Effectiveness of integrating HIV prevention within sexual reproductive health services with or without peer support among adolescents and young adults in rural KwaZulu-Natal, South Africa (Isisekelo Sempilo): 2 × 2 factorial, open-label, randomised controlled trial

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Summary

Background Approximately 200 000 South Africans acquired HIV in 2021 despite the availability of universal HIV test and treat and pre-exposure prophylaxis (PrEP). The aim of this study was to test the effectiveness of sexual and reproductive health services or peer support, or both, on the uptake of serostatus neutral HIV services or reduction of sexually transmissible HIV.

Methods We did an open-label, 2 × 2 randomised factorial trial among young people in a mostly rural area of KwaZulu-Natal, South Africa. Inclusion criteria included being aged 16–29 years, living in the mapped geographical areas that were accessible to the area-based peer navigators, being willing and able to provide informed consent, and being willing to provide a dried blood spot for anonymous HIV testing and HIV viral load measurement at 12 months. Participants were randomly allocated by computer-generated algorithm to one of four groups: those in the standard-of-care group were referred to youth-friendly services for differentiated HIV prevention (condoms, universal HIV test and treat with antiretroviral therapy, and PrEP if eligible); those in the sexual and reproductive health services group received baseline self-collected specimens for sexually transmitted infection (STI) testing and referral to integrated sexual and reproductive health and HIV prevention services; those in the peer support group were referred to peer navigators for health promotion, condom provision, and facilitation of attendance for differentiated HIV prevention services; and those in the final group received a combination of sexual and reproductive health services and peer support. Coprimary outcomes were linkage to clinical services within 60 days of enrolment, proportion of participants who had sexually transmissible HIV at 12 months after enrolment, and proportion of sampled individuals who consented to participation and gave a dried blood spot for HIV testing at 12 months. Logistic regression was used for analyses, and adjusted for age, sex, and rural or peri-urban area of residence. This study is registered with ClinicalTrials.gov (NCT04532307) and is closed.

Findings Between March 2, 2020, and July 7, 2022, 1743 (75·7%) of 2301 eligible individuals were enrolled and followed up. 12-month dried blood spots were collected from 1168 participants (67·0%). The median age of the participants was 21 years (IQR 18–25), 51·4% were female, and 51·1% had secondary level education. Baseline characteristics and 12-month outcome ascertainment were similar between groups. 755 (43·3%) linked to services by 60 days. 430 (49·8%) of 863 who were in the sexual reproductive health services group were linked to care compared with 325 (36·9%) of 880 who were not in the sexual and reproductive health services group (adjusted odds ratio [aOR] 1·68; 95% CI 1·39–2·04); peer support had no effect: 385 (43·5%) of 858 compared with 370 (43·1%) of 885 (1·02, 0·84–1·23). At 12 months, 227 (19%) tested ELISA-positive for HIV, of whom 41 (18%) had viral loads of 400 copies per mL; overall prevalence of transmissible HIV was 3·5%. 22 (3·7%) of 578 participants in the sexual and reproductive health services group had transmissible HIV compared with 19 (3·3%) of 590 not in the sexual and reproductive health services group (aOR 1·12; 95% CI 0·60–2·11). The findings were also non-significant for peer support: 21 (3·3%) of 565 compared with 20 (3·3%) of 603 (aOR 1·03; 95% CI 0·55–1·94). There were no serious adverse events or deaths during the study.

Interpretation This study provides evidence that STI testing and sexual and reproductive health services create demand for serostatus neutral HIV prevention in adolescents and young adults in Africa. STI testing and integration of HIV and sexual health has the potential to reach those at risk and tackle unmet sexual health needs.

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Introduction

By implementing combination HIV prevention at scale, UNAIDs aims to reduce HIV diagnoses to 500 000 per year globally. Reality has fallen far short of this aim, with 1·3 million new HIV diagnoses in 2022.[1] Despite freely available safe and effective antiretroviral therapy (ART)-based HIV prevention (ie, universal HIV test and treat 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 South Africa in 2021, the highest number in the world, with people aged 15–24 years accounting for 32% of these new cases.[2,3] Moreover, young people are often missing from the HIV treatment cascade.[4,5] The demographic shift and the predicted doubling in the number of young people over the next 20 years underscores the urgency of developing scalable models of delivery for HIV prevention alongside treatment.[6]

There is a high unmet sexual and reproductive health-care need in young people.[7,8] Our 2016 population-based study of young people aged 15–24 years in rural South Africa found a high burden of sexually transmitted infections (STIs): 20% of women and 10% of men had curable STIs.[7] In the same survey, we found a high incidence of teenage pregnancy: 6·4 per 100 person-years. We also reported that home-based self-sampling and treatment for STIs was acceptable and desirable for young people.[7] We hypothesised that sexual and reproductive health services could encourage engagement with HIV prevention among sexually active young people.

A growing body of evidence shows effectiveness of community-based HIV care. A meta-analysis found that HIV care delivery by community health-care workers significantly improved HIV viral suppression compared with facility-based care, which also reduces HIV transmission.[9] The DOART trial showed that

Research in context

Evidence before this study

Before our trial, the evidence showed a suboptimal uptake of HIV pre-exposure prophylaxis (PrEP) in southern Africa, in part due to challenges in identifying and creating demand among those adolescents and young adults who would most benefit from PrEP. PubMed and Google Scholar were searched from Jan 1, 2015, to Nov 1, 2023, with the terms "oral PrEP" OR "pre-exposure prophylaxis" AND "demand creation" AND "reviews" (MESH terms in PubMed). We separately searched PubMed for "sexually transmitted infections" OR "STIs" OR "reproductive health" OR "sexual and reproductive health" OR "SRH" OR "SRHR" AND "oral PrEP" OR "pre-exposure prophylaxis" AND "trial" AND "clinical trial" AND "randomised controlled trial" (MESH terms). We searched for reviews of PrEP demand creation in low-income and middle-income settings and randomised controlled trials that included sexually transmitted infection (STI) testing to create demand for PrEP. The consolidated WHO differentiated and simplified PrEP for HIV prevention technical brief from 2022 and a 2023 scoping review of delivery models to promote PrEP uptake in adolescent girls and young women found that offering PrEP through family planning or antenatal and postnatal services improved the uptake of PrEP for adolescent girls and young women, and community-based delivery was preferred by both young men and women. However, none of the studies identified either in the scoping review or the WHO brief evaluated STI testing or sexual and reproductive health services to create demand for PrEP, particularly among young men. We did not find any additional trials that specifically looked at STIs for demand creation. The high unmet burden of curable STIs amongst adolescent girls and young women who use PrEP in Africa, and concerns around unmet sexual and reproductive health needs raised by the community in rural KwaZulu-Natal, suggest that STI testing should be used as an effective way to engage and attract sexually active adolescents and young adults to PrEP services.

Added value of this study

This study provides further evidence to accelerate the integration of HIV prevention with sexual and reproductive health services as a way to engage sexually active adolescents and young adults into services that tackle their unmet HIV and sexual health needs. Specifically, this study has shown that home-based STI self-sampling was acceptable and increased the uptake of differentiated and person-centred HIV prevention through mobile integrated sexual and reproductive health services and HIV services by 60% among a representative sample of adolescents and young adults. Notably, STI testing was effective in both young men and women. Peer support did not increase uptake but helped support retention in the integrated sexual and reproductive health and HIV clinical services.

Implications of all the available evidence

This study provides some of the earliest evidence of the value of STI testing as a means to create demand and identify those who would benefit the most from PrEP and not just to monitor STIs among 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 among adolescents and young adults in southern Africa.

a community-based HIV test-and-treat approach, 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 than older people.[11] Community-based approaches might 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 Africa.[12,13]

Evidence supporting 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 of HIV, sexual behaviour, and condom use across 12 studies.[16] Building on this evidence, we used community-based participatory research to develop Talk to Me (*Thetha Nami*), a peer-navigator-led area-based health promotion and peer mentorship intervention that was acceptable and feasible to deliver in rural South Africa.[17]

We hypothesised that biomedical HIV prevention and care (including universal HIV test and treat and PrEP), when integrated with services to improve adolescents and young adults' sexual and reproductive health and supported by peer navigators, will improve uptake of risk-differentiated HIV prevention in young people and reduce sexually transmissible HIV in rural South Africa. We report here results of our study, the Isisekelo Sempilo randomised controlled trial of integrated HIV prevention and peer support.

Methods

Study design

Between March 2, 2020, and July 7, 2022, we enrolled and followed up 1743 participants in an open-label 2×2 randomised factorial trial examining the effectiveness of integration with sexual and reproductive health services or peer support, or both, on the uptake of risk-informed ART-based HIV prevention (universal HIV test and treat and PrEP) and prevalence of sexually transmissible HIV among young people aged 16–29 years in a mostly rural area of uMkhanyakude, KwaZulu-Natal, South Africa. Consenting individuals were randomly assigned to one of four groups, to receive one of two delivery models (clinic referral only [enhanced standard of care] or peer navigator support), with or without a comprehensive sexual and reproductive health package (appendix p 7). The trial was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (approval number BREC/00000473/2019) and UCL Research Ethics Committee (approval number 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. All staff were provided with training on research ethics including confidentiality, voluntary participation, and good clinical practice. 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 the institutional review boards. Community-based participatory research was used to provide youth input into the final peer navigator intervention and sexual and reproductive health services. Peer navigators assisted in making the study clinics accessible, non-judgemental, and welcoming places for adolescents and young adults, identifying the sites for the mobile clinics, and designing 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, the community advisory committee, and the research community. Participants did not receive any reimbursement for their time or participation in any part of the trial.

Participants

The trial protocol and procedures have been published previously.[18] In brief, the trial was embedded in the Africa Health Research Institute health and demographic surveillance system in the uMkhanyakude district in KwaZulu-Natal, South Africa.[19] The study area is mostly rural and has low economic resources and a high prevalence of HIV; the area also includes scattered peri-urban areas of small roadside townships. We used the health and demographic surveillance system as a sampling frame to randomly sample 3000 men and women aged 16–29 years and invite them to participate in the study. Inclusion criteria included being aged 16–29 years, living in the mapped geographical areas that were accessible to the area-based peer navigators, being willing and able to provide informed consent, and being willing to provide a dried blood spot for anonymous HIV testing and HIV viral load measurement at 12 months. On the basis of our previous studies on the health and demographic surveillance system, we expected that 2000 participants would be contactable and eligible, and 1500 would enrol in the study.

Randomisation and masking

In January, 2020, a list of all young people aged 16–29 years living in the mapped areas (appendix p 8) was generated from the December 2019 Africa Health Research Institute health and demographic surveillance system census. From that list, 3000 young people,

See Online for appendix

stratified by sex, were selected, with the probability of being selected being proportional to the number of young men or women residing in the area, to reflect the population distribution in the health and demographic surveillance system. The trial statistician (NMt) generated a random allocation list (1:1:1:1) to one of the four trial groups. The allocation list was uploaded by the data manager (JD) into the electronic data collection tool (REDCap) and was only visible after the participant consented to enrolment. Randomisation and allocation were done by different people throughout, and the investigators and trial statistician were masked to allocation throughout. The participants and intervention delivery teams were not masked to the intervention type.

Procedures

Trial recruitment started on March 2, 2020. On March 24, 2020, South Africa went into national lockdown and the trial was paused, including clinical services, and peer support was made virtual.[20] On Sept 1, 2020, we restarted clinical services, but peer support continued to be delivered virtually. On Nov 17, 2020, we restarted enrolment, and in-person peer support was resumed on Nov 24, 2020.

Researchers visited the sampled individuals in their homes to invite them to participate in the study. The participants completed a brief eligibility screen, including self-reported sex, and provided potential participants with information about the trial. After informed consent was obtained, 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 receiving an information sheet for that group. HIV testing or status was not part of the inclusion criteria (appendix p 7).

In the standard-of-care group, 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 standard of care, free adolescent and young adult friendly services were provided by study nurses in two primary health clinics in accessible commercial areas, and through mobile clinics that visited fixed sites across the health and demographic surveillance system area every 2 weeks. All clinic attendees (irrespective of trial group) were offered HIV counselling, HIV point-of-care testing, and the immediate initiation of ART if they tested positive for HIV or PrEP if they tested negative and were eligible according to 2020 South African National PrEP guidelines. If the participant agreed to PrEP or ART initiation, the nurse issued them with a month's supply of generic tenofovir disoproxil fumarate and emtricitabine or ART on the same day. Follow-up by telephone was done 7 days after initiating PrEP or 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 or HIV viral load testing, or both, if needed; safety blood tests to be done; clinic-based counselling; adherence support; and PrEP or 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, as per national guidelines. Support and referral systems were available for detection and management of gender-based violence and safe abortion services.

In the peer support intervention group, participants who were randomly assigned to the peer navigator support (*Thetha Nami*) intervention were offered support of named peer navigators residing in their area. *Thetha Nami* consisted of 54 area-based men and women aged 18–30 years (13 men and 41 women) who had completed high school and 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 on to the peer navigators to contact them within 7 days. The peer navigators were trained to provide participants with one-to-one health promotion (including identification of gender-based violence), and support in accessing the clinical service; and, for those who started PrEP or ART and consented, they were provided with adherence and appointment scheduling support and reminders.

In the sexual and reproductive health intervention group, participants who were randomly assigned to the sexual and reproductive health intervention provided self-taken samples for STI testing at enrolment (three to four vaginal swabs or urine for women, and urine for men) and made an appointment to attend the study clinic for sexual and reproductive health care. The researcher, at enrolment, promoted sexual health and wellbeing and emphasised the sexual and reproductive health services that would be provided at the clinic. They encouraged the participant to attend the clinic, irrespective of the result of their STI test. Samples were sent to Africa Health Research Institute laboratories to be tested for gonorrhoea, chlamydia, and trichomonas with GeneXpert (Cepheid, Sunnyvale, CA, USA). 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); an 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 or injectable contraception, the implant, or an intrauterine device), and condoms. HIV point-of-care testing was offered as part of sexual health

counselling. The focus of PrEP counselling was on sexual wellbeing through remaining HIV negative, and the focus of ART counselling was on sexual wellbeing through the undetectable equals untransmissible message and staying healthy. In addition to the standard-of-care procedures, adherence support in this group included undetectable equals untransmissible counselling informed by HIV viral load result before ART refills. Participants had access to a clinic hotline and clinics for medical concerns during the trial.

To ascertain the outcome of linkage to clinical services, participants' clinic attendance was captured at the mobile study clinics and the two primary health clinics, where they received HIV testing, treatment, and risk-informed prevention (all groups), and additionally the integrated HIV and sexual and reproductive health package in the sexual and reproductive health group. This linkage to clinical services was assessed 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, serious adverse events, 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 adverse events and serious adverse events were monitored, categorised on the basis of the Division of AIDS adverse event grading system,[21] and followed up by the study team and principal investigator. A clinical monitor based at the Africa Health Research Institute reviewed all adverse events to confirm follow-up and reporting.

All participants, irrespective of whether they initiated PrEP or 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 Patient Health Questionnaire version 9),[22] and quality of life. They were asked to provide a dried blood spot 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 point-of-care testing, and referral to a clinical service of their choice if found to be living with HIV.

Outcomes

There were three coprimary outcomes: first, linkage to clinical services (attendance at one of the mobile study clinics or two primary health clinics in the health and demographic surveillance system, where participants were offered HIV testing and risk-informed HIV care and prevention) within 60 days of enrolment; second, the proportion of participants who had sexually transmissible HIV (HIV viral load ≥400 copies per mL) at 12 months after enrolment; and third, the proportion of sampled individuals who consented to participation and gave a dried blood spot 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 was successful, there would be fewer young people who acquired 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 acceptability and feasibility of recruiting and retaining young people for 12 months in a health and demographic surveillance system-embedded HIV prevention trial platform. We defined acceptability of recruitment to a health and demographic surveillance system-embedded platform trial as more than 75% of eligible people consenting to participate in the trial, and feasibility of retaining young people recruited in a health and demographic surveillance system-embedded trial as obtaining HIV ELISA and viral load results in more than 75% of participants 12 months after enrolment.

Secondary outcomes reported here include the effectiveness of the intervention in improving: first, treatment outcomes in participants living with HIV, measured as the proportion of participants living with HIV who started treatment with ART during the study; second, the provision of risk-informed HIV prevention, measured as the proportion of eligible participants who were negative for HIV who start PrEP, and the proportion of all participants who tested negative for HIV at any point before the 12 month survey who subsequently tested positive at 12 months; and third, the retention in risk-differentiated HIV prevention, measured as attending at least two clinical appointments during the 12-month follow-up. We did a process evaluation of acceptability, feasibility, fidelity, reach, and coverage of the intervention components reported in a separate paper (unpublished).

Statistical analysis

With 2000 eligible individuals and the assumption that 75% of them 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 randomly assigned participants (375 per group), assuming that 10% in the standard-of-care only group 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 sexual and reproductive health services only). We also had more than 90% power to detect an increase in uptake from 22% in the groups with only one intervention, to 38% in the group with both interventions (peer support and sexual and reproductive health services). Assuming follow-up of 80% of participants 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 version 12.[23] 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 had an audit trail. The data from REDCap were uploaded to a MySQL database server within a secure server cluster at the Africa Health Research Institute. Statistical analyses were conducted in Stata version 16.0. A detailed analysis plan was finalised before the trial ended.

Analyses were mainly by intention-to-treat. Baseline characteristics were tabulated by trial group. For the first two 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% CI for the main effects of peer navigator support and the sexual and reproductive health package, assuming no interaction. As a secondary analysis, we fitted a four-level categorical variable to estimate the ORs and 95% CIs for peer navigator alone, sexual and reproductive health services alone, and peer navigator combined with sexual and reproductive health services, all relative to the standard-of-care alone group. We also tested whether the peer navigator and sexual and reproductive health interventions interacted 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 have strong associations with HIV infection.

For the primary analysis of linkage to care within 60 days, we used the date of resumption of clinic services (Sept 1, 2020) as the entry date for participants who enrolled before the COVID-19 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 log-rank tests to compare time to linkage between groups.

To assess the acceptability and feasibility of the intervention, we calculated the proportions and 95% CIs for consent to participate in the trial and for provision of a dried blood spot 12 months after enrolment. Characteristics of participants who provided a dried blood spot at 12 months were compared between groups by use of χ^2 tests. 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, because participants had no post-enrolment data that could be

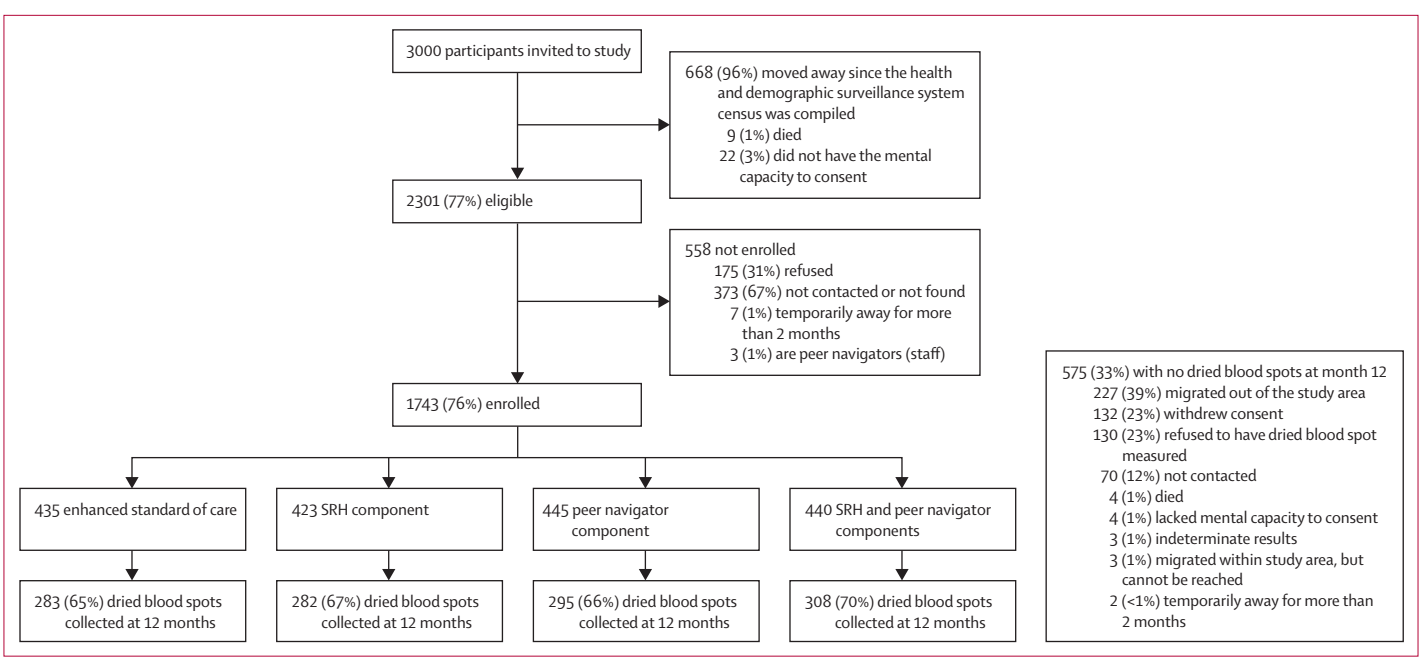

Figure 1: **Isisekelo Sempilo 2 × 2 factorial randomised controlled trial consort diagram**
SRH=sexual and reproductive health services.

used as auxiliary variables in the imputation model. For the secondary outcome of seroconversion, we calculated the number of HIV tests conducted during the trial and used a Wilcoxon rank-sum test to compare the number of HIV tests between participants in the sexual and reproductive health group and those who were not in the sexual and reproductive health group. This trial is registered with ClinicalTrials.gov (NCT04532307).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 2, 2020, and May 18, 2021, we successfully contacted 2627 (87·6%) of the 3000 young people sampled and invited them to enrol in the trial (figure 1). Of those, 2301 (87·6%) were eligible and 1743 (75·7%, 95% CI 73·9–77·5%) consented to enrolment; therefore, we achieved the more than 75% acceptability threshold. 346 participants were enrolled before the trial was paused on March 24, 2020; all other participants were enrolled after enrolment resumed in Nov 17, 2020.

There were no substantial differences in baseline characteristics by group (table 1). Median age of participants was 21 years (IQR 18–25); approximately half were female, and approximately half had secondary level education. Most participants aged 18 years or older were unemployed (1012/1157 [87·5%]), consistent with the population in the health and demographic surveillance system. STI testing at baseline was offered to the 863 participants in the two sexual and reproductive health groups; among the 797 (92·4%) who accepted it, 177 (22·2%) were positive for at least one STI. Peer support was offered to 885 participants in the two peer support groups, of whom 556 (62·8%) met the peer within 60 days.

1168 participants (67·0%; 95% CI 64·7–69·2%) provided a dried blood spot at 12 months for the second primary outcome of transmissible HIV at 12 months, lower than the 75% predefined feasibility threshold. However, there were no significant differences between groups in the characteristics of those that provided dried blood spot (appendix p 2).

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 the sexual and reproductive health group than any other group (table 2). There was no evidence of an effect of peer navigator support on linkage (table 2). Results were similar in the sensitivity analysis based on the actual date of enrolment for participants who enrolled before lockdown (appendix p 3). Our process evaluation found that fidelity of peer support was most affected by COVID-19 public health measures, and if linkage was measured from the date the participant linked with the peer there was some evidence of an effect (47·7% *vs* 43·1%, adjusted odds ratio 1·21, 95% CI 1·00–1·46; appendix p 4). These findings were similar when those who had tested positive for any of the three STIs were excluded (appendix p 4).

Overall, 1178 (67·6%) participants ever attended the clinic and median time to linkage was 3·0 months (IQR 0·4–14·2). Linkage was significantly higher in participants allocated to sexual and reproductive health groups compared with those who did not receive sexual and reproductive health services (p<0·0001; table 2, figure 2).

Of the 1168 participants who provided a dried blood spot at 12 months, 227 (19·4%) tested ELISA-positive for HIV, of whom 41 participants (3·5%) of 1168 had

	Total (N=1743)	Enhanced standard of care (n=435)	SRH (n=423)	Peer support (n=445)	SRH and peer support (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%)
Age, years	21 (18–25)	21 (18–25)	21 (18–25)	21 (18–24)	21 (18–25)
Sex					
Female	896 (51·4%)	220 (50·6%)	220 (52·0%)	227 (51·0%)	229 (52·0%)
Male	847 (48·6%)	215 (49·4%)	203 (48·0%)	218 (49·0%)	211 (48·0%)
Highest education level					
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%)
Higher than 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 status*					
Unemployed	1012/1157 (87·5%)	252/293 (86·0%)	249/287 (86·8%)	259/288 (89·9%)	252/289 (87·2%)
Employed	145/1157 (12·5%)	41/293 (14·0%)	38/287 (13·2%)	29/288 (10·1%)	37/289 (12·8%)
Marital status†					
Single	499/1233 (40·5%)	115/313 (36·7%)	118/304 (38·8%)	146/309 (47·2%)	120/307 (39·1%)
Married or informal union	734/1233 (59·5%)	198/313 (63·3%)	186/304 (61·2%)	163/309 (52·8%)	187/307 (60·9%)
Location of residence					
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 STI‡					
No	620/797 (77·8%)	NA	302/394 (76·6%)	NA	318/403 (78·9%)
Yes	177/797 (22·2%)	NA	92/394 (23·4%)	NA	85/403 (21·1%)

Data are n (%) or median (IQR). NA=not applicable. SRH=adolescent and youth friendly sexual and reproductive health services. STI=sexually transmitted infection. *Data were only available for 1157 patients who had left school. †Data were only available for 1233 patients who were aged 18 years or older. ‡Positive for chlamydia, gonorrhoea, or trichomoniasis at enrolment among 797 participants tested; only offered to those in groups that received SRH (863 participants).

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

	Number with primary outcome	Unadjusted OR	Adjusted OR*
Attended clinic within 60 days			
Overall	755/1743 (43·3%)	..	..
SRH			
No	325/880 (36·9%)	1	1
Yes	430/863 (49·8%)	1·70 (1·40–2·05)	1·68 (1·39–2·04)
p value	..	<0·0001	<0·0001
Peer support			
No	370/858 (43·1%)	1	1
Yes	385/885 (43·5%)	1·02 (0·84–1·23)	1·02 (0·84–1·23)
p value	..	0·873	0·853
Trial group			
Enhanced standard of care	158/435 (36·3%)	1	1
SRH alone	212/423 (50·1%)	1·76 (1·34–2·31)	1·75 (1·33–2·30)
Peer support alone	167/445 (37·5%)	1·05 (0·80–1·38)	1·06 (0·80–1·39)
SRH and peer support	218/440 (49·5%)	1·72 (1·31–2·26)	1·71 (1·30–2·25)
p value	..	<0·0001	<0·0001
Transmissible HIV at 12 months†			
Overall	41/1168 (3·5%)	..	..
SRH			
No	19/578 (3·3%)	1	1
Yes	22/590 (3·7%)	1·14 (0·61–2·13)	1·12 (0·60–2·11)
p value	..	0·682	0·719
Peer support			
No	20/565 (3·5%)	1	1
Yes	21/603 (3·5%)	0·98 (0·53–1·83)	1·03 (0·55–1·94)
p value	..	0·958	0·916
Trial group			
Enhanced standard of care	9/283 (3·2%)	1	1
SRH alone	11/282 (3·9%)	1·24 (0·50–3·03)	1·25 (0·51–3·09)
Peer support alone	10/295 (3·4%)	1·07 (0·43–2·67)	1·16 (0·46–2·92)
SRH and peer support	11/308 (3·6%)	1·13 (0·46–2·76)	1·17 (0·47–2·88)
p value	..	0·892	0·801

Data shown are n/N (%) or OR (95% CI), unless otherwise stated. OR=odds ratio. SRH=adolescent and youth friendly sexual and reproductive health services. *Adjusted for sex, age group, and location of residence. †Tested positive for HIV and a viral load of 400 copies per mL or higher.

Table 2: **Effect of intervention on primary outcomes: attending clinical services for risk differentiated HIV prevention within 60 days and transmissible HIV at 12 months**

detectable HIV viral loads of 400 copies per mL or more (table 2). There was no evidence of an effect of either intervention on the prevalence of transmissible HIV (sexual and reproductive health group adjusted OR 1·12, 95% CI 0·60–2·11; peer support adjusted OR 1·03, 0·55–1·94). There was no statistically significant evidence of interaction between peer support and sexual and reproductive health services for either primary outcome (p≥0·69).

During the trial, 1391 (79·8%) participants tested for HIV at least once, and 243 (17·5% of those tested) were 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 of participants starting ART (sexual and reproductive health adjusted OR 0·99, 95% CI 0·34–2·89; peer support adjusted OR 0·98, 0·35–2·79; table 3).

1161 participants tested HIV negative during the trial, of whom 909 (78·3%) ever attended a clinical service, of which 152 (16·7%) started PrEP (13·1% of the 1161 testing negative). There was no evidence of an effect of sexual and reproductive health services (adjusted OR 1·23, 95% CI 0·87–1·74) or of peer support (adjusted OR 0·99, 95% CI 0·70–1·40) on PrEP uptake (table 3). 12 participants (1·0%) seroconverted to HIV during the trial. Although a larger number of HIV seroconversions were observed in the sexual and reproductive health group compared with those who did not receive sexual and reproductive health services this is probably owing to ascertainment bias, since participants in the sexual and reproductive health group 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 sexual and reproductive health group had an average of 1·42 HIV tests during the trial, versus 1·23 in any other group (p=0·01 by Wilcoxon rank-sum test).

519 (29·8%) of 1743 participants attended more than one clinic appointment. Retention in care was highest among those allocated to both sexual and reproductive health services and peer support (adjusted OR 1·51 compared with standard of care, 95% CI 1·13–2·03; appendix p 5), although there was no evidence of an interaction between the interventions (p=0·91). 102 (67·1%) attended clinic for at least one PrEP refill and 42 (27·6%) attended clinic for at least two PrEP refills. There was no significant difference in the number who attended clinic for one or two PrEP refills between groups (appendix p 6).

There were no serious adverse events or deaths during the trial. One participant had discrepant results for the HIV point-of-care testing and the laboratory dried blood spot ELISA test; however, this was rapidly resolved through confirmatory ELISA testing and the participant's clinical management was not adversely affected. There were three times that a challenge was encountered with regard 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 young adults aged 16–29 years from a mostly rural area of South Africa, we found strong evidence that sexual and reproductive health services, including home-based STI self-sampling and testing, increased uptake of

differentiated HIV prevention. HIV prevalence was high and outcomes that reflected the UNAIDS 90-90-90 goals were reached across all groups by 12 months. However, neither sexual and reproductive health services nor peer support appeared to reduce transmissible HIV compared with the accessible adolescent and young adult friendly clinical services provided in the enhanced standard of care. 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 health-care worker administration and monitoring. Tenofovir disoproxil fumarate and emtricitabine is affordable, widely available, safe to use in pregnancy, and requires only regular HIV testing, which can be conducted by lay health-care workers or through HIV self-tests.[24] These characteristics make it easy to decentralise care.[24,25] Differentiated models of HIV prevention are recommended by WHO and to date there have been nearly 5 million PrEP initiations, according to the global PrEP tracker. Our trial similarly shows the high levels of acceptability of decentralised adolescent and youth friendly services, with high uptake among young men as well as young women, across different intervention types.[26] By integrating sexual and reproductive health 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 randomly assigned to receive sexual and reproductive health services had attended the adolescent and youth friendly services for differentiated HIV prevention and care. Moreover, our study, similar to other trials, found a high burden of unmet sexual health need and STIs.[8,27] Taken together, this evidence supports accessible integrated sexual and reproductive health and HIV services, not only to create demand for HIV prevention and treatment services, but also to tackle the unmet sexual and reproductive health needs among young men and women.[26]

We found that differences in uptake of adolescent and youth friendly services by group did not translate into a difference in starting ART-based prevention and treatment. One reason might be the accessibility and the non-judgemental and welcoming nature of the services, and the provision of referral slips for these services by study teams who enrolled participants at home, which might have encouraged the uptake of services among those aware of their HIV prevention needs, irrespective of the group they were randomly assigned to. This finding would be in keeping with data emerging that adherence, and therefore uptake, might be aligned with HIV risk.[28] Moreover, although we did not find any evidence that the intervention (either sexual and reproductive health or peer support) reduced transmissible HIV compared with adolescent and youth friendly services (enhanced standard of care), our overall prevalence of transmissible HIV was 3·5%. This is a third of 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 (aged 15–30 years) from the health and demographic surveillance system in 2022, a year after the trial ended.[29] 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 intervention groups, including enhanced standard-of-care groups.[28]

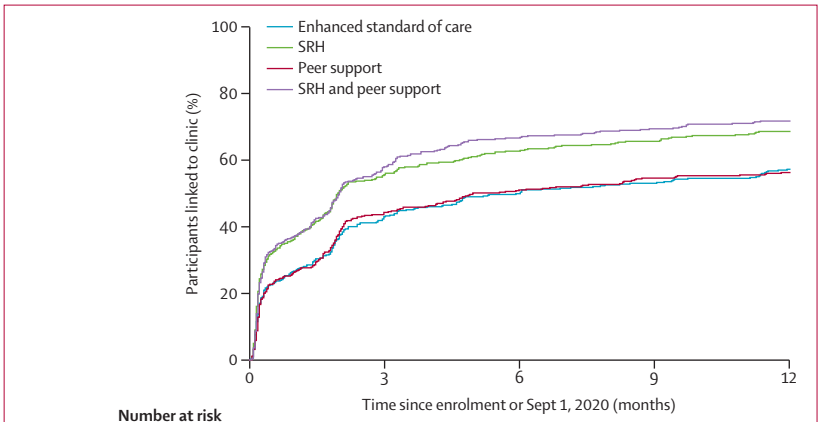

Figure 2: **Kaplan–Meier estimates of time to linkage to clinic, by trial group**
SRH=sexual and reproductive health services.

One of the challenges to oral PrEP is that the association between oral PrEP for HIV prevention and ART for HIV treatment—namely, the associated stigma, as well as the emphasis on 100% daily adherence, which might not be necessary even among cisgender women—drives high PrEP discontinuation rates.[30,31] Interestingly, although peer support did not improve the uptake of services, retention was slightly higher among participants who were randomly assigned to receive both peer support and sexual and reproductive health services.

Our trial showed that a health and demographic surveillance system can be used as a sampling frame for a platform trial offering public health interventions to a representative sample of adolescents and youth, with three-quarters of those sampled accepting to be randomly assigned, and their unique health and demographic surveillance system 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 health and demographic surveillance system might not be feasible for individual randomised trials of HIV prevention among this age group. Our trial found high levels of acceptance of both interventions, with more than 90% acceptance and uptake of the STI testing and peer support. Our mixed-method process evaluation

For the **global PrEP tracker** see https://data.prepwatch.org/

	Overall	SRH		Peer support	
		No	Yes	No	Yes
Started ART during the trial					
Tested positive during the trial	243	118	125	127	116
Not on ART	61 (25·1%)*	28 (23·7%)	33 (26·4%)	32 (25·2%)	29 (25·0%)
Started ART	25/61 (41·0%)	12/28 (42·9%)	13/33 (39·4%)	13/32 (40·6%)	12/29 (41·4%)
Unadjusted OR	..	1	0·87 (0·31–2·41)	1	1·03 (0·37–2·87)
p value	..	..	0·784	..	0·952
Adjusted OR†	..	1	0·99 (0·34–2·89)	1	0·98 (0·35–2·79)
p value	..	..	0·991	..	0·975
Started PrEP during the trial					
Tested negative during the trial	1161	575	586	555	606
Seroconverted	12 (1·0%)	2 (0·3%)	10 (1·7%)	9 (1·6%)	3 (0·5%)
Started PrEP	152/1161 (13·1%)	69/575 (12·0%)	83/586 (14·2%)	74/555 (13·3%)	78/606 (12·9%)
Unadjusted OR‡	..	1	1·21 (0·86–1·70)	1	0·96 (0·68–1·35)
p value	..	..	0·274	..	0·816
Adjusted OR†‡	..	1	1·23 (0·87–1·74)	1	0·99 (0·70–1·40)
p value	..	..	0·247	..	0·953
Remained in care during the trial					
Enrolled	1743	880	863	858	885
Ever attended clinic	1178 (67·6%)	544 (61·8%)	634 (73·5%)	573 (66·8%)	605 (68·4%)
Attended clinic more than two times	519/1743 (29·8%)	234/880 (26·6%)	285/863 (33·0%)	246/858 (28·7%)	273/885 (30·8%)
Unadjusted OR	..	1	1·36 (1·11–1·67)	1	1·11 (0·90–1·36)
p value	..	..	0·0033	..	0·320
Adjusted OR†	..	1	1·35 (1·10–1·66)	1	1·12 (0·91–1·38)
p value	..	..	0·0047	..	0·266

Data are n (%) or OR (95% CI), unless otherwise stated. ART=antiretroviral therapy. OR=odds ratio. PrEP=pre-exposure prophylaxis. SRH=adolescent and youth friendly sexual and reproductive health services. *The other 182 participants who tested HIV positive during the trial were already on ART at the time of testing. †Adjusted for sex, age group, and location of residence. ‡OR for the effect of the intervention on starting PrEP during the trial, among all who tested HIV negative.

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

provides further insights around acceptability, feasibility, fidelity, and experience of the intervention components. Future work will look at measuring the population effect of the intervention on transmissible HIV, using the health and demographic surveillance system as a framework for cluster randomised trials.[29]

The strengths of our study are that we tested the implementation of different community-delivered strategies to increase PrEP demand, through integration with sexual and reproductive health services or peer support, or both, among a representative sample of adolescents and young adults 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 COVID-19 lockdown (March 24, 2020), all study activities ceased, and peer support was moved to telephone calls, short messaging service, and WhatsApp messages. Although we were able to resume the mobile clinical services in September, 2020, peer support remained virtual, which our process evaluation has showed adversely affected the quality of the peer mentorship relationship and affected the fidelity of the peer support group 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 group, we were unable to comment on the effect of the intervention on HIV incidence by group. Finally, our overall prevalence of undetectable HIV viral load was substantially lower than observed in similar cohorts in other trials done both before and after this trial, suggesting that the enhanced standard of care (referral slips to mobile adolescent and youth friendly services) might 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 groups is consistent with the absence of an intervention effect on this outcome.

In summary, integrating HIV and sexual and reproductive health services improved uptake of adolescent and youth friendly services. Nearly 20% of those attending the clinics were eligible for and started PrEP. When, in addition to peer mentorship, peer navigators mobilised young people, this percentage has been higher.[32,33] 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 led to the further co-development of the intervention since the end of the trial, with the peer navigators decentralising differentiated HIV prevention further and including differentiated support for unmet social needs.[29] We are evaluating the effect of this optimised intervention, named *Thetha Nami ngithethe nawe* or Let's Talk (a peer-led mobilisation into decentralised integrated sexual and reproductive health and HIV services), on sexually transmissible HIV at a population level.[29]

Contributors

MS conceived the study. MS, J-MM, TZ, CH, NO, JD, AC, KB, NMt, JS, NC, NMc, 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. JD, JB, and KB verified the data. JD, JB, KB, NMt, and GC had access to the raw data and no authors were prohibited from accessing the raw data. NC, JB, GC, NMt, CH, NO, JD, TZ, ML, DG, SH, SMd, SMs, TS, J-MM, TK, NMc, JS, GH, LS, and AC read and critically revised the manuscript. All authors read and approved the final manuscript. MS had the final decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All datasets generated from this study are publicly available through the Africa Health Research Institute data repository site (https://data.ahri.org/index.php/home). The full study protocol, study data collection tools, and consent forms are available from the corresponding author (m.shahmanesh@ucl.ac.uk).

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