*Isisekelo Sempilo* 2x2 factorial randomised controlled trial of the effectiveness of integrating HIV prevention within sexual reproductive health (SRH) services with or without peer support amongst adolescents and young adults in rural KwaZulu-Natal

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# Keywords

Peer navigator, HIV prevention, community-based care, contraception, Pre-Exposure Prophylaxis

**Evidence before this study**

Prior to our trial the evidence showed sub-optimal uptake of PrEP in southern Africa, in part due to challenges to identify and create demand amongst those adolescents and youth who would most benefit from HIV pre-exposure prophylaxis (PrEP). The consolidated WHO differentiated and simplified PrEP for HIV prevention technical brief (2022) and a recent (2023) scoping review of delivery models to promote PrEP uptake adolescent girls and youth found that offering PrEP through family planning or antenatal and postnatal services improved uptake of PrEP for adolescent girls and young women, and community-based delivery was preferred by both young men and women. The high unmet burden of curable sexually transmitted infections (STIs) amongst adolescent girls and young women PrEP users in Africa, and the concerns around unmet sexual and reproductive health needs raised by the community in our setting, suggested STI testing as an effective way to engage and attract sexually active adolescents and young adults to PrEP services. However, none of the studies identified in the scoping review and the WHO brief evaluated STI testing or SRH services to create demand for PrEP, particularly amongst young men. In November 2023 we conducted an updated search through PubMed and Web of Science using broad terms that included sexually transmitted infections and PrEP. We did not find any additional trials that specifically looked at STIs for demand creation.

**Added value of this study**

This study has shown that homebased STI self-sampling was acceptable and increased uptake of differentiated and person-centred HIV prevention through mobile integrated SRH/HIV services by 60% amongst a representative sample of adolescents and young adults. Notably STI testing was effective in both young men and women. Peer support didn’t increase uptake but helped support retention in the integrated SRH/HIV clinical services.

**Implications of all the available evidence**

This study provides further evidence to accelerate the integration of HIV prevention with SRH services as a way to attract sexually active adolescents and youth into services that tackle their unmet HIV and sexual health needs. Specifically, this study provides some of the earliest evidence of the value of sexually transmitted infections testing as means to create demand and identify those who would benefit the most from PrEP and not just to monitor STIs amongst those already using PrEP. As HIV incidence declines, finding innovative and scalable ways to deliver differentiated HIV prevention to those who need it will become increasingly challenging. STI testing and integrating HIV and sexual health has the potential to reach those at risk and tackle unmet sexual health needs amongst the adolescents and youth in southern Africa.

**Abstract**

**Background:** Approximately 200,000 South Africans acquired HIV in 2021 despite universal HIV test and treat (UTT) and Pre-Exposure Prophylaxis (PrEP).

**Methods:** We conducted a 2x2 factorial open label randomised controlled trial. N=3000 potentially eligible 16-29-year-olds, randomly sampled from a population surveillance area in a mostly rural part of KwaZulu-Natal, were randomised to one of 4 arms: 1) enhanced Standard of Care (SoC): access to mobile youth-friendly services for differentiated HIV prevention (condoms, UTT, PrEP if eligible); 2) Sexual and Reproductive Health (SRH): baseline self-collected specimens for sexually transmitted infection testing and referral to differentiated HIV prevention services; 3) Peer-support: referral to a peer navigator for support, condom provision and facilitation of attendance for differentiated HIV prevention services; 4) SRH + peer-support. Co-primary effectiveness outcomes were: 1) linkage to differentiated HIV prevention services within 60 days of enrolment; 2) transmissible HIV (HIV viral load ≥400 copies/mL) measured from dried blood spots (DBS) at 12 months. **3)** the proportion of sampled individuals who consented to participation and gave a DBS for HIV testing at 12 months. Logistic regression was used for analyses, adjusted for age, sex and rural/peri-urban area.

**Findings:** Between March 2020 and August 2022, 1743/2301(76%) eligible individuals were enrolled, with a 12-month DBS collected from 1168 (67%). Baseline characteristics and 12-month outcome ascertainment were similar by arm. 755 (43.3%) linked to services by 60 days; SRH increased linkage (aOR 1.68;95%CI=1.39-2.04) but peer-support had no effect. At 12 months, 227 (19%) tested ELISA-positive for HIV, of whom 41 (18%) had a viral load ≥400 copies/ml. The overall prevalence of transmissible HIV was 3.5%. There was no evidence of an effect of either intervention on transmissible HIV (main effects: SRH aOR 1.12; 95%CI=0.60-2.11; peer-support aOR 1.03; 95%CI=0.55-1.94).

**Interpretation:** In this representative sample of adolescents and youth in a mostly rural area of South Africa, STI testing and SRH (but not peer support) increased uptake of differentiated HIV prevention. While the UNAIDS target of 90:90:90 was exceeded, neither SRH nor peer support showed evidence of reducing transmissible HIV.

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Trial Registry: clincialtrials.gov. Trial registration*:* NCT04532307

<https://clinicaltrials.gov/ct2/show/NCT04532307>

Registered: March 2020

# Background

By implementing combination HIV prevention to scale, UNAIDs aims to reduce HIV diagnoses to 500,000 per year globally. This has fallen far short with 1.3 million new HIV diagnoses in 2022.1 Despite freely available safe and effective anti-retroviral based HIV prevention i.e. universal HIV test and treat (UTT) that reduces mortality and prevents all onward transmission and HIV Pre-Exposure Prophylaxis (PrEP) that reduces HIV acquisition, there were an estimated 200,000 new infections in SA in 2021, the highest number in the world, with youth aged 15-24 accounting for 32% of these.2,3 Moreover, young people are often missing from the HIV treatment cascade.4,5 The demographic shift and doubling in number of young people over the next 20 years underscores the urgency of developing scalable models of delivering HIV prevention alongside treatment.6

There is a high unmet sexual and reproductive health (SRH) need.7,8 Our 2016 population-based study of 15-24-year-olds in rural SA found a high burden of sexually transmitted infections (STI) (20% of women and 10% of men had a curable STI7) and an extremely high incidence of teenage pregnancy 6.4/100 person-years. The same study also found that home-based self-sampling and treatment for STIs was acceptable and desirable for young people.7 We hypothesised that sexual and reproductive health (SRH) services could create demand for HIV prevention amongst sexually active young people.

There is growing evidence on the effectiveness of community-based HIV care. A meta-analysis found that community healthcare worker HIV care delivery significantly improved HIV viral suppression, which also reduces HIV transmission.9 The DOART trial showed that community-based HIV test-and-treat, in which people were tested in the community and started on ART treatment without needing to visit a clinic, was superior to facility-based HIV treatment (in which once diagnosed, people need to attend a clinic for treatment) in suppressing HIV viral load, particularly among men, in South Africa and Uganda.10 Similarly, the SEARCH trial in Kenya and Uganda showed the acceptability and feasibility of universal testing and provision of risk-informed PrEP, albeit with lower uptake among young people.11 Community-based approaches may be particularly important for adolescents. A study of a peer-led service delivery intervention integrated with psychosocial support in Zimbabwe was the first to show significant improvements in virological suppression in adolescents living with HIV in the African region.12,13

Evidence for peer-led interventions to support HIV prevention is also emerging.14,15 A systematic review of peer-based interventions with young people found improvements in knowledge, sexual behaviour, and condom use across 12 studies.16 Building on this evidence we used community-based participatory research to develop *Thetha Nami* (Talk to Me), a peer-navigator led area-based health promotion and peer mentorship intervention that was acceptable and feasible to deliver in rural SA.17

We hypothesised that biomedical HIV prevention and care (including UTT and PrEP) integrated with services to improve adolescents and young adults’ sexual and reproductive health (SRH) and supported by peer navigators will improve uptake of risk-differentiated HIV prevention in young people and reduce sexually transmissible HIV in rural SA. We report here the results of the *Isisekelo Sempilo* randomised controlled trial of integrated HIV prevention and peer support.

**Methods**

**Study design**

This was an open-label 2x2 randomised factorial trial of the effectiveness of integration with SRH and/or peer support on the uptake of risk-informed antiretroviral based HIV prevention (UTT/PrEP) and sexually transmissible HIV among young people aged 16-29 years in a mostly rural area of SA. Consenting individuals were randomised to one of 4 arms, to receive one of 2 delivery models (clinic referral only [enhanced standard of care (SOC)] or peer navigator support), with or without a comprehensive SRH package (Supplemental Figure 1). The trial was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000473/2019) and UCL Research Ethics Committee (5672/003). Written informed consent was obtained from participants aged 18-29 years; written assent was obtained from participants aged 16-17 years, with written consent from a parent or guardian.

**Participants**

The trial protocol and procedures have been published previously.18 In brief, the trial was embedded in the Africa Health Research Institute (AHRI) Health and Demographic Surveillance System (HDSS) in the uMkhanyakude district in KwaZulu-Natal, SA.19 The study area is mostly rural and with limited economic resources, with a high prevalence of HIV; the area also includes scattered peri-urban areas of small road-side townships. We used the HDSS as a sampling frame to randomly sample 3000 men and women aged 16-29 years old and invite them to participate in the study. Eligibility criteria included being aged 16-29, living in the mapped geographical areas that were accessible to the area-based peer navigators, willing and able to provide informed consent, and willing to provide a dried blood spot (DBS) for anonymous HIV testing and HIV viral load measurement at 12 months. Based on our previous studies in the HDSS, we expected that 2000 would be contactable and eligible, and 1500 (75%) would enrol.

**Randomisation**

In January 2020, a list of all young people aged 16-29 living in the mapped areas was generated from the December 2019 AHIR HDSS census. From that list, 3000 young people, stratified by sex, were selected with probability proportional to the number of young men or women in the area, to reflect the population distribution in the HDSS. The sampled individuals were then randomly allocated in a 1:1:1:1 ratio to the 4 trial arms, stratified by sex and broad geographical area (6 strata). The allocation list was uploaded into the electronic data collection tool (REDCap) and was only visible after the participant consented to enrolment. The investigators and trial statistician remained blinded to allocation throughout. The participants and intervention delivery teams were not blinded.

**Procedures**

Trial recruitment started on 02 March 2020. On 24 March, South Africa went into national lockdown and the trial was paused, including clinical services, and peer support was made virtual20. On 01 September 2020, we restarted clinical services, but peer support remained virtual. On 17 November 2020, we restarted enrolment, and in-person peer support was resumed on 24 November 2020.

Researchers visited the sampled individuals in their homes to invite them to participate in the study. They completed a brief eligibility screen and provided potential participants with information about the trial. Following informed consent, participants received a unique study identifying number, and completed a brief electronic enrolment questionnaire. After the questionnaire was completed, the individual’s trial allocation was revealed, with the participant information sheet for that arm. HIV testing or status was not an inclusion criteria.

All enrolled participants were provided with a barcoded clinic referral slip and an appointment to attend a clinic of their choice. As part of enhanced SOC, free adolescent, and youth friendly services (AYFS) were provided by study nurses in two primary health clinics in accessible commercial areas, and through mobile clinics that visited fixed sites across the HDSS area every 2 weeks. All clinic attendees (irrespective of trial arm) were offered HIV counselling, HIV point of care testing (POCT), and immediate initiation of ART if positive or PrEP if negative and eligible according to 2020 South African National PrEP guidelines. If the participant agreed to PrEP/ART initiation, the nurse issued them with a month’s supply of generic tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) or ART on the same day. Follow-up by telephone was conducted 7 days after initiating PrEP/ART to complete a standard symptom screen for adverse effects. Participants were asked to attend the clinic at months 1, 2, 6, 9 and 12, for repeat HIV testing (if on PrEP), ELISA confirmation and/or HIV viral load if needed, safety bloods, clinic-based counselling, adherence support and PrEP/ART refills. All clinic attendees were also offered family planning support (counselling and free provision of family planning methods) and syndromic management for STIs, partner notification documentation and, if male and HIV-negative, referral to voluntary male medical circumcision (VMMC), as per national guidelines.

Participants who were randomised to the peer navigator support (*Thetha Nami*) intervention were offered support of named peer navigators residing in their area. *Thetha Nami* were 54 area-based men and women aged 18-30 years (13 men), post matriculation, who were employed to provide peer-mentorship. Participants were offered the peer navigators’ contact details and told that, unless they objected, their contact details would be passed onto the peer navigators to contact them within 7 days. The peer navigators were trained to provide participants with one-to-one health promotion and support in accessing the clinical service and, for those who started PrEP/ART and agreed, adherence and appointment scheduling support and reminders.

Participants who were randomised to the SRH intervention provided self-taken samples for STI testing at enrolment (3-4 vaginal swabs or urine for women; urine for men) and an appointment to attend the study clinic for SRH care. The researcher at enrolment promoted sexual health and wellbeing and emphasised the SRH services that would be provided at the clinic. They encouraged the participant to attend irrespective of the result of their STI test. Samples were sent to AHRI laboratories to be tested for gonorrhoea, chlamydia, and trichomonas, using GeneXpert. If positive, a nurse contacted the participant to provide them and their partners with the appropriate STI treatment at a place convenient to them. At the clinic, they received tailored sexual health counselling with an emphasis on tackling the multiple health-related behaviours that affect fertility and sexual pleasure (STIs, mental health, alcohol, diet, and exercise); assessment of fertility desire and as appropriate preconception or contraception counselling. The nurses at the clinics dispensed free contraception on site, this included emergency contraception, a choice of contraception (including oral, injectable, implant or IUD), and condoms. HIV POCT was offered as part of sexual health counselling: The focus of PrEP counselling was on sexually well-being through staying negative and ART counselling on sexual well-being through Undetectable=Untransmissible (U=U) and staying healthy. In addition to the SOC procedures, adherence support in this arm included HIV viral load result-informed U=U counselling before ART refills. Participants had access to a clinic hotline and the clinics for medical concerns during the trial.

Participants’ clinic attendance was captured at the mobile study clinics and all the 11 primary health clinics serving the HDSS, where they would receive HIV testing, treatment and risk-informed prevention. Linkage was measured by scanning the barcode on their clinic referral slip. Participants who did not bring their referral slips were identified using an algorithm based on their unique demographic surveillance identifier number, name, date of birth, residential address, telephone number, and identity of the research assistant who recruited them in their enrolment. Adverse events (AE), serious adverse events (SAE) and social harms were captured through clinic staff (during monitoring visits and refills) and peer navigators, as well as the process evaluation, community engagement units, community advisory boards and a hotline, and were recorded up to 18 months after the start of the intervention. Reported AEs and SAEs were monitored, categorised based on an established grading system, and followed-up by the study team and principal investigator. A clinical monitor based at AHRI reviewed all AEs to ensure follow-up and reporting.

All participants, irrespective of whether they initiated PrEP/ART, were visited at home by the study team 12 months after enrolment. Participants completed a survey regarding their uptake and experience of HIV prevention and care services, uptake of contraception and incidence of pregnancy, mental health (using PHQ9), and quality of life. They were asked to provide a DBS for anonymous HIV ELISA and HIV viral load testing. All participants were offered self-sampling for STI testing (gonorrhoea, chlamydia, and trichomonas) and HIV counselling and POCT, and referral to a clinical service of their choice if found to be living with HIV.

Our participant-public engagement continued throughout the research process. The study was presented to the Community Advisory Board, peer navigators and the District Department of Health, to provide input into the relevance and importance of the research question and outcome measures before submission to Institutional Review Boards. Community-based participatory research (CBPR) was used to provide youth input into the final peer navigator intervention and SRH. Peer navigators assisted in making study clinics youth-friendly, identifying the sites for the mobile clinics, and designed the information and educational materials. The process evaluation explored the burden of the intervention, priorities, experiences, and preferences of young people throughout the trial. Results dissemination included peer navigators, youth stakeholders, community advisory committee, and the research community through local and international symposia. Participants did not receive any reimbursement for their time or participation in any part of the trial.

**Outcomes**

There were three co-primary outcomes: **1**) linkage to clinical services (where they are offered HIV testing, and risk-informed HIV care and prevention) within 60 days of enrolment; **2)** proportion of participants who had sexually transmissible HIV (HIV viral load ≥400 copies/mL) at 12 months after enrolment; and **3)** the proportion of sampled individuals who consented to participation and gave a DBS for HIV testing at 12 months.

The first outcome provided a measure of the effectiveness of the intervention to increase demand for HIV testing and risk-informed HIV prevention and treatment. The second outcome captured the effect of the intervention on both incident HIV and untreated HIV: if the intervention is successful there would be fewer young people who acquire HIV, and those living with HIV would be identified and promptly started on treatment, thus the overall number of individuals with unsuppressed (transmissible) HIV virus would be reduced. The third outcome measured the acceptability and feasibility of recruiting and retaining young people for 12 months in an HDSS-embedded HIV prevention trial platform. We defined acceptability of recruitment to an HDSS embedded platform trial as >75% consent to participate in the trial, and feasibility of retaining young people recruited in an HDSS-embedded trial, as obtaining a HIV ELISA and viral load result in >75% of participants 12 months after enrolment.

Secondary outcomes reported here include the effectiveness of the intervention in improving: 1) treatment outcomes in participants living with HIV, measured as the proportion of participants living with HIV who started treatment during the study; 2) provision of risk-informed HIV prevention, measured as the proportion of eligible HIV-negative participants who start PrEP, and the proportion of seroconversions at 12 months; and 3) retention in risk differentiated HIV prevention, measured as attending at least two clinical appointments during the 12 month follow-up. We conducted a process evaluation of acceptability, feasibility, fidelity, reach, and coverage of the intervention components reported in a separate paper.

**Statistical analysis**

With 2000 eligible and assuming that 75% consent to trial participation, we could estimate the consent rate with a precision of ±1.9%. With 1500 enrolled, assuming that 80% attended at 12 months, we could estimate retention with a precision of ±2.0%. With 1500 randomised participants (375 per arm), assuming that 10% in the SOC only arm access clinical services, we had 90% power to detect an increase in uptake to 22% with the addition of one intervention (peer navigator support only, or SRH only). We also had >90% power to detect an increase in uptake from 22% in the arms with only one intervention, to 38% in the arm with both interventions (peer support and SRH). Assuming 80% follow-up and no interaction between the interventions, we had 80% power to detect a reduction in the proportion of individuals with transmissible HIV due to either intervention (main effects analysis) from 7.0% (baseline prevalence) to 3.4%, or from 5.0% to 2.0%.3

Data were captured electronically on tablets using REDCap software.21 Automatic checks for invalid values, internal consistency and implausible responses were programmed into REDCap, and additional data validation checks were run after data collection. All changes have an audit trail. The data from REDCap was uploaded to a MySQL database server within a secure server cluster at AHRI. Statistical analyses were conducted in Stata version 16.0. A detailed analysis plan was finalised before the trial ended.

All analyses were conducted on an intention-to-treat (ITT) basis. Baseline characteristics were tabulated by trial arm. For the first 2 primary outcomes (proportion linked to care in 60 days and prevalence of transmissible HIV at 12 months), we fitted logistic regression models to jointly estimate the odds ratio (OR) and 95% confidence interval (CI) for the main effects of peer navigator support and the SRH package, assuming no interaction. As a secondary analysis, we fitted a 4-level categorical variable to estimate the OR and 95% CI for peer navigator alone, SRH alone, and peer navigator combined with SRH, all relative to SOC. We also tested whether the peer navigator and SRH interventions interact for each outcome. Similar methods were used in the analyses of the secondary outcomes. For all outcomes, analyses were adjusted for age, sex and area of residence (peri-urban vs rural), since these are known a priori to be strongly association of HIV infection.

For the primary analysis of linkage to care within 60 days, we used the date of resumption of clinic services (01 September 2020) as the entry date for participants who enrolled before the COVID lockdown. As a sensitivity analysis, we used the date of actual trial enrolment for all participants. In a secondary analysis, we used Kaplan-Meier methods to estimate time to linkage to care and used the log-rank test to compare time to linkage between arms.

To assess the acceptability and feasibility of the intervention, we calculated the proportions and 95% confidence intervals for consent to participate in the trial and for provision of a DBS 12 months after enrolment. Characteristics of participants who provided a DBS at 12 months were compared between arms using a Chi-squared test. For all outcomes based on data collected at the 12 month visit, participants who were lost to follow-up were excluded from the analysis (complete case). Missing data were not imputed since participants had no post-enrolment data that could be used as auxiliary variables in the imputation model.

**Role of funders**

The study was funded by a National Institute for Health R01 to MS and the Bill and Melinda Gates Foundation. The HDSS is supported by a Wellcome Trust core grant. None of the funders had any role in the design of the study or interpretation of the findings.

**Results**

Between 02 March 2020 and 18 May 2021, we successfully contacted 2627 (88%) of the 3000 young people sampled and invited them to enrol in the trial (Figure 1). Of those, 2301 (88%) were eligible and 1743 (75.7%, 95%CI=73.9%-77.5%) consented to enrolment, thus we achieved the >75% acceptability threshold. 346 participants were enrolled before the trial was paused on 24 March 2020; the remainder were enrolled after enrolment resumed in November 2020.

There were no important differences in baseline characteristics by arm (Table 1). Median age of participants was 21 years (interquartile range [IQR]=18-25); 51% were female and 51% had secondary education. The majority of participants were unemployed (58%), consistent with the population in the HDSS. STI testing at baseline was offered to the 863 participants in the two SRH arms; among the 797 (92%) who accepted it, 22% were positive for at least one STI. Peer support was offered to the 885, of which 556 (62.8%) met the peer within 60 days.

**Table 1: Baseline characteristics of study participants by arm**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total** | **Enhanced SoC1** | **SRH2** | **Peer support** | **SRH2 + peer support** |
|  | N=1743 | N=435 | N=423 | N=445 | N=440 |
| Age group |  |  |  |  |  |
| <20 years | 647 (37.1%) | 155 (35.6%) | 151 (35.7%) | 178 (40.0%) | 163 (37.0%) |
| 20-24 years | 612 (35.1%) | 161 (37.0%) | 149 (35.2%) | 157 (35.3%) | 145 (33.0%) |
| ≥25 years | 484 (27.8%) | 119 (27.4%) | 123 (29.1%) | 110 (24.7%) | 132 (30.0%) |
| Median (IQR) years | 21 (18-25) | 21 (18-25) | 21 (18-25) | 21 (18-24) | 21 (18-25) |
| Sex |  |  |  |  |  |
| Male | 847 (48.6%) | 215 (49.4%) | 203 (48.0%) | 218 (49.0%) | 211 (48.0%) |
| Female | 896 (51.4%) | 220 (50.6%) | 220 (52.0%) | 227 (51.0%) | 229 (52.0%) |
| Education |  |  |  |  |  |
| Primary | 644 (36.9%) | 155 (35.6%) | 161 (38.1%) | 168 (37.8%) | 160 (36.4%) |
| Secondary | 890 (51.1%) | 219 (50.3%) | 225 (53.2%) | 214 (48.1%) | 232 (52.7%) |
| Post secondary | 135 (7.7 %) | 44 (10.1%) | 26 (6.1 %) | 37 (8.3 %) | 28 (6.4 %) |
| Other | 73 (4.2 %) | 17 (3.9 %) | 11 (2.6 %) | 26 (5.8 %) | 19 (4.3 %) |
| Employment |  |  |  |  |  |
| Unemployed | 1012 (87.5%) | 252 (86.0%) | 249 (86.8%) | 259 (89.9%) | 252 (87.2%) |
| Employed | 145 (12.5%) | 41 (14.0%) | 38 (13.2%) | 29 (10.1%) | 37 (12.8%) |
| Marital status |  |  |  |  |  |
| Single | 499 (40.5%) | 115 (36.7%) | 118 (38.8%) | 146 (47.2%) | 120 (39.1%) |
| Married/informal union | 734 (59.5%) | 198 (63.3%) | 186 (61.2%) | 163 (52.8%) | 187 (60.9%) |
| Residence location |  |  |  |  |  |
| Rural | 1082 (62.1%) | 261 (60.0%) | 272 (64.3%) | 261 (58.7%) | 288 (65.5%) |
| Peri-urban | 661 (37.9%) | 174 (40.0%) | 151 (35.7%) | 184 (41.3%) | 152 (34.5%) |
| Any STI3 |  |  |  |  |  |
| No | 620 (77.8%) | – | 302 (76.6%) | – | 318 (78.9%) |
| Yes | 177 (22.2%) | – | 92 (23.4%) | – | 85 (21.1%) |

1Enhanced standard of care. 2Adolescent and youth friendly sexual and reproductive health services. 3Positive for chlamydia, gonorrhoea or trichomoniasis at enrolment, among 797 participants tested; only offered to those in SRH arms (863 participants).

1168 participants (67.0%; 95%CI:64.7-69.2%) provided a DBS at 12 months for the second primary outcome of transmissible HIV, lower than the 75% pre-defined feasibility threshold. However, there were no significant differences between arms in the characteristics of those that provided DBS (supplementary Table 1).

755 participants (43.3%) linked to clinical services for risk differentiated HIV prevention within 60 days. Linkage to risk differentiated HIV prevention was higher among participants allocated to SRH (49.8% vs 36.9%, adjusted main effect OR (aOR)=1.68, 95% CI=1.39-2.04). There was no evidence of an effect of peer navigator support on linkage (43.5% vs 43.1%, aOR=1.02, 95% CI=0.84-1.23). Results were similar in the sensitivity analysis based on the actual date of enrolment for participants who enrolled before lockdown (supplementary Table 2) and excluding those who tested positive for any of the three STIs (supplementary analysis 3). During the sensitivity analysis of linkage within 60 days of enrolment, measured from the date the participant linked to a peer navigator there was some evidence of an effect of peer navigator support on linkage to care (47.7% vs 43.1%, aOR=1.21, 95% CI=1.00-1.46). (supplementary table 4)

Overall, 1178 (67.6%) participants ever attended the clinic and median time to linkage was 3.0 months (IQR=0.4 to 14.2). Linkage was significantly higher in participants allocated to SRH (p<0.001; Table 2, Figure 2).

Of the 1168 who provided a DBS at 12 months, 227 (19%) tested ELISA-positive for HIV, of whom 41 participants (3.5%) had a detectable HIV viral load of ≥400 copies/mL (Table 2). There was no evidence of an effect of either intervention on the prevalence of transmissible HIV (SRH aOR=1.12, 95%CI=0.60-2.11; peer support aOR= 1.03, 95%CI=0.55-1.94). There was no clear (statistically significant) evidence of interaction between peer support and SRH for either primary outcome (p≥0.69)

**Table 2. Effect of intervention on primary outcomes: attending clinical services for risk differentiated HIV prevention within 60 days, and transmissible HIV**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Number with outcome/total (%)** | **Unadjusted OR  (95% CI)** | **Adjusted OR1  (95% CI)** |
| **Attended clinic within 60 days** | | | |
| Overall | 755/1743 (43.3) |  |  |
| SRH2 |  | P<0.001 | P<0.001 |
| No | 325/880 (36.9) | 1 | 1 |
| Yes | 430/863 (49.8) | 1.70 (1.40; 2.05) | 1.68 (1.39; 2.04) |
| Peer support |  | P=0.873 | P=0.853 |
| No | 370/858 (43.1) | 1 | 1 |
| Yes | 385/885 (43.5) | 1.02 (0.84; 1.23) | 1.02 (0.84; 1.23) |
| Trial arm |  | P<0.001 | P<0.001 |
| Enhanced SoC3 | 158/435 (36.3) | 1 | 1 |
| SRH2 | 212/423 (50.1) | 1.76 (1.34; 2.31) | 1.75 (1.33; 2.30) |
| Peer support | 167/445 (37.5) | 1.05 (0.80; 1.38) | 1.06 (0.80; 1.39) |
| SRH2 + peer support | 218/440 (49.6) | 1.72 (1.31; 2.26) | 1.71 (1.30; 2.25) |
| **Transmissible HIV at 12 months4** | | | |
| Overall | 41/1168 (3.5) |  |  |
| SRH2 |  | P=0.682 | P=0.719 |
| No | 19/578 (3.3) | 1 | 1 |
| Yes | 22/590 (3.7) | 1.14 (0.61; 2.13) | 1.12 (0.60; 2.11) |
| Peer support |  | P=0.958 | P=0.916 |
| No | 20/565 (3.5) | 1 | 1 |
| Yes | 21/603 (3.5) | 0.98 (0.53; 1.83) | 1.03 (0.55; 1.94) |
| Trial arm |  | P=0.892 | P=0.801 |
| Enhanced SoC3 | 9/283 (3.2) | 1 | 1 |
| SRH2 | 11/282 (3.9) | 1.24 (0.50; 3.03) | 1.25 (0.51; 3.09) |
| Peer support | 10/295 (3.4) | 1.07 (0.43; 2.67) | 1.16 (0.46; 2.92) |
| SRH2 + peer support | 11/308 (3.6) | 1.13 (0.46; 2.76) | 1.17 (0.47; 2.88) |

1Adjusted for sex, age group, and location of residence. 2Adolescent and youth friendly sexual and reproductive health services. 3Enhanced standard of care. 4HIV positive and viral load ≥400 copies/mL

During the trial, 1391 (79.8%) participants tested for HIV at least once, and 243 (17.5% of those tested) were found to be living with HIV, of whom 61 (25.1%) were not on ART at first attendance at clinics or endline. Among those, 25 (41.0%) started ART through the study clinics. There was no evidence of an effect of either intervention on the proportion starting ART (SRH aOR=0.99, 95%CI=0.34-2.89; peer support aOR=0.98, 95%CI=0.35-2.79; Table 3)

1161 participants tested HIV negative during the trial, of whom 909 (78.3%) ever attended a clinical service and 152 (16.7%) started PrEP (13.1% of those testing negative). There was no evidence of an effect SRH (aOR=1.23, 95%CI=0.87-1.74) or of peer support (aOR=0.99, 95%CI=0.70-1.40) on PrEP uptake (Table 3). 12 participants seroconverted to HIV during the trial. While a larger number of HIV seroconversions were observed in the SRH arm this is likely owing to ascertainment bias, since participants in the SRH arm were more likely to attend the clinics and more likely to be tested for HIV. Among those who tested HIV negative during the trial, those in the SRH arm had an average of 1.42 HIV tests during the trial, vs 1.23 if not in the SRH arm (p=0.01 by Wilcoxon rank-sum test).

**Table 3. Effect of intervention on secondary outcomes**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Started ART during the trial** | | | | | |
|  | **Tested positive during trial** | **Not on ART (%)** | **Started ART (%)** | **Unadjusted OR  (95% CI)** | **Adjusted OR1  (95% CI)** |
| Overall | 243 | 61 (25.1%)2 | 25/61 (41.0%) |  |  |
| SRH3 |  |  |  | P=0.784 | P=0.991 |
| No | 118 | 28 (23.7%) | 12/28 (42.9%) | 1 | 1 |
| Yes | 125 | 33 (26.4%) | 13/33 (39.4%) | 0.87 (0.31 -2.41 ) | 0.99 (0.34 -2.89 ) |
| Peer support |  |  |  | P=0.952 | P=0.975 |
| No | 127 | 32 (25.2%) | 13/32 (40.6%) | 1 | 1 |
| Yes | 116 | 29 (25.0%) | 12/29 (41.4%) | 1.03 (0.37 -2.87 ) | 0.98 (0.35 -2.79 ) |
| **Started PrEP during the trial** | | | | | |
|  | **Tested negative during trial** | **Seroconverted** | **Started PrEP (%)** | **Unadjusted OR4  (95% CI)** | **Adjusted OR1,4  (95% CI)** |
| Overall | 1161 | 12 (1.0%) | 152/1161 (13.1%) |  |  |
| SRH3 |  |  |  | P=0.274 | P=0.247 |
| No | 575 | 2 (0.3%) | 69/575 (12.0%) | 1 | 1 |
| Yes | 586 | 10 (1.7%) | 83/586 (14.2%) | 1.21 (0.86 -1.70 ) | 1.23 (0.87 -1.74 ) |
| Peer support |  |  |  | P=0.816 | P=0.953 |
| No | 555 | 9 (1.6%) | 74/555 (13.3%) | 1 | 1 |
| Yes | 606 | 3 (0.5%) | 78/606 (12.9%) | 0.96 (0.68 -1.35 ) | 0.99 (0.70 -1.40 ) |
| **Retention in care** | | | | | |
|  | **Enrolled** | **Ever attended clinic (%)** | **Attended clinic >2 times (% of enrolled)** | **Unadjusted OR  (95% CI)** | **Adjusted OR1  (95% CI)** |
| Overall | 1743 | 1178 (67.6%) | 519/1743 (29.8%) |  |  |
| SRH3 |  |  |  | P=0.003 | P=0.005 |
| No | 880 | 544 (61.8%) | 234/880 (26.6%) | 1 | 1 |
| Yes | 863 | 634 (73.5%) | 285/863 (33.0%) | 1.36 (1.11 -1.67 ) | 1.35 (1.10 -1.66 ) |
| Peer support |  |  |  | P=0.320 | P=0.266 |
| No | 858 | 573 (66.8%) | 246/858 (28.7%) | 1 | 1 |
| Yes | 885 | 605 (68.4%) | 273/885 (30.8%) | 1.11 (0.90 -1.36 ) | 1.12 (0.91 -1.38 ) |

1Adjusted for sex, age group, and location of residence. 2The remaining 182 participants who tested HIV positive during the trial were already on ART at the time of testing. 3Adolescent and youth friendly sexual and reproductive health services. 4OR for the effect of the intervention on starting PrEP during the trial, among all who tested HIV negative.

519 out of 1743 participants (29.8%) attended more than one clinic appointment. Retention in care was highest among those allocated to both SRH and peer support (aOR 1.51 compared with SOC, 95% CI=1.13-2.03; supplementary Table 3), although there was no evidence of an interaction between the interventions (p=0.91). 102 (67.1%) and 42 (27.6%) attended clinic for at least one or two PrEP refils respectively. This was not different per arm (supplementary table 5).

There were no SAEs or deaths during the trial. There was one participant with discrepant results between the HIV POCT and the laboratory DBS ELISA test; however, this was rapidly resolved through confirmatory ELISA testing and the participant’s clinical management was not adversely impacted. There were three challenges to peer navigators engaging a participant. In one, the peer navigator and participant were related; in another the peer navigator and participant’s family were not on good terms; and in the third, a member of the participant’s household had assaulted the peer navigator in the past. In all cases, an alternative peer navigator was successfully allocated to the participant.

**Discussion**

In this representative sample of adolescents and youth aged 16-29 from a mostly rural area of South Africa we found strong evidence that SRH including home-based STI self-sampling and testing increased uptake of differentiated HIV prevention. HIV prevalence was high and UNAIDS 90:90:90 was reached across all arms by 12 months. However, neither SRH nor peer support showed evidence that they reduced transmissible HIV compared to the AYFS enhanced SOC. Peer support and STI self-sampling were acceptable.

Effective long-acting PrEP such as injectable cabotegravir is on the horizon. However, it will be more expensive and requires healthcare worker administration and monitoring. TDF/FTC is affordable, widely available, safe in pregnancy and requires only regular HIV testing, which can be conducted by lay health care workers or through HIV self-tests.22 These characteristics make it easy to decentralise care.22,23 Differentiated models of HIV prevention are recommended by the WHO and to date there have been nearly 5 million PrEP initiations to date, according to the global PrEP tracker24. Our trial similarly demonstrates the high levels of acceptability of decentralized AYFS, with high uptake amongst young men as well as young women, across arms25. By integrating SRH services, including STI testing, with HIV care and prevention within the same mobile health services, uptake improved even further. By 12 months nearly three quarters of all young people (male and female) randomised to SRH had attended the AYFS for differentiated HIV prevention and care. Moreover, our study like others found a high burden of unmet sexual health need and STIs.8,26 Taken together, this evidence supports accessible integrated SRH/HIV services not only to create demand for HIV prevention and treatment services, but also to tackle the unmet SRH needs amongst adolescents and young men and women25.

We found that differences in uptake of AYFS by arm did not translate into a difference in starting ART-based prevention and treatment. One reason maybe that accessibility and youth friendliness of the services, and the provision of referral slips for these services by study teams who enrolled participants at home, may have encouraged uptake of services amongst those aware of their HIV prevention needs, irrespective of the arm they were randomised to. This would be in keeping with data emerging that adherence, and therefore uptake, may be aligned to HIV risk.27 Moreover, whilst we did not find any evidence that the intervention (either SRH or peer support) reduced transmissible HIV compared to AYFS (enhanced SoC), our overall prevalence of transmissible HIV was 3.5%. This is one-third the 9% prevalence in a similar random sample from the same setting in 2019,3 and half the 7% prevalence in a random sample of young people (15-30 years) from the HDSS in 2022 a year after the trial ended.28 Thus, our finding a lower prevalence of transmissible HIV is consistent with uptake of differentiated HIV prevention aligned to HIV risk among participants in all the trial arms.27

One of the challenges to oral PrEP is the association between oral PrEP for HIV prevention and ART for HIV treatment – the rattling pill bottle and the associated stigma, as well as the emphasis on 100% daily adherence, which may not be necessary even amongst cis-gender women – drives high PrEP discontinuation rates.29,30 Interestingly, whilst peer support did not improve uptake of services, retention was slightly higher amongst participants who were randomised to receive both peer support and SRH.

Our trial showed a HDSS can be used as a sampling frame for a platform trial offering public health interventions to representative sample of adolescents and youth, with three quarters of accepting to be randomised and the HDSS unique identifier allowing us a high ascertainment of the service uptake outcome. However, we were only able to measure the transmissible HIV outcome in 67% of trial participants at 12 months, suggesting that the HDSS may not be feasible for individual randomised trials of HIV prevention amongst this age group. Our trial found high levels of acceptance of both interventions, with >90% acceptance and uptake of the STI testing and peer support. Our mixed method process evaluation provides further insights around the acceptability, feasibility, fidelity and experience of the intervention components. Future work will look at measuring the population impact of the intervention on transmissible HIV, using the HDSS as a framework for cluster randomised trials.28

Strengths of our study are that we tested the implementation of different community-delivered strategies to increase PrEP demand, through integration with SRH and/or peer support, amongst a representative sample of adolescents and youth in a high HIV burden, mostly rural setting. There were several limitations to our study. The trial started in March 2020, just when South Africa went into the highest level of COVID19 lockdown (24 March 2020), all study activities ceased, and peer support was moved to telephone calls, SMS and WhatsApp messages. Whilst we were able to resume the mobile clinical services in September 2020, peer support remained virtual, which our process evaluation has showed adversely effected the quality of the peer-mentorship relationship and impacted on the fidelity of the peer support arm of the intervention, since peer navigators were less able to build rapport.20 Furthermore, peer navigators felt unable to provide support for the primarily psychosocial issues that arose for study participants. We did not do HIV testing at enrolment, and therefore given the difference in uptake of services by arm we are unable to comment on the effect of the intervention on HIV incidence by arm. Finally, our overall prevalence of undetectable HIV viral load was substantially lower than observed in comparable cohorts in this same area both before and after the trial, suggesting that the enhanced SoC (referral slips to mobile AYFS) may have diluted any effect. Furthermore, the trial was not adequately powered to detect small reductions in transmissible HIV, although the similar prevalence of transmissible HIV across the trial arms is consistent with the lack of an intervention effect on this outcome.

In summary, integrating HIV and SRH services improved uptake of AYFS. Nearly 20% of those attending the clinics were eligible for and started PrEP. This was lower than when in addition to peer mentorship, peer navigators mobilised youth in the areas.31,32 During the process evaluation peer navigators shared that they wanted to provide more person-centred and individualised referral, and that tackling the unmet social needs of young people was a priority for them. This has led the peers to decentralise differentiated HIV prevention further, including differentiated support for unmet social needs, in *Thetha Nami ngithethe nawe* (let’s talk).28 We are evaluating the impact of this optimised intervention (peer-led mobilisation into decentralised integrated SRH/HIV services) on sexually transmissible HIV at a population level.28

# Declarations

**Ethical approvals and consent to participate**

Ethical approval has been obtained the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000473/2019) and UCL Research Ethics Committee (5672/003). All staff (including peer navigators) were provided with training on research ethics including confidentiality, voluntary participation and good clinical practice. Written informed consent is obtained from all participants aged 18-29 years. For those aged 16-17 we obtain written informed assent from participants and written informed consent from their parents or guardian. This is an 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.

## Consent for publication

Not applicable

## Availability of data and materials

All datasets generated from this study will be in the study will be presented in the final manuscript and will thereafter be made publicly available through the AHRI data repository site. The full study protocol, study data collection tools and consent forms are available from the author.

## Competing interests

The authors declare that they have no competing interests.

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**Authors’ contributions**

MS conceived the study. MS, JMM, TZ, CH, NO, JD, AC, KB, NM1, JS, DP, FT, NC, NM2, GH and LS designed and implemented the study. MS and JB wrote the first draft of the manuscript. JD was the data manager, JB, AC and KB did the data analysis. NC, JB, GC, NM1, CH, NO, JD, TZ, ML, DG, SH, SM1, SM2, TS JMM, TK, NM2, JS, GH, LS, and AC read and critically revised the manuscript. All authors read and approved the final manuscript.

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