Siyaphambili protocol: An evaluation of randomized, nurse-led adaptive HIV treatment interventions for cisgender female sex workers living with HIV in Durban, South Africa

Carly A. Comins1 | Sheree R. Schwartz2 | Deliwe R. Phetlhu2 | Vijayanand Guddera3 | Katherine Young4 | Jason E. Farley5 | Nora West1 | Lauren Parmley1 | Elvin Geng6 | Chris Beyrer1 | David Dowdy1 | Sharmistha Mishra7,8 | Harry Hausler5 | Stefan Baral1

1 Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland
2 University of Western Cape, Cape Town, South Africa
3 TB HIV Care, Durban, South Africa
4 TB HIV Care, Cape Town, South Africa
5 Johns Hopkins University, School of Nursing, The REACH Initiative, Baltimore, Maryland
6 University of California, San Francisco, California
7 Li Ka Shing Knowledge Institute, St. Michael’s Hospital, University of Toronto, Toronto, Canada
8 Division of Infectious Diseases, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence
Carly A. Comins, Department of Epidemiology, Johns Hopkins School of Public Health, 615 N Wolfe St E7133, Baltimore MD, 21205.
Email: ccomins1@jhu.edu

Funding information
National Institute of Nursing Research of the National Institutes of Health, Grant number: R01NR016650; Center for AIDS Research, Johns Hopkins University through the National Institutes of Health, Grant number: P30AI094189

ABSTRACT
In South Africa, 60% of female sex workers are estimated to be living with human immunodeficiency virus (HIV). Many of these women face structural and individual-level barriers to initiating, accessing, and adhering to antiretroviral therapy (ART). While data are limited, it is estimated that less than 40% of sex workers living with HIV achieve viral suppression, leading to suboptimal clinical outcomes and sustained risks of onward sexual and vertical HIV transmission. Siyaphambili, a NINR/NIH-funded study, focuses on studying optimal implementation strategies for meeting HIV treatment needs among cisgender female sex workers living with HIV who are not virally suppressed. Here, we present the study protocol of this sequential multiple assignment randomized trial. In total, 800 viremic female sex workers will be enrolled into an 18-month adaptive implementation study to 1) compare the effectiveness and durability of a nurse-led decentralized ART treatment program versus an individualized case management approach, in isolation or in combination to achieve viral suppression and 2) estimate incremental cost-effectiveness of interventions and combinations of interventions. The primary outcome is a combined intention-to-treat outcome of retention in ART care and viral suppression at 18 months with secondary implementation outcomes. Siyaphambili aims to inform the implementation of and scale-up of HIV treatment services for female sex workers by determining the minimal package of services needed to achieve viral suppression and by characterizing individuals in need of more intensive HIV treatment approaches.

KEYWORDS
adherence/compliance, community public health, cost and cost analysis, design development, epidemiology, health care delivery, infectious disease, recruit/retain participants, social and economic aspects of illness, women’s health
1 | INTRODUCTION

Female sex workers (FSW) across South Africa bear a high burden of human immunodeficiency virus (HIV), suboptimal treatment outcomes, and disenfranchisement from the health sector (Baral & Phaswana-Mafuya, 2012). FSW in sub-Saharan Africa are estimated to be 14-times more likely to be living with HIV than other women of reproductive age (Baral et al., 2012; Baral, Wirtz, Poteat, & Beyrer, 2013). In South Africa, an estimated 121,000–167,000 women are engaged in sex work of which approximately 90,000 (59.6%, 95%CI [56.2–63.1]) are estimated to be living with HIV (Baral et al., 2012; Mishra, Pickles, Blanchard, Moses, & Boily, 2013; Shannon et al., 2014; Taskforce & Consulting, 2013). Moreover, access to antiretroviral therapy (ART) among FSW is low (Baral et al., 2012; Baral & Phaswana-Mafuya, 2012; Kerrigan et al., 2013). An estimated 39% of FSW living with HIV in South Africa are currently on ART and available viral load results, while limited, indicate viral suppression may be poor (Schwartz, Lambert et al., 2015) with significant risk of onward HIV transmission (Arnott & Crago, 2009; Needle et al., 2008; Ngugi, Roth, Mastin, Nderitu, & Yasmin, 2012). The unmet HIV prevention and treatment needs among FSW and their clients are estimated to account for 20% of the 365,000 annual infections among South Africans (Taskforce & Consulting, 2013).

Large gaps exist in the HIV treatment continuum, especially among FSW. Yet there is little evidence of how to effectively implement and adapt ART services to maximize HIV viral suppression among FSW (Baral et al., 2012). An optimal HIV treatment intervention is defined as the lowest cost package (combination of services) that can achieve the greatest viral suppression. Varying levels of intervention intensity may be offered and determining who benefits from which enhanced interventions can help prioritize expansion, improve treatment outcomes among those living with HIV, and reduce risks of onward HIV transmission (Mishra et al., 2014).

Siyaphambili, meaning “pushing forward together” in Zulu, is a sequential multiple assignment randomized trial (SMART) to evaluate the impact and cost-effectiveness of two interventions in isolation and in combination to improve HIV treatment coverage, retention, and viral suppression for FSW living with HIV in Durban, South Africa. The two interventions include 1) a mobile van-based decentralized treatment program and 2) a peer-led individualized case management intervention. The decentralized treatment leverages South African priorities of community-based, nurse-led ART care and treatment distribution (Georgeu et al., 2012), addressing structural barriers to care and treatment uptake, including accessibility and various forms of stigma (Baral et al., 2014; Peitzmeier, Grosso, Bowes, Cesay, & Baral, 2015). The case management program builds on cognitive behavioral theory to address barriers to treatment uptake, adherence, and retention through individualized self-management strategies. Both approaches are resource intensive and are not scalable to all people living with HIV in South Africa. The Siyaphambili protocol was further developed in response to extensive community engagement and an extensive history of service engagement and intended to be responsive to the needs of the community.

The Siyaphambili study leverages an adaptive implementation strategy to characterize women who may need and benefit more from intensive approaches. Importantly, decentralized treatment and case management interventions address different barriers to HIV treatment, allowing for a meaningful comparison of which approach is more effective and durable at achieving viral suppression given resource constraints. The Siyaphambili study team has the potential to inform the appropriate combination of interventions to achieve viral suppression and to estimate the incremental health impact and cost-effectiveness of these interventions if they were scaled up. The study aims to 1) compare effectiveness and durability of the nurse-led decentralized treatment and peer-led case management in isolation or in combination to achieve viral suppression and 2) to estimate the incremental impact and cost-effectiveness associated with study interventions and combinations of interventions. The aim of this paper is to present the Siyaphambili research protocol.

2 | METHODS

2.1 | Study design overview

The Siyaphambili study utilizes a SMART design to answer the first study aim, to compare effectiveness and durability of decentralized treatment and case management alone and in combination to achieve viral suppression for FSW living with HIV (Figure 1). At enrollment, viremic participants are randomized to either intervention for 6 months. At 6 months, re-randomization occurs to assess the durability of the interventions as well as whether more intensive intervention strategies are required and effective. Participants who achieve viral suppression are deemed responsive to the assigned intervention, as denoted by 6-month viral load status, and are re-randomized to return to the standard of care (SoC) or to continue with the originally assigned intervention. Participants remaining viremic at 6 months are randomized to continue the originally assigned intervention (in isolation) or to receive the most intensive approach, both interventions together. Intervention(s) assigned at the 6-month visit continue for the duration of the study.

The second aim of the study is addressed through an economic evaluation of intervention arms, from a societal perspective, to estimate the incremental impact and cost-effectiveness associated with the study interventions and the combination of interventions. Finally, a risk stratification tool will be incorporated into the economic evaluation to identify an individualized (personalized) strategy for FSW living with HIV according to a woman’s baseline characteristics, which maximizes the proportion who achieves viral suppression using a graded approach under standard thresholds for cost-effectiveness.

2.1.1 | Formative work

Formative qualitative activities, as well as continued community engagement in Durban through a community advisory group and
program peer educators, have been paramount to protocol development, determination of implementation strategies, and study progress thus far. In-depth interviews were conducted with 24 FSW and 15 key informants, including service providers, policy makers, security and police officers, and brothel managers, to refine intervention approaches, characterize appropriate and acceptable implementation strategies, and ensure cultural appropriateness. Findings highlighted the need for differentiated service delivery models for FSW, as well as provided substantial input into the two interventions’ implementation strategies (i.e., when and where to park mobile vans, when and where to hold case management sessions, privacy and confidentiality concerns and strategies) (Comins et al., 2018). Moreover, in-depth interviews with FSW directly guided the hiring process of study staff, through input on preferences of case managers’ backgrounds, skill sets, and personal characteristics. Consultations with community advisory group members and FSW peers guided the refinement of the study protocol. These consultations included pilot and cognitive testing of surveys and implementation tools, determining cultural appropriateness of using biometric iris scanning technology for identification purposes, and assisting in the development of text messages and communication strategies utilized in the trial. The community advisory group was also instrumental in developing the study name (Siyaphambili), logo, and recruitment materials.

2.2 Study setting and population

2.2.1 Study site

The project site is located in the Durban metropolitan area, within the eThekwini Municipality in the South African Province of Kwa-Zulu Natal, which has the highest HIV prevalence among women and girls in any region of any country of the world (Karim et al., 2012). Since 2012, TB HIV Care, a South African nongovernmental organization, has been implementing a sex worker program providing HIV prevention and care for FSW in Durban. TB HIV Care maintains strong partnerships with the provincial Department of Health, engages in service delivery per national guidelines, and operates through community engagement and participation, and employment of FSW peers to support linkage to HIV care and treatment. TB HIV Care utilizes mobile vans, staffed by nurses and peer counselors, to provide community-based HIV counseling and testing alongside screening and management for tuberculosis and sexually transmitted infections. Although ART is not currently provided via the mobile clinics in Durban (Georgeu et al., 2012; Pope et al., 2010), TB HIV Care has provided ART treatment and care at their drop-in wellness center since 2015.

2.2.2 Study staff

This study leverages TB HIV Care’s experience and community rapport. Study staff are South Africans fluent in Zulu and English, the two most common South African languages spoken in the district, and includes peer case managers (PCMs), nurses, research assistants, and a peer retention officer. PCMs are comprised of women with prior or current sex work experience as well as experience with HIV peer education and/or counseling. PCMs have been trained to provide case management to participants as well as to support recruitment and enrollment. Female nurses, trained in primary care and certified in nurse-initiated and managed ART, support the study through assisting with blood collection during study visits and overseeing ART management through the decentralized treatment intervention.
2.2.3 | Study population

For this study, we have used the TB HIV Care programmatic definition of sex work, which includes women reporting that they exchange sex for money or goods as their primary source of income. The study focuses on cisgender FSW; ≥18 years of age, living with HIV and residing in Durban, with no plans to relocate or travel outside of Durban for more than 2 months in the next year. Participants must speak Zulu or English and may not be pregnant at the time of enrollment.

For this study, both ART-naïve and -experienced individuals on first line ART regimens are eligible for study participation. To ensure that women have had exposure to SoC and require further interventions, women are eligible for participation only if they were diagnosed with HIV at least 6 months prior to study enrollment. If already on ART at study enrollment, women must be initiated at least two months prior to be eligible to ensure an opportunity for viral suppression before offering more intensive interventions. Individuals on ART for less than 2 months are not immediately eligible but may be rescreened for eligibility at a later point. Eligibility is determined by a phased enrollment screening, reflecting study inclusion, and exclusion criteria (Figure 2). Women deemed to lack mental capacity to provide informed consent (i.e., drunk, high, or cognitively impaired) at point of recruitment are not screened.

2.2.4 | Sample size

The estimated minimum sample size required for a part-factorial SMART experimental design was calculated in the R package N. SMARTpilot, based on the probability (p = 0.8) that a minimum number of subjects (n = 50) will be observed in each cell of the final assessments at 18 months post-randomization (Figure 1). Given an assumed 10% loss to follow-up at each 6-monthly study visit (cumulative loss to follow-up of 27.5%), a minimum sample size of 782 viremic FSW living with HIV is required to achieve 80% power to detect a difference of ≥12% between the two interventions. Thus, to ensure a sufficient sample size, the study will randomize 800 viremic FSW living with HIV into the intervention. Based on local estimates of 60% HIV prevalence and 30% viral suppression/refusal at randomization (Almirall, Compton, Gunlicks-Stoessel, Duan, & Murphy, 2012; Cowan et al., 2014), it is estimated that at least 1,905 women will be screened to achieve the enrollment targets. Estimates are based on an intention-to-treat analysis of the primary outcome of viral suppression between the two initially randomized arms (decentralized treatment vs. case management).

2.2.5 | Recruitment procedures

Preliminary qualitative findings demonstrated the importance of recruiting FSW through peers familiar with FSW and sex work venues, given their stature in the community. Thus, recruitment is led by PCMs and supported by other study staff trained in recruitment and screening procedures. A standardized recruitment script is utilized (Figure 3). FSW are recruited in the community from the mobile van and from service recipients accessing TB HIV Care services at the drop-in center.

To identify recruitment sites, a mapping of all sex work venues was completed, and a ranked venue priority list created. Sex work venues were categorized into high, medium, and low priority sites based on several considerations, including: the estimated number of FSW living with HIV at a given site, the estimated numbers of treatment-naïve women, loss-to-follow-up cases by site, and non- or inconsistently-adherent FSW operating at each site.

Recruitment commenced at high priority sites, to be followed by medium and low priority sites, and will continue until enrollment targets are reached. All potentially eligible women present at the venues reached by the mobile van or attending the drop-in center are consecutively recruited and invited to screen for eligibility. Recruitment flyers and business cards (Figure 4) distributed at the mobile van, sex work venues, and drop-in center support participant recruitment. Recruited women are screened for eligibility, including administration of pregnancy testing.

2.2.6 | Enrollment

Eligible and consenting participants are enrolled and receive a unique study identification number, generated from a biometric iris scan. Scans are administered by staff trained on the iRespond® software 2.0 and the iris scanning device (iRespond, 2017). The device scans the iris of both eyes and generates a 12-digit unique identification number for each newly identified scan. The unique identification number is utilized throughout the study for identifying and tracking participants across study visits, ART administration, and viral load testing. Following enrollment, whole blood is drawn by a nurse or phlebotomist to assess baseline CD4 count and viral load. Finally, a trained research assistant administers the baseline survey and provides reimbursement. A follow-up visit is scheduled to review the participants’ results. Participants are categorized according to whether they are virally suppressed (viral load <50 copies/ml) at baseline. Participants virally suppressed at baseline continue to receive care and treatment through the existing SoC, while viremic participants are randomized into the trial.

Inclusion Criteria:
1. Sells sex for goods or money as their main source of income
2. Assigned female sex at birth
3. Living with HIV; diagnosed ≥6 months prior
4. Currently living in Durban
5. If on anti-retroviral therapy (ART), initiated ≥2 months prior
6. Able to understand English or Zulu

Exclusion Criteria:
1. Engagement in an ongoing HIV treatment research study
2. Planning on leaving Durban for more than three months in the following 12 months
3. Pregnant at enrollment
4. On a second line ART regimen
5. Participating in an adherence club

FIGURE 2  The Siyaphambili study inclusion criterion (left) and the exclusion criterion (right) are presented
Randomization is being achieved through a blocked design utilizing permuted blocks of random sizes. The design ensures equal representation of treatment assignment across groups and protects the study team and investigators from easily anticipating treatment allocation (Antognini, 2008; Antognini & Giovagnoli, 2004; Efron, 1971; Markaryan & Rosenberger, 2010). Randomization to decentralized treatment and case management is 1:1 at the first stage of randomization. At the second stage, among responders (those virally suppressed at 6 months), randomization is 1:1 to SoC versus continuation of the previously assigned intervention; similarly, among non-responders, randomization is 1:1 to continuation of the assigned intervention versus enhancement to receive both interventions.

2.2.8 | Interventions

Participants virally suppressed at baseline do not undergo randomization and continue their current treatment program as part of the South African SoC (South Africa Department of Health, 2013/2014, 2015). Viral load outcomes for SoC participants are collected through passive follow-up of electronic health records. Participants assigned SoC at baseline will have no further contact with the study.

Participants assigned to decentralized treatment receive their ART supply at or near designated sex work venues through the TB HIV Care mobile van. ART can also be obtained by participants at the drop-in center, if convenient or working nearby. For participants already accessing ART through Department of Health facilities, a transfer letter and medical records are obtained. All clinical care, including ART initiation and ART management, is provided per South African national guidelines by a nurse trained in ART initiation and management (South Africa Department of Health, 2013/2014, 2015). At decentralized treatment visits, FSW receive a 1-month supply of ART at their sex work venue. Women become eligible for a 2-month supply if virally suppressed for more than 6 months. Additionally, participants receive un-personalized text messages to remind participants of the date of their next ART delivery.

Participants randomized to the case management intervention receive a package of case management services delivered by PCMs to build treatment self-efficacy, engage participants in goal-setting and planning, develop life skills, and provide logistical support to optimize treatment uptake and/or adherence. Within 1 month after

---

**FIGURE 3** The recruitment script for the Siyaphambili study. The peer case managers lead the recruitment of cisgender female sex workers in Durban, South Africa and utilize the standardized recruitment script during the recruitment process.

---

**FIGURE 4** The Siyaphambili recruitment flyer (left) and business card (right) are used to support recruitment activities and are distributed throughout the community and at the TB HIV Care drop-in center.
randomization into the intervention, participants meet twice in-person with their assigned PCM for 30–45 min each time. Subsequent, in-person meetings are held every 3 months. All meetings occur at a private, predetermined community location, in the TB HIV Care mobile van or at drop-in center according to the participant's preference. Participants also receive automated, fortnightly informational and motivational text messages and clinic reminders. Participants further receive monthly phone calls from assigned PCMs and can directly contact PCMs or send a free "Please Call Me" text, for more frequent contact.

Participants assigned to case management will continue to receive their HIV care and treatment at a Department of Health clinic or the TB HIV Care drop-in center, per SoC. For participants not already on ART, the PCMs will support the participants through referral to ART services at the TB HIV Care drop-in center or at the nearest Department of Health clinic, based on the participant's preference and readiness.

2.2.9 Follow-up assessments

Follow-up study visits, inclusive of a survey, viral load assessment, and pregnancy test, occur at 6, 12, and 18 months for all participants randomized into the trial. Study visits are distinct from intervention activities. Participants are reimbursed ZAR 100 (~USD 7.90) for completed study visits, for their time and any associated travel costs. Reimbursement will not be provided for participation in intervention activities. A summary of study procedures can be found in Table 1.

Viral loads are processed in the South African National Health Laboratory System. After at least 6 months of documented ART, FSW with viral loads >1,000 copies/ml receive adherence counseling and repeat viral load monitoring in 2 months, per South African treatment guidelines (South Africa Department of Health, 2013/2014, 2015). Participants whose viral loads exceed 1,000 copies/ml after further adherence counseling undergo resistance testing.

Participants with HIV drug resistance require second line ART. All drug resistant participants continue with subsequent study visits, but those assigned to decentralized treatment are removed from the intervention and referred to SoC as nurses are not currently allowed to administer second line ART in South Africa (South African Department of Health, 2013). Participants with incident pregnancies are directly referred to antenatal care but may continue with their assigned intervention.

2.3 Outcomes and measures

The primary effectiveness outcome is a combined outcome of retention in ART care and HIV viral suppression at 18 months after initial randomization comparing those initially randomized to decentralized treatment versus case management. Viral suppression is defined using a quantitative viral load assessment of <50 copies/ml. Interim analyses at 6- and 12-months post enrollment will be completed. Additionally, a combined outcome of retention and HIV viral suppression at 18 months among early intervention non-responders will be compared between those receiving their sustained single intervention versus women randomized to combined interventions. The primary and secondary outcomes are outlined in Table 2.

Adherence to ART is primarily measured through viral load but also includes self-reported adherence and assessment of ART treatment delivery as secondary outcome measures. Moreover, participants who do not suppress but report adherence despite sustained viral loads of >1,000 copies/ml, are tested for resistance to ensure that viral load remains a valid marker of adherence.

2.3.1 Baseline characteristics and time-variant measures

Measures of demographics, health and well-being are collected at baseline and, if time-varying, measures are collected longitudinally through research assistant-administered surveys at 6, 12, and 18 months. Survey modules cover sociodemographic information, personal and sexual history, reproductive health, health behavior, physical and sexual vulnerability, stigma, and quality of life (the brief version of the WHO Quality of Life HIV instrument (World Health Organization, 2002), and the EuroQol 5 dimensions tool (Rabin & de Charro, 2001)). Other modules include: alcohol and drug use, social support and mental health (through the Medical Outcomes Study Social support scale (Drain et al., 2015), the Patient Health Questionnaire depression module (Kroenke, Spitzer, & Williams, 2001), and the Brief Resilience Coping Scale (Sinclair & Wallston, 2004)), and opportunity costing questions. Intervention-specific questions are also asked at 6, 12, and 18 months.

2.3.2 Costing components

Health systems costs are collected, including service delivery and treatment costs of decentralized treatment and case management in isolation and in combination. Costs are collected through budgetary analysis, surveys, time-stamped program logs, and direct observation using time-and-motion studies (Lopetegui et al., 2014). Patient costs are collected at baseline, at an intervention visit (e.g., mobile van ART delivery or in-person meeting with assigned PCM) at 3–6 months post enrollment, and at an intervention visit at 12–15 months post enrollment, using a standardized survey based on the Stop TB Partnership "Tool to Estimate Patients' Costs" (KNCV Tuberculosis Foundation, 2008). Participant costs include: (a) lost wages and productivity required to attend mobile versus clinic-based care; (b) transportation and other direct costs (e.g., food, childcare) necessary for attendance; and (c) time spent engaging with study staff (e.g., lost wages).

2.4 Data management and analysis

Data are electronically collected, managed, and secured using RedCap™ by study staff trained on REDCap data entry, management and security (Harris et al., 2009). Quality assurance measures, including built-in skip patterns, validation ranges, and logic checks, minimize data collection and data capturing errors. Quality control measures,
including internal monitoring systems and daily and weekly reporting, are run to ensure expedient error correction and to optimize data integrity.

### 2.4.1 Statistical analyses

The analytic strategy for primary and secondary outcomes is presented in Table 3. Missing data will be handled using multiple imputation if missingness is believed to be at random or conditional upon measured covariates and >5%. Interim analyses at 6- and 12-months post enrollment will also be completed.

### 2.4.2 Economic evaluation

The Siyaphambili study team will estimate the cost-effectiveness of each intervention in isolation, in combination, and with graduated intensity (i.e., assuming sequential increase in intensity), compared with the SoC. Moreover, a Markov microsimulation model will be developed (i.e., a simulated cohort of FSW in Durban, adopting a lifetime time horizon, and parameterized directly from study data, where available, and from literature otherwise (Mishra et al., 2014; Mountain, Mishra et al., 2014; Mountain, Pickles et al., 2014)) and calibrated to the initial study population. Analysis will follow standard guidelines for economic evaluations, as laid out in the Gates Reference Case for cost-effectiveness analyses, and will be reported as per the Consolidated Health Economic Evaluation Reporting Standards (Husereau et al., 2013; International, 2014).

The primary cost-effectiveness outcome is expressed as the incremental cost (in 2018 US dollars) per incremental quality-adjusted life years gained (incremental cost-effectiveness ratio). The modeled outcome will compare a graded approach as described in Figure 1 against: (a) SoC, (b) case management for all participants, (c) decentralized treatment for all participants, and (d) both interventions in combination for all participants. To evaluate conditions under which different interventions might be preferred on cost-effectiveness grounds, extensive sensitivity analyses will be performed to consider different core parameter values (e.g., HIV prevalence among FSW), different perspectives (e.g., health system, societal), different willingness-to-pay thresholds, different discount rates, and different time horizons (Hoaglin et al., 2011; Weinstein et al., 2003). Additionally, one-way sensitivity analyses on all model parameters, multiway sensitivity analyses on those parameters found to be most influential on the primary outcome, and a probabilistic uncertainty analysis in which simultaneously varying all model parameters over predefined

<table>
<thead>
<tr>
<th>TABLE 1  Summary of study procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Procedure</td>
</tr>
<tr>
<td>STUDY VISITS: All participants receiving either intervention</td>
</tr>
<tr>
<td>Eligibility Screening</td>
</tr>
<tr>
<td>Consent Process</td>
</tr>
<tr>
<td>Iris Scan</td>
</tr>
<tr>
<td>Questionnaire</td>
</tr>
<tr>
<td>Viral load testing</td>
</tr>
<tr>
<td>Pregnancy testing</td>
</tr>
<tr>
<td>Randomization</td>
</tr>
<tr>
<td>INTERVENTION VISITS: Participants assigned to decentralized treatment</td>
</tr>
<tr>
<td>Iris scan</td>
</tr>
<tr>
<td>ART deliverya</td>
</tr>
<tr>
<td>INTERVENTION VISITS: Participants assigned to individualized case management</td>
</tr>
<tr>
<td>In-person meeting</td>
</tr>
<tr>
<td>Phone call</td>
</tr>
<tr>
<td>Text messages</td>
</tr>
<tr>
<td>INTERVENTION VISITS: Participants assigned to both interventions (at month 6)</td>
</tr>
<tr>
<td>Iris scan</td>
</tr>
<tr>
<td>ART deliverya</td>
</tr>
<tr>
<td>In-person meeting</td>
</tr>
<tr>
<td>Phone call</td>
</tr>
<tr>
<td>Text messages</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy.

*Per South African Treatment Guidelines, individuals virally suppressed for 6 months or more may receive bimonthly medication delivery.

including internal monitoring systems and daily and weekly reporting, are run to ensure expedient error correction and to optimize data integrity.
ranges will be done (Wu, Dhingra, Gambhir, & Remais, 2013). Additionally, a value of information analysis will be performed using an extension of the probabilistic sensitivity analysis to describe the extent to which greater certainty in parameter values would help to inform decision-making based on thresholds of cost-effectiveness.

2.5 Ethics

The Siyaphambili protocol has been approved by the University of the Western Cape Biomedical Research Ethics Committee in South Africa; the Johns Hopkins School of Public Health Institutional Review Board in the United States, and the eThekwini Municipality and KwaZulu-Natal Provincial Departments of Health. All participants are required to provide written informed consent. Staff trained in protection of human subjects in research and good clinical practice conduct the consent in a private space after confirming eligibility. Consent is conducted in Zulu or English, in accordance with the participant’s preference.

3 EARLY INSIGHTS

The Siyaphambili SMART study commenced in July 2018, and early insights have developed around resource utilization, biometric validation, and phone-based communication. Geographic zoning is important for ensuring areas are visited on a weekly basis, maximizing resources, and facilitating implementation activities. Early data show, of the women enrolled into Siyaphambili thus far, most women are on ART and to-date around half are virally suppressed. The utility of the recruitment schedule, venue ranking, and enrollment targets needs to be weighed against baseline viral suppression rates to ensure an adequate number of women are screened to achieve the randomization target of 800 viremic FSW. Reinforcing formative qualitative insights, PCMs have been essential to the recruitment process. PCMs are continuously present on the mobile van to facilitate entry into sites, rapport building, and FSW engagement. Biometric iris scanning has been an acceptable means of identification by FSW and has been effective in tracking participants over time. Finally, early insights around phone-based communication have been identified. For all randomized participants, study visit reminders are sent to cell phones via text message. Moreover, decentralized treatment intervention visit text message reminders (to obtain ART), case management phone calls, and case management biweekly support text messages are all sent via cell phone, highlighting the potential importance of phone ownership among participants, though this is not required for study participation. Of those enrolled thus far, 88% of women report owning or having access to a cell phone. Enrollment will continue for the next year and data collection is expected to be complete in 2020.

4 DISCUSSION

The Siyaphambili study compares the effectiveness, durability, and cost-effectiveness of differential HIV treatment implementation strategies in isolation, or in combination, to achieve viral suppression
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Analysis plan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
</tr>
<tr>
<td>1) Retention and viral suppression (&lt;50 copies/ml) at 18 months in FSW initially randomized to decentralized treatment versus case management</td>
<td>A difference of proportions ITT analysis will compare retention and HIV viral suppression at 18 months between FSW randomized to decentralized treatment versus case management</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>2) Retention and viral suppression at 18 months among month 6 non-responders (viral load &gt;50 copies/ml) randomized to continuation of either intervention versus combined interventions</td>
<td>Difference of proportions ITT analysis comparing retention and HIV viral suppression at 18 months between FSW randomized to continuation of either single intervention (group 1) versus a combined approach (group 2).</td>
</tr>
<tr>
<td>3) Risk factors of uncontrolled viremia and/or loss-to-follow-up</td>
<td>Predictors of responding to individual versus combined interventions – including age, parity, migration history, years in sex work, health characteristics (enrollment CD4, side effects, STIs, mental health, etc.), stigma metrics and behavioral factors – will be assessed using a risk prediction GEE model with a binomial distribution and logit function to account for clustering within individuals across time periods. The result will be an individual risk score that can be applied to FSW to help identify women at greatest risk for poor treatment outcomes. Additionally, stratified models utilizing the same general approach will be run among treatment subsets of women (those assigned to decentralized treatment, case management, both interventions), with an outcome of responsiveness (retention/viral suppression) at 18 months. The purpose of these models will be to assess characteristics of women most likely to be successful or to benefit from decentralized treatment, case management or a combined intervention.</td>
</tr>
<tr>
<td>4) Durability of retention and viral suppression among 6-month responders continuing decentralized treatment or case management versus those randomized to revert to SoC</td>
<td>A log binomial model ITT analysis will be used to compare retention and HIV viral suppression at 18 months between FSW responders (viral load &lt;50 copies/ml at 6 months) randomized to continuation of decentralized treatment alone (β1), case management (β2) alone or South African standard of care (Reference group α).</td>
</tr>
<tr>
<td>5) Self-reported adherence and ART refill data to assess adherence across arms</td>
<td>GEE models with a binomial distribution and logit function which account for lack of independence within individuals over time will be used to compare reports of ≥95% self-reported adherence (≥95% = 1, &lt;95% = 0) between decentralized treatment and case management arms across study follow-up using an ITT analysis. This variable will be measured during 6-monthly visits. Additionally, similar models will be run using the outcomes of reported adherence percent from each visit, as well as on-time ART pick-up using pharmacy refill data. Furthermore, an “as treated” analysis will be run to assess the impact of the time-varying intervention exposure on the adherence outcomes; inverse probability of treatment weights will be applied.</td>
</tr>
<tr>
<td>6) Viral suppression among those retained in care at 18 months</td>
<td>Difference of proportions ITT analysis comparing HIV viral suppression at 18 months between FSW randomized to decentralized treatment versus case management.</td>
</tr>
<tr>
<td>7) Loss-to-follow-up at 18 months</td>
<td>Difference of proportions ITT analysis comparing loss-to-follow-up at 18 months between FSW randomized to decentralized treatment versus case management.</td>
</tr>
<tr>
<td>8) Participant reported intervention acceptability</td>
<td>Participants will report on the acceptability of the intervention at 6, 12, and 18 months. Acceptability data will be described and compared across arms among those receiving the intervention using an ITT analysis. GEE models assessing changes within individuals over time (increased or decreased acceptability) will also be assessed.</td>
</tr>
<tr>
<td>9) Report and compare ART resistance</td>
<td>Difference of proportions ITT analysis of ART resistance at 18 months between FSW randomized to decentralized treatment versus case management.</td>
</tr>
<tr>
<td>10) Comparative cost-effectiveness of interventions</td>
<td>Through modeling and simulation analyses based on trial data, we will assess the incremental cost-effectiveness of decentralized treatment, case management, and the combination of both interventions.</td>
</tr>
</tbody>
</table>

FSW, female sex worker; ITT, intention-to-treat; HIV, human immunodeficiency virus; CD4, T-cell count; STI, sexually transmitted infection; GEE, generalized estimating equation.
at 18 months. We hypothesize that an adaptive, graduated multicomponent intervention to achieve viral suppression is preferred over single-intensity interventions or intensive multicomponent interventions for all FSW, under standard willingness-to-pay thresholds from a societal perspective. The Siyaphambili study embeds key innovations in advancing implementation research for HIV treatment for sex workers in South Africa by integrating adaptive implementation strategies and testing these through a SMART design. Specifically, the SMART design facilitates evaluation of differentiated treatment strategies by facilitating assessment of graduated interventions and answer multiple research questions regarding intervention effectiveness within the same study. The emergence of differential care is predicated on the theory that different people living with HIV are likely to have different needs for achieving viral suppression. The SMART design allows use of patient responsiveness data, determined by viral load status, to decide how to adapt the intervention package through a priori decision rules, randomizing for known and unknown confounders (Almirall, Nahum-Shani, Sherwood, & Murphy, 2014; Kilbourne et al., 2014). Siyaphambili also provides insight into the appropriate combination of interventions for achieving viral suppression, combined versus single intensity. Additionally, the Siyaphambili study characterizes women who will benefit from an intervention or combination of interventions. Furthermore, intervention de-escalation and escalation assess durability, or how long someone needs a single intensity intervention, and does so in a real-life service delivery setting with a broadly representative urban population of FSW in South Africa.

Siyaphambili’s SMART design further facilitates understanding of how to best address sustained HIV treatment coverage support through differentiated HIV care interventions focused on ART provision and adherence support. ART coverage, a product of service availability and sustained uptake, is studied within Siyaphambili through implementation of nurse-led ART provision on the mobile van and peer-led case management to address linkage, adherence, and retention in HIV treatment. Decentralized ART distribution has shown high levels of ART adherence success among South Africans already virally suppressed, however the Siyaphambili study team implements the decentralized ART distribution model among viremic FSW (Lamb, El-Sadr, Geng, & Nash, 2012). Moreover, case management has been tested in South Africa, but not evaluated or incorporated as part of the SoC ART program as it is resource intensive (Farley et al., 2014; Schwartz, Clouse et al., 2015). Case management may, however, have scalable utility within subpopulations exhibiting ART adherence needs. The Siyaphambili study team evaluates whether case management, if directed at FSW at high risk for adherence challenges, is cost-effective.

Finally, Siyaphambili’s SMART design integrates effectiveness research and cost-effectiveness modeling. Results will inform scale up and provide a real-world contextual understanding of how to promote HIV viral suppression among FSW in South Africa. The several permutations of impact comparison, embedded within the SMART design, enable analyses of interventions in isolation, in combination, and in comparison to the SoC, an important economic nuance as dual interventions will cost more and may not be needed by everyone. Determining who benefits from the enhanced interventions to achieve viral suppression can help prioritize expansion, inform decision making in contexts of budgetary constraints, and provide insight into overall improvements of HIV treatment outcomes in South Africa. Moreover, the incorporation of the economic evaluation adds to overall knowledge gained and estimates potential health and cost impacts of differentiated service delivery models to achieve HIV viral suppression among FSW.

4.1 | Limitations

Siyaphambili has limitations which are closely monitored and addressed where possible. Although integration of research into a service delivery program is beneficial and will advance intervention scalability if successful, integrating research into routine care also poses coordination challenges. Thus, assessment of implementation outcomes, including fidelity of the interventions, are being monitored closely and evaluated. Furthermore, in the absence of reliable and high throughput point of care viral load technology, the study sends bloodwork to the laboratory, creating one to 2-week delays in randomization and re-randomization. An appointed peer retention officer helps to minimize the impact of these delays and to generally support retention activities given the high mobility of FSW. Finally, the Siyaphambili study team will not be able to directly compare the effectiveness of the decentralized treatment and case management interventions with the SoC. Although this limitation is recognized, the intention of the study is to understand how to more effectively and efficiently direct resources to those for whom the SoC services are failing, as only an estimated 39% of FSW are currently achieving viral suppression (Schwartz, Lambert et al., 2015).

5 | SUMMARY

The Siyaphambili study was developed in response to the South African government’s commitment to achieve the global 90-90-90 treatment targets: to diagnose 90% of persons living with HIV, treat 90% of those diagnosed with ART, and achieve viral suppression for 90% of those on ART to improve the quality of life of people living with HIV and reduce onward HIV transmission risks, (Bain, Nkoke, & Noubiap, 2017). Findings will inform differentiated service implementation strategies including studying which FSW living with HIV may benefit from more intensive decentralized treatment and/or case management interventions and providing information around the intervention intensity and duration needed to achieve viral suppression. Siyaphambili aims to inform the implementation of and scale-up of HIV treatment services for FSW by studying the effectiveness of differential implementation approaches for HIV treatment and then modeling the potential impact and cost-effectiveness of these services if delivered at scale across South Africa.

ACKNOWLEDGMENTS

We are grateful to the Community Advisory Group of female sex workers in Durban who have shared their time, experiences, and
expertise to inform the design and implementation of the study. Moreover, we are grateful to the support of Amrita Rao in the development of this protocol. Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under Award Number R01NR016650 as well as through support from the Johns Hopkins University Center for AIDS Research through the National Institutes of Health (award P30AI094189). The contents expressed here are the sole responsibility of the authors and may not represent the views of the NIH. Finally, we are grateful to the Centers for Disease Control and Prevention for their support of the TB HIV Care sex work program.

ORCID

Carly A. Comins http://orcid.org/0000-0003-2991-4423

REFERENCES


