Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial

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Summary

Background Strengthening engagement of female sex workers with health services is needed to eliminate HIV. We assessed the efficacy of a targeted combination intervention for female sex workers in Zimbabwe.

Methods We did a cluster-randomised trial from 2014 to 2016. Clusters were areas surrounding female sex worker clinics and were enrolled in matched pairs. Sites were randomly assigned (1:1) to receive usual care (free sexual-health services supported by peer educators, including HIV testing on demand, referral for antiretroviral therapy [ART], and health education) or an intervention that supported additional regular HIV testing, on-site initiation of ART, pre-exposure prophylaxis, adherence, and intensified community mobilisation. The primary outcome was the proportion of all female sex workers with HIV viral load 1000 copies per mL or greater, assessed through respondent-driven sampling surveys. We used an adapted cluster-summary approach to estimate risk differences. This trial is registered with Pan African Clinical Trials Registry, number PACTR201312000722390.

Results We randomly assigned 14 clusters to usual care or the intervention (seven in each group). 3612 female sex workers attended clinics in the usual-care clusters and 4619 in the intervention clusters during the study. Half as many were tested (1151 *vs* 2606) and diagnosed as being HIV positive (546 *vs* 1052) in the usual-care clusters. The proportion of all female sex workers with viral loads of 1000 copies per mL or greater fell in both study groups (from 421 [30%] of 1363 to 279 [19%] of 1443 in the usual-care group and from 399 [30%] of 1303 to 240 [16%] of 1439 in the intervention group), but with a risk difference at the end of the assessment period of only –2·8% (95% CI –8·1 to 2·5, p=0·23). Among HIV-positive women, the proportions with viral loads less than 1000 copies per mL were 590 (68%) of 869 in the usual-care group and 588 (72%) of 828 in the intervention group at the end of the assessment period, adjusted risk difference of 5·3% (95% CI –4·0 to 14·6, p=0·20). There were no adverse events.

Interpretation Our intervention of a dedicated programme for female sex workers led to high levels of HIV diagnosis and treatment. Further research is needed to optimise programme content and intensity for the broader population.

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Introduction

Worldwide, female sex workers have roughly 13·5 times higher odds of having HIV infection than women in the general population.[1] Many female sex workers, however, have reduced access to testing and treatment and face barriers to treatment adherence, including discrimination, stigma, and concerns about illegality of sex work.[1,2] In Zimbabwe, HIV prevalence among the general adult female population is 17%[3] and sex work is illegal. Female sex workers mainly work independently of gatekeepers, in bars or on the street, and brothels are uncommon. Since 2006, this population has been identified as important in Zimbabwe's National HIV and AIDS Strategic Plan.[4–6] Analysis of data from 2009 to 2013 showed HIV incidence among female sex workers was more than ten new cases per 100 person-years at risk.[7] Only 67% were aware of their HIV status and less than 50% living with HIV had an undetectable viral load (<1000 copies per mL).[8] Consistent condom use with clients was reported by 65–73% of female sex workers. Heterosexual transmission of HIV is unlikely to occur when viral load is less than 1500 copies per mL.[9] Modelling suggests that over 40% of new infections in the general population are attributable to unsafe sex work, because of high HIV incidence and high prevalence of infectious HIV.[10]

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Research in context

Evidence before this study

We searched PubMed with the terms "sex workers", "HIV prevention", "HIV treatment cascade", and "HIV care cascade", for articles published in English up to Aug 7, 2017. Systematic reviews of HIV prevention and community empowerment interventions targeting female sex workers show that they can reduce individuals' risk of HIV and sexually transmitted infections. Mathematical modelling suggests that the population-attributable fraction of new infections contributed through commercial sex is high even in generalised epidemics. No randomised studies have been done of the effects of dedicated programmes for female sex workers on HIV prevalence and suppression outcomes in Africa or elsewhere.

Added value of this study

To our knowledge this is the first cluster-randomised trial to assess the effects of a comprehensive programme targeting female sex workers. Additionally, it is one of the first trials to assess effects at the population level through respondent-driven sampling surveys.

Implications of all the available data

Female sex workers are at very high risk of HIV. We found that in the context of a dedicated programme, high levels of diagnosis and successful treatment of women with HIV are feasible. However, although our intensive mobilisation efforts did increase the number of women assessed, tested, and diagnosed, we saw no effects on outcomes of interest, at least over the time frame of the trial. Targeting subgroups to ensure that female sex workers who are most vulnerable (younger women, new female sex workers, and those with concomitant mental health or substance use issues) are prioritised for support and access to prevention and care might improve outcomes.

Although guidelines for interventions for female sex workers exist,[11] few assessments have been made of their effects on engagement with HIV prevention and care, particularly in Africa and since the preventive effects of ART and efficacy of oral pre-exposure prophylaxis (PrEP) have become clear.[12] Reducing the burden of infectious HIV among female sex workers requires interventions that strengthen demand, improve supply, and support optimum use of any prevention or treatment strategy adopted. Demand-side interventions should increase risk perception, support positive attitudes towards HIV prevention and treatment, foster positive social norms, and build social cohesion to improve risk reduction. Supply-side interventions should increase accessibility and availability of HIV testing, treatment, and prevention, such as condoms, contraception, and PrEP. To optimise adherence, interventions should support behavioural self-efficacy and skills.[13] Based on these principles, we developed the Sisters Antiretroviral Prevention Programme—an Integrated Response (SAPPH-IRe) combination HIV prevention and treatment intervention package to enhance the existing national sex work programme, Sisters with a Voice (Sisters), which was established in 2009. The Sisters programme provides HIV prevention and sexual health services plus assisted referral to HIV treatment.[7]

We assessed the effects of our intervention on the proportion of all female sex workers with HIV viral loads of 1000 copies per mL or greater in a cluster-randomised trial in Zimbabwe (appendix p 4). We tested the hypothesis that the targeted and dedicated delivery and support would reduce the proportion of female sex workers living with non-virologically suppressed HIV when compared with usual care. The study protocol is available online.

See Online for appendix

For **study protocol** see http://www.ceshhar.org.zw/sapph-ire-trial-protocol

Methods

Study design and participants

The SAPPH-IRe trial is a pair-matched, parallel, cluster-randomised controlled trial nested within the Sisters programme.[14] Clusters were selected from 36 sites around Sisters programme centres across Zimbabwe. They had to be sufficiently far apart (≥90 km) to minimise contamination, based on review of programme data to explore mobility between sites, and likely to have a comparable pairing. We matched pairs of clusters based on whether or not they had previously provided dedicated services for sex workers and type of site (eg, town, growth point, colliery, or army base).

Female sex workers were eligible for inclusion if they had exchanged sex for money in the previous 30 days, were aged 18 years or older, and had been living or working for at least 6 months in the cluster where they were interviewed. Written informed consent, in English, Shona, or Ndebele, was obtained for survey participation before interviews were done and blood samples were taken whenever possible, but was not required for programme participation. All female sex workers starting PrEP had to sign an agreement form before doing so because the regimen used had not been approved for prophylactic use by the Medicines Control Authority of Zimbabwe. Ethics approval was obtained from the Medical Research Council of Zimbabwe, University College London, London School of Hygiene & Tropical Medicine, and RTI International. Foreign researchers were registered with the Research Council of Zimbabwe.

Randomisation and masking

Clusters were randomly assigned (1:1) to the usual-care or the intervention group in a public ceremony on Jan 31, 2014 (appendix pp 2–3). Female sex workers could continue to receive available Sisters services

regardless of their participation in research activities. It was not possible to mask intervention status from survey teams, but all teams did surveys in intervention and control communities. Laboratory staff were unaware of intervention allocations.

Interventions

In clusters in the usual-care group, the Sisters programme provided targeted HIV services following the WHO guidelines,[11] including provision of free condoms and contraception, free HIV testing and counselling, syndromic management of sexually transmitted infections, health education, community mobilisation, and legal advice. Activities were supported by trained peer educators. Services were provided at drop-in centres based in primary-care clinics on the same day each week. Women who required HIV care, antiretroviral treatment (ART), or both, were referred to government services. Clinic attendees were not actively followed up.

In clusters in the intervention group, the Sisters programme was augmented with additional community mobilisation activities aimed at raising awareness of the benefits of ART and PrEP, strengthening support networks to encourage health-promoting behaviour, and building leadership skills (appendix pp 5–6). ART and PrEP users were encouraged to join the community-based Adherence Sisters programme. ART or PrEP users nominated a trusted "sister" to act as their adherence supporter and to attend Adherence Sisters training sessions together. Importantly, the Adherence Sisters programme is status neutral, that is, participants are unaware of who is taking ART and who is taking PrEP (appendix p 5). Activities designed to encourage HIV testing every 6 months among women who were HIV negative included mobile telephone messaging reminders. Clinical services were improved so that ART and PrEP could be started on site and ART would comply with local and international guidelines. PrEP was offered to all women who tested negative for HIV. Female sex workers opting for PrEP attended two screening visits before PrEP was started. Clinical and social support services were delivered by clinical staff. SMS and follow-up phone calls were used to support clinic attendance. Delivery of the intervention began in April, 2014. On-site initiation of ART and PrEP was rolled out from July, 2014 (except for in one site where local approval was delayed until November, 2014). Peer educators were trained to deliver the Adherence Sisters programme in May, 2014, with refresher training in November, 2014.

Implementation of the interventions in both groups was monitored through programme records that included checklists, staff and training records, clinic attendance records, logs of community mobilisation activities, registers of the Adherence Sisters programme, peer education contacts, qualitative research, and a programme diary to record key contextual factors (appendix p 7).

Sampling for outcome surveys

Because it was not feasible to assemble a population sampling frame, we used respondent-driven sampling to obtain representative samples of female sex workers.[15] A baseline survey was done in all 14 sites in the period Nov 13 to Dec 20, 2013, and another survey was done after 21 months of intervention in the period April 11 to May 6, 2016, by the same method. Sex workers in Zimbabwe are well networked with each other, which is a criterion for using the respondent-driven sampling survey method.[16] In each cluster, we used geographical and social mapping to select six to eight women per site to be "seeds". These women represented a range of ages, types of sex work, and geographical locations. We interviewed the women, gave each one two coupons to distribute to peers in the following 2 weeks, and read them a sample recruitment script. Women who received a coupon could attend an interview, and on intervew completion were given two coupons for their peers. In all clusters, this process was repeated in five waves after the initial recruitment of the seeds. Each participant received US$5 and a further $2 for each woman she recruited. Checks were included to ensure coupons were genuine and to minimise repeat participation.

The interviewer-administered questionnaire included questions on demographics, sex work, sexual behaviour and condom use, HIV testing history, ART use, stigma, experience of violence, quality of life, mental health, general health, relationships with other sex workers, and use of sexual and reproductive health services. Data were collected on tablet computers and uploaded to a database daily. To enable adjustment of respondent-driven sampling we asked each participant how many female sex workers older than 18 years they knew living in the site who they had seen in the past month and would consider recruiting to the study. We collected a finger-prick blood sample (dried blood spot) from each woman for HIV antibody testing and measurement of HIV viral load.

Laboratory assessments

Blood samples were air dried on filter papers and stored at room temperature until they were, taken every 2 weeks, to the Flowcytometry Laboratory (Harare, Zimbabwe). Testing for HIV antibodies was done with AniLabsystems EIA kits (OyToilette, Finland). Positive samples were retested with NucliSENS EasyQ HIV-1 version 2.0 (bioMérieux, Marcy L'Etoile, France) to confirm HIV positive status and quantify the viral load. For samples positive for HIV antibodies but with undetectable viral load, a confirmatory ELISA was done (Enzygnost Anti-HIV 1/2 Plus ELISA, Dade Behring, Marburg, Germany).

Outcomes

The primary outcome was the proportion of female sex workers with HIV viral loads of 1000 copies per mL or

greater, and was calculated as the number of survey participants with positive HIV antibody and viral loads of 1000 copies per mL or greater divided by the number of survey participants who had an HIV antibody test. We assessed nine prespecified secondary endpoints reflecting the aspects of treatment and prevention intended to be affected by the intervention, which were analysed with the same analytical framework as the primary outcome.

Statistical analysis

Our sample-size calculations have been described previously.[14] We estimated that we would need seven matched pairs of clusters and 200 women per site to provide 80% power to detect a reduction of a third in the proportion of female sex workers with viral loads of 1000 copies per mL or greater over the duration of the trial. The statistical analysis followed a prespecified analytical plan (appendix pp 8–13).[14] In brief, we assessed evidence of bias in our operationalisation of respondent-driven sampling by graphically examining the convergence of the primary outcome (appendix pp 14–15). All our analyses were done at the cluster level. We accounted for the respondent-driven sampling in our estimates of cluster characteristics with RDS-II weighting. We dropped the seed responses and weighted the results for each Wwoman in each site by the inverse of her network size (ie, the number of other women that she could have recruited).[17] We described key sociodemographic characteristics of the sample recruited through respondent-driven sampling at baseline and the end of the assessment period with seeds included, and reported the cluster means and ranges by study group after RDS-II weighting. We described clustering with the coefficient of intercluster variation, k,[18] summarised across pairs with and without RDS-II weighting.

For the outcome analyses, we used an adapted cluster-summary approach to estimate risk differences, comparing the adjusted and unadjusted means of the RDS-II-weighted site-specific proportions of the binary outcomes in each study group. We used a linear regression model with a treatment dummy variable, dummy variables for the pairs, and the outcome level at baseline as regressors. We adjusted the model for age and sex with the two-step method to adjust for individual-level covariates in the cluster-summary analysis.[18] The respondent-driven sampling diagnostics code for the primary analysis was written with the RDS package in R (appendix pp 9–13)[19] and shared with the trial data safety and monitoring board, and the analysis was done with treatment allocation masked. We did two sensitivity analyses: first running the analysis without weighting and second with a successive sampling approach.[20] These analyses suggested the results were robust in terms of how we treated the respondent-driven sampling data and are not discussed further (appendix p 22).

All analyses were done using R, version 3.4.3. This trial is registered with Pan African Clinical Trials Registry, number PACTR201312000722390.

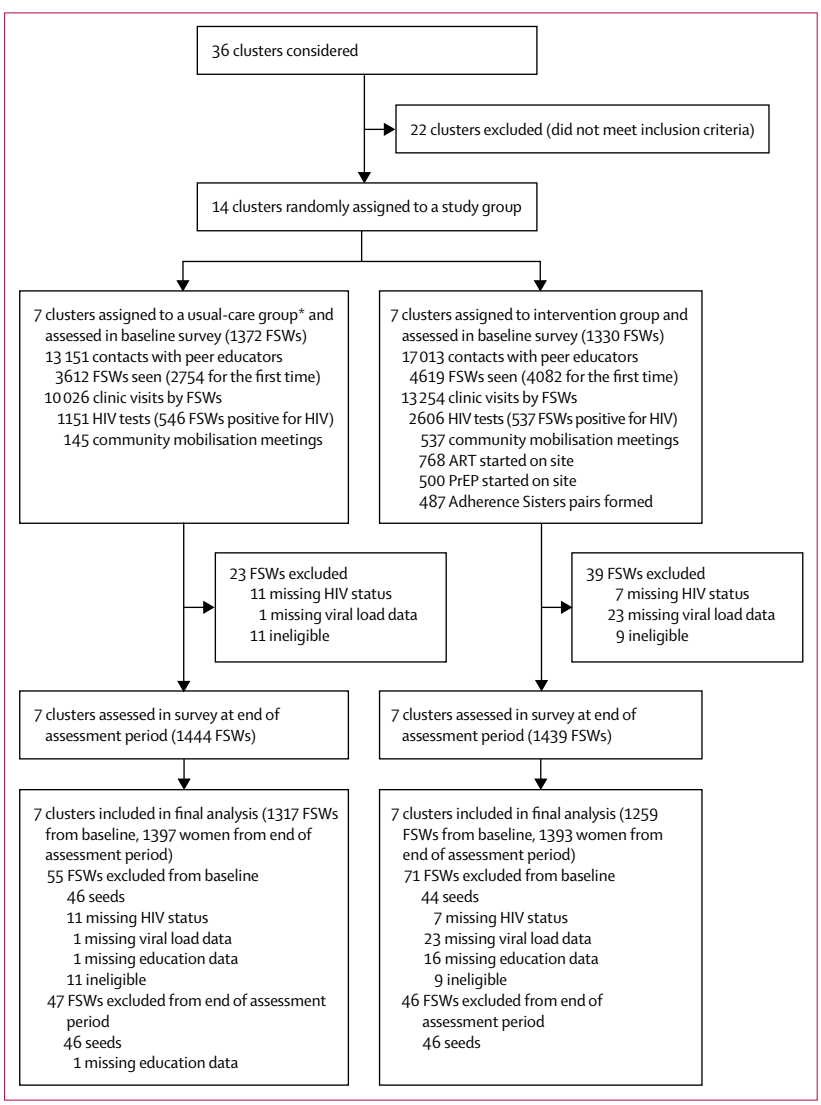

Figure 1: **Trial profile**
FSWs=female sex workers. ART=antiretroviral treatment. PrEP=pre-exposure prophylaxis. *No women started ART or PrEP on site or formed Adherence Sisters pairs, as these were only available as part of the intervention.

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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 36 clusters considered, 14 were randomised (seven in each study group) and remained in the study until the end (figure 1). The sample sizes were close to target at baseline and the end of the assessment period (figure 1), and sociodemographic and network characteristics were well matched across study groups (table 1, appendix p 20).

	Mean respondent-driven sampling weighted proportions (%, range)		Mean pair difference (range)
	Usual-care group	Intervention group	
Age (years)			
18–19	15/1444 (2·0%, 0·2 to 4·6)	36/1439 (2·6%, 0·1 to 8·0)	0·5% (–2·4 to 6·6)
20–24	211/1444 (13·4%, 9·0 to 18·7)	241/1439 (17·8%, 6·6 to 27·4)	4·4% (–6·6 to 9·3)
25–29	310/1444 (21·9%, 15·8 to 27·3)	300/1439 (19·3%, 14·1 to 25·6)	–2·6% (–12·5 to 9·8)
30–39	596/1444 (40·8%, 36·2 to 49·0)	562/1439 (38·1%, 31·9 to 44·4)	–2·7% (–15·8 to 3·7)
≥40	312/1444 (21·8%, 15·2 to 31·5)	300/1439 (22·2%, 9·2 to 40·1)	0·4% (–22·3 to 19·0)
Education			
None	419/1443 (33·9%, 27·2 to 41·5)	476/1439 (39·5%, 16·7 to 51·4)	5·6% (–14·2 to 23·6)
Primary	512/1443 (35·7%, 31·3 to 42·2)	497/1439 (34·4%, 26·9 to 49·0)	–1·3% (–13·8 to 10·1)
Secondary	512/1443 (30·4%, 22·1 to 40·6)	466/1439 (26·1%, 17·6 to 35·9)	–4·3% (–18·6 to 13·9)
Marital status			
Married	28/1443 (1·5%, 0·0 to 4·5)	14/1439 (1·1%, 0·0 to 6·2)	–0·3% (–4·0 to 6·2)
Divorced or separated	919/1443 (63·0%, 53·4 to 74·9)	930/1439 (63·9%, 49·3 to 79·8)	0·9% (–11·1 to 15·6)
Widowed	282/1443 (21·1%, 12·8 to 28·9)	282/1439 (21·1%, 9·7 to 36·2)	–0·1% (–17·5 to 23·4)
Never married	214/1443 (14·4%, 6·8 to 29·3)	213/1439 (13·9%, 6·6 to 34·8)	–0·5% (–15·3 to 20·9)
Age started sex work (years)			
<18	128/1443 (9·0%, 5·9 to 17·1)	160/1438 (12·2%, 7·2 to 17·8)	3·1% (–2·8 to 8·9)
18–19	153/1443 (9·9%, 6·4 to 16·7)	174/1438 (11·4%, 7·1 to 17·0)	1·6% (–9·6 to 6·8)
20–24	438/1443 (28·3%, 21·0 to 38·5)	420/1438 (28·4%, 21·9 to 36·9)	0·1% (–12·9 to 12·3)
25–29	351/1443 (23·8%, 15·9 to 27·1)	350/1438 (23·9%, 17·7 to 29·4)	0·1% (–9·3 to 78·2)
≥30	373/1443 (29·0%, 23·1 to 35·2)	334/1438 (24·2%, 14·3 to 33·1)	–4·9% (–15·1 to 9·3)
Time in sex work (years)			
<3	276/1443 (22·1%, 14·6 to 35·3)	295/1438 (22·1%, 7·4 to 28·4)	0·0% (–10·9 to 13·3)
3–5	420/1443 (28·7%, 23·8 to 34·2)	437/1438 (29·5%, 24·2 to 37·9)	0·8% (–9·8 to 8·3)
6–9	376/1443 (24·3%, 18·5 to 29·4)	347/1438 (22·4%, 14·0 to 29·1)	–1·9% (–9·5 to 5·5)
10–19	286/1443 (19·3%, 10·7 to 26·2)	284/1438 (20·6%, 11·4 to 29·7)	0·6% (–9·8 to 8·9)
≥20	85/1443 (5·6%, 3·5 to 9·5)	75/1438 (5·4%, 1·2 to 12·7)	–0·2% (–8·3 to 3·5)
Number of clients in the previous week			
0	84/1444 (6·2%, 3·3 to 9·1)	91/1439 (6·6%, 3·4 to 10·6)	0·4% (–1·8 to 3·3)
1–5	696/1444 (52·2%, 37·2 to 75·1)	749/1439 (54·7%, 42·7 to 72·1)	2·6% (–21·1 to 24·2)
6–10	371/1444 (24·6%, 13·9 to 34·2)	361/1439 (23·3%, 17·3 to 29·8)	–1·3% (–16·7 to 15·8)
11–15	126/1444 (7·2%, 2·4 to 11·2)	114/1439 (7·4%, 2·5 to 13·1)	0·2% (–4·3 to 6·1)
≥16	167/1444 (9·9%, 1·3 to 18·1)	124/1439 (8·0%, 2·7 to 16·0)	–1·9% (–11·4 to 2·8)

For mean respondent-driven sampling weighted proportions, crude values are reported as well as RDS-II-weighted cluster summary means and ranges. One participant in the control group had missing education and marital status data, and one woman in each group had missing data on age at which sex work was started. The pair differences were calculated by subtracting the mean for the control cluster from that for the intervention cluster within each pair and taking the mean of differences.

Table 1: **Sociodemographic characteristics of the full respondent-driven sample at the end of the intervention assessment period**

Eligibility data were missing for 70 participants, mostly from two sites (Chinhoyi n=3, Chivhu n=20, Gutu n=5, and Magunje n=42), who were interviewed at baseline and tested for HIV. We excluded these women from the analysis after confirming that excluding them did not meaningfully affect the results.

2883 women were recruited to the endline survey. Most (40% in each group) were aged 30–39 years, and many reported having no education, although over a quarter reported having completed secondary education (table 1). Around two-thirds of women were divorced, separated, or widowed. Just over half reported having started sex work before age 30 years and having had one to five clients in the previous week (table 1).

The respondent-driven sampling diagnostics analysis suggested that our estimates of the primary outcome had converged from the initial seed participant characteristics, with little evidence of biased recruitment (appendix p 19) or that recruitment by respondent-driven sampling differed by study group. We found some evidence that programme attendees might have been over-represented in the survey at the end of the assessment period, but to a similar degree in each group.

Before the trial started, attendance and uptake at clinics was higher in the usual-care group clusters than in the intervention group clusters but changed to more in the intervention clusters after the launch of the intervention (figure 2). Between April 1, 2014, and March 31, 2016,

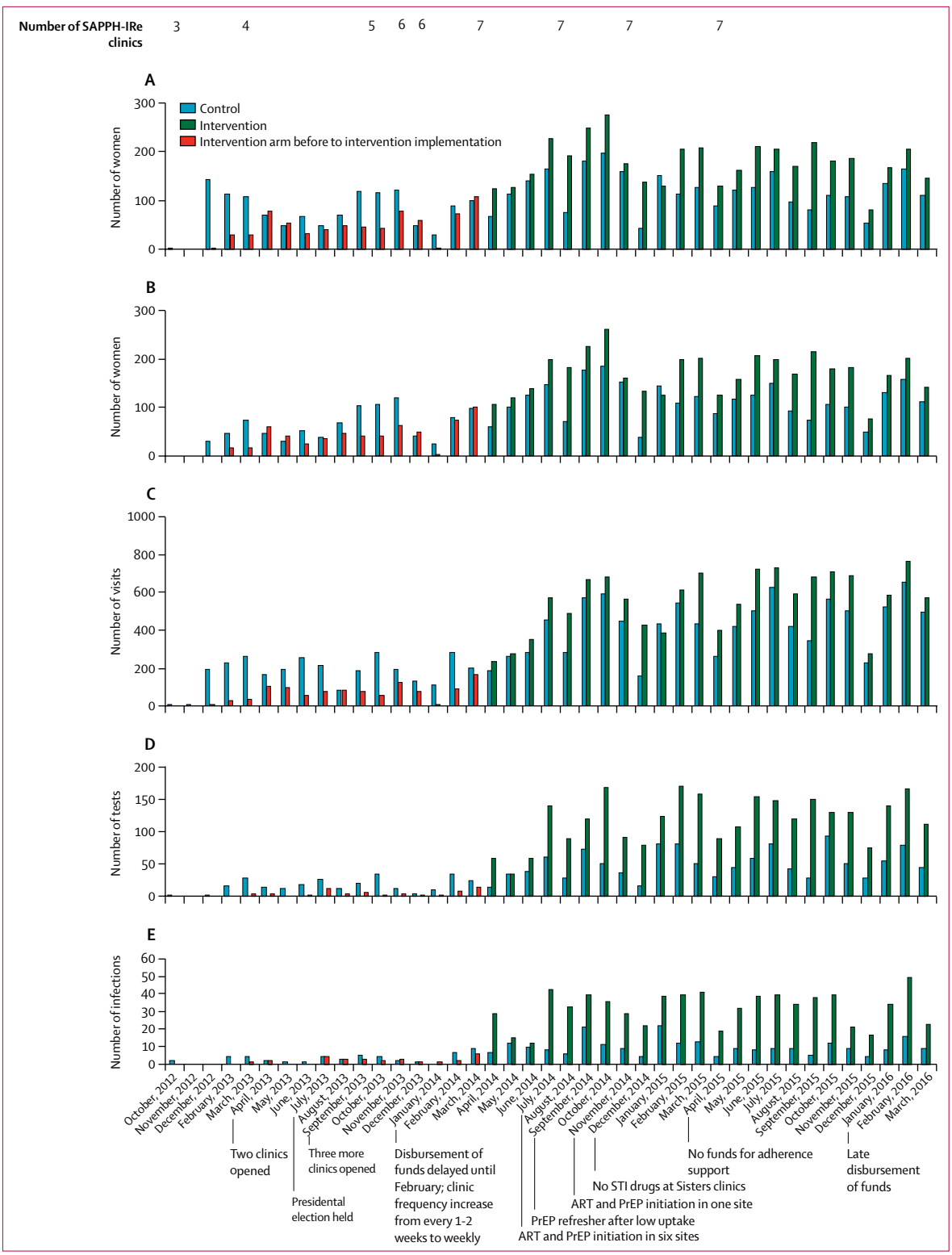

Figure 2: **Distributions of key programme indicators in the usual-care and intervention study groups over the trial period**
(A) Numbers of female sex workers seen in clinics. (B) Numbers of female sex workers attending clinics for the first time. (C) Numbers of clinic visits by clients. (D) Numbers of HIV tests. (E) Numbers of female sex workers with new HIV diagnoses. ART=antiretroviral treatment. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection.

	Mean respondent-driven sampling adjusted proportions (%, range)		Adjusted risk difference (% [95% CI])	p value
	Usual-care group	Intervention group		
Primary outcome				
Viral load ≥1000 copies per mL	279/1443 (19·1%, 13·6 to 25·1)	240/1439 (16·4%, 6·1 to 20·2)	–2·8% (–8·1% to 2·5)	0·23
Secondary outcomes				
HIV-positive test and reported being positive	695/869 (78·4%, 65·1 to 86·2)	669/828 (79·5%, 63·5 to 88·5)	0·2% (–8·8% to 9·3)	0·95
Reported being HIV positive and taking ART	580/695 (83·0%, 72·4 to 89·8)	594/669 (86·3%, 78·7 to 96·0)	3·4% (–2·9% to 9·7)	0·22
Reported taking ART and having viral load <1000 copies per mL	487/580 (86·5%, 80·9 to 90·0)	505/594 (85·9%, 78·7 to 96·7)	–0·5% (–6·8% to 5·9)	0·86
HIV positive with viral load <1000 copies per mL	590/869 (67·5%, 61·4 to 73·1)	588/828 (72·0%, 63·8 to 86·8)	5·3% (–4·0% to 14·6)	0·20
Knew HIV status	1068/1423 (74·6%, 65·1 to 80·2)	1063/1405 (75·7%, 68·8 to 85·2)	2·3% (–9·4% to 14·0)	0·63
Reported condomless sex with client in previous month	837/1358 (60·9%, 44·6 to 72·8)	715/1312 (54·0%, 36·2 to 79·2)	–7·2% (–18·0% to 3·7)	0·15
Reported good or very good relationships with other FSWs	949/1443 (66·9%, 55·7 to 75·0)	1013/1437 (68·6%, 46·8 to 85·5)	10·0% (–19·2% to 39·3)	0·42

Crude values include the seeds (ie, based on the survey at baseline, n=2576) and mean respondent-driven sampling proportions are calculated after exclusion of seeds and participants with missing primary outcome, education, and age data (ie, based on survey at the end of the intervention assessment period, n=2790). FSWs=female sex workers.

Table 2: **Effect estimates for the primary and secondary outcomes**

1007 more female sex workers were seen at outreach sites or drop-in centres in the intervention clusters than in the usual-care clusters (figure 1). In the usual-care clusters, substantially fewer female sex workers were seen for the first time, less than half as many HIV tests were done, around half as many new diagnoses of HIV were made, and fewer clinic visits were made overall than in the intervention clusters (figure 2). Additionally, in the intervention group there were 1·3 times more peer-educator contacts and 3·7 times as many community-mobilisation meetings (figure 1), and more than 7·2 times more women attended community mobilisation meetings (16 884 *vs* 2344) than in the usual-care group. 500 (38%) of the 1302 HIV-negative women offered PrEP and screened for eligibility opted to start PrEP in the intervention sites, and 405 (81%) returned for at least one follow-up visit. The total number of monthly visits by PrEP users by March 31, 2016, was 1844, and the median duration of follow-up was 3 months (IQR 1–5). 768 women started taking ART in the intervention sites, and 487 Adherence Sisters pairs were formed. 1405 mobile telephone text reminders were sent and 3741 calls for appointments for PrEP, ART, and repeat HIV testing were made.

In the survey at the end of the assessment period, 1263 (82%) of 1439 women in the intervention clusters reported contact with the programme in the previous 12 months, compared with 1243 (81%) of 1444 in the usual-care clusters. 188 (25%) of 608 HIV-negative women in the intervention group clusters reported that they had been offered PrEP compared with five (1%) of 572 in the usual-care group clusters, and 594 (86%) of 669 women who reported being HIV positive also reported they were taking ART in the intervention group, compared with 580 (83%) of 695 in usual-care group. At baseline in 2013, 30% of all women had viral loads of 1000 copies per mL or greater.[4]

Between baseline and the end of the assessment period, the proportions of women with viral loads of 1000 copies per mL or greater had reduced in both study groups: from 421 (30%) of 1363 women to 279 (19%) of 1443 in the usual-care group (35·1% reduction), and from 399 (30%) of 1303 women to 240 (16%) of 1439 in the intervention group (45·6% reduction). The weighted percentage risk difference, however, indicated little difference between groups (–2·8%, 95% CI –8·1 to 2·5, p=0·23). The value of the intercluster coefficient of variation, *k*, using baseline data was 0·14 with RDS-II weighting and 0·12 without.

590 (68%) of 869 HIV-positive women were virologically suppressed at the end of the assessment period in the usual-care group, compared with 588 (72%) of 828 in the intervention group, but the 95% CI for the risk difference included zero and negative effects (table 2). In both study

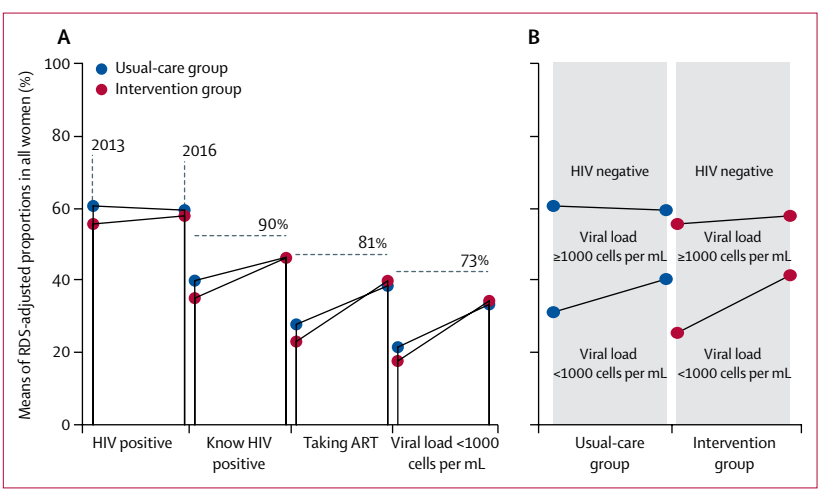

Figure 3: **Serrated HIV-treatment cascade diagram and comparison between study groups**
(A) Treatment cascades for both study groups in relation to the UNAIDS 90-90-90 targets. (B) Proportions of HIV-negative, HIV-positive and virally suppressed, and HIV-positive and not virally suppressed participants. All values were weighted by dropping the responses from seeds and weighting the values for each woman in each site by the inverse of her network size. In all bars, results on the left are for 2013 and those on the right are for 2016. ART=antiretroviral treatment.

groups, HIV prevalence remained the same between baseline and the end of the assessment period, but the proportions of HIV-positive women who reported being aware of their status, those taking ART, and those who were virologically suppressed increased (figure 3), with all changes being to a similar degree. The reductions in proportions of women with viral loads of 1000 copies per mL or greater were achieved by increases in the proportions of women virally suppressed rather than by reductions in HIV prevalence (figure 3). Similar proportions of women in the two study groups self-reported condomless sex with at least one client in the previous month (table 2). The proportions of female sex workers reporting good or very good relationships with other sex workers were lower in the usual-care group than in the intervention group, although the 95% CI for the difference between groups included zero and positive effects (table 2).

Discussion

In the context of an ongoing programme for female sex workers in Zimbabwe, we hypothesised that offering an enhanced prevention and treatment intervention package would lower the proportion of sex workers who had viral loads of 1000 copies per mL or greater. The intervention aimed to increase community mobilisation, active follow-up for repeat HIV testing, supply-side interventions that allowed starting of ART and provision of care on site in dedicated clinics for HIV-positive women, provision of prophylaxis with PrEP to HIV-negative women, and adherence to medications. The intervention strengthened engagement of female sex workers with services, but it did not lead to a significant population benefit beyond the ongoing usual care. There was some evidence, however, that the proportion of HIV-positive female sex workers with viral loads of 1000 copies per mL or greater was reduced.

Ours is among the first cluster-randomised trials of a targeted intervention for HIV control among female sex workers in any setting, and to our knowledge is the first done in Africa and since access to ART became widespread and oral PrEP was shown to be efficacious.[12] We used respondent-driven sampling to recruit research participants and a prespecified statistical analysis plan to adapt CONSORT principles for reporting and analysis.[14] We did an integrated, prospective process assessment alongside the trial to allow us to understand strengths and limitations of programme implementation.

Although our primary aim was not to track trends in engagement with care over time, we saw some patterns that might reflect the facilitating effect of the usual-care programme to increase uptake of HIV testing and lead to successful referral of female sex workers to treatment services in the context of the Ministry of Health's national treatment programme. In both study groups, female sex workers' engagement with services approached the UNAIDS 90-90-90 target for 2020. Of note, in the intervention group, the proportion of HIV-infected sex workers with viral loads lower than 1000 copies per mL was 72%, which is in line with the UNAIDS 90-90-90 targets.

The trial was done with programme funding but few additional resources to enhance usual care. For example, the numbers of peer educators supporting communities were low in both study groups. The potential for sustainability was integral to designing the intervention. We had planned to be able to support ART with viral load monitoring in the intervention clusters, but for logistical reasons this approach was impossible. Since the study ended, the standard of care for HIV-infected people in Zimbabwe has been strengthened by the revision of international[21] and national ART guidelines[22] and the commitment of the Zimbabwean Government to scale up differentiated care for ART supported by viral load results among those who need it most.[23] Provision must remain in place to maximise the coverage, engagement, and retention of female sex workers in health care, with increased resources for community-based demand creation and adherence support. The high uptake of ART services in the usual-care group suggests that sex workers, if supported, will attend services in the public sector. Of note, our approach did not attempt to identify the female sex workers who were most vulnerable and in greatest need of support. Therefore, although more women were seen, tested, and diagnosed as being HIV positive in the intervention group than in the usual-care group, we might not have reached those most in need of services. Interventions such as microplanning, which, by working with sex workers, maps hotspots, identifies all sex workers working in those areas, assesses their risk, and tailors outreach activities according to risk, have the potential to be more effective and efficient than our intervention, and might have a greater effect on the population.[24,25]

Our intervention incorporated one of the first projects to provide access to PrEP among female sex workers in Africa. Uptake was 38% among those women who tested HIV negative in intervention sites, which is high compared with 7% uptake among sex workers reported in South Africa.[26] Nevertheless, retention was low, with women taking PrEP for an average of just over 4 months. In South Africa, PrEP retention among female sex workers was only 22% at 12 months.[27] However, the primary outcome for the trial (proportion of female sex workers with viral load ≥1000 copies per mL) was predominantly driven by ART use rather than a decrease in the rate of new HIV infections, The relatively low proportion of women maintained on PrEP is, therefore, unlikely to have altered the population effect. When the trial was conceived, the evidence for effectiveness of PrEP in women was less clear than it has become,[28] and, therefore, our power calculations to determine population effect did not rely on a reduction in rate of new infections, but on increased coverage of ART. Rather than being

evidence of lack of PrEP effectiveness, therefore, our findings show the need for effective adherence support as PrEP is rolled out across the region, if coverage at the level required to reduce population incidence is to be achieved. The community-based support system we designed for adherence probably needs to be refined. Condom use is the mainstay of primary HIV prevention for sex workers and their clients. Although reported condom use with the latest client was reported by more than 95% of respondents in both study groups, consistent condom use with clients over the preceding month was suboptimum. Mathematical modelling suggests that increasing condom use among female sex workers in areas with generalised epidemics, even in the era of universal treatment, would have a substantial effect on population-level incidence of HIV.[24]

The study has limitations. First, we would have liked to do a larger trial over a longer period, but we faced resource constraints. Although the intervention effect among all female sex workers reported in our trial could be a result of chance, the weak evidence of effect among HIV-positive sex workers could potentially be important. Our intervention might have needed longer to have a population effect. We suggest more implementation studies of this type should be done to strengthen the evidence base, especially in Africa. Second, our use of respondent-driven sampling to recruit representative samples of female sex workers might have been subject to bias. Refusal rates are difficult to document with this design. Additionally, the intervention might have affected network structures differently from usual care and, in turn, affected recruitment. Our analyses into these dynamics suggested little evidence for bias and none for differential patterns by study group, but were not definitive, and indicated some areas for concern, most notably over-representation of female sex workers in contact with the Sisters services in both groups. Anticipating the effect of these potential biases on our estimate of intervention effect is difficult, but they highlight that caution is warranted. We are aware of only one other cluster-randomised trial that has used respondent-driven sampling surveys to determine population effect,[29] but no results have yet been published. Finally, most of the denominators for the secondary outcomes depended on characteristics after random assignment, such as HIV status, and, therefore, should not be interpreted as causal, especially where there is evidence that the denominator was changed by the intervention.

There is increasing recognition that the rigour of primary prevention programming needs to improve if the ambitious global goals for HIV elimination are to be reached.[30] Female sex workers in Zimbabwe, and, indeed, across Africa,[31] remain at high risk of HIV and other adverse outcomes. Encouragingly, we have shown that good outcomes are possible, at least within the context of providing comprehensive and dedicated services for sex workers. Intensifying community mobilisation to stimulate demand, supply, and adherence to primary prevention technologies, such as condoms and PrEP, and further improving treatment coverage, for example through use of status-neutral community-based differentiated care, are likely to strengthen population effects.

Contributors

FMC led the trial design, with involvement from VC, SN, JB, AP, and JRH. FMC led protocol development, with involvement from SN. FMC led the trial implementation with involvement from JB. JB led the process evaluation. JRH oversaw trial analysis and data interpretation. CD did the trial analysis, assisted by EF and SC. SC did the respondent-driven sampling diagnostic analysis and VC was involved in the sample size calculations. PM was the trial coordinator. JD was the trial data manager. FMC led data interpretation with involvement from VC, SN, DH, NM, TM, KH, OM, AP, and JRH. FMC, CD, and JRH wrote the paper and all authors were involved in the review of drafts.

Declaration of interests

We declare no competing interests.

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