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Improved Viral Suppression With Streamlined Care in the SEARCH Study

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Background: HIV differentiated service delivery (DSD) models are scaling up in resource-limited settings for stable patients; less is known about DSD outcomes for patients with viremia. We evaluated the effect on viral suppression (VS) of a streamlined care DSD model implemented in the SEARCH randomized universal test and treat trial in rural Uganda and Kenya (NCT:01864603).

Methods: We included HIV-infected adults at baseline (2013) who were country guideline antiretroviral therapy (ART) eligible (prior ART experience or CD4 \leq 350) with \geq 1 HIV clinic visit between 2013 and 2017 in SEARCH communities randomized to intervention (N = 16) or control (N = 16). We assessed the effect of streamlined care in intervention community clinics (patient-centered care, increased appointment spacing, improved clinic access, reminders, and tracking) on VS at 3 years. Analysis was stratified by the

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baseline care status: ART-experienced with viremia, ART-naïve with CD4 \leq 350, or ART-experienced with VS.

Results: Among 6190 ART-eligible persons in care, year 3 VS was 90% in intervention and 87% in control arms (RR 1.03, 95% CI: 1.01 to 1.06). Among ART-experienced persons with baseline viremia, streamlined care was associated with higher VS (67% vs 47%, RR 1.41, 95% CI: 1.05 to 1.91). Among ART-naïve persons, VS was not significantly higher with streamlined care (83% vs 79%, RR 1.05, 95% CI: 0.95 to 1.16). Among ART-experienced persons with baseline VS, nearly all remained virally suppressed in both arms (97% vs 95%, RR 1.01, 95% CI: 1.00 to 1.03).

Conclusions: Streamlined care was associated with higher viral suppression among ART-experienced patients with viremia in this randomized evaluation of ART-eligible patients who were in care after universal HIV testing.

Key Words: HIV, universal test and treat, differentiated service delivery, differentiated care, viral suppression, East Africa

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INTRODUCTION

Of the 37.9 million people living with HIV globally, over half live in eastern and southern Africa.¹ This region has made significant progress toward UNAIDS 90-90-90 targets over the past several years; however, 42% of people living with HIV in the region remain virally unsuppressed as of 2018.¹ To close this gap, interventions are needed across the HIV care cascade to diagnose the 15% who remain unaware of their HIV status, initiate antiretroviral therapy (ART) in the 21% of those diagnosed who are not yet on treatment, and achieve viral suppression (VS) among the 13% on ART but not yet suppressed.¹

Universal test and treat (UTT) is a promising and feasible strategy for achieving HIV epidemic control through population-level HIV testing and rapid initiation of ART, with results from several recent UTT trials exceeding 90-90-90 targets.² However, as we move toward universal ART coverage, health systems must adapt to accommodate greater numbers of patients while simultaneously addressing the needs of patients who do not achieve VS despite routine

ART care. Differentiated service delivery (DSD) models were developed to address this challenge by moving away from a "one size fits all" model to one focused on adapting HIV care to individual patient need.³ To date, DSD models have predominantly focused on deintensifying HIV care for stable, virally suppressed patients to reduce burden on the health system and decrease barriers to long-term retention in care for these individuals.^{4–6} DSD interventions to specifically address the needs of individuals with ongoing viremia despite ART have been less successful.^{3,4}

Although poor adherence is the most common reason for an unsuppressed viral load among patients on ART, a recent trial of an adherence counseling intervention was unsuccessful in improving VS in this population.⁷ Switch to second line therapy among patients with viral failure when adherence interventions are unsuccessful is also important for preventing morbidity and mortality, although delays in appropriate switch are common.^{8–10} Better DSD interventions are needed for viremic patients to most appropriately target services to improve population-level VS. Integrated DSD models are also needed that reduce common barriers to care for all patients and provide tailored services to viremic and virally suppressed patients alike.

In the SEARCH study, a cluster randomized UTT trial, all communities received comprehensive baseline HIV testing; intervention communities further received enhanced linkage to care and "streamlined care" interventions.¹¹ Streamlined care is a DSD model designed to reduce structural barriers, improve patient-provider relationships, and increase patient and provider HIV-related knowledge and skills, with the goal of improving care engagement and VS for all patients.¹² In this analysis, we sought to understand the effect of streamlined care on VS among HIV-infected persons who were ART eligible by country guidelines at study start in both intervention and control SEARCH trial communities. We evaluated the effect of streamlined care among those who were already on ART with or without VS and those who newly linked to care after universal HIV testing in the SEARCH trial.

METHODS

Study Setting

This analysis uses data from the SEARCH study (NCT:01864603), a community cluster randomized controlled trial in rural Kenya and Uganda conducted from 2013 to 2017 that evaluated a UTT strategy for reducing HIV incidence and improving community health outcomes.¹¹ SEARCH conducted baseline HIV testing in 16 intervention and 16 control communities through community health fairs, with health fair nonattendees receiving home visits during which HIV testing was offered. Individuals identified as HIV infected in both intervention and control received baseline CD4 and viral load testing, were introduced to a clinic staff member in person or by phone, were scheduled for an appointment at the local HIV clinic within 1 week or within 2 days if pregnant or with CD4 <200/µL, and were given a 1-time transportation to facilitate linkage to care. Intervention

participants were additionally given a phone number (staffed 24 h/d) to call with questions.¹³ Intervention participants who missed their initial clinic appointment received a phone call, or a home visit if the phone call was unsuccessful, to reschedule their appointment.¹⁴ SEARCH clinical staff were present at the primary government-run HIV clinics within both intervention and control communities.

ART Eligibility

In both Kenya and Uganda at study baseline (2013), persons were eligible for ART initiation if they met any of the following conditions: (1) were diagnosed with a WHO stage 3 or 4 condition, (2) CD4 count was \leq 350/µL, or (3) CD4 was >350, and the patient had active tuberculosis, hepatitis B virus co-infection, HIV-associated nephropathy, or pregnancy.^{15,16} ART eligibility expanded to include individuals with CD4 \leq 500 in all communities by 2014.^{17,18}

Study Population

For this analysis, we included adolescents and adults (age \geq 15 years) in all of the 32 SEARCH communities who were: (1) HIV infected at study baseline, (2) had at least 1 postbaseline HIV care visit at a SEARCH-supported health facility, and (3) were ART eligible based on either previous ART experience or CD4 count of \leq 350 at study baseline. Analyses were conducted in both the overall study population and in subgroups of patients defined by the baseline care status: ART experienced with baseline viremia, ART-naïve with CD4 \leq 350, or ART experienced with baseline VS. For purposes of this analysis, "ART experience" is defined as a baseline patient report or medical record indication of any previous ART, and "ART-naïve" is defined as both baseline patient report that they had not previously been on ART and no indication of previous ART in the medical record. Patients with a suppressed HIV viral load at baseline were considered ART experienced. The goal of this analysis was to isolate the effect of streamlined care from other interventions in SEARCH by restricting the study population to ARTeligible patients who linked to care and to understand the effects of streamlined care on different groups of treatment experienced and treatment naïve patients.

Streamlined Care Intervention (Differentiated Service Delivery Model)

Details of the SEARCH streamlined care model that was implemented in intervention communities have been published previously.¹² The primary objectives of streamlined care were to: (1) reduce structural barriers to care, (2) improve relationships between patients and the clinic, and (3) enhance patient and clinician knowledge of HIV and ART.

Streamlined care sought to address structural barriers, including long wait times, fixed clinic hours, lack of efficient appointment reminder and tracing mechanisms, and transportation cost and inconvenience associated with accessing care. A nurse-driven triage system was implemented to efficiently tailor clinic visits to what patients needed, with

the goal of reducing wait times. Scheduled visit intervals and ART pick-up were lengthened to every 3 months for stable patients to decrease wait times through reduced patient volume and increase convenience associated with less frequent clinic visits. Streamlined care also introduced integrated multidisease care for hypertension and diabetes, to reduce opportunity cost associated with accessing nonintegrated care for these comorbidities. Streamlined care included appointment reminders and phone access for health-related questions or appointment rescheduling. Patients unable to attend clinic during normal operating hours were accommodated with off-hours clinic access. Finally, for patients who missed a clinic visit, re-engagement efforts of increasing intensity were offered, including an initial phone call followed by physical tracing and facilitated transportation to return to care.

Streamlined care facilitated improved relationships with patients through provider and staff training on providing friendly care, including didactic lectures and role-playing exercises. Relationships with patients were also facilitated through improved communication with the clinic by appointment reminders, phone access to clinic, flexible clinic hours, and enhanced patient tracking after missed appointments.

Finally, streamlined care aimed to improve patient and clinician knowledge of HIV and ART through improved viral load counseling. HIV viral load was measured 6 months after ART initiation, then annually thereafter. Case-based training was conducted with providers to enhance provider knowledge and to improve providers' ability to communicate viral load results to patients. Phone access to clinic was also designed to answer patient questions that arose between clinic visits, further improving patient knowledge about HIV and ART.

Standard of Care

In control communities, standard HIV care was provided according to contemporary country ART guidelines. Recommended monitoring frequency included clinical evaluation on a monthly basis for the first 6 months after ART initiation, followed by return visits for ART refill and clinical evaluation every 1–2 months thereafter. Optional HIV viral load testing was conducted every 12 months or when viral failure was suspected.

Outcomes

Our primary outcome was VS (<500 copies/mL) 3 years after study baseline, among those with a measured HIV viral load. Extensive tracing efforts were made in both intervention and control communities to ascertain the vital status and measure HIV viral loads in all SEARCH participants at year 3. We conducted sensitivity analysis with a combined failure outcome of death or year 3 viral load \geq 500 copies/mL.

We also evaluated 2 measures of care engagement: time in care and missed visits by 90 days. To calculate these measures, we recorded all clinic visits for ART pick up and scheduled return dates. The follow-up time began at the patient's initial postbaseline visit and concluded at study end, transfer to another clinic, relocation out of the study area, or death. Patients were considered out of care during the period between a missed appointment and their return; they were considered in care otherwise. We then calculated the proportion of follow-up time that patients were in care ("time in care")¹⁹ and the occurrence of a missed visit without return to care for \geq 90 days.

We also report second-line ART switch among patients who were on first line therapy and viremic at study baseline. First-line therapy was defined as ART with a non-nucleoside reverse transcriptase inhibitor (NNRTI) and 2 nucleoside reverse transcriptase inhibitors (NRTIs). Second-line ART included a boosted protease inhibitor (PI, eg, lopinavir/ ritonavir or atazanavir/ritonavir).

Analysis

We describe baseline demographic characteristics among participants meeting inclusion criteria for this analysis in both intervention and control. We also describe implementation of streamlined care visit interval spacing by reporting the scheduled visit interval, defined as the time between a visit and the patient's scheduled return date.

We compared VS in intervention and control communities using a 2-staged approach, accounting for clustering and the matched-pair design.²⁰ We first calculated the percentage of participants in each community with a suppressed viral load. Next, we compared percent VS between intervention and control communities using community-level targeted maximum likelihood estimation.²¹

Secondary endpoints were assessed using a similar 2staged approach. We estimated the proportion of total "time in care" for each study participant and then calculated the mean "time in care" for each community. For each community, we used Kaplan–Meier to estimate the cumulative incidence of missed visits by \geq 90 days with censoring at transfer to another facility, permanent move out of the community, or death; point estimates were reported at 30 months of follow-up. Finally, we estimated the community-level proportion of participants with baseline ART experience and viremia who switched to second-line ART.

In an additional exploratory analysis, we compared year 3 VS between intervention and control communities, stratified by switch to second-line ART among participants with baseline ART-experience and viremia; these analyses were conducted with an individual-level targeted maximum likelihood estimation accounting for clustering by community.

RESULTS

Study Population

Baseline comprehensive HIV testing identified 7951 HIV-infected adults in intervention communities and 6981 HIV-infected adults in control communities (Fig. 1). Among those identified as HIV-infected on baseline testing, 5166 (65%) intervention participants and 4037 (58%) control participants linked to HIV care at a study-supported clinic within their community. Overall, 87% of intervention

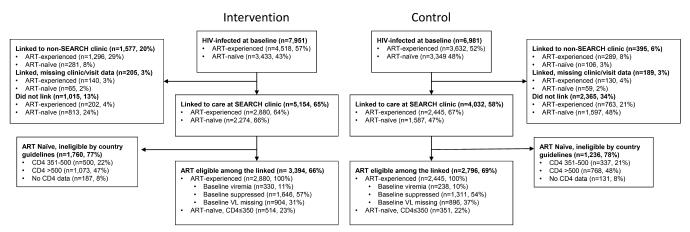


FIGURE 1. Study flow diagram.

participants and 66% of control participants had any record of linking to care after baseline HIV-testing, including those who linked to care outside the study area and were thus not included in this analysis. Among those linked to care at a SEARCH-supported clinic, 6190 were baseline ART-eligible according to country guidelines and included in this analysis: 3394 in intervention communities (85% treatment-experienced and 15% treatment-naïve with CD4 \leq 350) and 2796 in control communities (87% treatment-experienced and 13% treatment-naïve with CD4 \leq 350).

There were no significant differences between intervention and control community members who were HIV+ at baseline, ART-eligible, and linked to care (Table 1). The median age (IQR) was 37 years (30–45), and 34% were men. There was a slightly longer median time between initial community health campaign and the first or next clinic visit for intervention participants than control (51 vs 42 days). A lower proportion of intervention participants worked in "highrisk" informal occupations than control (10% vs 19%), and a slightly greater proportion of intervention participants were youth aged 15–24 (10% vs 8%).

Scheduled visit intervals were longer in the streamlined care arm than the control arm across all baseline care status groups and lengthened in the streamlined care arm over the duration of the study (Table 2).

Viral Suppression

In the overall study population for this analysis, year 3 VS was slightly higher in the streamlined care arm than control (90% vs 87%, respectively; relative risk (RR) 1.03, 95% confidence interval (CI) 1.01 to 1.06). Effects on VS were similar among men (87% vs 85%, RR 1.05, 95% CI: 0.99 to 1.05) and women (91% vs 88%, RR 1.04, 1.01 to 1.07). Year 3 viral load was measured in 82% of participants who were alive at the end of the study, with similar measurement in intervention and control (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B544).

In stratified analysis by the baseline care status (Table 3, see Table 2, Supplemental Digital Content, http://links.

lww.com/QAI/B544), individuals who were ARTexperienced with baseline viremia had substantially higher year 3 VS in the streamlined care arm compared with standard care (67% vs 47%, RR 1.41, 95% CI: 1.05 to 1.91), with similar effects for both men and women. Among ART-naïve persons with CD4 \leq 350, year 3 VS was similar in streamlined care and control (83% vs 79%, RR 1.05, 95% CI: 0.95 to 1.16). Among ART-experienced persons with baseline VS, both arms maintained high levels of VS at year 3 (97% vs 95%, RR 1.01, 95% CI: 1.00 to 1.03).

Sensitivity analyses using a composite failure outcome of viremia or death by year 3 yielded similar findings for the overall study population and each baseline care group (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B544). Additional sensitivity analysis among the ART-naïve group to include those with baseline CD4 count \leq 500 showed slightly higher year 3 VS in streamlined care compared with control (86% vs 80%, RR 1.07, 95% CI: 1.00 to 1.16; see Table 4 Supplemental Digital Content, http://links.lww.com/QAI/B544).

Care Engagement

Streamlined care was associated with more time in care and less frequent 90-day missed visits across all baseline care status groups (Table 3). Among ART-experienced patients with baseline viremia, "time in care" was higher in the streamlined care arm (RR 1.11, 95% CI: 1.02 to 1.19), corresponding to an average increase in 4 weeks per year of additional time adherent to appointment schedules. Among ART-experienced patients with baseline viremia, streamlined care was also associated with a 25% reduction in missed visits by \geq 90 days (RR 0.75, 95% CI: 0.58 to 0.98).

Second-Line ART Switch

Among ART-experienced patients with baseline viremia, 93% were on first-line, NNRTI-based ART and 5% were on second-line, PI-based ART at baseline. Among those on first-line ART at baseline, 17% of intervention participants and 10% of control participants switched to second-line therapy by year 3 (RR 1.64, 95% CI: 0.81 to 3.32). Among

	Intervention $(n = 3394)$		Control (n = 2796)	
	n or Median	% or IQR	n or Median	% or IQR
Region, n (%)				
Eastern Uganda	422	12%	302	11%
Kenya	2308	68%	1938	69%
Western Uganda	664	20%	556	20%
Male sex, n (%)	1130	33%	948	34%
Age category, n (%)				
15–24 yrs	327	10%	211	8%
25–49 yrs	2411	71%	2067	74%
\geq 50 yrs	656	19%	518	19%
Marital status, n (%)				
Single	198	6%	134	5%
Married	2267	68%	1875	67%
Widowed/Divorced/Separated	879	26%	773	28%
Occupation*, n (%)				
Formal sector	165	5%	113	4%
High-risk informal	327	10%	523	19%
Low-risk informal	2505	74%	1801	64%
No job or disabled	173	5%	193	7%
Other or missing	224	7%	166	6%
Baseline pregnancy, n (%, of women)	114	5%	99	5%
Time since ART initiation (yr), median (IQR)	3.2	2.6-3.7	3.5	3.1-3.8
Time from baseline community health fair to next clinic visit (d), median (IQR)†	51	24–93	42	20–103
Baseline CD4, n (%)				
<200	372	11%	304	11%
200–350	828	24%	606	22%
351-500	586	17%	499	18%
>500	1262	37%	1120	40%
Missing	346	10%	267	10%
Comorbid conditions, n (%)				
Hypertension	278	9%	222	9%
Diabetes	40	1%	39	2%
Baseline care status, n (%)				
ART-experienced, baseline viremia‡	330	10%	238	9%
ART-experienced, baseline suppression§	1646	48%	1311	47%
ART-experienced, baseline VL missing	904	27%	896	32%
ART-naïve, $CD4 \le 350$	514	15%	351	13%

*A formal sector occupation was defined as a teacher, student, government worker, military worker, health worker, or factory worker. A high-risk informal sector occupation was defined as a farmer, shopkeeper, market vendor, hotel worker, household worker, construction worker, or miner.

†A community health fair was conducted at baseline in all communities with nonattendees tracked in the community for baseline HIV testing. The time calculated from date of community health fair to the first/next clinic visit.

 $Viral load \ge 500 \text{ copies/mL}.$

§Viral load < 500 copies/mL.

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those who remained on first-line ART, year 3 VS was 65% in intervention and 46% in control (RR 1.43, 95% CI: 1.09 to 1.87). Among those who switched to second-line ART, year 3 VS was 78% in intervention and 58% in control (RR 1.35, 95% CI: 0.83 to 2.21) (Table 4).

DISCUSSION

Our study demonstrates that a multicomponent "streamlined care" intervention can achieve higher VS for ART- experienced patients with viremia than standard care while improving care efficiency for all patients. In particular, ARTexperienced individuals with baseline viremia had a 20% absolute increase in VS after 3 years in streamlined care compared with standard care. Individuals who were virally suppressed at study baseline maintained similar, very high levels of VS in both intervention and control communities, but with less frequent clinic visits in streamlined care. Streamlined care also achieved similar levels of VS as standard of care among individuals newly starting ART,

	ART-Experienced With Baseline Viremia*		ART-Naive With Baseline CD4 ≤350		ART-Experienced With Baseline VS†	
	Intervention (N = 330)	$\begin{array}{l} \text{Control} \\ (\text{N} = 238) \end{array}$	Intervention (N = 514)	Control (N = 351)	Intervention (N = 1646)	Control (N = 1312)
Visit interval, median days (IQR)						
Year 1	50 (37-62)	39 (32–50)	42 (31–50)	36 (28-46)	58 (47-70)	47 (36–56)
Year 2	63 (43-79)	43 (31–54)	70 (51-84)	50 (36-58)	75 (63-84)	51 (40-58)
Year 3	65 (42-83)	46 (33-57)	70 (55-84)	51 (38–58)	78 (64-84)	56 (43-62)

despite enhanced linkage efforts in intervention communities that may have brought more patients to care who had preexisting barriers to care engagement.¹⁴ Sensitivity analyses further suggest that VS may have been higher among ARTnaïve individuals in the streamlined care group when including those with baseline CD4<500, the threshold for initiating ART in control communities within 0–11 months after study baseline after country-level ART guideline changes.^{17,18}

Our findings suggest that streamlined care likely improved VS among ART-experienced patients with baseline viremia primarily through reduction in barriers to care engagement and improved adherence support. We observed both increased time in care and reduction in 90-day gaps in care, suggesting that streamlined care improved care engagement in this population. Although streamlined care was associated with a small, nonsignificant increase in switch to second-line ART, improvements in VS were similar regardless of whether or not patients switched to second-line ART. This finding suggests that the quality of care delivered may have been the most important factor in achieving VS, even among patients who did switch to second-line therapy.

Streamlined care was designed to improve care access and engagement through 3 primary mechanisms, namely (1) reduction of structural barriers to care, (2) improvements in relationships between patients and the clinic, and (3) enhanced patient and clinician knowledge of HIV and ART.¹² First, structural barriers such as transportation costs, wait times, and opportunity costs can reduce retention in care and VS.²² We have previously demonstrated that streamlined care reduced the average total time for a clinic visit from 155 minutes to 73 minutes, an "undifferentiated" intervention that reduces barriers for all patients.²³ Here, we show that streamlined care also reduced the frequency that patients needed to return to the clinic for medication pickup and provider visits, including for patients with ART experience and baseline viremia, further reducing structural barriers to care.

Second, poor relationships with clinicians have been shown to reduce retention in care and discourage patients from returning to care after a lapse.^{24,25} Furthermore, surveys of patient preference suggest that patients would be willing to travel further, wait longer, and pick up medications more frequently to receive care from a "nice" provider as opposed to a "rude" provider, suggesting that provider attitude is highly prioritized by patients.²⁶ Streamlined care aimed to directly improve patient–staff relationships through trainings to practice and encourage providers and staff to provide

	ART Experienced with Baseline Viremia*		ART Naive With Baseline CD4 ≤350			ART Experienced With Baseline VS†			
	Intervention (N = 330)	Control (N = 238)	RR (95% CI)	Intervention (N = 514)	Control (N = 351)	RR (95% CI)	Intervention (N = 1646)	Control (N = 1312)	RR (95% CI)
VS at year 3 [†]	67%	47%	1.41 (1.05 to 1.91)	83%	79%	1.05 (0.95 to 1.16)	97%	95%	1.01 (1.00 to 1.03)
Men	66%	55%	1.21 (0.89 to 1.65)	78%	72%	1.09 (0.91 to 1.30)	96%	95%	1.01 (0.98 to 1.03)
Women	66%	44%	1.52 (1.01 to 2.28)	88%	86%	1.03 (0.93 to 1.14)	97%	96%	1.01 (1.00 to 1.03)
Time in care (TIC)	81%	73%	1.11 (1.02 to 1.19)	74%	67%	1.10 (1.03 to 1.17)	86%	81%	1.07 (1.01 to 1.13)
Men	81%	71%	1.15 (1.01 to 1.30)	72%	66%	1.10 (0.98 to 1.22)	86%	83%	1.04 (1.00 to 1.09)
Women	81%	75%	1.08 (0.98 to 1.20)	75%	68%	1.10 (1.01 to 1.19)	86%	80%	1.08 (1.01 to 1.15)
Proportion with missed visit by ≥90 days‡	30%	40%	0.75 (0.58 to 0.98)	36%	46%	0.79 (0.65 to 0.96)	21%	29%	0.75 (0.46 to 1.20)
Men	34%	39%	0.87 (0.57 to 1.33)	37%	49%	0.75 (0.55 to 1.03)	23%	24%	0.96 (0.66 to 1.38)
Women	28%	40%	0.69 (0.47 to 1.03)	35%	43%	0.81 (0.62 to 1.07)	21%	30%	0.68 (0.40 to 1.16)

⁺Viral load ≥500 copies/mL. †Viral load <500 copies/mL.

‡Assessed at 30 months post-baseline

	ART Experienced With Baseline viremia*				
	Intervention (N = 330)	Control (N = 238)	RR (95% CI)		
ART regimen at study baseline					
First line (NNRTI- based)	310 (94%)	219 (92%)			
Second line (PI-based)	18 (5%)	12 (5%)			
Unknown	2 (1%)	7 (3%)			
Switch to second-line ART [†]	53 (17%)	23 (10%)	1.61 (0.81 to 3.32)		
Year 3 viral suppression by the switch status					
Remain on first-line ART	65%	45%	1.43 (1.09 to 1.87)		
Switch to second-line ART†	78%	58%	1.35 (0.83 to 2.21)		

TABLE 4. Switch to Second-Line ART Among ART

 Experienced Patients With Baseline Viremia

*Viral load \geq 500 copies/mL.

†Switch to second-line PI-based ART among those on first-line NNRTI-based ART at baseline.

friendly, patient-centered services, and through improved patient access to clinicians. We have previously reported the importance of friendly services for promoting retention in care among men within SEARCH.²⁷

Finally, improved patient and provider knowledge, motivation, and engagement are important for achieving optimal HIV outcomes and may also improve patient–provider interactions.^{22,28} In turn, greater patient activation may reduce stigma and encourage patients to become advocates for others in their community.²⁹ Streamlined care aimed to improve knowledge and reduce stigma by providing enhanced viral load counseling to help patients understand the meaning of suppressed and unsuppressed results. Integration of HIV and noncommunicable disease care may have also contributed to stigma reduction—both for patients with and without a noncommunicable disease.³⁰ Essentially, by broadening the services offered, clinics became not simply "HIV clinics," but rather "chronic care clinics."

Cost is a key consideration for adoption of any care intervention. Estimated costs of streamlined care are \$291 per-patient per-year, similar to or lower than that of PEPFAR-supported care elsewhere in sub-Saharan Africa.³¹ Some costs, such as direct cost for ART or viral load testing, may decrease over time; however, other costs may increase somewhat with scale, including costs associated with broader training and mentoring for clinicians to provide patient-centered care.

Previous evaluations of the SEARCH streamlined care intervention have shown high levels of retention in care and VS, although these evaluations lacked a comparison group.^{12,32} Here, we leverage the cluster randomized design of SEARCH to isolate the effect of streamlined care on care engagement and VS by comparing individuals who were ART-eligible in both intervention and control at baseline and who linked to care at a SEARCH-supported clinic. Although the randomized design strengthens our findings, our study may not be generalizable to all patients because we excluded those who linked to care outside their community of residence in order to ensure similar ascertainment of linkage to care between arms. Further, for those who were linked, our engagement in care measures do not account for care that may have been accessed at another clinic during an observed lapse in care. Nonetheless, these measures were ascertained in the same way in both intervention and control communities, and thus, differences in visit attendance and gaps in care are likely to reflect true differences in clinic access and engagement between study arms.

CONCLUSIONS

In conclusion, we found that a multicomponent streamlined care intervention increased care efficiency and maintained high levels of VS for virally suppressed and ARTnaïve patients, while simultaneously improving VS and care engagement for ART-experienced patients with viremia. The intervention components included in streamlined care are likely to have relevance for all HIV care systems in resourcelimited settings, including those that have scaled up other DSD models for stable patients. Beyond improving outcomes for HIV care, streamlined care also holds promise as a platform for low-barrier multidisease care that may further reduce HIV-associated stigma and barriers to addressing comorbid health conditions.

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REFERENCES

- 1. Global AIDS Update 2019: Communities at the Centre: UNAIDS; 2019: 316.
- 2. Havlir D, Lockman S, Ayles H, et al. What do the Universal Test and Treat trials tell us about the path to HIV epidemic control? *J Int AIDS Soc.* 2020;23:e25455.
- Grimsrud A, Bygrave H, Doherty M, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. J Int AIDS Soc. 2016;19:21484.
- Roy M, Bolton Moore C, Sikazwe I, et al. A review of differentiated service delivery for HIV treatment: effectiveness, mechanisms, targeting, and scale. *Curr HIV/AIDS Rep.* 2019;16:324–334.
- Fox MP, Pascoe S, Huber AN, et al. Adherence clubs and decentralized medication delivery to support patient retention and sustained viral suppression in care: results from a cluster-randomized evaluation of differentiated ART delivery models in South Africa. *PLoS Med.* 2019;16: e1002874.
- Jobarteh K, Shiraishi RW, Malimane I, et al. Community ART support groups in Mozambique: the potential of patients as partners in care. *PLoS One.* 2016;11:e0166444.
- Fox MP, Pascoe SJS, Huber AN, et al. Effectiveness of interventions for unstable patients on antiretroviral therapy in South Africa: results of a cluster-randomised evaluation. *Trop Med Int Health.* 2018;23: 1314–1325.

- Bell Gorrod H, Court R, Schomaker M, et al. Increased mortality with delayed and missed switch to second-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr. 2020;84:107–113.
- 9. Petersen ML, Tran L, Geng EH, et al. Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. *AIDS*. 2014;28:2097–2107.
- Hermans LE, Carmona S, Nijhuis M, et al. Virological suppression and clinical management in response to viremia in South African HIV treatment program: a multicenter cohort study. *PLoS Med.* 2020;17: e1003037.
- Havlir DV, Balzer LB, Charlebois ED, et al. HIV testing and treatment with the use of a community health approach in rural Africa. N Engl J Med. 2019;381:219–229.
- 12. Kwarisiima D, Kamya MR, Owaraganise A, et al. High rates of viral suppression in adults and children with high CD4+ counts using a streamlined ART delivery model in the SEARCH trial in rural Uganda and Kenya. *J Int AIDS Soc.* 2017;20(suppl 4):21673.
- 13. Ayieko J, Petersen ML, van Rie A, et al. Effect of a patient-centered phone call by a clinical officer at time of HIV testing on linkage to care in rural Kenya. *Open Forum Infect Dis.* 2018;5:ofy126.
- 14. Ayieko J, Petersen ML, Charlebois ED, et al. A patient-centered multicomponent strategy for accelerated linkage to care following community-wide HIV testing in rural Uganda and Kenya. J Acquir Immune Defic Syndr. 2019;80:414–422.
- 15. The Integrated National Guidelines on Antiretroviral Therapy, Prevention of Mother to Child Transmission of HIV and Infant & Young Child Feeding. Republic of Uganda: Ministry of Health; 2011.
- Guidelines for Antiretroviral Therapy in Kenya. Kenya: National AIDS/ STI Control Program (NASCOP); 2011.
- 17. Addendum to the National Antiretroviral Treatment Guidelines. Republic of Uganda: Ministry of Health; 2013.
- Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Invection. Kenya: National AIDS/STI Control Program (NASCOP); 2014.
- 19. Hickey MD, Salmen CR, Omollo D, et al. Implementation and operational research: pulling the network together: quasiexperimental trial of a patient-defined support network intervention for promoting engagement in HIV care and medication adherence on mfangano Island, Kenya. J Acquir Immune Defic Syndr. 2015;69:e127–e134.
- Balzer LB, Havlir DV, Schwab J, et al. Statistical Analysis Plan for SEARCH Phase I: Health Outcomes Among Adults. 2018. Ar-

Xiv180803231 Stat. Available at: http://arxiv.org/abs/1808.03231. Accessed September 1, 2020.

- Balzer LB, van der Laan MJ, Petersen ML, SEARCH Collaboration. Adaptive pre-specification in randomized trials with and without pairmatching. *Stat Med.* 2016;35:4528–4545.
- Roy M, Czaicki N, Holmes C, et al. Understanding sustained retention in HIV/AIDS care and treatment: a synthetic review. *Curr HIV/AIDS Rep.* 2016;13:177–185.
- 23. Shade SB, Chang W, Kahn JG, et al. SEARCH streamlined HIV care is associated with shorter wait times before and during patient visits in Ugandan and Kenyan HIV clinics. 21st International AIDS Conference. 2016; Durban, South Africa, Abstract FRAEO203.
- Ware NC, Wyatt MA, Geng EH, et al. Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: a qualitative study. *PLoS Med.* 2013;10:e1001369.
- Camlin CS, Neilands TB, Odeny TA, et al. Patient-reported factors associated with reengagement among HIV-infected patients disengaged from care in East Africa. *AIDS*. 2016;30:495–502.
- Zanolini A, Sikombe K, Sikazwe I, et al. Understanding preferences for HIV care and treatment in Zambia: evidence from a discrete choice experiment among patients who have been lost to follow-up. *PLoS Med.* 2018;15:e1002636.
- Brown LB, Getahun M, Ayieko J, et al. Factors predictive of successful retention in care among HIV-infected men in a universal test-and-treat setting in Uganda and Kenya: a mixed methods analysis. *PLoS One*. 2019;14:e0210126.
- Maclachlan EW, Shepard-Perry MG, Ingo P, et al. Evaluating the effectiveness of patient education and empowerment to improve patientprovider interactions in antiretroviral therapy clinics in Namibia. *AIDS Care*. 2016;28:620–627.
- 29. Camlin CS, Charlebois ED, Geng E, et al. Redemption of the "spoiled identity:" the role of HIV-positive individuals in HIV care cascade interventions. *J Int AIDS Soc.* 2017;20:e25023.
- Kwarisiima D, Atukunda M, Owaraganise A, et al. Hypertension control in integrated HIV and chronic disease clinics in Uganda in the SEARCH study. *BMC Public Health.* 2019;19:511.
- Shade SB, Osmand T, Luo A, et al. Costs of streamlined HIV care delivery in rural Ugandan and Kenyan clinics in the SEARCH Studys. *AIDS*. 2018;32:2179–2188.
- Brown LB, Havlir DV, Ayieko J, et al. High levels of retention in care with streamlined care and universal test and treat in East Africa. *AIDS*. 2016;30:2855–2864.