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Cluster randomized stepped-wedge trial of a multi-level HIV prevention intervention to decrease amphetamine-type stimulants and sexual risk in Cambodian female entertainment and sex workers

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Abstract

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Contributors

All authors contributed to this manuscript: KP, AWC, ES, JE, LM, and CM developed the protocol for this cluster randomized stepped-wedge trial with comments and feedback from the entire study team. KP, AWS, ES, MS, PM and SN developed and implemented standard operating procedures for conducting assessments as well as delivering the multi-level CIPI intervention and ensuring protocol fidelity. AWC and CS adapted evidence-based CCT and cognitive-behavioural interventions targeting stimulant use with substantial contributions by Ean Nil (see acknowledgements). ES and KP developed the ME opportunity protocol with substantial support from MS and SN to identify in-country collaborators to provide microloans. CS and NY led efforts to coordinate with local governmental officials and non-governmental organizations through orientation workshops conducted in each of the ten provinces for efficient implementation of this trial. Analyses were conducted by JE with substantial feedback from KP, CM, AWC, and ES. Preliminary trial results were presented in Cambodia to community partners by SM, PM, CS, NY, and SN. KP and AWC worked together on the first draft of this paper and all authors provided edits and feedback. All authors reviewed and approved the final draft.

*These authors have contributed equally to this manuscript

Conflict of Interest

All authors contributing to this manuscript have nothing to disclose.

Clinical Trial Number: NCT01835574; (www.clinicaltrials.gov)

Background: HIV prevention for female entertainment and sex workers (FESW) may be optimized by addressing individual and structural risks. We examined the impact of a sequentially delivered intervention to decrease sexual risk, amphetamine-type stimulant (ATS) use, and improve economic well-being in Cambodian FESW.

Methods: A cluster randomized stepped-wedge trial was conducted in 10 Cambodian provinces to test multi-level intervention in high risk FESW. After baseline screening in 1198 women, those screening positive for ATS use disorder were allocated to a 12-week conditional cash transfer intervention followed by a 4-week cognitive-behavioural aftercare group (CCT+AC). At six months, ATS abstinent participants were offered a microenterprise (ME) opportunity. Co-primary outcomes assessed in 600 FESW at each 6-, 12- and 18-month follow-up assessments, included: 1) number of sexual partners (past three months); and 2) ATS urine toxicology positive (Tox+) results. Secondary outcomes included indicators of economic well-being.

Results: Relative to baseline, FESW reported fewer sexual partners at all follow-up assessments with a significant 50% decrease at 12-months (Adjusted Rate Ratio [ARR]=0.50; 95%CI: 0.25, 0.95). Women had 60% lower odds of being ATS Tox+ (Adjusted Odds Ratio [AOR]=0.40; 95%CI: 0.25, 0.65) at 6-months, and continued but non-significant reductions at 12- and 18-months. Improvements in economic well-being indicators were observed at 12- and 18-months.

Conclusions: Findings support the robust effectiveness of the sequentially delivered CCT+AC and ME interventions for boosting HIV prevention for Cambodian FESW. Further research is needed to inform the scale up and improve durability of this comprehensive approach with FESW in Southeast Asia.

Keywords

Amphetamine-type stimulants; Conditional cash transfer; HIV prevention; Contingency Management; Microenterprise; Sex Work

1. Introduction

In Cambodia, women engaged in transactional sex continue to show heightened HIV risk (Vun et al., 2014). From 2007–2010, two prospective cohorts of young adult female entertainment and sex workers (FESW) in Phnom Penh observed high but declining HIV prevalence (23.0% to 15.5%) and incidence (3.5% to 1.2%) (Couture et al., 2012; Couture et al., 2011; Page et al., 2013). Amphetamine type stimulant (ATS) use is an established risk factor for HIV in Cambodian FESW (Couture et al., 2012; Couture et al., 2011) and economic pressures fuel its use (Maher et al., 2011a; Maher et al., 2011b). Despite the notable HIV risk associated with ATS for many key populations around the globe (Colfax et al., 2010), relatively little attention has been devoted to implementing evidence-based interventions to decrease ATS use.

Structural factors including poverty, negative impacts of public policy and policing, and violence, are also key barriers to HIV elimination among Cambodian FESW (Draughon Moret et al., 2016; Maher et al., 2015). The number of FESW has increased markedly, and anti-trafficking legislation aimed at suppressing sexual exploitation (Maher et al., 2015; Page et al., 2013), has paradoxically increased challenges to access the highest risk women and

hindered HIV prevention efforts (Maher et al., 2011a; Vun et al., 2014). To address HIV prevention in the large population of FESW (estimated at more than 40,000 women in Cambodia), an HIV prevention program called SMARTgirl was widely implemented in Cambodia, which used targeted communication tools to promote HIV prevention, HIV and STI testing, and reproductive health service uptake (FHI, 2011). Optimizing extant HIV prevention services like SMARTgirl with Cambodian FESW will require comprehensive, multi-level approaches that target structural barriers as well as individual-level sexual and drug risk exposures.

Because there is limited evidence for the effectiveness of pharmacotherapy for stimulant use disorders, research is needed to optimize existing behavioural interventions with ATS-using FESW. First, brief interventions such as that developed by the World Health Organization (WHO) achieve short-term reductions in ATS use (Humeniuk et al., 2012), but more intensive treatment may be necessary for those with stimulant use disorders. Second, conditional cash transfer (CCT) interventions provide cash incentives as positive reinforcement for health behaviour change (Lagarde et al., 2009), and may also address poverty as a structural barrier to HIV prevention (Baird et al., 2012). CCT is an evidence-based intervention that has demonstrated moderate effect sizes in decreasing stimulant use (Petry et al., 2012; Prendergast et al., 2006), but success has been mixed in HIV/AIDS prevention (Baird et al., 2012; Pettifor et al., 2016). Third, intensive outpatient cognitive-behavioural treatment reduces stimulant use and sexual risk in the United States (Carrico et al., 2016b), but scalable models are needed in resource-limited settings (Carrico et al., 2016a). Finally, given that FESW experience multiple other structural risks for HIV in addition to ATS, there is also a need for interventions to reduce the impact of these. Microenterprise (ME) opportunities have potential for this, and have been shown to reduce number of sex partners and facilitate departure from sex work (Odek et al., 2009; Sherman et al., 2006).

The effectiveness of multi-level HIV prevention approaches remains uncertain (Shannon et al., 2015). Among FESW, studies have targeted an array of individual, community, and structural factors relevant to reducing HIV risk (Kang et al., 2013; Kerrigan et al., 2016; Reza-Paul et al., 2008), and findings support potential benefits. Nevertheless, current evidence is limited by the fact that previous studies did not employ randomization to address possible bias in selecting communities to receive these types of interventions. Using an implementation science approach (Padian et al., 2011), we implemented a cluster randomized stepped-wedge trial to test the effectiveness of a multi-level intervention to optimize HIV prevention by reducing ATS use and improve economic well-being in Cambodian FESW (Page et al., 2016).

2. Materials and methods

2.1 Overview

An existing nationally disseminated HIV prevention program for Cambodian FESW, SMARTgirl, was leveraged as the delivery platform for the Cambodia Integrated HIV and Drug Prevention Implementation (CIPI) multi-level intervention (FHI, 2011). Launched in 2009 as a social marketing health promotion program, SMARTgirl uses targeted

communication tools to promote HIV and STI testing as well as reproductive health service uptake, and is implemented by local non-governmental organizations (NGO). The CIPI intervention was delivered to 10 randomized provinces selected based on: 1) active implementation of SMARTgirl services for FESW; and 2) the highest HIV prevalence. There was an enrollment target of 120 women in each province for a total of 1,200 women for baseline data collection (Page et al., 2016). The CIPI intervention aimed to provide additional intensive assessment and brief counselling for sexual and drug use risk behaviours, as well as the sequentially delivered CIPI CCT+AC and ME interventions to FESW (Figure 1). At baseline, all women completed interviewer-administered surveys, provided urine to test for recent ATS use (Innovacon Multi-Drug Screen Test Panel Dip Kit; Redwood Toxicology Laboratory, Inc., Santa Rosa, CA and Specimen Validity Testing from Innovation, Inc., San Diego, CA), and self-collected vaginal swabs to measure prostate specific antigen (PSA) using OneStep ABAcard® p30 rapid PSA test (Abacus Diagnostics, Inc., West Hills, CA) as an indicator of recent unprotected vaginal sex (Evans et al., 2013). PSA testing has been demonstrated to have high positive predictive value as a biomarker for unprotected sex (Macaluso et al., 1999).

HIV testing and counselling was offered to all women. Women reporting any recent (last 3 months) ATS use and those scoring moderate or high risk for an alcohol use disorder on the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) were provided with a brief prevention counselling message (Humeniuk et al., 2012).

Following baseline, a 16-week CCT+AC intervention was delivered to women who screened positive for an ATS use disorder (i.e., moderate or high risk on this ASSIST *and* were positive on urine toxicology screening (ATS Tox+) (Carrico et al., 2016a). All FESW who were abstinent from ATS at the 6-month follow-up were eligible for the ME opportunity (including those identified at baseline and those who met criteria after completing the CCT +AC intervention). Six hundred (of the projected 1200 enrolled at baseline) FESW were purposively sampled to complete three follow-up assessments every six months to measure the intervention effectiveness. Of the sixty women in each province that were selected for follow-up assessments, we attempted to retain all FESW who were eligible for CCT+AC and the remaining women were sampled based using convenience methods, including recontacting by mobile phone and in person by outreach workers. For the 12-month follow-up, women who participated in the 6-month assessment were sampled and similarly, women in the 18-month follow-assessments were sampled from those who participated in the 12-month assessment. The trial protocol was reviewed and approved by the Cambodian National Ethics Committee, and the Institutional Review Boards (IRBs) at FHI360 and University of California San Francisco (UCSF). Other participating academic partners (UNM, UNSW and UM) relied on UCSF IRB. Full details of the study design and protocol have been previously published (Carrico et al., 2016a; Page et al., 2016).

2.2. Recruitment, enrollment, and outcome assessments

The target population was Cambodian FESW who: (1) were biologically female; (2) aged ≥18 years; (3) reported ≥2 different sexual partners and/or transactional sex within the last month; (4) understood spoken Khmer language; and (5) were able to provide voluntary

informed consent (see Figure 1). Trained outreach workers provided a basic study description, answered questions, and invited women to attend the local study site (i.e., SMARTgirl Club) to be screened for eligibility.

Eligible women who consented to participate were asked to provide their fingerprint at enrollment (signed consent was waived) using a commercially available digital fingerprint reader that stores biometric images as an alphanumeric code (PersonID Fingerprint Identification System, Bayometric, San Jose, CA). Women who were not already members of the SMARTgirl program were invited to join. Women who attended follow-up assessments were remunerated for their time: $4 at the 6- and 12-month assessments, and $8 at the 18-month assessment. All participants were additionally offered $2 for transportation to the assessments, and refreshments and condoms at all assessments.

2.3. Primary and secondary outcomes

All outcomes were assessed at the individual-level among FESW who completed outcome assessments over the 18-month follow-up. Sexual risk was indexed using the primary outcome of recent (past 3 months) number of sexual partners. Secondary measures of sexual risk included: a PSA+ vaginal swab, number of new sexual partners, any unprotected sex with paying partners and any unprotected sex ith non-paying partners (past 3-months). ATS use was indexed using the co-primary outcome of ATS Tox+ urine results. Secondary measures were severity of ATS use (i.e., low, moderate, and high risk) measured by the WHO ASSIST, and self-reported binge ATS use. Economic well-being indicators were single-item measures of self-reported income, any housing instability, and any food insecurity. Food insecurity was defined as reporting “sometimes”, “always”, or “usually” “having no food to eat of any kind in your household because of lack of money or resources to get food in the last 3 months” (adapted from (Coates et al., 2007)). Housing instability was measured as “in the past 3 months, how often were you worried about having a place to stay for you or your family because of lack of resources or money for housing?” (adapted from (Centers for Disease and Prevention)).

2.4. Allocation to the sequentially delivered CIPI interventions

Immediately following the baseline assessment, women who screened positive for an ATS use disorder on the ASSIST and were ATS Tox+ were allocated CCT+AC. At the 6-month follow-up, women confirmed to be abstinent from ATS based on self-report and negative urine toxicology screening were eligible to participate in the ME opportunity. Women who had received the CCT+AC intervention were required to have completed at least half of the CCT urine screening visits (≥18) regardless of urine toxiclogy results and all AC group sessions to be eligible for AC.

2.5. CCT+AC intervention

The CCT intervention included thrice weekly ATS toxicology urine screening for 12-weeks (i.e., 36 possible screening visits). At each of these visits, women received $2 for each ATS-negative urine sample. For each week that a participant provided three ATS negative urine samples, she also received a cash bonus of $2 in weeks 1–4, a $4 bonus in weeks 5–8, and a $6 bonus in weeks 9–12. The cash bonus for continuous abstinence escalated over time

regardless of prior abstinence. The total possible reinforcement for ATS abstinence over the 12-weeks was $120. Participants received a mean of $39 (SD=$36) in incentives over the 12-weeks. Regardless of the urine toxicology results, those who completed at least half of the urine screening visits (i.e., >18) were eligible to participate in a 4-week, cognitive-behavioral AC group delivered immediately after CCT. Details of the CCT+AC intervention protocol and its development are provided elsewhere (Carrico et al., 2016a).

2.6. ME opportunity

The ME opportunity included a three-day financial literacy training focused on topics such as budgeting and savings. Participants who completed the training were eligible to apply for a microloan to start a small business through one of three registered Cambodian micro-lending institutions who partnered with the study. The ME opportunity was implemented in all ten provinces and delivered over a 12-month period between the six and 18 month follow-up assessments in each province.

2.7. Community engagement

We conducted extensive formative research with key stakeholders to guide study protocol development (Dixon et al., 2016). Once implementation began, the CIPI program was publically endorsed by governmental partners from the Ministry of Health, Department of Mental Health, and the National Authority to Combat Drugs. In each province, orientation workshops were delivered to stakeholders prior to or concurrent with implementation initiation. Stakeholders included local governmental and health leaders, NGO staff (heads and outreach workers), as well as police and sex worker advocates.

2.8. Fidelity Monitoring

Delivery of CCT+AC and ME in each province was guided by a detailed manual of operations, which included step-by-step procedures with detailed curricula and handouts for group-based exercises. Staff conducting CCT urine screening visits completed a comprehensive 5-day training that included an introduction to delivering low threshold services to active ATS users, providing urine screening results in a non-judgemental manner, and tracking incentives with participants to promote sustained engagement. A detailed treatment manual for the AC group was developed and monitored in collaboration with a Cambodian psychologist and a psychiatrist (Carrico et al., 2016a).

2.9. Statistical analyses

All analyses take into consideration clustering within provinces and individuals nested within provinces as random effects. All women screened at baseline constituted the enrolled population, and 600 women were purposively sampled from the basleine group to complete subsequent 6-, 12-, and 18-month outcome assessments. Treatment effects were assessed by comparisons of outcomes post-intervention time-points relative to the pre-intervention baseline data. We assessed post-intervention trends using tests of linear contrast across the four evaluation time points using two datasets. In what we term ‘Dataset 1’, the “intention-to-treat” (ITT) cohort, analyses used all available data from baseline and follow-up assessments. This larger dataset yields greater statistical power to detect a significant effect.

However, despite using all data, this dataset (1) did not fully utilize the randomized stepped wedge design, as control and outreach were not balanced over the follow up assessments. 'Dataset 2' presents a modified per protocol (mPP) approach, and includes only those women who attended baseline and the 6-month follow-up assessment (N=598) and excludes those not sampled for follow-up after baseline. It can also be construed as a sensitivity analysis. This analysis has the advantage of employing the study stepped wedge design, and also limiting potential bias due to differential drop out associated with participant characteristics, as each participant at the first post-intervention time point is balanced by a corresponding control time point.

The study was powered to detect between small and medium effect sizes according to Cohen's guidelines (Cohen, 1988). With ten clusters and 60 individuals per cluster and α=0.05, a t-test has 80% power to detect a standardized mean difference of d=0.216 between any two time points for a continuous outcome. For binary outcomes, assuming a proportion of 0.50 and n=600 per group and α=0.05, we had 80% power to detect a minimum decrease of 0.10. Sample size estimates were adjusted by a factor of 1.44 to account for the decreased efficiency of the stepped-wedge design and intra-cluster correlation. Mixed model logistic regression analysis was used to assess the change over time in each outcome measure. Time (baseline, 6, 12, and 18 months), calendar quarter (to adjust for time trend), and sex-work venue were included as fixed effects. Missing data were handled by listwise deletion in multivariable models. Rates of missing data were exceptionally low (<1%) for all of the outcomes. To assess the potential effects of the unbalanced design, we conducted sensitivity analyses restricting the analytic sample to participants who completed the 6-month assessment, and assessed demographic and risk behavior characteristics between the Datasets 1 and 2.

A Data Safety Monitoring Board (DSMB) conducted annual reviews of trial progress. The trial was registered at www.clinicaltrials.gov (NCT01835574).

3. Results

Participants were recruited between November 2013, and July 2015; data collection ended in November 2016. Of 1,559 women screened, 1,428 (92%) were eligible and 1,198 (84%) were enrolled (Figure 1). At each follow-up assessment,of 600 FESW were sampled from the baseline cohort, 596 (99%), 544 (91%) and 556 (93%) successfully completed the 6-, 12, and 18-month outcome assessments, respectively.

3.1. Demographics, behavioural, and clinical characteristics

Most of the 1,198 FESW enrolled at baseline were ≤30 years of age (79%, n=948), did not have a primary partner (68%, n=816), currently worked in an entertainment venue (81%, n=967), and reported an average monthly income of ≤ $250 (66%, n=772). Overall, women reported a median of seven recent male sex partners (Interquartile Range [IQR] = 4,17), and 28% (338/1193) of women tested PSA+ indicating unprotected vaginal sex in the previous 48 hours. Almost one in four (24%, n=286) tested ATS Tox+, indicative of ATS use in the past 72 hours. Based on the ASSIST, one-third (34%, n=408) of women screened positive for an ATS use disorder. Table 1 provides the demographic, behavioural, and clinical

characteristics of womenat baseline, including a comparison of participants in Dataset 1 (all enrolled women at baseline) and Dataset 2 (includes the baseline of 596 women who participated in 6-month follow-up). Women in Dataset 2 had had higher risk profiles for ATS, not unexpected as additional efforts were made to include all women who participated in CCT+AC in follow-up evaluations.

3.2. ATS and sexual risk outcomes

Table 2 shows primary and secondary sexual risk and ATS outcomes separately for Datasets 1 and 2. A significant, 60% reduction in the odds of testing ATS Tox+ was seen at 6 months (Adjusted Odds Ratio [AOR]=0.40; 95% CI: 0.25, 0.65; $p<0.001$). Women reported a lower number of sexual partners at all follow-up assessments, and at 12-months the 50% reduction was statistically significant relative to baseline (Adjusted Rate Ratio [ARR]=0.50; 95% CI = 0.25–0.95; $p=0.035$). Figure 2 also shows the adjusted mean number of sexual partners and the proportion providing testing ATS Tox+ over the 18-month follow-up in Dataset 1. Dataset 2 findings were consistent with Dataset 1 findings with the exception of significant reductions in the odds of testing ATS Tox+ at 18 months (AOR=0.30; 95% CI: 0.095, 0.97; $p<0.05$).

With respect to secondary sexual risk and ATS outcomes, women reported significant reductions in the number of new sexual partners over at each follow-up visit relative to baseline ($p<0.05$), although the overall trend did not reach statistical significance (p-value for trend 0.06). A significantly higher proportion of women reported stable primary partners at the 18-month assessment relative to baseline: 41% versus 32%, respectively in Dataset 1, and 42% versus 33% in Dataset 2. No significant reductions were seen in PSA+ results over any study follow-up assessments. There were also significant reductions in reports of unprotected sex with paying partners over the 18-month follow-up, but not for non-paying partners. Findings from Dataset 2 were comparable. No significant reductions were seen in the odds of screening positive for an ATS use disorder and any self-reported binge ATS use in Dataset 1. In Dataset 2, the declines in both self-reported ATS use measures were statistically significant at six months.

Intervention effects on indicators of economic well-being (Table 2) show no changes in median monthly income over the 18 months. Relative to baseline, women reported significantly lower odds of housing instability at 12-months. Women also reported significantly lower odds of food insecurity at 12- and 18-months.

3.3. CCT+AC Engagement

Overall, 281 FESW were eligible for CCT+AC. Of these, 79% (222/281) initiated CCT and provided a median of 12.5 (Interquartile Range [IQR]=4, 24) urine samples that were non-reactive for ATS, equivalent to a month of abstinence on average. Figure 3 shows the proportion of ATS negative urine toxicology screens among participants in CCT ATS over the 12-week intervention period. Among those who initiated CCT, 68%(151/281) were eligible to attend the cognitive-behavioural AC group; 69% (104/151) attended ≥3 group sessions (see Figure 1).

3.4. ME Opportunity Engagement

Of the 379 FESW who were eligible to complete the ME opportunity (Figure 1), 9% (35/379) had successfully completed CCT+AC with abstinence at six months. Approximately 64% of eligible women (244/379) completed the three-day financial literacy training. Of those who completed the three-day financial literacy training, 24% (59/244) applied for a microloan and 43 (18% of total and 73% (43/59) of those applying) received a microloan for an average amount of $265. Women who were older and had more children were more likely to attend the training, and subsequently to apply for loans (data not shown).

4. Discussion

The CIPI multi-level intervention was effective in achieving substantial reductions in sexual risk in a low income setting, which is encouraging because this remains a primary focus of HIV and STI prevention efforts with FESW (Maher et al., 2011a; Shannon et al., 2015; Strathdee et al., 2013). Although decreases in number of sexual partners were observed at six months these became statistically significant at 12-months after the sequential delivery of the ME opportunity. It may be that the explicit focus of the ME opportunity on structural barriers was essential to achieve meaningful reductions in sexual risk among Cambodian FESW. Secondary outcomes also provide support for sustained intervention-related reductions in sexual risk. Most notably, significant decreases in the number of *new* sexual partners and the odds of any unprotected sex with paying partners at 18 months. Reductions in sexual risk were observed in the absence of concurrent reductions in ATS use at 12 and 18 months. We also noted that women reported increases in unprotected sex with non-paying partners at 18 months as well as increases in steady primary male partners. We hypothesize that part of transitioning out of sex work in this setting may result in finding a stable male partner. Decreases in condom use with stable partners would be associated with negotiated safety. Delivering the CIPI multi-level intervention with existing HIV prevention services can achieve meaningful reductions in sexual risk with Cambodian FESW.

The CIPI multi-level intervention also decreased ATS use immediately following the delivery of CCT+AC, including substantial reductions at six months of testing ATS Tox+. Although the reductions seen at 12-and 18-months were sizeable, these were non-significant. Concurrent findings noted in Dataset 2 are important since this included a somewhat higher proportion of women with high-risk ATS use profiles. Additional research examining approaches to boost the intensity and duration of CCT+AC effects is needed to more effectively treat chronic, relapsing ATS use disorders.

Consistent with the focus of the CCT+AC and ME opportunity interventions on addressing structural barriers, women reported no losses of income over the 18-month follow-up. This was despite the fact that they reported significant decreases in the number of sexual partners, new partners and condomless sex with paying partners, and decreased ATS use. Providing CCT incentives as well as the financial literacy training during the ME opportunity may have offset any financial losses associated with decreasing sexual risk and ATS use. A substantive number of women participated in financial literacy training, however a small proportion (26%) of eligible women applied for micro-loans following that training. We

have hypothesized that improvements in “economic empowerment” may have been useful following financial literacy training, and women made informed choices about applying for these microloans. As older women were more likely to apply for loans, we also hypothesize that ME programs may be more appealing to women who are potentially aging out of sex work and or that family life may be a driver to explore alternative income strategies. In fact, significant reductions in the odds of housing instability at 12-months and food insecurity at 12-and 18-months relative to baseline provide further support for the success of the CIPI multi-level intervention in addressing structural barriers to HIV prevention.

Community engagement efforts were crucial to the success of this trial. First, our study builds on a decade of qualitative and epidemiological research with this population and additional formative qualitative research with key stakeholders, including FESW, was instrumental to informing key components of the CIPI intervention (Dixon et al., 2016). Second, integrating the CIPI multi-level intervention within the existing SMARTgirl HIV prevention program likely contributed both to engagement and high retention. Because the CIPI multi-level intervention built upon the SMARTgirl model, this underscores the importance of prioritizing funding for extant HIV prevention services for FESW as a platform for more comprehensive efforts to achieve more meaningful reductions in HIV risk. Third, implementation was supported by engagement with multiple partners, which was critical to assure FESW that they would not be arrested for seeking assistance with sexual risk reduction or ATS use (both highly stigmatized and criminalized in the Cambodian context).

Despite the overall positive outcomes, our study has limitations. There is potential for social desirability bias in self-reported outcomes of sexual exposures and drug use, which could have influenced our results. However, this would need to be systematic over the 18-month follow up, which we believe is unlikely over this long period. Further, our primary ATS outcome was based on a biological marker, and the concurrent declines in self-reported ATS use were observed among higher-risk women. Study design does not allow us to disaggregate the specific component(s) responsible for the robust effectiveness of the multi-level intervention. However, significant reductions in ATS use at six months were observed prior to the delivery of the ME opportunity. Finally, the design assessed outcomes following a re-sampled population of FESW. Our strategy of focused retention of women who at higher risk, i.e. ATS-using women - for follow up was undertaken to avoid the potential bias that can result from disproportionate losses in higher risk participants which is common in studies of drug using populations. We acknowledge that our strategy also has potential for bias, however by avoiding disproportionate losses this bias should be conservative. From a pragmatic perspective, we feel that ensuring follow up assessments of the highest risk women has potential to increase generalizability of our findings to this population. It is possible that observed reductions in primary and secondary outcomes partially reflect the impact of completing repeated outcome assessments or a regression to the mean, particularly in mPP analyses that focused on higher-risk women. Despite these limitations, the study has important strengths. This trial is the first to employ a randomized design to test a multi-level HIV prevention intervention with FESW, including in a low income setting characterised by a high burden of disease. We took advantage of the complex stepped-wedge design to analyze data using two Datasets, and results were largely consistent in these approaches, and

missing data was minimal. Regardless of the underlying mechanism(s) responsible for the observed efficacy, collectively results provide compelling support for this comprehensive, scalable approach to optimize HIV prevention with Cambodian FESW.

The CIPI intervention goes beyond education, communication and outreach and provides an important evidence base for effectively reducing sexual risk and ATS use, as well as improving economic well-being. The intervention engaged women in their occupational and cultural context by providing novel, evidence-based interventions that were adapted and implemented specifically for this population of women. The successful implementation of the mulltiple components across ten provinces demonstrates outstanding potential for scale-up. Adaptive designs may provide opportunities to disaggregate the effectiveness of specific components of the CIPI multi-level intervention.

Results of this trial also provide some important information on implementation of the CCT +AC and ME opportunity interventions. ATS prevention remains critical to successful HIV and other STI prevention among FESW in Cambodia and elsewhere. Further implementation science research is needed to test novel approaches such as CCT+AC with a boosted aftercare component, and assses durability. Integrating ME opportunities into existing HIV prevention programs is possible and has the potential to address structural barriers to HIV prevention with many key populations. Implementation and testing of the CIPI multi-level intervention or its components in other settings and with other key populations will also further inform HIV prevention globaly.

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Dedication

We dedicate this study to the memory of Dr. Willard Cates, who championed public health research which advanced women's health globally. His leadership with FHI360 helped promote HIV prevention and health for women in Cambodia and especially the women who participated in this study.

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Highlights:

- Female sex workers show reduced sexual and drug risk after multi-level intervention
- Women reported 50% fewer sex partners 1 year after the intervention
- ATS use decreased 60% after economic and cognitive-behavioural intervention.

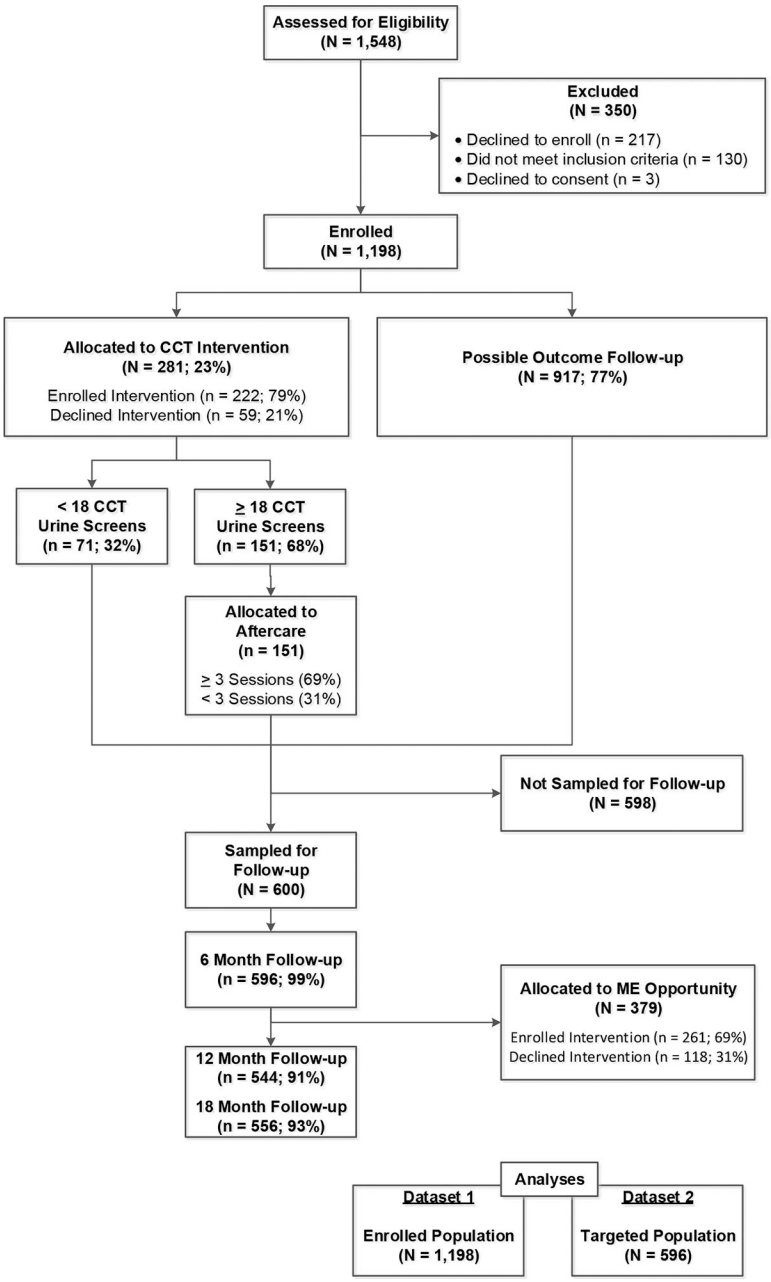

Figure 1:

Consort flow diagram of CIPI cluster randomized stepped-wedge trial with female entertainment and sex workers in 10 Cambodian provinces.

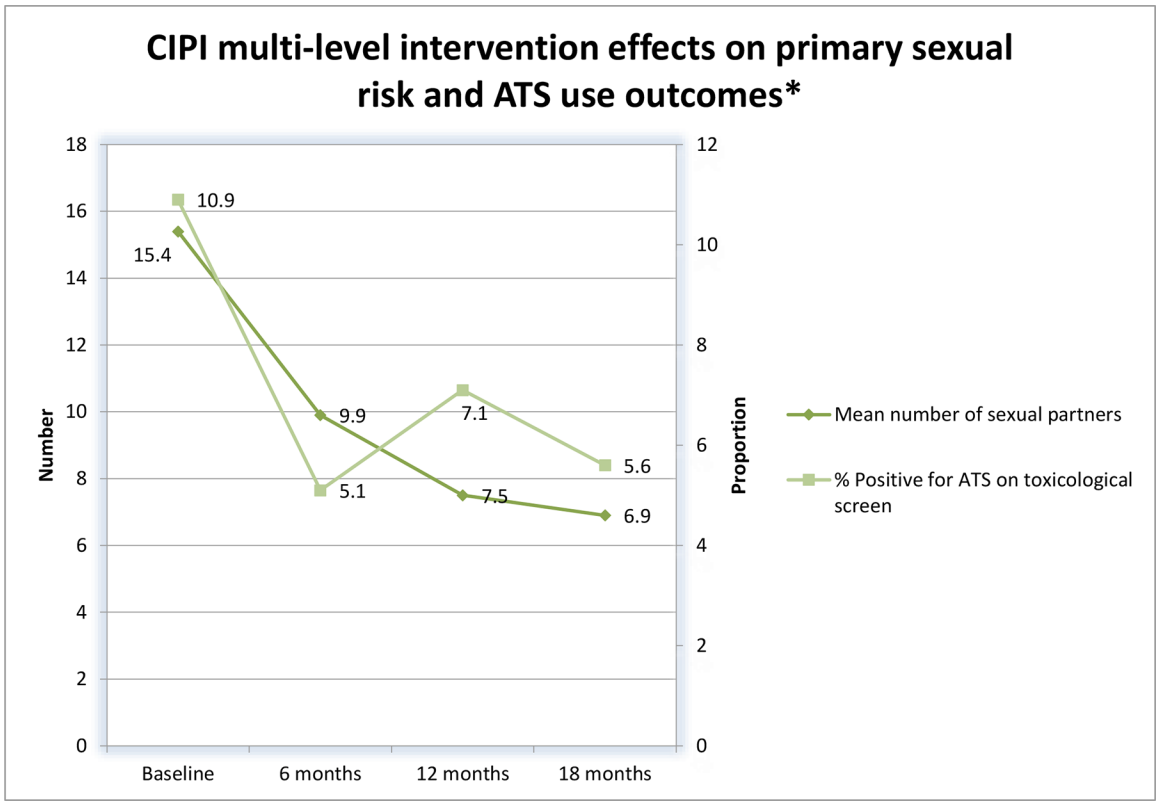

Figure 2:

Effect of CIPI multi-level intervention on primary sexual risk and ATS outcomes: number of sexual partners and ATS positive urine toxicological screen at 6-, 12- and 18-month follow up visits (Dataset 1).

* The values for mean number of sexual partners and percent positive for ATS on toxicological screen are adjusted for clustering by province and random effects.

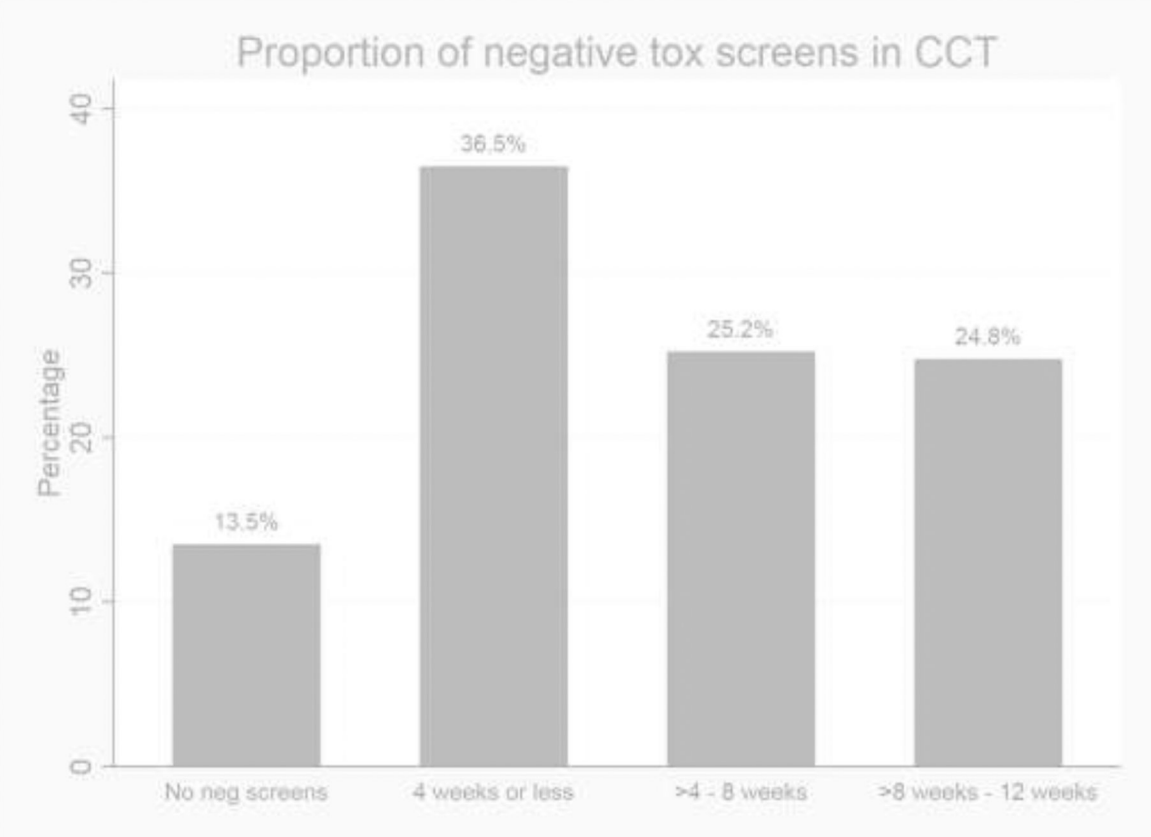

Figure 3:

Proportion of ATS negative urine toxicology screens in over 12 weeks among participants in Conditional Cash Transfer (CCT) ATS intervention

Table 1.

Baseline demographic, behavioral and health characteristics participating in the CIPI study at baseline overall (N=1198; Dataset 1) and those at baseline who completed the 6-month outcome evaluation (n=596; Dataset 2)

	Dataset 1		*Dataset 2*		
Characteristic	***N / median***	***% / (IQR)***	***N / median***	***% / (IQR)***	**p-value***
Median age (in years)	26	(22, 30)	27	(22, 30)	0.02
Marital (or partnership) status					
Married/Living together	382	31.89	153	25.67	0.02
Separated/Divorced/Widowed	494	41.24	305	51.17	
Single	322	26.88	138	23.15	
Years of school completed					
None	194	16.19	198	33.22	0.84
Primary (1–6)	634	52.92	223	37.42	
Secondary (≥7)	370	30.88	175	29.36	
Main sex work venue in the past month					
Entertainment	967	80.72	460	77.18	<0.01
Brothel/freelance (eg., park, street, guest house)	231	19.28	136	22.82	
Met with SMARTgirl outreach (past3 months)	946	79.0	489	82.1	<0.01
Registered SMARTgirl member	835	69.7	455	76.3	<0.01
Currently work for employer, boss, manager, or supervisor (yes)	872	72.8	412	69.13	<0.01
Currently working to pay off debt (yes)	650	54.26	306	51.34	0.04
Monthly Income (US$)					
<100	258	21.54	119	19.97	0.41
100–250	534	44.57	273	45.81	
>250	406	33.89	204	34.23	
Frequency of ≥5 drinks on 1 day in past 3 months					
Never	275	23	139	23.36	0.50
Less than monthly	77	6.4	34	5.71	
Monthly	88	7.4	43	7.23	
Weekly	263	22	122	20.50	
Daily/Almost daily	493	41.2	257	43.19	
Workplace requires drinking alcohol with customers (yes)	642	53.59	310	52.01	0.28
Number of male sex partners in past 3 months					
≤3	279	23.29	127	21.31	0.24
4 – 15	607	50.67	306	51.34	
≥16	312	26.02	163	27.35	
Number of new male sex partners in the past 3 months					
0	181	15.11	91	15.27	0.52
1 – 5	582	48.58	280	46.98	

	Dataset 1		Dataset 2		
Characteristic	***N / median***	***% / (IQR)***	***N / median***	***% / (IQR)***	**p-value***
≥6	435	36.31	225	37.75	
Prostate Specific Antigen result positive	338	28.2	174	29.34	0.44
Sex in exchange for drugs in past 3 months (yes)	103	8.6	57	9.58	0.24
Condom use with paying partners; always in past 3 months	862	76.62	435	78.80	0.09
Condom use with non-paying partners; always in past 3 months (among those with any non-paying partner)	113	18.52	53	17.55	0.54
ATS positive on urine screen					
No	912	76.1	430	72.15	<0.01
Yes	286	23.9	166	27.85	
ASSIST score for ATS					
Low (<4)	790	65.9	380	63.76	0.03
Moderate (4–26)	322	26.9	162	27.18	
High (≥27)	86	7.2	54	9.06	
Self-reported binge use of ATS in past 3 months	218	18.21	119	20.00	0.11
ASSIST Score for Alcohol					
Low (<11)	292	24.4	148	24.83	0.66
Moderate (11–26)	611	51	308	51.68	
High (≥27)	295	24.6	140	23.49	
HIV test result					
Among those who tested	16	1.34	6	1.01	0.48
Self-reported HIV positive	55	4.89	26	4.64	0.70
HIV-positive in national registry	75	6.26	40	6.71	0.52
Kessler psychological distress score (K10)					
No or low risk	708	59.65	344	58.31	0.34
Mild risk	260	21.9	125	21.19	
Moderate risk	112	9.44	61	10.34	
Severe risk	107	9.01	60	10.17	
Food insecurity in the past 3 months					
Never/rarely	1065	9.65	532	90.17	0.56
Some/often/always	123	10.35	58	9.83	
Housing insecurity in the past 3 months					
Never/rarely	747	62.93	371	62.99	0.97
Some/often/always	440	37.07	218	37.01	
Reproductive health visit past 3 months (yes)	668	55.8	343	57.55	0.21
Diagnosed with STI in the past 3 months (yes)	214	17.88	115	19.33	0.19

*Comparison is between all those enrolled at baseline (n=1198) and women at baseline (n=596) who were followed into the 6-month outcome assessment.

Table 2.

CIPI multi-level intervention effects on primary and secondary outcomes: sexual risk, ATS use and indicators of economic well-being

		6 months		12 months		18 months	
		Dataset 1	**Dataset 2**	**Dataset 1**	**Dataset 2**	**Dataset 1**	**Dataset 2**
Primary outcomes							
No. of sexual partners in the past 3 months	[a] ARR (95% CI)	0.647 (0.377, 1.109)	0.624 (0.370, 1.052)	**0.499 (0.252, 0.951)** *	**0.483 (0.251, 0.929)** *	0.448 (0.177, 1.136)	0.442 (0.180, 1.086)
Positive for ATS on toxicological screen	[b] AOR (95% CI)	**0.400 (0.247, 0.648)** *	**0.313 (0.177, 0.553)** *	0.584 (0.300, 1.137)	0.483 (0.206, 1.133)	0.443 (0.183, 1.072)	**0.303 (0.095, 0.970)** *,ℱ
Secondary sexual risk outcomes							
No. of new sexual partners in the past 3 months	[b] ARR (95% CI)	**0.347 (0.166, 0.728)** *	**0.336 (0.169, 0.668)** *	**0.184 (0.065, 0.525)** *	**0.180 (0.070, 0.459)** *	**0.151 (0.031, 0.740)** *	**0.144 (0.034, 0.611)** *
Positive prostate specific antigen (PSA) test	[b] AOR (95% CI)	0.988 (0.751, 1.300)	0.934 (0.682, 1.281)	1.002 (0.694, 1.445)	0.870 (0.558, 1.359)	1.439 (0.913, 2.269)	1.418 (0.813, 2.475)
Unprotected sex with paying partners in the past month	[b] AOR (95% CI)	0.678 (0.455, 1.008)	0.793 (0.488, 1.289)	**0.272 (0.141, 0.522)** *	**0.323 (0.140, 0.745)** *	**0.283 (0.126, 0.635)** *,ℱ	0.393 (0.137, 1.128) ℱ
Unprotected sex with non-paying partners in the past month	[b] AOR (95% CI)	0.677 (0.383, 1.197)	0.710 (0.391, 1.289)	2.110 (0.870, 5.114)	2.125 (0.862, 5.243)	**4.424 (1.306, 14.985)** *,ℱ	**5.143 (1.510, 17.518)** *,ℱ
Secondary ATS outcomes							
Moderate or high ASSIST score for ATS	[b] AOR (95% CI)	0.631 (0.334, 1.192)	**0.462 (0.216, 0.986)** *	0.603 (0.221, 1.648)	0.329 (0.093, 1.168)	1.436 (0.361, 5.716)	0.682 (0.117, 3.962)
Binge use of ATS in the past 3 months	[b] AOR (95% CI)	0.636 (0.344, 1.177)	**0.476 (0.244, 0.927)** *	0.953 (0.354, 2.568)	0.539 (0.181, 1.602)	1.164 (0.306, 4.432)	0.614 (0.143, 2.647)
Secondary Economic well-being indicators							
Monthly income (log10)	[a] ARR (95% CI)	1.124 (0.907, 1.393)	1.053 (0.843, 1.314)	1.212 (0.940, 1.563)	1.112 (0.884, 1.400)	1.080 (0.786, 1.485)	0.988 (0.750, 1.302)
Experienced housing insecurity in the past 3 months	[b] AOR (95% CI)	0.673 (0.405, 1.118)	0.585 (0.324, 1.055)	**0.319 (0.131, 0.775)** *	**0.267 (0.094, 0.757)** *	0.630 (0.187, 2.118)	0.426 (0.102, 1.787)
Experienced food insecurity in the past 3 months	[b] AOR (95% CI)	0.551 (0.282, 1.076)	0.580 (0.296, 1.137)	**0.179 (0.054, 0.592)** *	**0.147 (0.424, 0.506)** *	**0.105 (0.021, 0.528)** *,ℱ	**0.116 (0.023, 0.573)** *,ℱ

Multilevel regression models ([a] Mixed effects negative binomial regression; [b] Mixed effects logistic regression; [d] Multi-level mixed effects linear regression) were used to evaluate the main treatment effect between post-intervention outcomes relative to baseline outcomes, adjusting for calendar quarter (secular trends), and work venue (brothel or freelance). Province was fitted as a random effect to adjust for the cluster effect and the variability within province.

* $P < 0.05$.

$^{\mathcal{F}}$P-value for trend <0.05.