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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. Schwartz¹, Deliwe R. Phetlhu², Vijayanand Guddera³, Katherine Young⁴, Jason E. Farley⁵, Nora West¹, Lauren Parmley¹, Elvin Geng⁶, Chris Beyrer¹, David Dowdy¹, Sharmistha Mishra^{7,8}, Harry Hausler⁵, Stefan Baral¹

¹Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, Maryland

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

Abstract

In South Africa, 60% of female sex workers are estimated to be living with human immunodeficiency virus (HIV), many of whom 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 FSW 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 (FSW) 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; epidemiology; infectious disease; social and economic aspects of illness; design development; recruit/retain participants; community public health; health care delivery; cost and cost analysis; women's health

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 (S. Baral, Phaswana-Mafuya, N., 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 (S. Baral et al., 2012; S. D. Baral, Wirtz, A., Poteat, T., Beyrer, C., 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 (S. Baral et al., 2012; S. Mishra, Pickles, M., Blanchard, J.F., Moses, S., Boily, M.-C., 2013; Shannon et al., 2014; Taskforce & Consulting, 2013). Moreover, access to antiretroviral therapy (ART) among FSW is low (S. Baral et al., 2012; S. Baral, Phaswana-Mafuya, N., 2012; Kerrigan & Beyrer, 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 (S. Schwartz et al., 2015) with significant risk of onward HIV transmission (Arnott & Crago, 2009; Needle, 2008; Ngugi, 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 (S. 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 (S. 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 (DTP) and 2) a peer-led individualized case management (ICM) intervention. DTP leverages South African priorities of community-based, nurse-led ART care and treatment distribution (Georgeu et al., 2012), addressing structural barriers to linkage to care and treatment uptake, including accessibility and various forms of stigma (S. Baral et al., 2014; Peitzmeier, 2015). ICM 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 developed by a study team that includes balanced collaborations

between South African nursing investigators, implementing partners focused on leading nurse-led interventions for sex workers and other marginalized women, community and peer leads, and implementation researchers. The 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, DTP and ICM 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. Siyaphambili study team has the potential to inform 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 are to 1) compare effectiveness and durability of nurse-led DTP and peer-led ICM 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.

Methods

Study Design Overview

The Siyaphambili study utilizes a SMART design to answer the first study aim, to compare effectiveness and durability of DTP and ICM alone and in combination to achieve viral suppression for FSW living with HIV (Figure 1). At enrollment, viremic participants are randomized to either DTP or ICM for six months. At six 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 six-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 six months are randomized to continue the originally assigned intervention (DTP or ICM in isolation) or to receive the most intensive approach, DTP+ICM interventions together. Intervention(s) assigned at the six-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 achieve viral suppression using a graded approach under standard thresholds for cost-effectiveness.

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 DTP and ICM 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 ICM case managers' backgrounds, skill sets, and personal characteristics.

Consultations with community advisory group members and FSW peers guided the refinement of the study protocol. This 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.

Study Setting and Population

Study site.—The project site is located in the Durban metropolitan area, within the eThekweni 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 (DoH), 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 (George et al., 2012; Pope et al., 2010), TB HIV Care has provided ART treatment and care at their drop-in wellness center since 2015.

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 ICM 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 DTP intervention.

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 two 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 six 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 two 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 be screened.

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; F.M. Cowan, 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 (DTP verse ICM).

Procedures Recruitment.—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.

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.

Randomization.—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 DTP and ICM is 1:1 at the first stage of randomization. At the second stage, among responders (those virally suppressed at six months), randomization is 1:1 to SoC verse continuation of the previously assigned intervention; similarly, among non-responders, randomization is 1:1 to continuation of the assigned intervention verse enhancement to receive both DTP and ICM.

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 DTP 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 DoH 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 DTP visits, FSW receive a one-month supply of ART at their sex work venue. Women become eligible for a two-month supply if virally suppressed for more than six months. Additionally, participants receive un-personalized text messages to remind participants of the date of their next ART delivery.

Participants randomized to the ICM 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 one month after randomization into the intervention, participants meet twice in-person with their assigned PCM for 30–45 minutes each time. Subsequent, in-person meetings are held every three 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 ICM will continue to receive their HIV care and treatment at a DoH 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 DoH clinic, based on the participant's preference and readiness.

Follow-up assessments.—Follow-up study visits, inclusive of a survey, viral load assessment, and pregnancy test, occur at six, 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 (NHLS). After at least six months of documented ART, FSW with viral loads > 1000 copies/ml receive adherence counseling and repeat viral load monitoring in two months, per South African treatment guidelines (South Africa Department of Health, 2013/2014, 2015). Participants whose viral loads exceed 1000 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 DTP 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.

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 DTP versus ICM. Viral suppression is defined using a quantitative viral load assessment of < 50 copies/ml. Interim analyses at six- 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 > 1000 copies/ml, are tested for resistance to ensure that viral load remains a valid marker of adherence.

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 six, 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 [WHOQOL-HIV BREF] (World Health Organization, 2002), and the EuroQol 5 dimensions tool [EQ-5D] (Rabin & de Charro, 2001)). Other modules include: alcohol and drug use, social support and mental health (through the Medical Outcomes Study Social support scale [MOS:SSS] (Drain et al., 2015), the Patient Health Questionnaire depression module [PHQ9] (Kroenke, Spitzer, & Williams, 2001), and the Brief Resilience Coping Scale [BRCS] (Sinclair & Wallston, 2004)), and opportunity costing questions. Intervention-specific questions are also asked at six, 12 and 18 months.

Costing components.—Health systems costs are collected, including service delivery and treatment costs of ICM and DTP 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 verse 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).

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.

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 six- and 12-months post enrollment will also be completed.

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 (S. 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) ICM for all participants, (c) DTP for all participants, and (d) ICM and DTP 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 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.

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 eThekweni 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.

Early Insights

The Siyaphambili SMART study commenced July 21, 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, DTP intervention visit text message reminders (to obtain ART), ICM phone calls, and ICM 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.

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 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, Siyaphambili study characterizes women who will benefit from the 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 Siyaphambili study team implements the decentralized ART distribution model among viremic FSW (Lamb, El-Sadr, Geng, & Nash, 2012). Moreover, ICM 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; S. R. Schwartz et al., 2015). ICM may however have scalable utility within subpopulations exhibiting ART adherence needs. Siyaphambili study team evaluates whether ICM, 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.

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 closely being monitored 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 two-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, Siyaphambili study team will not be able to directly compare the effectiveness of DTP and ICM 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

which the SoC services are failing, as only an estimated 39% of FSW are currently achieving viral suppression (S. Schwartz et al., 2015)

Summary

The Siyaphambili study was developed in response to 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 DTP and/or ICM 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 female sex workers 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.

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Figure 1.

Siyaphambili SMART study design is presented across the top of the figure for the 18-month study duration. The anticipated sample size is also presented below each cell.

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 antiretroviral 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.

"Hello, my name is _____. I am working with TB HIV Care on a research study. We are interested in learning more about women's healthcare needs to inform services provided on the TB HIV Care mobile clinic and at the drop-in centre. This study will gather information to help us do that. Would you be interested in learning more about participating in the research study? I will first have to ask you a few questions to make sure you are eligible, and I will fully explain to you the details of the study so that you can decide if you are interested in taking part."

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.

Empowering communities to be healthy and free of TB and HIV

❖ LADIES ❖

If you are...

- 18 years old or older
- Living in Durban, and
- Not pregnant

You could join

SIYAPHAMBILI:

A Women's Healthcare

Study

- ❖ Nonjudgmental and confidential service
- ❖ Money for your time and transport

Questions? Want more info?
Want to participate?

Call, SMS, or Email _____
At (PHONE) | (EMAIL)
Or...Visit TB/HIV Care's Mobile Clinic

Questions? Want more info?
Want to participate?

Call, SMS, or Email _____
At (PHONE) | (EMAIL)
Or...Visit TB/HIV Care's Mobile Clinic

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.

Summary of Study Procedures

Table 1.

Study Procedure	Month																		
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
STUDY VISITS: All participants receiving either intervention																			
Eligibility Screening	✓																		
Consent Process	✓																		
Iris Scan	✓						✓						✓						✓
Questionnaire	✓						✓						✓						✓
Viral load testing	✓						✓						✓						✓
Pregnancy testing	✓						✓						✓						✓
Randomization	✓						✓												
INTERVENTION VISITS: Participants assigned to DTP																			
Iris scan	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART delivery ^a	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
INTERVENTION VISITS: Participants assigned to ICM																			
In-person meeting	✓			✓			✓		✓				✓			✓			✓
Phone call	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Text messages	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
INTERVENTION VISITS: Participants assigned to DTP+ICM (at month 6 or later)																			
Iris scan							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ART delivery ^a							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
In-person meeting							✓						✓			✓			✓
Phone call							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Text messages							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Note. DTP = decentralized treatment program; ART = antiretroviral therapy; ICM = individualized case management

^aPer South African Treatment Guidelines, individuals virally suppressed for six months or more may receive bimonthly medication delivery

Table 2.

Outcomes	
	Primary outcome
1) Retention and viral suppression at 18 months in those initially randomized to DTP versus ICM	
	Secondary outcomes
2) Retention and viral suppression at 18 months among month 6 non-responders randomized to continuation of either intervention versus combined DTP+ICM	
3) Risk factors of uncontrolled viremia and/or loss to follow up	
4) Durability of retention and viral suppression among 6-month responders continuing DTP or ICM versus those randomized to revert to South African standard of care	
5) Self-reported adherence and ART refill data to assess adherence across arms	
6) Viral suppression by arms among retained participants	
7) Loss-to-follow-up across arms	
8) Participant reported intervention acceptability	
9) Characterize and compare resistance across arms	
10) Comparison of intervention cost-effectiveness according to order of intervention delivery and duration of intervention received	
	Implementation outcomes
11) DTP delivery	
Number and proportion of DTP deliveries attended within 7-days of scheduled visit	
Number and proportion of DTP visits occurring at the TB HIV Care drop-in center	
12) ICM phone-based contacts	
Total number of ICM phone-based contacts attempted and successfully completed; proportion of monthly phone-based contacts successfully completed; proportion of participants initiating phone-based contact with their case manager during follow-up from 0–6 months, 6–12 months and 12–18 months.	
Number of participants randomized to ICM intervention who were without a phone	
13) ICM in-person meetings	
Number and proportion of in-person case manager sessions attended	

Note. DTP = decentralized treatment program; ICM = individualized case management

Table 3.

Data Analysis Plan by Outcomes

Outcome	Analysis plan
	Primary outcome
1) Retention and viral suppression (<50 copies/mL) at 18 months in FSW initially randomized to DTP versus ICM	A difference of proportions ITT analysis will compare retention and HIV viral suppression at 18 months between FSW randomized to DTP versus ICM
	Secondary outcomes
2) Retention and viral suppression at 18 months among month 6 non-responders (viral load >50 copies/ml) randomized to continuation of either intervention versus combined DTP+ICM	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).
3) Risk factors of uncontrolled viremia and/or loss-to-follow-up	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 DTP, ICM, DTP +ICM), 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 DTP, ICM or a combined intervention.
4) Durability of retention and viral suppression among 6-month responders continuing DTP or ICM versus those randomized to revert to SoC	A log binomial model ITT analysis will be used to compare retention and HIV viral suppression at 18 months between FSW responders (viral load <50 copies/ml at six months) randomized to continuation of DTP alone ($\beta 1$), ICM ($\beta 2$) alone or South African standard of care (Reference group [α]).
5) Self-reported adherence and ART refill data to assess adherence across arms	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, <95% = 0) between ICM and DTP 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.
6) Viral suppression among those retained in care at 18 months	Difference of proportions ITT analysis comparing HIV viral suppression at 18 months between FSW randomized to DTP versus ICM.
7) Loss-to-follow-up at 18 months	Difference of proportions ITT analysis comparing loss-to-follow-up at 18 months between FSW randomized to DTP versus ICM.
8) Participant reported intervention acceptability	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.
9) Report and compare ART resistance	Difference of proportions ITT analysis of ART resistance at 18 months between FSW randomized to DTP versus ICM.
10) Comparative cost-effectiveness of interventions	Through modeling and simulation analyses based on trial data, we will assess the incremental cost-effectiveness of ICM, DTP, and the combination of ICM and DTP.

Note. FSW = female sex worker; DTP = decentralized treatment program; ICM = individualized case management; ITT = intention-to-treat; HIV = human immunodeficiency virus; CD4 = T-cell count; STI = sexually transmitted infection; GEE = generalized estimating equation