention 3-monthly dispensing of ART within CAGs (3MC); and (3) 6-monthly dispensing of ART at community distribution points (6MCD). The study was approved by the Lesotho National Health Research Ethics Committee and the Advarra Institutional Review Board, USA.

Study Population

The study population consisted of HIV-infected adults (age ≥18 years) who had received first-line ART for at least 6 months, had baseline viral load <1000 copies/mL within the past 12 months (stable patient), provided written informed consent, and willing to participate in the arm their health facility was randomized to. Exclusion criteria included patients on second-line or third-line ART, those with comorbidities requiring more frequent facility visits, those who had ART modifications since the last viral load test, those who were pregnant and/or breastfeeding, those classified as WHO clinical stage 3 or 4 in the past 3 months, or those participating in another study requiring dispensing of drugs. Before study participation, participants received ART on a monthly basis as per national guidelines or received a 2-monthly supply if working in South Africa.

Study Intervention and Procedures

Study Interventions

The interventions in this study were the use of CAGs and community outreach distribution points for ART MMSD.[14,15]

Three-Month Dispensing Model at Health Facilities

Providers at facilities randomized to 3-month dispensing provided all enrolled patients with a 3-month supply of ART. All other aspects of care were part standard of care for the enrolling clinic, and routine visits occurred every 90 days instead of the standard-of-care interval.

CAG Model (3-Month Supply of Drug)

CAGs are groups of stable patients on ART who meet in the community and manage their own health by taking turns obtaining medications from the clinic for the entire group, self-monitoring medication adherence, and providing support to each other.[14,16,17] Study participants enrolled in this arm joined new/previously existing CAGs or were already members. The CAG consisted of 2–12 participants, who lived in a similar geographic location and attended the same health care facility. The members' appointments were synchronized to ensure that scheduled clinic visits were on the same day. Stable participants were required to have clinical consultation and viral load (VL) testing at the facility at 12 and 24 months after enrollment. Each member of the CAG collected their own 3-month supply of ART from the clinic on this day. Participants who were ill at any stage of the study reported to the clinic as soon as it was possible. A CAG representative distributed the drugs to the other members at the CAG meeting on the same day or the following day. The dates of these visits were noted by the facility to ensure that all drugs were predispensed and ready during this visit date.

Community ART Distribution Model by the Health Care Worker (6-Month Supply of Drug)

Participants were identified from the facilities and sensitized on collecting ART in the community. The distribution points are community outreach points used for health service delivery. Their next ART refill was conducted in 6 months in the community at an outreach post. These encounters in the community were on an individual provider–patient basis, not as part of a CAG. The ART refill was conducted by a health care worker, appropriately trained and certified for dispensing ART to stable patients. Study participants' adherence was assessed at this community distribution point. Participants continued to receive 6-month refills in the community if they remained stable (ie, have VL less than 1000 copies per mL). Stable participants were required to have a clinical consultation and VL done at the facility at 12 months and 24 months after enrollment.

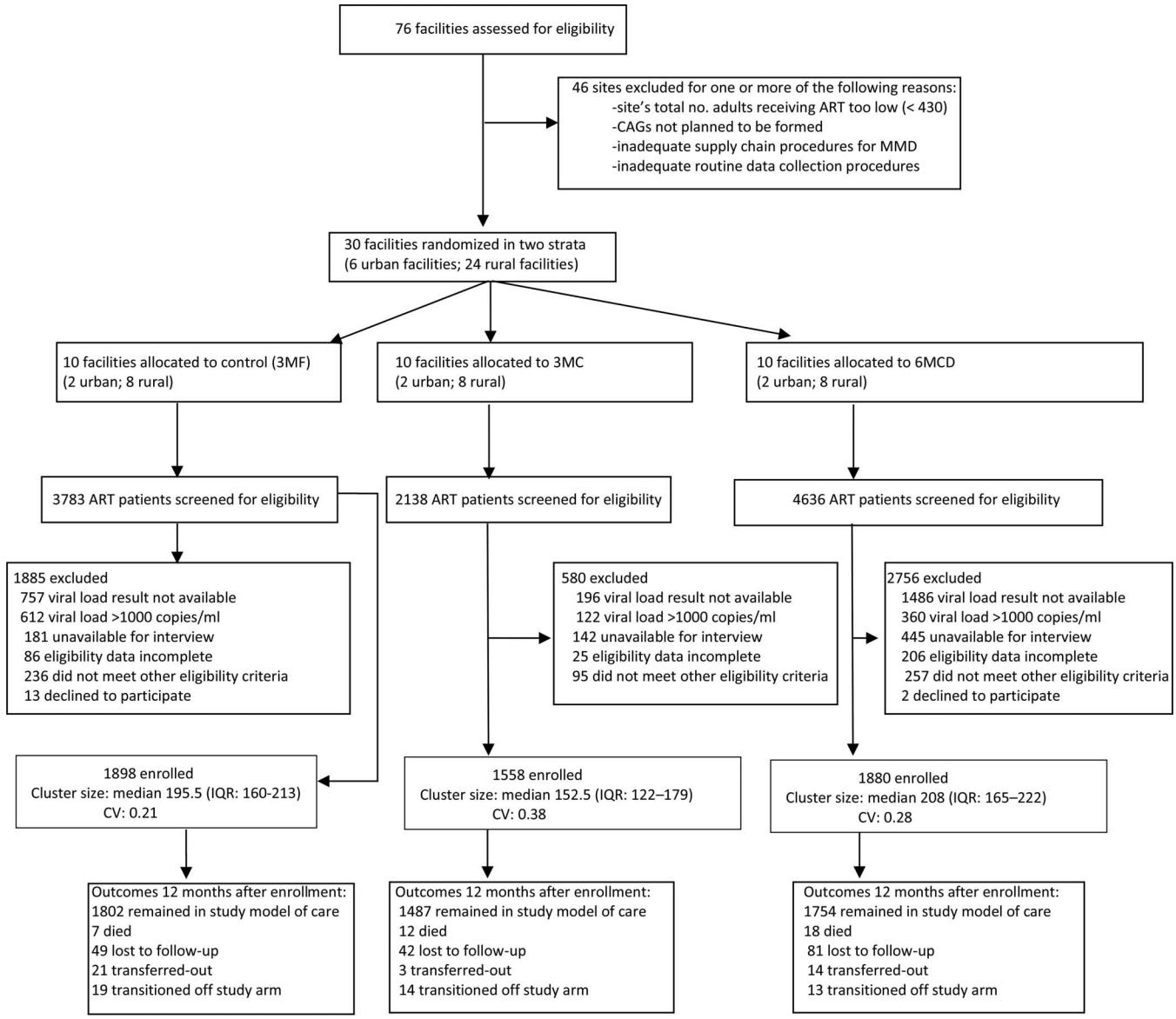

FIGURE 1. Trial flow diagram. CV, coefficient of variation of cluster size.

PROCEDURES

Screening and Enrollment

Study nurses, stationed at each study facility, reviewed each patient's clinical file to assess study eligibility. The nurses liaised with the facility health workers to refer all patients identified as potentially eligible for study enrollment. The study nurse invited referred patients to participate in the study and provided additional information on the study to all patients who expressed interest in the study. All study participants provided written informed consent before study screening and enrollment as part of the study informed consent process.

Patients who met the inclusion criteria and provided informed consent were enrolled in the study. Each participant received a unique study number for identification during follow-up and assessment of participants' records. All participants were enrolled from the facilities randomized to the 3 study arms. 3MF participants received the standard-of-care 3-monthly supply of ART at the facility. 3MC participants were enrolled from members of existing/newly formed CAGs and were given 3-monthly supply of ART. For the facilities randomized to the 6MCD arm, enrolled participants were given their first 6-monthly ART supply at enrollment. Patients only returned to the facility for annual clinical assessments that include viral load blood draws.

Follow-up Visits

During follow-up, the study nurses reviewed the patient files and completed both a paper and electronic monitoring tool for each participant. The monitoring tool captured

participants' vitals on the study outcomes. Tracing of all participants who missed ART appointments was performed as part of routine activities by an existing community implementing partner, Lesotho Network of AIDS Services Organizations (LENASO). Electronic data were captured using tablets and entered into a RedCap database onto a central server. Patients who were clinically unstable requiring more frequent or intense clinical follow-up were transitioned off the study arm and referred back to the facility.

Outcomes

The primary outcome was retention in ART care defined as the proportion of participants remaining in care 12 months after study enrollment. The secondary outcomes were (1) viral suppression, defined as the proportion of participants with viral load <1000 copies/mL 12 months after study enrollment, and (2) the proportion of participants retained in the study model of care (study arm) after 12 months, defined as participants alive and continuously receiving ART at 3- or 6-monthly intervals in the same study arm as at enrollment in the study. The primary outcome of retention in ART care considered both death and loss to follow-up (LTFU) as attrition. The secondary outcome of retention in the study arm considered all participants who died, were LTFU, who transferred out to other facilities, and those transitioning off the arm due to needing more frequent dispensing of ART for clinical reasons as losses to the arm. Participants who missed a pick-up date for their ART medication for more than 90 days after the last missed appointment and who were not known to have transferred out to another facility or service or died were considered LTFU. Follow-up continued until 15 months to calculate outcomes at 12 months, allowing participants not returning for the 12-month visit 3 additional months before being classified as LTFU.[15]

Statistical Analysis

Sample Size Estimation

Participant sample size estimates were calculated for the primary outcome of retention in ART care 12 months after enrollment, for a noninferiority test for the difference in 2 proportions in a cluster-randomized design using PASS v.14 software. Participant enrollment numbers were assumed to be equal in each cluster. The probability of participant retention 12 months after study enrollment in the control group was assumed to be 95%. The probability of retention in the intervention arms after 12 months was assumed to be 95%. An intracluster correlation coefficient of 0.01 for retention amongst stable ART patients associated with the same healthcare facility was assumed.[18] The noninferiority margin was prespecified as −3.25% [risk difference (RD)]. Assuming $\alpha = 0.05$, power of 85%, and using the 1-sided Z-test (unpooled) statistic, the cluster sample size target was 192 enrolled participants per facility, with 1920 participants per arm and a total sample size of 5760. As retention in care was the primary outcome, no adjustment for LTFU was made.

Data Analysis

Descriptive measures of the study population at baseline in each study arm were evaluated using medians and interquartile ranges for continuous variables and proportions for categorical variables. Individual-level outcome analyses were conducted by intention-to-treat (ITT) including all enrolled participants in the arm to which they were originally allocated. For retention in ART care and retention in the study arm, RDs were estimated using binomial population-averaged generalized estimating equations using an identity link and an exchangeable correlation structure, specifying for clustering by facility and using robust standard errors.[19,20] A small cluster size variance correction was used,[20] and randomization strata (urban/rural location) were included in all models as a fixed-effect parameter. Mortality and LTFU (as separate outcomes) were also analyzed by ITT using RDs estimated from binomial population-averaged generalized estimating equation models. Multivariable regression analyses were performed including individual-level and cluster-level covariates that displayed imbalance at baseline and were associated with the outcome in unadjusted analyses.

Two prespecified VL suppression analyses were conducted as follows: (1) ITT analysis including all enrolled participants as allocated and irrespective of whether they had available follow-up VL results or completed the study, and (2) an analysis restricted to participants having an available VL result 12 months after study enrollment. VL results performed between 9 and 15 months after study enrollment were considered as 12-month VL results. Where participants had more than 1 VL result during this period, the result closest to 12 months was analyzed.

For the ITT analysis of VS, a 3-level outcome variable was generated: VL suppressed, VL unsuppressed, and VL test not performed. Using a generalized structural equation framework, a multinomial logit model specified for clustering by facility was constructed to estimate the intervention effect of a suppressed vs. unsuppressed VL, specifying unsuppressed VL as the base category. For the analysis restricted to participants with available VL results, log-binomial regression with generalized estimating equations was used to estimate risk ratios of VS between study arms, specifying for clustering by facility. All regression models were adjusted for the randomization stratum. Statistical analyses were conducted using Stata 15. A Data Safety and Management Board oversaw the study (ClinicalTrials.gov Identifier NCT03438370).

RESULTS

From August 3, 2017, to April 30, 2018, a total of 3783, 2138, and 4636 ART patients were screened for eligibility, with 1898, 1558, and 1880 participants were enrolled in arms 3MF, 3MC, and 6MCD, respectively (Fig. 1). The most common reason for exclusion was nonavailability of viral load results (47% of those excluded), followed by having a viral load >1000 copies/mL (21% of those excluded). Enrollment in 6MCD was slightly slower than the other arms (median month of enrollment = November

TABLE 1. Characteristics of Participants at Enrollment in the Multimonth Scripting and Dispensing of ART Cluster-Randomized Trial in Lesotho

Baseline Characteristic	Arm 3MF (N = 1898)	Arm 3MC (N = 1558)	Arm 6MCD (N = 1880)
Age, yr, median (IQR) (n = 5336)	42.7 (34.7–54.0)	48.4 (39.4–57.8)	41.2 (33.3–51.4)
Age categories, n (%) (n = 5336)			
18–24 yrs	65 (3.4)	22 (1.4)	88 (4.7)
25–49 yrs	1223 (64.4)	821 (52.7)	1280 (68.1)
≥50 yrs	610 (32.1)	715 (45.9)	512 (27.2)
Gender, n (%) (n = 5336)			
Female	1158 (61.0)	1117 (71.7)	1264 (67.2)
Male	740 (39.0)	441 (28.3)	616 (32.8)
CD4 cell count at enrollment, cells/μL, median (IQR) (n = 3388)	515 (365.0–698.0)	560 (396.0–743.0)	535.5 (365.0–726.5)
CD4 cell count categories, n (%)			
<200 cells/μL	78 (4.1)	39 (2.5)	58 (3.1)
<200–499 cells/μL	546 (28.8)	415 (26.6)	366 (19.5)
500–749 cells/μL	429 (22.6)	396 (25.4)	314 (16.7)
750–3000 cells/μL	270 (14.2)	267 (17.1)	210 (11.2)
Not recorded	575 (30.3)	441 (28.3)	932 (49.6)
Weight, kg, median (IQR) (n = 5289)	60 (53.2–68.7)	59 (52.0–69.8)	61.5 (54.0–71.0)
WHO stage, n (%) (n = 5285)			
I	1841 (97.7)	1505 (98.2)	1809 (96.8)
II	43 (2.3)	28 (1.8)	59 (3.2)
Marital status, n (%) (n = 5327)			
Married	1051 (55.5)	726 (46.7)	958 (51.0)
Not married*	843 (44.5)	828 (53.3)	921 (49.0)
Current employment, n (%) (n = 5325)†			
Employed	676 (35.7)	464 (29.9)	877 (46.7)
Not employed	1218 (64.3)	1088 (70.1)	1002 (53.3)
Smoking, n (%) (n = 5316)			
Never smoked	1631 (86.1)	1412 (91.3)	1669 (89.0)
Current or previous smoker	263 (13.9)	135 (8.7)	206 (11.0)
Current alcohol consumption, n (%) (n = 5320)			
No	1447 (76.4)	1175 (75.9)	1511 (80.5)
Yes	446 (23.6)	374 (24.1)	367 (19.5)
Distance to facility, n (%) (n = 5317)			
<4 km	496 (26.2)	515 (33.3)	455 (24.2)
4–9 km	542 (28.6)	550 (35.6)	622 (33.1)
>9 km	527 (27.8)	346 (22.4)	405 (21.6)
Unknown	329 (17.4)	135 (8.7)	395 (21.0)
Time from ART initiation until study enrollment, mo, median (IQR) (n = 5464)	44.3 (20.1–86.3)	66.1 (31.8–103.6)	38.3 (18–77)
Time from HIV diagnosis till ART initiation, mo, median (IQR) (n = 4899)	1.5 (0.3–11.8)	2.3 (0.6–15.3)	1.2 (0–10.5)
Disclosed HIV status, n (%) (n = 5327)			
Yes	1790 (94.5)	1428 (92.0)	1790 (95.2)
No	104 (5.5)	125 (8.1)	90 (4.8)
Facility location, n (%) (n = 5336)			
Rural	1443 (76.0)	1125 (72.2)	1443 (76.8)
Urban	455 (24.0)	433 (27.8)	437 (23.2)
Health care level, n (%) (n = 5336)			
Clinic	1443 (76.0)	1277 (82.0)	1665 (88.6)
Hospital	455 (24.0)	281 (18.0)	215 (11.4)
District, n (%) (n = 5336)			
Maseru	1225 (64.5)	586 (37.6)	444 (23.6)
Mafeteng	280 (14.8)	671 (43.0)	1049 (55.8)
Mohale's Hoek	393 (20.7)	301 (19.3)	387 (20.6)

*Includes those never married, divorced, or widowed.
†Employment status was determined by self-report and recorded as a binary variable. Self-employment was considered employed.

TABLE 2. Analysis of Primary Outcome (Patient Retention) After 12 Months by Intention-to-Treat in the Multimonth Dispensing of ART Cluster-Randomized Trial in Lesotho*

				Unadjusted Analysis			Adjusted Analysis†		
Baseline Factor	**Enrolled (N)**	**Retained (n)**	**Retained (%)**	**Risk Difference**	**95% CI**	***P***	**Risk Difference**	**95% CI**	***P***
Arm (vs. 3MF)									
3MF (control)	1898	1842	97.1	Reference	—	—	Reference	—	—
3MC	1558	1504	96.5	−0.2%	−1.9 to 1.6	0.845	−0.1%	−1.6 to 1.5	0.924
6MCD	1880	1781	94.7	−2.3%	−4.1 to −0.4	0.016	−1.3%	−3.0 to 0.5	0.149
6MCD vs. 3MC									
3MC	1558	1504	96.5	Reference	—	—	Reference	—	—
6MCD	1880	1781	94.7	−2.1%	−3.9 to −0.3	0.023	−1.2%	−2.9 to 0.5	0.168
Gender									
Male	1797	1733	96.4	0.4%	−0.8 to 1.7	0.508			
Female	3539	3394	95.9	Reference	—	—			
Age category									
18–24 yrs	175	159	90.9	−5.2%	−9.3 to −1.1	0.013	−4.7%	−8.6 to −0.7	0.020
25–49 yrs	3324	3196	96.2	Reference	—	—	Reference	—	—
≥50 yrs	1837	1772	96.5	0.3%	−0.8 to 1.4	0.621	0.4	−0.8 to 1.6	0.501
CD4 cell count									
<200 cells/μL	175	168	96.0	−0.8%	−4.0 to 2.4	0.624			
<200–499 cells/μL	1327	1287	97.0	Reference	—	—			
500–749 cells/μL	1139	1101	97.0	−0.2%	−1.8 to 1.4	0.781			
≥750 cells/μL	747	719	96.3	−0.7%	−2.7 to 1.4	0.526			
Not recorded	1948	1852	95.1	−1.7%	−3.6 to 0.1	0.073			
WHO stage									
I	5155	4958	96.2	Reference	—	—			
II	130	124	95.4	−0.7%	−4.3 to 2.9	0.700			
Marital status									
Married	2735	2633	96.3	Reference	—	—			
Not married	2592	2486	96.0	−0.3%	−1.2 to 0.6	0.497			
Current employment									
Employed	2017	1940	96.2	Reference	—	—			
Not employed	3308	3117	96.0	−0.4%	−1.5 to 0.7	0.477			
Smoking									
Never smoked	4712	585	96.9	Reference	—	—			
Current/previous smoker	604	4525	96.0	1.0%	−0.7 to 2.8	0.253			
Alcohol consumption									
No	4133	3965	95.9	Reference	—	—			
Yes	1187	1147	96.6	0.8%	−0.4 to 2.1	0.175			
Distance to facility									
<4 km	1466	1409	96.1	Reference	—	—			
4–9 km	1714	1640	95.7	0.0%	−2.0 to 1.9	0.974			
>9 km	1278	1229	96.2	0.7%	−1.4 to 2.7	0.524			
Unknown	859	831	96.7	0.8%	−2.4 to 3.9	0.629			
Disclosed HIV status									
Yes	5008	4811	96.1	Reference	—	—			
No	319	308	96.6	0.7%	−1.4 to 2.7	0.525			
Facility location									
Urban	1325	1262	95.3	−1.0%	−3.1 to 1.2	0.377	−1.0	−2.8 to 0.7	0.240
Rural	4011	3865	96.4	Reference	—	—	Reference	—	—
Health care level									
Clinic	4385	4227	96.4	Reference	—	—			
Hospital	951	900	94.6	−2.3%	−6.0 to 1.9	0.219			

(*continued on next page*)

TABLE 2. (*Continued*) Analysis of Primary Outcome (Patient Retention) After 12 Months by Intention-to-Treat in the Multimonth Dispensing of ART Cluster-Randomized Trial in Lesotho*

				Unadjusted Analysis			Adjusted Analysis†		
Baseline Factor	**Enrolled (N)**	**Retained (n)**	**Retained (%)**	**Risk Difference**	**95% CI**	***P***	**Risk Difference**	**95% CI**	***P***
District									
Maseru	2255	2195	97.3	Reference	—	—	Reference	—	—
Mafeteng	2000	1894	94.7	−2.5%	−4.4 to −0.7	0.007	−2.1%	−3.5 to −0.6	0.006
Mohale's Hoek	1081	1038	96.0	−1.2%	−3.3 to 0.8	0.241	−1.1%	−2.4 to 0.3	0.127

The measured intracluster correlation coefficient for retention was 0.01.

*Outcome analyses were by intention-to-treat using population-averaged generalized estimating equations specified for clustering by facility and using robust standard errors. All models were adjusted for randomization stratum (rural/urban).

†Estimates adjusted for age category, district, and randomization stratum.

WHO, World Health Organization.

2017 vs. October 2017 in arms 3MF and 3MC). Participants' follow-up was closed on July 31, 2019.

At baseline, imbalance between the arms was apparent with respect to age (3MC participants were older, and 6MCD had a higher proportion of participants aged 18–24 years); 3MF participants were more likely to be enrolled at hospital-based facilities; and variation by district was apparent (3MF participants were less likely to be from Mafeteng) (Table 1).

The median duration of follow-up (from study enrollment to the last ART receipt) was 17.7 months [interquartile range (IQR): 15.1–19.1], 15.3 months (IQR: 12.1–18.2), and 12.4 months (IQR: 11.8–15.7) in arms 3MF, 3MC, and 6MCD, respectively. Enrollment in the 6MCD arm was slower compared with the other arms because of structural challenges and thus follow-up time was lower in this arm. Twelve months after enrollment, 1842 (97.1%), 1504 (96.5%), and 1781 (94.7%) participants enrolled in 3MF, 3MC, and 6MCD remained in ART care, respectively (Table 2). The measured intracluster correlation coefficient for retention in ART care was 0.01. Retention in 3MC did not

TABLE 3. Analysis of Secondary Outcome (Retention in the Study Arm) After 12 Months by Intention-to-Treat in the Multimonth Dispensing of ART Cluster-Randomized Trial in Lesotho*

				Unadjusted Analysis			Adjusted Analysis†		
Baseline Factor	**Enrolled (N)**	**Retained (n)**	**Retained (%)**	**Risk Difference**	**95% CI**	***P***	**Risk Difference**	**95% CI**	***P***
Arm (vs. 3MF)									
3MF (control)	1898	1802	94.9%	Reference	—	—	Reference	—	—
3MC	1558	1487	95.4%	0.9%	−1.3 to 3.1	0.445	1.1%	−0.6 to 2.8	0.192
6MCD	1880	1754	93.3%	−1.6%	−3.6 to 0.3	0.093	−0.6%	−2.4 to 1.1	0.495
6MCD vs. 3MC									
3MC	1558	1487	95.4%	Reference	—	—	Reference	—	—
6MCD	1880	1754	93.3%	−2.5%	−4.4 to −0.5	0.014	−1.9%	−3.6 to −0.2	0.032
Gender									
Male	1797	1715	95.4%	1.3%	−0.2 to 2.9	0.088			
Female	3539	3328	94.0%	Reference	—	—			
Age									
18–24 yrs	175	149	85.1%	−9.4%	−14.5 to −4.3	<0.0001	−9.0%	−14.0 to −4.0	<0.0001
25–49 yrs	3324	3143	94.6%	Reference	—	—	Reference	—	—
≥50 yrs	1837	1751	95.3%	0.7%	−0.7 to 2.1	0.309	0.6%	−0.9 to 2.1	0.438
CD4 cell count									
<200 cells/μL	175	164	93.7%	−1.2%	−5.3 to 2.9	0.565			
<200–499 cells/μL	1327	1263	95.2%	Reference	—	—			
500–749 cells/μL	1139	1085	95.3%	0.1%	−1.4 to 1.6	0.866			
≥750 cells/μL	747	708	94.8%	−0.3%	−2.4 to 1.8	0.762			
Not recorded	1948	1823	93.6%	−1.5%	−3.3 to 0.4	0.115			
WHO stage									
I	5155	4877	94.6%	Reference	—	—			
II	130	121	93.1%	−1.6%	−6.6 to 3.5	0.539			

TABLE 3. (*Continued*) Analysis of Secondary Outcome (Retention in the Study Arm) After 12 Months by Intention-to-Treat in the Multimonth Dispensing of ART Cluster-Randomized Trial in Lesotho*

				Unadjusted Analysis			Adjusted Analysis†		
Baseline Factor	**Enrolled (N)**	**Retained (n)**	**Retained (%)**	**Risk Difference**	**95% CI**	***P***	**Risk Difference**	**95% CI**	***P***
Marital status									
Married	2735	2587	94.4%	Reference	—	—			
Not married	2592	2448	94.6%	−0.1%	−1.1 to 0.9	0.812			
Current employment									
Employed	2017	1910	94.7%	Reference	—	—			
Not employed	3308	3123	94.4%	−0.5%	−1.8 to 0.7	0.415			
Smoking									
Never smoked	4712	4447	94.4%	Reference	—	—			
Current/previous smoker	604	579	95.9%	1.7%	−0.3 to 3.6	0.102			
Alcohol consumption									
No	4133	3899	94.3%	Reference	—	—			
Yes	1187	1130	95.2%	1.0%	−0.6 to 2.5	0.223			
Distance to facility									
<4 km	1466	1387	94.6%	Reference					
4–9 km	1714	1612	94.1%	−0.2%	−2.4 to 2.0	0.879			
>9 km	1278	1206	94.4%	0.3%	−2.0 to 2.5	0.820			
Unknown	859	820	95.5%	1.0%	−2.5 to 4.5	0.580			
Disclosed HIV status									
Yes	5008	4730	94.5%	Reference	—	—			
No	319	305	95.6%	1.2%	−1.1 to 3.6	0.309			
Facility location									
Urban	1325	1239	93.5%	−1.2%	−3.6 to 1.2	0.320	−1.3%	−3.4 to 0.7	0.202
Rural	4011	3804	94.9%	Reference	—	—	Reference	—	—
Health care level									
Clinic	4385	4161	94.9%	Reference	—	—			
Hospital	951	882	92.7%	−3.0%	−6.8 to 0.9	0.138			
District									
Maseru	2255	2167	96.1%	Reference	—	—	Reference	—	—
Mafeteng	2000	1868	93.4%	−2.9%	−4.5 to −1.3	<0.0001	−2.6%	−4.1 to −1.0	0.001
Mohale's Hoek	1081	1008	93.3%	−2.7%	−4.7 to −0.7	0.009	−2.5%	−4.2 to −0.8	0.004

*Outcome analyses were by intention-to-treat using population-averaged generalized estimating equations specified for clustering by facility and using robust standard errors. All models were adjusted for randomization stratum (rural/urban).

†Estimates adjusted for age category, district, and randomization stratum.

WHO, World Health Organization.

differ compared with control 3MF in both unadjusted and adjusted analyses, and the noninferiority limit was achieved, adjusted RD = −0.1% [95% confidence interval (CI): −1.6% to 1.5%]. Retention in 6MCD was reduced compared with control 3MF and 3MC in unadjusted analyses, RD = −2.3% (95% CI: −4.1% to −0.4%) and RD = −2.1% (95% CI: −3.9% to −0.3%), respectively. However, 6MCD had a higher proportion of participants aged 18–24 years and a higher proportion from Mafeteng district, and both factors were significantly associated with lower retention. After adjustment for age category and district, the noninferiority limit was achieved for both 6MCD vs. control 3MF and 6MCD vs. 3MC, adjusted RD = −1.3% (95% CI: −3.0% to 0.5%) and adjusted RD = −1.2% (95% CI: −2.9% to 0.5%), respectively.

After 12 months, 1802 (94.9%), 1487 (95.4%), and 1754 (93.3%) participants enrolled to 3MF, 3MC, and 6MCD continued to receive ART in their original arm, respectively (Table 3). The number of participants who transitioned off the arms due to needing increased frequency of ART receipt was low and similar between arms, 19 (1.0%), 14 (0.9%), and 13 (0.7%) in 3MF, 3MC, and 6MCD, respectively. In both unadjusted and adjusted analyses, retention in the arm did not differ between 3MC vs. control 3MF and also between 6MCD vs. control 3MF. However, retention in the study arm was lower in 6MCD vs. 3MC in the unadjusted analysis, RD = −2.5% (95% CI: −4.4% to −0.5%), and remained lower after adjusting for baseline imbalance, adjusted RD = −1.9% (95% CI: −3.6% to −0.2%).

TABLE 4. Viral Suppression 12 Months After Enrollment

	Enrolled (N)	VL Due* (N)	VL Done (N)	VL Suppressed (n)	VL Completion†	VS (ITT) (%)‡	VS Among Those with VL Results§	VS by ITT (N = 5336)‖						VS Among Those With VL Results (N = 3914)#		
								Unadjusted			Adjusted¶					
								RRR	95% CI	*P*	RRR	95% CI	*P*	RR	95% CI	*P*
Arm																
3MF	1898	1821	1503	1482	82.5%	78.1%	98.6%	Ref	—	—	Ref	—	—	Ref	—	—
3MC	1558	1501	1126	1104	75.0%	70.9%	98.1%	0.70	0.35–1.41	0.316	1.15	0.54–2.47	0.707	1.00	0.98–1.01	0.449
6MCD	1880	1767	1285	1263	72.7%	67.2%	98.3%	0.84	0.36–1.93	0.676	1.30	0.57–2.93	0.525	1.00	0.98–1.01	0.729
6MCD vs. 3MC								1.19	0.47–3.03	0.710	1.12	0.47–2.65	0.788	1.00	0.99–1.02	0.776
Facility location																
Urban	1325	1250	982	966	78.6%	72.9%	98.4%	Ref	—	—	Ref	—	—	Ref	—	—
Rural	4011	3839	2932	2883	76.4%	71.9%	98.3%	0.98	0.40–2.37	0.956	1.57	0.79–3.10	0.191	1.00	0.99–1.02	0.806
District																
Maseru	2255	2175	1797	1777	82.6%	78.8%	98.9%	Ref	—	—	Ref	—	—	Ref	—	—
Mafeteng	2000	1890	1343	1304	71.1%	65.2%	97.1%	0.37	0.18–0.72	0.004	0.30	0.17–0.55	<0.0001	0.98	0.97–0.99	0.002
Mohale's Hoek	1081	1024	774	768	75.6%	71.0%	99.2%	1.49	0.65–3.41	0.341	1.50	0.56–3.96	0.82	1.00	1.00–1.01	0.395

*Enrolled less died, LTFU, and TFO.
†Viral load done (N)/viral load due (N).
‡Viral load suppressed (n)/enrolled (N).
§Viral load suppressed (n)/VL done (N).
‖Estimates from a multinomial logit regression model specifying for clustering by facility and using unsuppressed viral load as the base category, adjusted for randomization stratum (urban/rural).
¶Adjusted for district and randomization stratum.
#Estimates using log-binomial regression with generalized estimating equations specifying for clustering by facility and adjusted for randomization stratum, including only participants with available viral load results.
RRR, relative risk ratio; RR, risk ratio; TFO, transferred out.

TABLE 5. Mortality and Loss to Follow-up 12 Months After Enrollment*

Arm	Enrolled (N)	Died, n (%)	LTFU, n (%)	Mortality						Loss to Follow-up					
				Unadjusted			Adjusted†			Unadjusted			Adjusted‡		
				RD	95% CI	*P*	RD	95% CI	*P*	RD	95% CI	*P*	RD	95% CI	*P*
3MF	1898	7 (0.4)	49 (2.6)	Ref.	—	—	Ref.	—	—	Ref.	—	—	Ref.	—	—
3MC	1558	12 (0.8)	42 (2.7)	0.4%	−0.1 to 0.8	0.090	0.3%	−0.1 to 0.6	0.162	−0.3%	−2.0 to 1.4	0.702	−0.2%	−1.4 to 1.0	0.739
6MCD	1880	18 (1.0)	81 (4.3)	0.5%	0.0 to 1.0	0.070	0.5%	−0.1 to 1.0	0.079	1.8%	−0.3 to 3.8	0.099	0.4%	−1.3 to 2.1	0.650
6MCD vs. 3MC				0.1%	−0.5 to 0.7	0.763	0.2%	−0.4 to 0.8	0.471	2.1%	0.1 to 4.1	0.037	0.6%	−1.0 to 2.2	0.479

*Outcome analyses were by intention-to-treat using population-averaged generalized estimating equations specified for clustering by facility and using robust standard errors. All models were adjusted for randomization stratum (urban/rural location).
†Estimates adjusted for age category, gender, and urban/rural location.
‡Estimates adjusted for age category, district, and urban/rural location.
Ref, reference category.

After 12 months, viral load completion was 1503 (82.5%), 1126 (75.0%), and 1285 (72.7%) in arms 3MF, 3MC, and 6MCD, respectively (Table 4). VS by ITT in 3MC and 6MCD was not different from 3MF; adjusted relative risk ratio (aRRR) = 1.30 (95% CI: 0.57 to 2.93) and aRRR = 1.12 (95% CI: 0.47 to 2.65), respectively. Adjusted models were adjusted for the randomization stratum and study district. Among participants with available viral load results after 12 months, 1482 (98.6%), 1104 (98.1%), and 1263 (98.3%) were virally suppressed in arms 3MF, 3MC, and 6MCD, respectively. No differences in viral suppression were found between any arms in analyses among participants with available viral load results (Table 4).

After 12 months, 7 (0.4%), 12 (0.8%), and 18 (1.0%) participants were recorded as having died in 3MF, 3MC, and 6MCD, respectively (Table 5). A further 49 (2.6%), 42 (2.7%), and 81 (4.3%) were LTFU in these same arms, respectively. The proportion of participants recorded as having died among those LTFU was slightly lower in 3MF than that in 3MC and 6MCD: 7 of 56 (12.5%), 12 of 54 (22.2%), and 18 of 99 (18.2%), respectively (P = 0.23). There was a borderline increase of mortality in 6MCD vs. control 3MF in the unadjusted analysis, RD = 0.5% (95% CI: 0.0% to 1.0%; P = 0.07). However, the difference in risk was small and was not significantly different at the 5% level both before and after adjustment, adjusted RD = 0.5% (95% CI: −0.1% to 1.0%; P = 0.07). Mortality in 6MCD was not higher when compared with 3MC. There were no differences in LTFU between the intervention arms vs. control. LTFU in 6MCD was higher compared with 3MC in the unadjusted analysis, but there was no difference after adjustment for age and district, adjusted RD = 0.6% (95% CI: −1.0% to 2.2%). Viral suppression was high (>98%) with no differences between arms.

DISCUSSION

This study is one of the first cluster-randomized trials to evaluate the outcomes of extended dispensing intervals of

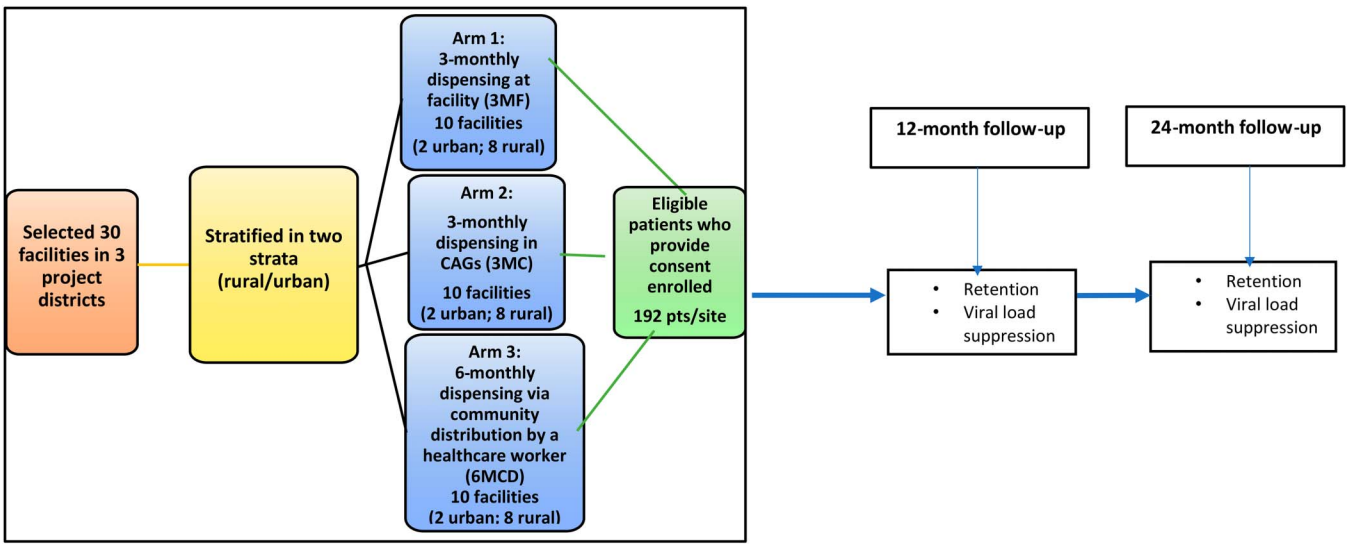

FIGURE 2. Study design. full color online

ART using community-based distribution in sub-Saharan Africa. This study showed the community-based models to have similar outcomes of retention and viral load suppression as the standard facility-based model, with no significant differences between the arms by adjusted ITT analyses. The results are congruent with a similar study, which was undertaken in Zimbabwe.[21] It is anticipated that the interventions will be cost-effective, as costs are expected to be reduced with extended intervals of community-based distribution vs. facility-based ART dispensing.

Community-based differentiated models of ART delivery (DMAD) in low-income countries were primarily designed to adopt HIV services to client needs in order to minimize barriers to adherence and retention on ART by bringing the services closer to the client and to reduce the rapidly increasing burden on the health systems caused by increasing numbers of patients initiating ART.[6,12,14,22–26]

Various observational studies have suggested that DMAD may offer other benefits beyond system and patient cost savings such as improved patient outcomes including lower death rates and LTFU, improved retention, improved health systems' operational efficiency, improved accessibility of services, shorter patient waiting times, patients' social support, and patient and provider satisfaction.[4,19,27–34] Studies further suggest that when a health system adopts client-centered DMAD, the limited facility-based resources are focused on the populations most at risk of adverse outcomes, thus providing better access to improved quality of care and treatment in a more effective way.[16,35] Studies have discussed the benefits of DMAD but have not rigorously investigated potential differences in patient outcomes between these models, with a lack of randomized studies to adequately assess the effects of DMAD within community ART dispensing models. Our study adds important public health evidence to the findings of other studies by demonstrating that community DMAD did not compromise the outcomes of retention and viral suppression for stable HIV patients.

In our study, nonavailability of viral load results was the most common reason for noneligibility for the study (Fig. 1). This was due to prolonged turnaround time of about 3 months. For a successful MMSD program, we recommend strengthening of the laboratory services to reduce viral load turnaround times and improve access to timely viral load results. In addition, as our study found similar outcomes among longer ART dispensing intervals (6 vs. 3 months), we recommend national policy change to allow stable HIV patients, including migrant populations, access to longer ART dispensing intervals (6 months) to minimize barriers to adherence and retention in care (Fig. 2).

The study limitation includes lower recruitment in 3MC than other arms because of limited availability of potentially eligible patients in the clusters randomized to the arm, and thus, study power for comparisons involving 3MC was lower than anticipated. As cluster allocation was not stratified by district, baseline imbalance with respect to district was apparent. Although baseline imbalance was controlled for in adjusted analyses, adjustment may not have fully corrected for baseline differences. Participant outcomes beyond 12 months after enrollment were not assessed as follow-up closed at 12 months. Caution should be taken when generalizing interpretation of our findings to other settings because there are varying definitions of stable patients. The sample of participants aged 18–24 years in our study was small, and thus, overall results may not be generalizable to this age group. In our study and similar to previous studies, retention among youth was low, and DSD models may need to be better tailored to this age group to achieve optimal outcomes.[36] Despite these limitations, this study's robust design is the first such study in Lesotho to explore the outcomes of retention and viral suppression among community-based MMSD models of ART.

CONCLUSIONS

The study shows that it is feasible to implement community-based differentiated models of MMSD of ART at 3- and 6-month intervals outside the standard facility model with high retention, minimum loss to follow-up, and high viral load suppression. Further evaluations should include longer participant follow-up to ascertain longer-term outcomes of community-based MMSD of ART.

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