Effectiveness and Acceptability of urine tenofovir drug-level feedback on HIV pre-exposure prophylaxis adherence in young South African women

by

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology: Infectious Disease Epidemiology

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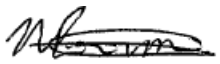
DECLARATION

I, Nicole Poovan, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Science in Epidemiology: Infectious Disease Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Nicole Poovan designed the research study with assistance by Sinead Delany-Moretlwe and Dorothy C. Nyemba. Nicole Poovan, Nontokozo H. Ndlovu, Connie Celum, Renee Heffron, and Sinead Delany-Moretlwe performed the research. Nicole Poovan, and Sue Peacock managed the data. Monica Gandhi provided essential tools. Nicole Poovan analysed the data with assistance from Dorothy C. Nyemba, and Sinead Delany-Moretlwe. Nicole Poovan drafted the initial manuscript and iterative reviews performed by Dorothy C. Nyemba, and Sinead Delany-Moretlwe



(Signature of candidate)

14th day of September 2025, Johannesburg

DEDICATION

I dedicate this report to my family, who provided me with support throughout this experience.

PRESENTATIONS AND PUBLICATIONS

The findings of this study were presented by Dr Nicole Poovan, as a virtual poster presentation at the 5th HIV Research for Prevention Conference in Lima, Peru, 6-10 October 2024. The findings of this study are yet to be published. In Chapter 2, the manuscript in submissible format is planned to be submitted to the Journal of International AIDS Society.

ABSTRACT

Background

Oral pre-exposure prophylaxis (PrEP) adherence in young African women has been suboptimal, necessitating interventions to improve PrEP adherence. We conducted a pilot randomised controlled trial to evaluate the effectiveness of drug-level feedback (DLFB) counselling based on a point-of-care (POC) urine tenofovir assay on PrEP adherence in young South African women.

Methods

Nested within the INSIGHT observational cohort in Johannesburg, South Africa, we randomised cisgender women aged 16-30 years one month after initiating PrEP to either DLFB based on a POC urine test or standard of care (SOC). The primary outcome of tenofovir diphosphate (TFV-DP) ≥700 fmol/punch in dried blood spots (DBS), indicating high adherence, was assessed two months later and analysed by intent-to-treat. Acceptability of DLFB counselling was assessed by self-administered questionnaire. Baseline characteristics associated with TFV-DP ≥700 fmol/punch at the outcome visit were assessed in multivariate analysis using modified Poisson regression.

Results

From Nov 2022 to Jan 2023, 103 participants (53 POCT; 50 SOC) were enrolled; 15% (15/103) with previous PrEP experience and a median age of 24 (IQR: 21-27) years. At randomisation 83% (44/53) had a positive POC urine test. Overall, median follow-up time to outcome visit was 51 days (interquartile range [IQR] 48-56), and 96% (99/103) completed follow up. At the outcome visit, 17% (17/103) had TFV-DP≥700 fmol/punch detected; 19% (10/53) in the DLFB group compared to 14% (7/50) in the SOC group (relative risk [RR] 1.35, 95% confidence interval [CI] 0.56-3.27) in the intent-to-treat analysis. Participants found DLFB based on the POC urine test highly acceptable. Participants liked receiving POC test results on the same day as PrEP refill (90%, 44/49) and reported that DLFB counselling would motivate more frequent PrEP use (92%, 45/49). No baseline characteristics were significantly associated with high adherence in multivariate analysis.

Conclusion:

In this pilot randomised evaluation, real-time adherence counselling based on a POC urine TFV test is a promising intervention that was highly acceptable to young women and associated with a trend towards higher adherence compared to SOC, but this was not statistically significant.

These findings should be confirmed in larger randomised studies with robust estimates of effectiveness, longer follow-up, and cost-effectiveness evaluations to inform program implementation on oral PrEP adherence support.

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LIST OF ABBREVIATIONS/NOMENCLATURE

AGWY: adolescent girls and young women

ART: antiretroviral therapy

CES-D-10: Center of Epidemiologic Studies Depression Scale, 10-item version

CI: confidence interval

CT: *Chlamydia trachomatis*

DAG: directed acyclic graph

DBS: dried blood spot

DLFB: drug-level feedback

EAMs: electronic adherence monitors

Fmol/punch: femtomole per punch

HIV: human immunodeficiency virus

IQR: interquartile range

LLOD: lower limit of detection

NG: *Neisseria gonorrhoea*

OR: odds ratio

POC: point-of-care

PrEP: pre-exposure prophylaxis

RR: relative risk

SMS: Short Message Service

SOC: standard of care

STI: sexually transmitted infection

TFV: tenofovir

TFV-DP: Tenofovir diphosphate

TV: *Trichomonas vaginalis*

WHO: World Health Organization

CHAPTER 1 - INTRODUCTION:

1.1. Introduction

This chapter introduces the burden of human immunodeficiency virus (HIV) in adolescent girls and young women (AGYW) and the barriers related to oral pre-exposure prophylaxis (PrEP). The literature review presents the existing evidence on barriers associated with oral PrEP in this population and strategies that have been evaluated to support PrEP continuation and adherence. It also describes drug monitoring methods for adherence monitoring, the rationale for drug monitoring for PrEP adherence, and the benefits and challenges of each approach. Importantly, the literature review presents the existing evidence supporting evaluation of counselling based on a point-of-care (POC) urine tenofovir (TFV) test for PrEP adherence. Finally, the problem statement, justification, research questions, aims and objectives are described for this research study.

1.2. Background

In 2023, the global HIV incidence was 1.3 million, with girls and women accounting for 44% new HIV infections [1]. However, girls and women accounted for an estimated 62% of HIV incidence among individuals aged 15 years and older in sub-Saharan Africa, indicating an ongoing disproportionate burden compared to males in this region [2]. In 2015, the World Health Organization (WHO) issued recommendations to provide oral PrEP to populations at substantial risk of HIV [3]. In South Africa, the National Department of Health implemented PrEP in 2016 [4] and since then approximately 1,3 million people have initiated oral PrEP [5]. AGYW are an important group that would benefit from PrEP. Despite South Africa having the highest oral PrEP uptake [5], PrEP discontinuation and suboptimal adherence remains high among cisgender girls and women [6]. Consequently, populations with high PrEP discontinuation rates are often associated with an increased incidence of HIV [6]. One potential strategy that may overcome the challenge of PrEP adherence among AGYW is drug-level feedback (DLFB).

1.3. Literature review

1.3.1. Factors associated with oral PrEP discontinuation and adherence

PrEP continuation is important during periods of risk and high adherence, defined as taking four or more doses per week, is needed to prevent HIV in women [7]. Reasons for PrEP discontinuation include individual barriers such as younger age, being female, low perception of HIV risk, side effects and pill burden; interpersonal barriers include lack of family support; and structural barriers such as cost and access to PrEP [6]. An open-label PrEP trial, identified

that high oral PrEP adherence was observed during periods when HIV risk was described, demonstrating that AGYW could use PrEP consistently when they experienced HIV risk [8]. Risk reduction and adherence counselling may have supported AGYW to use PrEP during periods of risk [8], underscoring the value of HIV risk awareness and PrEP education to support HIV prevention. Despite risk reduction and PrEP adherence counselling being standard components of PrEP provision, ongoing challenges with PrEP continuation indicate that barriers to oral PrEP use occur on multiple levels. Interpersonal challenges such as lack of support by family, partner and the community can influence motivation for PrEP use in AGYW [9]. Suboptimal adherence has also been observed when AGYW experienced symptoms of depression [10–12], furthermore transactional sex and intimate partner violence (IPV) are often reported in AGYW experiencing symptoms of depression [10]. Partner and family relationships, as well as mental health conditions significantly impacts individuals' decision-making capabilities, influencing not only their adherence but also their access to PrEP services [13]. Access to PrEP is a major structural barrier. Beyond those challenges influenced by the social environment, access barriers also occur at the healthcare provider and service delivery levels. These include long waiting times, stock shortages, negative attitudes by health professionals towards young women's sexual activity, and limited availability of PrEP services beyond clinical facilities [9]. Understanding the factors associated with PrEP continuation and adherence is crucial for identifying and implementing appropriate supportive measures to overcome these barriers.

1.3.2. **Interventions to support oral PrEP adherence**

Several innovative supportive strategies to overcome barriers associated with oral PrEP continuation and adherence have been evaluated in open-label PrEP trials but have not observed substantial effect on adherence. In South Africa, incentives using a shopping voucher were evaluated on oral PrEP adherence and observed that adherence was higher in the incentive arm but these findings were not statistically significant demonstrating that this incentive was not strong enough to motivate high adherence in AGYW [14]. An electronic decision support tool (DST) designed to guide users in assessing HIV risk and providing education on PrEP, demonstrated improved PrEP continuation at one month, with PrEP persistence of 19% among AGYW in the DST group compared to 10% in the control group [OR 1.79, 95% CI 1.08-3.69] [15]. This tool may have provided early support for individual PrEP barriers, including the management of side effects and understanding daily pill-taking [15]. However, the lack of difference in knowledge and satisfaction between the intervention groups suggests higher satisfaction with client-provider interactions, an important

consideration for the development and evaluation of oral PrEP adherence support strategies [15]. The PrEP SMART trial evaluated scalable PrEP adherence support strategies [16,17]. These included WhatsApp peer support groups, two-way short message service (SMS) communication with the health-care provider, monthly issue-focused counselling and quarterly DLFB on PrEP adherence [16,17]. Although there were no significant differences in high adherence observed between these interventions, overall adherence was improved compared to previous open-label PrEP studies, with rates of 55% at 2 months and 27% at 9 months [17]. Despite the improvements observed, these findings demonstrate an ongoing gap in achieving effective levels of oral PrEP in AGYW. Lessons learned from this trial suggest scaling additional support earlier at one month post PrEP initiation, and highlight the need for future research on how, when and to whom to provide scalable oral PrEP adherence support [17].

1.3.3. **Objective measures for PrEP adherence monitoring**

Motivations to use PrEP are unique compared to treatment of chronic conditions in that failure to use PrEP may or may not result in a health condition and as HIV risk changes over time, continuous use of PrEP may not be necessary [18]. In clinical trials evaluating daily oral PrEP among women in Africa, self-reported PrEP adherence was high while objective measurements utilizing tenofovir (TFV) plasma levels showed low adherence [19,20]. In the VOICE trial, women who received retrospective feedback on their plasma TFV results recommended real-time monitoring and feedback on their PrEP use to support adherence [21]. Self-report, pharmacy refills and pill counts are frequently used to assess adherence in practice, however these are limited by social desirability bias and inaccuracy [22,23]. To overcome these limitations feasible, cost-effective, acceptable, time-efficient and objective assessments for measuring adherence are required [24]. Objective methods for assessing adherence include electronic adherence monitors (EAMs) and monitoring drug levels [22]. EAMs provide adherence information based on bottle opening however they are costly and do not measure ingestion of pills [22]. Monitoring for the presence of drug in biological fluids is the most objective method for confirming adherence [25]. In the context of prophylaxis, drug monitoring has been used with lithium for prevention of manic or depressive episodes, phenytoin for preventing seizures and cyclosporine for preventing rejection of transplant organs [26].

Methods used for monitoring drug levels include plasma and urine that assess recent dosing over days, while drug levels in dried blood spots (DBS) and hair assess drug dosing for a

longer period, over weeks (**Table 1.1**) [22]. Analyses using plasma assays provide variable sensitivities and determine PrEP use in the last week [23]. While plasma is valuable in evaluating adherence in research, it is not practical for clinical implementation in resource-constrained settings. Sample processing and testing requires time, specialised training and expensive equipment, and due to its reflection on recent dosing, this method may be susceptible to "white-coat" adherence [27,28]. Methods that measure longer term adherence may be preferred such as DBS. Tenofovir diphosphate (TFV-DP) has a intracellular half-life of 17 days and is able to measure long-term PrEP dosing and adherence in the past 4-8weeks [29,30]. The iPrEx trial demonstrated that TFV-DP levels at a cut-off of 700 femtomole per punch (fmol/punch), corresponding to 4-7 tablets taken per week, was associated with a 100% reduction in HIV incidence during the study period [31]. This threshold and the long-term measure of adherence with DBS has provided value in PrEP studies evaluating adherence. Subsequent studies in cis-gender women have also demonstrated that taking 4 or more doses of PrEP is able to provide protective levels against HIV [7]. While DBS can be easily collected by finger prick [28], analysis of drug concentrations requires a specialised laboratory, and cannot be performed in real-time [22]. Due to the slow growth rate of hair, drug levels in the 1.5cm of hair proximal to the head provide information on dosing in the last 6 weeks [32]. The benefits of hair sample collection are that it is minimally invasive and can also be collected in non-clinical environments if required [22]. However, this method is also limited in that it requires a specialised laboratory and the need for 50-100 hair strands collected close to the scalp was not acceptable among participants in a previous trial conducted in South Africa [22,33].

Table 1.1. Methods for measuring drug concentrations of TFV-based oral PrEP.

Sample collection method	Adherence timeframe	Protective threshold
Plasma[6,23,34]	2-7 days	35-40 ng/ml
Urine POC assay[35,36]	4-7 days	≥1500 ng/mL
Dried blood spots (DBS) [29–31]	4-8 weeks	≥700 fmol/punch
Hair[37]	6 weeks	0.023 ng/mg

1.3.4. **Point-of-care urine TFV assay for adherence counselling**

While dried blood spots or hair samples could enable measurement of long-term PrEP adherence through TFV testing, the laboratory processing it requires is not practical for rapid testing in clinical practice. [27]. A validated point-of-care (POC) urine TFV assay was developed at high levels of specificity (97%) and sensitivity (99%) at a threshold of

1500ng/mL and assesses recent prep dosing in the previous 4-7 days [35]. This POC urine test costs less than forty rand, is easy to use and provides rapid results, enabling real-time PrEP adherence counselling [35]. The POC urine test could therefore address the barriers identified with DLFB using DBS or hair and be more feasible to implement within the package of PrEP services [36].

Qualitative data from the VOICE trial found that in the subset of women who received retrospective DLFB based on their plasma samples collected during the study, reported that DLFB was acceptable and understood by women taking PrEP [21]. In the HPTN 082 study, specialized counselling based on TFV concentrations in DBS did not improve PrEP adherence [38]. The use of DBS presented several challenges: the results were received a month after sample collection since testing was performed at a specialised laboratory [38]. There were difficulties transcribing drug level results to the corresponding counselling messages, and providing counselling based on results that reflected adherence in the prior 4-6 weeks may have been difficult for women to recall their PrEP use over that long period [38]. These findings highlight the need for tools that enable real-time testing and feedback to support oral PrEP adherence.

Qualitative findings from a study in Kenya identified that counselling based on the urine test may be feasible and acceptable by both PrEP users and providers [39]. Quantitative analysis in the PrEP SMART and PUMA trials demonstrated that women using PrEP found counselling based on the POC urine test to be acceptable [40,41]. In the PrEP SMART trial, counselling based on the urine test was liked by most participants (94%) and 98% would be willing to use this counselling method in the future if available [40]. Furthermore, the test's performance was evaluated in comparison to DBS, and a negative result from the POC urine test accurately identified individuals with suboptimal adherence who would require additional supportive measures. [40]. These acceptability and performance findings encourage further evaluation of the effectiveness of this counselling tool on oral PrEP adherence.

In Namibia, a pre-post intervention study among patients who were virologically unsuppressed on antiretroviral therapy (ART) showed that after receiving monthly counselling based on the POC urine TFV test, virological suppression was attained in 87% (p-value<0.001) at 3 months and 97% at 9 months (p-value<0.001) [42]. This was the first study to demonstrate improvement in adherence using this test. In the HIV prevention setting, a pilot randomised trial conducted in 100 PrEP users in Kenya recently published findings that

participant non-adherence at 12 months was 3.5-fold more likely in those who received SOC compared to those who received counselling based on the urine test [41]. In addition, the utility of the urine test for counselling was explored in another study conducted in Kenya that found counselling based on the urine test to improve self-report of condomless sex and PrEP adherence [43]. These findings suggest that POC urine testing and counselling may improve oral PrEP adherence, however the effect on high adherence has not been assessed and is needed to establish if the tool can assist AGYW to achieve protective PrEP levels for HIV prevention.

1.4. **Problem statement**

In sub-Saharan Africa, HIV incidence is highest among AGYW. Despite high oral PrEP uptake, PrEP adherence and continuation is low in women and may undermine the public health impact of PrEP. There are multiple barriers to oral PrEP adherence and continuation. Interventions to support daily oral PrEP continuation and adherence have not demonstrated substantial impact. Cost-effective and easy to use tools are needed to support PrEP adherence especially among young women who struggle with daily oral pill taking.

1.5. **Justification**

A validated, qualitative POC test detecting TFV in urine is low-cost, easy to perform and enables same-day counselling on recent PrEP use at a PrEP refill appointment [36]. To our knowledge, no other trial has demonstrated the effectiveness of counselling based on the POC urine test for oral PrEP on high adherence that is required to achieve protective levels for HIV prevention for women [7]. Currently adherence counselling based on drug measurement is not included in SOC PrEP adherence counselling, and evaluation of the effectiveness and acceptability of counselling based on this POC urine TFV assay on oral PrEP adherence is needed to inform use of this tool in young women living South African.

1.6. **Research Questions**

What is the 1) effectiveness and 2) acceptability of DLFB adherence counselling based on POC urine test results compared to SOC on oral PrEP adherence in young South African women? 3) What characteristics are associated with high adherence to oral PrEP?

1.7. **Aim**

To evaluate the effectiveness and acceptability of DLFB adherence counselling based on POC urine test results compared to SOC on oral PrEP adherence in young South African women.

1.8. **Objectives**

1.8.1. **Primary objective**

- To assess the effectiveness of DLFB adherence counselling based on POC urine test results compared to SOC on high adherence after 3 months of oral PrEP initiation (short-term adherence). The outcome is the proportion of women with high adherence (intracellular tenofovir diphosphate [TFV-DP] concentrations on DBS ≥700 fmol/punch) by study arm, at the outcome visit.

1.8.2. **Secondary objectives**

- To assess acceptability of DLFB adherence counselling based on a POC urine test among women.
- To evaluate the demographic and behavioural characteristics associated with high PrEP adherence.

CHAPTER 2 - MANUSCRIPT IN SUBMISSIBLE FORMAT

This manuscript is planned for submission to The Journal of The International AIDS Society (JIAS). The authorship guidelines for publication in JIAS are found in appendix 5. A declaration stating my contribution to the manuscript and agreement signed by the co-authors can be found in appendix 6.

Effectiveness of Point-of-Care Urine Tenofovir Testing to Improve PrEP Adherence in Young South African Women: a randomised pilot trial

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Abstract

Background

Oral pre-exposure prophylaxis (PrEP) adherence in young African women has been suboptimal, necessitating interventions to improve PrEP adherence. We conducted a pilot randomised controlled trial to evaluate the effectiveness of counselling based on a point-of-care urine tenofovir (POCT) assay on PrEP adherence in young South African women.

Methods

Nested within the INSIGHT observational cohort in Johannesburg, South Africa, we randomised cisgender women aged 16-30 years one month after initiating PrEP to either counselling based on POCT or standard of care (SOC). The primary outcome of tenofovir diphosphate (TFV-DP) ≥700 fmol/punch in dried blood spots (DBS), indicating high adherence, was assessed two months later and analysed by intent-to-treat. Acceptability of POCT counselling was assessed by self-administered questionnaire. Baseline characteristics associated with TFV-DP ≥700 fmol/punch at the outcome visit were assessed in multivariate analysis using modified Poisson regression.

Results

From Nov 2022 to Jan 2023, 103 participants (53 POCT; 50 SOC) were enrolled; 15% (15/103) with previous PrEP experience and a median age of 24 (IQR: 21-27) years. At randomisation 83% (44/53) had a positive POCT. Overall, median follow-up time to outcome visit was 51 days (interquartile range [IQR] 48-56), and 96% (99/103) completed follow up. At the outcome visit, 17% (17/103) had TFV-DP≥700 fmol/punch detected; 19% (10/53) in the POCT group compared to 14% (7/50) in the SOC group (relative risk [RR] 1.35, 95% confidence interval [CI] 0.56-3.27) in the intent-to-treat analysis. Participants found POCT-based counselling highly acceptable. Participants liked receiving POCT results on the same day as PrEP refill (90%, 44/49) and reported that POCT-based counselling would motivate more frequent PrEP use (92%, 45/49). No baseline characteristics were significantly associated with high adherence in multivariate analysis.

Conclusion:

In this pilot randomised evaluation, real-time adherence counselling based on POCT is a promising intervention that was highly acceptable to young women and associated with a trend towards higher adherence compared to SOC, but this was not statistically significant. These

findings should be confirmed in larger randomised studies with robust estimates of effectiveness, longer follow-up, and cost-effectiveness evaluations.

Clinical Trial Number: NCT05746065

Introduction

Adolescent girls and young women (AGYW) accounted for 44% of new HIV infections globally in 2023 [1]. In 2015, the World Health Organization (WHO) provided guidance to offer pre-exposure prophylaxis (PrEP) to those at substantial risk of HIV [2]. Despite the potential benefits of PrEP for AGYW, discontinuation rates are highest among AGYW significant risk factor for suboptimal PrEP adherence [3]. Reported reasons for oral PrEP discontinuation include side effects, pill burden, lack of support, cost and access barriers to PrEP [3]. Continued use of PrEP during periods of risk is essential for HIV prevention ('prevention-effective adherence') [4]; women with consistent daily or consistent high PrEP adherence (4-6 doses/week) experienced very low HIV incidence (<0.5/100 person-years) in a recent pooled analysis [5]. One potential strategy that may help overcome the challenges of oral PrEP adherence and continuation is adherence counselling based on objective measures of drug concentrations.

In clinical trials evaluating daily oral PrEP among women in Africa, there have been significant differences between high self-reported adherence and actual adherence based on objective measurements of tenofovir (TFV) plasma concentrations that were low [6,7]. In the VOICE trial, a subset of women who received retrospective feedback on their plasma TFV concentrations recommended implementing real-time monitoring and feedback to support PrEP adherence [8]. In the HPTN 082 study, counselling based on TFV-DP concentrations in dried blood spots (DBS) did not improve adherence compared to standard of care (SOC) counselling [9]. DBS-based counselling may not have improved adherence because of the long interval between the actual pill-taking behaviours associated with the result and the visit when counselling based on results was provided. DBS TFV-DP testing can only be performed in specialised laboratories and is not a scalable option [9]. However, a point-of-care urine TFV (POCT) assay has been validated and would be more feasible to implement in clinical settings [10]. This lateral flow assay with a cut-off of 1500ng TFV/mL of urine is able to provide information on PrEP use in the last 4-7 days [11]. The POCT is easy to use, low cost (<$2 per test) with a rapid turnaround time (3 mins), facilitating real-time adherence monitoring and PrEP adherence counselling [11]. In South Africa, the current guidelines for PrEP adherence counselling do not include any reference to counselling based on drug measurements [12]. We conducted a pilot randomised trial at a single site nested within the INSIGHT study to evaluate the effectiveness of real-time adherence counselling based on a urine POCT assay in young South African women using oral PrEP [13].

Methods

Study design and participants

INSIGHT was a prospective open-label cohort study assessing PrEP uptake, adherence, and persistence through 6 months among young women aged 16-30 years, conducted across 20 sites in six African countries that has been described elsewhere [13]. Young women were recruited through community events, primary health care clinics and social media. Participants without HIV who were interested in HIV prevention were initiated on oral PrEP at enrolment and attended follow-up visits at months 1, 3 and 6 aligned with the recommended national PrEP follow-up schedule [12].

From November 2022 to March 2023 participants at Wits RHI Ward 21 Clinical Research Site in Johannesburg were assessed for eligibility to participate in the nested pilot Type I effectiveness-implementation hybrid randomised controlled trial. Participants were eligible for randomisation to either POCT-based or SOC counselling if they attended their one-month PrEP follow-up visit, and were willing to consent to trial procedures. Evaluation of POCT-based counselling was incorporated in the PrEP visit schedule at this visit because studies have shown that AGYW who fail to establish PrEP adherence in the first three months of use seldom succeed later and frequently discontinue PrEP [9,14]. Long-term adherence outcomes were assessed at the visit three months after PrEP initiation i.e. approximately two months post-randomisation.

Study procedures

At PrEP initiation, baseline demographic and behavioural data were collected through interviewer-administered questionnaires. Swabs were collected and tested for *Chlamydia trachomatis* (CT) and *Neiserria gonorrhoea* (NG) using nucleic acid amplification and *Trichomonas vaginalis* (TV) using OSOM Trichomonas rapid test (Sekisui Diagnostics, USA). Blood samples were collected for syphilis serology and defined as positive if both non-treponemal and treponemal test were reactive.

Participants returning for their visit one month later were randomised 1:1 to receive either POCT-based or SOC adherence counselling following written informed consent (**Figure 2.S1**). SOC counselling was provided by a study counsellor or nurse and included assessment of pill taking, PrEP education regarding effective use, identification of barriers to effective use and provision of strategies to address barriers. Participants in the POCT group provided a urine sample for same day TFV testing at the randomisation visit. POCT testing was

performed at the clinical research site laboratory using the assay developed and validated by UCSF Hair Analytical Laboratory/Abbott Rapid Diagnostics [11]. After 3-5 minutes, results were reviewed and provided to the clinic staff for counselling. Results were recorded in the electronic database with a photo of the test uploaded for quality check by the central data manager. Trained study nurses provided POCT-based counselling using counselling messages adapted from the HPTN 082 and PrEP SMART studies (**Figure 2.S2**) [9,15]. For those with a negative test result, counselling focussed on recent adherence barriers and ongoing motivation for PrEP use, with support provided to help resolve challenges identified. Irrespective of the test result, supportive counselling was provided and consistent PrEP use was encouraged for HIV prevention. Following counselling, participants in the POCT group completed a computer assisted self-interview (CASI) on a tablet [16], to assess acceptability of the intervention. The CASI was based on a previously used tool in a similar population in the PrEP SMART trial [15,17]. This tool was adapted from tools assessing other aspects of PrEP delivery, including the questionnaire assessing acceptability of the MyPrEP decision support tool, which was evaluated in the POWER demonstration project [18]. The 9-item questionnaire used a 4-point Likert scale with response options of strongly disagree, disagree, agree, and strongly agree.

Participants were asked to return for PrEP refill and an outcome visit two months later. At both the randomisation visit and outcome visit, all participants received HIV testing, risk reduction and adherence counselling, condom provision, contraception and PrEP refill if indicated. At the outcome visit, DBS samples for TFV-DP assessment were collected from participants in both groups. DBS testing was performed at the University of Cape Town (UCT) laboratory [9,19]. TFV-DP has a long half-life of 17 days in red blood cells and reflects cumulative PrEP dosing and adherence in the last 4-8weeks [20,21]. TFV-DP levels of 700 fmol/punch corresponding to an average of ≥4 pills taken per week [22] has been shown to be associated with protective levels in cisgender women [5,23].

This study was reviewed and approved by the Human Research Ethics Committee at the University of the Witwatersrand. All participants provided written informed consent or assent with parental/legal guardian consent to participate.

Randomisation and blinding

A randomisation list using blocks of 8 was generated in Stata 17 by the study data manager and uploaded in to the REDCap randomisation module. Participants were randomised using

the REDCap randomisation CRF at the start of the randomisation visit. Participants and providers were not blinded to intervention group, but the outcome assessment was completed by laboratory staff who were blinded to allocation.

Outcomes

The primary outcome was the proportion of women with high adherence defined as DBS intracellular TFV-DP concentrations on ≥700 fmol/punch at the outcome visit. Secondary outcomes included (1) the proportion of women with detectable TFV-DP levels (≥16.6 fmol/punch, lower limit of detection [LLOD] indicating some PrEP use in the prior 4-8 weeks) by group, at the outcome visit; (2) acceptability of POCT-based counselling assessed as the proportion who agreed or strongly agreed to each item of the questionnaire and (3) baseline demographic and behavioural characteristics associated with TFV-DP levels ≥700 fmol/punch at the outcome visit.

Statistical considerations

We calculated the sample size needed for a two-sample comparison of proportions, at a statistical significance level of 0.05 and power of 0.80. Assuming that the proportion of women with TFV-DP levels ≥700 fmol/punch in the SOC group is similar to that observed in the HPTN 082 study (24%) after three months of PrEP initiation [9], a sample size of approximately 100 participants would have sufficient power at 80% to detect a two-fold increase in the proportion of participants with high adherence.

The intent-to-treat analyses included all participants. Missing DBS TFV-DP results at the outcome visit were set to 0 (not detectable) and assumed to be missing at random. A per-protocol analysis excluded those who did not receive their randomised counselling intervention and those with missing DBS results at the outcome visit. Risk ratios were calculated using a 2x2 contingency and differences in outcome assessed using chi-squared or Fishers exact test. During the main study, delays in importing POCT kits, contributed to fewer participants with POCT results. In those with POCT results available at the outcome visit, the proportion with positive urine POCT were compared by group. To assess acceptability of POCT-based counselling, questionnaire responses were dichotomised to measure the proportion of participants who agreed or disagreed for each item of the Likert-scale. Associations between baseline characteristics and high adherence were explored in bivariate analyses using generalised estimating equations to estimate relative rates. Models were fit

with a log link, Poisson distribution, and robust standard errors. Factors explored in multivariate analysis were informed through use of directed acyclic graphs (DAGs) and past literature on oral PrEP adherence (**Supplementary Material:**

Table 2.S1. Baseline predictors of oral PrEP adherence at the outcome visit among young women.

	TFV-DP in DBS		Unadjusted		Adjusted†	
	TFV-DP < 700 fmol/punch n=86 n (%) or median (IQR)	**TFV-DP ≥ 700 fmol/punch n=17 n (%) or median (IQR)**	**Relative Risk (95% CI)**	**p-value**	**Relative Risk (95% CI)**	**p-value**
Intervention arm						
SOC arm	43 (50.0%)	7 (41.2%)	ref	-	ref	-
POCT arm	43 (50.0%)	10 (58.8%)	1.35 (0.56-3.27)	0.509	1.37 (0.57-3.26)	0.479
Highest level of education						
Secondary school or below	14 (16.3%)	1 (5.9%)	ref	-	ref	-
Tertiary school or higher	54 (62.8%)	10 (58.8%)	1.80 (0.74-4.34)	0.194	1.78 (0.75-4.22)	0.191
CES-D-10 score ≥10‡	26 (30.2%)	8 (47.1%)	1.80 (0.76-4.26)	0.178	2.17 (0.90-5.22)	0.085
VOICE risk score§	7 (5-7)	5 (4-7)	0.90 (0.74-1.10)	0.308	0.88 (0.72-1.07)	0.194

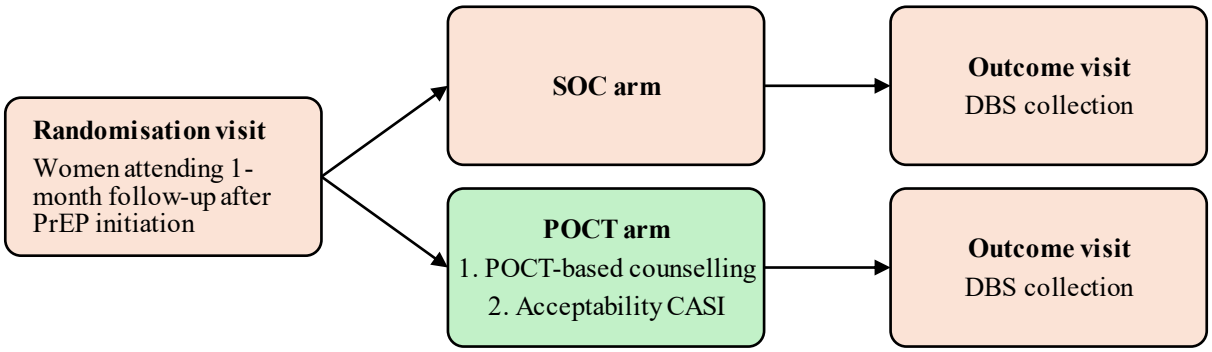
CES-D-10: Centre for Epidemiological Studies Depression Scale-10; CI: confidence interval; IQR: interquartile range; POCT: point-of-care urine tenofovir; SOC: standard of care; TFV-DP: tenofovir diphosphate.

† The VOICE risk score as a continuous variable, highest level of education, Centre for Epidemiological Studies Depression Scale-10 (CES-D-10) with a score ≥10 indicating high risk of depression and study arm were adjusted for in multivariate analysis.

‡ CES-D-10 scale, maximum score of 30; CES-D-10 ≥10 associated with high risk of depression.

§ VOICE risk score includes age ≤25, married or living with partner, partner provides financial and/or material support, primary partner has other partners, and alcohol use in the last 3 months. Excludes HSV-2 serostatus. Maximum score of 9; score of ≥5 associated with high risk of acquiring HIV.

Figure 2.S1. Study design



DBS: dried blood spots; CASI: computer-assisted self-interview; POCT: point-of-care urine tenofovir; PrEP: pre-exposure prophylaxis; SOC: standard of Care.

Figure 2.S2. Real-time adherence counselling messages.

Control line only (one line appears on test)
Key message: It looks like you took a PrEP pill recently, you are doing great! Remember that taking one PrEP pill every day is needed for strong protection against HIV. Are you still interested in taking PrEP today?

Control and tenofovir test line (two lines appear on test)
Key message: It looks like you haven't been able to take the PrEP medication in the past few days. Is PrEP something that you are still interested in? If yes, how can we help you?

Figure 2.S3). The VOICE risk score has been validated against HIV incidence, with a score ≥5 associated with high risk of acquiring HIV [24]. The VOICE risk score (including age) as a continuous variable [24], highest level of education, Centre for Epidemiological Studies Depression Scale-10 (CES-D-10) with a score □10 indicating high risk of depression [25] and study group were adjusted for a priori. Factors significant in bivariate analysis at 0.05 were included in an adjusted model. Statistical analysis was conducted using Stata® statistical package 17 [26].

Results

Participant characteristics at enrolment

Of 112 participants who initiated PrEP and were assessed for eligibility from 11 November 2022 to 17 January 2023, 103 (92%) were randomised (53 POCT, 50 SOC) one month post PrEP initiation (**Figure 2.1**). In the POCT group, 1 participant did not receive POCT-based counselling because of delays in test kit importation and 1 participant declined PrEP refill after receiving adherence counselling. In the SOC group, 1 participant received the POCT-based counselling in error. These participants were excluded from the per-protocol analysis.

At PrEP initiation, baseline characteristics were balanced across groups apart from CT prevalence which was lower in the POCT group (**Table 2.1**). The median age was 24 years (interquartile range [IQR] 21-27), 77% (79/103) had some secondary school education and 15% (15/103) had prior PrEP experience. Overall, 27% (28/103) reported two or more partners, 43% (44/103) had a primary partner with HIV or unknown status, 26% (27/103) reported intimate partner violence months and 6% (6/103) reported transactional sex in the past three months. The median VOICE risk score was 6 (IQR 5-7), 33% (34/103) had a CES-D-10 score ≥ 10 indicating symptoms of depression, and 28% (29/103) had either CT, NG or TV. At randomisation, 83% (44/53) in the POCT group had a positive POCT test.

Of those randomised, 96% (99/103) were retained at the outcome visit (51 POCT, 48 SOC) (**Figure 2.1**). The median follow-up time was 51 days (interquartile range [IQR]: 47.5-56) and did not differ by group. At the outcome visit, 2 participants in each group did not have DBS results and were excluded from the per-protocol analysis. Among those with a POCT test at the outcome visit, 83% (34/41) had a positive result, 91% (19/21) in the POCT group and 83% (15/20) in the SOC group (Relative risk [RR] 1.73; 95% CI 0.08-1.74; p-value 0.238).

Effectiveness of POCT-based counselling on oral PrEP adherence

At the outcome visit, 19% (10/53) in the POCT compared to 14% (7/50) in the SOC group had high adherence ((RR): 1.35; 95% confidence interval (CI) 0.56-3.27) (**Table 2.2**). Similarly, in the per-protocol analysis, 18% (9/49) in the POCT group had high adherence compared to 15% (7/47) who received the SOC (RR 1.23; 95% CI 0.50-3.04). With respect to the intervention effects on detectable TFV-DP , 91% (48/53) in the POCT compared to 84% (42/50) in the SOC group had TFV-DP detected on DBS (RR 1.08; 95% CI 0.93-1.25). Similar trends were observed in a per-protocol analysis (96% (47/49) POCT vs 87% (41/47) SOC; RR 1.10; 95% CI 0.97-1.24).

Acceptability of POC-based counselling

At the randomisation visit, 49/53 POCT participants completed the acceptability questionnaire (**Figure 2.2**). Participants mostly understood the results of the POCT testing (94%, 46/49) and expected the POCT result that they were shown during counselling (88%, 43/49). Most reported that POCT-based counselling improved communication with PrEP providers (90%; 44/49), with 92% (45/49) agreeing that the POCT would motivate more consistent PrEP use. Participants appreciated the real-time feedback (94%, 46/49), found POCT-based counselling helpful for HIV prevention (94%, 46/49), liked receiving same day results and counselling (90%, 44/49) and felt emotionally supported during counselling (78%, 38/49). Most participants (92%, 45/49) would choose POCT-based counselling in the future. There were no significant differences in acceptability reported when compared by urine TFV test result at randomisation.

Characteristics associated with high PrEP adherence

In bivariate and multivariable analyses there were no demographic or behavioural characteristics found to be associated with high adherence at a significance level of 0.05 (**Table 2.S1**).

Discussion

In this pilot randomised trial of real-time adherence measurement and counselling in young South African women, 83% of those randomized to the POCT had a positive result at randomisation. Despite this encouraging early evidence of recent PrEP use, POCT-based counselling was not associated with high PrEP adherence two months later, although the proportion of women with high adherence was 35% higher in the POCT group. This finding may reflect overall declining adherence in the first three months of PrEP adherence, as seen in

other studies [27], and/or that a single same-day counselling session about recent PrEP use is insufficient to overcome the adherence challenges women experienced in the subsequent two months.

Our results differ from a pilot trial of the POCT in 100 PrEP users in Kenya, but these differences may be due to differences in trial design. In that trial, 79% in the POCT group had detectable TFV in hair at 12 months compared to 63% in the SOC group, with the odds of undetectable TFV in hair being 3.53-fold higher in those not exposed to POCT (p=0.04) [28]. Similarly, in our pilot 96% in the POCT group had detectable TFV-DP in DBS compared to 87% in the SOC group after two months, with the absolute differences between the groups being smaller in our trial potentially explaining the difference in results. However, detectable TFV may be limited as an outcome, as high adherence is needed for HIV protection [23]. In our trial, the high proportion of participants with detectable TFV compared to the low proportion with TFV-DP ≥700 fmol/punch on DBS highlights the challenges with achieving HIV protection with inconsistent oral PrEP use. Inconsistent PrEP use may be influenced by young women's varying assessment of HIV risk as well as ongoing social and structural barriers to adherence that may be more difficult to change at an individual level. Trials comparing high adherence may be more informative in evaluating the potential benefits of this counselling intervention.

Notably in our trial, three months after PrEP initiation, 83% of participants had a positive urine POCT and the proportion of positive was significantly higher (73%) in the POCT group. By contrast, the proportion of positive tests at three months was lower in the Kenyan study and did not vary by study group. However, there were differences between the two groups in the Kenyan trials on urine POCT by 12 months, suggesting that multiple POCT-based counselling sessions over a prolonged period may have contributed to a more sustained benefit.

POCT-based counselling was highly acceptable to young women in this pilot irrespective of their POCT results, consistent with other studies [28,29]. A recent study of 500 young women in Uganda found that POCT improved self-report of PrEP adherence and condomless sex, highlighting the potential of this method to enhance client-provider communication[30]. However, qualitative data from young Kenyan women underscores the potential negative consequence of a negative test if women feel pressured to return for PrEP refills only if they have had recent dosing to ensure a positive test [29]. In INSIGHT, a positive POCT result

was associated with a higher likelihood of a positive test at a subsequent visit [13]. This could either be due to improved adherence or subsequent positive tests reflecting social desirability and "white coat adherence" [31]. In our trial most participants reported that counselling helped them communicate with their provider, but fewer felt emotionally supported. Almost a third of the participants in our trial reported symptoms of depression and 26% reported recent intimate partner violence, indicating a need for additional support beyond POCT-based counselling. Nevertheless, POCT-based counselling does appear to improve communication between PrEP users and providers, but efforts are needed to strengthen this relationship to ensure young women's additional support needs are not overlooked.

This study was powered to detect a two-fold difference in effectiveness between the counselling groups and was limited in its ability to detect smaller effect sizes as demonstrated by the smaller, non-statistically significant result. The overall low proportion with high adherence observed at the outcome visit, three months after PrEP initiation, is comparable to other recent studies in young African women but may also have contributed to this null finding [9,27]. Missing DBS samples at outcome visit may also have affected the validity of the results, however this was limited to a few participants who missed the visit or did not continue PrEP at follow-up in this trial. Additionally, processes to assess the fidelity of the counselling messages provided in this trial and experiences between those with a positive or negative test result were not included. A larger randomised trial would therefore be needed to demonstrate definitively the potential benefits of POCT-based counselling on adherence in young women.

Conclusion

In this pilot trial, real-time adherence assessment and counselling based on a POCT did not significantly increase the proportion of young women able to achieve protective levels of TFV two months after receiving the counselling intervention. POCT-based counselling was acceptable to young women using daily oral PrEP and could support adherence while access to long-acting PrEP methods is limited. Real-time adherence counselling using the urine POCT should be evaluated in larger randomised trials with robust estimates of effectiveness and cost to inform future support programs for young women who use oral PrEP for HIV prevention.

Competing interests

CC and RH have served as scientific advisors to Merck. All other authors report no conflicts of interest.

Authors' contributions

N.P., CC and S.D-M. designed the research study. N.P., N.H.N, M.L.K, IN, C.C., R.H., and S.D-M. conducted and/or supervised the research. N.P., and S.P. managed the data. M.G. provided essential tools. N.P., D.N.M., and S.D-M. analysed the data. N.P. drafted the initial manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

The data that support the findings of this study will be made available upon reasonable request. INSIGHT study data may be requested through icrc@uw.edu. Data specific to the nested study may be requested through the corresponding author at Wits RHI, University of Witwatersrand.

Supporting Information

Supporting Information file 1: Supplementary Material

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Table 2.1. Baseline characteristics of young women in the pilot randomised trial.

Baseline characteristic	POCT group (N=53) n (%) or median (IQR)	SOC group (N=50) n (%) or median (IQR)
Age (years), median (IQR)	24 (21-26)	23 (21-27)
Highest level of education		
Secondary school or below	39 (73.6%)	40 (80.0%)
Tertiary school or higher	14 (26.4%)	10 (20.0%)
Employed	7 (13.2%)	12 (24.0%)
≥2 sex partners in the last 3 months	12 (22.6%)	16 (32.0%)
Age difference with primary partner >5 years†	13/51 (25.5%)	8/48 (16.7%)
Primary partner living with HIV or unknown status‡	24/52 (46.2%)	20/48 (41.7%)
Any transactional sex in the past 3 months§	3 (5.7%)	3 (6.0%)
Vaginal sex act in the past 7 days, median (IQR)	1 (0-2)	1 (0-3)
Condom use at last sex act	15 (28.3%)	10 (20.0%)
Any Intimate partner violence (IPV) in the past year¶	12 (22.6%)	15 (30.0%)
CES-D 10 scale ≥10#	17 (32.1%)	17 (34.0%)
Prior PEP use	4 (7.6%)	2 (4.0%)
Prior PrEP use	10 (18.9%)	5 (10.0%)
Current contraceptive method use		
Oral	6 (11.3%)	2 (4.0%)
Injectable	18 (34.0%)	22 (44.0%)
Implant	5 (9.4%)	5 (10.0%)
IUD	0	1 (2.0%)
Condoms only	15 (28.3%)	16 (32.00%)
None	9 (17.0%)	4 (8.0%)
Pregnant at time of enrolment	1 (1.9%)	0
Any curable STI††	12 (22.6%)	17 (34.0%)
Chlamydia trachomatis	3 (5.9%)	13 (26.5%)
Neisseria gonorrhoea	4 (7.8%)	6 (12.2%)
Trichomonas vaginalis	6 (11.8%)	1 (2.0%)
Positive syphilis serology§§	1 (1.9%)	0
VOICE risk score¶¶ median (IQR)	7 (5-7)	6 (5-8)

CES-D-10: Centre for Epidemiological Studies Depression Scale-10; IQR: interquartile range; PEP: post-exposure prophylaxis; POCT: point-of-care urine tenofovir; PrEP: pre-exposure prophylaxis; SOC: standard-of-care; STI: sexually transmitted infection.

† 4 missing as 3 participants report does not have a primary partner and 1 participant did not report partner age.
‡ 3 missing as 3 participants report does not have a primary partner.
§ Transactional sex is defined as having sex with a man because he provided her with or she expected he would provide her with food, clothes, accessories, cell phone, items or children or family, transport, school or residence fees, somewhere to stay, cash, airtime, and/or other items.
¶ Any IPV includes physical IPV, emotional IPV, forced sexual contact, and or felt unsafe or in danger.
# CES-D-10 scale, maximum score of 30; CES-D ≥10 associated with high risk of depression.
†† Nucleic acid amplification testing for *C. trachomatis* and *N. gonorrhoea* and OSOM testing for *T. vaginalis*. 3 missing as 3 participants did not do STI swab testing at enrolment due to menstruation and STI swab testing was subsequently completed at month 1.
§§ Positive syphilis serology defined as positive if both non-treponemal and treponemal test were reactive.

¶¶ VOICE risk score includes age ≤25, married or living with partner, partner provides financial and/or material support, primary partner has other partners, and alcohol use in the last 3 months. Excludes HSV-2 serostatus. Maximum score of 9; score of ≥5 associated with high risk of acquiring HIV.

Table 2.2. PrEP adherence based on TFV-DP concentrations in DBS at the outcome visit, by intervention group.

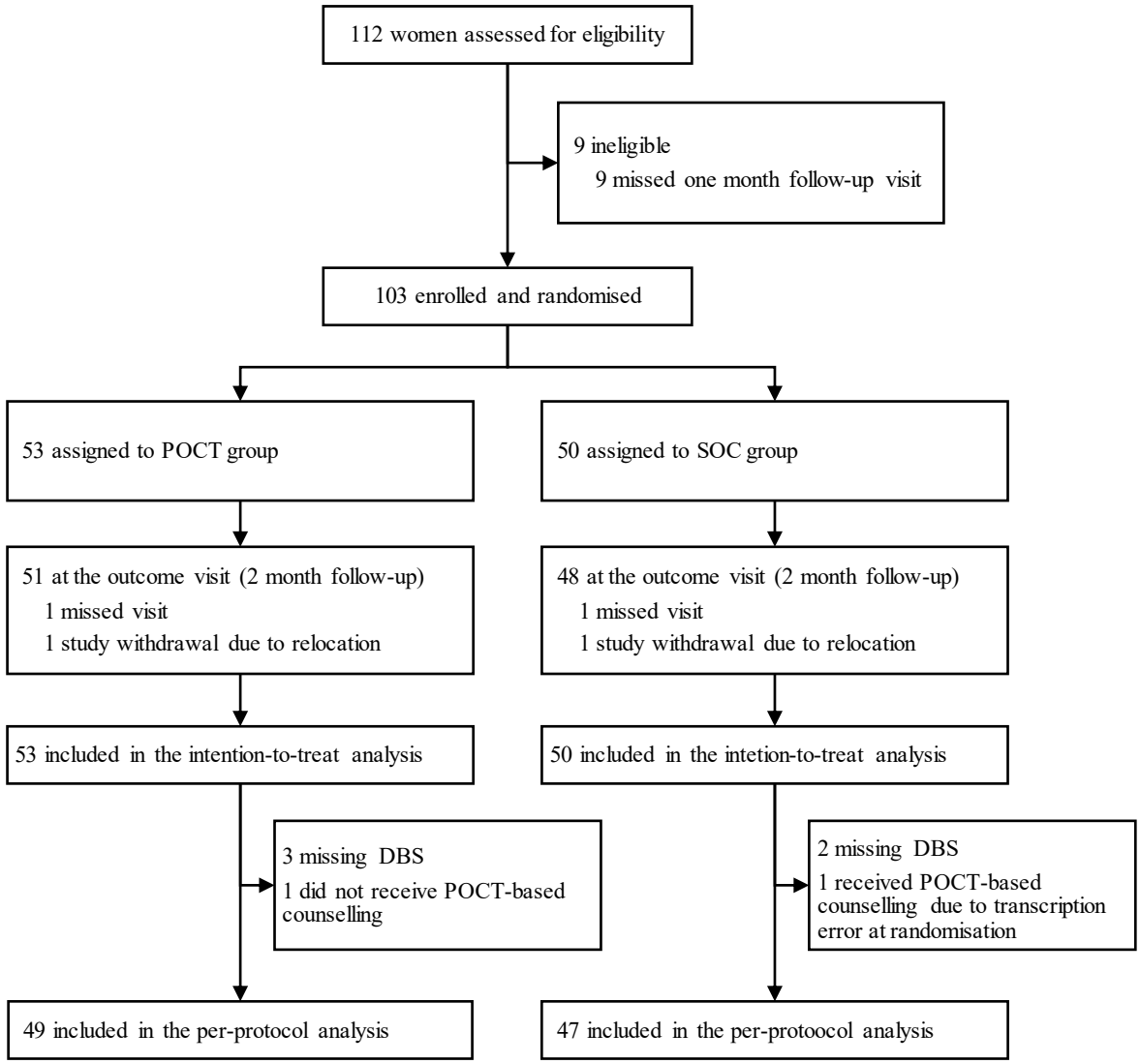
TFV-DP in DBS	POCT group N (%)	SOC group N (%)	RR (95% CI)	P-value
Intention-to-treat analysis N=103				
TFV-DP ≥ 700 fmol/punch	10/53 (18.9%)	7/50 (14.0%)	1.35 (0.56-3.27)	0.506
TFV-DP Detectable†	48/53 (90.6%)	42/50 (84%)	1.08 (0.93-1.25)	0.316
Per protocol analysis‡ N=96				
TFV-DP < 700 fmol/punch	9/49 (18.4%)	7/47 (14.9%)	1.23 (0.50-3.04)	0.648
TFV-DP Detectable	47/49 (95.9%)	41/47 (87.2%)	1.10 (0.97-1.24)	0.155

CI: Confidence Interval; TFV-DP: tenofovir diphosphate; POCT: point-of-care urine tenofovir; RR: risk ratio; SOC: standard-of-care.

† Detectable TFV-DP levels: TFV-DP ≥16.6 fmol/punch.

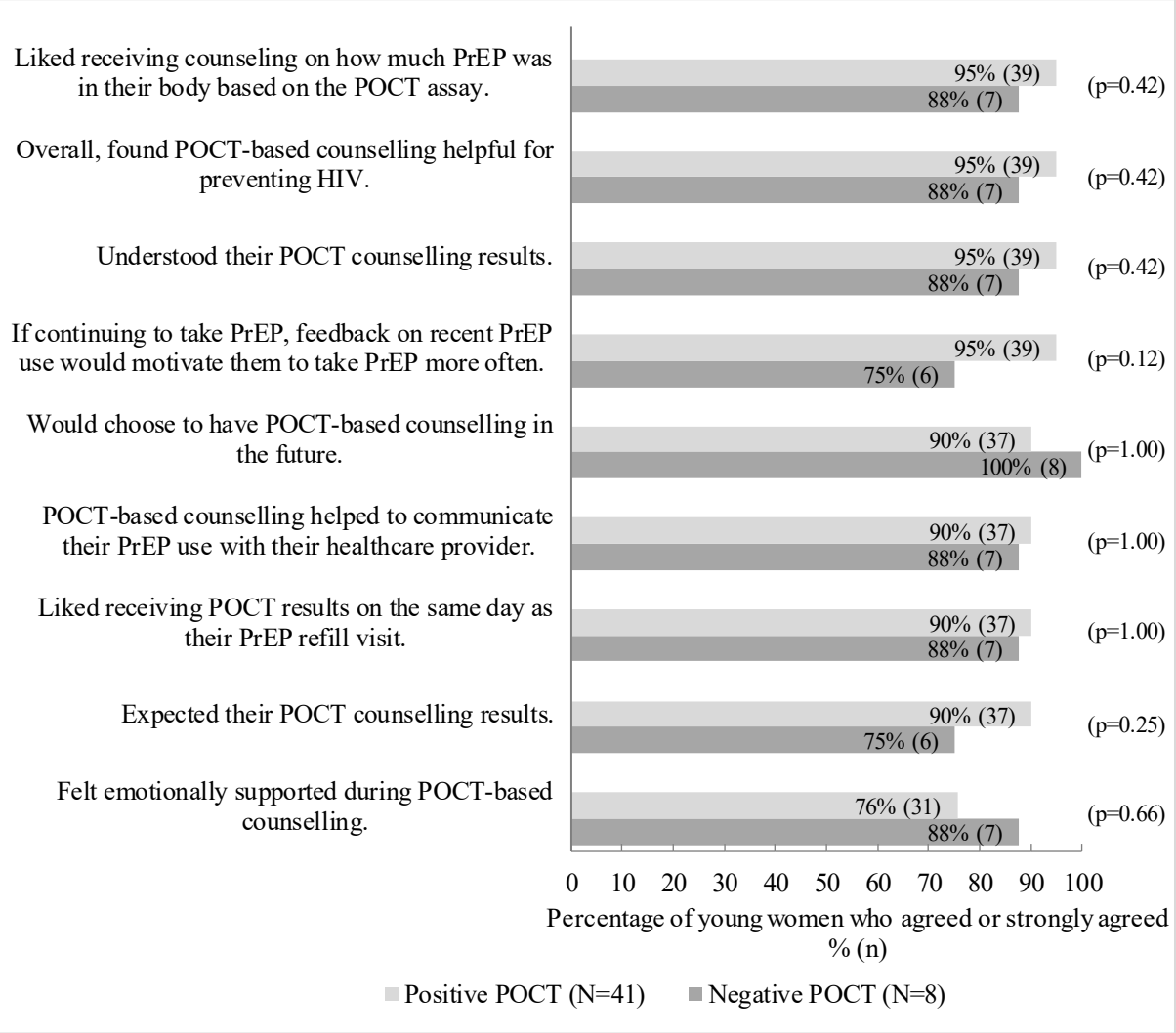
‡ Per protocol analysis excluded women who did not receive their assigned counselling intervention and those with missing outcome due to missed outcome visit of study withdrawal.

Figure 2.1. Participant flow chart for pilot randomised trial.



DBS: dried blood spots; PrEP: pre-exposure prophylaxis; POCT: point-of-care urine tenofovir; SOC: standard-of-care.
Missing DBS due to missed outcome visit, study withdrawal and 1 participant in POCT group declining PrEP after receiving POCT-based counselling at randomisation visit.

Figure 2.2. Acceptability of POCT-based counselling in the POCT group at the randomisation visit, by POCT result (N=49).



p: p-value; POCT: point-of-care urine tenofovir; PrEP: pre-exposure prophylaxis.

Supplementary Material:

Table 2.S1. Baseline predictors of oral PrEP adherence at the outcome visit among young women.

	TFV-DP in DBS		Unadjusted		Adjusted†	
	TFV-DP < 700 fmol/punch n=86 n (%) or median (IQR)	**TFV-DP ≥ 700 fmol/punch n=17 n (%) or median (IQR)**	**Relative Risk (95% CI)**	**p-value**	**Relative Risk (95% CI)**	**p-value**
Intervention arm						
SOC arm	43 (50.0%)	7 (41.2%)	ref	-	ref	-
POCT arm	43 (50.0%)	10 (58.8%)	1.35 (0.56-3.27)	0.509	1.37 (0.57-3.26)	0.479
Highest level of education						
Secondary school or below	14 (16.3%)	1 (5.9%)	ref	-	ref	-
Tertiary school or higher	54 (62.8%)	10 (58.8%)	1.80 (0.74-4.34)	0.194	1.78 (0.75-4.22)	0.191
CES-D-10 score ≥10‡	26 (30.2%)	8 (47.1%)	1.80 (0.76-4.26)	0.178	2.17 (0.90-5.22)	0.085
VOICE risk score§	7 (5-7)	5 (4-7)	0.90 (0.74-1.10)	0.308	0.88 (0.72-1.07)	0.194

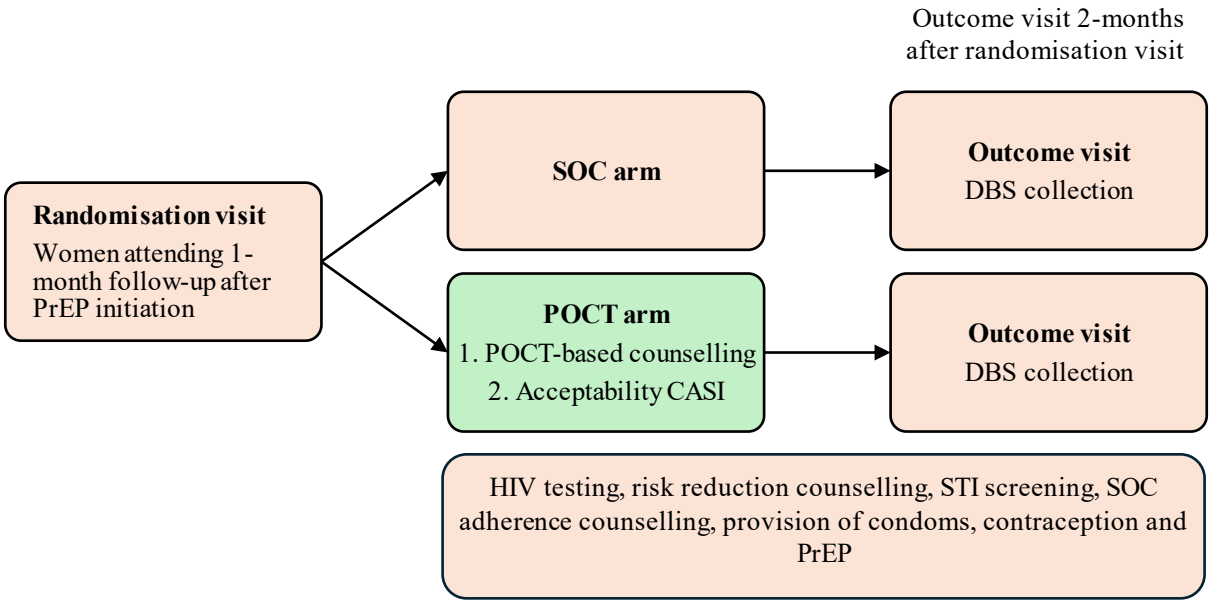
CES-D-10: Centre for Epidemiological Studies Depression Scale-10; CI: confidence interval; IQR: interquartile range; POCT: point-of-care urine tenofovir; SOC: standard of care; TFV-DP: tenofovir diphosphate.

† The VOICE risk score as a continuous variable, highest level of education, Centre for Epidemiological Studies Depression Scale-10 (CES-D-10) with a score ≥10 indicating high risk of depression and study arm were adjusted for in multivariate analysis.

‡ CES-D-10 scale, maximum score of 30; CES-D-10 ≥10 associated with high risk of depression.

§ VOICE risk score includes age ≤25, married or living with partner, partner provides financial and/or material support, primary partner has other partners, and alcohol use in the last 3 months. Excludes HSV-2 serostatus. Maximum score of 9; score of ≥5 associated with high risk of acquiring HIV.

Figure 2.S1. Study design



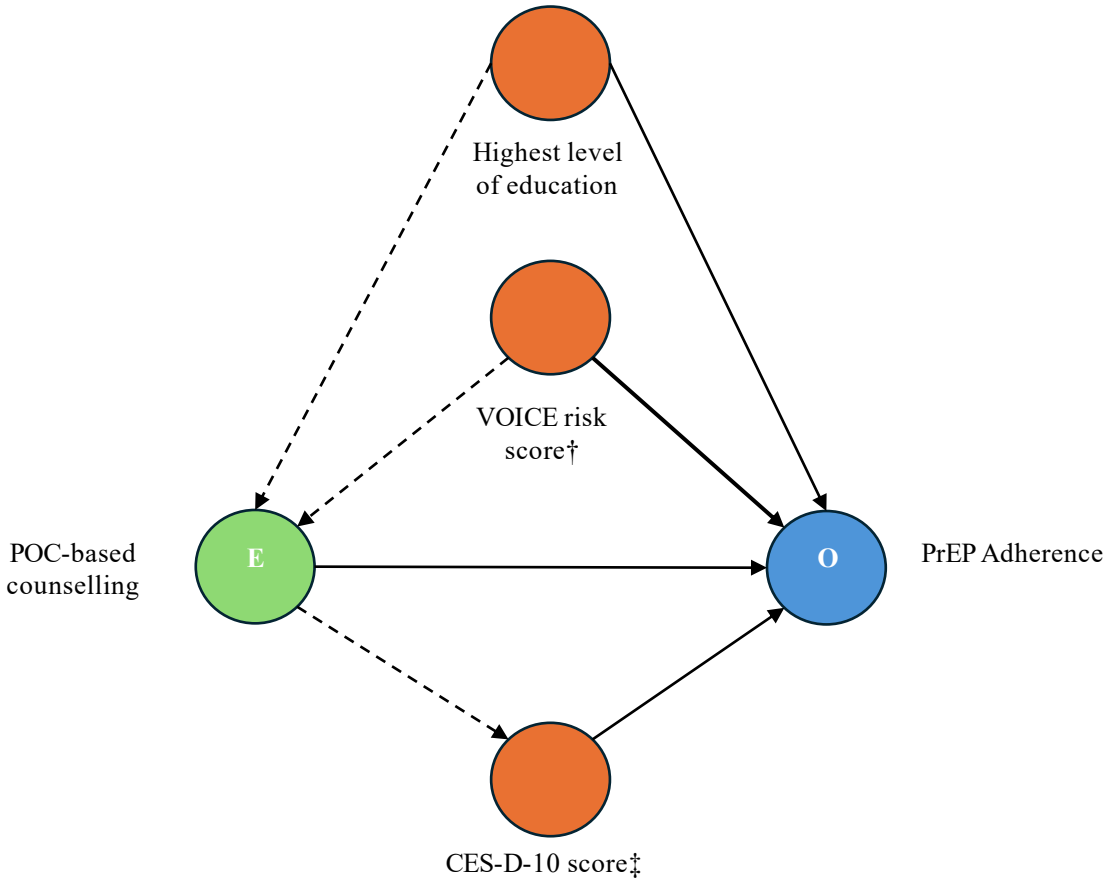
DBS: dried blood spots; CASI: computer-assisted self-interview; POCT: point-of-care urine tenofovir; PrEP: pre-exposure prophylaxis; SOC: standard of Care.

Figure 2.S2. Real-time adherence counselling messages.

Control line only (one line appears on test)
Key message: It looks like you took a PrEP pill recently, you are doing great! Remember that taking one PrEP pill every day is needed for strong protection against HIV. Are you still interested in taking PrEP today?

Control and tenofovir test line (two lines appear on test)
Key message: It looks like you haven't been able to take the PrEP medication in the past few days. Is PrEP something that you are still interested in? If yes, how can we help you?

Figure 2.S3. DAG of factors associated with high PrEP adherence, including POC-based counselling.



POC: point-of-care.
† VOICE risk score includes age ≤25, married or living with partner, partner provides financial and/or material support, primary partner has other partners, and alcohol use in the last 3 months. Excludes HSV-2 serostatus. Maximum score of 9; score of ≥5 associated with high risk of acquiring HIV.
‡ CES-D-10 scale, maximum score of 30; CES-D-10 ≥10 associated with high risk of depression.

CHAPTER 3 - DISCUSSION, CONCLUSION AND RECOMMENDATIONS

3.1. Introduction

The aim of this research report was to evaluate the effectiveness and acceptability of Drug-level feedback (DLFB) based on a POC urine TFV test on oral PrEP adherence. Additionally this report also evaluated the baseline characteristics associated with high adherence in a group of young women using oral PrEP in Johannesburg. DLFB has been used to describe an approach where oral PrEP users are provided with feedback on quantitative drug-level results from samples [17,38]. In contrast, the current study focuses on an adherence counselling intervention that utilises a qualitative POC urine TFV test to deliver rapid results. With emphasis on the counselling aspect of this tool, the above manuscript has termed this intervention "POC urine TFV test-based counselling", which aligns with recent publications on the urine test [41,44]. This chapter will provide additional discussion points and recommendations for each of the objectives of this research report to expand on the discussion and recommendations provided in the manuscript in Chapter 2.

3.2. Discussion

3.2.1. Effectiveness of counselling based on a POC urine TFV test on oral PrEP adherence

This pilot trial enrolled young women at risk of HIV, as demonstrated by the median VOICE risk score exceeding 5 and similar high STI prevalence to previous PrEP trials [17,38], who could benefit from HIV prevention interventions. Counselling based on a POC urine TFV test is a novel intervention that has the potential to improve oral PrEP adherence in AGYW, who have multiple challenges taking daily oral PrEP. In the setting of HIV treatment, counselling based on the urine test demonstrated improved adherence to ART, with suppressed viral loads at 3 months (87%, $p<0.001$) and 9 months (97%, $p<0.001$) in clients who initially had unsuppressed viral loads in a pre-post intervention study conducted in Namibia [42]. These findings encourage evaluation of counselling based on a POC urine TFV test on adherence for TFV based regimens used for HIV prevention. Although the pilot randomised trial presented in this research report observed a non-significant positive trend towards high PrEP adherence (TFV-DP ≥700 fmol/punch), a study in Kenya observed that the odds of detectable TFV in hair in the POC arm was 3.53 (p-value=0.04) compared to the SOC arm [41]. The Kenyan study also measured adherence by POC urine test, finding no significant difference at 3 months, similar to our trial at this time point, but found a significant difference at 12 months, suggesting the POC test may have a greater impact long-term [41]. While these result are

encouraging, they do not include an assessment of the impact of POC-based counselling on high adherence, corresponding to 4 or more doses taken per week, that is needed for HIV protection in cisgender women [7,20]. A larger randomized trial, with high adherence as the outcome, would definitively demonstrate the potential benefits of this intervention in AGYW.

Prioritisation of support for young women interested in oral PrEP is critical, as HIV prevention programmes are essential towards attainment of the 95-95-95 UNAIDS targets for ending AIDS in 2030 [45]. SMS reminders, including those triggered by missed doses using a Wisepill device, can improve adherence for HIV treatment [57] but did not improve adherence for oral PrEP [58]. The POWER study demonstrated that an electronic decision support tool, improved PrEP persistence at 1 month (odds ratio [OR] 1.97; 95% CI 1.08-3.69) [15] and encourages evaluation of strategies that can empower HIV risk awareness and decision making around choice of HIV prevention methods including PrEP [15]. The 3Ps for prevention study identified a positive effect on oral PrEP adherence using a shopping voucher, although not statistically significant [14]. This demonstrates that incentives would need to have a greater and longer lasting effect to impact PrEP adherence [14]. [14]

It has been noted that trials that have included multiple adherence support strategies have seen higher oral PrEP adherence. [14]In the PrEP SMART trial, AGYW received either two-way SMS communication or WhatsApp peer support [17]. Those with suboptimal adherence received additional support through quarterly DFLB based on DBS or monthly problem solving counselling [17]. Although no significant differences were found between the interventions, overall adherence to oral PrEP was higher compared to previous open-label PrEP trials [17]. The REACH cross-over study that provided oral PrEP and the monthly vaginal dapivirine ring for HIV prevention, observed high adherence to both oral PrEP and vaginal ring [46]. Participants attended monthly visits with counselling provided by trained counsellors who guided choice on PrEP use, provided DLFB based on DBS and residual TFV levels in the ring and addressed adherence barriers [47]. Qualitative interviews identified that competition amongst peers and accountability with the counsellor may have motivated adherence using this method [47], demonstrating the value of an objective measure to motivate PrEP adherence. In addition, participants were offered a choice of support in the form of weekly two-way SMS communication or phone calls, and peer support groups with in-person or virtual options [47]. This trial demonstrated that by building rapport through frequent contact with clinic staff and providing guidance on choice regarding product and adherence support strategies, participants were motivated to adhere to their choice of PrEP.

PrEP providers should consider providing a menu of supportive PrEP adherence strategies as AGYW face multiple challenges at different individual, interpersonal and structural levels,. The POC urine test is a simple-to-use tool that could be combined with other strategies to support oral PrEP adherence.

The continued challenges with oral PrEP among AGYW, despite numerous trials evaluating strategies for PrEP adherence, highlight the urgent need for access to long-acting HIV prevention products that offer fewer side effects and overcome the challenges of daily pill burden and related social challenges. Products such as Cabotegravir eight-weekly injection [48] and Lenacapavir two-yearly injection [49] have shown superior efficacy for HIV prevention compared to oral PrEP in clinical trials. While discrete choice experiments show that AGYW prefer longer-acting PrEP agents [50,51], the HPTN 084 open-label extension found that a third of participants chose oral PrEP [52]. Similarly, in the REACH study nearly a third of participants chose oral PrEP over the dapivirine ring during the choice period [46]. These trials show that there is still a group of AGYW that would prefer a pill to injections or rings, highlighting the continued need for feasible and effective interventions to support oral PrEP use in HIV prevention.

Currently, long-acting products are not accessible to most AGYW living in South Africa with cost being a major barrier, limiting choice in the tool-kit for HIV prevention. Likewise, effective adherence support strategies need to be cost-effective, feasible and acceptable for optimal impact. Many of the adherence strategies mentioned above may present several disadvantages that may not all be suitable for implementation in resource-constrained settings. Mobile health strategies require access to a phone, stable network and electricity; providing services with frequent contact may require additional clinic human resources; and DLFB using laboratory-based methods is costly. In contrast, a POC urine test, costing less than forty rands per test, may be an easy-to-use and affordable alternative. Further studies to establish cost-effectiveness of these interventions, including the POC urine test, are needed to inform implementation as PrEP providers will need to consider adherence strategies that are feasible and acceptable for implementation in their setting.

3.2.2. **Acceptability of POC urine test for oral PrEP adherence among young women**

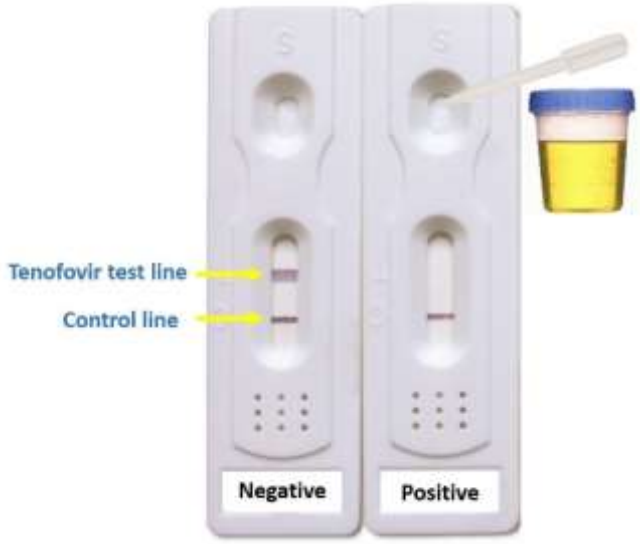
Counselling based on the urine test was acceptable among young women using PrEP and is consistent with results from the pilot trial conducted in Kenya [41]. In another qualitative

study conducted in Kenya, counselling based on the urine test was acceptable by both PrEP users and providers [39]. Women reported that the urine test would be preferred over a blood test and the test was believed to be easy to use [39]. However, PrEP providers and users expressed differing opinions regarding time spent at the clinic to do the test [39]. Women were concerned that some would not want to do the test as it would increase time at the clinic while providers felt that there would be sufficient time to do the test [39]. However, in our pilot trial majority of women reported that they liked receiving urine test results on the same day as PrEP refill. Strategic consideration of how to incorporate the urine test within PrEP follow-up visits is important to minimise additional clinic time. For example, urine may be collected while collection for additional testing such as pregnancy testing is occurring, or testing may occur simultaneously with HIV rapid testing, followed by comprehensive risk reduction and adherence counselling.

In this pilot trial, majority of women reported that they understood counselling based on the test result. The urine test requires careful attention in result interpretation because the number of lines on the rapid test does not follow the same logic as HIV or pregnancy rapid tests. The presence of two lines indicates a negative result (TFV not detected), while the presence of one line indicates a positive result (TFV detected) (

Figure 3.*1*) [35]. In our pilot trial, Counselling was provided by trained clinical research nurses using counselling messages adapted from HPTN 082 with a Wi-Fi signal visual (**Error! Reference source not found.**) to provide supportive counselling, irrespective of the t est result. Visual aids such as these counselling messages should be considered to guide supportive adherence counselling that is understandable to the PrEP client. In addition, implementation will require training of those providing POC-based counselling to have a non-judgemental and supportive approach to counsel on results that were not expected and explore barriers to recent PrEP dosing.

Figure 3.1. Urine TFV test results interpretation.



While most items on acceptability scored high among AGYW in this trial, a smaller proportion indicated that they got the results they expected, with only 75% of those with a negative test who expected the result received. The performance of the POC urine test has been compared to TFV-DP levels in DBS in the PrEP SMART trial, where there was 100% concordance between a negative POC urine test and TFV-DP levels <700 fmol/punch, however only approximately 50% of those with a positive POC urine test had TFV-DP levels ≥700 fmol/punch (high adherence) [40]. The reason for the discordance may be due to the POC urine test measuring recent PrEP use in the last week compared to DBS which measures PrEP adherence in the last 4-8 weeks [29,30]. The POC urine test has limitations, making it important to explore PrEP use in prior weeks, regardless of the test result. This approach helps to identify barriers and develop strategies to address them, while offering supportive counseling messages that encourage consistent PrEP use rather than punitive messaging. Our study findings also showed that approximately 80% of AGYW felt emotionally supported during the counselling sessions. This finding could relate to the concerns expressed from qualitative interviews conducted in Kenya where women feared that the test may only be like by those with a positive test result and that those with a negative test may face negative interactions from PrEP providers and compromise their future access to PrEP. However, in our trial this acceptability score was lower in both those with positive and negative tests results, perhaps highlighting that AGYW require support for psychosocial challenges beyond the scope of counselling using the POC urine test. Qualitative research would be valuable to understand the experiences of those who received counselling with a positive versus a negative POC urine test, to further guide counselling messages and inform considerations for the implementation of POCT-based counselling.

3.2.3. **Baseline characteristics associated with high oral PrEP adherence**

This pilot trial observed a positive association between depressive symptoms at PrEP initiation and high oral PrEP adherence after 3 months. Although not statistically significant, this association strengthened in a multivariable analysis that includes study arm, education and the VOICE risk score. This finding is different to other open-label PrEP studies in African women where elevated depressive symptoms were negatively associated with PrEP adherence at follow-up visits [10,11]. Furthermore, depressive symptoms were identified to be associated with those who reported transactional sex, IPV, and symptoms of traumatic stress [10] as well as heavy alcohol use, and lower levels of social or partner support [11]. In our pilot trial about a third of participants had depressive symptoms and a quarter had experienced any IPV in the last year, highlighting the prevalence of both mental health and social challenges in young women using PrEP. While POC-based counselling may not be able to address symptoms of depression, screening for depression with appropriate referral for additional care is important to support PrEP adherence. In South Africa, mental health care services are mostly concentrated at hospital level with fewer services available at the primary health care level where majority of the population seek care [53]. Primary health care clinics mostly consist of nursing staff who are unable to prescribe medication for depression, or provide specialist care, further limiting access to care for those who may need additional support [53]. It is therefore critical to include screening for depression in PrEP services at both PrEP initiation and follow up, using tools that are simple to use and time-efficient, to detect and refer for appropriate management. Psychosocial services should also be made more accessible to the population at a primary health care and community level especially for women, who suffer with the complexity of depressive symptoms together with other challenges related to alcohol use, transactional relationships, lack of support and IPV.

3.3. **Conclusion**

In this pilot trial, real-time counselling based on a POC urine TFV test did not significantly increase the proportion of young women able to achieve protective levels of TFV at a subsequent visit two months after receiving the counselling intervention, however a positive trend towards high adherence was observed. Real-time counselling based on a POC urine test was acceptable to young women using oral PrEP and could support adherence while access to long-acting products is limited.

3.4. **Recommendations**

The findings from this pilot trial together with previous studies on POC-based counselling substantiate the need for larger randomised trials on oral PrEP adherence. These trials should provide a robust estimate of the effectiveness and cost of this counselling tool, to inform its implementation in programmes providing oral PrEP to young women for HIV prevention. Future studies should evaluate the impact of this tool on high adherence, to achieve protective levels ultimately needed for HIV prevention. In addition these studies should evaluate the impact over extended follow-up periods beyond two months and assess the impact based on frequency of POC-based counselling delivery, either monthly or quarterly.

Future research evaluating real-time counselling based on the POC urine test should consider a hybrid randomised implementation-effectiveness approach to assess its impact and delivery in the real-world. The WHO has provided guidance on differentiated PrEP services that are client- and community-centred to enhance access to those who could most benefit [54]. For POC-based counselling to be effectively implemented within differentiated services, consideration is needed in the setting in which it is delivered, the personnel needed to perform the test and provide counselling, the frequency of testing, and the broader package of services it is integrated with [54]. The POC urine test kit could be delivered at a primary health care clinic, pharmacy or mobile clinic and delivered by a trained nurse or counsellor. Implementing POC-based counselling will require training of PrEP providers to delivery non-judgemental, supportive counselling and development of visual tools to guide the counselling process. POC urine testing and counselling alone may not be able to overcome the challenges of oral PrEP adherence. Therefore, a combination of supportive strategies may need to be offered within comprehensive services, that include psychosocial support, for young women using PrEP. Despite potential delays in expanding PrEP options for women, researchers and healthcare providers should be encouraged to optimise currently available interventions, such as oral PrEP, through the evaluation of supportive tools like POC-based counselling.

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APPENDICES

Appendix 1: Plagiarism declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Nicole Poovan (Student number: 2606475) am a student registered for the degree of MSc in Epidemiology, field of Infectious Disease Epidemiolgy in the academic year 2025.

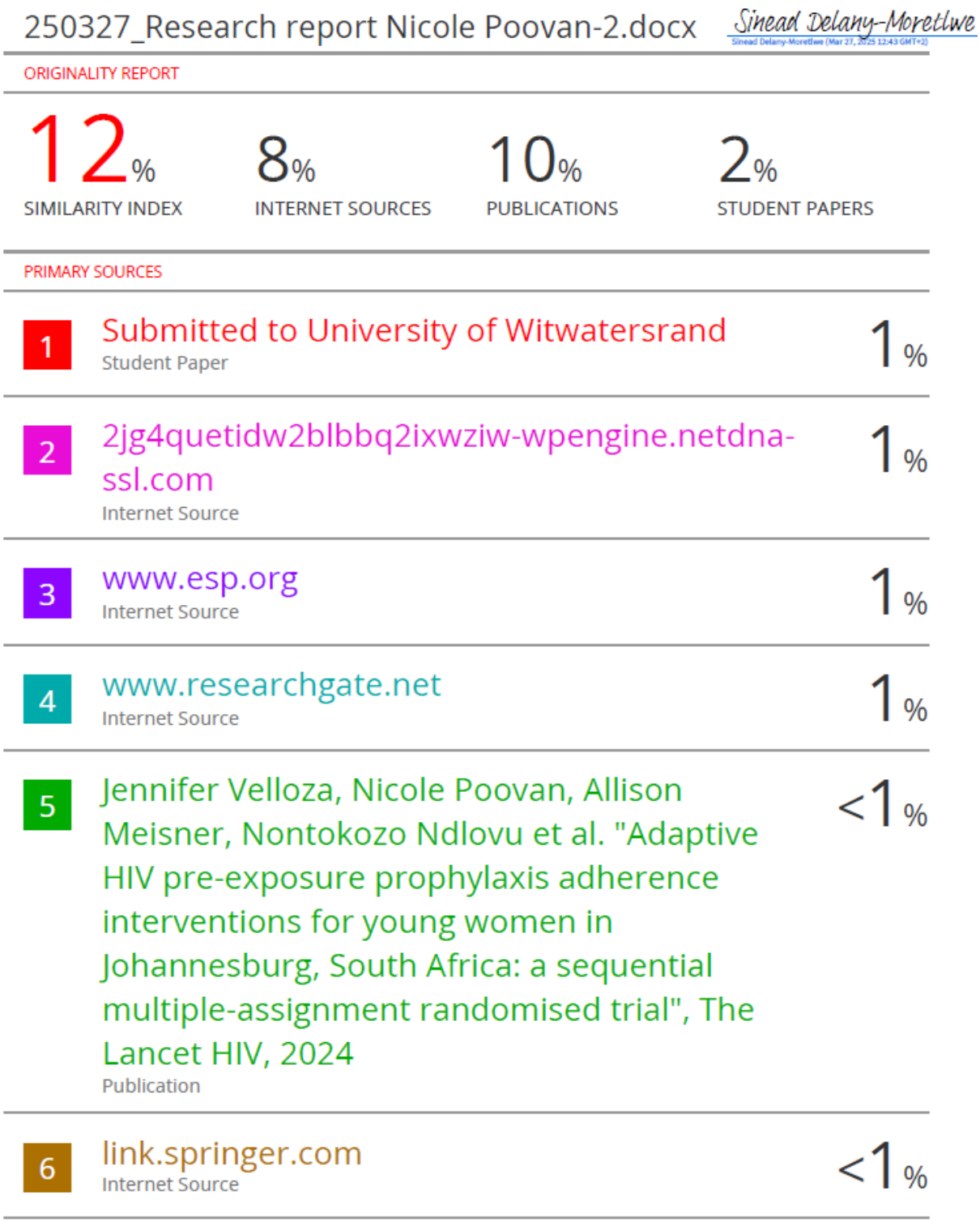
I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 27 Mar 2025

1

Appendix 2: Turnitin cover page



250327_Research report Nicole Poovan-2.docx

Sinead Delany-Moretlwe

Sinead Delany-Moretlwe (Mar 27, 2025 12:43 GMT+2)

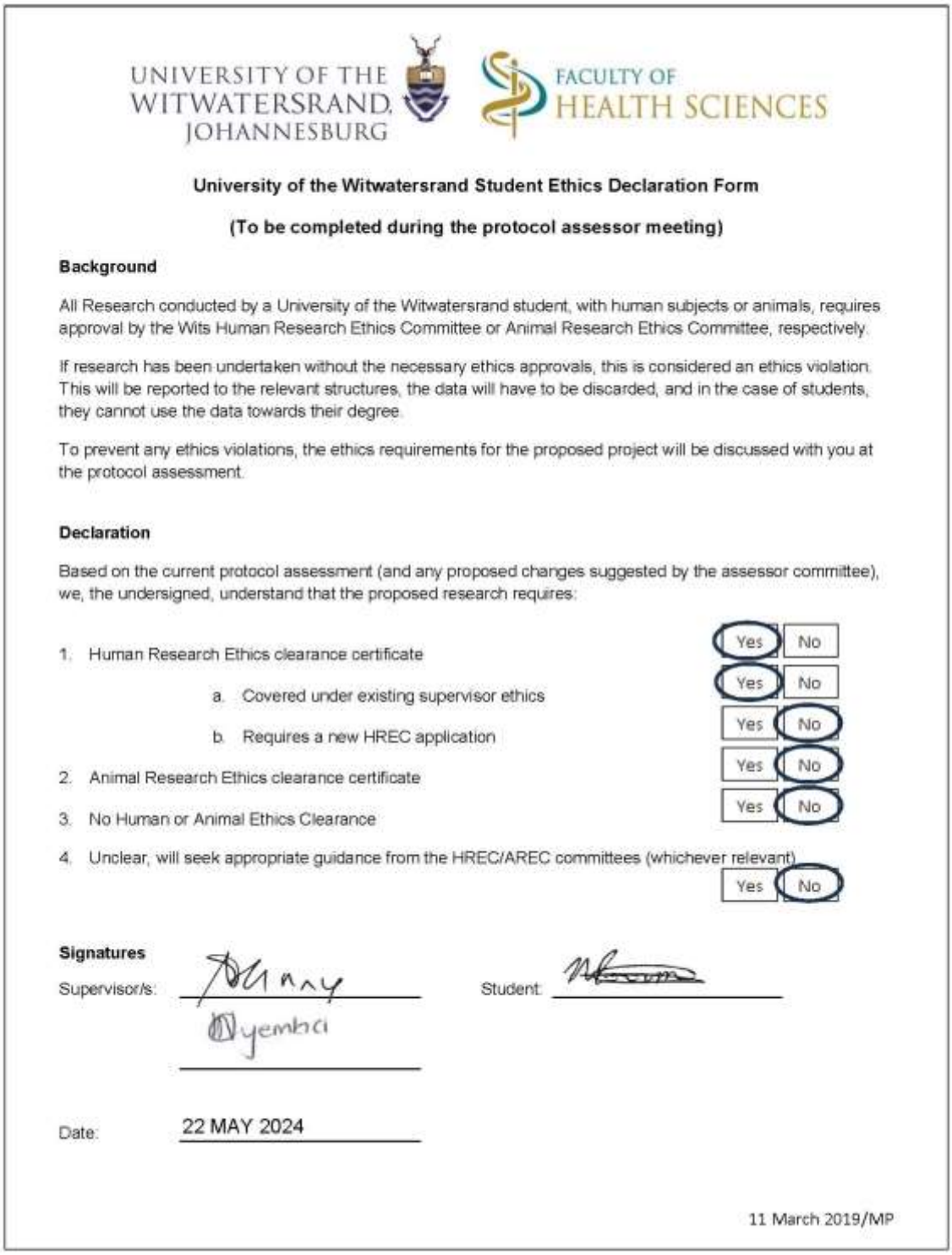
ORIGINALITY REPORT

12%	8%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to University of Witwatersrand Student Paper	1%
2	2jg4quetidw2blbbq2ixwziw-wpengine.netdna-ssl.com Internet Source	1%
3	www.esp.org Internet Source	1%
4	www.researchgate.net Internet Source	1%
5	Jennifer Velloza, Nicole Poovan, Allison Meisner, Nontokozo Ndlovu et al. "Adaptive HIV pre-exposure prophylaxis adherence interventions for young women in Johannesburg, South Africa: a sequential multiple-assignment randomised trial", The Lancet HIV, 2024 Publication	<1%
6	link.springer.com Internet Source	<1%

Appendix 3: Ethics clearance certificate



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

University of the Witwatersrand Student Ethics Declaration Form

(To be completed during the protocol assessor meeting)

Background

All Research conducted by a University of the Witwatersrand student, with human subjects or animals, requires approval by the Wits Human Research Ethics Committee or Animal Research Ethics Committee, respectively.

If research has been undertaken without the necessary ethics approvals, this is considered an ethics violation. This will be reported to the relevant structures, the data will have to be discarded, and in the case of students, they cannot use the data towards their degree.

To prevent any ethics violations, the ethics requirements for the proposed project will be discussed with you at the protocol assessment.

Declaration

Based on the current protocol assessment (and any proposed changes suggested by the assessor committee), we, the undersigned, understand that the proposed research requires:

1. Human Research Ethics clearance certificate — Yes / No
   a. Covered under existing supervisor ethics — Yes / No
   b. Requires a new HREC application — Yes / No
2. Animal Research Ethics clearance certificate — Yes / No
3. No Human or Animal Ethics Clearance — Yes / No
4. Unclear, will seek appropriate guidance from the HREC/AREC committees (whichever relevant) — Yes / No

Signatures

Supervisor/s: _____ Student: _____

Date: 22 MAY 2024

11 March 2019/MP

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

11 May 2022

EMAILED & COURIERED

Prof AS Delany-Moretlwe,
Ward 21 Clinical Research Site (CRS)
Wits RHI
22 Esselen Street
Hillbrow, Johannesburg
2001

Email: sdelany@wrhi.ac.za

Dear Prof Delany-Moretlwe,

PROTOCOL: INSIGHT - A COHORT FOR EVALUATION OF OPEN-LABEL PREP DELIVERY AND PREP PREFERENCES AMONG AFRICAN WOMEN

ETHICS REFERENCE NO: 220208

RE : FINAL ETHICS APPROVAL

This is to certify that the above-mentioned trial has been approved by the University of the Witwatersrand, Human Research Ethics Committee (HREC), and the Protocol/Expert Reviewer. Date of Meeting where trial was reviewed: 25 February 2022.

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. It is the responsibility of the Sponsor and Principal Investigator to ensure, where required, that relevant approvals are in place and compliance with the following is adhered to before a trial may begin:

- If trial is being conducted in Provincial Health facilities: Approval from the Hospital CEO / Clinic Manager / District Research Committee (whichever is applicable) be obtained.
- The study is submitted onto The National Health Research Database (NHRD).
- The relevant approvals are uploaded onto the NHRD system: Ethics Approval, SAHPRA Approval, Hospital CEO / Clinic Manager / District Research Committee Approval.

* A copy of the SAHPRA Approval and/or SAHPRA Notification letter must be submitted to the Ethics Secretariat Office for record purposes (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE).

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study.

1

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:
* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:
* The University of the Witwatersrand, Human Research Ethics Committee requests that the SAHPRA Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - email: EthicsRegulatory@witshealth.co.za and a report of the final results: at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:
* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the South African Health Products Regulatory Authority and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:
* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING:
* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE:
* The South African Department of Health, South African Health Products Regulatory Authority requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

8. THE SUPPORTING APPROVAL DOCUMENTS ARE ATTACHED:

8.1 Ethics Approval Form signed by the Chairperson of the HREC - Kindly return the copy of the Approval Form signed by the Principal Investigator(s) per email: EthicsRegulatory@witshealth.co.za for our records (this is applicable with the initial Approval).

8.2 List of members present at the HREC meeting held as per INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

1

9. WE AWAIT YOUR RESPONSES AS REQUESTED: Ensure to have these documents forwarded at the earliest for the HREC records.

* SAHPRA Approval letter and/or letter of Notification before the above study may commence / or where an Amendment may be implemented (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* Copy of independent Ethics Declaration Approval Form signed by the Principal Investigator. (this is applicable with the initial Approval).

* Kindly forward the above to the undersigned to email: EthicsRegulatory@witshealth.co.za at your earliest convenience.

Dr S Badal-Faesen declared a conflict of interest.

The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / SPONSOR / STUDY CO-ORDINATORS - WHERE APPLICABLE

Regards,

PROF CLEMENT PENNY

For and on behalf of the Human Research Ethics Committee: (Medical)

1

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

Ethics Reference No.	220208	Date of Meeting	25-Feb-2022
		Recertification Due	24 February 2023 (if applicable)

Principal Investigators:	Prof AS Delany-Moretlwe	Investigators:	Dr K Ahmed
	Dr M Jaggernath		Dr MI Ajayi
	Dr PL Kotze		Dr JJ Allegeppen
	Dr M Maseko		Dr S Badal-Faesen
	Dr NH Mwelase		Dr S Behariram
	Dr R Panchia		Dr JA Bennet
	Dr RAP Selepe		Dr C Innes
			Dr C Kritzinger
			Dr OS Letlape
			Dr CE Louw
			Dr MAC Makwela
			Dr M Malefu
			Dr NI Masingi
			Dr C Mathew
			Dr M Moyo
			Dr NM Mshele (Mvuma)
			Mrs T Nielson
			Dr PTD Nkosi
			Dr F Noor Mahomed
			Dr ZZ Ntseke
			Dr SA Pitsi
			Dr N Poowan
			Dr MS Rasool
			Dr EH Roos
			Dr N Zuma-Gwala
			Dr ZA Zwane

Co-Principal Investigator	Prof JA Smit

Protocol Title:	A cohort for evaluation of open-label PrEP delivery and PrEP preferences among African women

DOCUMENTS REVIEWED				Tick As Appropriate	Yes	No
Protocol Number	INSIGHT	Date:	02-Feb-2022			
Protocol	INSIGHT Protocol, Version 1.0	Date:	02-Feb-2022		☑	☐
Investigator's Brochure	Package Insert - Tenemine - Version: - - Dated: 15 Jun 2019				☑	☐
Subject Information/Consent Form	Participant Information Leaflet and Informed Consent Form - Version: 1.0 - Dated: 05 May 2022				☑	☐
	Participant Information Leaflet and Consent Form for Parents/Guardians - Version: 1.0 - Dated: 05 May 2022				☑	☐
	Participant Information Leaflet and Assent Form for Minors - Version: 1.0 - Dated: 05 May 2022				☑	☐
Advertisements						
Questionnaires						
Insurance/Compensation	N/A	Valid From:		To:	☐	☑
Synopsis of Study/Trial Summary	PrEP preferences among African women				☑	☐
Other Documentation	Protocol Synopsis - Dated: 04 Feb 2021				☑	☐
	HREC Application Form - Dated: 07 Feb 2022				☑	☐
	SANCTR Application Trial ID#6827 - Dated: 07 Feb 2022				☑	☐
Relevant Trial Hospital/(s)	Wits RHI - Esselen Street				☑	☐
	Setshaba Research Centre				☑	☐
	Mikhamba Gardens-The Qhakaza Mbokodo Research Clinic				☑	☐
	MatCH Commercial City Clinic				☑	☐
	Madibeng Centre for Research				☑	☐
	Helen Joseph Hospital				☑	☐
	Chris Hani Baragwanath Hospital				☑	☐
	Aurum Institute: Gavin J Churchyard Legacy Centre				☑	☐
Syndicate and/or Research Unit	Wits RHI - Ward 21 Clinical Research Site				☑	☐
	Setshaba Research Centre				☑	☐
	Qhakaza Mbokodo Research Clinic				☑	☐

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INDEPENDENT ETHICS COMMITTEE APPROVAL FORM

Perinatal HIV Research Unit - PHRU	☑	☐
MatCH Commercial City Clinic	☑	☐
Madibeng Centre for Research	☑	☐
Clinical HIV Research Unit, Wits - W CHRU	☑	☐
Aurum Institute: Gavin J Churchyard Legacy Centre	☑	☐

DETAILS OF COMMITTEE

Name	University of the Witwatersrand Human Research Ethics Committee: (Medical)
Address	Research Office, Senate House University of the Witwatersrand, 1 Jan Smuts Avenue, BRAAMFONTEIN, Johannesburg, 2000

DETAILS OF MEETING

	Yes	No
Is the Investigator a member of the committee ?	☑	☐
If "Yes" did he/she vote ?	☐	☑
Is the Committee organised and operated according to applicable laws and regulations together with ?	☑	☐
Local GCP requirements ?	☑	☐
ICH GCP requirements ?	☑	☐
FDA GCP requirements ? - FWA Registered No. IRB00001223	☑	☐
Progress reports required either in March and September or six monthly from start of study ?	☑	☐

DECISION ON APPROVAL : is approval given to conduct the trial ?	Tick As Appropriate
Yes - with no conditions	☑
Remarks : Our expectation is that our requirements are fulfulled once a company has submitted and uploaded relevant approvals onto NRRD. Dr S Badal-Faesen declared a conflict of interest.	
Yes - with conditions	☐
Specify conditions :	
No	☐
Specify reasons	

SIGNATURES

I confirm that the details on this form are correct.		Date
Name: Prof C Penny Chair / Deputy Chair of Committee	Signature: C B Penny	11 May 2022

DECLARATION OF INVESTIGATOR/(S)

To be completed and ONE COPY returned to the Secretariat for the HREC at Wits Health Consortium, 31 Princess of Wales Terrace, Parktown, 2193 or Email: EthicsRegulatory@witshealth.co.za

I/We fully understand the conditions under which I am/we are authorised to carry out and complete the above-mentioned research and I/we agree to ensure full compliance with those conditions. Should any amendment, alteration or departure be contemplated from the research procedure methodology or manner of execution, I/we will communicate with the Chairman of the Human Research Ethics Committee: (Medical) for approval prior to acting on any of the above mentioned proposed amendments, alterations or departures. I am/we are fully aware that any unauthorised amendment, alteration or departure as above will amount to misconduct and may lead to the institution of disciplinary procedures.

Any approval given by the HREC is conditional upon consent being obtained by the Investigators from the Superintendent (or equivalent official) of the Hospital, Clinic or Institution in which the research is, in part or all, to take place.

The Chairman may of course at his discretion place the matter before the full Committee.

DATE: 13 MAY 2022 SIGNATURE: NAME: Sinead Delany-Moretlwe

PROTOCOL NUMBER INSIGHT 5023MAY22 ETHICS REF.: 220208

Date Printed 11 May 2022

1

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Human Research Ethics Committee: (Medical)
FWA Registered No IRB 00001223

SECRETARIAT: Suite 189, Private Bag x2600, Houghton 2041, South Africa Tel: +27-11-274 9200 Fax: +27-11-274 9281

Ms D Ramjit

EMAILED

28 October 2022

Regulatory Manager
Wits Reproductive Health & HIV Institute
Hillbrow Health Precinct, Hugh Solomon Buil
Hillbrow Health Precinct, Hugh Solomon Buil
2001

Email: dramjit@wrhi.ac.za

Dear Ms Ramjit,

PROTOCOL: INSIGHT - A COHORT FOR EVALUATION OF OPEN-LABEL PREP DELIVERY AND PREP PREFERENCES AMONG AFRICAN WOMEN

ETHICS REFERENCE NO: 220208

RE : APPROVAL FOR LETTER OF AMENDMENT #1, VERSION 1.0 DATED 14 SEPTEMBER 2022

We acknowledge receipt of your letter dated 13 October 2022 with the following documentation pertaining to the above-captioned trial.

Amendment Date:	14-Sep-2022	Amendment Version:	1.0
Amendment Number:	#1	Received Date:	13-Oct-2022

The following has been approved by the Wits Human Research Ethics Committee: (Medical):

* Letter of Amendment #1, version 1.0 dated 14 September 2022
* INSIGHT CASI - Urine Drug-Level Feedback satisfaction, Version 1.0 dated 12 October 2022
* Participant Information Leaflet and Informed Consent Form, Version 2.0 dated 12 October 2022 (Tracked and Clean)
* Participant Information Leaflet and Consent Form for Parents/Guardians, Version 2.0 dated 12 October 2022 (Tracked and Clean)
* Participant Information Leaflet and Assent Form for Minors, Version 2.0 dated 12 October 2022 (Tracked and Clean)

Ethics Approval Date: Friday, 28 October 2022

The University of the Witwatersrand, Human Research Ethics Committee Approval Granted for the above mentioned study is valid for five years. Where required by Sponsor to have approval on a more frequent basis it remains the responsibility of the Sponsor and Investigator to apply for continuing review and approval, or for the duration of the Trial.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

1

* A copy of the SAHPRA Approval and/or SAHPRA Notification letter must be submitted to the Ethics Regulatory Office Secretariat before the study commences / or where an Amendment may be implemented (IF SAHPRA APPROVAL / NOTIFICATION IS APPLICABLE). It remains the responsibility of the Principal Investigator and/or Sponsor to ensure that the relevant approvals are in place.

* The study is conducted according to the protocol submitted to the University of the Witwatersrand, Human Research Ethics Committee. Any amendments to the protocol must first be submitted to the Human Research Ethics Committee for approval.

* During the study, the University of the Witwatersrand, Human Research Ethics Committee is informed immediately of :

- Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug. (Refer to POL-IEC–001 and SOP-IEC–005, Item 3.4).
- Any data received during the trial which, may cast doubt on the validity of the continuation of the study .

* The University of the Witwatersrand, Human Research Ethics Committee is notified of any decision to discontinue the study and the reason stated.

* The Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the University of the Witwatersrand, Human Research Ethics Committee for approval prior to their participation in the study.

* In the event of an authorised Investigator ceasing to participate in the study, the University of the Witwatersrand, Human Research Ethics Committee must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:

* The University of the Witwatersrand, Human Research Ethics Committee requires that in all studies, the Principles of Informed Consent are adhered to. This applies to volunteers as well as patients.

3. PROGRESS REPORTS:

* The University of the Witwatersrand, Human Research Ethics Committee requests that the MCC Progress Reports be submitted twice a year either in March and September or six monthly from start of study to the HREC Secretariat Office - email: EthicsRegulatory@witshealth.co.za and a report of the final results, at the conclusion of the study. (IF APPLICABLE)

4. REIMBURSEMENT TO PATIENTS FOR TRANSPORT:

* The Human Research Ethics Committee: (Medical) is in agreement that reimbursement per visit is according to the South African Health Products Regulatory Authority and that reimbursement should be appropriate according to the situation.

5. TRANSPORT AND STORAGE OF BLOOD AND TISSUE SAMPLES IN SOUTH AFRICA:

* If blood specimens are to be stored for future analysis and is planned that such analysis will be done outside Wits, then the blood must be stored at a facility in South Africa agreed with the relevant IRB, with release of sub-samples only once projects have been approved by the local Research Ethics Committee applicable to where the analysis will be done as well as by the Wits Human Research Ethics Committee: (Medical).

6. GENETIC TESTING

* The Human Research Ethics Committee: Medical; will not approve open-ended genetic testing as this does not fit the Human Research Ethics Committee criteria.

7. GOOD CLINICAL PRACTICE

1

The South African Department of Health, South African Health Products Regulatory Authority requires Good Clinical Practice (GCP) Training for all Investigators in Clinical Trials, and that GCP training be renewed every three (3) years.

As yet, there are no National Guidelines for the content of GCP courses. Until these are available the Wits Human Research Ethics Committee (Medical) will note courses completed by Investigators without approval of the content of the individual courses.

.

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The above has been noted for the Ethics Committee information and records.

KINDLY FORWARD TO THE RELEVANT INVESTIGATORS / CRA / STUDY CO-ORDINATORS

Regards,

PROF CLEMENT PENNY

For and on behalf of the Human Research Ethics Committee: (Medical)

Processed by: Kim Zara Mothiba - Tel: 011 274 9255

1

Appendix 4: Master of Science in Epidemiology - Approval of Title

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

01 July 2024
Person No: 2606475
PAG

Dr N Poovan
19 Stanmore Road
Nahoon
5241
South Africa

Dear Dr Nicole Poovan

Master of Science in Epidemiology: Approval of Title

We have pleasure in advising that your proposal entitled *Effectiveness and Acceptability of urine tenofovir drug-level feedback on HIV pre-exposure prophylaxis adherence in young South African women* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 5: Journal guidelines for authors

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY Open Access

Author Guidelines

Statement of Editorial Independence

The views expressed here are solely those of IAS - the International AIDS Society, and do not necessarily represent those of the publisher.

Statement in response to recent US executive orders

Effective 14 February 2025

In February 2025, an executive order was issued by the U.S. administration concerning the use of language related to sex and gender in official documents and communications, including peer-reviewed publications. This directive also has imposed communications restrictions on federally funded employees, including researchers. The *Journal of the International AIDS Society* (JIAS) recognizes these developments, but reinforces its commitment to uphold academic freedom and scientific integrity, irrespective of external political or ideological influences.

JIAS is committed to maintaining the highest standards of integrity, transparency, and inclusivity in scientific publishing. We affirm our dedication to ethical principles and responsible authorship.

The section below reiterates our editorial policies concerning manuscript submission, authorship, language use, and post-publication corrections.

1. Authorship and contributor roles

JIAS adheres to clear and consistent criteria for determining authorship and recognizing contributors:

- **Authorship criteria:** All individuals designated as authors must meet the conditions as described in the Editorial Policies and Ethical Considerations.
- **Authorship changes:** Requests for adding or removing authors after submission must be accompanied by a written statement of agreement from all listed authors, including those seeking to be added or removed.

2. Manuscript withdrawal

- **Pre-publication withdrawal:** Manuscript withdrawal requests before publication will generally be considered only if the request is submitted by the corresponding author and if all the authors are informed of the decision to withdraw. This policy ensures transparency and mutual agreement among collaborators.

- **Post-publication corrections and retractions:** Corrections will be only issued for factual errors that affect the scientific accuracy of the published work. Retractions will be considered in cases of significant errors that invalidate the study's findings or when scientific misconduct is confirmed.

3. Inclusive and respectful language

JIAS champions diversity, equity, and inclusion in scientific discourse. We encourage authors to:

- Use inclusive, respectful, and scientifically accurate language, particularly concerning sex, gender, and other identity-related descriptors.
- Use a people's first language following best practices, such as the recommendations of the People First Charter and the UNAIDS guidelines on terminology.
- Follow the Sex and Gender Equity in Research (SAGER) guidelines to ensure comprehensive and equitable reporting of sex and gender dimensions in research.

While JIAS recommends best practices for inclusive language, the final choice of terminology remains with the authors, provided it upholds scientific rigor and respect.

4. Ethical Standards and Compliance

JIAS aligns its editorial policies with international best practices, including guidance from the **International Committee of Medical Journal Editors (ICMJE)** and ethical publishing standards. We uphold the principles of:

- Academic freedom and the integrity of scientific communication.
- Transparency in authorship, peer review, and editorial decisions.
- Commitment to correcting the scientific record when necessary.

In addition to the above, the standard JIAS Author Guidelines can be found below:

Sections

1. SUBMISSION

Once the submission materials have been prepared in accordance with the author guidelines, new submissions should be made via the Research Exchange submission portal: **https://wiley.atyponrex.com/journal/JIAS**.

You may check the status of your submission at any time by logging on to **submission.wiley.com** and clicking the "My Submissions" button. **For technical help with the submission system**, please review our **FAQs** or contact **submissionhelp@wiley.com**.

For editorial enquiries, please contact the *Journal of the International AIDS Society* Editorial Office at **editorial@jiasociety.org**.

Please carefully read through the Instructions for Authors and prepare your manuscript according to the guidelines, including structuring it manuscript based on the chosen article category. Manuscripts that do not follow the instructions may be returned to the authors for corrections.

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Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

The submission system will prompt authors to use an ORCID iD (a unique author identifier) to help distinguish their work from that of other researchers. Click here to find out more.

You will be asked to suggest potential peer reviewers for your manuscript: they should be experts in the field and be able to provide an objective assessment of the manuscript. Any suggested peer reviewers should not have published with any of the authors of the manuscript within the past three years, should not be current collaborators, and should not be members of the same institution. Suggested reviewers will be considered alongside potential reviewers identified by the Editorial team.

2. AIMS AND SCOPE

The *JIAS* welcomes submissions on HIV-related topics from across all scientific disciplines, including but not limited to:

- Basic and biomedical sciences
- Behavioural sciences
- Epidemiology
- Clinical sciences
- Health economics and health policy
- Operations research and implementation sciences
- Social sciences and humanities, including political sciences and media

The *JIAS* prioritizes submissions from operational research and implementation science as publication of such material can provide valuable information on various algorithms for monitoring and providing support for comprehensive, yet affordable and sustainable treatment, prevention and care programmes in different contexts.

Submission of HIV research carried out in low- and middle-income countries is strongly encouraged.

3. FREE FORMAT

JIAS offers Free Format submission for a simplified and streamlined submission process.

Before you submit, you will need:

- Your manuscript: this should be an editable file including text, figures, and tables, or separate files—whichever you prefer. All required sections should be contained in your manuscript, including abstract, introduction, methods, results, and conclusions. Figures and tables should have legends. Figures should be uploaded in the highest resolution possible. If the figures are not of sufficiently high quality, your manuscript may be delayed. References may be submitted in any style or format, as long as it is consistent throughout the manuscript. Supporting information should be submitted in separate files. If the manuscript, figures or tables are difficult for you to read, they will also be difficult for the editors and reviewers, and the editorial office will send it back to you for revision. Your manuscript may also be sent back to you for revision if the quality of English language is poor.

- An ORCID ID, freely available at https://orcid.org. (Why is this important? Your article, if accepted and published, will be attached to your ORCID profile. Institutions and funders are increasingly requiring authors to have ORCID IDs.)
- The title page of the manuscript, including:
    - Your co-author details, including affiliation and email address. (Why is this important? We need to keep all co-authors informed of the outcome of the peer review process.)

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- Statements relating to our ethics and integrity policies, which may include any of the following (*Why are these important? We need to uphold rigorous ethical standards for the research we consider for publication*):
  - data availability statement
  - funding statement
  - conflict of interest disclosure
  - ethics approval statement
  - patient consent statement
  - permission to reproduce material from other sources
  - clinical trial registration

4. MANUSCRIPT CATEGORIES AND REQUIREMENTS

The *JIAS* accepts submissions in the following categories:

- Research
- Short report
- Review
- Debate
- Commentary
- Letter to the Editor
- Viewpoint
- Field notes

Research - full reports of data from original research studies

Abstract:
Headings: Introduction, Methods, Results, Conclusions
Word limit: 350 words

Main text:
Headings: Introduction, Methods, Results, Discussion, Conclusions
Word limit (quantitative): 3500 words; tables do not contribute to the word count
Word limit (qualitative): 5000 words if the manuscript includes substantial quotes; tables with quotes contribute to the word count; mixed and multiple methods reports may be included if there is a qualitative component with quotes
Numbers of figures and tables: Unlimited
Additional files: Yes

Download the manuscript template

Short report - brief reports of data from original research, such as follow-up or confirmatory studies, case series and negative results

Abstract:
Headings: Introduction, Methods, Results
Conclusions
Word limit: 350 words

Main text:
Headings: Introduction, Methods, Results, Discussion, Conclusions
Word limit: 2000 words
Numbers of figures and tables: 3
Additional files: No

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5. PREPARING THE SUBMISSION

Cover letter

In the cover letter, please explain why your manuscript should be published in the journal. If necessary, address any issues relating to our editorial policies ,and declare any competing interests (see **Editorial Policies and Ethical Considerations)**

Parts of the Manuscript

The manuscript should be submitted as a main text file including tables and figures. Appendices and supporting information should be submitted as separate files.

Main Text File

The text file should be presented in the following order:

1. Title page;
2. Keywords;
3. Abstract;
4. Main text;
5. Conflict of Interest Statement;
6. Authorship;
7. Acknowledgments;
8. References;
9. Tables;
10. Figures;
11. Supporting Information;

Title page

The title should not contain abbreviations, except commonly used abbreviations such as HIV or AIDS (see **Wiley's best practice SEO tips**).

On the title page, you should mention the title of the manuscript, list all authors' names in full, and list any study groups if applicable. Each authors' affiliation should be numbered in superscript consecutively and listed underneath, including department, institution, city and country.

The corresponding author should be marked with the symbol § in superscript and full contact details should be provided, including a telephone number with country code. Authors who have contributed equally to the work should be marked with the symbol * in superscript. Deceased authors should be marked with the symbol ^ in superscript. The email addresses of all authors should be listed by their initials.

Keywords

Please provide six keywords. Keywords should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at **https://www.nlm.nih.gov/mesh/**. Preferably alternate words to those found in the abstract in order to improve search hits for the article in repositories.

Abstract

The Abstract should not exceed 350 words and should be structured according to the headings of the selected article category (see above), excluding the heading "Discussion" for Research articles and Short Reports. Avoid using abbreviations and do not cite references in the Abstract.

Main Text

Article sections

Introduction

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The Introduction section should introduce the topic to readers without specialist knowledge in that area and must clearly outline the current state of knowledge in this field, the motivation and the aim of the study or the article.

Methods
The Methods section should include all information necessary to repeat the study, in particular, the study design, how data was collected and analyzed, clarifying the choice of methods that were made. If applicable, you should describe the setting of the study, the dates the study were conducted, and the sample or participants, as well as necessary power calculations and materials, including statistical packages, used. Interventions and programmes should be described in detail. Generic names for drugs or any molecules should be used.

All studies involving humans or animals require a statement on ethical approval, and for the former, the consent procedure that was followed. Please include the names of the ethics review board(s) that approved the study. If the research study was specific to one sex/gender, the reasons for this should be clearly stated.

Results
This section should include only data and findings from the authors' study. Presentation of statistical results should mention confidence intervals and levels of significance where appropriate. Quotes from qualitative study participants of less than three lines should be quoted in the text using quotation marks. For quotes longer than three lines, place the quote in a separate, indented paragraph and introduce it with a colon. No quotation marks are needed in this case. Details of the participant can be added in round brackets following the quote, but should not contain identifiable information to ensure confidentiality. Clarifications within the quotation should be placed in square brackets. In some cases, it may also be appropriate to organize quotes within a table. For details on the use of tables to display qualitative quotes, please see guidance below, under *Tables*.

Submitting authors should include data disaggregated by sex (and, whenever possible, by race or ethnicity) and provide a comprehensive analysis of gender and racial or ethnic differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results.

Discussion
In the Discussion section, you should discuss your main findings and place these within the context of the current body of knowledge in the field. Limitations of the study, for example, selection bias, can also be discussed, and should address how these influence the results and conclusions. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed.

Conclusions
In your Conclusions section, state your key messages from the study and explain their importance and relevance, as well as implications. Future studies and recommendations can be included in this section. The conclusions drawn must be strictly based on the data provided.

Conflict of Interest Statement
Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the **Editorial Policies and Ethical Considerations** section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

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Authorship

Please refer to the journal's Authorship policy in the **Editorial Policies and Ethical Considerations** section for details on author listing eligibility. The individual contributions of each author must be specified in the Authors' Contributions section. Please use authors' initials and state that all authors have read and approved the final manuscript. An example of a suitable statement is: "S.W., N.J., D.W. and S.S. performed the research. S.W., N.J., H.H. and T.L. designed the research study. H.H. and S.S. contributed essential reagents or tools. S.W., N.J. and D.W. analysed the data. S.W. and N.J. wrote the paper." Please see the 'Authorship' section in the Editorial Policies and Ethical Considerations section below for what constitutes authorship.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

References

All external sources of information should be referenced within the text, the tables and figures, using consecutive numbering in square brackets, e.g. [1], [3-5], [3,4]. The references should be up to date and adequately reflect the current state of knowledge in the field. Citation bias, for example, by country or point of view must be avoided. Numbers of references are unlimited for all article categories and should be formatted in standard Vancouver style; **see Sample references from ICMJE** . Unpublished observations, personal communications and manuscripts currently under consideration should be cited in the text in round brackets and not in the reference list.

Tables

They should be supplied as editable files, not pasted as images. Tables should be inserted into the text. They should have the header: "Table 1. Title of table". All tables should be cited in the text in consecutive order. The tables should not contain colour or shading, and no vertical, visible lines. If tables are copied or adapted from another source, permission must be sought by the authors prior to publication and these should be clearly cited as such. If a table spans more than one page, authors may want to consider uploading the table as an additional file instead. Tables should be self-contained and complement, not duplicate, information contained in the text. A legend can be provided underneath the title, listing any abbreviations or meanings of symbols used. If several tables are included, please ensure that symbols are used consistently. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Guidance on the use of tables to display qualitative quotes:

Quotes placed in tables should be organized thoughtfully and strategically, to aid the clear presentation of results. Displaying quotes in tables may be particularly useful when comparing and contrasting subgroup variations in responses or showing temporal variation. Tables may also help visually organize themes when they correspond to the order or way in which findings are described in the text. Please note that tables that present quotes will contribute to the overall word count of the manuscript, with intention to avoid excessively long tables in which quotes are placed without sufficient context. Accordingly, the word limit for qualitative and mixed methods submissions is 5,000 words, inclusive of tables with quotes.

Figures

Figures should be cropped as closely as possible and have the header: "Figure 1. Title of figure". All figures need to be cited in the text in consecutive order.

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. **Click here** for the basic figure requirements for

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figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements. We suggest as minimum font size Arial 9, Calibri 10, TNR 10.

Figure legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. If several figures are included, please ensure that symbols are used consistently. Post-peer review, the manuscript should be submitted as a main text file including tables and figures. Tables and figures should also be submitted separately as high-resolution versions.

Additional Files

Appendices

Appendices will be published after the references. For submission, they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, **and other relevant material. Authors are encouraged to be concise, to only include relevant content, and to avoid excessively long documents. Supporting information is not peer-reviewed or copy-edited. Click here** for Wiley's FAQs on supporting information.

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The following points provide general advice on formatting and style:

- **Abbreviations:** In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.
- **Acronyms:** Acronyms should be used sparingly, and not in headings or in the Abstract. Only commonly known acronyms may be used, and they should be spelt out at first use followed by the abbreviation in brackets. SI units should be used, with litre and molar being permitted.
- **Units of measurement:** Measurements should be given in SI or SI-derived units. Visit the Bureau International des Poids et Mesures (BIPM) website **here** for more information about SI units.
- **Numbers:** Numbers under 10 are spelt out, except for: measurements with a unit (8mmol/l); age (6 weeks old), or lists with other numbers (11 dogs, 9 cats, 4 gerbils).
- **Trade Names:** Chemical substances should be referred to by the generic name only. Trade names should not be used. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name and the name and location of the manufacturer in parentheses.
- **Footnotes:** Footnotes are not allowed in the text, the information shall be included directly into the text, where it fits best, and if these are references, to include in the reference section at the end.
- **Language**: All submissions must be in UK English (International) and UN-accepted terminology should be followed. No capitalization should be used except for grammatically correct use, official names and titles, and abbreviations. JIAS encourages the authors to use

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a people's first language following best practices, such as the recommendations of the People First Charter and the UNAIDS guidelines on terminology.

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6. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Editorial Review and Acceptance

The acceptance criteria for all papers are the quality and originality of the research and its significance to journal readership. Except where otherwise stated, manuscripts are single-blind peer reviewed, meaning that reviewers remain anonymous to the authors, although the authors' identity is known to the reviewers. Papers will only be sent to review if the Editors-in-Chief determine that the paper meets the appropriate quality and relevance requirements.

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Please note that changes should not be made to manuscripts after acceptance, with the exclusion of minor copy-editing corrections during production. When submitting their manuscript, authors are encouraged to consider any required clearance processes by governing agencies and ensure that no changes are requested after acceptance.

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The Journal of the International AIDS Society expects that data supporting the results in the paper will be archived in an appropriate public repository. Whenever possible the scripts and other artefacts used to generate the analyses presented in the paper should also be publicly archived. Exceptions may be granted at the discretion of the editor for sensitive information such as human subject data or the location of endangered species. Authors are expected to provide a data availability statement, including a link to the repository they have used, to accompany their paper. More details and templates of data availability statements can be found here.

Protein and nucleotide sequences

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For nucleic acid sequences, protein sequences or atomic coordinates, which are cited in the manuscript, and the accession number, together with the database where the information was deposited, should be cited in square brackets in the text, for example, [EMBL:AB026295, EMBL:AC137000, DDBJ:AE000812, GenBank:U49845, PDB:1BFM, Swiss-Prot:Q96KQ7, PIR:S66116]. Relevant databases are: EMBL Nucleotide Sequence Database (**EMBL**), DNA Data Bank of Japan (**DDBJ**), GenBank at the NCBI (GenBank), Protein Data Bank (**PDB**), Protein Information Resource (**PIR**) and the Swiss-Prot Protein Database (**Swiss-Prot**).

Mass spectrometry
Mass spectrometry data should be provided in the mzML format according to the **HUPO Protein Standards Initiative Mass Spectrometry Standards Working Group guidelines**. The data should also be deposited in the **ProteomeExchange** through the **PRIDE** website, and protein interaction data can be deposited through members of the IMEx consortium.

Structures
Protein structures can be submitted with one of the members of the **Worldwide Protein Data Bank**. Nucleic acid structures can be deposited with the **Nucleic Acid Database** at Rutgers. Crystal structures of organic compounds can be deposited with the **Cambridge Crystallographic Data Centre**.

Chemical structures and assays
Structures of chemical substances can be deposited with **PubChem Substance**. Bioactivity screens of chemical substances can be deposited with **PubChem BioAssay**.

Functional genomics data (such as microarray or ChIP-Seq data)
Please refer to standards proposed by the **Functional Genomics Data Society** and deposit your microarray data in MIAME-compliant format in one of the public repositories, for example, **ArrayExpress** or **Gene Expression Omnibus** (GEO). Deposition of high-throughput functional genomics sequencing data (such as RNA-Seq or ChIP-Seq data) with ArrayExpress or GEO in compliance with MINSEQE is also needed.

Computational modelling
Please prepare models of biochemical reaction networks using the **Systems Biology Markup Language** and submit your model to the **BioModels database**, as well as providing it as an additional file with your submission.

Plasmids
Please submit copies of your plasmids as DNA or bacterial stocks with **Addgene**, a non-profit repository, or **PlasmID**, the Plasmid Information Database at Harvard.

Ethical approval – Human and animal studies

Human Studies and Subjects
For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: **Declaration of Helsinki**; **US Federal Policy for the Protection of Human Subjects**; or **European Medicines Agency Guidelines for Good Clinical Practice**.

A statement on the ethical aspects, including the consent procedure followed, must be included in the Methods section of the manuscript. The Editors may reject manuscripts where the research has not been carried out within an ethical framework. Images and information from individual participants will only be published where the authors have obtained the individual's free prior informed consent. Confidentiality of study participants must be ensured at all stages of research and reporting. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a **standard patient consent form available for use**.

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A statement indicating that the protocol and procedures employed were ethically reviewed and approved, as well as the name of the body giving approval, must be included in the Methods section of the manuscript. Authors are encouraged to adhere to animal research reporting standards, for example the **The Gold Standard Publication Checklist from Hooijmans and colleagues** or the **ARRIVE reporting guidelines** for reporting study design and statistical analysis; experimental procedures; experimental animals and housing and husbandry. Authors should also state whether experiments were performed in accordance with relevant institutional and national guidelines for the care and use of laboratory animals:

- US authors should cite compliance with the US National Research Council's **Guide for the Care and Use of Laboratory Animals**, the US Public Health Service's **Policy on Humane Care and Use of Laboratory Animals**, and **Guide for the Care and Use of Laboratory Animals**.
- UK authors should conform to UK legislation under the **Animals (Scientific Procedures) Act 1986 Amendment Regulations (SI 2012/3039)**.
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The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

Research Reporting Guidelines

Standard of reporting

The *JIAS* endorses international standards of reporting. Please see the **Uniform Requirements for Manuscripts Submitted to Biomedical Journals** guidelines produced by ICMJE as a reference standard of reporting. Authors are also referred to the **EQUATOR** network website for further information on the available reporting guidelines for health research, and the **MIBBI** Portal for prescriptive checklists for reporting biological and biomedical research where applicable. A number of checklists are available for various study designs, including randomized controlled trials (**CONSORT**), interventional trials (**SPIRIT**), qualitative research (**COREQ**), systematic reviews (**PRISMA**), observational studies (**STROBE**), economic evaluations of health interventions (**CHEERS**), meta-analyses of observational studies (**MOOSE**) and diagnostic / prognostic studies (**STARD** and **TRIPOD**). For systematic reviews, an additional file should be provided by the authors listing all details concerning the search strategy. Please refer to the **Cochrane Reviewers' Handbook** for an example of how a search strategy should be presented.

Guidelines on mutation nomenclature are provided by the **Human Genome Variation Society** , and authors should use the recommended gene name by referring to the appropriate genetic nomenclature database, for example, HUGO for human genes, and the International Committee on Standardized Genetic Nomenclature for Mice. When describing human phenotypes, please use standardized terms, such as those proposed by the Elements of Morphology working group (see **http://research.nhgri.nih.gov/morphology/index.cgi**).

Contributions from pharmaceutical companies or other commercial organizations should follow the **Good Publication Practice guidelinEs for pharmaceutical companies**, which also apply to any companies or individuals that work on industry-sponsored publications, such as freelance writers, contract research organizations and communications companies.

The *JIAS* supports international standards of reporting of trials, in particular, prospective registering and numbering of clinical trials. Clinical trials are defined by the World Health Organization as all phase I to IV trials, which are research studies that prospectively assign human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Trials need to be registered prior to submission in a suitable, publicly available registry. Links to existing registries can be found through ICMJE **here** or through the primary registers that participate in the **WHO International Clinical Trials Registry**

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Platform. The trial registration number should be included as the last line of the manuscript Abstract.

Reporting by gender and race or ethnicity

Submitting authors should include data disaggregated by sex (and, whenever possible, by race) and provide an analysis of gender and racial differences. The authors should include the number and percentage of men, women and, if appropriate, transgender persons, who participated in the research study. Anatomical and physiological differences between men and women (height, weight, body fat-to-muscle ratios, cell counts, hormonal cycles, etc.), as well as social and cultural variables (socio-economic, education, access to care, etc.), should be taken into consideration in the presentation of data and/or analysis of the results. If statistically significant differences were found between men and women or between different racial or cultural groups in the effects of the studied intervention, the implications, if any, for clinical and/or public health should be adequately discussed. If the research study was specific to one sex/gender, the reasons for this should be clearly stated. Please refer to the SAGER guidelines for more information

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Upon its first use in the title, abstract, and text, the common name of a species should be followed by the scientific name (genus, species, and authority) in parentheses. For well-known species, however, scientific names may be omitted from article titles. If no common name exists in English, only the scientific name should be used.

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Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see varnomen.hgvs.org, where examples of acceptable nomenclature are provided.

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1. Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. Have been involved in drafting the manuscript or revising it critically for important intellectual content;
3.Have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
4. Have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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If a study group is listed in the authorship, the members that contributed to the study can be listed as "Collaborators," which will allow them to be searchable in PubMed (see example here).

Additional Authorship Options:
In the case of joint first or joint senior authorship, a footnote should be added to the author listing, e.g. 'X and Y should be considered joint first author' or 'X and Y should be considered joint senior author.' Joint first authorship together with joint senior authorship is not allowed. Three joint first authors or three joint senior authors are not allowed.

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7. AUTHOR LICENSING

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Appendix 6: Student's contribution to the manuscript and co-author agreement

Declaration: Student's contribution to article and agreement of co-author(s)

I, Nicole Poovan, student number 2606475, declare that this Research Report in the submissible format is my own work and that I contributed adequately towards research the article stated below which is included in my Research Report. N.P., D.C.N, and S.D-M. designed the research study. N.P., N.H.N, C.C., R.H., and S.D-M. performed the research. N.P., and S.P. managed the data. M.G. provided essential tools. N.P., D.C.N., and S.D-M. analysed the data. N.P. drafted the initial manuscript with iterative reviews by D.C.N, and S.D-M.

Signature of Student Nicole Poovan Digitally signed by Nicole Poovan Date: 2025.03.12 15:13:57 +02'00' **Date** 12 Mar 2025

Name of Primary Supervisor: Prof Sinead Delany-Moretlwe

Signature of Primary Supervisor Sinead Delany-Moretlwe Sinead Delany-Moretlwe (Mar 13, 2025 14:06 PDT) **Date** Mar 13, 2025

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article by the student as part of her Research Report.

Article 1: Title: Effectiveness of counselling based on a point-of-care urine tenofovir on HIV pre-exposure prophylaxis adherence among young South African women: a randomized pilot trial.

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Comments by primary supervisor:

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