Adaptive Randomized Evaluation of HIV Treatment Retention Interventions for Women Living With HIV

Siyaphambili

Protocol

NCT ID:
NCT03500172

9 April, 2018

Contents

1. Key Roles 4
2. Background Information and Scientific Rationale 4
3. Objectives 5
4. Study Design 6
5. Study Population 8
   5.1 Inclusion and exclusion criteria 8
   5.2 Selection of the Study Population 9
6. Study Procedures 9
   6.1 Screening 11
   6.2 Informed Consent 13
   6.3 Enrollment/Baseline 13
   6.4 Randomization and Re-Randomization 14
   6.5 Intervention Implementation and Study Visits 14
      6.5.1 South African Standard of Care 14
      6.5.2 Decentralized Treatment Program 17
      6.5.3 Individualized Case Management 19
   6.6 Endline Assessment 21
   6.7 Early Termination of Visit, if applicable 21
   6.8 Criteria for Discontinuation or Withdrawal of a Participant from the Study 21
7. Laboratory Evaluations 22
   7.1 Laboratory Evaluations/Assays 22
   7.2 Special Assays or Procedures 22
   7.3 Specimen Collection, Preparation, Handling and Shipping 23
8. Assessment of Outcome Measures 24
   8.1 Specification of the Appropriate Outcome Measures 24
      8.1.1 Primary Outcome Measures 24
      8.1.2 Secondary Outcome Measures 24
9. Safety assessment and reporting 26
   9.1 Definition of Adverse Event (AE) and Serious Adverse Event (SAE) 26
   9.2 Event Detection and Reporting Procedures 27
      9.2.1 Reporting of Pregnancy 27
      9.2.3 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings 27

9.2.4 Type and Duration of the Follow-up of Subjects After Adverse Events 27
9.5 Safety Oversight 28
10. Clinical Monitoring Structure 29
11. Statistical Considerations 30
11.1 Sample Size Considerations 30
11.2 Participant Enrollment and Follow-Up 30
11.4 Statistical Analysis Plan 31
11.4.1 Analysis Plan for Study Outcomes 31
11.4.2 Analysis Plan for Cost Effectiveness 33
12. Access to Source Data/Documents 34
13. Quality Control and Quality Assurance 34
14. Protection of Human Subjects 35
14.1 Declaration of Helsinki 36
14.2 Institutional Review Board 36
14.3 Potential Risks and Benefits 36
14.3.1 Potential Risks 36
14.3.2 Known Potential Benefits 38
14.4 Informed Consent Process 38
14.5 Exclusion of Women, Minorities, and Children (Special Populations) 39
14.6 Subject Confidentiality 39
14.7 Future Use of Stored Specimens 39
15. Data Handling and Record Keeping 40
15.1 Data Management Responsibilities 40
15.2 Data Capture Methods 41
15.3 Types of Data and Timing/Reporting 41
15.4 Study Records Retention 43
15.5 Protocol Deviations 44
16. Publication Policy 44
17. Literature References 44

1. Key Roles

The NIH/NINR-funded research study is to be conducted by Johns Hopkins University Bloomberg School of Public Health (JHU), in partnership with TB/HIV Care (THC) and in collaboration with University of the Western Cape, University of Toronto (Li Ka Shing Knowledge Institute), the National Health Laboratory System (NHLS), National Institute of Communicable Diseases (NICD) and the University of California in San Francisco (UCSF). THC will lead the data collection in Durban, South Africa and the study will be established utilizing the existing resources of the drop-in center and the mobile health van. They will thus oversee the implementation of the trial and collect biological and quantitative data from female sex workers (FSW) living with HIV. The University of Toronto will oversee the HIV intervention modeling and cost effectiveness analysis to assess the incremental benefits of this package of interventions. Collaborators from the University of the Western Cape and UCSF will provide expert guidance on nurse led and adaptive interventions respectively. NHLS and NICD will oversee the laboratory elements of the study.

Human subjects research oversight and approvals will be provided by the Human Research Ethics Committee at the University of the Western Cape and the Johns Hopkins University Institutional Review Board, as well as the Provincial KZN Ethics Committee and eThekwini district and municipality. All investigators and study staff involved with the data collection and analysis will be trained in human research subjects' protection and good clinical practice. Interviewers will receive training on the questionnaire, interviewing techniques, and working with FSW.

The principal investigators (PIs) and Co-Investigators will make regular site visits to the data collection site to provide training, review study progress, support ongoing implementation of activities, and provide technical assistance. The Project Manager will be based in Durban and hired by THC to ensure that the study team follows the protocol and that all data collection materials and forms are completed and stored in accordance with the protocol and standard operating procedures. These activities will be monitored by the local PI, JHU PI, and other investigators on site visits.

2. Background Information and Scientific Rationale

FSW represent a group of women in South Africa with a very high burden of HIV, high risks of onward HIV transmission, and disenfranchisement with significant marginalization from the health sector[1-3]. Across Sub-Saharan Africa (SSA), FSW are 14-times more likely to be living with HIV than other women of reproductive age[4, 5]. There are an estimated 121,000-167,000 women engaged in sex work in South Africa, of whom 90,000 (59.6%, 95% CI 56.2-63.1) are estimated to be living with HIV[4, 6-8]. Mathematical models using these data suggest that approximately 20% of the 365,000 annual infections among adults in South Africa are acquired by FSW and their clients[8]. The risk of onward HIV transmission due to poor antiretroviral therapy (ART) coverage is significant, highlighting the potential population-wide impact of HIV viral suppression among FSW[9-11]. HIV treatment initiation and retention represent complex challenges for FSW with individual level risk factors contextualized by higher order determinants, including stigma and discrimination[12].

Evidence suggests large gaps in the HIV treatment continuum across specific populations in SSA, but there is little evidence on how to effectively address these gaps – especially among FSW[13, 14]. The few available studies suggest that access to treatment among FSW is low[1, 4, 15]. Data suggest that only

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 even more limited[3]. Furthermore, systematic reviews have identified low ART coverage among FSW across SSA, again highlighting the breadth of treatment needs in this population[13, 14]. However, due to a paucity of data on the determinants of uptake, retention, and adherence in the ART continuum among FSW, we have yet to fully understand how to implement and adapt ART services to maximize HIV viral suppression for these marginalized women[4].

The optimal package of HIV treatment adherence interventions is defined by the lowest cost package that can achieve the most outcomes of viral suppression. Interventions maybe offered at different levels of intensity and determining who benefits from enhanced interventions to achieve viral suppression can help prioritize expansion and improve HIV treatment in South Africa.

Two interventions are proposed in this study, including a mobile van-based decentralized treatment program (DTP) model and a peer-led individualized case management (ICM) intervention. The DTP strategy leverages South African priorities of nurse-led ART care and treatment distribution within the community[16]. This is particularly important for marginalized women given the inherent structural barriers to linkage to care and treatment uptake, including accessibility and various forms of stigma[17-20]. The ICM strategy builds on cognitive behavioral theory and helps address barriers to treatment uptake, adherence and retention by working with individuals on self-management strategies including: a) setting treatment goals, b) building treatment literacy and self-efficacy to execute treatment plans, and c) providing social and logistics support to patients to achieve their goals. While both approaches are resource intensive and not scalable to all people living with HIV in South Africa, using an adaptive implementation strategy can help characterize the women who might need and benefit from more 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.

The Siyaphambili Study is a sequential multistage assignment randomized trial (SMART) to evaluate the impact and cost-effectiveness of mobile DTP and ICM in improving HIV treatment. The mediators of poor ART uptake and non-adherence vary across individuals, highlighting the need for patient-responsive and adaptive strategies. People who are the most marginalized and socially disenfranchised are among those most at risk of ART non-adherence and may require the most intensive support to achieve HIV viral suppression to prevent disparities in clinical treatment outcomes and reduce onward transmission within their networks[21]. This study has the potential to inform the appropriate combination of interventions to achieve viral suppression among women engaged in sex work, who are among the most marginalized women in South Africa, and to estimate the incremental health impact and cost-effectiveness of these interventions if brought to scale. The project site, Durban, in the South African Province of Kwa-Zulu Natal, has the highest HIV rates among women and girls in any country of the world[22], and is in urgent need of interventions to improve clinical outcomes.

3. Objectives

The objective of this trial is to evaluate the impact and cost-effectiveness of a mobile DTP and ICM in improving HIV treatment coverage, retention and viral suppression for marginalized women living with HIV in Durban, South Africa. The specific aims are as follows:

Aim 1: Compare the effectiveness and durability of nurse-led DTP and ICM in isolation or in combinations to achieve viral suppression.
Hypothesis: DTP and ICM will be equally effective at achieving viral suppression and will have a synergistic effect when combined and targeted at those who remained non-responsive to either isolated intervention.

Aim 2: Estimate the incremental impact and cost-effectiveness associated with study intervention arms to complement empiric data collection in Aim 1.
Hypothesis: An adaptive, graduated multicomponent intervention to achieve viral suppression is more cost-effective than single-intensity interventions or intensive multicomponent interventions for all FSW.

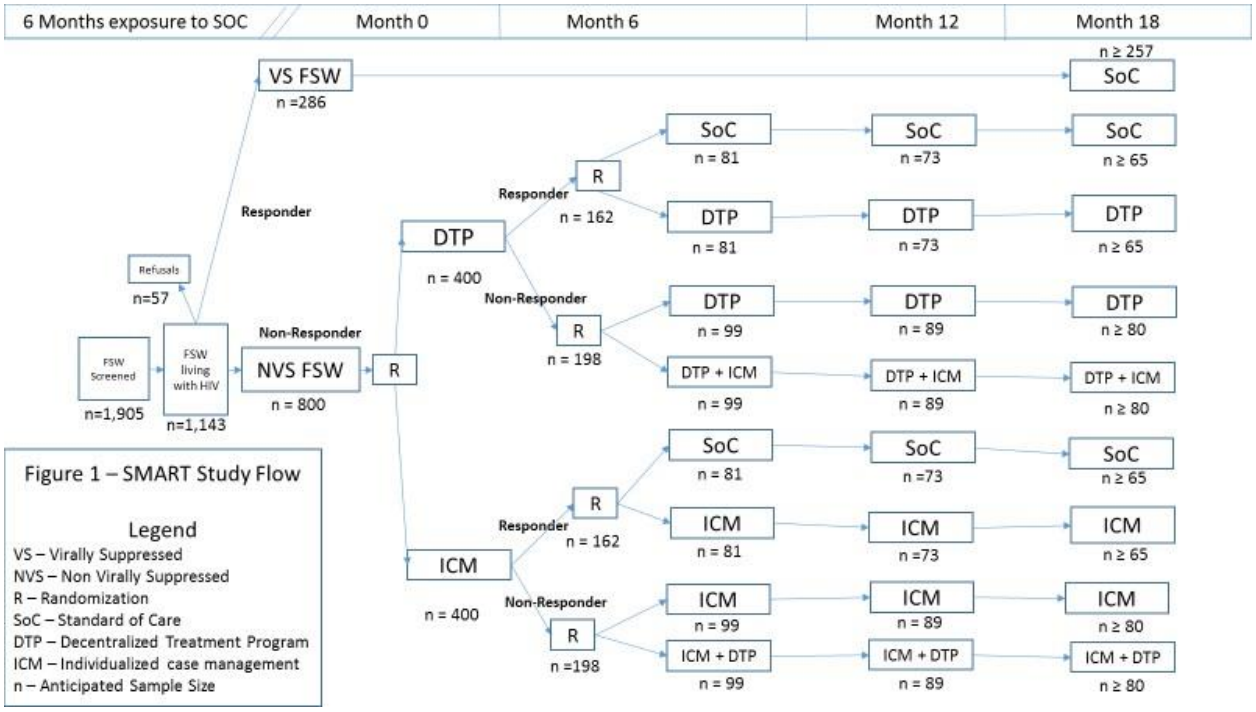
4. Study Design

As referred to above, this study is a sequential multistage adaptive randomized trial (SMART). Non-virally suppressed participants are randomized to one of two intervention arms and then re-randomized at six months into the study to continue, discontinue or amplify their intervention. This type of study design allows for the assessment of the effectiveness of the interventions, as well as the durability and necessary dose of the interventions for effectiveness.

The trial will evaluate the impact and cost-effectiveness of mobile van-based DTP and peer-led ICM in improving HIV treatment coverage, retention and viral suppression for FSW living with HIV in Durban, South Africa. Viral suppression is defined according to national Department of Health (DOH) ART Treatment Guidelines and refers to a viral load below 50 copies/mL[23]. HIV positive FSW, 18 years and older will be recruited at sex work venues through the THC mobile health team or at the THC drop-in center. Study staff will invite all potentially eligible women at FSW venues visited by the mobile van and the THC drop-in center to undergo eligibility screening. Participants will be eligible if they were diagnosed HIV positive at least six months prior to enrollment, and therefore all will have been exposed to South African standard of care (SoC) for at least six months prior to study commencement. Following eligibility screening, consenting participants will enroll into a longitudinal cohort of FSW living with HIV that will include an 18-month intervention for non-virally suppressed FSW. Once enrolled, participants will receive a unique identification number based on a biometric iris scan. All participants will engage in a baseline assessment and have their viral load (VL) assessed. Based on the VL results, virally suppressed participants will continue to receive the South African SoC and non-virally suppressed participants will be randomized to DTP or ICM. The baseline assessment will capture demographics, socioeconomic status, mobility and migration history, behavioral characteristics, mental health, social support, and health and treatment history. Additionally, the informed consent process will request permission to access health records from THC and HIV-related health data from the South African electronic HIV records, which will enable continued passive follow-up of SoC participants and participants LTFU in the study.

The study design is built on three approaches: (A) SoC; (B) DTP; and (C) ICM. Based on the results of the VL test, conducted at enrollment, participants will be separated by those who are virally suppressed and those who are not. Those who are virally suppressed will continue to engage in South African SoC for HIV and ART treatment. FSW who are not virally suppressed will be randomized to one of two

experimental conditions including (i) DTP or (ii) ICM interventions. Those who are randomized to DTP or ICM will receive the intervention for six months and then will receive an abbreviated questionnaire and VL at month six. At this point, the participants who are virally suppressed will have been deemed to have been responsive to the intervention and will be re-randomized to either revert to SoC or to continue to receive the DTP or ICM intervention initially assigned. This will assess both the necessity for continued intervention as well as the durability of the two interventions. For those who are not virally suppressed at six months, they will be randomized to continue receiving DTP or ICM alone or to receive the most intensive approach which is both the DTP + ICM interventions together. This will assess whether more exposure to the DTP or ICM intervention in isolation is needed to achieve viral suppression or whether a more intensive intervention strategy including DTP + ICM is required and effective. VLs will be completed at 12 and 18 months post-enrollment, alongside a 12-month abbreviated questionnaire and an endline assessment. No further randomization will take place beyond six months. While there is significant plausibility for the benefit of the DTP and ICM interventions, neither intervention is currently included as SoC in South Africa, nor have they been tested among FSW. It would not be sustainable to implement these interventions for all people initiated on ART every year in South Africa. Thus, the adaptive design facilitates understanding of what is the most efficient package to achieve viral suppression for those most marginalized. A visual depiction of the SMART study design can be found in Figure 1.



In all cases, we will abide by the South African treatment guidelines[23, 24]. Thus, for FSW who are virally suppressed and on ART for greater than six months, two-month ART pick-ups will be offered for DTP participants, versus monthly for those being initiated onto ART or initiated within the past six months. Additionally, for those initially assigned to the DTP or ICM arms who at six months or thereafter have a VL >1000 copies/mL and who report taking treatment will undergo adherence counseling and repeat viral load monitoring two months later, independent of their randomization. For those with VL still

>1000 copies/mL, we will conduct resistance testing and switch patients to drug sensitive regimens as required. SoC in South Africa would only support resistance testing with failure of second line regimens, however we are taking a cautious approach to ensure that participants are not unnecessarily switched to second or third line therapies which are expensive and cannot be initiated or managed by the study team[25]. Participants within the DPT intervention will be discontinued from the intervention and referred to SoC for ART management at a DOH facility. As the guidelines allow for nurses to initiate and manage second-line therapy, those individuals will no longer be discontinued from the intervention. All participants found to be resistant to first line regimen while enrolled in the study will still engage in subsequent study visits.

Furthermore, data will be collected as part of the study to assess the cost-effectiveness and incremental impact of the interventions, alone and in combination. Dynamic modeling (detailed in 11.4) will be used to accomplish these goals.

5. Study Population

5.1 Inclusion and exclusion criteria

There is no universally accepted case definition for a sex worker. For this study, we are using THC's definition of sex work as a primary source of income. To maximize the generalizability of the study, the study will focus broadly on FSW living with HIV. However, because we want the interventions, which are intensive, to focus on women who are most in need of additional support, only those women with at least six months exposure to South African SoC will be eligible for the study and only those not virally suppressed will be randomized to the two intervention arms. By ensuring that a woman has been aware of her HIV status for at least six months, we will ensure that those women enrolled into the study had an opportunity to seek out and take up ART treatment and thus if they are not on ART or are not virally suppressed, the SoC package has not been observed to meet their needs. Eligibility will be independent of current or past ART. Individuals on ART, but who were initiated within the past two months will not be eligible because if they are not suppressed it may be an adherence issue or it may be that they just have not had sufficient time on ART to become virally suppressed. Therefore, it is important that potential participants currently on ART have at least two months experience on ART. However, after being on ART for two months or more, the individual may be rescreened for study eligibility should they still be interested in study participation and should study enrollment still be ongoing.

A. *Inclusion Criteria:*
   1. Sells sex for goods or money as their main source of income
   2. Assigned female sex at birth
   3. ≥18 years of age
   4. Living with HIV; diagnosed ≥6 months prior
   5. Currently living in Durban
   6. If on ART, initiated ≥2 months prior

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

5. Participating in an adherence club

**Positive urine-based pregnancy test at screening*

5.2 Selection of the Study Population

FSW will be recruited into the study through routine THC services at the mobile van or drop-in center. Recruitment will occur during existing THC hours of operation at the drop-in center and on the mobile van. The sex worker outreach team, primarily comprised of peers, will be utilized as the primary entry point to engaging FSW. All peers will be trained on the goals and objectives of the study and recruitment script to ensure consistency of messaging across THC staff. Recruitment flyers will also be distributed at the mobile van and the THC drop-in center to invite FSW to screen for eligibility. Additionally, a business card with the study logo and contact information will be distributed at sex work venues by the THC mobile van and peers, as well as at the drop-in center. Finally, electronic records from the drop-in center ART clinic will be utilized to identify patients who are lost-to-follow-up (have missed appointments for three months or longer) and attempt to reinitiate in care and recruit through their provided contact information.

Given that other health services are provided at the mobile van and drop-in center, including HIV counseling and testing, family planning, STI screening and treatment and condom distribution, visiting the mobile van is not associated with being HIV positive and sex workers already attend the mobile van and drop-in center for services. As participants will be recruited through the mobile van located at sex work venues and the drop-in center, as well as through recruitment flyers to invite their peers to participate, we do not anticipate that others in the community will learn of their HIV or sex work status.

To identify recruitment sites, a map of all sex work venues served by the mobile THC van will be compiled. Sex work venues, identified by THC, will be categorized into high, medium, and low priority sites. Venues will then be ranked based on several considerations: the overall estimated number of FSW living with HIV as well as the estimated numbers of treatment naïve, loss-to-follow-up, and non- or inconsistent adherent FSW operating at each site. Recruitment will commence at high priority sites, followed by medium and low priority sites until FSW enrollment targets are reached. All eligible individuals attending venues reached by the mobile van or the drop-in center at the visit will be consecutively recruited or invited to screen for enrolment into the study until the intervention sample size has been met. Study staff will not screen or consent those who are deemed to lack capacity [e.g. if drunk or high] at the point of recruitment.

6. Study Procedures

The interventions being assessed include the South African SoC and two differentiated care models: mobile nurse-led DTP and ICM. Table 1 summarizes the main components of the interventions. Under the South African treatment guidelines[23, 24], everyone living with HIV is eligible for treatment and will either be initiated or maintained on treatment (DTP) or referred to initiate or continue treatment at existing DOH supported facilities, including the THC drop-in center clinic (ICM and SoC). South African treatment guidelines will be followed. VLs will be monitored every six months. FSW who have VLs >1000 copies/mL will undergo adherence counseling and repeat VL monitoring in two months per national guidelines, independent of their randomization. For those with VLs >1000 copies/mL during repeat monitoring, South African treatment guidelines prompt a switch to second line ART; however in

this study, we will conduct resistance testing at this stage and only refer those with resistant mutations for a regimen change[25]. A detailed description of each study procedure is presented in the subsequent sections.

Table 1. Summary of Interventions

Intervention	Key Elements
Current TBHIV Care (THC) program standard of care (SoC)	• HIV counseling and testing (HTC) • STI screening and treatment • TB screening and referral • Health education through peer educators and peer supported follow-up related to linkages to care • Referrals to DOH primary healthcare clinics or THC drop-in center for ART treatment initiation and management
Decentralized treatment program (DTP)	• Standard of care, minus clinic referrals for ART treatment initiation and management • Nurse initiated and managed ART within the community on mobile van at sites served by the mobile van which already provides SoC services
Individualized Case management (ICM)	• Standard of Care • Assignment of peer case manager • Face-to-face meeting to tailor ICM approach to FSW preference • Self-efficacy building in face-to-face sessions and bi-weekly text messages • Relational support through monthly calls, face-to-face meetings every three months, and additional support through FSW initiated interaction

For FSW randomized into the 18-month trial, there will be both study and intervention visits. Table 2 below illustrates the study schedule for viraemic FSW at baseline and receiving either intervention, highlighting that study visits will be conducted at baseline and 6, 12, and 18 months post enrollment and intervention visits will occur monthly or bimonthly, as noted and based on randomization. The study procedures and intervention specifics are detailed within the subsequent sections. FSW found to be virally suppressed at baseline will continue to receive South African SoC for HIV and ART treatment and will be passively followed through medical record review for the duration of the study.

Table 2. Study Schedule for Trial

Study Procedure	Enrol-ment	Month																	
		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	✓						✓						✓						✓
Blood Draw (15mL)	✓						✓						✓						✓
Pregnancy testing*							✓						✓						✓
Randomization/Intervention assignment		✓					✓												
INTERVENTION VISITS: Participants assigned to DTP:																			
Iris scan		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monthly ART pickup^		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
INTERVENTION VISITS: Participants assigned to ICM:																			
Face-to-face Meeting		✓			✓			✓			✓			✓			✓		
Monthly calls		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biweekly text messages		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
INTERVENTION VISITS: Participants assigned to DTP+ICM (at month 7 or later):																			
Iris scan								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monthly ART pickup^								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Face-to-face Meeting								✓			✓			✓			✓		
Monthly calls								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Biweekly text messages								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
*Pregnancy testing will also be conducted as part of eligibility screening procedures. ^ Per South African Treatment Guidelines, individuals virally suppressed for 6 months or more may receive bi-monthly medication pick-ups.																			

6.1 Screening

Following recruitment, screening for study eligibility will be conducted face-to-face in a private space using a structured screening tool reflecting the study inclusion and exclusion criteria (Section 5.1).

Eligibility Screening Tool

[Initially conduct pregnancy screening. Provide participant with cup and have her capture urine. Once urine sample provided, test for pregnancy per manufacturer's instructions. Complete the entire questionnaire and then assess eligibility. If pregnant, refer to ANC services and thank her for her time. If deemed ineligible, thank her for her time.]

No.	Question	Code	Response
1	Do you speak English or Zulu?	*00* No *[Not eligible]* 01 Yes	____

2	How many years old are you right now?	*[record age in years]* **<18 years–not eligible*	|__|__|
3	Were you born female?	*00* No *[Not eligible]* 01 Yes	|__|__|
4	Do you identify as a woman?	*00* No *[Not eligible]* 01 Yes	|__|__|
5	Do you live in Durban?	*00* No *[Not eligible]* 01 Yes	|__|__|
6	In the next 12 months, do you plan to leave Durban for more than 3 months?	00 No *01* Yes *[Not eligible]*	|__|__|
7	Does your main source of income come from sex work, i.e. exchanging sex for money or goods?	*00* No *[Not eligible]* 01 Yes	|__|__|
8	Are you HIV-positive?	*00* No *[Not eligible]* 01 Yes	|__|__|
9	Which month and year were you first told that you are living with HIV?	*[record month and year of diagnosis]* **participants with a diagnosis < 6 months - not eligible*	|__|__| |__|__||__|__|
10	Have you been initiated on ARV?	*00* No *[skip to Q12]* 01 Yes	|__|__|
11	Which month and year where you first initiated on ARVs?	*[record month and year of diagnosis]* **participants initiated 2 or more months prior are eligible*	|__|__| |__|__||__|__|
12	Are you taking a fixed dose combination? **confirm through an ARV pill chart or assessing her pills to confirm she is on a first line regimen. Those on a second or third line ARV regimen will not be eligible.*	00 No 01 Yes	|__|__|
13	Do you attend adherence club meetings or get your free ARVs at a local	*00* No *[skip to Q14]* 01 Yes	|__|__|

	CLICKS, Dischem, or another local pharmacy? **confirm by determining if she picks up her ARVs outside of a clinic*		
14	To participate in this study you will need to leave your adherence club. Do you want to leave your adherence club?	*00* No *[Not eligible]* 01 Yes	|__|_|
15	Are you currently pregnant? **Confirm with urine-based pregnancy test*	00 No *01* Yes *[not eligible]*	|__|_|
*[**Interviewer**: Read consent script if participant is eligible thus far. If the individual is ineligible based on the above criteria, enter 'No' ('00') in question 16 and please thank her for her time.]*			
16	Is this person eligible?	00 Not eligible [STOP] 01 Eligible [continue with survey]	|__|_|

6.2 Informed Consent

All women deemed eligible and competent and who are interested in participating will be consented into the study; written informed consent will be obtained from all women prior to enrollment. Consent will be conducted in a private space either at the THC drop-in center, mobile van or sex work venue. The study purpose and description, procedures, events, rights of participants, potential risks and benefits and duration will be explained, allowing for ample time to ask and clarify questions. Upon comprehension of the study information sheet, a copy of which will be provided to a participant if she decides to take it, participants' consent will be demonstrated by a signature or mark on the consent form. We will not attempt to enroll adults who lack capacity to give informed consent (e.g. drunk, high, emotionally disturbed) at that visit. For participants who speak and understand the language used in the consent document, but who are unable to read or write, all information in the consent form will be communicated verbally. Further details outlining the informed consent process are within Section 14.4.

6.3 Enrollment/Baseline

FSW consenting to participation will be enrolled into the study. At the point of enrollment, women will receive a unique study identification number generated based upon their biometric iris scan. Iris scanning will be administered by study staff, trained on iris scanning and the device. The device will scan and capture an image of the participant's eyes and generate a unique identification number for each newly identified iris. The unique identification number will be utilized throughout the duration of the study for tracking, linking, ART pickups, blood draws and provision of laboratory results.

All participants will complete a contact details form at enrollment for contacting, scheduling, and accessing participant electronic health records. Personal identifiers collected for this study include name, date of birth, phone number and address, clinic file number, and iris scan. Collection of personal identifiers is necessary to identify and follow-up participants at various time points and will be kept

separately from study information. A link log will be created linking personal identifiers to the unique identification number and will be kept in a secure, locked cabinet.

All participants will have blood drawn at the enrollment/baseline visit and will be administered a baseline questionnaire. Bloods will be sent to NHLS for VL and CD4 processing and be available to study staff within five days after drop-off. Laboratory evaluations are outlined in Section 7. At the end of the enrollment visit, study staff will schedule a follow up visit with the participant to review test results and proceed with the randomization into the trial for participants who are not virally suppressed. The follow up visit should be scheduled within 7 days of enrollment. Those who are virally suppressed (<50copies/mL) will continue with South African SoC. Participants who are not virally suppressed will be randomized to the DTP or ICM arms. This first enrollment/baseline visit will last approximately 90 minutes, and the follow up visit will last approximately 20 minutes. Both visits will occur at either the THC mobile van or THC drop-in center at the participant's choosing.

General SMS text messages will be automatically sent to all study participants throughout the duration of the study. An initial welcome message will be sent to the participant upon study enrollment, and follow-up messages will be sent annually during the holiday season.

6.4 Randomization and Re-Randomization

Within one week after enrollment, participants will have a follow up visit with study staff to review VL results and potentially undergo randomization. Virally suppressed women will continue with South African SoC. Participants who are viremic will be randomized to the DTP or ICM arms. The baseline randomization to DTP and ICM will be 1:1.

Six months after enrollment, re-randomization will occur based on participants' response to the assigned intervention. Responders are classified as those virally suppressed, following six months of the assigned intervention. Responders will be re-randomized to SoC or to continue on the previously assigned intervention. Re-randomization for responders will be 1:1. Similarly, non-responders are classified as those with VL ≥50 copies/mL, following 6 months of the assigned intervention. Non-responders will be re-randomized to continuation of assigned intervention or step-up to receive both DTP and ICM. Re-randomization for non-responders will be 1:1. A blocked design, utilizing permuted blocks of random sizes, will be used to ensure equal representation of treatment assignment across groups and to ensure that the study team and investigators cannot easily anticipate treatment allocation[26-29].

6.5 Intervention Implementation and Study Visits

The 18-month Siyaphambili Study is comprised of both scheduled study visits and intervention visits. As noted in Section 6.3 all participants, regardless of viral load, will have two initial study visits - a baseline visit for a blood draw and survey followed by a follow up visit to receive their results and be randomized.

6.5.1 South African Standard of Care

Participants virally suppressed will continue with South African SoC, and thus will continue to engage with care and treatment per the South African treatment guidelines[23, 24]. Study staff will access health screening records and HIV-related health data from the South African electronic health records to document VL results. Additionally, participants will continue to access treatment and undergo

management of their HIV as per South African treatment guidelines. Specifically, participants will pick up ART from the THC drop in center or DOH clinic as normal. Figure 2 fully details the number and type of participant visits within the SoC arm for the duration of the study.

Figure 2. South African Standard of Care (SoC) Arm

STANDARD OF CARE

VISIT 0: Enrollment, baseline CD4, VL testing
VISIT 1 [1 week]: VL results, baseline questionnaire
VISIT 2 [1 month]: **N/A** Passive follow-up of engagement in care
VISIT 3 [2 months]: N/A Passive follow-up of engagement in care
VISIT 4 [3 months]: N/A Passive follow-up of engagement in care
VISIT 5 [4 months]: N/A Passive follow-up of engagement in care
VISIT 6 [5 months]: N/A Passive follow-up of engagement in care
VISIT 7 [6 months]: N/A Passive follow-up of engagement in care
VISIT 8 [7 months]: N/A Passive follow-up of engagement in care
VISIT 9 [8 months]: N/A Passive follow-up of engagement in care

STANDARD OF CARE (continued)

VISIT 10 [9 months]: N/A Passive follow-up of engagement in care
VISIT 11 [10 months]: N/A Passive follow-up of engagement in care
VISIT 12 [11 months]: N/A Passive follow-up of engagement in care
VISIT 13 [12 months]: N/A Passive follow-up of engagement in care
VISIT 14 [13 months]: N/A Passive follow-up of engagement in care
VISIT 15 [14 months]: N/A Passive follow-up of engagement in care
VISIT 16 [15 months]: N/A Passive follow-up of engagement in care
VISIT 17 [16 months]: N/A Passive follow-up of engagement in care
VISIT 18 [17 months]: N/A Passive follow-up of engagement in care
VISIT 19 [18 months]: N/A Passive follow-up of engagement in care

Testing/VL testing: DIC/DOH clinic
Where they receive ART: DIC/DOH clinic
*Virally Suppressed ≥6 months can pick up a 2-month supply [adherence clubs available after ≥12 months of viral suppression]
Number of Contacts with Study Staff:
2 Study visits

6.5.2 Decentralized Treatment Program

Viremic participants will be randomized to receive the DTP or ICM intervention. Participants randomly assigned to DTP will be provided with a pre-packed ART drug supply from the THC mobile van. All HIV clinical care, including ART initiation and ART management will be provided per the South African national guidelines by a nurse trained in Nurse Initiated Management of ART (NIMART). For FSW newly initiated onto ART (within the prior six months), one-month supply will be offered, and two-month supply pick up will be offered for participants virally suppressed for great than 6 months[23]. All ART pick up will occur on the THC mobile van at or nearby FSW venues according to a pre-determined mobile van schedule. Pickups denote DTP intervention visits. If participants miss an ART pickup, study staff will contact the participant to reschedule pick up according to participants' availability and mobile van schedule within 14 days of missed ART pick-up. For participants on ART prior to enrolment in the study and currently receiving HIV care and treatment from a facility outside of THC, medical records and transfer letters will be facilitated by the study team in cooperation with the participant. This will be done in order to ensure proper ART management and to ensure participant is not registered as a defaulter at the facility where she previously received care. THC mobile van will frequent FSW venues on a biweekly basis for ART distribution. It will take approximately 15 minutes for FSW to receive their ART supply from the THC mobile van. Participants will receive impersonalized SMS treatment pickup reminders based on the THC mobile van schedule. The SMS reminders will not include the terms "HIV" nor "ART treatment".

Participants will also have study visits at 6, 12, and 18 months following enrollment. At each of these time points, VL testing, pregnancy testing, and a questionnaire will be administered by trained study staff. Study visits will be conducted at a private location, at THC mobile van or THC drop-in center, per the participant's choosing, and take approximately 60-90 minutes. Participants with incident pregnancies, during the 18-month intervention, will not be removed as a participant from the study. They will be directly referred to ANC in accordance with South African SoC and THC standard procedures, and efforts will be made by the study team to ensure that linkage to care occurs.

In all cases, FSW who have VLs >1000 copies/mL will receive adherence counseling and repeat viral load monitoring in two months, and those with persistent VLs >1000 copies/mL will undergo resistance testing. Those with demonstrated resistance will be referred to a DOH clinic to switch to a second line ART. THC does not administer second line ART. At this point, those participants referred out will be removed from the study intervention, though results will be passively followed. These participants will still engage with study staff for questionnaire administration and VLs as scheduled. As the guidelines allow for nurses to initiate and manage second-line therapy, those individuals will no longer be discontinued from the intervention. Figure 3 details the number and type of study visits for participants within the DTP arm.

Figure 3. Decentralized Treatment Program (DTP) Arm

DECENTRALIZED TREATMENT PROGRAM

VISIT 0: Enrollment, baseline CD4, VL testing, baseline questionnaire
VISIT 1 [1 week]: Mobile, VL results, randomization; pick up one-month supply of treatment
VISIT 2 [1 month]: Mobile, pick up one-month supply
VISIT 3 [2 months]: Mobile, pick up one-month supply
VISIT 4 [3 months]: Mobile, pick up one-month supply
VISIT 5 [4 months]: Mobile, pick up one-month supply
VISIT 6 [5 months]: Mobile, pick up one-month supply
VISIT 7 [6 months]: Mobile, pick up one-month supply, VL testing, pregnancy testing, 6-month questionnaire
VISIT 8 [6 months + 1 week]: Mobile, VL results, randomization
VISIT 9 [7 months]: Mobile, pick up one-month supply
VISIT 10 [8 months]: Mobile, pick up one-month supply

DECENTRALIZED TREATMENT PROGRAM (continued)

VISIT 11 [9 months]: Mobile, pick up one-month supply
VISIT 12 [10 months]: Mobile, pick up one-month supply
VISIT 13 [11 months]: Mobile, pick up one-month supply
VISIT 14 [12 months]: Mobile, pick up one-month supply, VL testing, pregnancy testing, 12-month questionnaire
VISIT 15 [13 months]: Mobile, pick up one-month supply
VISIT 16 [14 months]: Mobile, pick up one-month supply
VISIT 17 [15 months]: Mobile, pick up one-month supply
VISIT 18 [16 months]: Mobile, pick up one-month supply
VISIT 19 [17 months]: Mobile, pick up one-month supply
VISIT 20 [18 months]: Mobile, pick up one-month supply, VL testing, pregnancy testing, endline questionnaire

Testing/VL testing: Mobile
*Virally Suppressed ≥6 months can pick up a 2-month supply
[VL >1000 copies/mL – adherence counseling & repeat VL in 2 months]
[Repeat VL >1000 copies/mL → resistance testing]
Where they receive ART: Mobile
Number of Contacts with Study Staff:
6 Study visits + Intervention Visits (Number will vary)

6.5.3 Individualized Case Management

At enrollment, viremic participants will be randomized to receive the DTP or ICM intervention. Participants randomized to the ICM intervention will receive a standard monthly package of services for individualized coordinated care and support provided by a skilled, trained case manager. Within one-month post enrollment, participants within the ICM intervention will be randomly assigned a peer case manager and have an initial and follow up face-to-face meeting. Ongoing face-to-face meetings will subsequently take place every three months. Specifically, participants will have full-length in-person meetings one, three, six, nine, 12 and 18 months after assignment to the ICM intervention. The month six in-person meeting will occur prior to study visits and potential re-randomization. Each in-person meeting will last approximately 30-60 minutes at the THC mobile van, THC drop-in center, or at the sex work venue of the participant's choosing. Additionally, participants will receive automated SMS text messages (biweekly), phone calls (monthly), and clinic reminders 7 days and 24 hours prior to the appointment. Participants will also be able to directly contact the case manager or send a free "Please Call Me" text to the case manager for more frequent contact. Participants within the ICM intervention will continue to frequent the DOH clinic or THC drop-in center for ART care per South Africa SoC (as previously described).

Within the ICM arm, SMS text messages will be sent for two different purposes. Firstly, automated biweekly support SMS text messages will be sent to participants randomized to the ICM arm on tips for remembering to take treatment, nutritional advice, condom negotiation and information about signs of co-infection. The SMS text messages were purposefully developed in Durban, leverage existing SMS text messages utilized by THC, and were discussed with the investigative team, the Community Advisory Group, and the peers at THC for appropriateness and cultural and social sensitivity. Moreover, the messages have been developed strategically, in a way that reduces the risk of potential loss of confidentiality if someone else sees those messages on participants' phones. Examples of the case management biweekly support SMS text messages can be found below.

> *Case management support messages*
> *Message example #1: I hope u r feeling well today. I am here to support u. To talk to me, send a Please Call Me to this number.*
> *Message example #2: U have rights! To learn more about ur rights, send a Please Call Me to this number.*
> *Message example #3: When you feel like giving up, think about why you started. What are your reasons? What are your goals? To talk to me, send a Please Call Me to this number.*

Just as in the DTP arm, in addition to the ICM activities detailed above, participants will also have study visits at 6, 12, and 18 months following enrollment, lasting between 60-90 minutes per visit. At each time point, VL testing, pregnancy testing, and a questionnaire will be administered by trained study staff. In all cases, participants who have VLs >1000 copies/mL will undergo adherence counseling and repeat viral load monitoring in two months, and those with VLs >1000 copies/mL during repeat monitoring will undergo resistance testing and switch to a second line ART. At this point, participants with drug resistant virus that require a switch to second line treatment will be referred back to SoC, though these participants will still continue to receive the ICM intervention and engage with study staff for questionnaire administration and VLs as scheduled at 12 and 18 months. Women with incident pregnancies, during the

18-month intervention, will not be removed as participants from the study. They will be directly referred to ANC in accordance with South African SoC and THC standard procedures and efforts will be made by the study team to ensure that linkage to care occurs. Figure 4 details the type and frequency of study visits for participants within the ICM arm.

Figure 4. Individualized Case Management (ICM) Arm

INDIVIDUALIZED CASE MANAGEMENT

VISIT 0: Enrollment, VL testing, baseline CD4, baseline questionnaire
VISIT 1 [1 week]: VL results, randomization, assign case manager, monthly contact
VISIT 2 [1 week – 3 weeks]: initial case manager meeting
VISIT 3 [1 month]: Case manager meeting, monthly contact
VISIT 4 [2 months]: Monthly contact
VISIT 5 [3 months]: Case manager meeting, monthly contact
VISIT 6 [4 months]: Monthly contact
VISIT 7 [5 months]: Monthly contact
VISIT 8 [6 months]: Case manager meeting, monthly contact, VL testing, pregnancy testing, 6-month questionnaire
VISIT 9 [6 months + 1 week]: VL results, randomization

INDIVIDUALIZED CASE MANAGEMENT (continued)

VISIT 10 [7 months]: Monthly contact
VISIT 11 [8 months]: Monthly contact
VISIT 12 [9 months]: Case manager meeting, monthly contact
VISIT 13 [10 months]: Monthly contact
VISIT 14 [11 months]: Monthly contact
VISIT 15 [12 months]: Monthly contact, VL testing, pregnancy testing, 12-month questionnaire, Case manager meeting
VISIT 17 [13 months]: Monthly contact
VISIT 18 [14 months]: Monthly contact
VISIT 19 [15 months]: Case manager meeting, monthly contact
VISIT 20 [16 months]: Monthly contact
VISIT 21 [17 months]: Monthly contact
VISIT 22 [18 months]: Case manager meeting, monthly contact, VL testing, pregnancy testing, endline questionnaire

Testing/ VL testing: Mobile
*Viral Suppressed ≥6 months can pick up a 2-month supply
[VL >1000 copies/mL – adherence counseling & repeat VL in 2 months]
[Repeat VL >1000 copies/mL → resistance testing]
Where they receive ART: THC DIC/DOH clinic
Number of contacts with study Staff:
6 Study visits + Interventions visits
Monthly Intervention Components:
- 2 automated text (biweekly)
- 1 phone call (monthly)
- clinic reminders (7 days & 24 hours before)
- missed apt call (as needed)
- in person meeting (every 3 months)

6.6 Endline Assessment

All participants within the trial will have a final study visit at 18 months, either at THC mobile van or THC drop-in center, per the participant's choosing. At this visit, VLs will be taken, pregnancy testing conducted, and an endline questionnaire administered by a trained study nurse and staff, respectively. This final study visit will last approximately 60-90 minutes.

6.7 Early Termination of Visit, if applicable

Early termination of study visit will occur if the participant is deemed under the influence of alcohol or substances. The study team will do everything in their power to avoid commencing a study or intervention visit if the participant is under the influence of alcohol or substances. In the event that a visit is initiated before recognizing the participant is under the influence, the visit will be terminated immediately upon noticing. For any visit terminated early, a full visit will be rescheduled at the earliest convenience with the next two weeks. Moreover, if the participant is cognitively impaired for any other reason or exhibits signs of cognitive impairment during a study or intervention visit, the visit will be terminated early.

Additionally, visits will be terminated early at the discretion of research staff if the participant is emotionally distressed, excessively upset, and/or unable to continue the visit. If the participant exhibits any sign of exacerbated emotional distress or if the staff deems it not in the best interest of the participant to continue with research activities, the study or intervention visit will be terminated immediately. Alternatively, the study team will terminate a visit early if the participant requests to stop participating or for any other reason at the discretion of the study team.

6.8 Criteria for Discontinuation or Withdrawal of a Participant from the Study

Participants will be removed from the study and referred to facility-based care if they have an adverse reaction to antiretroviral therapy that requires clinical follow-up by a physician or monitoring not available at a mobile unit. Participants not virally suppressed after six months and with VL >1000 copies/mL after repeat monitoring will undergo resistance testing. If a switch to second line therapy is needed, participants within the DPT intervention will be discontinued from the intervention and referred to SoC for ART management at a DOH facility. As the guidelines allow for nurses to initiate and manage second-line therapy, those individuals will no longer be discontinued from the intervention. These participants will still engage with study staff for questionnaire administration and VLs as scheduled at 12 and 18 months.

Women with incident pregnancies during the 18-month intervention will not be removed from the study or prevented from engaging in the interventions. Urine-based pregnancy tests will be conducted at scheduled study visits at 6, 12 and 18 months. Participants with incident pregnancies will be directly referred to ANC in accordance with South African SoC and THC standard procedures and efforts will be made by the study team to ensure that linkage to care occurs. Women will be allowed to continue with the intervention given that we would not want to take away an adherence intervention that is working for a woman while she is pregnant.

7. Laboratory Evaluations

The South African NHLS at Inkosi Albert Luthuli Central Hospital (IALCH) will process all study-related laboratory tests and conduct all laboratory evaluations, with the exception of pregnancy tests which will be conducted in the THC mobile van or drop-in center. VL testing will be the predominate biological test conducted in the study, baseline CD4 assessment, resistance testing and routine monitoring and safety bloods will be conducted, as necessary and as outlined within the following sections. NHLS at IALCH will store all biological specimens.

7.1 Laboratory Evaluations/Assays

For participants indicating a prior HIV diagnosis for which no documentation of results or clinical care is available, rapid HIV testing will be conducted through the THC program during the screening process to confirm the individual's HIV status and eligibility. Should the individual screen HIV negative but reaffirm that they have been diagnosed, bloodwork will be sent to the laboratory for confirmation.

Biological testing will be completed by the South African NHLS and in accordance to South African guidelines of HIV treatment and management[23]. NHLS is a certified lab that provides diagnostic services for government clinics and hospitals across South Africa. Repeat bloods will be drawn for samples that are inadequate or unviable. It will be the responsibility of the study team to communicate with the participant and determine a convenient time and location to perform the repeat blood draw either at the drop-in center or at the mobile van.

CD4 testing will occur at baseline for all participants enrolled. VL tests will be conducted at baseline and 6, 12 and 18 months post enrolment for all randomized participants within the 18-month trial. All test results will be returned to participants along with routine and step-up adherence counseling for participants that are not virally suppressed (≥50 copies/mL) per South African SoC. All laboratory activities will be carried out in accordance to South African guidelines, this is inclusive of all routine monitoring and safety bloods[23, 24]. As South African national testing and treatment guidelines for people living with HIV evolve, laboratory activities will be adapted accordingly.

Urine-based pregnancy testing, conducted at baseline, 6, 12 and 18 months post-enrolment, will be done on the mobile van or THC drop-in center and results provided to participants. Pregnancy test results will measure the levels of beta human chorionic gonadotropin (HCG) hormone in the urine. Urine point of care pregnancy testing will be conducted as per the manufacturer's instructions and results provided immediately upon completion of the test.

7.2 Special Assays or Procedures

Per South African SoC, participants who have a VL of >1,000 copies/mL during study follow-up visits will receive a repeat viral load test in two months. For those with persistent VL >1000 copies/mL during repeat monitoring, resistance testing will be conducted. Participants within the DPT intervention will be referred to DOH clinics for switches to drug sensitive regimens if indicated. As the guidelines allow for nurses to initiate and manage second-line therapy, those individuals will no longer be discontinued from the study. Resistance testing will be conducted by the South African NHLS at IALCH.

7.3 Specimen Collection, Preparation, Handling and Shipping

South African Standard of Care

Participants in SoC arm will have 15mL of blood intravenously drawn for laboratory testing conducted by a qualified study nurse at the time of enrollment. As part of the informed consent process, participants will have the option of consenting to the storage of their remaining blood sample for potential future research use. For participants who do not consent to storage of their blood, any extra blood that is not used fully will be destroyed at study completion. Subsequent testing will be conducted per the SoC in South Africa at local DOH clinics or the THC drop-in center and the records will be accessible by study staff though South African electronic health records available within the NICD.

Decentralized Treatment Program and Individualized Case Management

Participants in DTP, ICM, and DTP+ICM arms will have a venous blood draw for laboratory testing conducted by a qualified study nurse at the time of enrollment and subsequent testing at 6 months, 12 months, and 18 months. Additionally, participants who have a viral load of >1,000 copies/mL at any follow-up study visit will receive an additional repeat viral load two months later and if indicated resistance testing as described above (Section 7.2). All laboratory activities will be carried out in accordance to South African guidelines[23, 24], this is inclusive of all routine monitoring and safety bloods. As South African national testing and treatment guidelines for people living with HIV evolve, laboratory activities will be adapted accordingly. At each specimen collection time point 15 mL of blood will be collected for all participants. As part of the informed consent process, participants will have the option of consenting to the storage of their blood sample after viral load testing for potential future research use. For participants who do not consent to storage of their blood, any extra blood that is not used fully will be destroyed at study completion.

Moreover, all participants within the intervention arms of the study will provide a urine specimen for point-of-care urine-based pregnancy testing at 6, 12, and 18 months. Pregnancy tests will occur at the sex work venue, THC mobile van or THC drop-in center. Participants will be provided with a small specimen jars to urinate into. Any extra urine that is not used will be appropriately discarded. Women with incident pregnancies during the 18-month intervention will not be removed as a participant from the study. They will be directly referred to antenatal care in accordance with South African SoC and THC standard procedures and efforts will be made by the study team to ensure that linkage to care occurs[23].

Shipping and Handling

Bloods will be collected by trained nurses on the THC mobile van or drop-in center. A log will track the blood collection, shipping and handling. The log captures the participant's unique ID, date and time of blood draw, NHLS barcode, name of staff collecting blood, temperature in cooler at time of storage and purpose of collection (e.g. specific tests to be processed). Bloods will be dropped at NHLS on a daily basis. The log will also capture when and where samples were dropped off, the total number of bloods submitted, and the signature of the individual receiving the bloodwork.

Sample Storage

For consenting participants, samples will be prepared for long-term storage at the NHLS at IALCH. Plasma will be aliquoted into storage tubes and stored on-site at -80°C for no longer than 10 years.

Retrieving results

Provision of routine HIV safety bloods and VL results will be available within 5 working days and HIV resistances test results within 14 working days to on the NHLS TrakCare WebView facility and within excel format.

8. Assessment of Outcome Measures

Primary, secondary and other prespecified outcomes will be measured at various time points throughout the study.

8.1 Specification of the Appropriate Outcome Measures

We will estimate the effectiveness and durability of interventions focused on achieving HIV viral suppression to inform the current South African SoC. The primary effectiveness outcome is a combined outcome of retention in ART care and HIV viral suppression at 18 months after initial randomization, defined using quantitative viral load assessment with <50 copies/mL, comparing those initially randomized to DTP vs. ICM. FSW who are lost to follow-up or experience death during study follow-up will be grouped with FSW who are not virally suppressed. This will ensure that non-differential loss to follow-up is accounted for in the design, since it is likely strongly associated with loss to ART care and viral rebound. Interim analyses at 6 and 12 months will also be completed. Additionally, combined retention and HIV viral suppression at 18 months among early intervention non-responders will be compared between those receiving continued single vs. combined interventions. Differences in retention and viral suppression outcomes will also separately be compared across groups.

8.1.1 Primary Outcome Measures

The primary outcome of the study is retention and viral suppression at 18 months in those initially randomized to DTP vs. ICM.

8.1.2 Secondary Outcome Measures

The secondary outcomes of the study include:

2. Retention and Viral Suppression of Non-Responders

- Retention and viral suppression at 18 months among month 6 non-responders randomized to continuation of either intervention vs. combined DTP+ICM
- Time Frame: 18 months after enrollment

3. Risk factors of uncontrolled viremia and/or lost to follow-up

- Risk stratification tool to identify FSW at highest risk for uncontrolled viremia and/or loss to follow-up
- Time Frame: Up to 18 months after enrollment

4. Durability of Retention and Viral Suppression of Responders

- Durability of retention and viral suppression among 6-month responders continuing on DTP or ICM vs. those randomized to revert to SoC
- Time Frame: Up to 18 months after enrollment

5. Adherence Assessment

- Self-reported adherence and refill pick-up data to assess adherence across arms
- Time Frame: 6, 12 and 18 months

6. Viral Suppression of Retained Participants

- Among those retained, comparison of viral suppression across arms
- Time Frame: Up to 18 months after enrollment

7. Loss-to-Follow-Up

- Loss-to-follow-up across arms
- Time Frame: 18 months after study enrollment

8. Intervention Acceptability

- Participant reported intervention acceptability
- Time Frame: Up to 18 months after enrollment

9. ART Resistance

- Report and compare resistance across arms
- Time Frame: Up to 18 months after enrollment

10. Comparative cost-effectiveness of interventions

- Comparison of intervention cost-effectiveness according to order of intervention and duration of intervention received
- Time Frame: Up to 18 months after enrollment

Other prespecified implementation outcomes to be measured include:

11. DTP Pick-Ups

- Number and proportion of DTP pick-ups attended within 7-days of scheduled visit
- Number and proportion of DTP pick-ups obtained from THC drop-in center

12. ICM Phone-Based Contacts

- Total number of ICM phone-based contacts; proportion of monthly phone-based contacts attended; 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 without phone

13. ICM In-Person Meetings

- Number and proportion of face-to-face case manager sessions attended

9. Safety assessment and reporting

All study members will be trained and will understand the potential risks to participant safety, how to minimize them and how to detect and report adverse events and serious adverse events that may or may not be related to the study. These will be reported to the PIs, the Data Safety Monitoring Board (DSMB)and the relevant ethics committees in a timely and standardized manner.

9.1 Definition of Adverse Event (AE) and Serious Adverse Event (SAE)

As this study does not include an investigational medical product, adverse event reporting will be limited to events considered of significance, related to study participation, and which could affect the risk/benefit profile of the study or negatively impact the study conduct.

1) *Adverse Event (AE)* - An unfavorable or unexpected sign, including an abnormal laboratory finding or behavioral experience that is temporally associated with the use of an investigational product or intervention activity, whether or not considered related to the product/intervention. AEs will be recorded on a four-point scale based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (potentially life-threatening)[30].

2) *Serious Adverse Event (SAE*) An SAE is an AE that:
   - Results in death or
   - Is life-threatening (i.e. the patient was at risk of death at the time of the AE) or
   - Requires prolongation of existing hospitalization or
   - Requires new inpatient hospitalization or
   - Results in persistent or significant disability/incapacity

   All SAEs, regardless of study relatedness, will be reported to the relevant ethics committees within 72 hours of the study team becoming aware of the event.

3) *Expedited Adverse Experiences (EAEs)*: EAEs are AEs of special interest related to study participation which require expedited reporting to the study PIs, the DSMB and the Ethics committees. These events include:
   - Serious adverse events (SAEs)
   - Non-serious adverse events of special interest resulting from study participation:
     - Physical assault, regardless of severity grade
     - Sexual assault, regardless of severity grade
     - Suicide
     - Parasuicide
   - Non-medical adverse experiences (Social harms) resulting from study participation, specifically:
     - Negative outcomes resulting from inadvertent disclosure of HIV status;
     - Negative experience at healthcare facilities due inadvertent disclosure of sex work status;
     - Negative outcome related to inadvertent disclosure of study participation;
     - Reported theft or confiscation of ARVs by clients, other sex workers, sex work managers (e.g. pimps) or law enforcement;
     - Psychosocial stress related to the addressing of adherence barriers;
   - Any adverse or unexpected events judged by the study team to have, or potentially have, a negative impact on the safety of study participants, the study team, or the community; or which could negatively impact the scientific integrity of the study.

4) *Uncommon events of clinical significance:* Adverse drug reactions (side effects) of special interest in the DTP arm:
    - Grade 2 or higher laboratory assays (renal and liver functions);
    - Renal or liver failure;
    - Worsening of hepatitis B virus infection;
    - Grade 2 or higher psychiatric disorders;
    - Any grade 2 or higher adverse drug reaction;
    - Immune reconstitution inflammatory syndrome (IRIS);

9.2 Event Detection and Reporting Procedures

All adverse events and adverse experiences reported by study participants will be documented in participant files and will receive appropriate clinical and programmatic management and referrals. All expedited adverse experiences related to the study or directly related to the antiretroviral treatment will be reported to the PIs, the Data Safety Monitoring Board (DSMB) and the relevant ethics committees within 72 hours of the study team becoming aware of the event. Other non-serious adverse events or adverse experiences (such as physical and sexual assault) which are not related to participation in the study but reported during the 6-monthly surveys or through other means (e.g. to study staff, to case managers, to a study nurse, etc.) will be reported to the relevant ethics committees within periodic, annual progress reports.

Uncommon events of clinical significance will be documented and reported to PIs in an expedited manner. These will be also reported to DSMB on 6-monthly basis and South African pharmacovigilance, as needed. Uncommon events of clinical significance will be reported to ethics only as it aligns with their reporting requirements.

9.2.1 Reporting of Pregnancy

Participants will be tested for pregnancy at screening for study eligibility. At enrollment, pregnant participants will be excluded from the study. Pregnancy testing will be conducted at 6, 12, and 18 months following enrollment. Women with incident pregnancies, during the 18-month intervention, will not be removed from study participation. Instead, participants will be directly referred to ANC in accordance with South African SoC and THC standard procedures and efforts will be made by the study team to ensure that linkage to care occurs.

9.2.3 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

This study is not testing an investigational medical product and therefore adverse event reporting will be limited to events considered of significance and which could affect the risk/benefit profile of the study or negatively impact the study conduct. Uncommon events of clinical significance related to the ART regimen currently provided as part of South African SoC, will be reported to South African pharmacovigilance, as needed (as outlined within section 9.1).

9.2.4 Type and Duration of the Follow-up of Subjects After Adverse Events

The range of actions that may be taken include an administrative hold on the study pending receipt of further information from the PI in a time period not to exceed 90 days, modification of the protocol,

provision of additional information to past participants, requiring current participants to re-consent, and in extreme cases, stoppage of the trial. The ethical review committees will have the authority to suspend or terminate approval of any research that has been associated with unexpected serious harm to participants. Conditions that would lead to stoppage of the trial include a direct causal link between study procedures and hospitalization or death of any research participants.

9.5 Safety Oversight

The primary responsibility of the DSMB is to review study progress and interim safety. In adaptive SMART designs, traditional stopping rules typically do not apply. Thus, efficacy will be reported to and reviewed by the DSMB, but review of efficacy data is not a primary function of the DSMB. The DSMB will meet prior to the launch of the study at which time the DSMB Charter will be reviewed and consensus on the Charter reached prior to study launch. The DSMB will meet 6-monthly to review study progress and data, as well as on an ad-hoc basis as requested by the DSMB Chair or Principal Investigator.

The DSMB Chair will be the contact person for the DSMB and will be responsible for overseeing the meetings and developing the meeting agenda in consultation with the study team. No member of the DSMB will have direct involvement, financial, scientific, or otherwise, with the study to avoid conflict of interest. Written documentation attesting to absence of conflict of interest will be required.

The DSMB is comprised of members with a range of expertise, including clinical expertise, members who work closely with the sex work community, and a statistician. The members have collective expertise in HIV, research with female sex workers, and HIV trials.

The DSMB will receive updated enrollment data every six months and will review the cumulative data in relation to safety, study conduct, and scientific validity. A DSMB meeting may be requested by DSMB members or the Principal Investigators at any time to discuss safety concerns or changes in external factors as noted below. The DSMB may also review overall study operations, including data quality, completeness, and timeliness, adherence to the protocol, and compliance with projected targets for recruitment and retention. As described in detail above, adverse events and interim outcomes will be submitted to all ethical review committees in a timely manner for their independent review. Based on the enrollment data, adverse events reported, and the performance of overall study operations, the DSMB will determine whether to recommend continuation, modification or termination of the trial. The DSMB will not only consider study-specific data and procedures but will also weigh the specific needs of this key population in their review in order to adequately minimize research-associated risk. All materials, discussions, and proceedings of the DSMB will be completely confidential. Confidentiality of participant data will be a high priority of the DSMB, and DSMB members will maintain strict confidentiality concerning all trial results.

External factors relating to participant safety will be weighed in the recommendations made by the DSMB. The DSMB will continuously monitor the literature for potential changes that may affect the ethics of the research study. External factors include legal contexts affecting marginalized women, HIV prevention and treatment guidelines in South Africa, and novel research findings that may affect the intervention design and implementation and will be reviewed at the regularly scheduled meetings. Ad

hoc meetings may be called if there are external factors that might impact continuation of the trial as designed.

Within two weeks of each DSMB meeting, the DSMB chairperson will generate two reports, 1) A Letter describing the DSMB findings and recommendations to the corresponding PI, and 2) a detailed interim analysis report. The letter will be based on each DSMB meeting and will include a recommendation to continue the trial without modification, continue the trial with modification, stop the trial due to safety concerns, or stop the trial for another reason. The PI will review and respond to the DSMB recommendations, and the PI will disseminate all DSMB reports, responses and final decisions to the relevant ethics committees according to the reporting requirements of those committees. In addition, a DSMB Report will be generated which will contain the date and time of DSMB meeting, the DSMB members and other individuals in attendance during the open and closed sessions, the verification that all analyses mandated for review by this Charter was received and reviewed by the DSMB, documentation of any other analyses requested and reviewed by the DSMB, all data analyses reviewed, comments by the DSMB on reviewed analyses, and recommendations of the DSMB. The Interim Analysis Report will be kept by the DSMB chair until the study has been terminated and the report will be given to the corresponding PI to be filed with other study documents.

10. Clinical Monitoring Structure

Antiretroviral therapy and treatment for participants in the DTP arm will be managed by a study nurse certified in provision of ART initiation and management. South African treatment guidelines will be followed including all routine procedures for monitoring side effects, safety bloods and responsiveness to ART[23, 24].

Specifically, in accordance with the national guidelines, the baseline and routine clinical and laboratory assessment for women will depend on the phase of HIV management. At enrollment, women who present without documented proof of HIV status will receive rapid HIV test according to the regional testing algorithm. All participants will receive a baseline CD4 test, regardless of when diagnosis occurred, to obtain a baseline understanding of participant's immune status. Moreover, participants with CD4 count <100/µl will be eligible for Cryptococcus Antigen (CrAg) test to assess if there is disseminated cryptococcal infection. If CD4 ≤200, co-trimoxazole will be provided and stopped after one year if CD4 >200 and patient is well on ART. To identify any concomitant chronic diseases, all participants will receive an assessment of hypertension and diabetes with blood pressure and urine glycosuria, TB screen using TB screening tool, screen for HBV, STIs and syphilis. All women will have weight and height captured. THC administers the generic ART regimen, a Efavirenz + tenofovir disoproxil fumarate (DF) + FTC single-pill combination. Therefore, a creatinine and alanine transaminase (ALT) test will also be provided to assess renal sufficiency and exclude liver dysfunction, respectively. ART should be initiated as soon as patient is ready and within two weeks of CD4 count being done.

Furthermore, in accordance with the national guidelines for routine clinical and laboratory monitoring, if already on ART, participants should be screened for TB symptoms at each visit to identify for TB/HIV co-infection, asked about side effects, and creatinine should be tested at month 3, 6, 12 and then every 12 afterwards to identify for tenofovir DF-related renal toxicity. CD4 testing will also be conducted annually.

Should the South African national HIV treatment guidelines change over the duration of the study, the prescribed routine procedures are subject to change and will be adapted accordingly.

11. Statistical Considerations

Statistical considerations, specifically around sample size and participant recruitment and retention, will ensure the study is able to detect important differences in the outcomes outlined in Section 8. Moreover, the statistical analysis plan will outline the analyses that will be conducted to address the main aims of the study.

11.1 Sample Size Considerations

We estimated the minimum sample size required for a part-factorial SMART experimental design using an R package[31]. The sample size was based on the probability (k=0.8) that a minimum number of subjects (m=50) will be observed in each cell of the final assessments at 18 months post-randomization (Figure 1). We posit that the interventions will improve viral suppression by 40% at 18 months post-randomization. Thus, with a sample size of 601, we will have 80% power to detect a difference of ≥12% between the two interventions. We assume a cumulative 30% loss to follow-up at the end of the study period and distributed equally across each 6-month study visit, resulting in a total minimum sample size required for randomization of 782 FSW living with HIV who are not virally suppressed. Thus, to ensure a sufficient sample size we will enroll 800 FSW living with HIV into the sample. Based on local estimates of 60% HIV prevalence (Figure 1), and 30% viral suppression/refusal at randomization[32], we estimate that the number needed to screen within THC services is 1905 to achieve our enrollment targets. This will require screening an average of 40 FSW per week in Durban and its surrounding area at mobile sites and drop-in centers, which is in line with current service delivery targets. All estimates are based on an intention-to-treat (ITT) analysis of the primary outcome of viral suppression between the two initially randomized arms. Note that the difference in detectable effect sizes between DTP and ICM groups will be affected by the overall ability of the interventions to improve retention and viral suppression. As stated above, we have posited an improvement in overall retention and viral suppression among participants of 40%. By designing for a minimum of 50 subjects per final cell, we will be able to conduct sub-group analyses of secondary outcomes comparing results of intensification in non-responders.

11.2 Participant Enrollment and Follow-Up

Viremic participants will be enrolled into the trial. Given the high mobility of FSW, we anticipate 10% loss to follow-up will occur between each study 6-month study visit, resulting in an expected cumulative retention of 70% of FSW undergoing intervention assignment.

To reduce loss of follow up over time, retention will be closely monitored by a retention officer, the peer navigator on the study team, and the entire study team will proactively attempt to ensure retention of all study participants. The study team will work to cultivate positive relationships with participants and whenever possible the same study staff will engage with the same participant over time. Building rapport with the participants will build good trust and encourage participation and retention, without being coercive. Moreover, loss to follow up will be incorporated into the primary outcome through an intention-to-treat analysis.

11.4 Statistical Analysis Plan

We will estimate the effectiveness and durability of interventions focused on achieving HIV viral suppression. The primary effectiveness outcome is a combined outcome of retention in ART care and HIV viral suppression at 18 months after initial randomization, defined using quantitative viral load assessment with <50 copies/mL, comparing those initially randomized to DTP vs. ICM. FSW who are lost to follow-up or experience death during study follow-up will be grouped with FSW who are not virally suppressed. This will ensure that non-differential loss to follow-up is accounted for in the design, since it is likely strongly associated with loss to ART care and viral rebound. Interim analyses at 6 and 12 months will also be completed. Additionally, combined retention and HIV viral suppression at 18 months among early intervention non-responders will be compared between those receiving continued single vs. combined interventions. Differences in retention and viral suppression outcomes will also separately be compared across groups. These and other secondary outcomes (including alternate adherence measures) are outlined in section 8 (Outcome Measures).

11.4.1 Analysis Plan for Study Outcomes

A summary of the analysis plan for each outcome is provided below:

Primary outcome:

1. *Retention and viral suppression (<50 copies/mL) at 18 months post-enrollment in those initially randomized to DTP vs. ICM*

- Difference of proportions intention-to-treat (ITT) analysis comparing retention and HIV viral suppression at 18 months between FSW randomized to DTP vs. 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 vs. combined DTP+ICM*

- Difference of proportions intention-to-treat (ITT) analysis comparing retention and HIV viral suppression at 18 months between FSW randomized to continuation of either single intervention (group 1) vs. a combined approach (group 2).

3. *Risk factors of uncontrolled viremia and/or lost to follow-up*
    - Predictors of responding to individual versus combined interventions - including age, parity, migration history, years in sex work, health characteristics (baseline 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), however this time 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 on DTP or ICM vs. those randomized to revert to SoC.*
    - A log binomial model intention-to-treat (ITT) analysis will be used to compare retention and HIV viral suppression at 18 months between FSW responders (viral load <50 copies/mL at 6 months) randomized to continuation of DTP alone (β_1), ICM (β_2) alone or SOC (Reference group [α]).

5. *Self-reported adherence and refill pick-up 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 100% self-reported adherence (100%=1, <100%=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 pick-ups using pharmacy refill data.
    - Additionally, an 'as treated' analysis will be run to assess the impact of the time-varying 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 intention-to-treat (ITT) analysis comparing HIV viral suppression at 18 months between FSW randomized to DTP vs. ICM.

7. *Loss-to-Follow-Up at 18-months*
    - Difference of proportions intention-to-treat (ITT) analysis comparing loss to follow-up at 18 months between FSW randomized to DTP vs. 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 intention-to-treat (ITT) analysis of ART resistance at 18 months between FSW randomized to DTP vs. ICM

10. *Comparative cost-effectiveness of interventions*
    - Through modeling and simulation analyses based on trial data, we will assess the impact of the order and duration of interventions on viral suppression. *See section 11.4.2 for further details.*

Other prespecified implementation outcomes to be measured include:

12. DTP Pick-Ups

- Number and proportion of DTP pick-ups attended within 7-days of scheduled visit
- Number and proportion of DTP pick-ups obtained from THC drop in centre

13. ICM Phone-Based Contacts

- Number of ICM phone-based contacts; proportion of participant initiating phone-based contacts at 6, 12 and 18 months
- Number and proportion of participants randomized to ICM intervention without phone

14. ICM In-Person Meetings

- Number and proportion of face-to-face case manager sessions attended

11.4.2 Analysis Plan for Cost Effectiveness

To estimate the incremental impact and cost-effectiveness associated with study intervention arms to complement empiric data collection, we will develop, parameterize, calibrate, and analyze a Markov-based microsimulation model of FSW who will transition through health-states after becoming infected with HIV. The primary outcome of the model will be to estimate the incremental health benefits (estimated life-years and quality-adjusted life years gained) of achieving HIV viral suppression among FSW, per added cost of scaling-up the proposed intervention arms (DTP, ICM, DTP+ICM) compared to the costs of maintaining the SoC. The model will keep track of FSW in each health state over time, and convert these into generic, scaled, and preference-based measures of health using quality-adjusted life years (QALYs) from existing weights for HIV-related changes in health status in South Africa[33]. Program costs from the health system perspective will also be collected during the trial and include service delivery and treatment costs together with marginal costs of ICM and mobile DTP separately and in combination. Patient-costs will be collected using a standardized questionnaire based on the World Health Organization's "Tool to Estimate Patients' Costs"[34]. Participant costs will include: (a) lost wages and productivity required to attend mobile vs. clinic-based care; (b) transportation and ancillary costs (e.g., food, childcare) necessary for attendance; (c) cell phone use charges to organize attendance; (d) time spent engaging with case managers (e.g., lost wages). An important measure of the intervention will include sustainability. During follow-up visits as well as through evaluations of case managers and mobile nurses, measures of maintenance and routinization of the interventions will be measured. To measure changes in the quality of life associated with the implementation of the interventions, we will use two brief instruments carried out at baseline and 18 months: the brief version of the WHO Quality of Life HIV brief instrument (WHOQOL-HIV BREF) and the EQ-5D to assess participants' quality of life and health utility, respectively[35, 36]. The WHOQOL-HIV BREF is a 31-item instrument that measures quality of life for persons living with HIV across six broad domains: physical health, psychological health, level of independence, social relationships, environment, and spirituality/religion/personal beliefs; the EQ-5D is a five-item survey that can provide estimates of health utility (score from 0 = death to 1 = perfect health). The modeling and economic evaluation will be conducted and reported as per the Consolidated Health Economic Evaluation Reporting Standards[37].

The time-horizon for model analysis will be 24 months, 5 years, 10 years, and life-time. The implementation parameters will include 'effect size' estimates of the different interventions under study, via the primary and secondary outcomes (See 8.1.1 and 8.1.2). The model will be calibrated to the initial study population (observed numbers of FSW diagnosed with HIV, and the cascade under SoC).

12. Access to Source Data/Documents

Study documentation, including but not limited to the research plan, consent form, study tools, standard operating procedures, etc., will be securely shared between the coordinating center and all partners by means of a preset Dropbox Business folder specifically developed for this study. Access to the Dropbox folder will be by email invitation only. As study documents are changed, official amendment requests will be put through to both the JHU IRB and the IRB at the University of the Western Cape.

Source data will be collected, managed and protected using REDCap[38], and in accordance with a detailed Standard Operating Procedure (SOP) for Data Management. All computers with data will be protected by passwords, data files will be stored in encrypted folders on JHBox, and hard copies of data kept in a secure cabinet or room with limited access by individuals on the study team. All consent forms will be stored separately from other study documents, in a discrete secure cabinet or room. Additionally, a link log will be created and will be kept isolated in a secure, locked cabinet and electronic versions in a password protected database stored on a secure sever with minimal individuals who know the password or have access to the key (Project Manager, Data Manager, and Head of Research for emergencies). JHU team members will not have access to the link log. All data available to JHU or collaborators outside of THC will be de-identified.

Tablets and computers will be password protected and returned to the office on a basis and stored in a locked cabinet. Hard paper copies will be available as back-ups in the event that the electronic systems are not working and then entered within two business days into the electronic data collection system. Paper copies will be returned to the office on a nightly basis by a designated study staff, trained in data security, and stored securely in a locked cabinet.

13. Quality Control and Quality Assurance

Data quality control and quality assurance is imperative to ensuring that all research results in the trial are of high quality and are valid. Moreover, systematic and continuous quality control measures and a detailed quality assurance plan is central to making sure that trial activities are conducted as planned and to avoid poor data results, wasted time, effort, and resources and potential harm or risk to participants or the target population. Therefore, the study has enacted a number of quality assurance and control measures.

Furthermore, all study staff will undergo good clinical practice training, focusing on data quality control and quality assurance, and follow daily quality control measures put forth within the protocol, data monitoring plan, and directly by the program coordinator and investigative team. All study staff will be held accountable for data quality.

Inbuilt measures will help support and ensure quality assurance. Data will be collected, managed and protected using REDCap[38]. Data from study visits will be collected on tablets. This will help reduce transcription errors. The questionnaires and other log files will be programmed with built in skip patterns and validation rules. Validation rules (e.g. valid data ranges or logic checks) assist in ensuring that data is captured and recorded in a standardized way. The questions will also be programmed to ensure no question is left blank and/or skipped by ensuring that data collector indicates some sort of refusal or do not know to the unanswered question. Electronic data collection will allow for real-time data monitoring and review to ensure that quality assurance and quality control measures are effectively being implemented and possible issues are being appropriately being addressed. For source data collected with paper-based tools (e.g. data documenting delivery of the intervention), the study staff will enter the data into REDCap and will be specifically trained to reduce transcription errors. Paper-based source documentation will be kept, for verification of possible transcription errors, for up to 10 years following completion of data collection.

Ongoing internal monitoring will be conducted on a daily basis, led by the program coordinator based in Durban, and presented to the investigative team on a weekly basis. The internal monitoring will ensure quality control by actively identifying and mitigating issues, ensuring proper informed consent documents are in place, eligibility criteria preserved, randomization balance, and data quality. Additionally, a source documentation checklist will be employed to ensure all study related activities are carried out as stipulated in the protocol and in a consistent way. The source documentation checklist will also make sure all activities of a visit are completed before participants leaves.

Development of a structured procedures manual will also act as a data quality control strategy. Study procedures will be presented in an instruction-based format and anticipated unexpected circumstances and potential solutions are presented. Moreover, there will be a specific SOP in place to guide and ensure quality control systems. The team will run daily and weekly quality control reports that will identify and flag potential issues.

Moreover, periodic auditing of data collectors and participant files will be conducted. Data collectors will be reviewed to ensure all are abiding by protocol and maintaining the intervention fidelity. Similarly, participant files will be routinely checked for completeness and auditing. This includes, but is not limited to, an inbuilt auditing process for informed consent and other source documentation process.

The entire team is involved in data quality and data management. Open team communication, from data collector to PI, will facilitate uniformity in understanding and facilitating data quality. Research staff are responsible for effectively implementing the data monitoring plan and ensuring data quality measures are upheld. Investigators are responsible collecting and reporting inconsistencies with data and data monitoring plan, and the PIs are ultimately responsible for data quality and integrity. The DSMB, sponsors and ethics may also review overall study operations, including data quality, completeness, and timeliness, adherence to the protocol, and compliance with projected targets for recruitment and retention.

14. Protection of Human Subjects

This study will take preemptive and ongoing measures to ensure the protection of human subjects before, during and after the research study. The study team will ensure participants' privacy is safeguarded and the confidentiality of their data are protected. Moreover, through the process of informed consent, all

women participating in the study will be participating voluntarily and with full knowledge of the study procedures, duration, risk and benefits.

14.1 Declaration of Helsinki

The ethical principles outlined with the Declaration of Helsinki guide this research[39]. The wellbeing of the participants takes upmost importance and precedence over the proposed research and interest of science and society. This research is held to ethical standards that promote respect for persons and protect their health and human rights. Moreover, given that this research involves vulnerable populations, specific and special attention has been inbuilt to ensure the protection of these individuals. As a result, the study has been reviewed and approved by the ethical review boards at Johns Hopkins Bloomberg School of Public Health and University of Western Cape. Participation in the study is voluntary and all subjects must provide informed consent to enroll.

14.2 Institutional Review Board

The clinical site will use the Human Research Ethics Committee of the University of Western Cape for this study. Approval has also been provided by the JHU IRB, which will collect IRB approvals and renewals from the University of the Western Cape.

Johns Hopkins Bloomberg School of Public Health
Institutional Review Board
FWA: FWA0000287
Address: 615 N. Wolfe Street
Suite E1100
Baltimore, Maryland 21205
Telephone number: +1-888-262-3242

University of the Western Cape
Biomedical Research Ethics Committee
FWA: FWA00003205
Address: Robert Sobukwe Road
Top Floor - C Block, Room 28
Private Bag X17, Bellville, South Africa
Telephone number: +27 021 959 2709

14.3 Potential Risks and Benefits

The study has identified a number of potentially direct and indirect risks and benefits to the participant and the larger target population on a whole.

14.3.1 Potential Risks

Participants could be harmed if individuals outside of the study found out about their participation in the study and therefore discovered that they are FSW and are living with HIV. Risks include negative impact on social standing with peers and family, loss of relationship with partner, arrest/incarceration/fine, or discrimination from medical personnel, friends or family members if confidentiality is breached and HIV status or involvement in sex work is disclosed to others. For this reason, the mobile van will only attend sex work hotspots where women are working and already accessing the mobile van for condoms, STI

screening and other health interventions. Moreover, as sex work remains illegal in South Africa and a stigmatized profession, the researchers acknowledge the vital importance of protecting the confidentiality of participants' profession, behaviors, and HIV status.

To minimize risks of psychological and physical harm, all staff will complete sensitivity training on working with FSW. Questionnaires will be conducted in a discrete and secure setting to ensure risks are minimized. In all communications, including text messages, with participants outside of the meeting, questionnaires or other study activities, the investigators will not mention sex work or HIV. Questionnaires will cover topics related to personal health, and stigma and discrimination that may trigger difficult emotions for interview participants, but support will be provided by the nurses and counselors and if additional support is necessary a referral will be offered by THC to a local social worker. During phone calls to schedule study meetings, the staff will only speak to the participant and will not leave a voice message or a message with another person. If necessary, the staff will simply call back another time. When the study is mentioned over the phone or while reminding an FSW of an appointment, it will only be referred to as a study that aims to improve health care for women. Phone numbers utilized to send SMS support messages will be recorded and any messages sent to study participants will be non-specific so as not to disclose anything about the participant should someone else be using her phone. During the case managers monthly calls with participants, the case manager will first establish that they are talking with the correct participant and that the participant is in a safe space to talk. In order to identify that the participant is correct, there will be a code word assigned to each woman which she must identify; should she forget the code word the FSW will be requested to provide her date of birth and mother's first name in order to confirm her identity. Furthermore, a component of the study's interventions includes SMS text messages that will be to send to either remind participants to pick up treatment, attend schedule clinic or study visits, generally support adherence. To protect participants' confidentiality and reduce the risk of potential loss of confidentially, the study name – Siyaphambili – will be utilized to associate these messages to the study and words such as HIV, ARVs and treatment will not be included in the SMS messages.

There are minimal physical risks associated with blood draw for the biological component of the study which may include minor pain or bruising at the site where blood is collected. Some participants may feel faint. These risks are rare. Participants may feel discomfort providing urine samples in the community, especially at the outdoor venues. THC currently conducts urine-based pregnancy testing on the mobile van at the Durban sites and other THC operational sites and will leverage this experience. FSW operating at both indoor and outdoor venues have been able to access this modality with relative ease.

Additionally, participants may face risk or discomfort receiving ART in the community as there may be more of a chance of unwanted disclosure. There may be a potential risk that others in the community may try to mug the participant for ART. FSW may also face risks in returning to their venue of operation with ART. There is a risk ART may be found and would disclose participants' status and could lead to social or physical harms.

Participants will be offered a copy of the information sheet and consent form but will not be required to take it. All participation will be voluntary, and declining participation will not affect access to existing health services available through THC or other partners.

In addition to all data being reported anonymously, we will ensure that any contextual information that might identify a particular individual will not be reported in publications or reports that result from this study.

14.3.2 Known Potential Benefits

Participants in the study will have the opportunity to be a part of the intervention and receive baseline CD4 testing, ongoing viral load testing, pregnancy testing, referrals to care, and pending their randomization, ART management and care at the site that they are working (thus not having to separately go into the clinic) or individualized treatment and adherence support.

Additionally, this study may indirectly benefit participants, as it will inform ART and adherence-focused service scale-up for FSW in South Africa.

14.4 Informed Consent Process

Written informed consent will be obtained for all participants. All participants must be capable of providing informed consent and will be required to provide written informed consent to participate in the study. Individuals must be able to understand English or Zulu in order to participate. Study staff, trained in protection of human subjects in research and good clinical practice, will conduct the informed consent process using the written information sheet and consent scripts and will include a full explanation of the study and what their involvement will be, as well as descriptions of the potential benefits and risks. Participation in the study is completely voluntary. Additionally, part of the informed consent process will request the right to access to health screening records from THC and HIV-related health data from the South African National electronic health records. The consent script will be read to the participants, who will also be allowed to read the printed form, to ensure comprehension. A paper copy of the consent will be made available to all participants for personal records.

Consent will be conducted privately, one-on-one, after confirming eligibility. The consent process will be conducted either in a private room at the THC drop-in center, in a private space at the mobile van or at the sex work venue if that is the preference of the participant and confidentiality can be secured. We will not attempt to enroll adults lacking capacity to give informed consent (e.g. drunk, high, emotionally disturbed). Study staff members will use an information sheet and consent form, approved by the University of the Western Cape Biomedical Research Ethics Committee and the Johns Hopkins School Bloomberg School of Public Health Institutional Review Board. Trained staff will explain the study in detail, outlining the purpose, sequence of events, rights, and potential risks and benefits to participants. This information, along with a local study phone number that can be called with questions or concerns, will be available on a paper version of the approved version of the information sheet. The information sheet and consent form will be given to the participant for review and will be read-aloud by the researcher, who will provide an opportunity for the potential participant to ask questions and seek clarification. Participants will be provided with an opportunity to take a paper consent form and information sheet home with them, though this will not be required. For participants who speak and understand the language used in the consent document, but are unable to read or write, all of the information in the consent form will be communicated verbally. Participants will be asked to demonstrate their informed consent by placing their signature or a mark. If the eligible subject accepts to participate,

he or she will sign or mark the informed consent document on the signature line of the consent form prior to any procedures being done specifically for the study.

14.5 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals less than 18 years of age are not included in the study. In South Africa, the legal age for adults is 18 years. Below 18 years of age, parental consent is required. The determination of the study team was that given parental consent would disclose the occupational and HIV status of potential participants, inclusion in the study was inappropriate. Furthermore, many FSW under 18 years operate as emancipated minors for which parental consent would not even be possible. Enrollment of minors into research without parental consent, even in cases of emancipated minors, is very rarely granted by human research ethics committees in South Africa.

14.6 Subject Confidentiality

Names and contact information will be collected from FSW participating in the study, however all contact information will be kept in a link-log file which will be kept in a locked location separate from other study related data. iRespond iris scans will generate a unique twelve-digit ID per participant (participant ID)[40]. Biometric iris scans will be taken at enrollment and utilized at various points to verify participant identity for ART pick up, questionnaire administration and viral load testing. A link log will be created to link participant ID number and names, and will be kept in a secure, locked cabinet in THC's office and electronic versions in a password protected database stored on a secure sever with minimal individuals who know the password or have access to the key (Project Manager, Data Manager, and Head of Research for emergencies). JHU team members will not have access to the link log. All data available to JHU will be de-identified.

Geographic identifiers will be captured for the sex work venues where FSW primarily operate and the general neighborhood where participants reside for costing analysis. Access to health records and HIV-related health data will be captured from the South African EHR for participants, as well. All computers with data will be protected by passwords, data files will be stored in encrypted folders on JHBox, and hard copies of data kept in a secure cabinet or room with limited access by individuals on the study team. In addition to all data being reported anonymously, we will be extremely careful to ensure that any contextual information that might identify a particular individual not be reported in publications or reports that result from this study (e.g. for FSW: a specific neighborhood where they spend time, a church or organization they attend, or the name of the clinics where they receive care).

14.7 Future Use of Stored Specimens

As part of the informed consent process, participants will have the option of consenting to the storage of their blood sample after viral load testing for potential future research use. For participants who do not consent to storage of their blood, any extra blood that is not used fully will be destroyed.

Blood samples from participants who consent will be stored in-country with our collaborating partners at NHLS at IALCH. Biospecimens will be stored for a period of no longer than 10 years and will be destroyed at the end of this period. The samples will not be used for commercial purposes and non-collaborating partners will not have access to samples. The specimens will not be identifiable and will be

linked to study data only through the unique identifier code previously mentioned. A participant can withdraw consent for use of a biospecimen following consent and this sample will be destroyed.

15. Data Handling and Record Keeping

There will be two main data sources within the study, (1) existing health service data from THC and the national electronic health records; and (2) data collected during study activities. Routinely collected health assessment data will be used from THC and electronic health records (permission to use this data will be requested as part of the study informed consent). Data from THC and the electronic health records will also be used to assess FSW retention in care and adherence to HIV treatment. Existing health service data from THC will be obtained from the THC data capturer and stored into the de-identified patient file. National electronic health records will be utilized for participants passively followed and still engaging in SoC. Data will be extracted from the national health records and stored into the de-identified patient file. Data collected during study health activities are outlined within section 15.3.

All study staff are responsible for appropriate record management, with the project coordinator taking accountability of all record management and associated activities, as outlined in the SOP for Record Management. All participant patient files will be stored in a locked cabinet, with the project coordinator responsible for unlocking access.

15.1 Data Management Responsibilities

Johns Hopkins University (JHU) will serve as the Data Coordinating Center. JHU will support the development and monitoring of data collection systems and will provide technical expertise around data collection including training prior to study launch, setting up quality assurance and quality control systems for the study, and troubleshooting during data collection. JHU will also provide data cleaning support. JHU will work with in-country partners regarding submission to the IRBs, including any amendments to the study protocol, materials, consent forms, etc. and will work with partners to ensure IRB amendments are submitted in a timely manner.

Study modeling partners

University of Toronto will oversee the HIV intervention modeling and cost effectiveness analysis to assess the incremental benefits of this package of interventions.

Study implementation partners

TB/HIV Care (THC) will administer the data collection in Durban, South Africa. They will thus oversee the implementation of the SMART study design and collect biological and quantitative data from FSW living with HIV in accordance with the study protocol and the study SOPs.

Study laboratory partners

The NHLS and the NICD will oversee the laboratory aspects of the study and will run all of the laboratory tests.

15.2 Data Capture Methods

Data will be collected, managed and protected using REDCap[38]. All computers with data will be protected by passwords, data files will be stored in encrypted folders on JHBox, and hard copies of data kept in a secure cabinet or room with limited access by individuals on the study team.

Tablets will be password protected and be returned to the office on a nightly basis and stored in a locked cabinet. Tablets will be backed up immediately upon return to the office or if returned after hours, first thing the following day. Tablets will not be taken into the field if the previous days interviews have not been backed up. Hard paper copies will be available as back-ups in the event that the electronic systems are not working and then entered within two business days into the electronic data collection system. If this is the case, paper copies will be returned to the office on a nightly basis by a designated study staff, trained in data security, and stored securely in a locked cabinet. Paper based deidentified participant data will be stored in the participant file. Consent forms and link logs will be store separately from one another and also stored separately from the patient file.

15.3 Types of Data and Timing/Reporting

The types of data, instrument of data collection, means of data collection and timing of data collection is detailed in Table 2.

Table 2. Siyaphambili Data Sources

Type of Data	Tool/Instrument	Means of collection	Timing of collection
Screening	1. Screening log 2. Eligibility screening questionnaire	1 - 2. Tablet-based (REDCap - Siyaphambili Screening)	Screening - pre-enrollment
Consent	1. Information Sheet 2. Consent form	1 - 2. Paper-based	Pre-enrollment
Participant identification	1. Linking log	2. Paper-based	Enrollment
Contact information	1. Enrollment contact sheet 2. ICM contact sheet	1 - 2. Paper-based	1. Enrollment 2. Upon randomization to ICM
Baseline data (Month 0)	1. Blood collection log 2. Result log (VL, CD4) 3. Baseline questionnaire 4. Source documentation 5. Reimbursement log	1. Paper-based 2 - 3. Tablet-based (REDCap - Siyaphambili Study) 4. Paper- and tablet-based 5. Paper-based	Baseline
Month 6 data	1. Blood collection log 2. Result log (VL, pregnancy test) 3. Month 6 questionnaire	1. Paper-based 2 - 3. Tablet-based (REDCap - Siyaphambili Study)	6 months post enrollment

	4. Source documentation 5. Reimbursement log	4. Paper- and tablet-based 5. Paper-based	
Month 12 data	1. Blood collection log 2. Result log (VL, pregnancy test) 3. Month 12 questionnaire 4. Source documentation 5. Reimbursement log	1. Paper-based 2 - 3. Tablet-based (REDCap - Siyaphambili Study) 4. Paper- and tablet-based 5. Paper-based	12 months post enrollment
Endline data (Month 18)	1. Blood collection log 2. Result log (VL, pregnancy test) 3. Month 18 questionnaire 4. Source documentation 5. Reimbursement log	1. Paper-based 2 - 3. Tablet-based (REDCap - Siyaphambili Study) 4. Paper- and tablet-based 5. Paper-based	18 months post enrollment
Passive follow up of participants within SoC Arm	1. M6 passive follow up log 2. M12 passive follow up log 3. M18 passive follow up log	1 - 3. Tablet-based (REDCap - Siyaphambili Study)	6, 12, 18 months post enrollment
Iris scans	4. IRespond software	1. Iris scanner	At enrollment and prior to: all blood draws, laboratory results administration, questionnaire administration, and ART distribution
DTP pickups	1. DTP log 2. ARV inventory log	1. Paper-based 2. Paper-based	Each scheduled ARV pick up and management of ARV inventory in pharmacy
ICM interactions	1. ICM in-person meeting form 2. ICM call form 3. ICM log 4. ICM SMS log	1 - 2. Tablet-based (REDCap - Siyaphambili Study) 3. Paper-based 4. Paper-based	For each scheduled and unscheduled in-person meeting or phone call with case manager and each text message sent
Randomization	1. Baseline randomization log 2. Month 6 randomization log	1 - 2. Tablet-based (REDCap - Siyaphambili Study)	Upon results of baseline VL and upon results of month 6 VL.
Opportunity Costing Assessment	1. Opportunity costing questionnaire - part 1 2. Opportunity costing questionnaire - part 2	1. Tablet-based (REDCap - Siyaphambili Study)	1. For all participants randomized into trial, 3-6 months after enrolment 2. For all participants randomized into trial, 9-

			15 months after enrolment

Enrolment and randomization numbers, as well as interim analyses and quality control checks will be presented to the investigative team on a weekly basis. Every six months the following will be presented to the DSMB:

1. Summary of logistical issues, review of data quality and any new information that may impact the research being investigated.
2. Protocol violations
3. Study Status: Number of subjects screened, enrolled, randomized across intervention arms, lost to follow-up, discontinued study (with time from entry to discontinuation and reason for discontinuation), and completed study; we will also report on numbers re-randomized after 6 months of study participation
4. Comparison of actual to planned enrollment
5. Demographics of subjects enrolled
6. Primary outcome: viral suppression and loss to follow-up across arms (ITT)
7. Secondary outcomes:
8. Rates and types of grade 2, 3 and 4 adverse events
9. SAE reports filled for all grade 4 adverse events.
10. Evidence of social harm (SAEs, any relevant reports filed by quantitative or qualitative interviewers related to negative impact of the study on participants)
11. Any other data the DSMB chooses to review

Every year the follow will be presented in a progress report to the ethical review board at Johns Hopkins University:

1. Conflict of interest
2. Good clinical practice training and HIPAA training
3. Study status since last IRB review and approval
4. Information on subjects, records and/or samples studied
5. Study activities during this approval period
6. Data security
7. Adverse events and unanticipated problems posing risk to subjects or others, and protocol deviations
8. Data safety monitoring (DSMB) or other monitoring reports
9. Approved amendment summary
10. Funding
11. Progress report summary for this approval period

15.4 Study Records Retention

All analyses will be conducted on de-identified datasets. Two years after the closeout of the study, personally Identifiable Information (PII) and the corresponding link logs will be destroyed. Paper-based source documentation will be kept, for verification of possible transcription errors, for up to 10 years

following completion of data collection. Biospecimens will be stored for a period of no longer than 10 years and will be destroyed at the end of this period.

15.5 Protocol Deviations

The study team will keep a log of protocol deviations throughout the duration of the study. The log will be used for record keeping, reporting, and tracking deviations over time. As the primary grant recipient and the data coordinating center, JHU will report protocol events and deviations to the IRB and to the DSMB in an expedited manner. The study team will do everything possible to ensure that protocol deviations are minimized. All study staff will be trained on how to recognize and report a protocol deviation and open communication between study staff members will facilitate reporting.

The Durban Project Manager will be responsible for ensuring compliance to the study protocol and procedures on a day-to-day basis. The Durban site coordinator, South African investigators, JHU investigators and the JHU Research Coordinator will all be tasked with monitoring compliance during their study visits and reporting any issues noted to the South African and JHU PIs.

16. Publication Policy

Data will be published collaboratively by the investigative team. Both PIs will provide approval prior to publication of any data related to this study. Investigators external to the study, interested in conducting analyses from the data, should contract the PIs for further inquiry and approval.

17. Literature References

1. Baral, S. and N. Phaswana-Mafuya, *Rewriting the narrative of the epidemiology of HIV in sub-Saharan Africa.* SAHARA J, 2012. **9**(3): p. 127-30.
2. Fonner, V.A., et al., *Social cohesion, social participation, and HIV related risk among female sex workers in Swaziland.* PLoS One, 2014. **9**(1): p. e87527.
3. Schwartz, S., et al. *Engagement in the HIV care cascade and predictors of uptake of antiretroviral therapy among female sex workers in Port Elizabeth, South Africa (WEAC01)*. in *International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention* 2015. Vancouver, British Columbia.
4. Baral, S., et al., *Burden of HIV among female sex workers in low-income and middle-income countries: a systematic review and meta-analysis.* Lancet Infect Dis, 2012. **12**(7): p. 538-49.
5. Baral, S.D., et al., *Was the HIV infection burden in female sex workers in China overestimated? - authors' reply.* Lancet Infect Dis, 2013. **13**(1): p. 13-4.
6. Mishra, S., et al., *Distinguishing sources of HIV transmission from the distribution of newly acquired HIV infections: why is it important for HIV prevention planning?* Sexually Transmitted Infections, 2013.
7. Shannon, K., et al., *Global epidemiology of HIV among female sex workers: influence of structural determinants.* Lancet, 2014.
8. Taskforce, S.W.E.A. and I. Consulting, *Sex Workers in South Africa: A Rapid Population Size Estimation Study*. 2013, South Africa National AIDS Council: South Africa.
9. Arnott, J. and A.L. Crago, *Rights not Rescure: A Report on Female, Male, And Trans Sex Workers' Human Rights in Botswana, Nambiia, and South Africa*. 2009, OSI: New York City, USA.
10. Needle, R., et al., *Sex, drugs, and HIV: rapid assessment of HIV risk behaviors among street-based drug using sex workers in Durban, South Africa.* Soc Sci Med, 2008. **67**(9): p. 1447-55.

11. Ngugi, E.N., et al., *Female sex workers in Africa: epidemiology overview, data gaps, ways forward.* SAHARA J, 2012. **9**(3): p. 148-53.
12. Baral, S., et al., *Modified social ecological model: a tool to guide the assessment of the risks and risk contexts of HIV epidemics.* BMC Public Health, 2013. **13**(1): p. 482.
13. Mountain, E., et al., *Antiretroviral Therapy Uptake, Attrition, Adherence and Outcomes among HIV-Infected Female Sex Workers: A Systematic Review and Meta-Analysis.* PLoS One, 2014. **9**(9): p. e105645.
14. Mountain, E., et al., *The HIV care cascade and antiretroviral therapy in female sex workers: implications for HIV prevention.* Expert Rev Anti Infect Ther, 2014. **12**(10): p. 1203-19.
15. Kerrigan, D., et al., *The Global HIV Epidemics among Sex Workers*, G.A.M.a.E. Team, Editor. 2012: Washington, DC:.
16. Georgeu, D., et al., *Implementing nurse-initiated and managed antiretroviral treatment (NIMART) in South Africa: a qualitative process evaluation of the STRETCH trial.* Implementation Science : IS, 2012. **7**: p. 66-66.
17. Baral, S., et al., *Enhancing benefits or increasing harms: community responses for HIV among men who have sex with men, transgender women, female sex workers, and people who inject drugs.* J Acquir Immune Defic Syndr, 2014. **66 Suppl 3**: p. S319-28.
18. Beyrer, C., et al., *Expanding the space: inclusion of most-at-risk populations in HIV prevention, treatment, and care services.* Journal of acquired immune deficiency syndromes, 2011. **57 Suppl 2**: p. S96-9.
19. Holland, C.E., et al., *Antiretroviral treatment coverage for men who have sex with men and female sex workers living with HIV in Cameroon.* J Acquir Immune Defic Syndr, 2015. **68 Suppl 2**: p. S232-40.
20. Peitzmeier, S.M., et al., *Associations of stigma with negative health outcomes for people living with HIV in the Gambia: implications for key populations.* J Acquir Immune Defic Syndr, 2015. **68 Suppl 2**: p. S146-53.
21. Mishra, S., et al., *Exploring the population-level impact of antiretroviral treatment: The influence of baseline intervention context.* AIDS, 2014. **28**(Suppl 1): p. S61-72.
22. Karim, Q.A., et al., *HIV incidence in young girls in KwaZulu-Natal, South Africa-Public health imperative for their inclusion in HIV biomedical intervention trials.* AIDS and behavior, 2012. **16**(7): p. 1870-1876.
23. Africa, D.o.H.R.o.S., *National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents, and Adults*. 2015: Pretoria, South Africa.
24. Africa, D.o.H.R.o.S., *Primary Care 101*. 2013/2014: The National Department of Health Privay Bag x828 Pretoria 0001.
25. Africa, D.o.H.R.o.S., *The South African Antiretroviral Treatment Guidelines*. 2013: Johannesburg, SA.
26. Efron, B., *Forcing a Sequential Experiment to be Balanced.* Biometrika, 1971. **58**(3): p. 403-417.
27. Markaryan, T. and W.F. Rosenberger, *Exact properties of Efron's biased coin randomization procedure.* 2010: p. 1546-1567.
28. Antognini, A.B. and A. Giovagnoli, *A New 'Biased Coin Design' for the Sequential Allocation of Two Treatments.* Journal of the Royal Statistical Society. Series C (Applied Statistics), 2004. **53**(4): p. 651-664.
29. Antognini, A.B., *A theoretical analysis of the power of biased coin designs.* Journal of Statistical Planning and Inference, 2008. **138**(6): p. 1792-1798.
30. Division of AIDS, N.I.o.A.a.I.D., National Institues of Health, US Department of Health and Human Services, *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events*. 2017.

31. Almirall, D., Compton, S. N., Gunlicks-Stossel, M., Duan, N., & Murphy, S. A. , *Designing a pilot sequential multiple assignment randomized trial for developing an adaptive treatment strategy.*, T.M. Center, Editor. 2011, The Pennsylvania State University: niversity Park, PA:.
32. F.M. Cowan, C. Davey, S. Napierala Mavedzenge, P. Mushati, S. Mtetwa, T. Chiyaka, V. Cambiano, N. Masuka, M. Chemhuru, O. Mugurungi, D. Hanisch, K. Hatzold, J. Busza, A. Phillips, J. Hargreaves. *Estimation of the HIV care cascade for female sex workers in Zimbabwe: baseline results of the SAPPH-Ire trial (Abstract THAC0305LB)*. in *International AIDS Conference*. 2014. Melbourne: IAS.
33. Eaton, E., et al., *Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models.* Lancet Global Health, 2013. **2**(1): p. e23-34.
34. KNCV Tuberculosis Foundation, W., Japan Anti-Tuberculosis Association. *Tool to Estimate Patients' Costs*. 2008; Available from: http://www.stoptb.org/wg/dots_expansion/tbandpoverty/assets/documents/Tool%20to%20estimate%20Patients'%20Costs.pdf.
35. Rabin, R. and F. de Charro, *EQ-5D: a measure of health status from the EuroQol Group.* Ann Med, 2001. **33**(5): p. 337-43.
36. Organization, W.H., *WHOQOL-BREF Introduction, Administration, Scoring and Generic Version of the Assessment*, in *Program on Mental Health*. 1996, World Health Organization: Geneva.
37. Husereau, D., et al., *Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.* Int J Technol Assess Health Care, 2013. **29**(2): p. 117-22.
38. Harris, P.A., et al., *Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of Biomedical Informatics, 2009. **42**(2): p. 377-381.
39. Organization, W.H., *Declaration of Helsinki*. 2001.
40. iRespond. *iRespond*. 2017; Available from: https://www.irespond.org/.