Pilot study of the feasibility and acceptability of an adherence promotion package for postpartum women on pre-exposure prophylaxis (PrEP)

Study Investigators:

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1. Background and rationale:

Pregnant and breastfeeding women in South Africa are at very high risk of HIV acquisition and vertical HIV transmission during pregnancy, labour and breastfeeding[1]. One-third to half of perinatal HIV transmission occurs in women who are seroconvert during the pregnancy and post-partum period[2]. Effective use of pre-exposure prophylaxis (PrEP) could contribute to eliminating maternal HIV acquisition, and hence mother to child transmission (MTCT) of HIV[3,4]. However, PrEP efficacy requires high levels of adherence, and adherence requires high levels of acceptability, yet there are few data on how best to promote adherence to PrEP in postpartum women[5].

We propose to conduct a pilot study of the feasibility and acceptability of an adherence promotion package in n=200 postpartum women enrolled in an ongoing PrEP study (PrEP-PP; ongoing, HREC Ref 297/2018; PI Myer) to evaluate the feasibility, acceptability and efficacy of a package of interventions to improve PrEP adherence in pregnancy and postpartum women. Specifically the package of interventions will include:

(1) SMS/Whatsapp messages with reminders about PrEP,

(2) HIV self-testing (for the participant and her partner) and

(3) immediate feedback on PrEP adherence using a urine lateral flow assay that tests the level of tenofovir taken in the past 48 hours.[6-8]

The sub-study will take place in Gugulethu Midwife Obstetric Unit (MOU). We will enroll n=200 HIV-uninfected postpartum women (1-6 months postpartum) at their regular PrEP-PP study visit and follow them for 1 month. We will randomize 1:1 to the intervention arm (n=100) to compare with the standard of care arm. The adherence promotion intervention package will include provision of a HIV self-test for the woman and her partner, SMS messaging about PrEP taking, and adherence based feedback following the urine lateral flow assay (that measures recent tenofovir in past 48 hours). In the standard of care arm, n=100 will receive standard of care PrEP-PP services including: HIV counseling and testing in the facility by the PrEP study staff, face-to-face counseling that is based on self-reported adherence, without any SMS interventions or urine assay.

At baseline and endline (1 month) we will administer a brief 15-20 minute survey about recent PrEP adherence in the standard of care and intervention groups, and feasibility and acceptability of the package of interventions in the intervention group. Participants will receive an option to participate in the interview on the phone instead of returning to the health facility.

Outcomes include a comparison of objective PrEP adherence using tenofovir measure in the urine assay at 14 and 30 days following baseline. We will analyze the survey responses to evaluate acceptability and feasibility alongside the efficacy data to inform the development of a larger randomized control trial in postpartum women.

COVID-19 and study implications. Our PrEP-PP study (HREC Ref 297/2018) has continued during the COVID-19 lockdown in South Africa as PrEP provision is considered to be an essential service. We continue to effectively and safely recruit ~15 women/week and ~20 retention visits/week during the COVID lockdown and observe all UCT and Department of Health infection prevention and control methods. The proposed intervention is designed to promote adherence to PrEP in high risk postpartum

women, whilst minimising contact with the health facility, healthcare workers and study staff through HIVST, phone based SMS counselling, and phone interviews.

2. Study objectives:

The objectives of the proposed pilot sub-study are to evaluate the feasibility and acceptability of a package of interventions to improve PrEP adherence in postpartum women.

1. Evaluate acceptability and feasibility of adherence promotion package in women randomized to the intervention arm including:
    a. SMS: # of messages received, # responded to, feedback from women about responses to messages and utility in improving adherence
    b. HIV self-testing in women and their partners: # of women who report self-testing at home, and # who report their partners testing (and test results), and feedback from women in surveys about their experience with using self-tests for themselves and partners, and feasibility as reported by study staff to explain HIVST in their counseling
    c. Integrating urine based lateral flow assays in reporting back adherence levels to PrEP in women: Measured by the time the test takes, correlation with self-reported recent adherence, the feasibility as reported by study staff to read the test and feedback from the woman about the satisfaction and understanding following the bio-feedback
2. Evaluate objective PrEP adherence levels following intervention and compare with standard of care arm:
    a. Evaluate tenofovir levels in urine assay at 2 weeks and 4 weeks following baseline intervention in intervention arm and compare with standard of care arm at 1 month

3. Study design

Randomized control pilot sub-study of n=200 postpartum women in the PrEP-PP study.

Inclusion Criteria:

1. Currently enrolled in PrEP-PP study and on PrEP
2. 18+ years old
3. confirmed HIV-negative (confirmed with a 4th generation antigen HIV test)
4. confirmed to be postpartum (1-6 months postpartum)
5. confirmed to currently have a male partner
6. confirmed to have a cell phone that can read and respond to SMS/Whatsapp messages
7. without psychiatric or medical contraindications to PrEP

Exclusion criteria: Failure to meet all of inclusion criteria

Eligible, consenting women will receive up to R120 in grocery vouchers and transportation costs, and refreshments for their time and effort in the study at baseline and each follow up visit (1 visit for standard of care arm, 2 visits for intervention arm).

Procedures for the informed consent process are outlined below. Throughout, trained study staff will ensure that women are aware of their right to refuse and/or withdraw from the study at any time. In addition, study staff will emphasize that all study activities are entirely separate from routine postnatal care services received and that refusal or withdrawal from the study will have no impact on their ability to access any services provided at any public-sector health facility.

4. Study procedures

The study will be integrated into the MOU in Gugulethu. Women will be recruited directly from the PrEP-PP study (ongoing, Ref 297/2018). We will not recruit nor enroll new participants, but will draw a sub-sample from our ongoing cohort study. Further, we will not hire new staff, all trained staff are already working in the facility part of the ongoing current PrEP-PP study. The PrEP-PP study recruiter will recruit eligible directly from women in the cohort study, and if interested and eligible after the screening process, the women will go to the study trailer (Green Clinic) in Gugulethu for the sub-study consent and study enrolment procedures.

Randomization: We will randomize enrolled PrEP-PP participants who are eligible (see above additional eligibility requirements) and consent to participate in the adherence promotion intervention in a 1:1 ratio to the intervention or standard of care arm. Randomization will be performed using dynamic permuted blocks, with sealed randomization envelopes. The participants will open the envelopes sequentially.

Table 1. Sub-study list of visits and assessments per arm

Visit	Intervention Arm	Standard of care Arm
Baseline	1. ICF for sub-study 2. Survey 3. HIV self-test for self and partner with counselling 4. Urine TDF test with adherence based counselling	1. ICF for sub-study 2. Survey 3. Invitation for partner testing 4. Urine TDF test (no counselling or feedback)
30 days	1. Endline survey 2. Urine TDF test with adherence based counselling	1. Endline survey 2. Urine TDF test (no counselling or feedback)

Intervention arm: Consented, enrolled women in the intervention group (n=100) will receive an adherence promotion intervention package that includes the following visits/assessments:

1. **At baseline:**
    a. HIV self-test for herself and her partner(s) with instructions on how to use, and instructions on how to report the result to the study on the SMS/Whatsapp messages.

b. Adherence based counseling and feedback from a urine tenofovir test (that measures recent tenofovir in past 48 hours)

2. **Weekly:** SMS messaging with counseling and reminders about taking daily PrEP
3. **At 2-weeks (extra visit- not part of standard of care):** adherence based feedback and counseling following the urine lateral flow assay

Standard of care arm: In the standard of care arm, women will receive normal PrEP-PP services as per study protocol including facility based HIV testing and counselling with a letter to refer their partner for testing in the facility. Women in the standard of care PrEP-PP arm will not receive SMS reminders or messages, nor will they get feedback following the urine assay on their tenofovir levels. Participants will receive standard counselling about importance of adherence, prescription for 3 months of PrEP, and invitations for the study appointment in 4 weeks' time.

Baseline and endline adherence evaluation (both arms): All participants, regardless of study arm, will receive urine lateral flow testing of tenofovir levels at baseline and again at 1 month.

Baseline and endline survey (both arms): At baseline and endline (1 month) we will administer a brief 15-20 minute survey about recent PrEP adherence in the standard of care and intervention groups, and feasibility and acceptability of the package of interventions in the intervention group. A trained study staff will ask the survey questions in isiXhosa using RedCap. Participants will receive an option to participate in the interview on the phone instead of returning to the health facility.

Table 1. Pilot study timeline

	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**
HREC proposal submission, review and approval	X					
Train study staff in pilot study SOPs	X					
Develop RedCap survey in isiXhosa and pre-test with staff	X					
Recruit and enroll n=200 postpartum women in PrEP-PP study (per eligibility criteria), n=~70/month		X	X	X		
Baseline test for DBS and urine tenofovir levels (all participants)		X	X	X		
Survey (baseline and endline)		X	X	X	X	
Deliver intervention package (SMS, HIVST and biofeedback counseling) to intervention group at day 0, 14 and 30		X	X	X	X	
Study endline: test for DBS and urine tenofovir levels in all participants (at 1 month after follow-up)			X	X	X	
Analysis and dissemination					X	X

5. Ethical considerations

The study protocol, informed consent form, all data collection tools, and other requested documents will be reviewed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT-HREC).

Informed consent

The study informed consent for the study and questionnaire are modelled after that used in previous studies and will be delivered in participants' home language (isiXhosa or Afrikaans) by trained interviewers. This study ICF details the purpose of the study, study procedures, and the risks and benefits to mothers that participants may encounter at the second study visit.

Here, study staff will emphasize to participants that:

- Participation is entirely voluntary, and their choice regarding participation will in no way influence the quality of routine medical care for mothers or their infants
- Women may exit the study at any time for any reason without compromising the quality of health care received.

Risks

The potential risks to participants in the study include:

- Risks associated with collection of self-reported behavioural and psychosocial information, related to psychosocial distress raised by questionnaire items involving social support, mental health, or disclosure of HIV status
- Risks due to loss of confidentiality due to study procedures—for instance, in the process of data collection
- Risk associated with asking participants to disclose their status, and potential for interpersonal violence by the partner resultant from the disclosure.

All participants will be informed of these risks, and the strategies to minimize these, as part of the informed consent process. These strategies draw directly from prior experiences conducting research on HIV prevention and treatment in Gugulethu and similar communities across Cape Town.

6. Benefits

Direct benefit: The primary direct benefit from participating in this pilot study is that postpartum women in the intervention arm will receive best possible HIV prevention support including ongoing counseling, SMS messages, HIV self-tests, and biofeedback on adherence to improve their PrEP use and prevent HIV acquisition and infant transmission. The proposed intervention is designed to promote adherence to PrEP in high risk women, while minimising contact with the health facility, healthcare workers and study staff through HIVST, phone based SMS counselling, and phone interviews. Therefore, the direct benefit also includes limiting potential COVID exposure in the health facility by postpartum women and their infants, by providing them services that they can use in their home (HIVST, SMS and phone interviews).

Indirect benefit: By identifying the optimal strategy for improving PrEP adherence in postpartum women, this study has the potential to lead to improved HIV prevention interventions to protect against HIV acquisition and vertical transmission in HIV-uninfected women and their infants in Cape Town, the Western Cape Province, and across South Africa. Further, if the pilot works and is implemented more widely, it will reduce COVID exposure in the health facility by postpartum women and their infants, by providing them services that they can use in their home.

Confidentiality: The following steps will be taken to minimize the risk of any loss of confidentiality throughout study design and conduct.

- All personnel involved in data collection and management will undergo specific training for the study in confidentiality and related patient protection issues.

- Following standard practice, all patient- and study-related information will be kept in locked cabinets at either the study office in Gugulethu or at UCT.

- Anonymous participant identification numbers will be used on all study documents. Collection of participant names and other identifiers will be restricted to informed consent documents, patient tracing materials, and a study identification key, all of which will be kept in a locked cabinet in the study office at Gugulethu and at UCT separate from other study documentation and accessible only by the project coordinator and PI. No CRF will include participant name, including CRF that may reflect HIV status of women or their children.

- All electronic records will be kept in password-protected files. All electronic communications of study data will be through password-protected, encrypted files. All data storage at the University of Cape Town will be within a firewall-protected server.

While efforts will be made to minimize the loss of confidentiality, in the event that staff learn that the participant is a threat to themselves or to others or of possible abuse by partners, the proper authorities will be notified. This exception will be included in all study informed consent forms.

References:

1. Graybill LA, Kasaro M, Freeborn K, et al. Incident HIV among pregnant and breast-feeding women in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS (London, England)* 2020; **34**(5): 761-76.
2. Johnson LF, Stinson K, Newell ML, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. *Journal of acquired immune deficiency syndromes (1999)* 2012; **59**(4): 417-25.
3. Joseph Davey DL, Pintye J, Baeten JM, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? *Journal of the International AIDS Society* 2020; **23**(1): e25426.
4. Joseph Davey D, Linda-Gail Bekker, Nyiko Mashele, Yamkela Qayiya, Pamina Gorbach, Thomas Coates, Landon Myer. HIGH RISK PREGNANT WOMEN INITIATE & PERSIST ON PREP IN CAPE TOWN SOUTH AFRICA COHORT In: Society IA, editor. AIDS (London, England). Virtual conference; 2020.
5. Mofenson LM. Tenofovir Pre-exposure Prophylaxis for Pregnant and Breastfeeding Women at Risk of HIV Infection: The Time is Now. *PLoS Med* 2016; **13**(9): e1002133.
6. Drain P, Ngure K, Mugo N, et al. Testing a Real-Time Tenofovir Urine Adherence Assay for Monitoring and Providing Feedback to Preexposure Prophylaxis in Kenya (PUMA): Protocol for a Pilot Randomized Controlled Trial. *JMIR Res Protoc* 2020; **9**(4): e15029.
7. Spinelli MA, Rodrigues WC, Wang G, et al. Brief Report: High Accuracy of a Real-Time Urine Antibody-Based Tenofovir Point-of-Care Test Compared With Laboratory-Based ELISA in Diverse Populations. *Journal of acquired immune deficiency syndromes (1999)* 2020; **84**(2): 149-52.
8. Gandhi M, Wang G, King R, et al. Development and validation of the first point-of-care assay to objectively monitor adherence to HIV treatment and prevention in real-time in routine settings. *AIDS (London, England)* 2020; **34**(2): 255-60.

TITLE OF RESEARCH: Evaluation of the feasibility and acceptability of an adherence promotiote package for postpartum women on PrEP

INTRODUCTION

Good Morning/Afternoon. My name is _____. I work for the University of Cape Town. We would like to ask you to participate in a research study. The purpose of the study is to evaluate the feasibility and accpetabitliy of SMS reminders, HIV self testing and adherence tests in women on PrEP. This study is being run by public health researchers from the University of Cape Town, South Africa. We have selected Gugulethu Midwife Obstetric Unit to recruit study participants. Before you decide if you want to take part, I will tell you more about the study participation including the benefits and risks to you and what would be expected of you. This information is described in the consent form, which I will give to you now. If you agree to participate, I will ask you to sign the form confirming your willingness to participate. I will give you a copy of the signed consent form to keep.

Why is this study being done?

The purpose of the study is to evaluate how best to improve adherence to pre-exposure prophylyaxis (PrEP) in postpartum women and to evaluate how acceptable it is to send SMS messages about adherehce, HIV self tests for the participant and partner, and a test of adherence using urine. By taking part in this study you will help us collect data that will help determine how to best to prevent HIV in women and children.

Why are you being asked to take part?

Because you are in the PrEP-PP study and are on PrEP and are HIV-negative.

How many people will take part in the study?

200 HIV-negative postpartum women.

How long will the study last?

The study lasts 1 month after you start.

What do we do to decide if you are eligible to take part?

For you to participate in this study you must be:

1. Currently enrolled in PrEP-PP study and on PrEP
2. 18+ years old
3. confirmed HIV-negative (confirmed with a 4th generation antigen HIV test)
4. confirmed to be postpartum (1-6 months postpartum)
5. confirmed to currently have a male partner
6. confirmed to have a cell phone that can read and respond to SMSs
7. without psychiatric or medical contraindications to PrEP

What will happen if you decide to take part in the study? You will then be randomly allocated to participate in the same study group as before (PrEP-PP, referred to as standard of care), or a new group (intervention arm) that will access to certain new information and procedures (see table 1 below). Both groups will have a new study visit in 1 month to follow you up to learn more about your experiences.

Table 1. Sub-study list of visits and assessments by study arm

Visit	**Intervention arm (new study arm)**	**PrEP-PP standard of care arm**
Baseline	1. Consent form for sub-study 2. Survey 3. HIV self-test for self and partner with counselling 4. Urine test with adherence based counselling	1. Consent form for sub-study 2. Survey 3. Invitation for partner testing 4. Urine test (no counselling or feedback)
Weekly (*no visit—only SMS)*	SMS messaging with counselling and reminders to take PrEP	None
14 days	Urine test with adherence counselling	No visit
30 days	1. Endline survey 2. Urine test with adherence based counselling	1. Endline survey 2. Urine test (no counselling or feedback)

Are there any benefits to you for being in the study?

The biggest benefit is for women in the intervention arm will receive best possible HIV prevention support including ongoing counseling, SMS messages, HIV self-tests, and biofeedback on adherence to improve your PrEP use and prevent HIV acquisition and infant transmission.

For women in the standard of care group, there is no direct benefit to participating in this sub-study.

What are the risks and discomforts of this study?

The potential risks to participants in the study include:

- Risks associated with collection of self-reported behavioural and psychosocial information, related to psychosocial distress raised by questionnaire items involving social support, mental health, or disclosure of HIV status
- Risks due to loss of confidentiality due to study procedures—for instance, in the process of data collection
- Risk associated with asking participants to disclose their status, and potential for interpersonal violence by the partner resultant from the disclosure.

The participants will be informed of these risks and the strategies to minimize these as part of the informed consent process. These strategies draw direction from prior experience with HIV research in Gugulethu.

What other choices do you have?

Taking part in this study is voluntary. If you choose not to participate, your care at this clinic or in the PrEP-PP study will NOT be affected today or in the future. If after you join the study, you decide that you no longer want to be involved, you can speak with one of the nurses or study staff, and we will take you off our list and you will not be contacted about the study again.

What will happen when the study is over?

When the study is over, you will continue in the PrEP-PP study until your baby is 12 months old as planned.

Will your test results be shared with you?

- If you are part of the standard of care arm: We will share your HIV test results, but we will not share your urine tenofovir test results for adherence
- If you are part of the new intervention arm: Yes, all results will be shared with you including HIV testing, urine tenofovir for adherence

Will the results of the research be shared with you?

Once all participants have finished the study, we will write a summary of the results and have it at the MOU. If you want a copy, we will let you know when it is ready and can provide it to you.

Will any of your blood, tissue or other samples be stored and used for research in the future?

No.

Will you receive any reward for taking part in this study?

At the end of each visit, you will be given a R100 grocery voucher, R20 for transport, and food and drink while you are at the visit. There is no payment for participation.

Who will see the information which is collected about you during the study?

All information that will be collected from your will be kept confidential. No one but the researchers will be able to see it. We will not tell anyone about your participation. Your name will not be linked to your information. Only the special study number we give you will be able to identify you, and only the researchers will know what your number is. We will lock this information up with a lock and key.

What happens if I get hurt taking part in this study?

This research study is covered by an insurance with the University of Cape Town if you suffer a bodily injury because you are taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury. The insurer will pay without you having to prove that the research was responsible for your injury. You may ask the study doctor for a copy of these guidelines.

Who do I speak to if I have any questions about the study?

If there is anything that is unclear or if you need further information, please ask us and we will provide it.

FOR ADDITIONAL INFORMATION:

The UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

If you have any questions or have any problems while taking part in this research study, you should contact:

Professor Landon Myer
School of Public Health and Family Medicine
Faculty of Health Sciences, University of Cape Town
Tel: 021 406 6661
Email: Landon.Myer@uct.ac.za

CONSENT FOR STUDY PARTICIPATION

CONSENT STATEMENT:

I have read this form, or someone has read it to me. I have been offered a copy of this consent form. I was encouraged and given time to ask questions. I agree to participate in the pilot study, including regular data collection. I agree to provide urine specimens as explained in the consent form. I know that I may withdraw my consent at any time. My participation is voluntary. I understand that whether or not I take part will not affect my health care services received today, or at any time in the future.

Please indicate your consent with your signature.

Volunteer's name _____

_____

Signature of Volunteer Date (DD/MM/YYYY)

Staff member's name_____

_____

Signature of study staff Date (DD/MM/YYYY)

If the volunteer is unable to read or write the entire counselling process must be observed by an independent witness who can then confirm the procedure once the she has given consent.

Fingerprint of volunteer:

Witness:

I confirm that I am independent of the study and that I witnessed the entire informed consent counselling process in the home language of the volunteer

Name: _____

Signature: _____

Date (DD/MM/YYYY): _____

Thank you