Isisekelo Sempilo: HIV prevention embedded in sexual health: A pilot trial to optimize peer *(Thetha Nami)* delivery of HIV prevention and care to adolescents and young adults in rural KwaZulu-Natal.

Protocol Version 5
dated 20th of Jan 2020

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Funders 3ie and NIH

Executive Summary of project

Background: Despite advances in efficacious, efficient and safe biomedical tools to reduce HIV transmission and acquisition the HIV epidemic in South Africa (SA) remains an intractable problem, with the lifetime risk of infection approaching 70% for a 15-year-old girl currently living in northern KwaZulu-Natal Province, the Africa Health Research Institute (AHRI) research setting. This is at least in part due to the difficulty in engaging adolescents and youth in HIV interventions. The demonstration of efficacy of interventions in selected populations has not been confirmed when these interventions have been applied at population level.

We aim to integrate novel advances in intervention design, process evaluation and adaptive trials to answer the question, "will innovative and tailored HIV prevention interventions developed in partnership with young people arrest the HIV epidemic as well as improve wellbeing?" We will use the unique opportunity provided by the AHRI longitudinal population cohort of ~20,000, 16-29-year olds located in the epicentre of the HIV epidemic and in whom we are able to longitudinally measure HIV incidence and health outcomes.

We have used participatory methods with realist process evaluation to develop and tailor the interventions to young people's needs. Findings suggested that young people want us to focus on sexual and reproductive health (SRH), including fertility and family planning, sexual and reproductive infections testing and treatment (not HIV necessarily). The also value peer support and health promotion delivered by people of their own age-group and background. We now aim to assess the feasibility, acceptability, and preliminary effectiveness of multiple interventions using a 4-arm factorial trial within a common intervention delivery platform. This approach will motivate rapid selection of interventions to prioritise for further evaluation or scale-up.

The content of the intervention has emerged from formative work conducted between January – June 2019 that demonstrated acceptability and feasibility of :

1. Delivering HIV prevention within *Thetha Nami*, an area-based peer-navigator intervention to promote and support psychosocial well-being, youth development, social welfare, and sexual health to young people aged 15-29.
2. Adolescent and youth friendly clinics (***Isisekelo Sempilo***) that are linked to existing primary care clinics (PHC). These clinics included fixed buildings situated within urban and peri-urban primary health care clinics, and mobile clinics that visit the peer navigators' areas on a two-weekly basis and are closely aligned with the area PHC clinic. The clinics deliver adolescent-friendly, nurse-led HIV testing, prevention and care integrated with sexual and reproductive health services.
3. Home-based Sexually Transmitted Infection (STI) self-sampling, testing to address the high prevalence of asymptomatic and treatable infections amongst 15-24-year-old men and women living in the study area.

Study design: We will conduct a 2x2 factorial design intervention pilot trial including 1500 men and women aged 16-29-years old and living in the AHRI surveillance area. The study duration will be 18 months. For our primary outcomes of interest, we will assess uptake of comprehensive HIV prevention services, including Pre-Exposure Prophylaxis (PrEP) and Universal Test and Treat (UTT) and the reduction of the proportion of individuals at a population level with infectious HIV (population viral load).

Study Population and Recruitment: Research assistants will approach n=3000 16-29-year old males and females selected from the demographic surveillance area at their homesteads. We expect that 2000 will still be eligible, i.e. aged 16-29 and still living in the surveillance area. Research assistants will provide information about the study to all eligible participants and consent them to the random offer of HIV or sexual health interventions (Table 1) and follow-up with a survey and HIV testing at 12 months. We anticipate that n=1500 [75% (73-77%)] will consent to participate.

Table 1: Summary of interventions

Group	*Name*	*Content*
1	*SOC*	Research assistants refer the consenting participants to ***Isisekelo Sempilo*** adolescent and youth friendly services with HIV testing, treatment if positive and PrEP eligibility screening and offer if negative and family planning
2	*SRH enhanced Isisekelo Sempilo*	Self-collected vaginal and urine samples are collected at enrolment. Research assistants then provide an ***Isisekelo Sempilo*** clinic referral appointment for results, treatment, HIV testing, sexual health, fertility, and family planning counselling, including the personal benefits of ART and Undetectable=Uninfectious among those infected, and PrEP for those eligible and who are negative.
3	Peer-support *(Thetha-Nami)*	The research assistants refer the participant to a *Thetha Nami* peer-navigator in their community. Peer navigators will assess their health, social and educational needs, provide mentorship, and help them access

		the services they need. The peer navigator will facilitate attendance, adherence and retention at the ***Isisekelo Sempilo*** clinic.
4	*SOC + SRH + peer-support*	A combination of interventions 2 and 3, to include both self-collected STI testing, nurse led testing and counseling, and referral to a Thetha Nami peer navigator to encourage clinic attendance and sexual health promotion.

Data. Collection: Over a period of 12 months after randomisation we will collect routine data on uptake of *Thetha Nami* and Clinical Services as well as adverse events. At 12 months we will approach all those who consented at baseline by phone, in their homes or wherever they prefer to be seen. Following Informed Consent we will conduct a brief redcap survey to collect information on uptake and experience of HIV prevention and care services, uptake of contraception and incidence of pregnancy, mental health (using PHQ9), and quality of life. We will also offer point of care HIV testing and linkage to care, collect dry blood spot for HIV ELISA and HIV viral load, and offer STI testing and treatment to all. In addition, we will conduct a mixed-method process evaluation to collect data on uptake and retention and fidelity of each component of the intervention; assess service users and providers and the community experience, i.e. which facets of the package are valued; and any social harms. Finally, a costing analysis will be undertaken to establish the cost of delivering the intervention through the different models of care.

Analysis: With n=1500 we have 90% power to show an increase from 10% linkage to clinical services (current value) in SoC to 22% with the addition of one intervention (peer navigator support only, or SRH only) and 38% in the arm with two interventions (peer support and SRH). We also have the power to detect a reduction of proportion of 16-29-year olds with a detectable HIV viral load from 7% to 3.5% at 12 months.

Our experienced multidisciplinary team of clinical researchers, epidemiologists, social scientists, and biostatisticians will conduct the study over 18 months. By taking a HIV status neutral approach to enrolling participants we will mitigate the effects of stigma on study participation and thus reduce selection bias. By taking a holistic prevention approach - keeping those HIV-ve virus free and identifying those HIV+ve and fast tracking them onto antiretroviral therapy - we will generate high-quality evidence for the effectiveness in reducing population-level risk of acquiring and transmitting HIV. Secondary analysis will look at the effect of the interventions on individual sexual and well-being outcomes. The process evaluation will identify feasibility and fidelity of the intervention components. Ultimately, it will generate evidence on scalable, cost-effective interventions to reduce the impact of HIV on youth in SA.

Background and work leading to trial:

Why is the study needed now: South Africa (SA) has an estimated 7.2 million people living with HIV – the highest number globally; HIV remains the leading cause of death. HIV incidence has remained stubbornly high, especially in KwaZulu-Natal (KZN) where we have shown an annual incidence of 8% amongst females aged 20-24 and 4% in males aged 25-29[1]. There has been considerable progress in developing efficacious and cost-effective HIV prevention tools. These include HIV point of care tests (POCT) and self-tests; the use of daily oral tenofovir/emtricitabine for Pre-Exposure Prophylaxis (PrEP) which can reduce the risk of acquiring HIV by up to 90%[2]; and HIV treatment with antiretroviral therapy (ART) that reduces mortality and eliminates onward transmission of HIV to sexual partners. However, there remains a disparity between the vulnerability of different subpopulations to HIV and their demand for, access to, and support for optimal use of HIV care and prevention tools. Adolescents are particularly vulnerable. While mathematical models of the study setting predict that reaching those aged <30 with PrEP and universal HIV test and treat (UTT) will be most effective in reducing HIV incidence, multiple trials and demonstration projects of UTT and PrEP have shown that those aged <30 are the hardest to reach and retain. In parallel primary health care systems, particularly in rural setting are failing to reach young people with contraception, resulting in high levels of teenage pregnancy.

Effectiveness of PrEP depends on high uptake and optimal use. There are several challenges to delivering PrEP to young people. First, while PrEP is effective, low levels of adherence resulted in no observed benefit in PrEP trials among women in SA. A meta-analysis of 24,000 PrEP trials found that only 34% of participants aged <30 adhered to PrEP[3]. Second, public health clinics are not effective in linking young men and non-pregnant young women to HIV care. The AHRI population cohort (the study site) despite over 94% knowing where to get ART, we consistently find that <50% of 15-24-year olds have tested for HIV within the previous 12 months, with pregnancy being the strongest predictor of HIV-testing in women[1]. In our UTT trial, where community-based testing improved HIV testing uptake fewer than 25% and 30% of HIV positive men and women aged <25 linked to care[4].

HIV programmes in rural SA haven't successfully tackled health and social needs of youth: In the AHRI setting over 85% of school-leavers are unemployed[1]; there are high levels of common mental disorders (CMD) which increase with age (rising to 32% of those aged 20-22). Attempting to reduce structural vulnerabilities through multi-level interventions (social asset building and parenting interventions) has been unsuccessful in reaching older adolescents, those out of school, and those with CMD were less likely to access structural interventions. So, young people are disproportionately affected by both facility-level barriers, such as provider attitudes, financial and time costs of visiting a facility, waiting times and stigma of sitting in a clinic waiting room, and delayed service uptake due to competing priorities. In the meantime, fertility and sexual health remain important for young people.

The burden of Sexual and Reproductive (SRH) morbidity is high in young people: In a 2016 population-based study of 15-24-year olds in the study area we found 20% of women and 10% of men had a curable STI with 75% of these reporting no symptoms, and 40% of the women had bacterial vaginosis[5]. Primary health care systems, in rural setting are failing to reach young people with contraception. In the study area teenage pregnancy levels are persistently high, with an annual incidence of teenage pregnancy of

6.4% (5.7-8.6) (unpublished data) and the majority of young women 15-24 only start contraception after their first pregnancy[1]. The barriers to seeking sexual and reproductive health (SRH) services through health facilities (time and cost of travel, waiting times, stigma and attitude of health care providers) mirror the social costs for seeking HIV treatment in young people. We found that home-based self-sampling and treatment for STIs was acceptable and desirable to young people[5] and forms the basis for creating demand for care and prevention of sexually transmitted HIV within community-based SRH services.

Community-based care can optimise access and support adherence: Systematic reviews have looked at factors influencing uptake, retention and ART adherence, finding that a) community-based delivery of HIV care (e.g. adherence clubs or community health workers) improve both uptake and retention in low and middle-income settings and are cost effective[6,7,] and b) peers are effective in supporting adherence and virologic suppression including amongst adolescents. However, none of these promising interventions have been tested in young adults for HIV prevention outside of key populations, where there is some evidence that tailored, personalized community-based, peer-led approaches are effective[8]. Since then our formative work has found that community-based delivery of HIV care and prevention with peer support are acceptable and feasible.

In summary we have found that:

- The acceptability and feasibility of *Thetha Nami*, an area-based peer-navigator intervention promoting wider psychosocial well-being and sexual health promotion in addition to HIV prevention to young people aged 15-29: over a four month period 24 pairs of peer navigators approached 5872, 15-29-year-old men and women, of which 5272 (90%) accepted the rapid psychosocial and health needs assessment. Based on this they were identified to need referral or support for health needs n=2419; social welfare needs n=395; educational (skills) support needs 2058; and legal and advocacy support n=294. N=3634 were referred to the *Isisekelo Sempilo* clinics.
- *Isisekelo Sempilo* clinics which are adolescent and youth friendly clinics that are linked to existing primary care clinics (PHC) and include clinics situated within two accessible and busy urban and peri-urban primary health care clinics and mobile clinics that visit the peer navigators areas on a two weekly basis and are closely aligned with the area PHC clinic. The clinics deliver nurse-led HIV testing, prevention and care integrated with sexual and reproductive health services. To date n= 337 of those referred from the community (~10%) have attended the clinic.
- The acceptability of home-based Sexually Transmitted Infection (STI) self-sampling, testing and the high prevalence of asymptomatic and treatable infections amongst 15-24-year-old men and women living in the study area[5]

Hypothesis

The evidence suggests that an effective intervention for young people will need to be co-developed with service users and providers to ensure it is acceptable for users and feasible to deliver. Our formative work suggests that 1) The content should focus on fertility and sexual health and 2) the intervention should be community-based and peer-led. We hypothesise that integrating *HIV prevention and care* (including UTT and PrEP) with youth-led services to improve adolescents and young adults *sexual and reproductive health* will improve uptake of HIV prevention and contraception. This will reduce HIV incidence and improve SRH outcomes. The challenges to initiation, adherence and retention of young

people in complex prevention behaviours supports the need to test and refine this hypothesis in a pilot trial prior to full evaluation.

Study setting:

This study will be embedded in Africa Health Research Institute's (AHRI) HIV prevention programme based in the uMkhanyakude district of KwaZulu-Natal, South Africa. Here where we have established an open cohort of > 20,000 16-29-year olds, in whom we are able to measure exposure to HIV prevention interventions, HIV incidence and health related outcomes. Using the setting as a platform for delivering intervention allows us to offer various combinations of interventions and measure the difference in prevalence of infectious HIV (defined as the population HIV viral load – a HIV status neutral measure which captures the dual aims of a holistic HIV prevention intervention -i.e. staying negative if HIV negative and initiation and retention on ART if HIV positive) associated with intervention delivery as well as response to the different components of the intervention on intermediate outcomes such as uptake and retention in HIV care, PrEP and contraception, and drug levels.

The study area is mostly rural and poor compared with other parts of South Africa, with high levels of unemployment (over 85% of young adults aged 20-24 are unemployed). In the study area 8 out of 100 women aged between 20 and 24 acquire HIV in one year and 4 out of 10 women attending antenatal clinics are found to be infected with HIV. Data between 2011 and 2015 in the study area suggests that sexually active women aged 16-29 and young adult men have an HIV incidence above the threshold of eligibility for PrEP. Within this context, the AHRI has developed the largest population-based HIV incidence cohorts in the world. Moreover, through a Memorandum of Understanding with the Department of Health AHRI has also embedded data collection clerks within the public health clinics to capture electronically any clinical attendance and linking it with the surveillance platform on all consenting attendees. This allows us to measure linkage of individuals to HIV care and use of contraceptive services.

Study Goals and objectives

Study aim:

The overarching goal is to arrest the HIV epidemic and reduce its negative impact on young people in SA through *rapidly developing and testing the efficacy and efficiency of tailored HIV care and prevention (including PrEP and UTT) that address demand, optimise access and support adherence in adolescents and young people*. Our aim in this phase of the programme is to integrate exciting advances in participatory intervention development, process evaluation and adaptive trials to explore the hypothesis that, innovative and tailored HIV prevention interventions developed with and for young people will optimize models to deliver HIV prevention and care to men and women aged 16-29 living in a high HIV incidence area of rural South Africa. We will use the pilot to optimize the intervention and understand the relative importance of the different components in supporting the uptake of HIV care, prevention and contraception.

Research questions for the pilot trial

1. Will innovative and tailored HIV prevention interventions developed with young people reduce infectious HIV (measured as population HIV viral load) in 16-29-year-old men and women in rural KZN?

2. Are youth-led models of care effective in increasing demand for ART based prevention?
3. Will delivering HIV care and prevention through sexual and reproductive health services increase demand and improve sexual health?
4. What are the costs of delivering this community-based model of integrated care?
5. Is it feasible to deliver interventions with high fidelity and acceptability?
6. Can we adapt novel methodological approaches to rapidly evaluate the efficacy, sustainability and equity of interventions to reduce infectious HIV?

Specific objectives for the pilot trial:

1. Measure the effectiveness of innovative and tailored HIV prevention interventions developed with young people to reduce infectious HIV in 16-29-year-old men and women in rural KZN
2. Evaluate the effectiveness and efficiency of sexually transmitted infection tests with sexual health focused HIV prevention counselling to increase uptake of HIV prevention in eligible 16-29-year-olds in rural KZN.
3. Evaluate the effectiveness and efficiency of area-based peer-navigator psychosocial support to increase uptake for HIV prevention in 16-29-year-olds in rural KZN
4. Assess the acceptability and feasibility of evaluating the effectiveness of multiple combinations of interventions on reducing infectious HIV using multi-arms within a common platform.

Study Outcome

Primary outcomes

1. Preliminary data on effectiveness of the intervention in reducing infectious HIV measured as the proportion with a detectable HIV viral load (>400 copies per ml) per arm

2. The effectiveness of different components of the intervention to improve demand for HIV prevention and treatment: Measured as the proportion who link to clinical services for HIV testing and PrEP/ART counselling within 60 days per arm

3. The acceptability and feasibility of recruiting and following up adolescent and youth participants in an HIV prevention trial platform.
    a. Acceptability of randomizing to an offer of interventions >75% consent to participate in trial
    b. Feasibility of collecting the population HIV viral load in > 75% in an intention to treat analysis (i.e. of all trial participants irrespective of engagement in any intervention), 12 months after enrollment.

Secondary outcomes

1. On treatment estimates and comparison of the proportion with an HIV viral load that is undetectable per arm
2. HIV treatment outcomes: Proportion with HIV positive test who start treatment per arm; time from randomization to HIV test and treatment initiation per arm
3. PrEP outcomes: Proportion of those eligible (based on the South African PrEP eligibility criteria) who initiate PrEP when tested negative; Proportion who remain on PrEP at the end of follow-up; and proportion of new HIV diagnosis per arm.

4. SRH outcomes: Proportion start contraception; new pregnancy; and diagnosed with any STI per arm
5. The proportion screening positive for mental health outcome per arm
6. Proportion retained, defined as attending at least 3 out of 4 follow-up visits (month 1, 3, 6, 9) and receiving appropriate HIV test per arm

Process evaluation

Process evaluation of the intervention fidelity; description of acceptability of the intervention components (what works for whom and in which context); unexpected adverse events to the individual and community; and what were the sociodemographic patterns of uptake, retention and adherence?

Cost

What is the cost of the comprehensive SRH component? What is the cost of the peer navigator component? What is the incremental cost per additional person starting and retained in UTT and PrEP at 6 months in each of the arms compared to SoC.

The output of this pilot study will be a costed model of ***delivering and evaluating HIV prevention and care through comprehensive SRH for young people (aged <30) living in rural and semi-urban areas of SA.*** We anticipate that this will not only inform a large-scale evaluation of the intervention but will provide SA and other southern Africa health policy-makers with evidence for delivering ART-based HIV prevention, which synergize with their planned moves to shift care for long term conditions into the community. This will fill an evidence gap for delivery models to **tackle unmet SRH needs, including unplanned pregnancies, STIs and HIV in young people.**

Method

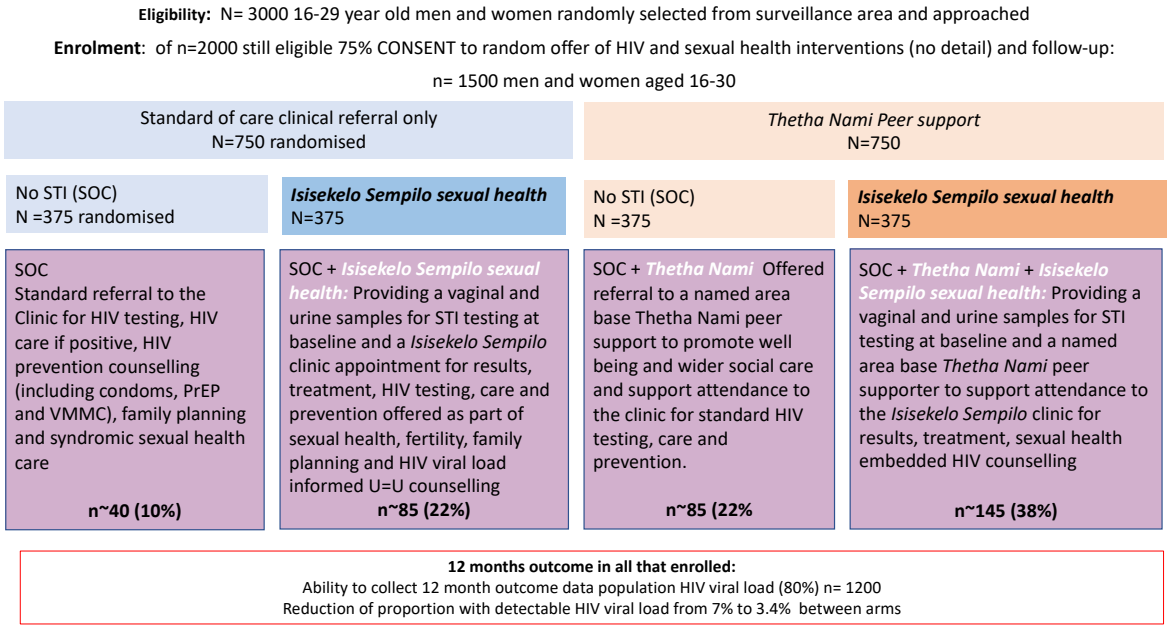
Study design:

We used participatory methods with realist mixed method process evaluation to iteratively tailor the interventions to young people's needs and refine the theory of change (Fig. 3). We will now use a **2x2 factorial design** to conduct a **pilot trial** over 18 months to look at effectiveness of each intervention on uptake of PrEP/ART based HIV prevention and population viral load. This design will allow us to efficiently measure the effect of different delivery models, and of offering a comprehensive SRH package, on a number of HIV care and prevention outcomes, requiring a smaller sample size that in 2 separate trials.

We will use a **process evaluation** of a pilot intervention to evaluate the extent to which the different approaches support *uptake, retention and adherence to ART based care and prevention* in young people using the Behaviour Change Wheel, APEASE (acceptability, practicability, effectiveness, affordability, safety/side-effects, equity) criteria. We will assess which facets of the package are valued and clarify the causal assumptions of their effectiveness. The *causal assumptions* we anticipate are that: 1) individual barriers to uptake of PrEP/UTT and contraception can be overcome through an approach that emphasizes HIV prevention and care as a means to improve sexual health and fertility and 2) the

health system barriers can be overcome through a peer-led approach to strengthen the pathways to safe and effective community-based care as part of wider psychosocial support. Testing the causal assumptions underlying the ToC (*Figure 3*) is fundamental to interpreting the pilot results and informing scalability.

Figure 2: Pilot study flow diagram



Study population:

A random sample of N=3000 men and women aged 16-29 years old from the Population Intervention Platform Surveillance Area will be selected, stratified by sex and approached to participate in the study. Based on our recent experience of recruiting for a nested cohort of a similar age range we will expect that ~2000 will still be eligible i.e. alive, still aged 16-29 and residing in the demographic surveillance area. Of these we expect 75% (n=1500) to be contactable and able to provide informed consent; and willing to be traced at one year. Recruitment and outcome ascertainment will be independent of HIV status. Consenting individuals will be randomized in a 2x2 factorial trial to receive one of two delivery models (clinic referral only or peer navigator support), with or without a comprehensive SRH package, with 375 individuals per arm (Figure 2).

Figure 3: Thetha Nami and Isisekelo Sempilo Theory of change

Thetha Nami and ***Isisekelo Sempilo*** **Theory of Change**				
The problem	Underlying drivers	Mechanism of action	Activities	Level
Continued high incidence of HIV in adolescents girls and young men and women in rural KwaZulu-Natal, South Africa	• External stigma • Unemployment & Mobility • Adolescent transition • Lack of social cohesion • Health facilities not suitable for young people	• Enabling environment • Skills for employability • Educational opportunities • Positive social norms • Social resilience (group efficacy) • Support health care delivery	• Community youth champions • *Thetha Nami* map social services and educational opportunites • *Thetha Nami* mentoring • *Thetha Nami*- youth groups • *Thetha Nami*-led structured activities • *Thetha Nami* delivery of care and follow-up	Society/ community
	• Internalised stigma • Common mental disorders • Low contraception/condoms • Low SRH knowledge (but fertility matters)	• HIV status neutral interventions • Increase SRH knowledge • Address wider health concerns • Increase self efficacy	• *Thetha Nami*: Peer Navigators promote mental and sexual health • *Isisekelo Sempilo:* sexual health embedded HIV status neutral care and U=U promotion	Individual
	• High community viral load in young men and women • Low condom use • STIs and BV are common	• Reduce STIs • Increase uptake and retention in biomed interventions	• *Thetha Nami* adherence support • *Isisekelo Sempilo:* Point of care HIV viral loads • *Isisekelo Sempilo:* STI test & treat	Biological

Study inclusion and exclusion criteria

Table 2: Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Participant must be between 16-29 years old	Participants under 16 years or older than 30 years
Participant willing and able to consent to participate	Participant unable or unwilling to consent to participate
Participant willing and able to be followed up at 12 months and provide a sample for HIV viral load ascertainment	Participant unable or unwilling to be followed up at 12 months or provide a sample for HIV viral load ascertainment at that time
Both males and females can be included	None

Randomisation

A simple random sample (n=2500 eligible men and women aged 16-29) stratified by sex and distributed across the 24 areas will be selected from the demographic surveillance eligibility framework. As explained above and based on our experience of recruiting a sample with a similar age range for our DREAMS impact evaluation we expect to find that 2000 are still eligible, of which 75% are contactable and able to consent. Following informed consent, they will be randomised by sex to one of the four arms.

Sample size calculation

Based on recent studies at AHRI, we expect that 75% of individuals who are approached will consent to enroll in the study (N=1500), and 80% of those enrolled will be followed up successfully at 12 months (N=1200). We estimate that 10% of those in the SOC arm will access clinical services, and 5-7% (overall) will have a detectable HIV viral load.

With 2000 eligible and assuming that 75% consent to being randomized, we can estimate this proportion (i.e. acceptability of randomisation) with a precision of 1.9%. With 1500 enrolled, assuming that 80% of those enrolled are followed up at 12 months, we can estimate this proportion (i.e. feasibility of collecting outcome data in all enrolled participants) with a precision of 2.0%

With 1500 randomised to one of the 4 arms (375 per arm), assuming that 10% in the SOC only arm access clinical services, we will have 90% power to detect an increase in uptake to 22% with the addition of one intervention (peer navigator support only, or sexual health only). We will also have >90% power to detect an increase in uptake from 22% in the arms with one intervention, to 38% in the arm with two interventions (peer support and sexual health).

With 750 allocated to each delivery model (SOC or peer navigation), assuming no interaction between the sexual health component and the peer navigator support, we will have 80% power to detect a reduction in the proportion of individuals with detectable viral load from 7.0% to 3.4%, or from 5.0% to 2.0%.

Study process

The interventions:

During the formative phase one we have worked closely with a team of 57 peer navigators (who have undergone confidentiality training, research ethics, HIV prevention PrEP/ART/SRH clinical training), social scientist facilitators and in liaison with the Department of Health to identify the following intervention components to test in a pilot trial.

Standard of Care (SOC): Clinic based initiation and follow-up with standard HIV prevention and treatment package. Care provided in a nurse led adolescent and youth friendly clinical space linked to the primary health care system. This includes two primary health clinics (PHC) in a busy commercial area with adolescent and youth friendly services (e.g. Mtubatuba and KwaMsane) and two mobile clinics that visit fixed sites across the more remote areas of uMkhanyakude on a once per two-week model. Everyone regardless of randomization arm is offered HIV counselling and point of care testing, immediate initiation of ART if positive and PrEP if negative and eligible according to South African National PrEP guidelines. This is followed by a telephone follow-up at day 7, months 1, 2, 6, 9 and 12 for repeat HIV testing, laboratory HIV viral load or Elisa confirmation, safety bloods, clinic-based counselling and adherence support and PrEP/ART refills (BFC311/18). All clinic attendees are offered family planning support and syndromic management for STIs and if male referral to voluntary male medical circumcision (as per South African National Department of Health Guideline).

Intervention one: *Thetha Nami* peer navigator support (BF515/18) In addition to the SOC at the point of randomisation the participant will be offered the support of a named pair of *Thetha Nami peer-navigators* who work in their area. They will be offered the peer navigators contact details and that unless they object their contact details (name, phone number and place of residence) would be passed onto the named peer navigators who would be attempting to contact them within 7 days.

Thetha Nami are 24 pairs of area-based men and women aged 18-30, post matriculation, who are employed on a part-time basis (24 hours per week) to provide a package of health and social support to youth aged 16-29 living in their areas. They were recruited following written and oral assessments from n=108 men and women aged 18-30 who were selected by their local traditional and municipal leadership to represent the 24 intervention implementation areas. Participants underwent a 16-week training programme which covered: HIV and sexual health information, HIV counselling, confidentiality, ethics and research methods. The peer navigators sit within the AHRI clinical research department and are supervised directly by trained counsellors and are overseen by a professional nurse. They also undergo biweekly team debriefings and ongoing supervision and training. As the peer navigators age out or migrate out of the area, new members are inducted.

During two participatory workshops, participants were divided into small groups of 6-8, moderated by a social scientists, to discuss the vignettes and brainstorm solutions (1st workshop), and map the intervention components to their own area (2nd workshop). The candidate interventions were plotted to a Theory of Change. The *Thetha Nami* intervention that was co-created through this process had the following components:

- Fostering (community-level) positive social norms and resilience through mentorship, youth-groups with structured skills-building and recreation activities; mapping the social services within their communities; and identifying educational opportunities for young people along the life-course,
- Identifying adult champions to advocate on their behalf with community leaders, parents and guardians. Advocate for young people with the department of health, social development and basic education,
- Supporting (individual-level) promotion of sexual and mental health, self-efficacy, and health literacy and
- Supporting retention and adherence through provision of peer support as community lay counsellors and supporting 3 monthly ART/PrEP/contraception refills, with or without HIV status neutral adherence clubs to those who accept.

Intervention 2: *Isisekelo Sempilo* with SRH: At the point of randomisation the research assistants will provide the participants with STI self-sampling at enrolment. This will include STI testing for *gonorrhoea and chlamydia* and *trichomonas* on 3-4 self-taken virginal samples (women) and a first catch urine (men). The samples will then be labelled with a unique identifier and the bar codes scanned into red-cap and sent by the research assistants to the laboratories in Durban. Participants will be provided with a clinic appointment at a clinical space most convenient for them in 7 days to receive their results. They will be informed that if they default the appointment and any of the results are positive a nurse or research assistant will attempt to contact them by phone or in person to ensure that they and their partners receive the appropriate therapy to treat the infection.

During the clinic appointment they will receive counselling around sexual health, fertility intention, contraception, HIV counselling and testing as part of sexual health counselling with PrEP to stay negative and ART in the context of staying well and Undetectable = Uninfectious. They will also receive aetiological treatment and partner notification if any of the STI or HIV results are positive. Everyone regardless of randomization arm is offered HIV counselling and point of care testing, immediate initiation of ART if positive and PrEP if negative and eligible according to South African National PrEP/ART guidelines. This is followed by a telephone follow-up at day 7, months 1, 2, 6, 9 and 12 for

repeat HIV testing, laboratory HIV viral load or Elisa confirmation, safety bloods, clinic-based counselling and adherence support and PrEP/ART refills (BFC311/18). The three-monthly follow-up and adherence support in this arm will include in addition to SOC HIV viral load-based U=U and adherence counselling prior to PrEP/ART refills.

Eligibility screening and recruitment

Study Enrolment: Using procedures that we have used in recruiting for our DREAMS nested cohorts[1] research assistants will approach eligible individuals in their home or a place of their choosing. They will complete a brief eligibility screening questionnaire on RedCap (confirm they are the person randomised, age 16-29, and able to consent). They will be provided with information, i.e. that they have been randomly selected and will be offered a variety of health interventions that they can choose to uptake if they want. HIV testing at baseline is not a condition of participating, however they need to agree to be followed up 12 months following consent to provide a dry blood test for HIV testing and HIV viral load, a POCT HIV test would be offered at the same time. Irrespective of whether or not they consent to the study individuals who test HIV-negative will receive counselling around the benefits of PrEP and HIV-positive individuals will receive counselling around the benefits of immediate starting of ART. Following informed consent, the participant will receive a unique study id and id card. They will be asked to complete a brief enrolment questionnaire, to be completed within REDCAP on a tablet. This will include the date of recruitment, and the id of research assistant who recruited them their area of residence; name, ID (DSID or SA national number), and telephone contact and basic demographics (age, gender). Following which the tablet will reveal the individuals 2X2 randomisation and related participant information sheet. The research assistant will then proceed to explain the intervention/s that the participant is being randomly offered and seek their consent for each component.

1. Standard of Care (SOC): The participant will be provided with information about and a bar-coded referral slip to a clinical space linked to a primary health clinic (PHC) they can attend – either in a busy commercial area with adolescent and youth friendly opening times (e.g. Mtubatuba or KwaMsane) or *nurse-led mobile clinic test* that visits fixed sites across uMkhanyakude on a once per two-week model where they can receive HIV testing and family planning and start ART or PrEP with three monthly follow-up and refills at mobile clinic. If they agree the bar code will be scanned into the tablet.
2. *Thetha Nami* Peer navigator support: The participant will be provided with information about the peer navigator team that are allocated to their area, and informed that unless they object their contact details (name, phone number and place of residence) would be passed onto the named peer navigators who would be attempting to contact them within 7 days. If they agree the details of the peer navigator will be entered into the REDCAP survey on the tablet and the participant details will be electronically shared with the peer navigator. The peer navigator will then contact them within 7 days and provide them with any support they require including supporting them to access the clinical service they have been referred to. They will use a brief *service recipient questionnaire* to be completed within REDCAP on a tablet to identify the participants needs and services required, including the clinical service they are allocated to and the support needed.
3. *Isisekelo Sempilo* with SRH: The participant will receive information around sexual health and STI testing by the research assistant. If they agree to both the testing and being contacted with the results and treatment for the testing they will be provided with a barcoded kit that contains 3-4

self-taken vaginal swabs or urine to test for *gonorrhoea and chlamydia* and trichomonas on self-taken virginal samples (women) and urine (men). The bar codes will be scanned into the tablet. If the participant is willing, they will provide the samples to the research assistant who will label them and return them for testing. The participant will be informed that they need to attend the clinical services to receive the results and treatment. They will also be reminded that if they default from the clinic and they have an untreated positive laboratory result then a study nurse or research assistant will attempt to find them, by phone and in person to deliver the antibiotics needed and to organize partner notification.

4. ***SOC + Thetha Nami*** + ***Isisekelo Sempilo with SRH:*** The research assistant will sequentially introduce both intervention 2 and 3 above.

Clinical Follow-up SoC: Participants who agree will undergo arm specific clinical screening for PrEP eligibility and ART. Screening is based on the South African National guidelines for HIV care and PrEP and includes Point of Care (POC) tests for HIV, creatinine to assess renal function and Hepatitis B, with vaccination offered to those who are negative, pregnancy test for women and sexual behaviour questionnaire to assess eligibility. Patients who are eligible for PrEP will be started in the three clinics that are currently providing PrEP (the mobile vans or the fixed urban adolescent and youth friendly clinic). Everyone will receive contraception; condoms; and HIV negative men are also counselled around the benefits of voluntary medical male circumcision (VMMC) and referred accordingly. A professional nurse will initiate PrEP or ART usually on the same day. The nurses or clinic-based counsellors will provide counselling on adherence and develop an individualized adherence plan.

If the participant agrees to immediate PrEP/ART initiation, s/he will be issued with a month's supply of generic tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) or ART. Baseline and follow-up bloods will be taken and processed as per national guidelines; The professional nurse will register the participant at the clinic (or update the record if the participant is already registered) so that the participant's records are available should the participant seek care there. Participants will receive a phone call seven days after initiating PrEP/ART to complete a standard symptom screen for adverse effects and be referred to clinic for care if necessary. Participants will have a clinic appointment scheduled one month, after PrEP/ART initiation, as per national guidelines; appointments for refills and monitoring will be at two and then three-monthly thereafter. Neutral text message reminders will be provided for participants who have access to private messaging and phone calls. Contact information will be provided for the clinic which participants can contact at any time.

Patients randomised to ***Thetha Nami*** will be offered their peer navigator support as part of their individualised adherence plan and to support the refills and/or appointment scheduling and reminders. It will be made clear that this referral is conditional to the participant agreeing and can be HIV status neutral.

Participants randomized to ***Isisekelo Sempilo*** arm will at first and subsequent visits receive in addition to SOC, the results (and where appropriate treatment) of their STI test and tailored sexual health counselling with an emphasis on tackling the multiple health-related behaviours that will affect fertility and sexual pleasure (STIs, mental health, alcohol, diet and exercise); partner notification if found to have a curable STIs and/or HIV; assessment of fertility desire and as appropriate preconception or contraception counselling; a choice of contraception and condoms. Those who are HIV positive will have HIV viral load result informed additional adherence and U=U counselling.

Referral to the clinic for symptoms and clinical events: Participants will be encouraged to visit the clinic

for medical concerns outside of the study. During participant resupply and monitoring visits, they will complete a standardized symptom screening questionnaire for adverse effects of PrEP as per South African clinical guidelines. Further, all participants will receive regular creatinine tests to monitor their renal function. Participants who have severe (grade 3/4) adverse effects, according to the DAIDS guidelines (https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-%28daids%29-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2) and serious adverse effects, will be referred to the clinic for medical evaluation. All participants who experience adverse events will receive follow-up until the adverse event is resolved. The study Clinical Monitor, based at AHRI, will review all severe (grade 3/4) and serious adverse events to ensure follow-up and reporting. This will include any adverse events recognised through the community-based process evaluation or the community engagement unit.

Follow-up for outcome ascertainment: All participants (including those who do not initiate PrEP or ART) will be traced at 12 months after enrolment. Following informed consent they will undergo a 20-30 minute interviewer administered REDCAP survey in IsiZulu, based on an existing survey tool that has been used in our DREAMS impact evaluation (ethics registration). Sensitive questions in this survey are self-filled. Questions will include HIV prevention and care service awareness, uptake and experience, condom use, contraception uptake, pregnancy, mental health (using PHQ9) and quality of life. Following this they will be asked to provide a DBS for HIV Elisa testing and HIV viral load if positive. Everyone will also be offered STI testing and a point of care HIV test and referral to a clinical service of their choice according to a protocol that we have been using.

Process evaluation:

We will use mixed methods including self-filled questionnaires by participants; programme data to quantify the uptake of each component of the intervention; and the recorded activities by the intervention teams. We will conduct in-depth interviews with participants (n=40; 20 per gender and 10 per arm); and intervention delivery teams; nurses/clinical research assistants (n=6); research assistants (n=5) and peer navigators n= 10; conduct natural group discussions with community group and intervention delivery staff (n=7; 1 with clinic staff, 2 peer navigators groups and 4 community groups [older men, older women and younger men and younger women]). A satisfaction survey will be administered as part of the end-line survey. The process evaluation will explore the following:

- Acceptability / experience.
- Feasibility
- Reach/coverage – for whom it worked and didn't work
- Fidelity

Cost

We will measure the costs in both interventions and control arm, to compare the two arms in their cost in achieving endpoints, i.e., cost per case linked to PrEP (HIV-) and cost per case linked to ART (HIV+). To establish costs, we will use a top-down costing approach using the study budgets and expenditure reports.

Data Collection Methods

This study employs the following data collection methods:

(1) Participant Survey and Clinic Linkage

A short survey (described above under enrolment and procedures) will be administered to consenting people participating in the study. The questionnaire will be used to collect data on participant's demographic info and two levels of randomisation identification. The data will be captured on REDCAP on a tablet. The survey will take approximately 5 minutes to complete and will be administered in both English and isiZulu.

The primary outcome of linkage and follow-up by ITT analysis will be measured through identifying the consenting eligible young people who link for PrEP/ prevention counselling or ART initiation. We will use the bar coded referral vouchers as well as other identification within REDCAP to confirm linkage. Using bar coded vouchers and the ClinLink software which is used in all the clinics in the demographic survey area and has been effective to data in linking individuals in the surveillance area when they attend clinic. We will use an algorithm to identify which arm the individual came from, including the bar code on the coupon they bring, their name, age, phone number, id number, area of residence, and the identity of the researcher that recruited them.

The primary outcome of population viral load will be collected from all consenting and contactable participants 12 months after enrolment using the REDCAP survey and Dried Blood Spots as described above. Secondary intervention exposure, sexual health and mental health outcomes will be collected through the same tool.

(2) Programmatic Data

In addition to the questionnaire, we will collect the programme data records from the clinical tool and the peer navigators daily reporting of their outreach activities and the clinical programme data. We will use the programme data in an aggregate way (disaggregated only by gender) to understand the reach and coverage of the programme and compare that with those who link to care.

(3) Participant in-depth interviews (IDI) and group discussion

IDIs will be conducted peer navigators (n=10), AHRI nurses/clinical research assistants (n=6) stationed in clinics in the participating communities, trackers (n=5) and a purposive sample of young people aged 16-29 years (n=40; 20 per gender and 10 per arm). The interviews will be conducted by ARHI trained fieldworkers including a senior social scientist in English and isiZulu and will take approximately 60 minutes in length depending on the participant's responses, and this will enable the researchers to understand, contextualize and explore some of the issues around the trial. To limit disturbances and ensure privacy, the IDI will be conducted in a private space suitable for the participant, and audio recorded with interviewees' consents. We will conduct natural group discussions with community group and intervention delivery staff (n=7; 1 with clinic staff, 2 peer navigators groups and 4 community

groups (older men, older women and younger men and younger women). We will ensure representativeness of both sexes in both IDIs and group discussions. The group discussion will contain 6-8 people and will last approximately 120 minutes. Prior to the interview, participants will be encouraged to use pseudo names instead of their real names to ensure anonymity. Also, participants in group discussions will be encouraged to respect individual's opinion and confidentiality where necessary.

DATA COLLECTION PLAN

Data Collection Team

This study will be managed by the project research team at ARHI. Depending on need, the data collection team will consist of AHRI trained research assistants and trackers; and ARHI trained social science research assistants. Data collectors will be selected based on their experience with both quantitative and qualitative data methods.

Data Collection Training Requirements

The data collectors will undergo a 2-day training which will include the following content:

1. ***Protocol training***: this entails the study objectives, the administration of the short survey and IDI guide as well as participant confidentiality and voluntary participation.

2. ***Redcap training:*** This will cover familiarization with survey questions and how it can be captured successfully on Redcap. This will also involve data quality, fidelity and analysis exercise.

3. ***IDI Data Collection refresher training:*** this covers IDI guide content, including training on probing and interview techniques in order to collect quality data. The IDI guide will be available in English and isiZulu, and the training of interviewers will entail a question-by-question discussion exercise as well as relevant terminologies to be used. This process will be led by the Senior Social Scientist.

Approvals

Institutional Ethical Review Board

Ethical approval will be sort from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC) and University College London (UCL) ethics board.

See section Ethics and Informed consent

DATA MANAGEMENT

Electronic Capture of Data and Storage of Electronic Data

Data collectors will administer the short survey using tablets thereby ensuring capturing of real time data. The questionnaire will be loaded onto REDCap and will be accessed for data collection as an application on the tablet. The data management system for these will be based on REDCap (research electronic data capture) developed at Vanderbilt University. The REDCap database resides within a single MySQL database server within a secure server cluster at the Africa Centre. Laboratory data collected for the trial will be output electronically directly from the analyser and imported into the database. Data extractions will be converted to Stata for analysis. Data can be extracted in a variety of formats for analysis. Qualitative data will be stored in the form of Word files or in Excel both of which can be uploaded into Nvivo qualitative data management and analysis programme; the use of MS Word will ensure that data can in future be shared for use in different analysis programmes. These files will be kept on a secure access-controlled folder on a file server at AHRI.

Hardcopy Data and Storage

All study-specific data will be stored on a server at AHRI, access to which is strictly controlled. Users are given individually-tailored access only. AHRI has a comprehensive set of SOPs covering the use, validation and security of their computer systems. To avoid loss of data during power fluctuations, servers are installed with stable UPS batteries, with a standby generator in case of power cuts. The server is backed up daily with twice weekly off-site backups. While the study is in progress, study-related forms will be maintained in locked cabinets; access to these cabinets is limited, at study conclusion these documents will be digitized, and the original paper documents destroyed. Digitized document images are indexed and stored indefinitely on the central server. Identifying information will be held by the field team and not kept with the questionnaires. Study-specific electronic laboratory results will be transferred directly from the LIMS. These data will be stored on the AHRI server after transfer. Qualitative data will be managed, stored and archived in consultation with the data manager

Audio Data and Storage

The IDI will be tape recorded after prior consent has been obtained from the participant. The audio files will be stored on password protected ARHI PCs and only authorized personnel will have access to them. It is important to mention that audio files will be used for the purpose of this study only. Once the audio files have been transcribed and translated and quality controlled they will be destroyed.

Formal information/data security standards

Physical security is maintained through access control for all rooms where data are held. The Institution use industry standard malware and intrusion detection with at least annual penetration tests by a reputable outside security audit company. A software update policy ensures that all operating, data management and malware detection systems are up to date. All servers use a two tier uninterruptable power supplies (UPS). Tier 1 UPS allows switch-over to a local diesel-powered generator, Tier 2 UPS allows for controlled shutdown of all servers if both Tier 1 and generator backups fail. Data on mobile devices are encrypted and unlocked through individual passwords. Communication with the data repository use secure SSL encrypted links. All data will be anonymised. Any personally identifiable information (including names, identity numbers, address, geolocation data, telephone numbers) will

be stored in a separate data enclave in the database with restricted access and identified by separate identifier.

Main risks to data security

i. Physical loss of device/data. Mobile devices can be lost or stolen, this risk is managed by encrypting devices and daily logging individual participant records so that data can be recollected in the case of a device being lost before the data is synchronised. Risk: Low.

ii. Unauthorised system intrusion and data theft. Intrusion detection systems are in place with annual audit by an external security auditor. Risk: Low

Identity or attribute disclosure risk. Datasets will be assessed for disclosure risk using SDCMicro prior to release on the institutional data repository. Risk: Low

Data for sharing

Anonymized quantitative data-sets collected in the study will be suitable for sharing. Sharing qualitative transcripts is more challenging. However, we are committed to open access data and so we have developed systems described below to support researchers that may want to use the qualitative data to answer research questions.

Discovery by potential users of the research data: The results of the study will be published in a peer-reviewed journal. Potential users of the research data will be able to contact the investigators for further information. Furthermore, in accordance with the AHRI Data Sharing Policy, the data will be registered with the AHRI Data Repository. Details of the project and data collected will be available through a URL that will be cited in published papers.

Governance of access: The data custodian at AHRI has the administrative control over granting access to the data to researchers. Anonymized electronic quantitative datasets will be archived and made available to interested external researchers under a data-sharing agreement, after a period of use by the study team. Interested researchers will be required to submit a proposal to use any data for independent analyses. Applicants will be asked to state their analysis objectives, demonstrate they have the capacity to conduct the intended investigations, and to show they understand the local study context to be able to interpret the results appropriately. Qualitative data is more challenging to anonymize. Investigators who are interested in using existing data to answer research questions will be asked to submit letters of intent, with an AHRI named Faculty member as a collaborator. If approved the study would have to undergo relevant IRB and ethical review processes. If analysis is to be undertaken, qualitative data will be stripped of any information that can identify participant before sharing. All data sharing, even those without identifiers, will be through a secure and password-controlled data sharing site, with access strictly limited to transcripts that are relevant to the analysis planned. Requests for data sharing are reviewed by the data custodian and a Data Sharing committee at AHRI. All AHRI staff are bound by the AHRI Data Access Policy, which prohibits any sharing of data with third parties, unless a formal Data Use Agreement has been signed with the third party. For all

analyses, AHRI researchers sign a specific Data Use Agreement that defines the analyses to be undertaken.

The study team's exclusive use of the data: The study team will have exclusive use of the data for 2 years after the study and/or once the primary analysis of the study has been published, whichever comes first. Data may be made available sooner at the discretion of the investigators, where this does not conflict with the publication plans for the study. After the period of exclusive use, data will be made available to potential new users on request.

Restrictions or delays to sharing, with planned actions to limit such restrictions: Data sharing will follow the procedures outlined above. All data available for sharing will be anonymized. Consent forms will include a statement to inform study participants that their data may be shared with other users for secondary analyses, with the goal of advancing knowledge

Regulation of responsibilities of users: Users will be asked to abide by the AHRI Data Access and Sharing Policy.

DATA ANALYSIS

Participant Survey

The data from the client survey captured on REDCap dashboard will be exported into STATA, cleaned and analyzed. Descriptive analysis will be performed. Identified variables captured via programmatic monitoring tool will also be exported and analyzed using STATA to compare data and linkage to care.

A detailed statistical analysis plan will be completed prior to the end of data collection

In-depth Interview and group discussion

Data from the IDIs and group discussions will be managed using NVIVO software. The software will be used for categorization and coding of identified themes from the interview transcripts. Identified themes (including participants' quotes) and interview transcripts will be reviewed and compared by the research team for inconsistencies and adequate representation of participants' comments. Emerging themes that address the key focus of the study will be examined and analysed following an interpretivist approach.

ETHICAL CONSIDERATIONS

All staff (including peer navigators) will be provided with training on research ethics such as confidentiality, voluntary participation and good clinical practices. We will ensure anonymity and confidentiality at all levels of the research process, and none of our reports, presentations or articles will contain study participants identifying information. Pseudo names will be used when reporting the data particularly qualitative data. Each participant will be assigned a unique non-identifying participant identification number. Prior to their involvement in the study, participants will be provided with adequate information about the study and they will be allowed to ask questions for clarifications. Voluntary informed consent will be ensured once participants have the full understanding of the study procedures and a copy of the signed consent form will be given to them. Also, participants will be informed about the importance of the confirmatory diagnostic testing. The study will conform to the ethical guidelines and standards of ARHI, UKZN, and UCL.

CONFIDENTIALITY

All staff (including peer navigators) will be provided with training on research ethics such as confidentiality, voluntary participation and good clinical practices. Each participant will be assigned a unique identifier to be recorded on all questionnaires and samples. Study-specific data will be captured electronically using tablets. Study participants will not have their names used during any stage of data collection except in consent forms, which will be electronic and kept securely in password controlled, encrypted and secure data havens. The data management system for these will be based on REDCap (research electronic data capture) developed at Vanderbilt University. The REDCap database resides within a single MySQL database server within a secure server cluster at the Africa Centre. Laboratory data collected for the trial will be output electronically directly from the analyser and imported into the database. Data extractions will be converted to Stata for analysis. Data for individuals surveyed in health facilities are similarly captured on REDCap using tablets and stored. Data can be extracted in a variety of formats for analysis. Qualitative data will be stored in the form of Word files or in Excel both of which can be uploaded into Nvivo qualitative data management and analysis programme; the use of MS Word will ensure that data can in future be shared for use in different analysis programmes. These files will be kept on a secure access-controlled folder on a file server at AHRI. All data will be anonymized at the time of transcription with names of respondents replaced by a unique anonymized participant identifier. Any names of other persons mentioned during interviews/discussions will be recorded in the text with a single initial. Names of areas will be replaced with the general location (district or ward). We will ensure confidentiality at all levels of the research process, and none of our reports, presentations or articles will contain study participants identifying information. Pseudo names will be used when reporting the data particularly qualitative data.

INFORMED CONSENT

Prior to their involvement in the study, all the randomised participants aged 16-29 and in the case of those aged 16-17 their parents or guardians will be provided with adequate information about the study in both written and oral form from the research assistants about the study and they will be allowed to ask questions for clarifications. In the first instance they will be asked to consent to two

things only: 1. To receive an offer of sexual health, peer support and HIV care and prevention intervention and 2. Consent to be followed up at 12 months for an end-line survey on health service uptake, sexual and mental health, experience of the intervention and provide a sample for HIV testing and viral load. If they agree have the full understanding of the study procedures and they are aged 18-29 written voluntary informed consent will be taken and a copy of the signed consent form will be given to them. If they are aged 16-17, they will provide assent and written consent will be taken from their parents or guardians. In addition their parents or guardians will be informed of the clinical services that are available in the clinics, sexual health, HIV testing, ART and PrEP and will be asked if they consent to their child receiving these services at the clinic (with or without their attendance). The second step of consent will be after the randomisation is revealed when participants will be asked if they agree to each component of the intervention that they have been offered. 1. Clinic referral; 2. Peer navigator contact, and 3. STI self-sampling and notification of results if they do not attend clinics.

If written consent is required, the investigator will first provide the potential participant with an explanation of the study as well as an information sheet with study details. The investigator will also explain that any individual-level data collected by the study may be shared publicly but will not contain the name of the individual. The investigator will answer any questions raised by the individual and allow them sufficient time to come to a decision. Participants will then be required to give consent. In cases where participants are illiterate, they will be asked to give verbal consent plus a thumb print certified by a witness. The study will conform to the ethical guidelines and standards of ARHI, UKZN and UCL.

Respect for Autonomy: potential participants have the right to make an informed decision whether or not to participate in this study. Voluntary participation will be ensured, and we will provide participants with the required information such as detailed information sheet and informed consent document prior to commencing any research activity. The research assistants will be available to assist with reading and understanding the informed consent if needed. At this point the individual can decide whether or not to participate in the study. If they decide to participate in the study, participants and research assistants must sign and date the informed consent form, as written proof. The information sheet and informed consent will be provided to individuals in English and isiZulu and they will not be disadvantaged in any form if they do not want to participate in the study.

Justice: it will be stated clearly to participants that their refusal to participate in the study will not affect them or any other health related services they are currently accessing.

COMPENSATION

None will be provided to the participants in the trial. Participants of semi-structured interviews will receive refreshments and be reimbursed for any travel costs.

Trial management and oversight

Day to day management of the trial will be supervised by the PI (Shahmanesh) and the trial co-ordinator (Natsayi Chimbindi) and her project management group which includes: *Carina Herbst (deputy project*

co-ordinator); Eskindir Shumbullo (trial statistician); Jaco Dreyer (Data Manager), Nonhlanhla Okesola (clinical co-ordinator); and Oluwafemi Adeagbo and Thembelihle Zuma (social science

We will establish a trial advisory group with clinical trials, PrEP, and statistical, and social science expertise to oversee the trial. This is a pilot effectiveness trial of different models of service delivery and all tests and drugs used are approved for clinical use in South Africa. All clinical care follows South African clinical guideline. The risk of harm is anticipated to be low. However, a sub-group of the trial advisory group will also oversee the data safety and monitoring (DSMB) aspects of the trial.

ADVERSE EVENT REPORTING AND MANAGEMENT

STI and HIV testing and PrEP is well established and known to have a high level of safety. However, harmful reactions can occur.

AEs and Serious Adverse Events (SAE) will be captured through the process evaluation, community engagement units and community advisory boards, the hotline, as well as the peer navigators and clinic staff and logged using our incident reporting form for up to up to 18 months after the start of the intervention. Reported AEs and SAEs will be monitored, categorized based on an established grading system, and followed-up accordingly by AHRI.

The Standard Level of Serious Adverse Event will be used for reporting the following to study leadership within two working days of becoming aware of the event:

- All deaths.
- All disabilities/incapacities.
- All hospitalizations that are “suspected adverse drug [procedure] reactions” (cannot rule out relationship to study procedures).
- All other Grade 4 events that are “suspected adverse drug [procedure] reactions” (cannot rule out relationship to study procedures).

SAEs will be logged, with the Clinical Monitor and Principal Investigator evaluating the SAE for seriousness and likely relationship to the intervention. Related SAEs will be reported to UKZN and UCL Ethics Review Boards. All SAEs will also be reported though six-month progress reports to Trial Advisory Group members and local and international collaborators. Annual reports with full listings of SAEs will also be submitted to Ethics Review Boards.

Risk and Benefits

There are no significant risks for potential participants in this study. The following risks are discussed with mitigation plans:

Biological risks: Vaginal swabs and urine tests if used correctly, it will be painless. Pictures on how to use the swabs are provided in isiZulu in the accompanying pamphlet to show the correct use. Previous study by the PI in this area found that home based self-sampling in this age group was highly acceptable and feasible[5].

Psychological risks: There are potential risks to becoming aware of one's HIV status. People who learn that they are HIV-infected may suffer from mental stress and depression as a result. They may also be stigmatized by their family and community and may, despite legal protection, be discriminated against. In order to minimize the risk of mental stress and stigma, HIV testing will be provided to individuals only within the context of voluntary clinical testing. A hotline linked to a couple of stand-by AHRI nurses will be created and other referral information will be provided. Information on referral channels for under 18's, will be provided and peer navigators will be trained to deal with that.

Social Risks: Our field staffs have been trained in sensitive data collection and confidentiality. To minimize risks of psychological and physical harm, all staff have completed additional training on working with young people at risk of HIV and child protection procedures. Additionally, all health care workers employed by the study, including the peer navigators and all facilities receiving referrals of study participants for treatment have received cultural and clinical competence training by trained AHRI team members, to address stigma reduction and specific health needs for adolescent girls and boys.

Data collection in public places is conducted through general, non-personal conversations and discussions about general community issues (not only related to HIV and sexual health) and any interviews that may be of a more sensitive nature will be conducted in a private and secure. In all communications with participants outside of the interviews, surveys, or other study activities, the investigators will not mention HIV. During phone calls and through text messages, the staff will only speak to the participant and will not leave a voice message or a message with another person. If necessary, the staff will simply call back another time. When the study is mentioned over the phone or text messages sent as part of the case management program, direct references to HIV will not be included. Phone numbers utilized to send SMS support messages will be recorded but will be kept in the link-log as well and any messages sent to study participants will not disclose anything about the participant should someone else be using his/her phone.

We will build on our close relationship with the community and our community advisory board as well as our peer navigators to ensure that our study design, all the study tools, and the ways in which we approach, and recruit are appropriate and acceptable.

If any study participants express the need for emotional support during or after the survey, interview, they will be referred to trained AHRI psychologist and/or counselors.

Study participants can leave the study at any time and continue to receive care through our clinical services. We have a close relationship with the MoU and will ensure that systems are in place for transition in and out of the study.

Legal risks: We have extensive experience of undertaking research in the research area including HIV testing and linkage to care and we have very rigorous system to ensure confidentiality. All data will have unique numerical identifier and no personal identifying data or information. Any items with personal identifying features such as consent forms will be kept separate from the research data as described under data management.

Financial risks: no financial risk for participants

Having mentioned the above risks, the study's is very important and timely given that HIV incidence rate is high in our environs. The benefits of this study outweigh its risks.

Child protection issues: For the purposes of this grant we will not be recruiting anyone under the age of 16. The field workers and research team are trained in issues related to child protection and clear standard operating procedures are in place to guide the research teams as to what they should do if any issues of concern are raised. These include appropriate referral pathways within the AHRI to social workers, psychologist and trained counselors, and in liaison with the Department of Social Welfare or the Department of Health clinics. As has been our practice to date the research and clinical teams will undergo regular debriefing with the project management team and child protection issues will be discussed and overseen by the clinical governance team and a dedicated child protection lead at AHRI.

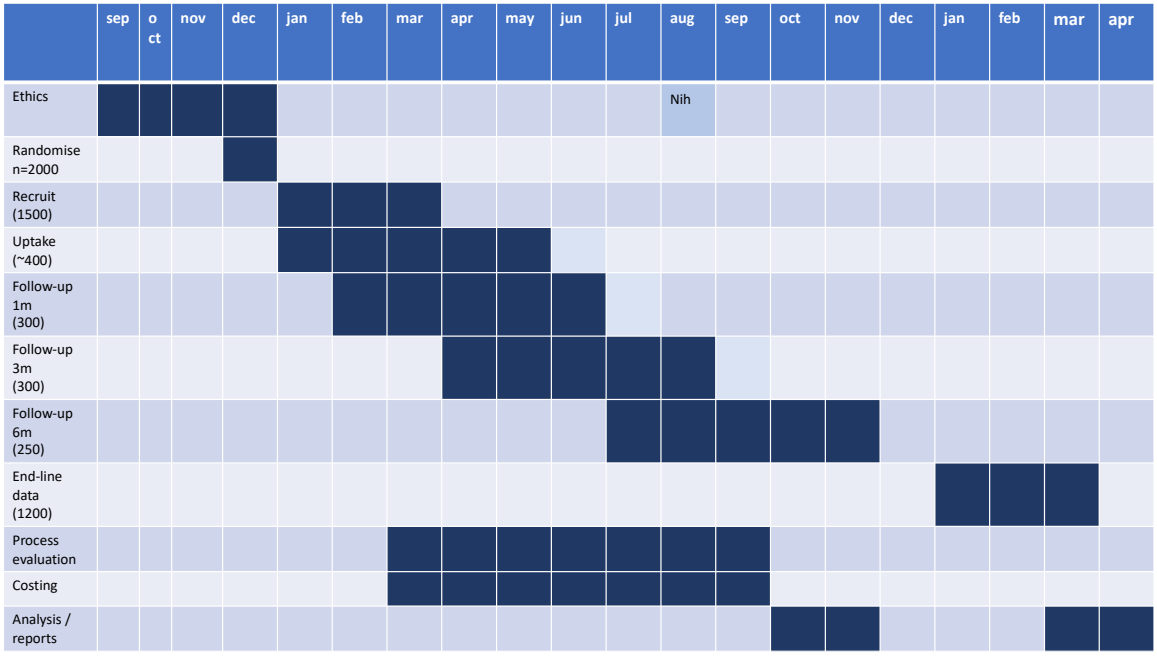
DISSEMINATION AND USE OF STUDY FINDINGS

The results of the proposed study will be disseminated through traditional academic channels (journal publications) as well as on different information dissemination platforms such as conferences, workshops and symposia. Particularly, the findings of this study will be documented in form of success stories, reports as well as articles in accredited peer reviewed journals. This will also be presented at both national and international platforms.

The following steps will be undertaken to ensure the dissemination of the findings of the study:

- The study report will be shared with stakeholders from NDoH, ARHI, community advisory boards (CABS) and other partners.
- Presentation of findings in local and international conferences/symposia/seminars and through academic and non-academic articles.

TIMELINE



Output: The findings of this grant will inform the scale up of community-based sexual and reproductive health interventions optimized to support the uptake and retention of adolescents and young adults in long term HIV treatment, HIV pre-exposure prophylaxis and other prevention, and contraception. This will potentially harness the full HIV incidence and mortality reducing potential of antiretroviral therapy.

Risk mitigation

We are aware that introduction of multiple interventions during scale up, may make it challenging to isolate the relative effect of the different components of our intervention compared to the wider intervention implemented in this setting. We will mitigate this by having randomised individual to each component and by documenting each step in the chain between exposure to the intervention, demand for SRH and HIV prevention services, uptake of services, and health outcomes, as a way to build plausibility for the intervention effect. Moreover, we will conduct a detailed process evaluation to understand the fidelity of the intervention and any unexpected adverse events.

Disclosure of abuse or violence: Clearly this is a risk in any study where we ask young people about sexual behaviour and sexual health. We will mitigate this by providing clear referral pathways and training to all field workers on this and the AHRI child protection protocol. We will create an incident reporting format similar to that used in clinical settings that will be reviewed by the project management team and will be shared with the investigators on a quarterly basis. These reports and discussions around them with the field teams and counsellors will be fed back into the research team and be used for awareness raising and further training.

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