Study Protocol

Adherence to HIV Treatment Postpartum: The Implications of Transitions Among Women Living with HIV in South Africa

ClinicalTrials.gov #: NCT04846569

Version 5.0

November 5, 2021

IRB Federalwide Assurance Numbers:

- FWA00004460 (Brown University)
- FWA00001637 (University of Cape Town)

Study Sponsor: National Institute of Mental Health (K01MH112443)

Protocol Summary

Adherence to HIV Treatment Postpartum: The Implications of Transitions Among Women Living with HIV in South Africa

Study Aims:

Aim 1: Identify contextual, interpersonal, clinic, and individual-level factors that influence women's HIV treatment adherence during periods of key points of transition during pregnancy and postpartum, using longitudinal in-depth qualitative interviews among a cohort of pregnant women (N=25-30) following them up to 12 months postpartum.

Aim 2: Evaluate the feasibility and preliminary efficacy of a Transition Theory-based ART adherence intervention for postpartum women living with HIV, using a small scale randomized controlled trial (RCT; N=60).

Aim 3: Assess participants' experiences of the intervention, perceived usefulness, and identify ways to refine the intervention for future evaluation, using in-depth individual interviews will be conducted with all participants in the intervention condition after follow-up assessments have been completed.

Sample size for RCT: 62 participants consented; 43 randomized

Study population: Adult (≥ 18 years), HIV-positive, pregnant (23-34 weeks) women attending antenatal services at the study site, prescribed ARVs

Participating site: Gugulethu Midwife Obstetric Unit, Cape Town, South Africa

Study design: Small-scale two-arm randomized control trial, assessing feasibility and preliminary efficacy.

Study timeline for RCT: April 2021-December 2022

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Abstract From NIH Application

Prevention of mother-to-child transmission (PMTCT) efforts have reduced the rates of vertical transmission to 2.7%, however, optimal antiretroviral therapy (ART) adherence remains a difficult goal to reach, particularly postpartum. The contribution of the proposed research is expected to be two-fold: 1) to gain an understanding of how influential contextual, interpersonal, clinic, and individual level factors change during key moments of transition during pregnancy and postpartum and influence ART adherence and 2) to develop bio-behavioral interventions to assist mothers in maintaining their adherence to ART postpartum. Candidate: I am a social psychologist with a background in ART adherence socially disadvantaged groups in the United States. I am applying for a five-year K01 Career Development Award to obtain training, mentorship, and research experience to become an expert in maternal health among women living with HIV in resource limited settings and an independent investigator capable of obtaining R01 funding. Mentoring: I have put together an exceptional mentoring team with extensive experience in HIV treatment and prevention research in South Africa that integrates epidemiology, qualitative methods, and clinical science. Drs. Don Operario and Mark Lurie will serve as co-Primary mentors and bring complementary expertise in international HIV behavioral intervention development and infectious disease epidemiology. In addition to my two Primary mentors, my co- mentors provide expertise in specific content areas and methodologies and are based in both the U.S. and South Africa (ZA). My co-mentorship team includes: Dr. Susan Cu-Uvin (U.S.-based, clinical management of HIV, obstetrics and gynecology), Dr. Landon Myer (ZA-based, perinatal epidemiology, postpartum ART adherence), Dr. Abigail Harrison (U.S.-based, longitudinal qualitative methods, sexual and reproductive health), and Dr. Christopher Colvin (ZA-based, qualitative methods, maternal child health). Training: Specific training in perinatal epidemiology, longitudinal qualitative methods, theory-based interventions, cross-cultural intervention development and evaluation will be achieved through intensive mentored training, coursework, workshops and directed readings and primary ZA research. Guided by my excellent mentorship team, these training and research experiences will establish my independent investigator career as an expert in developing HIV treatment and prevention interventions to address maternal health in high impact, low resource settings, that take into account key moments of transition and change that impact health behaviors. Research: The goals of the proposed project are to (1) identify contextual, interpersonal, clinic, and individual level factors that influence women's HIV treatment adherence during key period of transition during pregnancy and postpartum; (2) evaluate a Transition Theory-based bio-behavioral intervention to improve ART adherence postpartum using a small scale randomized controlled trial; (3) assess participants' experiences of the intervention, perceived usefulness, and identify ways to refine the intervention for future evaluation

Introduction

It is a critical time in the South African HIV epidemic to increase HIV treatment adherence among postpartum mothers. During pregnancy and postpartum, women living with HIV are eight times more likely to die than women who are HIV negative.[1] Prevention of mother-to-child transmission (PMTCT) efforts have reduced rates of vertical transmission to 2.7% in South Africa (ZA),[2] however, optimal postpartum adherence to HIV treatment, a key

component of PMTCT, remains difficult.[3,4] There are significant consequences of non-adherence postpartum including viral rebound,[5-7] which increases infectiousness to sex partners[8] and infants while breast-feeding,[9] and an increased chance of drug resistance,[10-14] which is particularly concerning in resource-limited settings where additional lines of ART may be limited.[15] Women who are non-adherent are also at risk for AIDS-related complications, including tuberculosis,[16] candidiasis,[17] and cytomegalovirus,[18] which can create high-risk pregnancies and jeopardize maternal and infant health.

Option B+ policies, which provide antiretroviral therapy (ART) to all HIV positive pregnant women for life, regardless of CD4 T cell count, have been adopted in many countries as a way to simplify health services and increase access and uptake.[19,20] There is major concern, however, about suboptimal engagement in care postpartum after mothers transfer from antenatal clinics to regular adult HIV care and the ability for women to adjust to lifelong treatment.[21-25] In Cape Town, ZA, 49% of women living with HIV have disengaged from care by six months postpartum[26] and a meta-analysis[3] of 51 studies found that only 53% of the women had optimal adherence postpartum. Additionally, it is hard to determine with precision when drop-offs in ART adherence occur due to the wide range of time points (3 days to 12 months) used to denote "postpartum" adherence in the literature.[27-33] In order to fully capitalize on the potential that Option B+ has for simplifying HIV treatment, it is necessary to identify when and why women become non-adherent to ART and how influential factors may change as HIV positive mothers transition from pregnancy to postpartum.

Pregnant and postpartum women are faced with individual, contextual, and systems-level facilitators and barriers to HIV treatment adherence.[34,35] Evidence shows lower education,[36] difficulties managing the practical demands of ART,[37] perceptions of being healthy, and the use of alcohol and drugs[29,31] are associated with suboptimal adherence. A major gap in evidence, however, is that previous studies rarely distinguish between pregnancy and postpartum, providing little information about the changes that occur during this crucial transitional window period.[35] A longitudinal perspective is necessary to accurately capture the complexities of women's lives and how motivations and behaviors change across this transition from pregnancy to early motherhood.[38] Additionally, balancing self-care with infant care, changes in familial roles, and finding out the infant's HIV status are all associated with this transition and may influence adherence, however, discussion of these factors is minimal in the ART adherence literature.[35] Furthermore, the extendibility of previous ART adherence interventions for general populations may not be appropriate for the special individual and contextual barriers that pregnant and postpartum mothers face.[35] Globally, ART adherence interventions tailored for pregnant and postpartum women are severely lacking.[39-41]

The contribution of this K01 research is expected to be two-fold: 1) to gain an understanding of how contextual, interpersonal, clinic, and individual level factors change during key moments of transition during pregnancy and postpartum and impact ART adherence and 2) to develop bio-behavioral interventions to assist mothers in maintaining their adherence to ART postpartum. The contribution of the proposed research will be significant because optimal ART adherence decreases rates of HIV transmission to infants and sexual partners, increases maternal general health and immune functioning, and decreases maternal mortality. Postpartum mothers are an ideal, high-risk population for achieving 90-90-90 targets, as they are already engaged within the health system and may be uniquely motivated by the life transition of birth.[42]

Theoretical Framework. Transition Theory[43] provides an innovative framework to guide the current research on HIV treatment adherence among pregnant and postpartum women.

Transition Theory (Figure 1) allows us to characterize and describe the transitions that occur during this window period by clearly delineating the relevant personal and environmental characteristics that may facilitate or impede a successful transition, which could lead to sub-optimal ART adherence. With Transition Theory, we can conceptualize pregnancy and postpartum among women living with HIV as a time with multiple related health and developmental transitions. Women experience transition into motherhood (for a first child) or transitions in family roles (for a subsequent child). These women will also experience other transitions such as receiving the results of their infants' HIV PCR test and shifting their own healthcare from antenatal clinics to HIV care clinics. These transitions can present significant challenges for ART adherence. There are also properties of transition experiences that contribute to how well an individual is able to adhere to ART, including awareness about an impending transition – such as being aware for the need to transfer care to an HIV care clinic – and engagement in the processes inherent in the transition – such as seeking out information about infant care. Transition experiences influence outcomes, such as adherence to ART, via transition conditions. Transition conditions are personal and environmental factors that can facilitate or inhibit progress towards a successful transition. These conditions are: (a) personal meanings, including appraisals of the anticipated event and the effect it will have on an individual's life, (b) cultural beliefs/attitudes, (c) socioeconomic status, (d) preparation for the transition, such as actively preparing for the infants' arrival, (e) community factors including family and partner support and (f) societal factors such as marginalization of people living with HIV. Transition Theory also specifies potential intervention techniques, termed nursing therapeutics, including providing knowledge, role modeling, social support, and creating a healthier environment at the familial and community levels. This innovative framework will guide both the informative longitudinal qualitative phase (Aim 1) of this study as well as the development and evaluation of the intervention (Aims 2 & 3).

This K01 application is innovative in several ways. First, this project focuses specifically on women living with HIV postpartum. Previous literature has largely been focused on pregnant women and child/mother dyads within the context of PMTCT and maternal ART adherence has often been considered a secondary outcome, particularly postpartum.[44] Furthermore, there is a dearth of information regarding ART adherence beyond 6 weeks postpartum,[45] which is too narrow a window period for understanding or targeting long-term treatment behaviors. This project aims to expand upon the current view of postpartum ART adherence by studying HIV treatment adherence and the factors that influence this behavior up to 12 months postpartum. In doing so, this project seeks to shift the current PMTCT research paradigm to focus on longer-term engagement in care for women of reproductive age. Additionally, we will use Transition Theory to guide both the informative qualitative research phase and intervention development. This theory has been used to understand the process of first time motherhood and fatherhood[46-48], chronic illness,[49-52] cancer,[53,54] and old age,[55,56] and is a conceptual framework guiding mine and Dr. Operario's current work on PrEP behaviors among young adults in ZA. However, Transition Theory has not been used to study PMTCT and HIV treatment among pregnant and postpartum women and is a novel contribution of the current work. This theory allows for the examination of behavior as personal and contextual factors change across time which provides new insights into how these factors impede adherence and represents a significant advantage over health behavior theories used to study ART adherence previously, particularly for this population.

2. STUDY AIM & OBJECTIVES

Study aim

The objective of this study is to identify how influential factors change during key moments of transition during pregnancy and postpartum and to construct an intervention that effectively addresses these moments of transition to bolster ART adherence for mothers living with HIV.

Study approach

This study includes two phases:

1. A longitudinal qualitative cohort to identify and characterize factors that influence women's adherence behaviors as well as perceptions and motivations for continued treatment and engagement in care and examine participants' preferences of adherence intervention structure and delivery, in order to shape the design components of the bio-behavioral intervention.
2. Conduct an open pilot and small scale RCT of the intervention to determine feasibility, and preliminary efficacy of the intervention to improve ART adherence among pregnant and postpartum women living with HIV and in-depth interviews with intervention participants to determine acceptability and to identify ways to refine the intervention for future evaluation.

Note that Phase 1 received ethical approval from UCT HREC previously (HREC: 344/2017). This protocol focuses on Phase 2 (Aims 2 & 3).

For Phase 2, the key outcomes are:

Primary Outcomes

1. Feasibility: Feasibility will be assessed through the number of counseling sessions completed.
2. Preliminary efficacy - ART Adherence: Preliminary efficacy will be assessed as the correlation between study arm and self-reported HIV adherence on the 3 item Wilson ART adherence scale (self-report, 3 item scale recoded as 0-100, 100 indicating perfect adherence in the past month) at 6 months postpartum.
3. Preliminary efficacy- Retention in HIV services: Preliminary efficacy will be assessed as the correlation between study arm and retention in HIV services at 6 months postpartum. Retention in HIV services is measured by clinic records. Retention at 6 months postpartum is measured as attended HIV clinic appointment in the past 3 months.
4. Preliminary efficacy-viral suppression: Preliminary efficacy will be assessed as the correlation between study arm and viral suppression at 6 months postpartum. Viral suppression will be measured by clinic records, with viral suppression defined as HIV viral load less than 200 copies/mL.

Secondary Outcomes

1. Adherence self-efficacy - confidence in taking medications: Adherence self-efficacy will be measured using the AACTG adherence self-efficacy scale, 15 items, using 5 point Likert scale ranging from not confident at all to very confident. Total scores range from 15-75, with higher scores indicating higher self-efficacy.

2. Acceptability/Utility of the Intervention: Acceptability of the Transition Theory-based intervention, assessed during in-depth interviews among participants in the intervention condition to gauge general feelings of acceptability and perceived usefulness of the intervention.

3. Study Design

Overview

We propose to address these objectives using a two phase design in which we identify how influential factors change during key moments of transition during pregnancy and postpartum and to construct an intervention that effectively addresses these moments of transition to bolster ART adherence and engagement in care for mothers living with HIV.

Phase 1 (Aim 1)

Phase 1 involved a longitudinal qualitative cohort design with interviews with 30 pregnant and postpartum women at 4 time points to identify contextual, interpersonal, clinic, and individual-level factors that influence women's HIV treatment adherence during periods of key points of transition during pregnancy and postpartum. (HREC 344/2017)

Phase 2 (Aims 2 & 3)

Aim 2: *Evaluate the feasibility and preliminary efficacy of a Transition Theory-based ART adherence intervention for postpartum women living with HIV*

Informed by Aim 1, this intervention will be tested using an open pilot (n=5) and a small scale randomized controlled trial (RCT; n=60 to complete baseline). The purpose of the open pilot is to pretest all study procedures, particularly recruitment and retention, to increase the feasibility of the RCT, as well as to pilot test the intervention content. Primary hypothesis if the RCT: The intervention will be feasible to conduct with postpartum women living with HIV in Cape Town, South Africa. Secondary hypothesis: Postpartum women in the intervention condition will have better ART adherence than women in the control condition at follow-up.

For the RCT, pregnant women living with HIV (n=60 to complete baseline; up to n=100 will be approached) will be approached to participate. Following informed consent, women will complete an enrollment study visit and will then be randomized to one of two arms:

- Arm A (Transition theory-based intervention): Women randomized to this arm will receive monthly one-on-one meetings with a community health worker for four months during late pregnancy and early postpartum
- Arm B (enhanced standard of care): Women randomized to this arm will receive one meeting with a community health worker in addition to the local standard of care.

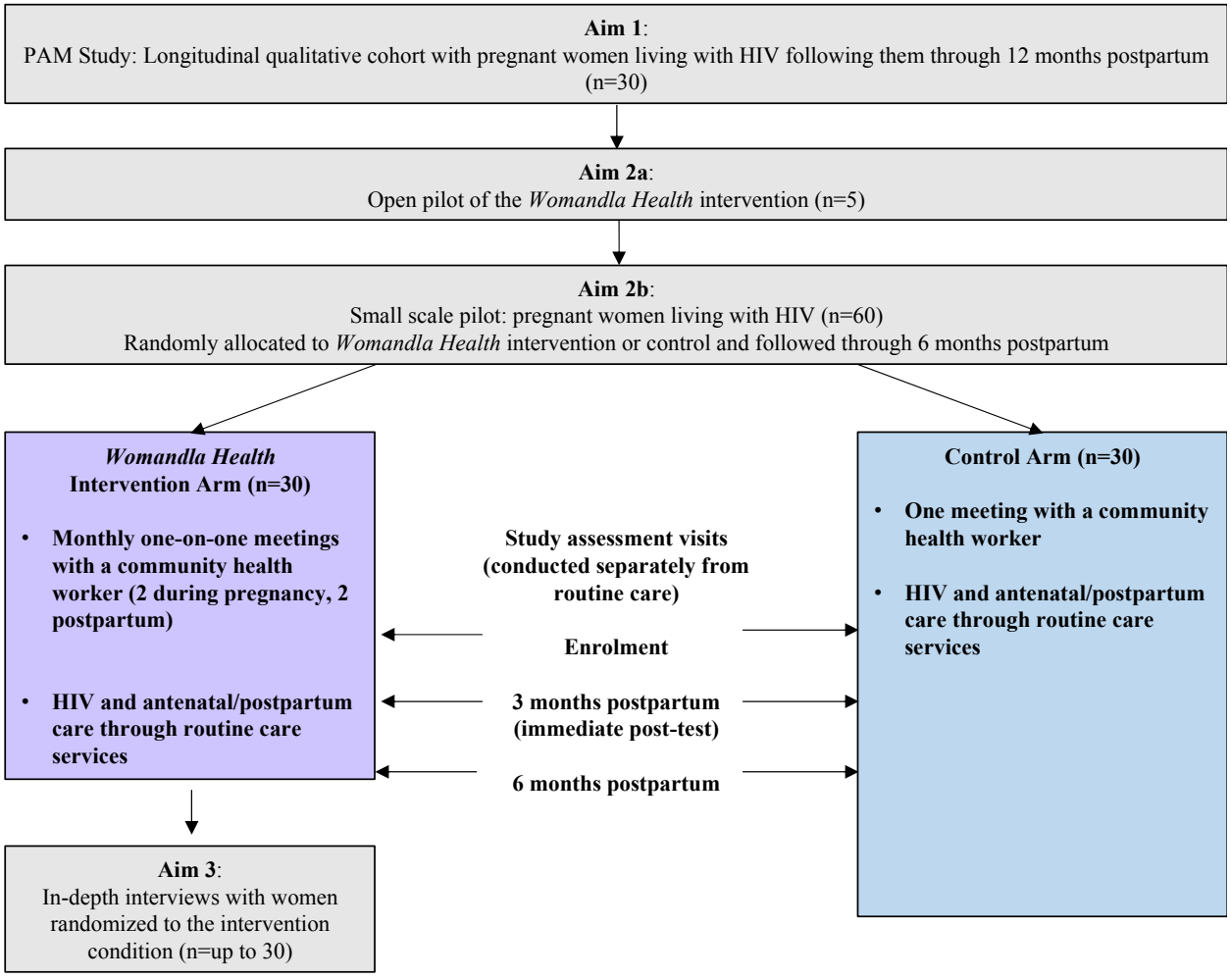
Women randomized to each arm will be asked to attend two additional assessment study visits at 3- and 6-months postpartum. The primary outcome will be self-reported ART adherence and secondary outcomes will be retention in routine HIV care (from routine electronic medical records) and HIV viral load using dried blood spots.

Participation will have no impact on any aspect of women's routine antenatal and obstetric care during pregnancy, or on any aspect of their postpartum care. In addition, participation will have no impact on their routine HIV care. Women randomised to the Transition intervention will receive the intervention separate from any routine medical visits. Women randomised to the enhanced standard of care will attend all routine medical visits and will receive one meeting with a community health worker separate from any routine medical visits.

Aim 3: *Assess participants' experiences of the intervention, perceived usefulness, and identify ways to refine the intervention for future evaluation.*

This aim will be accomplished using in-depth individual interviews with all participants who were randomized to the intervention condition after all follow-up assessments have been completed (n= up to 30)

The study schema is summarized in the diagram below:



Setting

The proposed study will take place in the community of Gugulethu in Cape Town. Aim 1 was successfully conducted in this community and our team has actively collaborated with local

health services in this setting for over 10 years. The antenatal HIV prevalence rate in Gugulethu is between 26-30%. Participants will be recruited during pregnancy from the Gugulethu Midwife Obstetrics Unit (MOU), which is a public sector facility that serves more than 4800 pregnant and postpartum women annually.

4. Study Population

For Phase 2 of this study (Aims 2 & 3), inclusion criteria are as follows:

- 18 years of age or older
- HIV positive status (based on clinic records)
- Confirmed pregnant (based on clinic records) and estimated to be 23-34 weeks gestation (clinic records or self-report)
- Currently prescribed ART
- Planning on remaining a resident of Cape Town for at least 6 months postpartum
- Able to provide informed consent for research including:
    - Willingness to be randomly allocated to the Transition intervention or enhanced standard of care
    - Consent to have study personnel access medical records under confidential conditions and for the purposes of the study only
    - Consent to other study procedures, including follow-up for at least 6 months
    - Ability to speak isiXhosa or English

Note: no restrictions will be made based on timing of HIV diagnosis or prior exposure to ART.

Exclusion criteria include:

- Failure to meet any of the inclusion criteria
- Significant pre-existing psychiatric comorbidity at enrolment that may impact ability to consent according to the judgement of study personnel (including cognitive impairment or known psychotic disorder)

Note: mothers will not be withdrawn from the study following foetal complications or death

5. Recruitment

Women attending the Gugulethu MOU who have documented HIV infection and clinical indication of pregnancy according to a provider will be told about the study by staff at the MOU. If women express interest in the study, they will be asked to approach study staff. Study staff will provide basic information about the study, and women who are interested in participating will be screened based on the inclusion/exclusion criteria detailed above. Women who are eligible will undertake the informed consent process described below. Study staff will emphasize that all study activities are entirely separate from routine antenatal/postpartum and HIV care and that refusal or withdrawal from the study will have no impact on their ability to access any of these services.

6. Study Arms

Open Pilot

All women recruited for the open pilot (n=5) will receive the Transition intervention (see below). All open pilot participants will receive 4 monthly one-on-one meetings with the community

health worker. As a reminder the purpose of the open pilot is to pretest all study procedures, particularly recruitment and retention, to increase the feasibility of the RCT, as well as to pilot test the intervention content. Participants will fill out end of session questionnaires that inquire about specific content and design features of the intervention. This information will guide the next iteration of the intervention to be tested in the small-scale RCT.

Randomized Controlled Trial Study Arms

Enhanced standard of care

Women randomized to the enhanced standard of care condition will receive the local standard of care plus a one-on-one meeting with the community health worker. All antenatal services at the Gugulethu MOU follow the local standard of care. Labor and delivery take place at either the MOU or nearby obstetric hospitals. Following delivery, all women make a routine postnatal visit to the Gugulethu MOU within 7 days postpartum; this is the only form of maternal postnatal care in this setting.

HIV services are integrated into antenatal care at the Gugulethu MOU, but women are referred to their nearest ART clinic at their first postpartum clinic visit, following the local standard of care in this setting. Women attend ART visits 1-2 monthly in these services. Individual ART counselling is provided before ART initiation and again when clinicians identify adherence concerns. Infants are referred for routine infant care to local primary care clinics.

As part of the enhanced standard of care condition, participants will also receive a one-on-one session during pregnancy with the community health worker. This session will include brief education about HIV, PMTCT, and ART, brief motivation interviewing for any adherence issues, as well as a basic assessment for any necessary referrals (i.e. psychological distress, substance use issues, food insecurity).

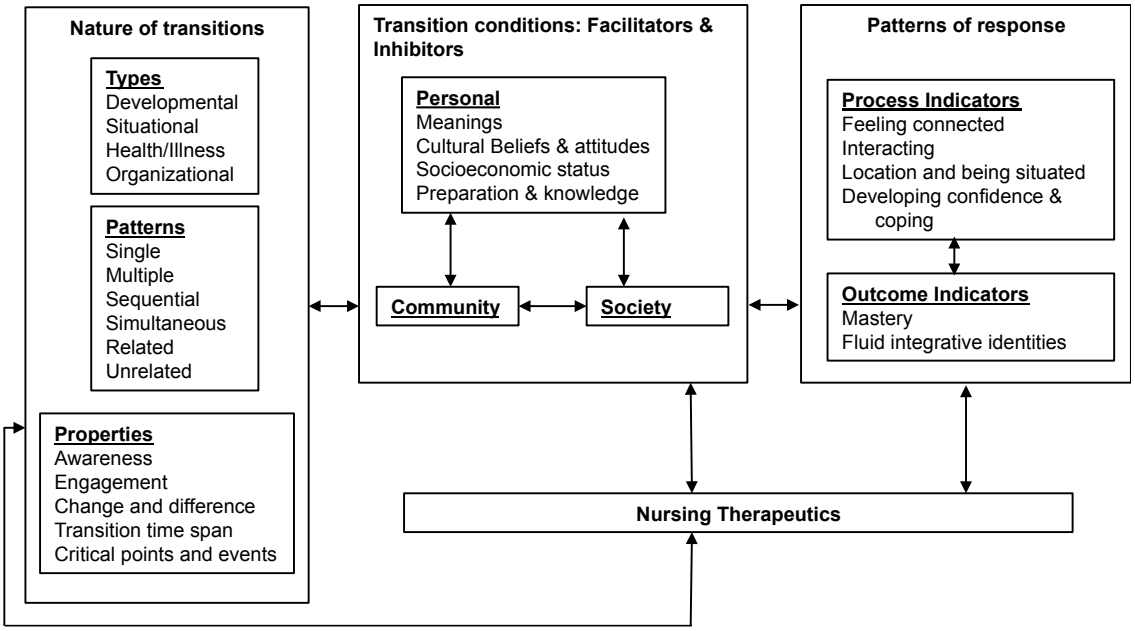
Transition intervention/ CHW intervention

This intervention draws on Transition Theory as an overarching framework (Figure below) and was developed using data provided by participants in Aim 1 as well as an extensive literature review.

Theoretical underpinnings

Transition Theory is a middle range nursing theory which posits that individuals in transition may be particularly susceptible to risks that impact their health (Chick & Meleis, 1986; Meleis, Sawyer, Massias, & Schumacher, 2000). Transition Theory allows us to characterize and describe the transitions that occur during this window period by clearly delineating the relevant personal and environmental characteristics that may facilitate or impede a successful transition, which could lead to sub-optimal ART adherence. With Transition Theory, we can conceptualize pregnancy and postpartum among women living with HIV as a time with multiple related health and developmental transitions. Women experience transition into motherhood (for a first child) or transitions in family roles (for a subsequent child). These women will also experience other transitions such as receiving the results of their infants' HIV PCR test and shifting their own healthcare from antenatal clinics to HIV care clinics. These transitions can present significant

challenges for ART adherence. There are also properties of transition experiences that contribute to how well an individual is able to adhere to ART, including awareness about an impending transition – such as being aware for the need to transfer care to an HIV care clinic – and engagement in the processes inherent in the transition – such as seeking out information about infant care. Transition experiences influence outcomes, such as adherence to ART, via transition conditions. Transition conditions are personal and environmental factors that can facilitate or inhibit progress towards a successful transition. These conditions are: (a) personal meanings, including appraisals of the anticipated event and the effect it will have on an individual's life, (b) cultural beliefs and attitudes, (c) socioeconomic status, (d) preparation for the transition, such as actively preparing for the infants' arrival, (e) community factors including family and partner support and (f) societal factors such as marginalization of people living with HIV.



Transition Theory also specifies potential intervention techniques, termed nursing therapeutics, including providing knowledge, role modeling, social support, and creating a healthier environment at the familial and community levels. In the present intervention we use both the individual one-on-one sessions with the community health worker to enact these techniques.

Qualitative Findings from Aim 2

Preliminary analyses of the data from the longitudinal qualitative cohort (Aim 2) reveal a variety of facilitators and barriers to the transition from pregnancy to postpartum. Preliminary results from the pregnancy interview showed high adherence motivation. Anticipated barriers postpartum were employment/financial concerns, logistical concerns around childcare and breastfeeding, worries about vertical transmission and difficulties bonding. Additional concerns included forgetting their ART medications and confusion about where to receive HIV care postpartum. At 6 weeks postpartum, women reported experiencing many of the barriers that they had anticipated, particularly financial and logistical challenges. Adherence motivation remained high postpartum, but some women reported issues remembering to take medications while caring for infants. Most women seem to have successfully transitioned, at least in terms of the initial

transition from pregnancy to early postpartum. Factors that appeared to facilitate this transition include supportive partners and families during pregnancy and postpartum and a sense of preparation during pregnancy. Factors that seemed to inhibit successful transition include unsupportive partners or a change in partner support from pregnancy to postpartum and lack of financial support.

Given the wide ranging and multi-level factors that both inhibit and facilitate successful transitions from pregnancy to postpartum and subsequent adherence to ART, we felt that a typical manualized individual level intervention would not fully address the varying issues arising in these women's lives. Our intervention design includes a one-on-one component with a community health worker who through motivational interviewing will help the participant identify her own individual barriers and her self-identified strategies for overcoming those barriers. Furthermore, the community health worker will be able to provide tangible support both in terms of referrals to other services (social services, governmental aid programs) as well as physically assisting with linkage to care and navigating clinical environments depending upon the needs of each individual participant.

Furthermore, during the Time 4 interview we asked Aim 2 participants about their preferences for a number of different formats and intervention components. Of the 10 interviews that have been translated and transcribed thus far, all participants have spoken in favor of a group component of an intervention for pregnant and postpartum women living with HIV both for a sense of social support as well as to share experiences and provide advice to one another. Additionally, when asked to rank what topics they would like covered in an intervention for women like them (pregnant and postpartum women living with HIV) education and substance use came up amongst many participants, but there was little consensus on any additional topics. At least one participant mentioned each of the following: intimate partner violence, depression, strategies for taking ART, baby care (including caring for an HIV-exposed infant- nevirapine, testing, etc.), employment issues, HIV care transfers postpartum, social support, and family planning. The design of this study will allow for several topics common to many women to be discussed within the group setting but also allows for individual tailoring in the one-on-one session with the CHW, particularly for topics that may be sensitive to discuss in a group setting, such as substance use or IPV.

Despite participants' preference for a group component in light of the COVID-19 pandemic, we will no longer including a group component to this study.

Background Literature

Our comprehensive review of the literature (Pellowski et al., 2019) supports a number of the findings from our qualitative work. Behavioral interventions for women living with HIV that contained a group component were more effective than interventions that did not include any group component. Furthermore, interventions that included some alteration of the healthcare system were also more effective than intervention that did not. Examples of types of alterations of the healthcare system included in this review were task-shifting from physician centered care to nurse/peer counselor care as well as the use of trained lay workers to deliver education, monitor barriers to ART adherence and to provide assistance in accessing healthcare, including accompanying women to the district hospital.

Role of Community Health Workers

This intervention draws on the growing cadre of community health workers within the South African health care system. A recent review (Schmitz et al., 2019) of HIV specific maternal and child health programmes delivered by lay health worker in Africa found a number of strategies utilized including: community engagement and sensitization, psychosocial support, linkage to care, encouraging women to bring their infants back for HIV testing and supporting default tracing. These interventions found improvements on community awareness of mother-to-child transmission, condom use, clinic attendance/retention in care, and infant testing. However, very few of these interventions measured maternal ART adherence as an outcome.

Current South African community health worker education does not include integrated training in maternal and child health and ART adherence focused on the transition from pregnancy to postpartum. This intervention would specifically provide additional training to community health workers in this area. Furthermore, this intervention will add to the literature by measuring ART adherence as a key outcome for a community health worker-based intervention.

Proposed model

After enrollment, participants will receive monthly one-on-one sessions. During the one-on-one sessions, the CHW will utilize motivational interviewing to understand the biggest barriers to ART adherence in women's lives and to assist the women in coming up with the best strategies or approaches. These sessions will also be used to assess if any referrals need to be made such as to social services or governmental aid programs. Importantly, there is no set agenda or topical areas that must be discussed within these sessions. The topics are entirely driven by the needs of the participant.

Training for CHW

We will hire a CHW who has experience working with both pregnant/postpartum women and persons living with HIV. Training specific to this interview will take place over the course for 2 weeks. Week 1 will include training on motivational interviewing and Week 2 will focus on training in the specific topics to be covered in both the one-on-one meetings. Trainings will consist of mock intervention sessions to develop skills and provide a setting for role playing. These mock intervention sessions will be critiqued by the PI to ensure proficiency in the intervention content and consistency in delivery.

Curriculum

A manual will be provided to the CHW. For the one-on-one sessions, the manual will describe possible areas to investigate where women may be having difficulties and information about procedures for referrals and availability of resources in the local area.

Educational materials will be adapted from the WHO and HHS/CDC Prevention of Mother-to-Child Transmission of HIV (PMTCT) Generic Training Package.[57] This training package was created as a comprehensive approach to the training of healthcare workers and provides guidelines for customized content to reflect local realities.

Process measures

The community health worker will complete logs for monitoring uptake and utilization of the intervention making note of session completion rates and dropouts. After individual sessions the CHW will also take extensive notes on topics focused on, common barriers experienced by women, and engagement within the sessions.

We will also audio record all counseling sessions to assess fidelity to the intervention. All counseling sessions will be coded using validated measures that have been adapted for this study. [58] [59]

The following figure displays the differences in exposure between the Transition intervention and the enhanced standard of care as well as the assessments

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8
			Postpartum 1	Postpartum 2	Postpartum 3	Postpartum 4	Postpartum 5	Postpartum 6
Assessments								
Enrollment Appointment: Informed Consent, Baseline Survey Assessment, Locator Form	X							
Follow-up Quantitative Survey					X			X
Follow-up DBS								X
Transition Intervention								
One-on-one session with CHW	X	X	X	X				
In-depth interviews								X
Enhanced Standard of Care								
One-on-one session with CHW	X							

7. Study Procedures

The purpose of the study measurement visits will be to evaluate the study objectives. These study measurement visits will be carried out separately from any routine care, including antenatal, postpartum, or HIV-related care.

Following recruitment and informed consent, all participants will be assigned unique study identification numbers. Women will complete the enrolment study visit and will then be randomized to either the Transitions intervention or control (enhanced standard of care).

Randomization

Randomization will take place at the end of the enrolment study visit. Women will be randomly allocated to either the Transitions intervention or control using a 1:1 randomization scheme. Randomization numbers will be generated prior to the start of the study and will be placed in sequentially numbered opaque envelopes. Randomization envelopes will be stored in a locked cabinet in the study office at UCT and will be accessed by the project manager when a woman is fully consented and has completed the enrolment visit. Women will be informed of their random allocation at the end of the enrolment visit. Ideally, a one-on-one meeting with the CHW (first visit for those in the Transitions intervention, only visit for those in the enhanced standard of care) would occur the same day as enrolment to aid in retention. If this is not possible the CHW will contact the participant using tracing information detailed below to inform them of the date and time of the first or only one-on-one meeting.

Quantitative measures

At each study measurement visit, a trained interviewer will administer questionnaire-based measures using paper and pencil. The trained interviewer will be blinded to participants' allocation. All study measurement visits will be conducted at a space that is separate from routine care. Most measures have been used previously by our group in this setting (see references in Table of measures, below), and have been translated into isiXhosa and back-translated into English following standard procedures. An additional scale[46] developed to measure the theoretical constructs of Transition Theory has been adapted for use with women living with HIV for this study and will be translated into isiXhosa and back-translated to English prior to use in the trial.

Linkage of routinely collected clinical data

Our team has extensive experience in utilizing data from routinely collected electronic medical records in this setting, including for ART and PMTCT outcome assessment. [60,61] Data will be requested from the Western Cape Provincial Data Centre, and we will use participants' provincial folder number (requested as part of tracing information) to facilitate an accurate electronic data request. Permission to review electronic clinical records of participants will be included in informed consent documents. Following standard procedures, we will request approval from the Provincial Department of Health to access electronic medical records. Established procedures are in place to ensure patient confidentiality. The project manager will link these data to participants' unique participant identifiers.

For the primary outcomes obtained from routine medical records (engagement in care and HIV viral suppression), we will use the following definitions:

- Engagement in care will be classified as any evidence of engagement in routine HIV services, including evidence of: HIV visit attendance; ART collection at a pharmacy; laboratory testing of HIV viral load or CD4 cell count
- HIV viral suppression will be classified as a viral load <200 copies/mL

For the primary outcome, we will use a window of up to 3 months around the 6-month postpartum study visit. In cases where there is evidence of multiple HIV viral load results in this window, we will use the result closest to the 6-month postpartum study visit for the primary outcome. For women who are lost to follow-up, we will use the median time of visits attended among those who are retained at study measurement visits to assess engagement in care and HIV viral suppression. As the primary outcome data will come from routine medical records, all women will have outcome data regardless of retention at study measurement visits.

Routinely collected clinical data will be linked with the written permission of (a) the participant (via informed consent), (b) the research oversight body of the Provincial Government of the Western Cape including the Provincial Data Centre, and (c) the HREC. Established procedures are in place to ensure patient confidentiality.

Aim 3 Qualitative Component

In-depth interviews will be conducted with participants randomized to the intervention condition (n=up to 30) after the completion of follow-ups in order to assess participants' experiences of the

intervention, perceived usefulness, and identify ways to refine the intervention for future evaluation. Participants will complete a separate informed consent form for the qualitative interview. Extra efforts will be made to capture participants who were not retained in the intervention to gain insight into elements of the intervention that may have contributed to disengagement from the intervention and to generate ideas for boosting retention in future evaluations.

The goal of these interviews is to evaluate the participants' views of the acceptability of the intervention and how useful they felt the intervention was with respect to medication adherence and retention in care. Content from these interviews will also allow us to better understand the quantitative outcomes of the intervention, regardless of the efficacy of the intervention. The in-depth interviews may also inform selection of future mediator or moderator variables to test in a full-scale RCT.

All study measures are detailed in the table below.

	Measure	Enrolment	3 months postpartum	6 months postpartum
Quantitative component				
Sociodemographic characteristics	Tool developed and used by our team previously [60]	X		
Pregnancy intentions	London Measure of Unplanned Pregnancy and measures of family planning use and fertility intentions [63] Used by our team previously [64]	X	X	X
Maternal health	Tool developed and used by our team previously [60] Includes measures of self-reported health issues and health service use	X	X	X
Child questionnaire	Tool developed and used by our team previously [60] Includes measures of breastfeeding, health issues and health service use		X	X
Non-disclosure	Tool developed and used by our team previously [65]	X	X	X
Partner questionnaire	Tool developed and used by our team previously Includes measures of relationship status, partner HIV testing, and partner substance use	X	X	X
COVID-19 impacts of engagement in care	Items are detailed below this table	X	X	X
Intimate partner violence	WHO Violence Against Women Questionnaire [66] Used by our team previously [67]	X	X	X
Depressive symptoms	Edinburgh Postnatal Depression Scale [68] Used by our team previously [67 69]	X	X	X
Substance use	Alcohol Use Disorders Identification Test [70] Drug Use Disorders Identification Test [71] Both used by our team previously [67 72]	X	X	X
Adherence self-efficacy	Adherence Self-Efficacy [73] Used by our team previously [74]	X	X	X
Self-reported adherence	Tool developed and used by our team previously [75] and the Visual Analog Scale [76] Includes measures of side effects and self-reported adherence	X	X	X
Pregnancy and Postnatal Well-being in Transition Questionnaire	Validated tool that we adapted for HIV [46] Includes measures of Transition Theory constructs	X	X	X
Alcohol-ART toxicity beliefs	Tool validated in Cape Town [77] Includes measures of beliefs about mixing alcohol and ART	X	X	X
Routine medical data				
Maternal health service use	Accessed from routine medical records		X	
Infant health service use	Accessed from routine medical records		X	
HIV viral load results	Accessed from routine medical records		X	
Qualitative Component				

In-depth interviews (IDI)	IDI guide, conducted with all participants randomized to the intervention	After all study procedures and assessments have been completed

COVID-19 impacts of engagement in care

1. Because of the COVID-19 pandemic, did you miss an appointment at your clinic for HIV treatment or care in the last 3 months? (Yes/No)

2. How do you access/have you accessed your ART tablets/your HIV medication during lockdown? (1=I buy them from someone on the street, 2=I get them from the clinic/hospital as I used to, 3= I borrow pills from a friend/household member/neighbor)

3. Has accessing your ART tablets/your HIV medications during lockdown been more challenging than before COVID-19? (Yes/No)

4. Are you worried that you will run out of ART tablets/your HIV medications because of challenges associated with COVID-19 (i.e. lockdown, don't want to go to the clinic during COVID-19) (Yes/No)

Identification of health needs during study procedures

At every study measurement visit, any woman found to have an unmet health need (whether medical, obstetric, postpartum family planning, or related to mental health or substance use) will be referred to the relevant service within the Gugulethu Community Health Centre or higher levels of care, as appropriate. In particular:

- Any woman found to have defaulted ART will be re-referred to her most recently attended ART service.
- Any woman found to be non-adherent to ART at any study measurement visit will receive intensive counselling on ART use, and will be referred to the relevant ART service for follow-up.
- Any woman found to be experiencing domestic or partner violence in any form will be referred to the main local NGO supporting victims of domestic violence and the South African Police Service with follow-up to ensure adequate attention.
- If any infant health care needs are identified, the infant will be referred to the appropriate paediatric health services via the Gugulethu Community Health Centre.

All referral processes are documented in an SOP for Referrals.

Staff training

Prior to initiation of the study, all staff that will have contact with participants will take part in a multi-day study-specific training. The curriculum of the training will include: rationale, purpose and scientific objectives of the study; study design and methodology; conduct of study assessments, tracking of participants, completion of study forms, and data collection; staff responsibilities; recruiting participants; procedures for enrolling participants into the study; randomization; universal precautions; communication skills; safety in the field; ethical guidelines for research including participants' rights; procedures for obtaining informed consent; and confidentiality requirements. Study staff will receive hands-on training, including mock interviews. Study staff will be given opportunities to practice both the English and isiXhosa versions of all assessments.

In addition, all staff members will complete training related to Good Clinical Practice and Human Subjects Protection. All staff who through the course of their work will have knowledge of, or access to, personal information about participants will be required to complete training on confidentiality and will sign a confidentiality agreement before the start of data collection.

All staff will be trained on the SOP for Referrals as well as management of crisis situations, including reports of abuse and domestic violence, that may be disclosed during study participation.

For all study staff, there will be additional training days scheduled during the study for refresher training. During these refresher trainings, study staff will review study procedures.

Contamination and masking

Contamination between groups is a concern and blinding participants to this type of psychosocial intervention is not possible. Contamination would mean that women in the enhanced standard of care control group may be aware of the Transitions interview, or vice-versa, and change their

behaviours related to their own ART use or retention in care. Some of the primary outcomes (retention in ART care and HIV viral suppression) are objective, thus reducing detection bias. Self-reported ART adherence is subjective and thus we acknowledge that this measure may be biased, however, other behavioral interventions (particularly pilot interventions) have utilized self-reported adherence to understand the behavioral antecedent to viral suppression. Insofar as possible, we will mask study personnel involved in the study measurement visits; in particular, the interviewer administering study measures will be blinded to participants' allocation All study measurement visits will be conducted at a space that is separate from routine care.

8. Participant retention

Study follow-up & retention

Participants will be followed for 8 months (6 months postpartum). Participants in both arms will attend study measurement visits at enrollment, 3 months postpartum, and 6 months postpartum. These visits will be scheduled and conducted separately from any routine care. Retention activities will focus on study measurement visits. At enrolment, the interviewer will collect detailed tracing information, including participants' full names, addresses, all telephone details; the names, addresses and contact details for two individuals who the participant lives with, and one alternate individual who the participant does not live with. Participants will also be asked to provide their provincial folder number used on routine medical records, for linkage with electronic medical records. At the 3-month postpartum follow-up visit, participants will be asked to update their contact information if needed. Throughout the study, tracing information will be kept in locked filing cabinets, separate from other participant information.

Following established procedures, we will maintain a simple electronic visit schedule database in Microsoft Access for the study team. Based on participant visits logged in the database, a schedule of expected participant study measurement visits is generated that can be used to provide reminders to participants before visits, or identify missed study visits that require tracing. The database will contain only unique participant identification numbers, and reference to the tracing information (kept in a locked study cabinet in the project office) will be made by the study coordinator. Following our previous approach, retention activities will include reminder phone calls to participants prior to study measurement visits. For women who do not attend scheduled study visits, we will attempt to contact the participant via telephone. If unsuccessful, we will contact one of the pre-designated alternate individuals. If telephone attempts fail, fieldworkers will visit the home address of the participant to trace the participant in person. Note that all participant tracing efforts by fieldworkers (via phone or home visit) do not mention the reason for the contact, or anything regarding HIV/AIDS or ART, under any circumstances (even if the participant themselves is traced). All contacts simply request that the participant come to the clinic the next working day for a health-related issue.

Participants will only be traced by study staff if they are found to have missed a study measurement visit. Tracing of participants who default routine care will be managed by public sector health services. However, if a participant is found to have defaulted ART at a study visit, study staff will urgently refer the participant to the service which they last attended.

Participant withdrawal

All participants may refuse or voluntarily withdraw from the study for any reason and at any time. As part of the informed consent process, staff will state specifically that participation in the study is voluntary and that a participant may refuse participation or withdraw from study participation at any time. Participants will be told that withdrawal from the study will have no effect on their access to health facilities providing any services. All study staff will be trained to ensure that participants have a firm understanding of this concept at the time of the informed consent process, and the informed consent forms will include a statement to this effect.

9. Analytic considerations

Sample size considerations: pilot study

The overall goal of this pilot study is to determine feasibility and potential efficacy to support future larger, fully-powered tests of the intervention's efficacy. We fully acknowledge the exploratory nature of this pilot. With a sample size of 60, between two groups, 2 follow-up measurements, controlling for self-reported baseline adherence, p=0.05, we will have 29% power of finding a small effect (Cohen's d=0.30), 65% power of finding a moderate effect (d=0.50), and 98% power of finding a large effect (d=0.80). This study will be underpowered to find significant small and moderate effects however, we will be able to calculate an effect size and the direction of its impact to support a larger scale test of the intervention.

The facility that is participating in this study, the Gugulethu MOU, sees approximately 4800 pregnant and postpartum women annually, with an antenatal HIV prevalence of 28%. Thus, we do not anticipate difficulty recruiting this sample within the allotted timeframe.

Sample size considerations: In-depth Interviews (Aim 3)

We propose to interview all of the women randomized to the intervention condition (n=up to 30). Based on our follow-up rates for the longitudinal qualitative cohort (HREC 344/2017), we anticipate at least an 80% retention rate at 6 months postpartum, which equates to an anticipated 24 participants completing in-depth interviews. Based on our previous experiences working with this population, we feel that 24 participants will be enough to reach saturation on key themes related to acceptability of the intervention.

Data management

The study includes data from four sources: (1) interviewer-administered questionnaires; (2) routine electronic medical records; (3) dried blood spots; and (4) IDI with participants randomized to the intervention condition. The collection of data will be conducted by (1) a fieldworker; (2) the project manager; (3) lab-based researcher; and (4) a qualitative interviewer, respectively. Procedures for data collection (regardless of source) will be outlined in SOPs. We have a bank of well-developed SOPs that our group has developed for previous studies. All data management will take place at UCT following procedures established by our group for multiple previous studies.

Quantitative data will be captured into a custom designed Microsoft Access database. The database will be password-protected following standard password safety procedures, and will be maintained in a firewall-protected UCT server with daily backups. The database will be designed and maintained by the project manager. The study coordinator will direct queries and data

quality assurance (QA)/quality control (QC) activities, and supervise data entry, with oversight from the project manager. Data QA will be in the form of robust database structure and platform, and 'front-end' data checks including real-time database queries. QC will be through data checking scripts to identify out-of-range values, logic violations and missing observations. Queries will be resolved based on reference to the completed questionnaires in question; all data queries and responses will be logged, and edits will be implemented through separate program files.

Qualitative data from IDI will be transcribed verbatim and translated into English. Translations will use unique participant identifiers, not participant names. All electronic files will be encrypted and password protected.

Data analysis

Quantitative data will be exported to Stata Version 14.0 (Stata Corporation, College Station, Texas) for analysis. We will analyze all primary and secondary outcomes preliminarily using simple means and standard deviations and point-biserial correlations to estimate effect sizes where appropriate. For outcomes that are indicative of a possible difference by condition, we will utilize more advanced analytic techniques, i.e generalized estimating equations (GEE), as follows:

To compare the impact of intervention condition on self-reported ART adherence, engagement in ART services and HIV viral suppression, we will utilize a series of generalized estimating equations (GEE) using Poisson distributions where appropriate. Outcome analyses will control for baseline self-reported adherence and any baseline differences on demographic variables. Intervention condition, time of assessment, and condition*time interaction will be entered as model effects. We will use GEEs to predict key psychosocial outcomes (adherence self-efficacy) by intervention condition. If there is evidence of an intervention effect we will explore factors that may modify intervention effects, we will compare intervention effects within subgroups of women based on key demographic clinical and psychosocial characteristics.

To determine feasibility, we will calculate rates for session attendance, as well as retention, withdraws, and assessment completion.

To determine acceptability of the intervention, we will use NVivo (QSR International Pty Ltd) to conduct our qualitative analysis. Data analysis will be iterative including open coding, axial coding, marginal remarks, constant comparison, and memo-writing. Analyses will be brought to the larger research team for critique and interrogation which will result in further queries and data checks to ensure appropriate interpretation of the qualitative data.

10. Ethical considerations

Ethical review

The study protocol, informed consent forms and data collection tools will be reviewed and approved by the Faculty of Health Sciences Human Research Ethics Committee (HREC) at UCT. Subsequent to the initial review and approval, the HREC will review progress of the study at least annually.

Preliminary research in this setting

As described above, our team has collaborated with district and provincial health services in the community of Gugulethu for >10 years, including the Gugulethu MOU at which this research will be based. During this time, we have formed strong local relationships including with a community advisory board. In Phase 1 of this study we found a variety of facilitators and barriers to the transition from pregnancy to postpartum for women living with HIV. Barriers included employment/financial concerns, logistical concerns around childcare and breastfeeding, worries about vertical transmission and difficulties bonding, forgetting ART medications, confusion about postpartum HIV care. Factors that appeared to facilitate this transition include supportive partners and families during pregnancy and postpartum and a sense of preparation during pregnancy. Given the wide-ranging and multi-level factors that both inhibit and facilitate successful transitions from pregnancy to postpartum and subsequent adherence to ART, we feel that a component of the intervention that includes a one-on-one component with a community health worker who through motivational interviewing will help the participant identify her own individual barriers and her self-identified strategies for overcoming those barriers in needed. Furthermore, the community health worker will be able to provide tangible support both in terms of referrals to other services (social services, governmental aid programs) as well as physically assisting with linkage to care and navigating clinical environments depending upon the needs of each individual participant. Additionally, when asked about formats of potential interventions, women spoke in favour of a group component of the intervention with other women living with HIV to provide both a sense of social support as well as to share experiences and provide advice to one another.

Informed consent

After eligibility is confirmed, all participants will complete informed consent prior to enrollment. All informed consent procedures will follow protocol approved by the University of Cape Town HREC and the Brown University IRB. The consent process will be conducted with a staff member fluent in both English and isiXhosa who has been trained in research ethics and the specific consenting protocol for this study. The consent process will be conducted in the language of the participant's choosing. The informed consent process will highlight the specific risks associated with the study, including discomfort from in-depth discussions of HIV infection and mother-to-child transmission and risk of breaches in confidentiality. The participants will be informed about the precautions put in place to reduce the risk of breaches in confidentiality including: the use of unique PIDs on all research data and that her name will not be used in relation to her data and that all data will be kept safe in a locked filing cabinet or password-protected computer in a locked office. It will also be noted that research study staff are not doctors, nurses, or any other type of trained medical personnel and, thus, cannot diagnose, treat, or change medications. The participant will be allowed to ask questions and the staff member will probe for complete understanding during key points of the consent form. The participant will be allowed to take as much time as she needs to make a decision and she will be reminded that her participation is completely voluntary, will not impact her medical care in any way, and if she does decide that she would like to participate she may change her mind at any time without penalty. All participants will be provided the contact numbers of the Principal Investigator Dr. Pellowski and University of Cape Town HREC chairs to answer questions that the participant might have about the study or one's rights as a human subject. Completed, signed consent forms

will be kept in a locked filing cabinet in our secured research office. The participant will be allowed to take a copy of the consent form home to have as a reference, but will also be reminded that someone finding the form may result in a breach of confidentiality.

Potential Risks to Participants

There are several potential risks in participant in this study. Discussing sensitive topics such as pregnancy and HIV infection may cause psychological distress. Study staff will be trained in counseling and will continually monitor the participant for signs of distress. If signs of distress are apparent, the interviewer will offer to pause the session until the participant feels well enough to carry on. The participant will also be reminded that they may stop the session or un-enroll from the study at any time without penalty. If needed, referrals will be made to social services. We will also emphasize that participants may pause the interview at any time or may un-enroll from the study at any time without penalty.

To reduce risks of accidental disclosure of HIV status, all study activities (i.e. eligibility screening, interviews, assessments) will take place in a private room. During recruitment, eligibility questions will be embedded in a larger set of foil questions so that ineligible individuals will not be able to decipher why they were not eligible for the study. All data collected will not contain the name of the participant and will instead be identified by their unique PID number. All data will be stored in locked file cabinets and encrypted computers. Although this study is centered around HIV medications and adherence behaviors, study staff will not be prescribing medications and they will not change dosing of medications in any way. Optimal adherence to medications will always be encouraged. If the participant discloses issues with side effects or HIV symptoms, study staff will refer the participant back to their HIV care doctor.

Additionally, during the consent process, risks of breaches in confidentiality will be highlighted including legal norms that would require a break in confidentiality. All ethical issues requiring urgent attention will be reported to the PI immediately. All unanticipated ethical situations that do not need immediate attention will be discussing the weekly team meeting.

Protections Against small risk of loss of privacy or confidentiality of data**.** All interview cohort participants will be assigned a unique participant ID (PID). These PIDs will be used to identify participants on all research materials, surveys, transcripts, tracking forms and all databases. Separate from research records, an identifier key will be created to link the PID to participant names and contact information in order to facilitate follow-up with participants. This identifier key will only contain contact information and will NOT include any research data and it will be stored separately from any research data or research-related forms (e.g. informed consent forms). All research data, research-related forms, and the identifier key will be secured in a locked cabinet or a password protected and encrypted laptop in a locked room. Data will also be backed up daily by a designated staff member and transferred a firewall protected secure UCT server. Only the PI, mentors, and essential project staff will have access to any project data. Participants' names or other individually identifying information will never appear in any report resulting from this project.

Electronic data, including digital voice recordings, will have several protections: (1) all data will be stored on password-protected computers; (2) all files on project computers will be protected through encryption; (3) all study staff will be trained in participant data confidentiality protocols and will be consistently monitored by the PI on data safety and confidentiality; (4) audio files generated from the qualitative interviews will be designated with a code to ensure

name confidentiality and delivered securely to the transcribers who will establish a memorandum of understanding (MOU) to ensure their compliance with confidentiality procedures (e.g. maintaining files on an encrypted computer in a locked office when not being actively transcribed, deleting all identifiers from the transcripts and using the unique PID).

For qualitative data collected in the in-depth interviews (i.e. transcripts), all identifiers within the text will be replaced with the PID. To ensure data quality of qualitative data, DVR recordings of the interviews will reviewed within 48 hours of the interview by the PI or study manager. Additionally, after the data is transcribed, transcripts will be checked for accuracy against the voice data files. Voice files will be destroyed after transcripts are thoroughly checked for accuracy.

Training in Confidentiality. The PIs will provide the study team with training in all ethical procedures including informed consent, maintaining confidentiality, and protecting confidential data. This training includes for example, the importance of securing participants' privacy, the separation of data from identifiers, and protocols for using locked offices, filing cabinets, and password-protected files to avoid unauthorized use of participant data. The study team will meet regularly to discuss protocols for maintaining participants' privacy. The study team will also follow institutional policies for requiring mandatory training in human subjects protection before conducting any study activities.

Alternative Treatments. The purpose of this study is to expand upon the standard of care for pregnant and postpartum women living with HIV. Participation or non-participation will not impact health care or clinic services in any way.

Addressing Risks to Participants

Planned Procedures for Protecting Against or Minimizing Potential Risks. We will minimize discomfort associated with discussing potentially distressing topics (e.g. pregnancy, HIV infection, mother-to-child transmission of HIV) by notifying eligible individuals about the types of topics that will be discussed prior to signing the consent form. Participants will also be reminded that they can discontinue participation in the study at any time. Additionally, staff members will be trained procedures to minimize distress within the interview and will be trained in how to identify discomfort in the participant. If a participant appears to be becoming too distressed, the staff member will offer to pause the assessment. These procedures will also be used in the counseling sessions to minimize the distress of those enrolled in the behavioral trial.

We will minimize breaches in confidentiality by using unique PIDs on all data resulting from this project and will not use identifying information (i.e. participants' names) in databases or forms that contain data. We will also let participants know that they may use a pseudonym in the interview to keep their identity unknown on the recording. Regardless, all names and other identifying information will be expunged from the transcripts of the interviews. All data generated from this project will be kept in a locked filing cabinet or a password-protected computer in a locked office. To minimize the risks of accidental HIV status disclosure, all study procedures will occur in a private room.

Additional Considerations for Pregnant Women. As a research project, we will have no part in making medical decisions regarding the health of the pregnant woman or her fetus, including but not limited to determination of the viability of the fetus or need for inducing labor. Additionally, we will have not part in making any diagnoses related to pregnancy or other conditions such as preeclampsia or cytomegalovirus. Although we will be conducting a study about medication adherence during pregnancy and postpartum, we will not change medication

prescriptions. If a participant complains about their current prescriptions or states that they would like to stop their prescription, they will be told by the study staff to continue taking their medications as prescribed and instructed to bring these concerns to their antenatal care physician for the protection of themselves and their fetus. Because this study will be conducted in a health care setting, study staff will remind study participants that we are not related to their pregnancy or HIV care in any capacity, when necessary.

Medical or Professional Intervention in Event of Adverse Event**.** Although we do not anticipate any events in need of medical intervention associated with our study activities, due to our special population of pregnant and postpartum women living with HIV we do recognize the need for some safeguards. All participants will be under the care of a physician as our study site is based in a SA-DOH clinic (Gugulethu MOU) and prescription of ART is an eligibility criteria of our study. We will emphasize that research staff members are not medically trained and medical concerns should be discussed with the participant's doctor. If a medical event does arise during our research activities (e.g. labor pains), with the participant's permission, we will consult with the medical staff in the clinic and transfer her to their care, if necessary. All adverse events will be immediately reported to the PI. Serious adverse events will be reported to the University of Cape Town HREC and Brown IRB by phone and followed by a written report of notification within 24 hours of the event. The PI will also notify the NIH Program officer and will report adverse event in writing to the NIH funding institute. The Adverse event will also be reviewed with co-Primary Mentors Drs. Lurie and Operario with input from the entire mentorship team to determine subsequent actions and if revisions to current protocols are needed.

Benefits

Direct Benefit

There may be little or no direct benefit to participants from this study. For those enrolled in the intervention we hope that receiving support from a community health worker and support from other women living with HIV may lead to improvements in ART adherence and engagement in care, however, this benefit is unknown. All participants will be given information on HIV infection, pregnancy, and preventing mother-to-child transmission of HIV as well as references to local health and social services. Referrals to more intensive resources will be made as needed. The risks associated with this research are reasonable in relation to the anticipated benefits of advancing empirical knowledge about ART adherence during the transition from pregnancy to postpartum and behavioral intervention approaches to improve ART adherence for this high priority population and setting.

Indirect Benefit

This study will fill key gaps in scientific knowledge about behavioral ART adherence interventions for pregnant and postpartum women living with HIV. In the literature there are few behavioural intervention that have been effective in increasing ART adherence and retention in care among postpartum women. Given this lack of effective interventions, there are significant indirect benefits to filling key gaps in scientific knowledge and, if the intervention is successful, this study has the potential to lead to the roll out of this intervention for pregnant and postpartum women living with HIV, which could benefit the population as a whole. Thus, the risks of the proposed study are reasonable and balanced by the potential contribution of providing important information that can advance our knowledge of ART adherence among pregnant and postpartum

women and whether or not the proposed behavioral intervention will aid in increasing ART adherence during this critical time for HIV treatment and prevention.

Compensation

At each study measurement visit, participants will be given R20 in cash for transport costs and R80 in the form of grocery vouchers for their time and effort. At the final study measurement visit, women will be given a small gift up to the value of R100 for their child. Refreshments will be provided at all study measurement visits and at the one-on-one sessions. No reimbursement will be given for attendance at the one-on-on sessions for the intervention arm but participants will be reimbursed for their transportation costs for each session (R20).

Internal monitoring

The study team involved in day-to-day activities will meet weekly to discuss progress and operational aspects, led by the principal investigator; and the project manager will report back to the principal investigator and core team of study investigators on a weekly basis. Quarterly teleconferences will be held with the scientific advisory board for their specific inputs into the study.

Use of information and publications

Publication or presentation of the results of this study will be agreed upon in collaboration with the study investigators. Note that the funding agency has no input in the decision to present or publish study data or the nature of the data that are presented or published.

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