Link4Health
A combination strategy for linkage and retention in Swaziland

The Link4Health Study: Evaluation of a Combination Strategy for Linkage and Retention in Swaziland

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PEPFAR

SIYINQABA

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Cover photo:

A Link4Health community interviewer en route to the home of a study participant to conduct a follow-up interview.

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Acronyms

ART	Antiretroviral therapy
BCPP	Basic care and prevention package
CIS	Combination intervention strategy
DBS	Dried blood spot
FI	Financial incentive
HCT	HIV counseling and testing
HCW	Health care worker
HIV	Human immunodeficiency virus
IQR	Interquartile range
POC	Point-of-care
RR	Relative risk
SMS	Short Message Service
SOC	Standard of care
WHO	World Health Organization

Acknowledgements

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Executive Summary

Gaps in continuum for HIV care contribute to poor health outcomes and increase the risk of HIV transmission. A combination of evidence-based interventions targeting multiple steps in the continuum is needed to achieve the desired impact of HIV treatment. The Link4Health study was conducted by ICAP at Columbia University in collaboration with the Ministry of Health in Swaziland.

The Link4Health Study, a cluster-randomized controlled trial, evaluated the effectiveness of a combination intervention strategy (CIS) versus the standard of care (SOC) on the primary outcome of linkage to care within one month *plus* retention in care at 12 months after HIV-positive testing. Ten clusters of HIV clinics in Swaziland were randomized 1:1 to the CIS versus the SOC. The CIS included:

- Point-of-care (POC) CD4+ cell count testing at time of HIV-positive test
- Accelerated antiretroviral therapy (ART) initiation for treatment-eligible individuals
- Mobile phone appointment reminders
- Health educational packages
- Non-cash financial incentives

A total of 2,197 adults 18 years of age or older who newly tested HIV-positive were enrolled from August 2013–November 2014, with 1,096 randomly assigned to CIS arm and 1,101 to the SOC arm. All participants were followed for 12 months. Median age was 31 years (interquartile range [IQR] 26–39) and 59 percent were women. An intention-to-treat analysis including 2,197 participants showed that 64 percent (705/1096) of participants at CIS sites achieved the primary outcome versus 43 percent (477/1,101) at SOC sites (absolute difference 21%, adjusted relative risk [RR] 1.52, 95% CI 1.19–1.96, p = 0.002). Participants in CIS versus SOC sites also had improved secondary outcomes, including a higher proportion assessed for ART-eligibility (100% versus 84%, p = 0.004), shorter time from HIV testing to ART initiation among eligible patients (seven versus 14 days, p<0.0001), and higher 12-month retention (66% versus 45%, RR 1.48, 95% CI 1.18–1.86, p = 0.002). No difference was noted in viral load suppression among those on ART for at least 6 months (RR 0.97, 95% CI: 0.88–1.07, p = 0.55).

A combination of behavioral, structural, and biomedical interventions aimed at multiple steps in the HIV care continuum was associated with a 50 percent increase in the combined outcome of prompt linkage to care and 12-month retention. This strategy offers promise for enhanced treatment outcomes and decreased HIV transmission.

Introduction

Background

The Kingdom of Swaziland has one of the world's most severe HIV epidemics, and HIV-related illness is the leading cause of death in the country. In 2011, the year the Link4Health study began, Swaziland had a population of 1.1 million people, an estimated HIV prevalence of 32 percent among adults aged 18–49 years, and an estimated annual HIV incidence of 2.4 percent.[2] At that time, a cumulative 93,295 adults had been initiated on antiretroviral therapy (ART)[3], but the rates of linkage to care and retention at 12 months after ART initiation were suboptimal.[4] Swaziland has since made substantial advances in responding to the HIV epidemic. By 2016, the cumulative number of adults on ART had increased to 171,266, with 85 percent of the adults who were aware that they were living with HIV self-reporting ART use.[5] While annual HIV incidence has declined to 1.4 percent, HIV prevalence in the adult population remains high at 31 percent.[5] Therefore, ensuring sustainable linkage to care and retention on ART remains a priority in this population.

Swaziland's Ministry of Health is committed to improving retention along the HIV care continuum to decrease the impact of HIV on morbidity and mortality, and to decrease the alarming HIV incidence rate in the country. The Link4Health study aimed to use implementation science to assess the effectiveness of a combination strategy comprising five evidence-based interventions designed to improve linkage to and retention in care among adults newly tested HIV-positive in Swaziland.

Study Objectives

The **primary objective** of the study was to evaluate effectiveness of the Combination Intervention Strategy (CIS,) compared to the Standard of Care (SOC), on the combined outcome of linkage to HIV care within one month and retention in care at 12 months among adults after testing HIV-positive.

The **secondary objectives** of the study were to identify socio-demographic, clinical, and facility determinants of key study outcomes, and to evaluate the effectiveness of the CIS compared to the SOC in relation to:

a) Linkage to HIV care within one month of HIV-positive test
b) Retention in care at 12 months after HIV-positive test
c) Median time to linkage
d) Time from HIV testing to ART eligibility assessment
e) Time from HIV testing to ART eligibility
f) Time from ART eligibility to ART initiation
g) Consistency of engagement in HIV care

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[2] Bicego GT, Nkambule R, Peterson I, et al. Recent patterns in population-based HIV prevalence in Swaziland. *PloS One.* 2013; 8(10):e77101; Swaziland HIV Incidence Measurement Survey (SHIMS) Final Findings Report. Mbabane Swaziland: Swaziland Ministry of Health, ICAP at Columbia University, PEPFAR, SCHARP; 2012.
[3] Annual HIV Programs Report 2013. Mbabane, Swaziland: Swaziland Ministry of Health; 2013.
[4] MacKellar DA, Williams D, Storer N, et al. Enrollment in HIV care two years after HIV diagnosis in the Kingdom of Swaziland: an evaluation of a national program of new linkage procedures. *PloS One.* 2016; 11(2):e0150086;
[5] Nkambule R, Nuwagaba-Biribonwoha H, Mnisi Z, et al. Substantial Progress in Confronting the HIV Epidemic in Swaziland: First Evidence of National Impact. 9th International AIDS Society (IAS) Conference on HIV Science, July 23-26, Paris, France. Abstract# MOAX0204LB, Late Breaker Oral Presentation.

h) Disease progression (new World Health Organization [WHO] stage III/IV event, hospitalization, CD4+ count, death)
i) Cost-effectiveness (disease progression and infections prevented), intervention feasibility, and participant acceptability

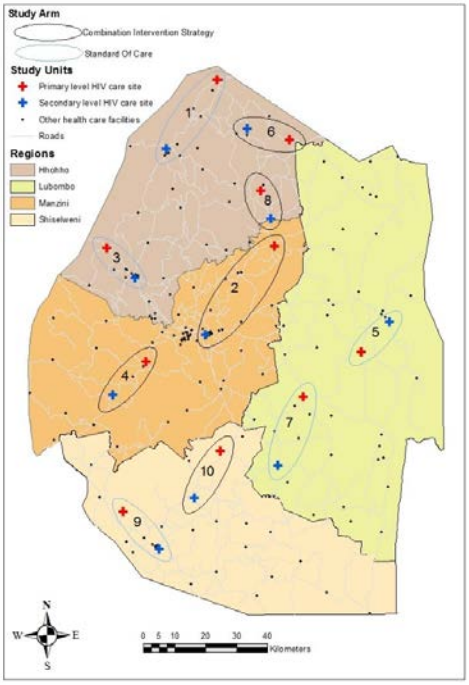
Study Design

Link4Health was a cluster site-randomized trial that built on Swaziland's hub-and-spoke model for HIV care and treatment services.[6] The unit of randomization was a network of secondary HIV clinics (mother clinics) paired with affiliated primary-level HIV clinics (baby clinics), which are referred to as study units. Study units were randomized to the CIS or SOC arm.

Study Unit

The study unit reflects the decentralization of HIV care from larger facilities to primary-level facilities in Swaziland. Ten of the 11 existing secondary HIV care clinics were selected based on affiliation with at least one primary-level HIV care clinic (Figure 1). Affiliated primary-level HIV care clinics were chosen based on HIV program size (volume of patients testing HIV-positive), patient volume (based on 18-month historic data, with special attention given to the most recent six months), and Ministry of Health concurrence.

Figure 1: Map of Link4Health Study Units



Randomization

Study units were randomized to the CIS or SOC arm using matched-pair randomization balanced by the following factors: facility location (rural, urban), expected number of adults enrolled in HIV care at each facility per month, and implementing partner supporting the facility. The study facilities, matching criteria, and enrollment targets are summarized in Table 1.

Study Population

The study population included adults who tested HIV-positive at the HIV counseling and testing sites at facilities participating in the study. Eligibility criteria for the study are outlined below:

Inclusion Criteria:

- Age ≥18 years
- Testing HIV-positive at an HIV counseling and testing site within a study unit
- Willing to be referred to an HIV care clinic associated with the study unit
- Willing to provide locator information

[6] Auld, AF, Kamiru H, Baughman AL, et al. Implementation and operational research: evaluation of Swaziland's Hub-and-Spoke Model for decentralizing access to antiretroviral therapy services. *JAIDS*. 2015; 69(1):e1-e12.

- Willing to adhere to study procedures, including a baseline interview, home-based interviews at one and 12 months after study enrollment, home-based CD4+ count assessment 12 months after enrollment, and abstraction of data from their medical records
- Able to provide informed consent

Exclusion Criteria:

- Planning on leaving the community where they currently reside in the next 12 months, for a period greater than six months
- Enrolled in HIV care in the past six months at any HIV care clinic
- Initiated ART (for any duration) in the past six months at any HIV care clinic
- Currently on ART
- Does not speak or understand English or siSwati
- Reports being pregnant at time of study enrollment

Table 1: Study Unit Matched Pairs

Matched Pair	Study Unit	Study Facility	Study Arm	Implementing Partner	Location	Enrollment Target
A	1	Pigg's Peak Government Hospital	SOC	ICAP	Urban	579
		Horo Clinic				
	2	Raleigh Fitkin Memorial Hospital	CIS			
		Mliba Clinic				
B	3	Mbabane Government Hospital	SOC	ICAP	Urban	579
		Motshane Clinic				
	4	Mankayane Hospital	CIS			
		Luyengo Clinic				
C	5	Good Shepherd Hospital	SOC	ICAP	Rural	376
		Mpolenjeni Clinic				
	6	Mkhuzweni Health Center	CIS	ICAP	Rural	
		Mangweni Clinic				
D	7	Sithobela Rural Health Centre	SOC	ICAP	Rural	376
		Siphofaneni Clinic				
	8	Dvokolwako Health Centre	CIS	ICAP	Rural	
		Bhalekane Clinic				
E	9	Nhlangano Health Centre	SOC	Médecins Sans Frontières	Urban	145
		Mashobeni Clinic				
	10	Hlatikhulu Hospital	CIS	Médecins Sans Frontières	Urban	145
		Kamfishane Clinic				

Study Outcomes

The **primary study outcome** was the combined outcome of linkage to HIV care within one month after testing HIV-positive *plus* retention in care 12 months after testing.

Secondary outcomes included:

1. Linkage to care within one month of HIV testing (at any clinic within the assigned study unit, or at any other clinic)
2. Retention in care 12 months after HIV testing, independent of linkage at one month (at any clinic within the assigned study unit, or at any other clinic)
3. Median time to linkage to care
4. Time from linkage to ART eligibility assessment
5. Time from HIV testing to ART eligibility
6. Time from ART eligibility to ART initiation
7. Proportion of participants who consistently engage in care, defined as attending >75 percent of their scheduled appointments
8. Proportion of participants with new WHO stage III/IV event or hospitalization
9. Median CD4+ cell count 12 months after HIV diagnosis (by ART status)
10. Mortality rate 12 months after HIV diagnosis
11. Cost-effectiveness
12. Proportion of participants randomized to study units receiving the CIS who report receipt of each intervention
13. Proportion of participants randomized to study units receiving the CIS who report that interventions were highly acceptable

Methods

Study Interventions

The study had two arms: the CIS and SOC arms. At study units assigned to the SOC arm of the study, participants were managed as per country guidelines (see Table 2). Participants at study units assigned to the CIS study arm received five evidence-based interventions in addition to the SOC interventions: 1) POC CD4+ count testing on the same day as HIV diagnosis; 2) accelerated ART initiation for eligible patients with CD4+ count <350 cells/milliliter, the prevailing ART eligibility threshold during study implementation; 3) mobile phone appointment reminders; 4) care and prevention bags; and 5) non-cash financial incentives for linkage and retention. Table 2 summarizes the interventions included in the study, the type of barrier addressed, and the targeted step in the HIV care continuum.

Trainings and Advisory Group Meetings

All study staff received training on study procedures, good clinical practice, and refresher topics. Additionally, Study Advisory Group meetings were held approximately quarterly to assist in the monitoring of existing and future study implementation, and will continue to support the translation of study findings into relevant policy recommendations for the country. The Advisory Group consisted of representatives from the Ministry of Health, Swaziland National AIDS Programme (SNAP), PEPFAR/CDC in Swaziland, and various HIV testing, care, and treatment implementing partners.

Recruitment and Eligibility Screening

Recruitment and enrollment occurred at HIV counseling and testing sites within each participating study unit. During the enrollment period, health care workers informed all individuals aged 18 years or older who tested HIV-positive about the study and referred those interested in participation to study staff, who determined eligibility, provided further information regarding the study, and obtained written informed consent from those wishing to participate. Participants were enrolled in order of consenting until the sample size per study unit was reached.

Table 2: Summary of Study Interventions

Intervention	Standard of Care (SOC)	Combination Intervention Strategy (CIS)	Type of Intervention	Step Targeted in HIV Care Continuum
Point of Care CD4+ Count Testing	• POC CD4 assays available in some primary care clinics and some secondary health centers/hospitals for patients enrolled in HIV care, but only used once a patient has linked to care • CD4 (Cyflow, FACS Caliber) after linkage to HIV care in the clinic or lab • Turn-around time approximately two weeks	• POC CD4 assays at the HIV testing site at time of HIV testing • Turnaround time immediate	Structural and biomedical	Linkage, ART eligibility assessment, and ART initiation
Accelerated ART Initiation	• ART initiation per national guidelines for patients with CD4 $\leq$350 cells/uL or WHO stage III/VI • Requires three counseling sessions and receipt of baseline lab tests • Initiation two weeks to one month from testing	• Accelerated ART initiation for patients with POC CD4 $\leq$350 cells/uL within one week from testing • Two counseling sessions (one at time of HIV testing and other at first HIV clinic visit) and collection of blood for other baseline lab tests, but initiation prior to return of results for patients who do not meet criteria for waiting for receipt of lab results prior to ART initiation	Structural and biomedical	ART initiation and retention
Cellular Appointment Reminders	• Telephone call within seven days of missed appointment for ART patients only	• Short message service (SMS) (or voice if illiterate) appointment reminders one day prior to each scheduled appointment • SMS (or voice if illiterate) reminder within seven days after a missed appointment	Behavioral	Linkage and retention
Basic Care and Prevention Package (BCPP)	• Cotrimoxazole prescribed for all patients once enrolled in HIV care • Condoms available	• Basic care and prevention package provided approximately every three months for HIV clinic attendance. Package includes: condoms, soap, cotrimoxazole, pill box, and pictorial education about use of materials and HIV, such as family testing tools and information	Biomedical and behavioral	Retention
Non-Cash Financial Incentive	• None	• Non-cash financial incentive (mobile airtime) provided for linkage within one month of testing and retention at six and 12 months	Structural	Linkage and retention

Data Collection

All participants completed a baseline interview at time of study enrollment, which included information on socio-demographics, HIV history, barriers to care, travel time to clinic, depression, social and family support, and HIV-related knowledge. Follow-up interviews were conducted at home at one and 12 months after enrollment to collect information on changes in socio-demographic characteristics, utilization of HIV services (including whether linked to care), visit completion, and acceptability of the study interventions. A CD4+ cell count and dried blood spot (DBS) sample for viral load was obtained at 12 months. Additional clinical and laboratory data were extracted from paper-based patient medical charts.

Facility assessment surveys were conducted at the beginning of the study and every six months to document any changes in clinical services that occurred during the study period that may influence study outcomes.

Costs of delivering the SOC and CIS were estimated based on the cost of outpatient HIV care, the cost of hospitalization, and the cost of delivering each intervention component.

Data Management

Study staff collected study information on paper forms, and data were entered into a database that included all of the study variables for participants, indexed by unique participant ID number. All study data were double-data entered in an encrypted database on password-protected computers. Study data were accessible only to study staff directly involved in the Link4Health study (data manager, study coordinators, study director, principal investigators, and co-investigators).

Quality Assurance Activities

Numerous quality assurance activities were conducted throughout the study period, including:

- Monitoring of study enrollment on a weekly basis
- Data quality checks of all completed questionnaires before data entry
- Monitoring the rate of completion of baseline, one-, and 12-month questionnaires
- Reviewing completed study process forms (e.g., tracking logs, phone call logs)
- Ensuring POC CD4+ machines were appropriately calibrated
- Reviewing the number of participants who were eligible to receive each intervention versus the number who actually received it
- Reconciliation of the number of consent forms and the number of participants
- Reconciliation of signatures on consent forms and other forms signed by participants
- Reconciliation of data entry between first and second entry
- Filing field incident reports for any unexpected occurrences
- Reconciling study exits from the study exit form with the Field Incident Database
- Review of patient medical charts with the regional mentoring team to ensure completion of documentation
- Conducting logic and data validation checks with entered data before analysis

Data Analysis

An intent-to-treat analysis compared the relative risk (RR) of achieving the primary outcome between study arms, with each arm having five clusters. Within study unit clustering was accounted for using random-intercept multilevel models. For dichotomous outcomes, log-poisson models with robust standard error were used. For continuous outcomes, random-intercept linear regression models were used. Assessment of potential confounding despite cluster randomization was performed by constructing multivariable random-intercept regression models, including covariates found statistically different between treatment arms at an alpha of 0.01. Additionally, a per-protocol analysis was conducted comparing the RR of achieving the primary outcome among participants who received the full CIS for the duration of study participation. Sensitivity analysis assessed any changes to the intent-to-treat analysis after including self-reported linkage and retention obtained from follow-up surveys. In post-hoc analyses, assessment of the RR for achieving the primary outcome by key subgroups was done using interaction contrast ratios.

For costing analyses, the study team incorporated the observed effects and costs of the Link4Health strategy into a computer simulation of the HIV epidemic in Swaziland, comparing a scenario in which the strategy was scaled up to a counterfactual scenario with no implementation of the Link4Health strategy. The simulation combined a deterministic compartmental model of HIV transmission with a stochastic microsimulation of HIV progression, and was calibrated to Swaziland's epidemiological data with the goal of replicating trends in HIV prevalence, incidence, and deaths from 1997 to 2015. It incorporated downstream health costs potentially saved, and infections potentially prevented, due to improved linkage to treatment and, because it is the mediating effect that leads to lower viral load, treatment adherence. The team assessed the incremental cost-effectiveness ratio from a programmatic and societal perspective using $2015, a time horizon of 20 years, and a discount rate of 3 percent.

Ethical Considerations

This study was approved by the institutional review boards of Columbia University, the U.S. Centers for Disease Control and Prevention, and the Swaziland Scientific and Ethics Committee.

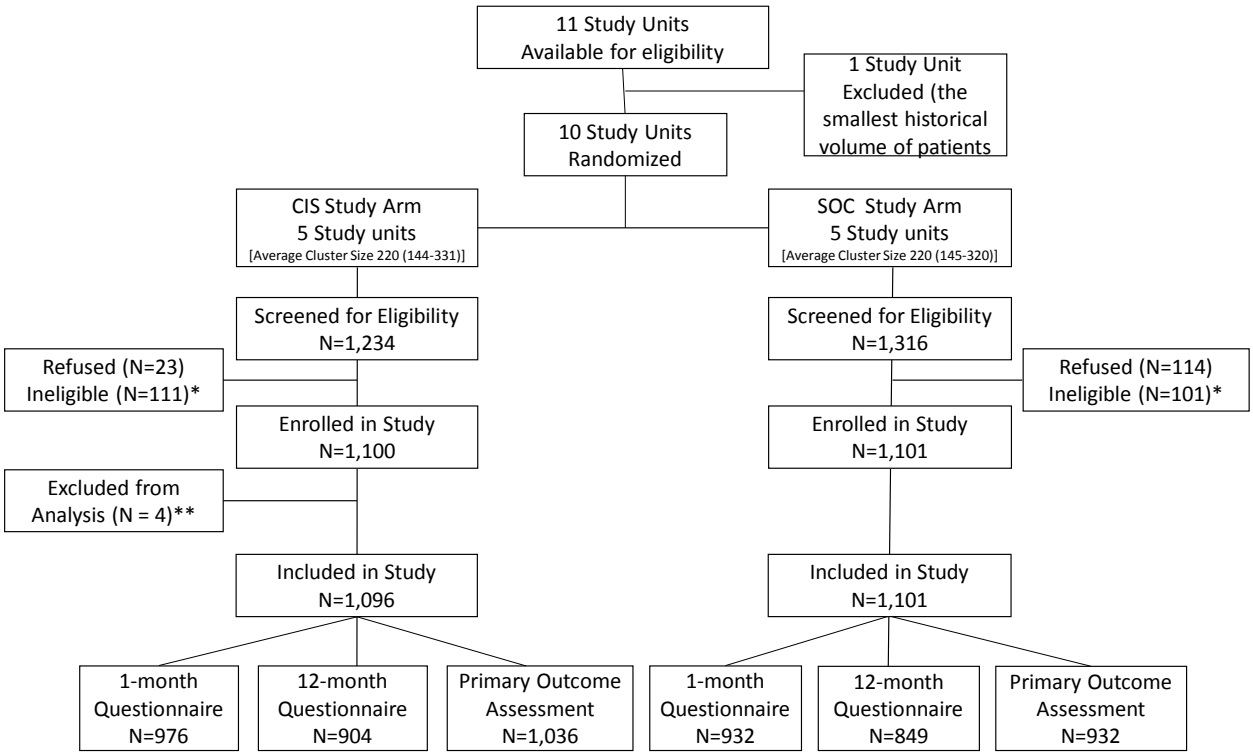
Trial Registration

The study is registered at Clinicaltrials.gov under NCT01904994.

Results

Of the 10 study units included in the study, six were located in urban areas and four in rural areas. At study units randomized to the CIS study arm, a total of 1,234 individuals were screened for eligibility, with 1,100 (89%) enrolled in the study from August 2013 to November 2014 (Figure 2). At study units assigned to the SOC study arm, a total of 1,316 were screened, with 1,101 (84%) enrolled. Study refusal differed by study arm, with 23 refusals (1.9%) in the CIS arm and 114 refusals (8.7%) in the SOC arm ($p<0.0001$). Reasons for ineligibility are shown in Figure 2; the number did not vary by study arm. Figure 2 also shows the proportion of participants who completed month one and month 12 questionnaires by study arm.

Figure 2: Flow Diagram of Study Enrollment and Follow-up



*Reasons ineligible: CIS arm: < 18 yrs (N = 4), not HIV-positive (N = 3), refuse referral to SU (N = 26), refuse to provide contact information (N = 4), plans to move in next year (N = 22), recent history of HIV care or ART (N = 12), other (N = 40) . SOC arm: < 18 yrs (N = 2), not HIV-positive (N = 1), refuse referral to SU (N = 28), plans to move in next year (N = 21), recent history of HIV care or ART (N = 13), other (N = 34)

**Reasons for exclusion: enrollment technical issues

Characteristics of participants are shown in Table 3. Among 2,197 participants included in the analysis, 1,294 (59%) were female and the median age was 31 years (IQR 26–39), with 445 (20%) of the participants aged 18–24 years. Forty-five percent reported no education or only primary schooling, and approximately half were unemployed. Median individual weekly income was $9 (IQR $0–37). Eighty-four percent reported living in their current residence for more than one year, with 16 percent reporting travel away from home for over one month during the past year. Median travel time from residence to the HIV clinic was 30 minutes (IQR 20–50). The majority (80%) were diagnosed with HIV through a voluntary counseling and testing site, with

Table 3: Participant Characteristics at Time of HIV Testing

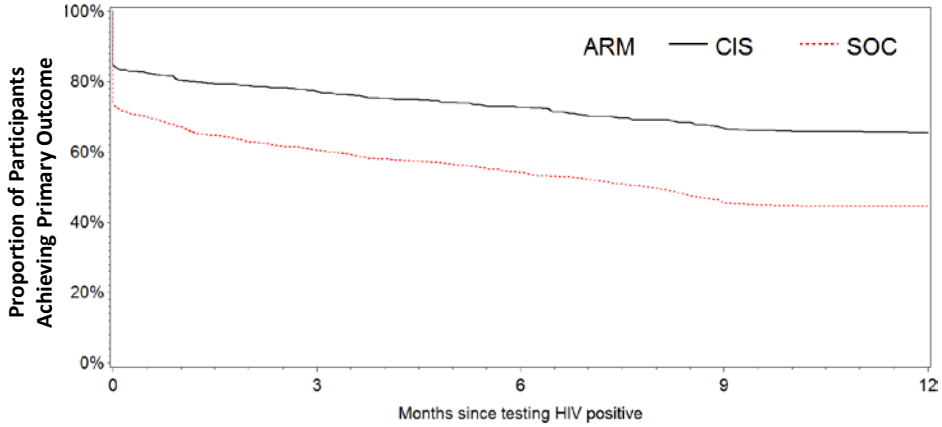
Characteristics		CIS Arm		SOC Arm		Total	
		N	%	N	%	N	%
	Number Enrolled	1,096		1,101		2,197	
Female		657	60%	637	58%	1,294	59%
Age (years)	Median (IQR)	32 (26–40)		30 (25–39)		31 (26–39)	
	18-24	210	19%	235	21%	445	20%
	25-39	612	56%	604	55%	1,216	55%
	40-49	158	14%	166	15%	324	15%
	>50	116	11%	95	9%	211	10%
	Missing/refused	-	-	1	0%	1	0%
Education	None/primary	478	44%	519	47%	997	45%
	Secondary or higher	617	56%	581	53%	1,198	55%
	Missing/refused	1	0%	1	0%	2	0%
Weekly Income	Median (IQR), USD	$9 ($0–$37)		$14 ($0–$37)		$9 ($0–$37)	
Unemployed		624	57%	531	48%	1,155	53%
Married		400	36%	408	37%	808	37%
Number of Living Children	0	206	19%	207	19%	413	19%
	1 to 3	645	59%	680	62%	1,325	60%
	>3	243	22%	214	19%	457	21%
	Missing/refused	2	0%	0	0%	2	0%
Lives Alone		116	11%	160	15%	276	13%
Away from Home >1 Month in Past Year		179	16%	170	15%	349	16%
Time at Current Residence	1 year or less	164	15%	192	17%	356	16%
	Greater than 1 year	930	85%	906	82%	1,836	84%
	Missing/refused	2	0%	3	0%	5	0%
Travel Time to Clinic	Median (IQR) time minutes	30 (20–45)		30 (20–60)		30 (20–50)	
	<30 minutes	690	63%	584	53%	1,274	58%
	31-60 minutes	330	30%	323	29%	653	30%
	>60 minutes	62	6%	191	17%	253	11%
	Missing/refused	14	1%	3	0%	17	1%
Currently on TB Treatment		8	1%	14	1%	22	1%
HIV Testing Site	Voluntary testing and counseling	937	85%	820	74%	1757	80%
	Provider-initiated counseling and testing	159	15%	280	25%	439	20%
	Missing/refused	0	0%	1	0%	1	0%
First HIV Test		642	59%	539	49%	1181	54%
First Positive HIV Test		967	88%	978	89%	1945	89%
Household Member with HIV		427	39%	348	32%	775	35%
Alcohol Consumption Last 7 Days	Every day	16	1%	18	2%	34	2%
	Some days	235	21%	234	21%	469	21%
	Never	845	77%	849	77%	1694	77%

the remaining having received HIV testing through provider-initiated testing and counseling at outpatient clinics within the study units. Over half (54%) of participants reported that this was their first HIV test, while 84 percent indicated that it was their first HIV-positive test.

Primary Outcome

In intent-to-treat analysis, 705 (64%) participants at sites randomized to the CIS arm and 477 (43%) participants at sites randomized to the SOC arm achieved the primary study outcome of linkage to HIV care within one month of HIV testing plus retention in HIV care at 12 months after HIV testing, for a RR of 1.48 (95% CI 1.37–1.61, p<0.0001). Accounting for clustering within study units, the RR was 1.52 (95% CI 1.19–1.96, p = 0.002) (Figure 3 and Table 4). Adjusting for covariates listed in Table 1 did not appreciably change the results.

Figure 3: Proportion of Patients Who Achieved the Primary Outcome of Linkage to HIV Care Within One Month of HIV Testing Plus Retention in HIV Care at 12 months After HIV Testing, Compared Among Participants in the CIS Versus SOC Study Arms



	0 months	3 months	6 months	9 months	12 months	TOTAL
			CIS			
Number	1096 (100%)	929 (85%)	848 (77%)	800 (73%)	738 (67%)	1096
Linked/Retained	929 (85%)	848 (91%)	800 (94%)	738 (92%)	720 (98%)	720 (66%)
Death	2 (0%)	19 (2%)	6 (1%)	2 (0%)	6 (1%)	35 (3%)
Transfer	1 (0%)	6 (1%)	6 (1%)	4 (1%)	6 (1%)	23 (2%)
Lost to follow-up	164 (15%)	56 (6%)	36 (4%)	56 (7%)	6 (1%)	318 (29%)
			SOC			
Number	1101 (100%)	815 (74%)	670 (61%)	603 (55%)	513 (47%)	1101
Linked/Retained	815 (74%)	670 (82%)	603 (90%)	513 (85%)	498 (97%)	498 (45%)
Death	8(1%)	18 (2%)	7 (1%)	5 (1%)	5 (1%)	43 (4%)
Transfer	6 (1%)	8 (1%)	7 (1%)	0 (0%)	5 (1%)	26 (2%)
Lost to follow-up	272 (25%)	119 (15%)	53 (8%)	85 (14%)	5 (1%)	534 (49%)

Table 4: Primary and Secondary Outcomes between the CIS and SOC Study Arm

		CIS Arm (N = 1,096)		SOC Arm (N = 1,101)		Relative Risk		
		N	%	N	%	Relative Risk	95% CI	P-value
Primary Outcome	Intention to treat	705	64%	477	43%	1.48	(1.37–1.61)	<0.0001
	Intention to treat, accounting for clustering[1]	705	64%	477	43%	1.52	(1.19–1.96)	0.002
	Intention to treat, accounting for clustering and differences in covariates	705	64%	477	43%	1.50	(1.12–1.99)	0.009
	Per protocol[1,2]	672	69%	447	43%	1.68	(1.32–2.15)	0.0003
	Sensitivity analysis[1,3]	761	69%	557	51%	1.41	(1.13–1.74)	0.004
Secondary Outcomes								
Linkage	Linked same day of HIV test[1]	887	81%	760	69%	1.22	(0.89–1.68)	0.20
	Linked within one month[1]	1,010	92%	918	83%	1.12	(0.96–1.30)	0.14
	Linked ever[1]	1,032	94%	957	87%	1.08	(0.97–1.21)	0.13
	Mean (std) time from HIV testing to linkage	2.5 days (19.5)		7.5 days (46.6)				0.189
ART Eligibility	Assessed for ART eligibility[1]	1,096	100%	920	84%	1.20	(1.07–1.34)	0.004
	Became ART Eligible[1]	833	76%	721	65%	1.18	(1.01–1.37)	0.038
	Mean (std) time from HIV testing to ART eligibility assessment[4]	0 (0)		6.3 (35.5)				<0.0001
ART Initiation*	Initiated ART (within one year)[1]	682	62%	597	54%	1.18	(0.97–1.43)	0.092
	Initiated ART (ever)[1]	710	65%	635	58%	1.16	(0.96–1.40)	0.12
	Median (IQR) time from testing HIV-positive to ART Initiation among ART eligible, days[5]	7.0 (3.0–21.0)		14.0 (7.0–31.0)				<0.0001
Retention Regardless of ART Status	Six months after HIV testing[1]	785	72%	580	53%	1.39	(1.14–1.70)	0.002
	12 months after HIV testing[1]	720	66%	498	45%	1.48	(1.18–1.86)	0.002
Deaths within 12 Months of HIV Testing	Total deaths[1]	35	3%	43	4%	0.80	(0.46–1.35)	0.41
	Death before ART initiation[1]	10	1%	23	2%	0.44	(0.19–1.01)	0.05
	Death after ART initiation[1]	25	2%	20	2%	1.18	(0.57–2.47)	0.63
Transfers within 12 Months of HIV Testing	Total transfers[1]	23	2%	26	2%	0.88	(0.44–1.77)	0.71
	Transfers before ART initiation[1]	7	1%	19	2%	0.37	(0.16–0.85)	0.02
	Transfers after ART initiation[1]	16	1%	7	1%	2.10	(0.72–6.18)	0.16
Lost to Follow-up within 12 Months of HIV Testing	Total lost to follow-up[1]	318	29%	534	49%	0.56	(0.40–0.79)	0.002
	Lost to follow-up before ART initiation[1]	240	22%	357	32%	0.60	(0.40–0.89)	0.014
	Lost to follow-up after ART initiation[1]	78	7%	177	16%	0.51	(0.31–0.85)	0.013
Viral Load Suppression	On ART for > 6 months	419	88%	406	90	0.97	(0.88-1.07)	0.55

Table 4 Notes:

1. Accounting for within-study unit clustering using random intercept log-Poisson regression models with robust standard error.
2. The per-protocol analysis compares all patients in the SOC to those in the CIS self-reporting receipt of all interventions: POC PIMA CD4, accelerated ART initiation (if eligible), BCPP, SMS, and financial incentives. A total of 937 of the 1,100 in the CIS arm were included. Patients were excluded for missing the following: PIMA (2), ART counseling session #1 (24), ART counseling session #2 (14), BCPP1 (7), financial incentive #1 (86), BCPP2 (12), financial incentive #2 (8), financial incentive #3 (4), BCPP3 (4), BCPP4 (2).
3. The sensitivity analysis considers participants linked to HIV care or retained in HIV care if they are recorded as linked and retained in their medical records or if they self-reported linkage or retention in the one- and/or 12-month study questionnaire.
4. All participants in the SOC arm were assessed for ART eligibility at time of testing HIV-positive. 920/1,101 (84%) of SOC participants were assessed at enrollment into HIV care or clinical follow-up.
5. Time To ART initiation measured from date of HIV-positive test to ART initiation among those becoming ART eligible. P-values are Wilcoxon tests of differences between medians.

* In the CIS arm, 85 percent of those ART-eligible initiated ART. In the SOC arm, 88 percent of those eligible initiated ART.

The RR in the per-protocol analysis accounting for clustering for achieving the primary outcome was 1.68 (95% CI 1.32–2.15, p = 0.003) (Table 4). The RR in the sensitivity analysis accounting for clustering, which included participants who self-reported linkage and retention in the one- and 12-month surveys at a clinic other than one with their assigned study unit, was 1.41 (95% CI 1.13–1.74, p = 0.004) (Table 4).

The CIS intervention was delivered according to study protocol to 937 (85%) of the 1,096 participants enrolled in study units assigned to the CIS. Reasons for not receiving all of the CIS intervention components included missing POC CD4+ cell count testing (<1% CIS participants), missing an ART counseling session per accelerated ART procedures (3%), missing receipt of one health care bag (2%), and missing receipt of one financial incentive (9%). There was heterogeneity in the primary outcome across the five pairs of matched study units. The proportion of participants who achieved the primary outcome in study units randomized to the CIS ranged from 49 to 82 percent, while this ranged from 22 to 57 percent in the study units randomized to the SOC.

Secondary Outcomes

A similar proportion of participants linked to care anytime within the study period in both study arms: 1,032 (94%) in the CIS arm compared to 957 (87%) in the SOC arm (RR 1.08, 95% CI 0.97–1.21), with no significant differences in linkage within the same day or one month after testing (see Table 4). The mean time to linkage to care was shorter in the CIS arm versus the SOC study arm, but was not statistically different (2.5 compared to 7.5 days, p = 0.189). However, among those who ever linked to care (1,032 in the CIS and 957 in the SOC), significantly fewer patients (13%) in CIS sites versus SOC sites (18%) did not return for subsequent visits after the first clinic visit (p = 0.008).

Assessment for ART eligibility through either a CD4+ cell count or WHO staging was done for all participants in the CIS arm compared to 84 percent of participants in the SOC arm (RR 1.20, 95% CI 1.07–1.34, p = 0.004). Mean time to ART eligibility assessment was zero days in the CIS study arm compared to 6.3 days in the SOC arm (p <0.0001). Median CD4+ cell count among 1,096 participants in the CIS arm who had POC CD4+ cell count testing done at the time of HIV testing was 311 cells/microliter (IQR 159–443).

Among the 907 (82%) participants in the SOC arm who linked to HIV care and had a CD4+ cell count done, the median CD4+ cell count was 285 cells/microliter (155–444, p = 0.07).

A total of 710 (85% of ART-eligible participants) in the CIS arm, compared to 635 (88% among ART-eligible participants) in the SOC arm, initiated ART within the study follow-up period (RR 1.16, 95% CI 0.96–1.40, p = 0.12) (see Table 4). The median time from HIV testing to ART initiation among eligible patients was seven days (IQR 3.0–21.0) in the CIS arm, compared to 14 days (IQR 7.0–13.0) in the SOC study arm (p<0.0001).

Retention in care at 12 months, regardless of ART status or time of linkage, was significantly greater in participants in the CIS compared to the SOC study arm, with a RR of 1.48 (95% CI 1.18–1.86, p = 0.002). Loss to follow-up during pre-ART care (RR = 0.60, 95% CI: 0.40–0.89, p = 0.014) and after ART initiation (RR = 0.51, 95% CI: 0.31–0.85, p = 0.013) was significantly lower in the CIS versus the SOC.

For participants on ART for at least six months during follow-up, regardless of retention status, viral load data were available for 97 percent (N = 477/493) of participants in CIS arm and 98 percent (N = 451/458) in the SOC arm. Viral suppression among participants was similar by study arm: 88 percent in the CIS and 90 percent in the SOC (RR 0.97, 95% CI 0.88–1.07, p = 0.55).

There were 78 deaths (3.6% of the study population) that occurred during follow-up and this did not differ by study arm (35 deaths [3%] in the CIS study arm versus 43 deaths [4%] in the SOC arm, with a RR of 0.80, 95% CI 0.46–1.35, p = 0.40) (see Table 4). However, there was a trend toward significantly lower mortality among participants prior to ART initiation in the CIS arm (10 deaths) compared to the SOC arm (23 deaths), with a RR of 0.44 (95% CI 0.19–1.01, p = 0.05).

The effect of the CIS, as compared to the SOC, was consistent across all pre-specified subgroups, including by age, sex, income, employment, marital status, travel away from home in the past year, travel time to clinic, past HIV testing history, household members with HIV, and type of clinic (Figure 4).

Acceptability of CIS Interventions

Among the 977 participants (89% of participants in the CIS arm) who received a one-month questionnaire, 314 (32%) reported that POC CD4 testing was the most helpful in terms of encouraging linkage to care, followed by the financial incentive (24%), same-day ART counseling as part of accelerated ART procedures (21%), SMS appointment reminders (12%), and the basic health care bag (9%). At 12 months, among the 905 CIS participants (82%) receiving a 12-month questionnaire, 870 responded to questions about acceptability. Of these, 277 participants (32%) reported that receiving the non-cash financial incentive was the most helpful in terms of encouraging retention in care, followed by SMS text reminders (21%), same-day ART adherence counseling (17%), and POC CD4 testing (16%).

Receipt of Study Interventions

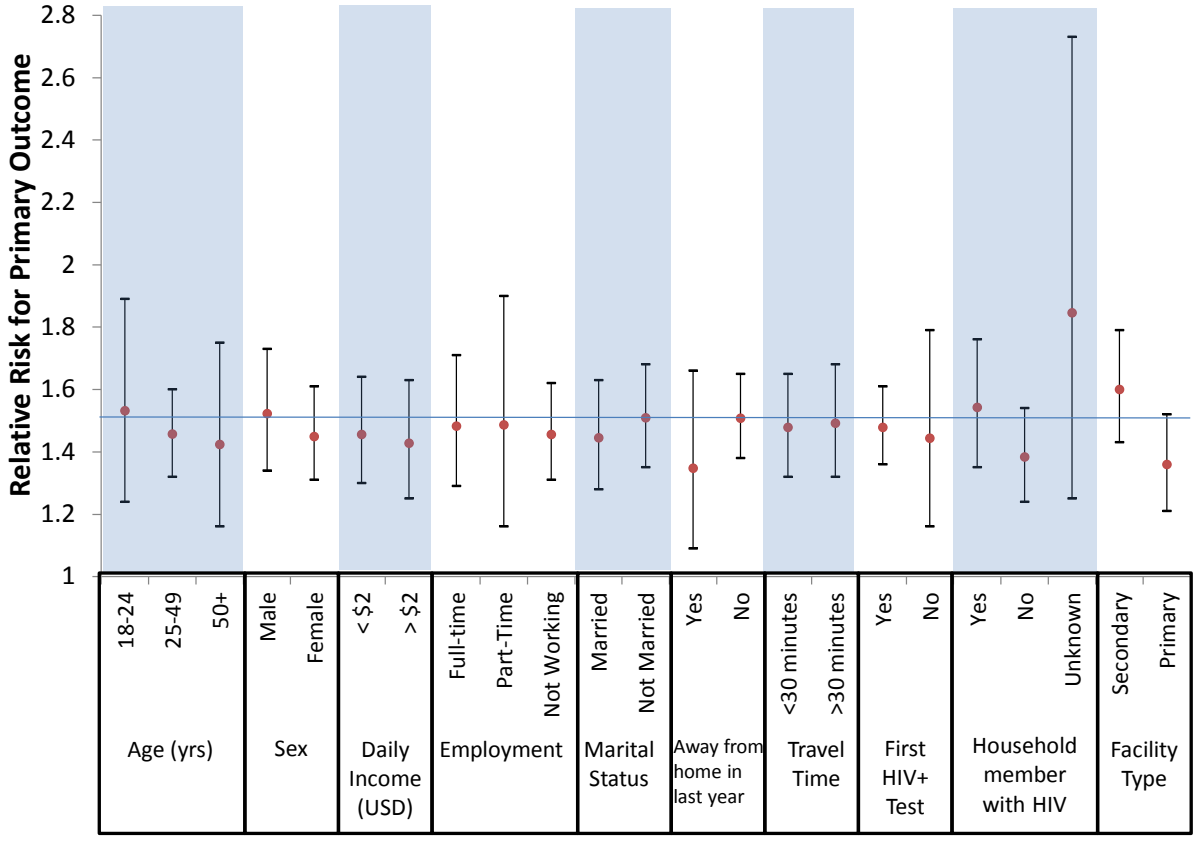
Among the 1,100 participants enrolled at the CIS study facilities, 99.8 percent received POC CD4+ cell count tests. Among those eligible for ART, 98 percent received the first ART counseling session and 99 percent received the second ART counseling session. Overall, more than 90 percent of eligible participants received the BCPP bags and non-cash financial incentives. Ninety-nine percent of eligible participants received the first and second BCPP bags and 100 percent received the third and fourth. Ninety-one percent of eligible

participants received the first financial incentive and 99 and 100 percent received the second and third, respectively.

Cost and Cost-Effectiveness

Based on the model, scale-up of the Link4Health CIS reduced the number of new HIV infections over 20 years by 959 infections (from 12,164 infections to 11,205 infections) and prevented 5,077 deaths (from 50,663 to 45,586 deaths). The CIS resulted in an incremental cost per infection prevented of $922 and an incremental cost per quality-adjusted life year gained of $4,201/quality-adjusted life year. In one-way and multi-way sensitivity analyses, results regarding costs and benefits were highly stable, with the Link4Health CIS remaining cost-effective and improving health outcomes across a range of assumptions.

Figure 4: Subgroup Analysis for the Primary Endpoint



Discussion

In this cluster-randomized study, a novel combination strategy, inclusive of five evidence-based components, was 50 percent more effective than the SOC in enhancing linkage to care plus retention in care among HIV-positive individuals. The robustness of this outcome is supported by the finding of a similar effect in the per-protocol and sensitivity analyses, and by the consistency of the effect noted across the pre-specified subgroups of participants. In addition, the CIS was associated with improvements across multiple steps of the care continuum, with an increased proportion of participants who were assessed for ART eligibility, decreased time to ART eligibility assessment, decreased time to ART initiation, increased retention at 12 months after HIV testing (regardless of time to linkage and ART status), and a trend for decreased mortality among participants prior to ART initiation. However, high rates of viral suppression were similar among ART patients across study arms.

In the Link4Health study, the primary effect of the CIS was noted on retention, rather than on linkage to care. One reason for this finding may be due to the high proportion of participants who linked to care within one month of HIV testing (87% in the SOC arm and 92% in the CIS arm)—thus our sample size was insufficient to show a difference between the arms. The high proportion of linkage was likely influenced by a national campaign to improve linkage and retention that was being implemented in Swaziland during the study period.[7]

The CIS significantly reduced loss to follow-up among participants, regardless of their ART status. Loss to follow-up in both study arms was higher among pre-ART participants as compared to participants who had initiated ART. This is consistent with findings from a large study that included 390,603 HIV-positive adults in Kenya, Mozambique, Rwanda, and Tanzania, where 34.8 percent of all patients who had not initiated ART were lost from care at 12 months, compared to 5.8 percent among patients on ART.[8] The study findings remain relevant even though recent WHO guidelines now recommend offering ART to all HIV-positive patients irrespective of CD4+ cell count or WHO disease stage, as studies have shown that retention in care and on ART remains a challenge in this context.[9] For example, while adoption of Option B+, which entails prompt initiation of ART for all HIV-positive pregnant women, has been associated with an increase in the number on ART, loss to follow-up has remained a challenge. Among 21,939 HIV-infected pregnant women who started ART as per Option B+ in Malawi, 17 percent were lost to follow-up at six months after treatment start, with a five-fold higher loss to follow-up compared to those who initiated ART at a more advanced stage of HIV disease.

Viral suppression was high among participants who were on ART for a minimum of six months (84 and 90% in the CIS and SOC arm, respectively). This confirms the potency of a first-line regimen consisting of tenofovir, lamivudine, and efavirenz or nevirapine, and suggests that participants who had initiated ART were highly adherent to these medications. These findings are consistent with those from the Population-based HIV Impact Assessment (PHIA) surveys conducted in Malawi, Swaziland, Zambia, and Zimbabwe, which

[7] MacKellar DA, Williams D, Steror N, et al. Enrollment in HIV care two years after HIV diagnosis in the Kingdom of Swaziland: an evaluation of a national program of new linkage procedures." *PloS One.* 2016; 11(2):e0150086.
[8] McNairy, ML, Lamb MR, Abrams EJ, et al. Use of a comprehensive HIV care cascade for evaluating HIV program performance: findings from 4 sub-Saharan African countries. *JAIDS.* 1999; 70(2):e44.
[9] Guidelines on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: WHO; 2015.

included nationally representative samples of adults and children and which noted high viral load suppression (HIV RNA <1,000 copies/milliliter) among HIV-positive patients who reported being on ART.[10] The finding of similar proportions of viral suppression among participants by study arm may be due to the fact that suppression was very high in both arms and the sample size was insufficient to detect a difference. The CIS used in the study was not designed with a focus specifically on medication adherence and viral suppression. Lastly, it is also possible that the CIS arm included a higher proportion of participants who struggled with medication adherence, or who would not have otherwise started ART in the absence of the CIS strategy, as compared to participants in the SOC arm.

Mortality was an important outcome in this study and every effort was made to ascertain accurate mortality outcomes. It should be noted, however, that reporting of loss to follow-up and mortality by HIV programs has been a controversial topic. This is due to the fact that when attempts were made to trace individuals reported as lost to follow-up by HIV programs, a substantial proportion of such individuals were found to have either died or transferred care to another health facility.[11] However, such misclassification is unlikely to have occurred in this study, since home tracing was conducted for all study participants to determine their outcomes. While the study was not powered to detect a difference between the study arms in terms of mortality, the CIS appeared to have a meaningful, albeit not statistically significant effect, with as much as 50 percent lower mortality noted among pre-ART patients ($p = 0.05$). This may be due to better retention in care among participants in the intervention arm. Poor retention in care has been demonstrated to be associated with increased mortality—likely due to missed clinic visits that deprive patients of clinical and laboratory assessments for diagnosis of early complications, to determine ART eligibility in a timely manner, and to allow for prompt initiation of ART.[12]

To date, most intervention studies to address gaps in the HIV care continuum have focused on a single step in the continuum, usually ART initiation. The Rapid Initiation of Treatment (RapIT) trial showed that single-visit ART initiation that included POC CD4+ cell count testing was associated with significantly higher ART initiation (97%) compared to the SOC (72%).[13] The START-ART trial was a stepped-wedge, cluster-randomized trial of 20 clinics in Uganda evaluating an intervention aimed at improving ART initiation among eligible patients, which included opinion-leader-led training, POC CD4+ cell count testing, and reduced counseling sessions prior to ART initiation.[14] The intervention was associated with a higher proportion of patients initiating ART (80%) within 14 days after ART eligibility determination, compared to 38 percent in the control group. Finally, the Same Day ART Initiation study in Haiti, which evaluated the effect of same-day ART initiation on the day of HIV diagnosis among asymptomatic HIV-positive adults with CD4+ cell count <500 cells/microliter and WHO Stage I or II disease on retention in care with viral suppression (HIV RNA <50 copies/milliliter) at 12 months after HIV diagnosis, noted that a higher proportion (54%) of patients randomized to the same-day intervention achieved the primary outcome compared to the SOC

[10] The Population HIV Impact Assessment (PHIA) Project. http://www.phia.icap.columbia.edu. Accessed May 31, 2017.
[11] Geng EH, Glidden DV, Bwana MB, et al. Retention in care and connection to care among HIV-infected patients on antiretroviral therapy in Africa: estimation via a sampling-based approach." *PloS One.* 2011;6(7):e21797.
[12] Giordano TP, Gifford AL, White AC Jr, et al. Retention in care: a challenge to survival with HIV infection. *Clinical Infectious Diseases.* 2007;44(11):1493–1499.
[13] Rosen, S, Maskew M, Fox M, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: the RapIT randomized controlled trial. *PLoS Medicine.* 2016;13(5):e1002015.
[14] Amanyire G, Semitala F, Namusobya J, et al. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. *The Lancet HIV* 3.11 (2016): e539-e548.

(42%).[15] Unique to the Link4Health study is the delivery of multiple interventions aimed at multiple steps in the HIV care continuum, packaged as a single strategy. The strategy includes accelerated ART initiation, but also aims to improve downstream steps in the continuum, such as retention in care (regardless of ART status). Thus, implementation of an effective strategy, such as the one assessed in this study, has the potential to achieve prompt ART initiation and better retention in care and on ART, consequently enhancing the potential for individual and society benefits from the "treat all" approach.

The study had several strengths, including the use of a pragmatic approach consistent with implementation science design. Specifically, the study utilized broad eligibility criteria, was conducted within established health facilities, tested feasible interventions that were delivered primarily by available staff (rather than research staff), and assessed the primary outcome largely through routinely available data. In addition, the study included the majority of clinics in Swaziland and involved cluster-randomized design, rather than randomization of individual participants, which allowed for ease of implementation and avoided the disruption of services within clinics. Lastly, the study evaluated a combination strategy of multiple evidence-based interventions that targeted multiple steps in the care continuum and assessed the effect on a combined primary outcome of linkage and retention.

The study also had limitations, including that it involved a limited number of clusters; however, these were all the available clusters in the country. The design focused on evaluating a package of interventions as one strategy and thus it did not allow for the evaluation of the effectiveness of individual components of the combination approach.

[15] Koenig S, Dorvil N, Severe P, Riviere C, et al. Same-day HIV testing and antiretroviral therapy initiation results in higher rates of treatment initiation and retention in care. Abstract presented at AIDS 2016; Durban, South Africa.

Conclusions

The Link4Health study demonstrated that a combination strategy of evidence-based interventions aimed at gaps in various steps of the HIV care continuum was highly effective in enhancing linkage of HIV-positive individuals to care, as well as their retention in care and on ART. The study also showed that, once participants initiated ART, viral load suppression was remarkably high irrespective of study arm. Thus, interventions such as our combination strategy to support ART initiation through linkage, rapid initiation, and ongoing retention remain relevant even in the context of recommendation for initiation of ART among all persons living with HIV. Qualitative analyses are ongoing in order to offer insight into provider and participant perceptions for decision-makers considering adoption of this strategy.

The study findings offer an effective strategy that can advance the quality of HIV programs in Swaziland and that can be adapted to other, similar contexts. The scale-up of the Link4Health strategy would substantially reduce HIV-related deaths and prevent new HIV infections in Swaziland. With a favorable value over a 10-year timeframe or longer, the Link4Health strategy is a cost-effective strategy for confronting the HIV epidemic in Swaziland and other low-income countries.

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