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BMJ Open Treatment And Prevention for female Sex workers in South Africa: protocol for the TAPS Demonstration Project

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ABSTRACT

Introduction: Updated guidelines from the WHO recommend antiretroviral treatment for adults with HIV at any CD4 count and daily oral pre-exposure prophylaxis (PrEP) for people at substantial risk of HIV infection. However, implementation challenges may hinder the ability of programmes to translate these recommendations into successful practice. This demonstration project is the first to integrate PrEP and immediate treatment (ITx) for female sex workers (FSWs) in South Africa to answer operational research questions.

Methods and analysis: This is a prospective cohort study where the main outcome is retention at 12 months. The study population is recruited into two arms across two urban sites: (1) PrEP for HIV-negative FSWs (n=400) and (2) ITx for HIV-positive FSWs with CD4 greater than national guidelines (n=300). We investigate process and other health indicators, uptake and use of PrEP and ITx through qualitative research, and evaluate cost-effectiveness analysis combined with estimates of impact through epidemiological modelling.

Ethics and dissemination: The Treatment And Prevention for female Sex workers in South Africa (TAPS) Project was designed as an implementation study before emtricitabine/tenofovir disoproxil fumarate was licenced as an indication for PrEP in South Africa. Therefore, clinical trial requirements for ethical and South African Medicines Control Council approvals were followed. Results will be disseminated to participants, local health officials and other stakeholders, as well as in peer-reviewed journals and at conferences.

INTRODUCTION

Globally, UNAIDS data have shown a significant and continuous decline (35%) in the number of new HIV infections since 2000.¹ In sub-Saharan Africa, this trend is even more pronounced with a 41% decline. However, in this region of the world, where women make up for more than half of all people living with HIV, incidence rates remain high.¹ In particular, the HIV epidemic in South Africa continues to be the

Strengths and limitations of this study

- The Treatment And Prevention for female Sex workers in South Africa study incorporates a multidisciplinary service delivery evaluation within an implementation science paradigm.
- Success will be measured using several outcomes enabling triangulation of data.
- The study was designed to adapt to shifts in South African antiretroviral therapy guidelines and clinical standards.
- The study will not measure the effectiveness of any service delivery model as there is no comparison arm.
- Our sample size is relatively small and might not be representative of the national population of female sex workers.

highest in the world, based on both HIV incidence (with a currently estimated rate of up to 4 per 100 women-years^{2 3}) and total number of people living with HIV (6.8 million estimated in 2014.^{4 5}

The South African National Strategic Plan on HIV, sexually transmitted infections (STIs) and tuberculosis for 2012–2016⁶ prioritises interventions with the aim to reduce new infections on a national level by 50% using combination prevention while scaling up treatment to cover at least 80% of the population. It also identifies key populations as a major focus of the strategy, which calls for a multifaceted approach to ending the epidemic. Sex workers are among the key populations identified in the past and current National Strategic Plans. Globally, female sex workers (FSWs) are 13.5 times more likely to be living with HIV than women in the general population.⁷ The 2013 South African Key Populations Report estimates that HIV prevalence among FSWs is between 44 and 69%,^{8–11} with 19.8% of all new infections being attributed to sex work, including infections among clients and partners of clients.¹²

A study conducted in 2008 in a cohort of high-risk women in KwaZulu-Natal Province, estimated incidence to be as high as 7.2/100 person-years.¹¹ More recently, a prevalence study conducted among populations of sex workers found a 72% HIV prevalence with low treatment uptake in Gauteng Province.¹³ This high vulnerability is rooted in the many structural drivers of HIV risk affecting this population including: restricted access to healthcare, criminalisation and lack of legal protection, unsafe working conditions, stigma, and economic hardship.¹² As a marginalised population who are stigmatised and criminalised, sex workers require specialised programmes sensitive to their needs for interventions in HIV prevention, care and treatment as well as support to access other health and legal services.

Following the positive results of antiretroviral (ARV)-based prevention studies in reducing both HIV transmission (through ITx) and acquisition (through PrEP),^{14–20} global and national authorities updated HIV guidelines to recommend antiretroviral therapy (ART) be initiated at any CD4 count in adults and daily oral PrEP as an additional prevention strategy for people at substantial risk of HIV infection.^{21–23} While modelling studies have shown that the scaling up of new prevention and treatment tools across the HIV continuum of care could have a significant impact on the epidemic,^{24–26} implementation challenges relating to health service capacity, acceptability and financing and resource allocation may hinder the ability of the programmes from making a significant difference to the HIV epidemic.^{27 28}

The evaluation of existing and innovative models of care to implement new technologies for prevention and treatment through demonstration projects is being conducted around the world.²⁹ These projects represent a spectrum of designs from clinical trial-like protocols to 'real-world' implementation science studies, yet all have similar goals: to test delivery models of new technologies and interventions to inform policy and programming. In particular, projects tend to cater to key populations where acceptability and uptake of technologies such as oral PrEP may be higher and intersect with those populations who might benefit the most initially, such as men who have sex with men, sex workers, serodiscordant couples and young women. These prevention-focused projects are situated within a landscape of evolving HIV treatment guidelines, as treatment is now recognised as the major contributor to prevention and thus many include treatment components.^{21 30}

The demonstration project described here is the first to integrate a combination prevention intervention including oral PrEP and ITx (for those with CD4 counts higher than current national guidelines) for FSWs in South Africa.¹ The interventions are being delivered at

two clinic-based sites for FSWs in Gauteng Province. Gauteng is the most densely populated province of South Africa, also home to both the economic and political capitals of the country.³¹ This implementation study seeks to understand the 'real-world' implications of introducing PrEP and ITx into an existing service delivery structure. By combining PrEP and ITx, we aim to leverage, in a novel way, the service delivery areas needed to support these programmes which primarily include outreach for testing and counselling and clinic services. The overall aim will be to answer operational questions: whether FSWs will accept ITx or combination prevention including PrEP, whether the service delivery mechanism is capable of handling the increase in resource needs these interventions might lead to, and what kind of implications this strategy would have on overall costs, should they be considered for scale up.

METHODS AND ANALYSIS

Population and setting

FSWs are the study population defined as women self-identifying as sex workers, and who have received goods or money in exchange for sex in the past 3 months, age 18 or above, operating in the areas surrounding two existing clinics providing services for sex workers in Hillbrow, Johannesburg and the central business district in Pretoria. These clinics are run by Wits Reproductive Health and HIV Institute (RHI), one of the largest research Institutes of the University of Witwatersrand; since 1994, Wits RHI has pioneered health programmes with a strong community focus. The Hillbrow site is connected to the Esselen Clinic which is home to the well-established Wits RHI Sex Worker Project.³² The Sex Worker Project is a comprehensive reproductive health, HIV and STI prevention and treatment service programme partnered with City of Johannesburg and the South African Department of Health (DoH). It provides services such as: HIV counselling and testing and condom distribution, nurse-initiated and managed ART (NIMART), tuberculosis screening, human papillomavirus screening, clinical services for minor ailments, psychosocial support and referrals to both clinical and legal services. The programme accesses several brothels, with mobile units to serve street-based sex workers and a stationary clinic space. The actual clinic space for the Treatment And Prevention for female Sex workers in South Africa (TAPS) Demonstration Project is located in the Wits RHI Research and Training Centre, which is adjacent to the Esselen Clinic. At the time we initiated the study, renovations at the Esselen Clinic had begun and the building was closed which is the reason for housing the TAPS Project in the Research Centre.

The Pretoria site is located in Sediba Hope Medical Centre, a private non-profit clinic affiliated with the Department of Health, which has been serving the local community in the heart of the inner city of Pretoria. Wits RHI's Sex Worker Project has now opened a sex

¹Recently (June 2016), the NDoH started the piloting at 10 sites of new National guidelines for treatment, where all people infected with HIV independent of their CD4 count are eligible and pre-exposure prophylaxis is available for female sex workers. This demonstration project is informing the roll out pilot directly.

Table 1 Sample size considerations

PrEP arm			ITx arm		
Retention at 12 months (%)	Precision (%)	Number	Retention at 12 months (%)	Precision (%)	Number
65	2.5	1398	75	2.5	1152
65	5.0	350	75	5.0	288
65	7.5	155	75	7.5	128
65	10.0	87	75	10.0	72

Numbers in bold are the numbers taken to develop the sample size.

ITx, immediate treatment; mo, months; N, number; PrEP, pre-exposure prophylaxis.

worker clinic at Sediba Hope which is also linked to the Community Health Clinic in the same building.

Design

The study design is a prospective, observational cohort study, with two study arms:

1. PrEP intervention as part of a combined prevention approach for recently documented HIV-negative FSWs;
2. ITx intervention for HIV-positive ART-naïve FSWs not eligible for ART at the currently implemented CD4-defined standard of care.

The PrEP intervention arm will seek to protect HIV-negative FSWs from acquiring HIV through the use of PrEP and other available prevention options (such as condoms). The ITx intervention arm will seek to link FSWs directly to care to reduce and avoid loss to follow-up within the treatment cascade. Indirectly, it will seek to prevent HIV-positive FSWs from transmitting the virus to clients and other sex partners through the use of ARVs.

Sample size and eligibility criteria

Table 1 shows the sample size considerations for both study arms. We aim to enrol 400 FSWs in the PrEP arm of the study. With an expected retention rate of 65% (precision of $\pm 5\%$) at 12 months, we need 350 participants, which we have increased to 400 to account for variability across the two sites. To achieve this sample size, we should aim to screen 1600 FSWs, of which 800 are expected to be HIV-negative (assuming an HIV prevalence of 50%) and we estimate conservatively that 50% accept to participate. For the ITx arm, we aim to enrol 300 FSWs with an expected retention rate of 75% (precision of $\pm 5\%$) at 12 months, assuming a 25% default rate which reflects recent research on the treatment cascade.³³ To achieve this sample size, we should aim to screen 3600 FSWs, of which 1800 are expected to be HIV-positive (assuming an HIV prevalence of 50%), one-third with CD4 counts over 350 ($n=600$) and 50% accept to participate. In practice, the screening process is a joint step in the recruitment of both the PrEP and the ITx arms. As such, we will aim to screen 3600 FSWs to be able to achieve the required sample sizes. PrEP enrolment will stop as soon as the required sample size is achieved. Note that the original calculations for this study were performed assuming a national CD4 count initiation threshold of 350.

A summary of eligibility criteria is presented in **table 2**. We excluded patients at risk of documented serious side effects of the regimes used. This includes patients with abnormal kidney function (eg, a creatinine clearance rate above 60.0 mL/min), taking medication for multidrug-resistant tuberculosis, testing positive for hepatitis B (PrEP only) or being prescribed any other drugs contraindicated for taking with any of the drug regimens prescribed in the study. Patients are also excluded at clinician's discretion according to their assessment of the patient's safety. We also exclude FSWs pregnant at enrolment. All pregnant women are referred to antenatal care, where HIV-positive FSWs are started on ART as per guidelines and HIV-negative FSWs counselled.

Intervention

Recruitment

Participants for both arms of the study are recruited from the local Wits RHI Sex Worker Project clinics as well as the surrounding community, and in particular places of business such as hotels/brothels, bars and streets. We leverage the existing peer educator-based outreach services currently provided by the Sex Worker Project to reach out and inform them of the study. Each potential participant completes a DoH HIV counselling and Testing (HCT) consent form first as part of standard HCT practice, to determine HIV status through the

Table 2 TAPS Project eligibility criteria

PrEP arm	ITx arm
18 years or older	18 years or older
Creatinine clearance above 60.0 mL/min	Creatinine clearance above 60.0 mL/min
Negative for hepatitis B	CD4 count above national standard for ART initiation
Not pregnant	Not pregnant
Not presenting signs or symptoms of or taking medication for MDR-TB	Not presenting signs or symptoms of or taking medication for MDR-TB
Not prescribed other drugs contraindicated for taking with emtricitabine and tenofovir disoproxil fumarate (FTC/TDF)	Not prescribed other drugs contraindicated for taking with tenofovir disoproxil fumarate/lamivudine/emtricitabine/efavirenz (TDF+3TC/FTC+EFV)

ART, antiretroviral therapy; ITx, immediate treatment; MDR-TB, multidrug resistant tuberculosis; PrEP, pre-exposure prophylaxis.

point-of-care rapid testing process. Discordant HIV rapid test results are then confirmed using ELISA using standard local algorithms (ie, algorithm: two rapid tests are performed simultaneously for confirmation. In case of discordant, indeterminate or positive results, blood is drawn for an ELISA).³⁴ Once HIV status is established, participants sign either the PrEP or ITx TAPS study informed consent form according to HIV status. Participants in the PrEP arm are counselled and informed about adherence and effectiveness of PrEP, the need to use condoms with PrEP in order to ensure a high level of protection against HIV infection as well as to prevent STIs and unwanted pregnancies. Participants in the ITx arm are also counselled about adhering to their treatment regimens and using condoms.

We aimed to balance the 'real world' aspect of the demonstration project with the consent and information gathering needs for research purposes. Therefore, at the screening visit, participants are asked to complete a demographic and behaviour questionnaire, as well as a short medical history for screening purposes. Blood samples are taken for creatinine levels, hepatitis B, syphilis testing, HIV confirmation with ELISA and viral load testing. All participants also take a point-of-care pregnancy test as part of eligibility requirements.

Participants are asked to return in 1-week, within a maximum window of up to 30 days if needed, after the screening visit for enrolment if eligible. At the enrolment visit, participants are scheduled for regular study visits to monitor medication adherence and safety. We also take a clinical history, offer syndromic STI screening and any other clinically indicated assessments such as for cervical cancer as per DoH guidelines. Potential participants are asked about fertility intentions; however, future pregnancy plans are not a part of study exclusion. Contraception is offered to those requiring a method as per standard of care, but use of a contraceptive is not a requirement for study eligibility.

The participants have access to counselling services, as well as all other services provided by the Sex Worker Project as standard of care, including but not limited to reproductive health services, referrals for legal services, substance use and violence counselling and support and post-rape care. Support groups are not currently planned as an official service of this study; however, FSWs may elect to form support groups and project staff make an effort to support this with space if requested.

Medication and adherence

HIV-negative participants fulfilling all eligibility criteria are started on co-formulated emtricitabine and tenofovir disoproxyl fumarate FTC/TDF (Truvada) in the PrEP arm. The medication for the ITx arm is tenofovir disoproxyl fumarate plus lamivudine/emtricitabine plus efavirenz combination (TDF+ 3TC/FTC+EFV), or Atripla, as per current guidelines. The drugs for the TAPS study have been donated by Gilead.

We measure adherence to PrEP through several modes of self-report as well as plasma drug level testing. Treatment adherence is measured through self-report and monitoring viral load suppression.

As adherence support, all participants have the option to receive SMS. Two types of SMS may be sent to participants. The first type is visit reminders, three sent per visit—two as reminders before the visit and one to thank the participant for attendance or to remind them to reschedule if they missed a visit. The second type is aimed at providing information and support on a weekly basis and within the following themes—adherence/side-effects/informational, health education, healthy living, referral services and affirmations. All participants are offered each type of messaging services and those who are willing to participate sign an additional consent form. Participants are able to opt out at any time and feedback on the utility of the messages is solicited throughout the study.

Management of pregnancy

Guidance from major organisations, such as the WHO and Centers for Disease Control and Prevention (CDC), USA, has made surveillance of PrEP use in pregnancy a priority.^{35 36} If a participant becomes pregnant during the course of the project in the PrEP group, she will be given the option to either continue or discontinue taking PrEP. If she decides to discontinue PrEP, she will be given the option to remain in the project using other HIV prevention options, but is referred for antenatal services or termination of pregnancy services as selected. The potential for harm due to unknown risks of taking PrEP while pregnant is noted in the main study's informed consent forms.

If a participant in the treatment group becomes pregnant during the course of the project, she will also be given the option to remain in the study and be referred for antenatal services, where participants will continue lifelong treatment as per the current guidelines. If the participant decides to discontinue participation in the study, she will be referred to the clinic of her choice for continued treatment.

Follow-up visits and loss to follow-up

Participants are scheduled for clinic visits on a 3-month basis and receive a prescription refill once a month in both arms. Monitoring visits include HIV testing (PrEP arm only), CD4 and viral load tests (ITx arm only), creatinine levels, syndromic screening and treatment for STIs as required, and adherence counselling. All these services are standard of care for monitoring patients on treatment and are the minimum monitoring requirement in the newly published PrEP and ITx guidelines.²³ At each scheduled visit, participants are asked to complete a short questionnaire to record any side effects, changes in risk behaviour, fertility intentions, time of last menstrual period and adherence to ARVs. Participants may also request an unscheduled visit to report safety

events at any time. We are not collecting quantitative information on diversion of medications (eg, selling or giving ARVs to others), but we are both collecting qualitative information on this important issue as part of the in-depth interviews (IDIs) and providing intensive adherence counselling.

Loss to follow-up is defined as a participant missing two consecutive visits with no contact. Efforts will be made to contact participants by phone in the PrEP and ITx arms to understand the reasons for missed visits. However, only additional efforts, which may include a home visit, will be made to encourage participants in the ITx arm to return. If participants are contacted in the PrEP group and decide not to return, we will ask if they are willing to participate in a brief exit interview to understand the reasons for dropout and to ensure there are no safety concerns.

Final visit and withdrawal from the project

At the final project visit, all participants will be asked to answer final behavioural, violence and participant costing questionnaires. Those in the PrEP arm will have creatinine test, STI screening and treatment as necessary; while those in the treatment arm will have CD4 and viral load tests, creatinine test, STI screening and treatment as necessary, and counselling for continued adherence to their treatment regimen. They will be offered a choice to remain at the same clinic for continued care and treatment, or be transferred to another clinic of their choice. If a participant in the PrEP arm sero-converts, we will offer a full resistance testing. The participant will not be rolled on to the ITx arm but will be offered a choice to remain at the same clinic for continued care and treatment, or be transferred to another clinic of their choice. All participants will also be informed as to when they can expect a report of the project's results.

As of 1 June 2016, PrEP and the test and treat approach has been prioritised for sex workers. As a result, we are now able to transition all of the women in our study to PrEP and HIV treatment services in our Sex Worker Programme or to other clinics of their choosing offering these services, either at the end of the study or should they choose to leave the study early for any reason.

For ease of reference, we mapped all events and provided a visit schedule for both PrEP arm and ITx arm in the online supplementary appendix.

Analysis

The project is being evaluated through a mixed methods approach. This approach examines the deliverability of the interventions and their integration into a comprehensive prevention and treatment package, and includes quantitative analysis of process and questionnaire data (behaviours, uptake, linkage and retention in care and adherence), qualitative assessment of providers and user feedback on the interventions, and an economic evaluation from a societal perspective.

Quantitative analysis of process and questionnaire data

The primary outcome for both arms is the number of women retained at 12 months of follow-up (a participant is considered retained at 12 months if she attended a scheduled follow-up visit between 10.5 and 13.5 months after enrolment). In the PrEP arm, we note that a participant is considered retained even if not on PrEP but continuing the combination prevention visits. Secondary outcomes for both arms are shown in [table 3](#).

We can expect three types of bias in cohort studies: selection bias, information bias and misclassification bias. It is possible that participants 'auto-select' (ie, a selection bias), meaning that those FSWs feeling most vulnerable will be most likely to enrol and continue participation. Since this is a demonstration project, we expect participants to decide whether to participate based on their risk perception and we will aim to document these motivations and perceptions as much as possible through qualitative research. We do not expect an information bias to be present as we are collecting the same information for all participants. Finally, misclassification could arise from a participant being considered not retained in care as per her participation in our study; however, she might be in care at another clinic. We will aim to ascertain if this is a potential bias while contacting by phone those participants missing two consecutive clinic visits in either the PrEP or the ITx arm to understand the reasons for missed visits.

Qualitative research

Data from qualitative research conducted during the PrEP efficacy trials indicate multiple and varying reasons for lack of adherence on the part of participants, thus illustrating the imperative to understand how PrEP may be best implemented in a given context from the point of view of potential consumers.^{37 38} In this regard, we are conducting a multifaceted qualitative research with participants from the two project arms as well as providers at the clinics to gain perspectives on using and implementing PrEP and ITx. Methods include IDIs with participants, waiting-room observations and provider group discussions. These methods will serve as a means to compare and contrast sources of data to develop a narrative as to the feasibility, and more specifically, the motivations and barriers of implementing PrEP and ITx. We will also be able to compare these qualitative data with data from the structured questionnaires to explore different aspects of adherence to medication. All data collection tools have been piloted and adjusted as required.

Participant IDIs

We use an adapted socioecological model as a framework to explore themes related to motivations and barriers to the use of PrEP and ITx based on the multiple spheres influencing women's lives from community, household, work and clinic settings. A subset of women from the PrEP and ITx arms are being randomly invited to participate in the qualitative research component in

Table 3 TAPS Project secondary outcomes

Variable	PrEP arm	ITx arm	Type of data
Knowledge	Assessment of HIV knowledge including PrEP	Assessment of HIV knowledge including ITx	Qualitative data (IDIs) and questionnaire data
Uptake and acceptability	Description of reasons for ineligibility after first eligibility assessment	Description of reasons for ineligibility after first eligibility assessment	Questionnaire data, complemented by qualitative data
	Proportion of women accepting PrEP at baseline	Proportion of women accepting ITx at baseline	Programme data, complemented by qualitative data
	Comparison demographic characteristics of women accepting PrEP vs refusing at baseline	Comparison demographic characteristics of women accepting ITx vs refusing at baseline	Questionnaire data
Retention	Proportion of women retained and adherent to PrEP at 3, 6, 18, 24 months	Proportion of women retained and adherent to ART at 3, 6, 18, 24 months	Programme data
Patterns of use	Proportion of women using PrEP continuously for 12 months	NA	Programme data
	Description of length of use and repetitive uptake for women not using PrEP continuously for 12 months		Programme data and IDIs
Adherence	Proportion of women reporting taking >85% of pills (self-reported) at each routine visit during 12 months	Proportion of women reporting taking >85% of pills (self-reported) at each routine visit during 12 months	Questionnaire data
Side effects	Proportion of women with drug level detectable in plasma at 12 months	Proportion of women with undetectable viral load at 12 months	Clinical (laboratory) data and IDIs
	Number (by type) of all side effects reported at routine visits for 12 months	Number (by type) of all side effects reported at routine visits for 12 months	Clinical data, IDIs and clinic observations
HIV status	Number of seroconversion cases at 12 months and description of all resistance profiles	Proportion of women with plasma HIV-1 RNA level ≥ 1000 copies/mL at 6 months or after initial suppression and description of all resistance profiles	Clinical (laboratory) data
Pregnancy Sexual behaviour	Pregnancy rates during follow-up	Pregnancy rates during follow-up	Clinical data
	Comparison of proportion of women reporting consistent condom use (stable partners, regular/new clients): baseline vs PrEP use after 12 months	Comparison of proportion of women reporting consistent condom use (stable partners, regular/new clients): baseline vs ART use after 12 months	Questionnaire data and IDIs
Cell phone technology for adherence support	Proportion of women presenting with STI symptoms at each routine visit during 12 months	Proportion of women presenting with STI symptoms at each routine during 12 months	Questionnaire data
	Proportion of women opting-out of SMS reminders at baseline and throughout the duration of the project	Proportion of women opting-out of SMS reminders at baseline and throughout the duration of the project	Programme data and IDIs
Cost of intervention	Cost per person-year on PrEP (health service perspective)	Cost per person-year on ITx (health service perspective)	Costing data
	Cost per person-year on PrEP (participant perspective)	Cost per person-year on ITx (participant perspective)	Costing questionnaire data

ART, antiretroviral therapy; IDIs, in depth interviews; ITx, immediate treatment; NA, not applicable; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

each arm (up to 40 for PrEP and up to 30 for ITx). Each participant is asked to sign a separate consent form and is reimbursed for her travel costs since this will be outside of regular clinic visit requirements. This is the only form of participant reimbursement offered since the purpose of the TAPS project is to assess retention in the programme in a 'real-world' clinic setting.

Interviews are conducted individually with each participant by a research assistant who is conversant in the participant's language.

Interviews will be conducted longitudinally at months 3, 6 and 9 for each participant in order to explore themes emerging over time.³⁷ Interview questions will seek data related to reasons for participating in the

study, motivations and barriers to uptake and use of the interventions, acceptability of the SMS technology, perceived gaps in service delivery and HIV prevention method preferences over time. Interviews will be audio taped, and later translated into English, as needed, and transcribed.

Waiting-room observations

Informal conversations held by participants in settings such as waiting-rooms have provided invaluable information for the triangulation of qualitative data thus enriching narratives of participant behaviour during studies.³⁷ We are conducting waiting-room observations at the two project sites for a period of 1-week on a quarterly basis. Permission to conduct these observations is obtained from the clinic managers, and researchers conducting the observations provide study participants in the waiting-rooms with notification of who they are, what they are doing and for what purpose. The purpose of these observations is to gather informal data on participants' perspectives of the study, the interventions and issues they may be experiencing that influence their interest in the programme and ability to maintain participation. Information will be recorded in the researcher's field notebook and later uploaded into NVIVO for coding and analysis.

Provider group discussions

A recent guidance illustrates the importance of service delivery providers as an important target group for promoting and managing the dissemination and uptake of PrEP.³⁹ As such, we are convening informal group discussions at each site in order to explore provider experiences, including primarily the community health workers/counsellors, nurses, pharmacists, coordinators and medical officers, in delivering PrEP and ITx. All potential provider-participants are asked to complete the informed consent process and have the option to decline participation. The research is being conducted by an external contractor and does not include evaluation of providers on performance. As themes for discussion may evolve over time, a more structured discussion guide is being used initially and subsequent guides will build on emerging themes.

Analysis

All qualitative research components will be analysed using thematic analysis as defined by Braun and Clarke.⁴⁰ This approach to thematic analysis features a six-phase process: familiarisation with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and finally producing the report. Translated and transcribed transcripts from the IDIs, waiting-room observations and provider group discussions will be uploaded into NVIVO software and coded according to the coding manual created. Researchers will assemble the coding manual first by developing overarching data categories based on

research objectives, then by systematic and iterative review of the data to elicit primary and subthemes. We will aim to have at least two coders per transcript. Any discrepancies in coding will be discussed between the coders with input from the senior investigator to gain consensus. Once all the data have been coded, researchers will synthesise the findings to explore commonalities and differences across participant perspectives.

Economic evaluation

The introduction of an integrated HIV prevention and care service is likely to involve several trade-offs between costs and efficiencies. We are measuring empirically the costs for participants and the healthcare providers in the two sites of the TAPS study to then model total costs, impact and cost-effectiveness of this intervention both in our cohort and at a population level. The evaluation is carried out from a societal perspective.

Healthcare provider costs

All costs will be estimated using an ingredient costing approach to define the cost per person receiving each service. Data are collected through directly observed resource use (observations of practice at sites and interviews with the healthcare workers before implementation, at early stages of implementation and 1-year after the interventions are implemented). We also review clinic costs (such as utility bills) over the duration of the study. We include capital costs (equipment, buildings, non-recurrent training), as well as recurring costs (personnel, supplies, operations and maintenance of buildings) in our estimates. We aim to include costs incurred above the direct service level, such as monitoring and evaluation and coordination costs as well as cost incurred during start up activities such as community mobilisation and training before the service delivery starts. The current micro costing approach allows us to record in detail all processes happening at each visit and their purpose (for research or service delivery). The unit cost will then be reported disaggregating research-related costs.

Participant costs

Data are collected through voluntary questionnaires administered to all participants in the PrEP and ITx cohorts at one visit (follow-up at 12 months). In the questionnaires, we collect general information regarding the participant's household, employment and income, out-of-pocket expenditures including transportation fees, consultation fees, non-HIV laboratory tests, non-HIV medication (vitamins, antibiotics and others) and food, any time lost due to PrEP or ITx appointments, including travel time, consultation time and loss of income: the participant's time and that of her family/friends will be ascertained. Family/friends time will be estimated from the proportion of visits where a family member/friend escorted the participant.

Modelling

All modelling exercises will be informed from the data collected during the TAPS study on behaviour, uptake, linkage, retention and medication adherence as well as the costing data. A decision analytic economic modelling approach will be used to look at issues of health system capacity (staff constraints) and equity (poverty analysis using patient-related costs within the cohort). The direct impact on costs and health gains that the introduction of PrEP and ITx might have had on the study cohorts and the service provided in the clinics will be explored.

A population-level transmission model fitted to the South African epidemic will be used, with a special emphasis on transmission within FSW groups with high mobility model focusing on the estimated impact that the introduction of PrEP and ITx might have, should the intervention be scaled up nationally. Population-level data will be gathered from the literature. Outputs of the transmission model will include cost-effectiveness and budget impact measures. A series of scenario analyses might be needed to reflect the different strategies for scale up that policymakers might consider. We will consult all stakeholders (both users and policymakers) during the process of defining the scenarios for scale up to ensure that the most realistic scenarios are tested. We will aim to estimate the reduction in health costs of implementing both interventions. Therefore, we expect savings from infections averted while on PrEP and from less 'other' HIV care if treatment is started early.

ETHICS AND DISSEMINATION

Ethical considerations

As an implementation science research study including human subjects and medication, this study has taken all ethical issues into consideration in line with ICH-GCP (The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) - Good Clinical Practice) guidelines. These include the risks and benefits of taking the study medications as well as the participation in the study itself, the informed consent process, maintaining confidentiality and participation reimbursement. This protocol has been reviewed and approved by the Wits Human Research Ethics Committee (HREC—reference number: 140502) and the Medicines Control Council (MCC—reference number: 20140740), South Africa. The protocol was initially approved by both committees on 8 September 2014, and 15 October 2014 respectively. An amendment was approved subsequently (16 March 2016) following MCC approval of new indication for FTC/TDF and changes in DoH treatment-eligibility criteria.

As this project is not a clinical trial but rather an implementation study, using a product not registered for the relevant indications in South Africa at the time of ethical and MCC applications, the requirements for ethical and MCC approvals were unclear. As with other demonstration projects globally, the project was held to clinical trial

standards during the course of the review with questions about procedure, monitoring and participant support throughout the process. In particular, the project is seeking to evaluate the willingness of FSW's to take up and use PrEP and ITx; therefore, we were strongly committed to delivering the interventions in a 'real-world' context which meant excluding reimbursements for clinic visits. This had to be negotiated with the ethics and MCC committees, where a participant fee was suggested, based on the guarantee of minimal invasive procedures (eg, nothing outside of what would be carried out routinely in a public health clinic) and limited waiting time spent in the clinics. In the end, it was agreed that participants would not be paid given the project was offering new interventions for free on top of routine services, but those participants participating in the IDIs would be reimbursed for transport costs at R50.

Owing to the vulnerable nature of this population, confidentiality was an important factor to incorporate into all aspects of the project, but in particular the design of clinical processes. All staff members, whether in contact with participants or not, were trained on how to maintain confidentiality of participants and all patient files, questionnaire data and specimens are being labelled and managed in such a way to safeguard identities.

Dissemination

A stakeholder engagement plan has been implemented as part of the project, which includes the formation of a sex-worker focused community advisory board (CAB), engagement with officials in the South African health sector both at the national and local levels, engagement with partners and stakeholders at the international level, and continuous community outreach and education including sensitisation trainings for community members and Wits RHI staff. The engagement nationally and internationally has included participation on WHO guidelines committees, South African DoH guidelines committees for PrEP and ITx and the new National Sex Worker Plan, as well as plenaries and other presentations at international and local conferences.

The stakeholder engagement plan also includes the dissemination of information about the study as it progresses through the channels mentioned above, as well as eventual dissemination of results. Once the study is completed, study staff will first disseminate results to TAPS participants. This may be carried out through meetings or SMS. Results will be presented to local health officials and stakeholders at meetings, and then sent out through press releases to other partners.

Finally, investigators will publish the main study results as well as findings from the multiple research components of the study, namely the economic evaluation, qualitative research and other clinical and process data. Results from the study will also be presented at various conferences. We will aim to follow STROBE guidelines in the presentation of results; these guidelines were followed in developing the protocol.⁴¹

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Contributors RE, GBG, WDFV and HR conceived and designed the study. RE, GBG and JM managed the study and data collection. RE, GBG and JM analysed the data. RE, GBG, GA and JM developed materials and analysis tools. RE and GBG wrote the initial draft. RE, GBG, GA, JM, WDFV and HR reviewed the final draft.

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Competing interests GBG, RE, GA and JM declare no competing interests. WDFV has served on Gilead advisory boards; in addition, he is designing a study that requests a donation of a Gilead product. HR was the protocol chair of a microbicide trial involving a Gilead product and has been and is the principal investigator for several trials involving study drug donations from Gilead.

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