RESULTS OF THE SAPPH-IRE TRIAL: A CLUSTER RANDOMISED TRIAL OF A COMPREHENSIVE TARGETTED COMBINATION PREVENTION INTERVENTION TO SUPPORT FEMALE SEX WORKERS IN ZIMBABWE TO LINK AND ADHERE TO ANTIRETROVIRALS FOR TREATMENT AND PREVENTION

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ABSTRACT (WORD COUNT 259, MAX 250)

BACKGROUND

Strengthening female sex workers' (FSW) engagement with services is needed to eliminate HIV. We aimed to determine the impact of a targeted combination intervention for FSW in Zimbabwe.

METHODS

We conducted a cluster-randomised trial between 2014-2016 randomising 14 clusters (areas surrounding FSW clinics) in matched pairs to usual-care (free sexual-health services supported by peer educators, including HIV testing on demand, referral for antiretroviral therapy (ART), and health education) or enhanced-intervention arms (regular HIV testing, on-site ART and pre-exposure prophylaxis; adherence support, and intensified community mobilization).

Primary outcome: proportion of all FSW with HIV viral load (VL) >=1,000 copies per mL, assessed through respondent driven sampling surveys. We used an adapted cluster-summary approach to estimate risk differences.

RESULTS

At intervention sites, 4,619 FSW attended clinics compared to 3,612 in comparison sites, twice as many were tested (2,606 vs 1,151) and diagnosed HIV positive (1,052 vs 546). The proportion of all FSW with VL >=1,000 copies per mL fell in both arms, (29.5% (407/1317) to 19.1% (272/1397) in usual-care and 30.2% (384/1259) to 16.4% (232/1393) in enhanced intervention arm) but with a risk difference of only -2.8% (95% CI: -8.1%, 2.5%) at endline, *p*-value=0.23. Among HIV-positive women, the proportions with VL<1000 copies per mL rose to 72.0% (562/794) in the enhanced-intervention and 67.5% (569/841) in the usual-care arm, adjusted risk difference of 5.3% (95% CI: -4.0%, 14.6%), *p*-value=0.20. There were no adverse events.

INTERPRETATION

Within a dedicated FSW programme, high levels of HIV diagnosis and treatment are achievable. Further research is required to optimise programme content and intensity for population impact.

FUNDING

The Sisters Antiretroviral therapy Programme for Prevention of HIV: an Integrated Response (SAPPH-IRe) trial was funded by United Population Population Fund (UNFPA) via Zimbabwe's Integrated Support Fund which received funds from DfID, Irish Aid and SIDA. A small amount of funding for survey work is from GIZ. USAID supported the cost of PSI Zimbabwe to deliver ART and PrEP to sex workers as part of the trial. We received a donation of Truvada for PrEP use for the trial from Gilead Sciences.

INTRODUCTION

Worldwide, female sex workers have approximately 13.5-times higher odds of HIV infection than women in the general population[1]. Many have reduced access to testing and treatment, and face barriers to adherence[1,2]. In Zimbabwe, analysis of data from 2009-2013 found HIV incidence among female sex workers to be over 10 new cases per 100 person-years at risk[3]. Only 67% were aware of their HIV status, while less than 50% living with HIV had an undetectable viral load, defined as <1000 copies per mL[4]. Consistent condom use with clients was reported by 65-73%. Heterosexual transmission of HIV is unlikely to occur with viral load of <1500 copies per mL[5]. Modelling suggests that over 40% of new infections among the general population are attributable to unsafe sex work, because of both high HIV incidence and high prevalence of infectious HIV among this group, leading to transmission to others[6]. While guidelines for interventions for female sex workers exist[7], few evaluations have assessed impact on engagement with HIV prevention and care, particularly in Africa and since the preventative effects of ART and efficacy of oral pre-exposure prophylaxis (PrEP) have become clear[8]

Reducing the burden of infectious HIV among female sex workers requires interventions that strengthen demand, enhance supply, and support optimal 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 enhance risk reduction. Supply-side interventions should increase accessibility and availability of HIV-testing and treatment, and of HIV prevention tools such as condoms, contraception, and PrEP. For adherence, interventions should support behavioural self-efficacy and skills[9]. Based on these principles, we enhanced the existing *Sisters* programme to develop the *S*isters *A*ntiretroviral *P*revention *P*rogramme – an *I*ntegrated *Re*sponse (*SAPPH-IRe*) combination-HIV-prevention-and-treatment-intervention package, and evaluated its impact on the proportion of all female sex workers with an HIV viral load >=1000 copies per mL in a cluster-randomised trial in Zimbabwe (see Theory of Change Webappendix 2 page 4). Our hypothesis was that the targeted and dedicated delivery and support of our enhanced intervention would reduce the proportion of female sex workers living with an HIV viral load >=1000 copies per mL when compared with the current WHO-guideline-based usual care.

METHODS

TRIAL DESIGN

We conducted a pair-matched, 1:1 allocation-ratio, parallel, cluster-randomised-controlled trial. Trial sites were purposively selected from 36 *Sisters* sites. Sites were at least 90 kilometres apart to minimise contamination, confirmed through review of programme data to explore mobility between sites. Sites were pair-matched based on 'type' of site (e.g. town, growth point, colliery/army base) and on whether the site was providing services for sex workers for the first time or has been providing dedicated sex worker services before the trial. Female sex workers accessing dedicated services would receive services available in that site, regardless of participation in research activities (protocol available at http://www.ceshhar.org.zw/sapph-ire-trial-protocol. Randomisation was conducted in a public ceremony on 31st January 2014 (see **Webappendix 1**, page 2). A baseline survey was conducted in all 14 sites in 13th November- 20th December 2013 using respondent driven sampling (RDS)[4]. Trial outcomes were assessed using RDS surveys conducted in 11th April – 6th May 2016 after 21 months of intervention.

SETTING

The SAPPH-IRe trial was conducted across 14 sites in Zimbabwe, where the national adult HIV prevalence among women is 16.7%[10] and sex work is illegal. Sex workers mainly work independently of gatekeepers in bars or on the street, with brothels relatively uncommon. Female sex workers have been identified as a key population in Zimbabwe's National HIV and AIDS Strategic Plan since 2006[11–13]. In 2009, the National Sex Work Programme, Sisters with a Voice (*Sisters*), was established, providing HIV prevention and sexual health services plus assisted referral to HIV treatment[3]. The SAPPH-IRe trial was nested within this programme[14].

INTERVENTIONS (SEE **WEBAPPENDIX 3** PAGE 5)

In the usual-care arm, the *Sisters* programme provided targeted HIV services following WHO guidelines[7],including provision of free condoms and contraception, free HIV testing and counselling, syndromic management of sexually-transmitted infections, health education, community mobilization, and legal advice. Activities were supported by trained peer educators. Services were provided at drop-in centres based at primary care clinics on the same day each week. Women who required HIV care and/or antiretroviral treatment (ART) were referred to government services. Women were not actively followed up.

In the enhanced-intervention arm, the *Sisters* programme was augmented with additional elements. Extra community mobilisation activities aimed to increase use of prevention and treatment modalities by (i) raising awareness of the benefits of ART and PrEP; (ii) strengthening support networks to encourage health-promoting behaviour including adherence; and (iii) building leadership skills (see **Webappendix 3** page 5 and **Webappendix 4** page 6). ART and PrEP users were encouraged to join a community-based 'Adherence Sisters' programme (see **Webappendix 3** page 5). Activities designed to encourage 6-monthly repeat HIV testing, including SMS-messaging reminders, were implemented for women testing HIV-negative. We enhanced clinical services so that ART and PrEP could be initiated on-

site. ART initiation complied with local and international guidelines. PrEP was offered to all women testing HIV-negative. Female sex workers opting for PrEP attended two screening visits prior to PrEP initiation. Clinical and social support services were delivered by clinical staff. SMS and follow-up phone calls were used to support clinic attendance.

Enhanced-intervention delivery in the seven sites began in April 2014. On-site initiation of ART and PrEP was rolled out to enhanced-Sisters sites from July 2014 (in one site, 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.

PROGRAMME DATA

Implementation of the interventions in both arms was monitored through programme records that included checklists, staff and training records, clinic attendance records, logs of community mobilization activities, adherence sisters programme registers, peer education contacts, qualitative research, and a programme diary to record key contextual factors (see Monitoring and Evaluation Framework **Webappendix 5** page 7).

INCLUSION CRITERIA AND SAMPLING FOR OUTCOME SURVEYS

Endline surveys were undertaken during 11th April-6th May 2016. Female sex workers were eligible for inclusion if they had exchanged sex for money in the past 30 days and were aged 18 or older. Of note, they had to have been living or working in the site where they were interviewed for at least 6 months.

Since it was not feasible to assemble a population sampling frame, we used RDS to obtain a representative sample of the female sex worker population[15]. Sex work in Zimbabwe is not primarily venue-based, and sex workers are well-networked[16]. In each site, we conducted geographic and social mapping. We purposefully selected initial 'seeds' of 6 or 8 women per site representing a mix of ages, sex-work types, and geographic locations. We interviewed seeds, gave them two coupons to distribute to peers within two weeks, and read them a sample 'recruitment script'. Women who received a coupon could attend an interview, and would subsequently be given two coupons for their peers. In all 14 sites, five iterations of this process ("waves") were performed, excluding seeds. Participants were given US$5 incentives for participation and US$2 for each participant recruited. Checks were included to ensure coupons were genuine and minimize repeat participation.

Interviewer-administered questionnaire data were collected on tablet computers and uploaded to a database daily. The 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. We collected data to determine personal network size for RDS adjustment: we asked each participant how many female sex workers she knew whom were aged over 18, lived at the site, whom she had seen in the last month, and whom she would consider recruiting to the study. A finger-prick blood-sample (dried-blood spot) was collected from each woman for HIV antibody testing and measurement of HIV viral load.

Procedures for the baseline survey conducted in 2013[4] were identical to that of the endline surveys in 2016. While it was not possible to blind survey teams to intervention status, all four teams conducted surveys in both intervention and control communities.

Laboratory Methods

Blood samples were air-dried on filter papers and stored at room temperature until transported bi-weekly to the Flowcytometry Laboratory in Harare. If HIV antibodies were detected using AniLabsytems EIA kit (AniLabsystems Ltd, OyToilette 3, FIN-01720, Finland) then the sample was retested for HIV viral load using NucliSENS EasyQ HIV-1 v2.0, both to confirm HIV positive status and to quantify the viral load. For samples with a positive HIV antibody test using Anilab EIA, but an undetectable viral load, a second confirmatory ELISA was performed (Enzygnost Anti-HIV 1/2 Plus ELISA (Germany). Laboratory staff were blind to intervention allocation.

Primary outcome

We hypothesised that, after 21 months of intervention, a lower proportion of female sex workers from sites randomised to the enhanced-intervention arm would have a HIV viral load >=1000 copies per mL than female sex workers in the usual-care arm.

The primary outcome variable was calculated as:

$$\text{Primary outcome} = \frac{\text{No. survey participants with positive HIV antibody \& viral load } >= \text{ 1000 copies per mL}}{\text{No. survey participants who had an HIV antibody test}}$$

Secondary endpoints

Nine pre-specified secondary endpoints, including the proportion of HIV positive female sex workers with a HIV viral load >=1000 copies per mL, were analysed using the same analytic framework as the primary outcome, described below (see tables for details). Secondary outcomes reflected aspects of treatment or prevention intended to be affected by the intervention. For many of these, the denominators depended on post-randomisation characteristics, such as HIV status, and therefore causal interpretations should be cautioned, especially where there is evidence that the denominator was changed by the intervention.

Sample size justification

Our sample-size considerations have been published[14]. We estimated that we would require 200 women per site, and 14 matched pairs to have 80% power to detect a one third reduction in proportion of female sex workers with a viral load >=1000 copies per mL over the duration of the trial.

Statistical analysis

The statistical analysis followed a published analytical plan[14] (see **Webappendix 6** page 8 for details). In brief, we assessed evidence of bias in our operationalisation of RDS (see **Webappendix 7** page 14). All of our analyses were conducted at the level of the cluster. To account for the RDS in our estimates of cluster characteristics, we used the RDS-II method: dropping seed responses and weighting each woman

in each site by the inverse of her network size, i.e. the number of other women that she could have recruited[17]. We described key sociodemographic characteristics of the sample recruited through RDS at both baseline (see **Web Appendix 8** page 20) and endline (**Table 1**) with the seeds included, and reported the cluster-means and ranges, by trial arm, by applying RDS-II weighting – which excluded the seeds.

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 arm. We used a linear regression model with a treatment dummy variable, dummmy variables for the pairs, and the baseline level of the outcome as regressors. We adjusted for age and sex using the 'two-step' method to adjust for individual-level covariates with a cluster-summary analysis[18]. The primary analysis code was written, shared with the trial Data Safety and Monitoring Board and conducted blind to treatment allocation (see **Webappendix 6** page 9 for details). We conducted two sensitivity analyses: running the analysis without weighting, and using a 'successive sampling' approach[19]. These analyses suggested the results were robust to how we treated the RDS data, and these analyses are not discussed further here (see **Webappendix 9** page 22 for details).

All analyses were conducted using R R version 3.4.3 (2017-11-30)[20], and RDS diagnostics used the 'RDS' R package[21].

ETHICS AND REGULATORY APPROVALS

Written informed consent was obtained from all survey participants, in English, Shona or Ndebele prior to conducting interviews and collecting blood samples. Signed consent was not required for programme participation. All female sex workers who initiated PrEP signed an agreement form since Truvada was not yet approved for use as PrEP by Medicines Control Authority of Zimbabwe. Ethical approval was received for the trial from the Medical Research Council of Zimbabwe, University College London, London School of Hygiene and Tropical Medicine and RTI International. Foreign researchers were registered with the Research Council of Zimbabwe. The trial was registered at Pan African Clinical Trials Registry (PACTR201312000722390) on December 9th, 2013.

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

STUDY PROFILE AND BASELINE BALANCE

No sites dropped out during the trial (**Figure 1**). At baseline (**Webappendix 8** page 20) and endline (**Table 1**) the recruited sample sizes were close to target, and socio-demographic and network characteristics were well-matched across trial arms. There was little missing data. However, at baseline 70 participants, mostly from two sites, were missing data on eligibility who were interviewed and tested for HIV. We included these women in the analysis after confirming that excluding them did not meaningfully affect the results. At endline, 2,883 women were recruited from across 14 sites. Recruited female sex workers were most commonly 30-39 years old (39.9% across both arms), and many reported no education (36.3%); although a substantial proportion also reported having completed secondary education (28.3%). The women were most commonly divorced, separated, or widowed (63.6%). The majority reported having started sex work before the age of 30, and most had 1-5 clients in the previous week (53.4%).

RDS-diagnostic analysis suggested that our estimates of the primary outcome had converged from initial seed participant characteristics. There was little evidence of biased recruitment (**Webappendix 7** page 14) or that the RDS recruitment differed by trial arm. There was some evidence that programme attendees may have been overrepresented in the endline survey, though this was similar in each arm.

INTERVENTION IMPLEMENTATION

Programme records show that between 1st April 2014 and 31st March 2016 28 more FSW were seen at outreach sites/drop-in centres in enhanced-intervention sites compared to usual-care sites (Figure 1). Enhanced-intervention sites saw 48% more female sex workers for the first time. Enhanced-intervention sites performed over twice as many HIV tests, and newly diagnosed nearly twice as many cases of HIV. There were 1.3 times more peer-educator contacts, 3.7 times as many community-mobilisation meetings held in the enhanced-intervention sites, and 16,884 community mobilization meeting attendances in enhanced-intervention arm compared to 2,344 in usual-care arm. By 31 March 2016, 500 women initiated PrEP at enhanced-intervention sites of 1,302 whom were screened (38%), and 405 (81%) returned for at least one follow-up visit. Overall, PrEP users had attended for 1,844 monthly follow up visits by 31 March 2016 (average of 4.37 months on PrEP). 768 women were initiated on ART at enhanced-intervention sites, and 487 Adherence Sisters pairs were formed. 16,759 SMS text reminders and 3,741 calls for appointments for PrEP, ART and repeat HIV testing were sent or made. **Figure 2** depicts how programme uptake changed over time from one year prior to the baseline survey to end of the trial. Of note, prior to commencing the trial, programme attendance and uptake was higher in control arm sites and this trend reversed with the introduction of the enhanced intervention.

In endline surveys, 82.4% (1217/1393)% of women in enhanced-intervention sites reported contact with the programme in the past 12 months, compared to 80.7% (1199/1398) in usual-care arm; 40.5% (182/363) of HIV-negative women reported that they had been offered PrEP (compared to 5.3% (5/84) in usual-care arm), and 86.7% (565/639) of all HIV-positive women reported they were on ART

(compared to 83.1% (563/672) in usual-care arm). At baseline, 29.7% of all women had a viral load greater than or equal to 1000 copies per mL overall[4].

PRIMARY OUTCOME

Between baseline and endline, there was a reduction in the proportion of women with a viral load greater than 1000 copies per mL in both arms. In the usual care Sisters arm, there was a 35.1% reduction (from 29.5% (407/1317) to 19.1% (272/1397)) compared to a 45.6% reduction in the enhanced-intervention arm (from 30.2% (384/1259) to 16.4% (232/1393)). However, there was little evidence of a difference between arms, with a weighted percentage risk difference at endline (95% CI) of -2.8% (-8.1%, 2.5%), *p*=0.23 (see **Table 3**).

The value of the intercluster coefficient of variation, *k*, using baseline data was 0.14 when accounting for the RDS-II weighting, and 0.12 without.

SECONDARY OUTCOMES

The proportion of all HIV positive women who were virologically suppressed at endline was 67.5% (569/841) in the usual-care arm and 72.0% (562/794) in the enhanced-intervention arm (see **Table 2**), an adjusted risk difference of 5.3% (-4.0%, 14.6%), *p*=0.20.

The left-hand portion of **Figure 3** shows the change in engagement with the treatment cascade between 2013 and 2016 using a 'serrated' cascade diagram with the baseline on the left of each bar and endline on the right. The results for the two arms are superimposed. While HIV prevalence remained the same between baseline and endline (flat slope of the first column of the cascade), in both arms there were increases in the proportion of HIV positive women who reported being aware of their status (upward slope of the second column), on ART (slope of third column), and who were virologically suppressed (slope of fourth column). Again, there is little evidence of a difference for any of these outcomes. The right-hand portion of Figure 3 shows the main trial outcomes for the two arms side-by-side, emphasising that the overall proportion of women with a viral load >1000 copies per mL was reduced in both arms by an increase in the proportion of women virally suppressed, and not a reduction in HIV prevalence.

Self reported condomless sex with at least one client in the previous month did not differ by arm: 60.9% (810/1313) in the usual-care arm, 54.0% (695/1269) in the enhanced-intervention arm: adjusted risk difference -7.2% (-18.0%, 3.7%), *p*=0.15.

There was a bigger increase in the proportion of female sex workers reporting 'good' or 'very-good' relationships with other sex workers in the enhanced-intervention arm (56.9% (723/1259) to 68.6% (980/1391)) compared to the usual-care arm (65.2% (862/1316) to 66.9% (921/1397)) although again there was little of a difference between the arms, with an adjusted risk difference of 10.0% (-19.2%, 39.3%), *p*=0.42.

DISCUSSION

In the context of an on-going programme for female sex workers in Zimbabwe, we hypothesized that offering an enhanced-intervention would lower the proportion of sex workers who have a viral load of >=1000 copies per mL. The enhanced intervention included more intensive community mobilization; active follow up for repeat HIV testing; supply-side interventions to provide ART-initiation and care on site for HIV-positive women and pre-exposure prophylaxis to HIV-negative women, and efforts to improve adherence to these medications. While our enhanced intervention strengthened engagement of female sex workers with services it did not lead to a significant population benefit beyond the on-going usual care in the proportion of female sex workers with a HIV viral load of >=1000 copies per mL in 2016. There was some evidence however that the proportion of HIV positive female sex workers was reduced.

Ours is among the first cluster-randomised trial of a targeted intervention for HIV control among female sex workers in any setting, and to our knowledge the first conducted in Africa and in the era of widespread access to ART and evidence of the efficacy of oral PrEP. We deployed a novel cluster-randomised trial design using RDS to recruit research participants, and published a statistical analysis plan to show how we would adapt CONSORT principles for reporting and analysis[14]. We conducted an integrated, prospective process evaluation 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 in care over time, these trends were striking and it seems plausible that this reflects the facilitating effect of the usual-care programme to increase uptake of HIV testing and of successful referral to treatment services of female sex workers, in context of the Ministry of Health's successful national treatment programme. In both arms, sex worker engagement as reflected in the treatment cascade was approaching the UNAIDS 90-90-90 target for 2020. Of note, in the enhanced-intervention arm the proportion of HIV infected sex workers with a viral load <1000 copies per mL was 72.3% (95% CI: 64.0%, 87.0%), mirroring the UNAIDS 90-90-90 target.

The trial was undertaken with programme funding and few additional resources to enhance the intervention; for example, the number of peer educators supporting communities was few and similar between trial arms. 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 enhanced-intervention arm, but for logistical reasons this proved impossible. The standard of care for HIV infected persons in Zimbabwe has since been strengthened by the revision of international[22] and Zimbabwean ART guidelines[23], and the commitment of the Zimbabwean government to scale up viral-load-supported differentiated care for ART among those who need it most[24]. It is critical that provision remains in place to maximize the coverage, engagement and retention of female sex workers, with increased resources for community-based demand creation and adherence support. The high uptake of ART services in the usual-care arm suggests that sex workers, if supported, will attend services in the public sector. Of note, our approach did not attempt to identify those sex workers who were most vulnerable and therefore in greatest need of support, so although more women were seen, tested, and diagnosed HIV positive in the enhanced-intervention arm, it is possible that we did not reach those most in need of services. Interventions such as microplanning that work with sex workers to map hotspots, identify all sex workers working in that

hotspot, assess their risk, and tailor outreach activities according to levels of risk have the potential to be more effective and efficient, thus having greater population impact[25,26].

The enhanced intervention incorporated one of the first demonstration projects of 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 in South Africa[27], but retention was low; on average women retained on PrEP for less than 4 months. Again in South Africa, PrEP retention among female sex workers was only 22% at 12 months[28]. However, the primary outcome for the trial (proportion with viral load of >=1,000 copies per mL) was predominantly driven by ART use rather than a decrease in the rate of new infections, therefore the relatively low proportion of women retained on PrEP is unlikely to have effected population impact. When the trial was conceived, the evidence for effectiveness of PrEP in women was less clear than it is now[29], and therefore our power calculations to determine population impact did not rely on a reduction in rate of new infections, but on increased coverage of ART. The lack of impact in the female sex workers population should not be taken as evidence of lack of PrEP effectiveness, but as demonstrating the need for effective adherence support as PrEP is rolled-out across the region, if we are to achieve coverage at the level required to reduce population incidence. It is likely that our community-based support for adherence needs to be refined. Condom use is the mainstay of primary HIV prevention for sex workers and their clients, and although reported condom use at last sex with a client was in excess of 95% in both arms, consistent condom use with clients over the preceding month was sub-optimal. Mathematical modeling suggests that increasing condom use among female sex workers in generalised epidemics, even in the era of universal treatment, would likely have a substantial impact on population-level incidence[25].

The study has limitations. First, we would have liked to have conducted a larger trial over a longer period but there were resource constraints. While the intervention effect among all female sex workers reported in our trial could be due to chance, the weak evidence of effect among HV positive sex workers is tantalizing and potentially important. It is possible our enhanced intervention may have needed longer to have a population impact. We suggest more implementation studies of this type should be conducted to strengthen the evidence base, especially in Africa. Second, our use of RDS to recruit representative baseline and endline samples may have been subject to bias. It is difficult to formally document refusal rates using this design. It is also possible that the enhanced intervention may have influenced network structures differently than the usual-care intervention and, in turn affected recruitment patterns. Our analyses into these dynamics were largely reassuring, suggesting little evidence for bias and none for differential patterns by trial arm. Nevertheless, these analyses are not definitive, and there were some areas for concern, notably that those recruited to the surveys appeared to over-represent those in contact with the *Sisters* services in both arms. It is difficult to anticipate the effect of these potential biases on our estimate of intervention effect, but they highlight that caution is warranted. We are aware of only one other cluster randomised trial to that used respondent driven sampling surveys to determine population impact[30].

There is increasing recognition that the rigor of primary prevention programming needs to improve if the ambitious global goals for HIV elimination are to be reached[31]. Female sex workers in Zimbabwe, and indeed across Africa[32], 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 mobilization to stimulate demand, supply and adherence to primary prevention technologies such as condoms and PrEP as well as further improving treatment coverage for example through use of status-neutral community-based differentiated care will likely further strengthen population impact.

DECLARATION OF INTERESTS

We received a donation of Truvada from Gilead Health Sciences to allow the provision of PrEP in intervention sites. We declare no other competing interests.

RESEARCH IN CONTEXT

Evidence before this study

Systematic reviews of HIV prevention and community empowerment interventions targeting female sex workers show these can reduce individual risk of HIV and sexually transmitted infections. Mathematical modeling suggests that the population attributable fraction of new infections contributed through commercial sex is high even in generalized epidemics. However, there are no previous randomized studies of the impact of dedicated sex worker programmes on HIV prevalence and suppression outcomes in Africa or elsewhere. To explore engagement of female sex workers with prevention and care PubMed was searched using the terms “sex workers” “HIV prevention”, “HIV treatment cascade”, “HIV care cascade”, with last search on August 7th 2017.

Added value of this study

To our knowledge this is the first cluster randomised trial to determine the impact of comprehensive programming targeting female sex workers. Additionally, it is one of the first trials to determine population level impact among sex workers through respondent driven sampling surveys.

Implications

Female sex workers are at very high risk of HIV. This trial clearly demonstrates that in the context of a dedicated programme, high levels of diagnosis and successful treatment of women with HIV are feasible. While our intensive mobilization efforts did increase the number of women seen, tested for and diagnosed with HIV, this did not translate into impact on outcomes of interest at least over the time frame of the trial. It is also possible that efforts need to be better targeted to ensure that those sex workers who are most vulnerable (younger women, newer entrants to sex work, with concomitant mental health or substance use) are prioritized for support to link them to prevention and care.

DECLARATION OF INTERESTS

We declare that we have no conflicts of interest.

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SAPPH-IRE TRIAL ANALYSIS - TABLES

04 April, 2018

ENDLINE CHARACTERISTICS

	Intervention n/N; mean RDS-weighted proportions (min-max)	Control n/N; mean RDS-weighted proportions (min-max)	Mean pair diff. (min-max)
Age			
18-19	36/1439; 2.5% (0.1%, 7.9%)	15/1444; 2.0% (0.2%, 4.5%)	0.6% (-2.3% - 6.6%)
20-24	241/1439; 17.9% (6.4%, 27.3%)	211/1444; 13.4% (8.3%, 19.9%)	4.5% (-6.4% - 8.3%)
25-29	300/1439; 19.2% (14.3%, 25.6%)	310/1444; 21.6% (15.4%, 28.9%)	-2.5% (-14.6% - 10.2%)
30-39	562/1439; 38.5% (32.5%, 44.2%)	596/1444; 41.3% (36.0%, 48.2%)	-2.8% (-14.4% - 5.7%)
40+	300/1439; 21.9% (9.1%, 39.4%)	312/1444; 21.7% (16.9%, 31.0%)	0.2% (-21.9% - 18.7%)
Education			
None	476/1439; 39.1% (16.5%, 51.1%)	419/1443; 33.5% (26.2%, 38.4%)	5.6% (-15.9% - 23.3%)
Primary	497/1439; 34.6% (26.8%, 48.6%)	512/1443; 36.3% (31.8%, 42.5%)	-1.6% (-15.8% - 10.3%)
Secondary	466/1439; 26.3% (18.0%, 36.7%)	512/1443; 30.3% (23.8%, 40.7%)	-4.0% (-18.7% - 12.9%)
Marital status			
Married	14/1439; 1.5% (0.0%, 6.1%)	28/1443; 1.6% (0.0%, 4.3%)	-0.1% (-3.9% - 6.1%)
Divorced/separated	930/1439; 63.8% (49.6%, 79.7%)	919/1443; 63.3% (54.6%, 76.1%)	0.5% (-11.5% - 16.6%)
Widowed	282/1439; 20.9% (9.6%, 36.3%)	282/1443; 20.7% (12.7%, 28.7%)	0.3% (-17.4% - 23.7%)
Never married	213/1439; 13.8% (6.5%, 34.7%)	214/1443; 14.4% (8.0%, 28.4%)	-0.6% (-14.8% - 21.1%)
Age started sex work			
<18 yrs	160/1438; 12.0% (7.1%, 18.0%)	128/1443; 9.2% (6.1%, 16.4%)	2.9% (-2.0% - 9.3%)
18-19 yrs	174/1438; 11.3% (6.9%, 16.8%)	153/1443; 9.6% (6.6%, 16.2%)	1.7% (-9.3% - 6.8%)
20-24 yrs	420/1438; 28.5% (22.3%, 36.5%)	438/1443; 29.0% (22.6%, 38.0%)	-0.5% (-12.6% - 12.3%)
25-29 yrs	350/1438; 24.3% (17.6%, 28.6%)	351/1443; 23.6% (15.4%, 26.7%)	0.7% (-9.1% - 8.7%)
30+ yrs	334/1438; 23.9% (14.0%, 32.3%)	373/1443; 28.6% (22.4%, 34.6%)	-4.8% (-16.3% - 7.4%)
Number of years in sex work			
<3 yrs	295/1438; 22.3% (7.2%, 28.0%)	276/1443; 21.5% (14.4%, 34.3%)	0.8% (-10.3% - 13.5%)
3-5 yrs	437/1438; 29.3% (24.0%, 37.7%)	420/1443; 28.5% (23.7%, 34.4%)	0.8% (-10.4% - 8.5%)
6-10 yrs	347/1438; 22.6% (14.5%, 30.3%)	376/1443; 24.6% (19.0%, 29.3%)	-2.0% (-9.3% - 7.6%)
10-20 yrs	284/1438; 20.5% (11.4%, 29.7%)	286/1443; 19.9% (12.8%, 26.8%)	0.6% (-9.8% - 8.9%)
20+	75/1438; 5.3% (1.3%, 12.4%)	85/1443; 5.5% (3.4%, 9.4%)	-0.2% (-8.1% - 3.5%)
Number of clients in the previous week			
0	91/1439; 7.1% (3.3%, 11.2%)	84/1444; 6.3% (3.8%, 9.0%)	0.8% (-1.6% - 7.0%)
1-5	749/1439; 54.6% (42.0%, 72.4%)	696/1444; 52.2% (36.9%, 74.2%)	2.3% (-20.0% - 22.4%)
6-10	361/1439; 23.2% (17.4%, 29.7%)	371/1444; 24.1% (15.0%, 32.6%)	-0.8% (-15.0% - 14.7%)

11-15	114/1439; 7.3% (2.5%, 12.9%)	126/1444; 7.4% (2.3%, 12.3%)	-0.1% (-4.2% - 4.9%)
16+	124/1439; 7.9% (2.6%, 15.7%)	167/1444; 10.1% (1.3%, 19.5%)	-2.2% (-11.5% - 2.8%)

Table 1: Socio-demographic characteristics of the full RDS sample at endline, N=2,883. Crude figures are reported with the mean of the RDS-weighted cluster-summaries, and the range. There was missing education data for one participant in the control arm, and also for marital status. The pair differences were calculated by subtracting the mean for the control cluster from the intervention cluster within each pair. The mean of the pair differences and the range is reported.

EFFECT ESTIMATES

	Intervention n/N; mean RDS-adjusted proportions (min-max)	Control n/N; mean RDS-adjusted proportions (min-max)	Adjusted-Risk Difference (95% CI)	p-value
Primary outcome				
Proportion of all FSW with VL >=1000 copies / ml	240/1439; 16.3% (6.0%, 20.2%)	279/1443; 18.9% (16.3%, 23.2%)	-2.8% (-8.1%, 2.5%)	0.23
Secondary outcomes				
Proportion of HIV-positive FSW who report being positive	669/828; 79.8% (63.6%, 89.0%)	695/869; 78.8% (62.8%, 87.4%)	0.2% (-8.8%, 9.3%)	0.95
Proportion of FSW who report being HIV-positive who also report being on ART	594/669; 86.5% (79.3%, 96.1%)	580/695; 82.0% (74.3%, 89.8%)	3.4% (-2.9%, 9.7%)	0.22
Proportion of FSW who report being on ART with VL < 1000 copies /ml	505/594; 85.9% (78.7%, 96.5%)	487/580; 86.9% (81.5%, 90.7%)	-0.5% (-6.8%, 5.9%)	0.86
Proportion of HIV-positive FSW with VL < 1000 copies /ml	588/828; 72.3% (64.0%, 87.0%)	590/869; 67.8% (60.1%, 73.4%)	5.3% (-4.0%, 14.6%)	0.20
Proportion of all FSW who know their status	1063/1405; 75.8% (68.5%, 85.6%)	1068/1423; 74.9% (66.4%, 80.7%)	2.3% (-9.4%, 14.0%)	0.63
Proportion of all FSW who report condomless sex with client in last month	715/1312; 53.7% (35.5%, 77.7%)	837/1358; 60.9% (47.1%, 73.0%)	-7.2% (-18.0%, 3.7%)	0.15
Proportion of all FSW with good or very good relationships with other FSW	1013/1437; 68.2% (46.4%, 85.3%)	949/1443; 66.0% (55.8%, 72.5%)	10.0% (-19.2%, 39.3%)	0.42

Table 2: Effect estimates for the primary and secondary outcomes using baseline and endline RDS surveys with seeds and participants with missing primary outcome, education, and age data removed (baseline N=2,576, endline N=2,790).

SAPPH-IRE TRIAL ANALYSIS - FIGURES

10 May 2018

FIGURE 1 - PARTICIPANT FLOW

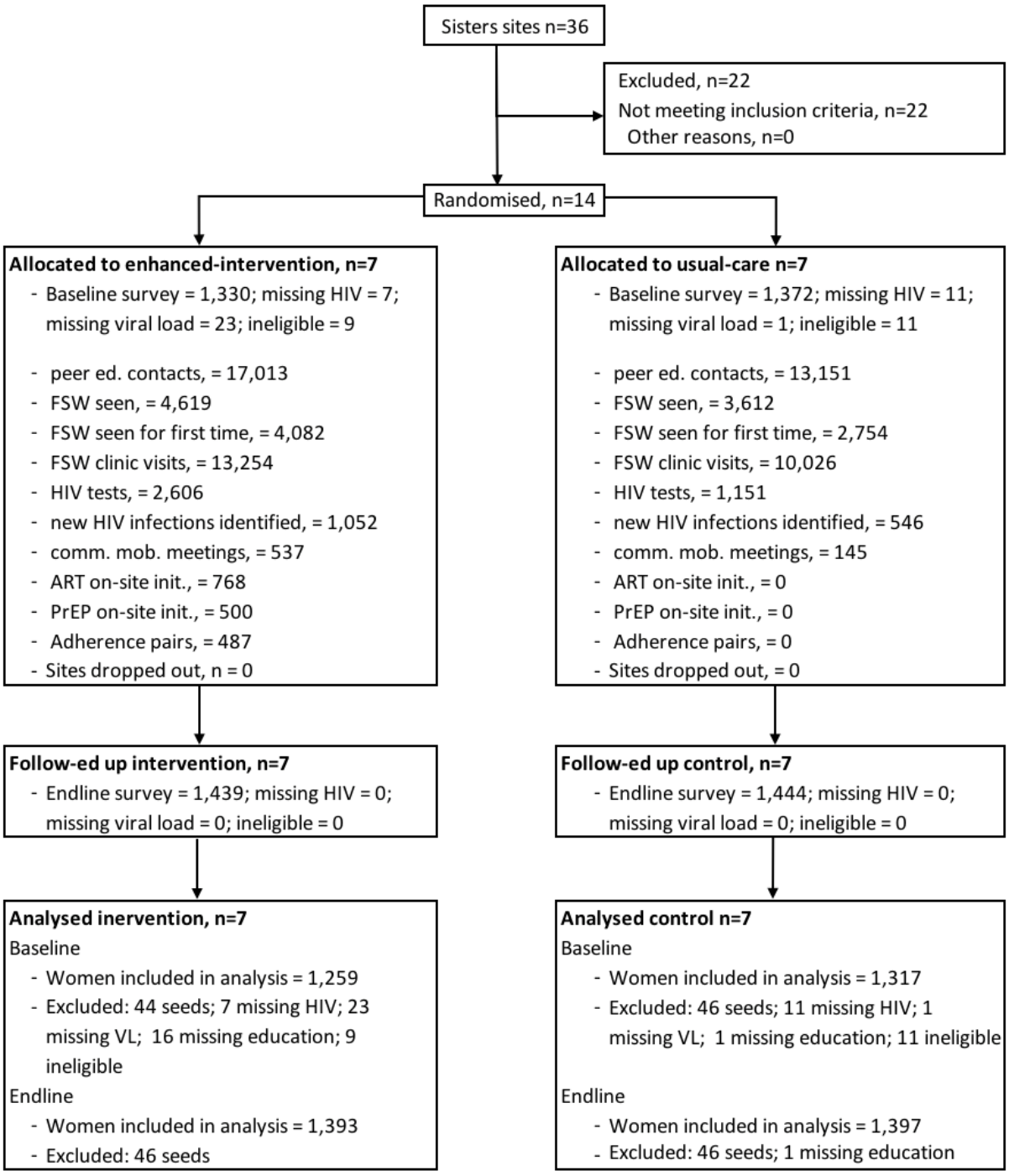

FIGURE 2 – KEY SISTERS PROGRAMME INDICATORS OVER TRIAL PERIOD

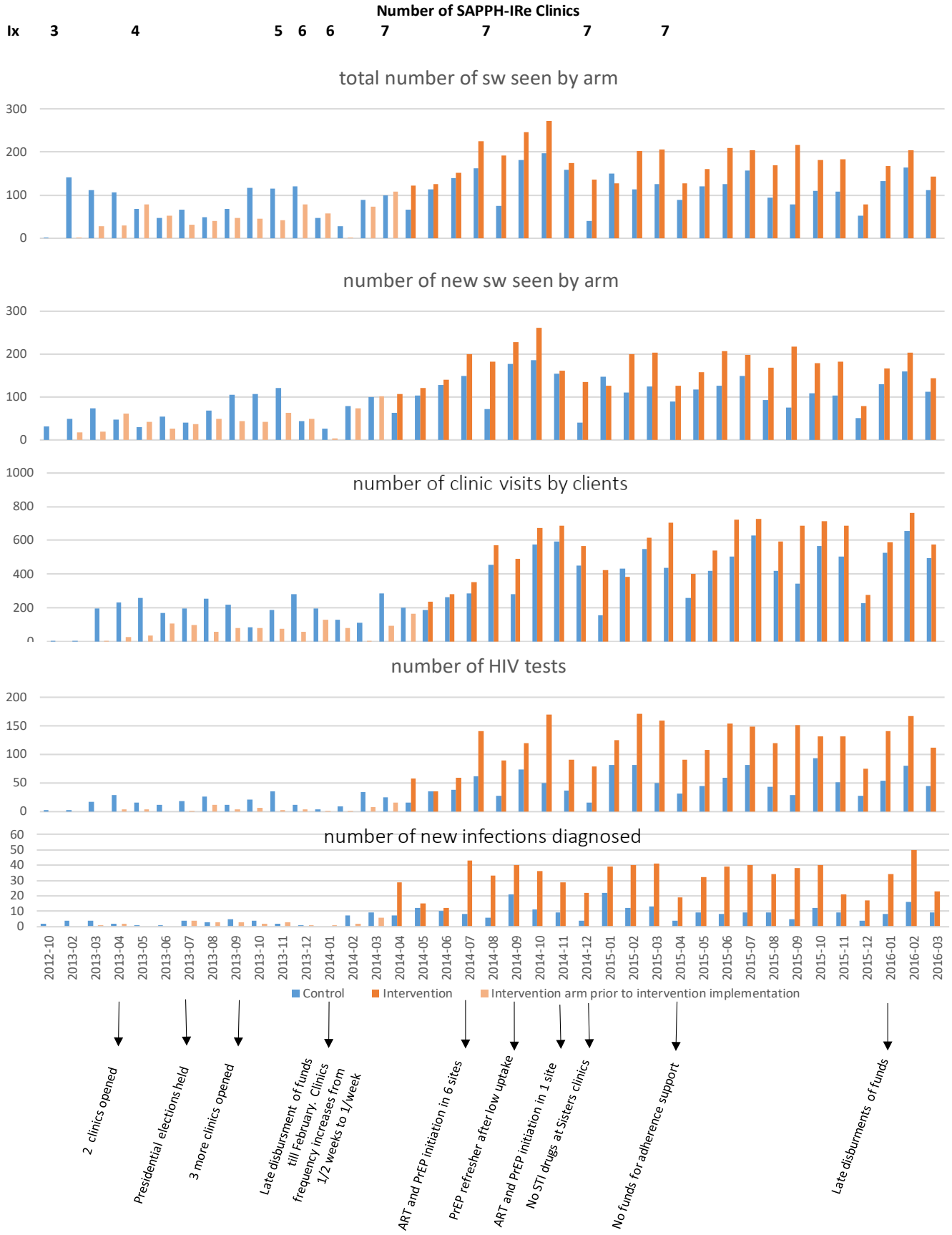

FIGURE 3: SERRATED HIV-TREATMENT CASCADE DIAGRAM AND COMPARISON BETWEEN ARMS

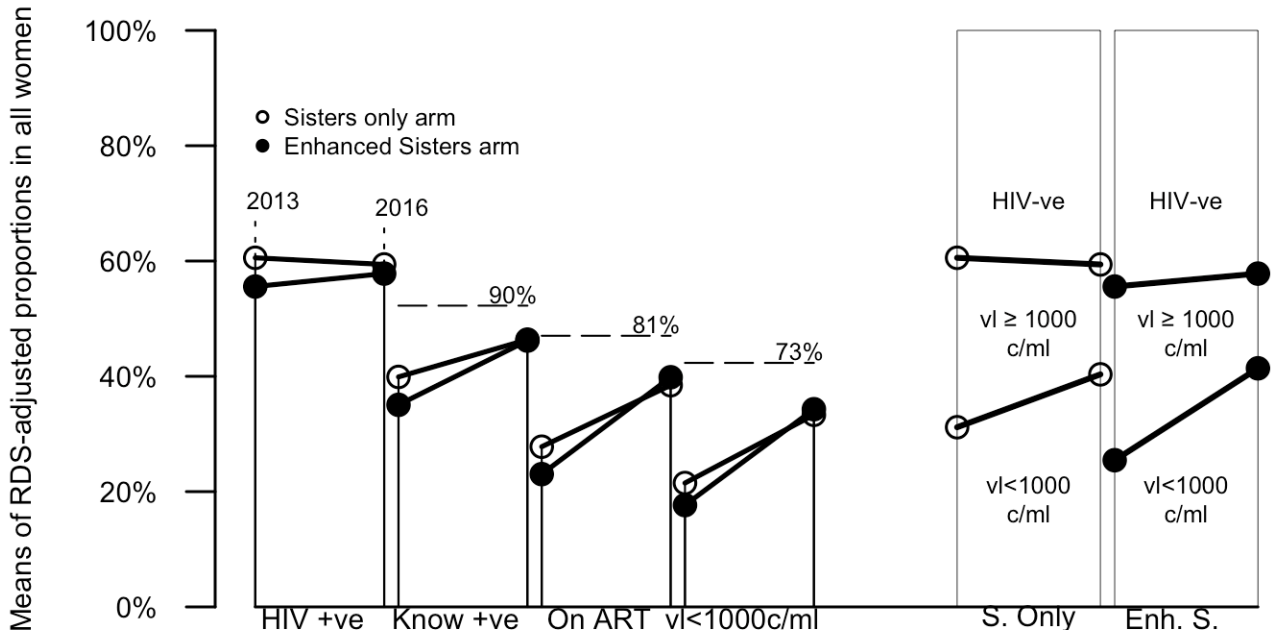

Figure 4: on the left of the figure, the treatment cascades for the two arms are superimposed, with the left of each bar showing results for 2013 and the right 2016. The cascades are shown for all women, with the 90:90:90 targets indicated with horizontal dotted lines. On the right of the figure, the proportions of female sex workers who are HIV-negative, HIV-positive and virally-suppressed, and HIV-positive and not virally-suppressed, for the two trial arms are shown side-by-side, with 2013 on the left of each bar and 2016 on the right. All values were adjusted with RDS-II.