SUPPLEMENTARY MATERIAL

Table of content

1. Background

2. Methods:

A) Data collection

B) Mathematical modelling

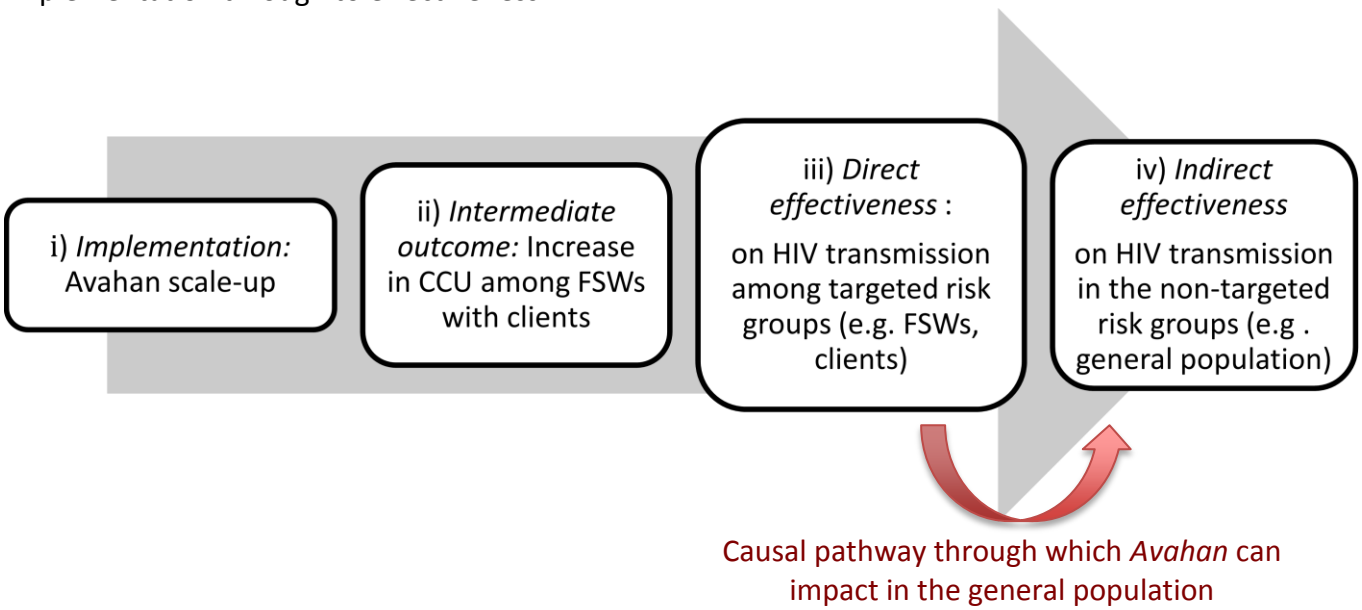
C) Detailed fitting procedure and likelihood methods

D) Validation of hypothesis testing procedure

1. BACKGROUND: Complementary information on intervention, scale-up and impact on different outcomes

Flowchart A represents the overall evaluation framework used to assess the impact of the Avahan intervention, from implementation through to effectiveness. The flowchart summarises the logical sequence of evaluation activities that occurred following the implementation of Avahan to assess the programme implementation (using programme outcomes: service provision, utilisation and coverage); change in HIV risk behaviour (using intermediate behavioural outcomes such as consistent condom use); impact on HIV (using biological outcomes - HIV and STIs); and cost-effectiveness analysis. Given the nature of the intervention (i.e. core group intervention that aims to directly reduce transmission and HIV prevalence in the targeted high-risk groups in order to subsequently reduce transmission in the lower risk population), it is important to assess the impact of the intervention among the targeted groups before estimating impact in the general population (not targeted by the intervention). (Note: the overall impact take into account the direct and herd effects among those reached and not reached by the intervention in the given population).

Flowchart A: Overall evaluation flowchart to assess each component of the intervention, from implementation through to effectiveness.



Summary of evidence of Avahan impact in Karnataka at each stage

Here, we present some evidence that Avahan implementation and scale-up has been adequate (stage i), that consistent condom use (CCU) among FSWs has increased following Avahan and that this increase is at least partly attributable to the Avahan intervention (stage ii) in Karnataka state (Flowchart A). This information is complementary to the results presented in the main manuscript, where we assess and demonstrate that in many districts the observed changed in HIV prevalence from the serial cross-sectional IBBA studies are unlikely to have occurred without the increases in condom use reported by FSWs over time. This information strengthens the evidence of an intervention impact on HIV among FSWs (see main manuscript). Following this, we estimate the effectiveness of the increase in condom use in preventing HIV transmission firstly among FSWs and clients (direct impact among the risk groups targeted by the

intervention) (stage iii) and in the general population (stage iv) (indirect impact due to the prevention of secondary transmissions).

Box 1: Summary of results on implementation, secondary outcomes and biological outcomes for Karnakata & strength of evidence

The findings of the different studies are interpreted within our overall evaluation framework combining the concepts of adequacy, plausibility and probability developed by Habicht and Victora[1] , for public health programme evaluations (Details in Box 2), and the logical sequence of events defined in flowchart A.	**Strength of evidence**[1] **Adequacy**	**Plausibility**	**Probability**
(i) Implementation: Coverage and scale-up due to Avahan • Did *Avahan* achieve *rapid, planned* scale-up to 80% coverage of target FSW population, with sufficient intensity?	✔		
Methods: Routine programme monitoring data from the *Avahan* monitoring information system (MIS) and denominator estimates (size of FSW population) were collected from all 18 Karnataka intervention districts (Figure S1) on a monthly basis and aggregated[2,3]. These data were used to estimate indicators of service provision, availability and utilization; condom distribution / provision; and rate and extent of scale-up of coverage of the target population. Detailed methodologies, and aggregated data for all *Avahan* districts, are described elsewhere[3].			
Results: By December 2008, five years after the start of *Avahan*, there were 11 NGO implementing agencies, 179 drop-in centres and 99 static STI clinics in operation in the 18 Karnataka *Avahan* intervention districts, with 837 active FSW peer educators and over 400 outreach staff (Figure S2A). The ratio of FSWs to peer educators decreased from about 200 in January 2005 to 72 in December 2008 (Figure S2B). The number of FSWs ever contacted by the programme increased from ~25,000 to over 95,000; and the number having ever visited the clinic increased from zero to over 79,000 (NB: these numbers are larger than the estimated number of ~60,000 FSWs in areas covered by *Avahan* in Karnataka, due to turnover of the population) (Figure S2C). The proportion of the estimated total FSW population contacted monthly by peer educators or outreach workers increased from 11% to 77%, and the proportion visiting the clinics monthly from zero to 27% (Figure S2D). During the same period, the mean number of condoms distributed monthly per FSW increased from three to 43 (Figure S2B). The estimated mean requirement of 34 condoms per month per FSW (based on number of reported clients by typology in IBBAs) was achieved by January 2007.			
Conclusion: The data indicate that successful scale-up of the programme has been achieved in Karnataka, with rapid expansion of services through increases in numbers of NGOs, drop-in centres and STI clinics; as well as in numbers of active peer educators and outreach workers employed by the programme; and condoms distributed.	✔		

(ii) Intermediate outcomes: Condom use by FSWs during commercial sex acts due to Avahan • Is there evidence of increases in condom use over time among FSWs following the start of the *Avahan* intervention? - *Assessment of time trends in condom use – 1st data source ("estimated CCU trends")* Methods: Serial cross-sectional bio-behavioural surveys (Integrated Behavioural and Biological Assessments - IBBAs) were carried out among FSWs in five representative intervention districts: Bellary, Belgaum, Mysore, Shimoga and Bangalore (Figure S1). Programmes were initiated in each district between January 2004 and June 2005, with baseline surveys conducted 7-19 months later[5]. Due to the lack of baseline and comparable pre-intervention condom use data 'reconstruction' of condom use time trends using retrospctive (historical cohort) analyses of the IBBA data was carried out[2]. Pooled data from round 2 IBBA surveys in Bellary, Belgaum, Mysore and Shimoga were used: sample size was 1,482 FSWs who had sold sex to occasional clients in the month preceding interview; of whom 1,236 reported sex with regular clients. Data on length of time consistently using condoms, and length of time selling sex, were converted into number of FSWs using condoms (numerator) and selling sex (denominator) by year, to give yearly rates of consistent condom use (CCU) from 1998 to 2007. Linear regression with generalised estimating equations was used to assess time trends and compare the rate of increase in CCU before and after *Avahan* initiation in 2003, Detailed methodology, with district-specific and pooled analyses for all *Avahan* districts are described elsewhere[2]. Results: Figure S3 shows the reconstructed rates of consistent condom use (CCU) by FSW with occasional and regular clients from 1998 to 2007. The rate of increase in CCU with both occasional and regular clients, from 1998 to 2007, was highly significant ($p<0.0001$). Estimated CCU with occasional clients rates increased from 12.2% [95% confidence interval (95%CI): 9.0% - 15.3%] in 1998, to 49.1% (95% CI: 45.1% - 53.1%) in 2004, to 80.1% (95% CI: 77.5% - 82.7%) in 2007. The average yearly rate of increase in CCU was significantly greater after [slope 2003-2007: 11.5% (95% CI: 10.6% - 12.4%) per year] than prior to implementation of *Avahan* [slope 1998-2003: 3.7% (95% CI: 3.0% - 4.4%) per year] ($p<0.0001$). Similar results were observed for regular clients, with only a slightly lower level of CCU (Figure S3). - *Assessment of time trends in condom use – Second data source* Methods & Results: Another study used data on condom availability for all five districts, from both private sector condom sales and Avahan condom distribution[6]. Assuming 20% condom wastage, the number of available condoms rose from 7.7 million in 2004 to 20.8 million in 2008, with Avahan accounting for 11.5 million (88%) of the additional 13.1 million condoms available. • Can increases in condom use rates be attributed to exposure to *Avahan* intervention? - *Exposure of FSWs to the intervention and dose-response analyses* Methods: Pooled data (total n=988) from cross-sectional behavioural surveys of FSWs (Special Behavioural Surveys, SBS) carried out 1.5 – 2.5 years after *Avahan* implementation in Belgaum (n=208), Bellary (n=198), Bangalore (n=369) and Mysore (n=213) districts were used (Figure S1). Cross-sectional analyses of the relationship between self-reported measures of degree of exposure to intervention (explanatory variables) and consistent condom use (CCU) with occasional clients (outcome variable) were carried out, controlling for potential confounders, using bivariate and multivariable	✔	✔	

logistic regression. Detailed methodology and analyses of data from Belgaum, Bellary and Bangalore are described elsewhere[7]**.** Results: Overall, 734 (76.6%) women reported CCU with occasional clients in the SBS surveys carried out 1.5-2.5 years after the start of *Avahan*. Reported CCU with clients was higher among FSWs who had ever been contacted by intervention staff (79.1%) compared to those who had not been (55.3%, p<0.001 and p=0.005 in univariate and multivariate analyses, respectively); and among those who had ever seen a condom demonstration by intervention staff (80.9%) compared to those who had not (55.2%, p<0.001 and p=0.004 in univariate and multivariate analyses, respectively). Figure S4a-b demonstrates how CCU increased as the duration of time since first contacted by intervention staff and the number of times contacted by staff in the past month increased. CCU rates also increased with the number of condom demonstrations given by staff and observed by FSWs in the past month, but started leveling off at twice per month (Figure S4c). There were significant positive dose-response relationships in univariate and multivariate analyses between CCU and (a) duration since first contacted by intervention staff, and (b) the number of condom demonstrations given by staff in the past month. The level of CCU reported by those who have not been in contact with the Avahan intervention (~55%) are coherent with the average level of CCU with occasional clients estimated for the five districts combined in 2003-2004 (around the time that Avahan started) using the condom reconstruction method (Figure S3-S4). Conclusion: Different independent data sources suggested "adequacy and "plausibility" of change in intermediate behavioural outcomes: Analyses using reconstructed time trends indicate significant increases in condom use rates over time. Use of historical ('before-after') control groups provides evidence at the level of plausibility that *Avahan* itself may have positively impacted on condom use rates by FSWs. These analyses indicate a more rapid rate of increase in condom use rates by FSWs following the start of *Avahan*, than before *Avahan* Figure S3). District-specific analyses published elsewhere show similar trends[2]. The demonstration, using internal control groups, of a positive dose-response relationship between the duration and degree of exposure to the programme, and consistent condom use rates, provides further plausible evidence for a positive effect of *Avahan* in the Karnataka districts studied. *Similar conclusions can be drawn from the analysis of a different set of districts published elsewhere[7*] The above findings are supported by data presented elsewhere on analyses of condom availability over time in Karnataka[6], as well as analyses of IBBA data examining the relationship between exposure to *Avahan* and biological outcomes (STI rates)[5].	✔		
(iii) Effectiveness of Avahan on HIV among core groups • Have there been changes in HIV prevalence/incidence over time among FSWs during the *Avahan* intervention? How many HIV infections are averted by the increase in condom use during Avahan? Methods & Results: Main manuscript - Time trend analysis of STI and HIV prevalence over study rounds controlling for confounding factors. - Transmission dynamics modeling assessed the likelihood that the change in HIV prevalence occurred due to the increase in condom use among FSWs during Avahan (Hypothesis testing of different CCU trends and model estimates of the number of HIV infections averted over the course of the program.		✔	

(iv) Impact among the general population: • What is the likely impact of the FSWs intervention among the general population? <u>Methods & Results:</u> Main manuscript - Transmission dynamics modeling to estimate the number os secondary HIV infections averted in the lower risk groups due to the reported change in condom use among FSWs Conclusion: The empirical and modelling results provides rather strong "plausible" evidence that condom use during commercial sex has increased during Avahan, and contributed to reducing HIV transmission between FSWs and clients. These assertions are strengthened by strong evidence for the successful implementation of the Avahan program in Karnataka, and that increases in condom use amongst FSWs are associated with program exposure. Our results have important policy implications: they support the notion that HIV prevention programmes targeted at high-risk groups are feasible and can have considerable impact.	✔	✔	

[1] See details in Box 2

Figure S1: Map of Karnataka state, India, indicating districts covered by *Avahan*. *Avahan* is the sole implementer in these 18 districts, apart from Bangalore, where there is joint programme implementation in conjunction with the Karnataka AIDS Prevention Society (KSAPS). Targeted interventions are also implemented in the non-*Avahan* districts by KSAPS, and the *Avahan* lead implementing partner in Karnataka has provided technical assistance to KSAPS in these districts since 2007.

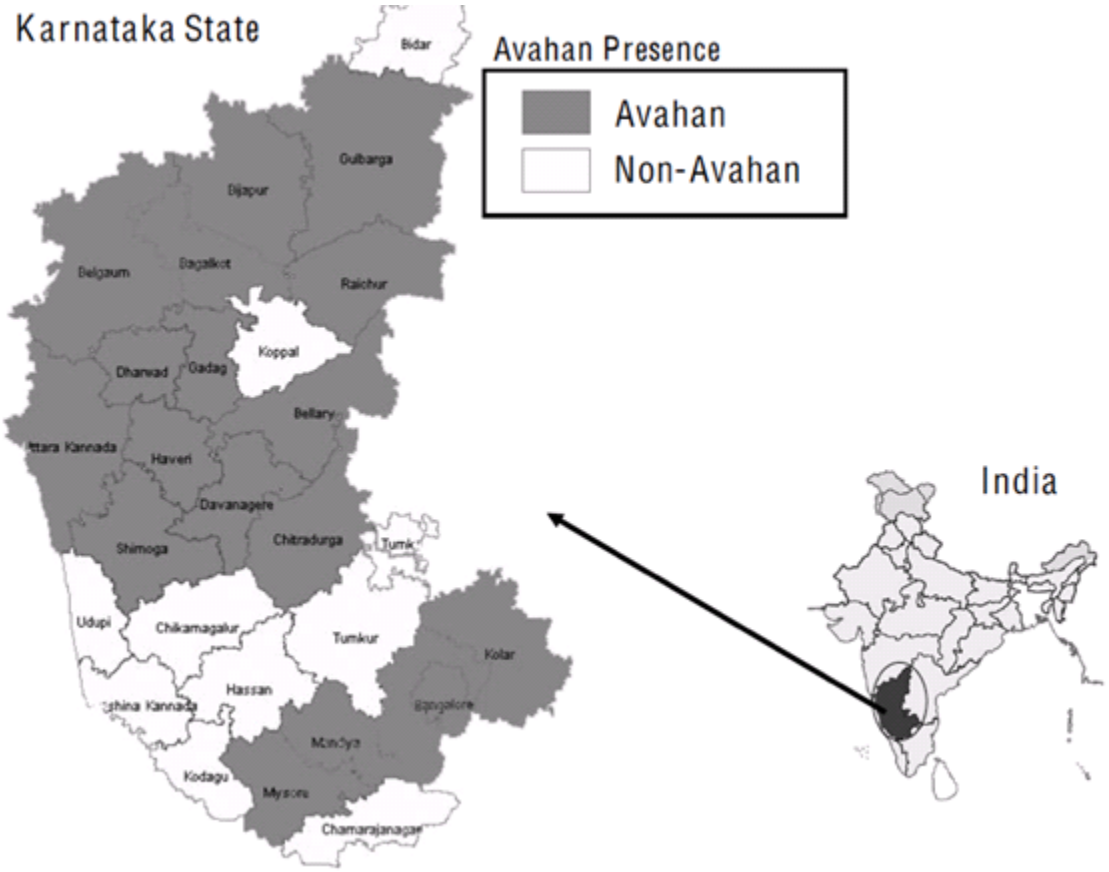


Figure S2: Evolution of *Avahan* intervention coverage indicators over time, 2005-2008, in Karnataka state. A) Number of active outreach workers and FSW peer educators. B) Ratio of number of FSWs to the number of FSW peer educators (PE) and mean number of condoms distributed each month per FSW. C) Number of FSWs ever contacted and ever having visited a programme STI clinic. D) Proportion of FSWs contacted at least once per month in the field and visiting a programme STI clinic at least once per month (denominator based on 2008 FSW population size estimate).

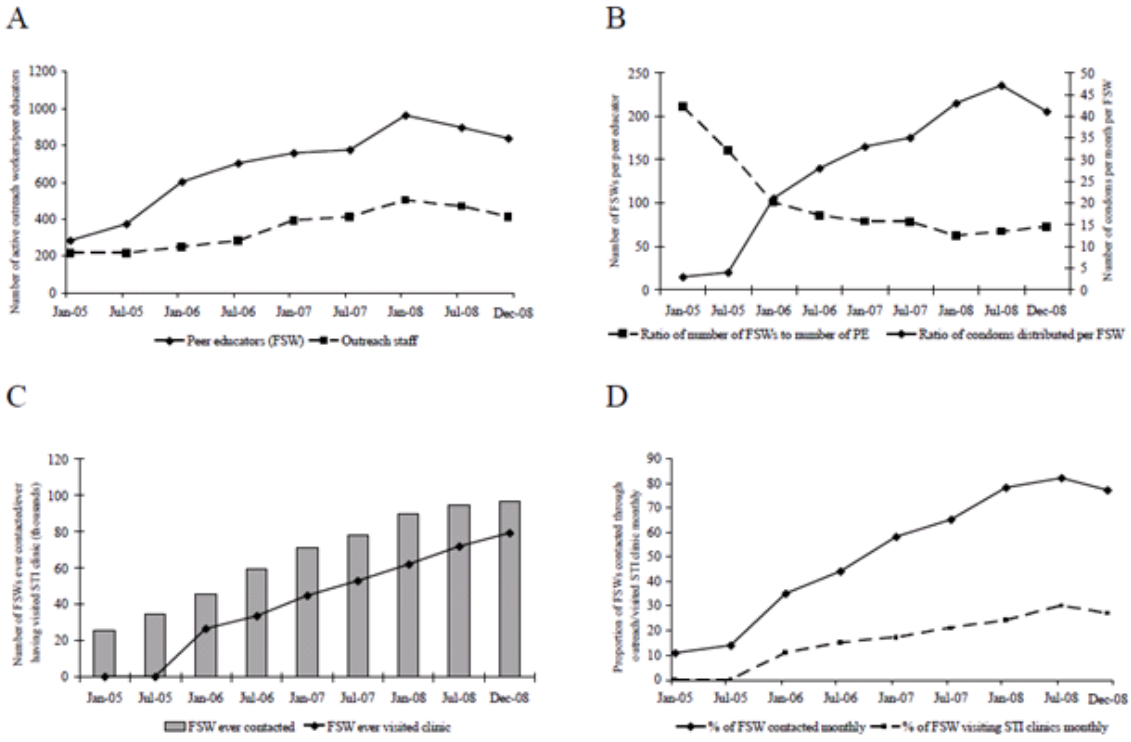


Figure S3: Estimated time trends in consistent condom use with occasional and regular clients by female sex workers, 1998-2007, based on retrospective analysis of data from the integrated behavioural and biological assessment (IBBA) surveys in Karnataka state (all five districts combined). The vertical arrow indicates the last pre-intervention time point. Consistent condom use (CCU) was defined as 'always' condom use, *vs*. 'less than always' condom use – 'often, sometimes, never', when FSWs were asked the question "how often do you use condoms with your new / repeat clients?".

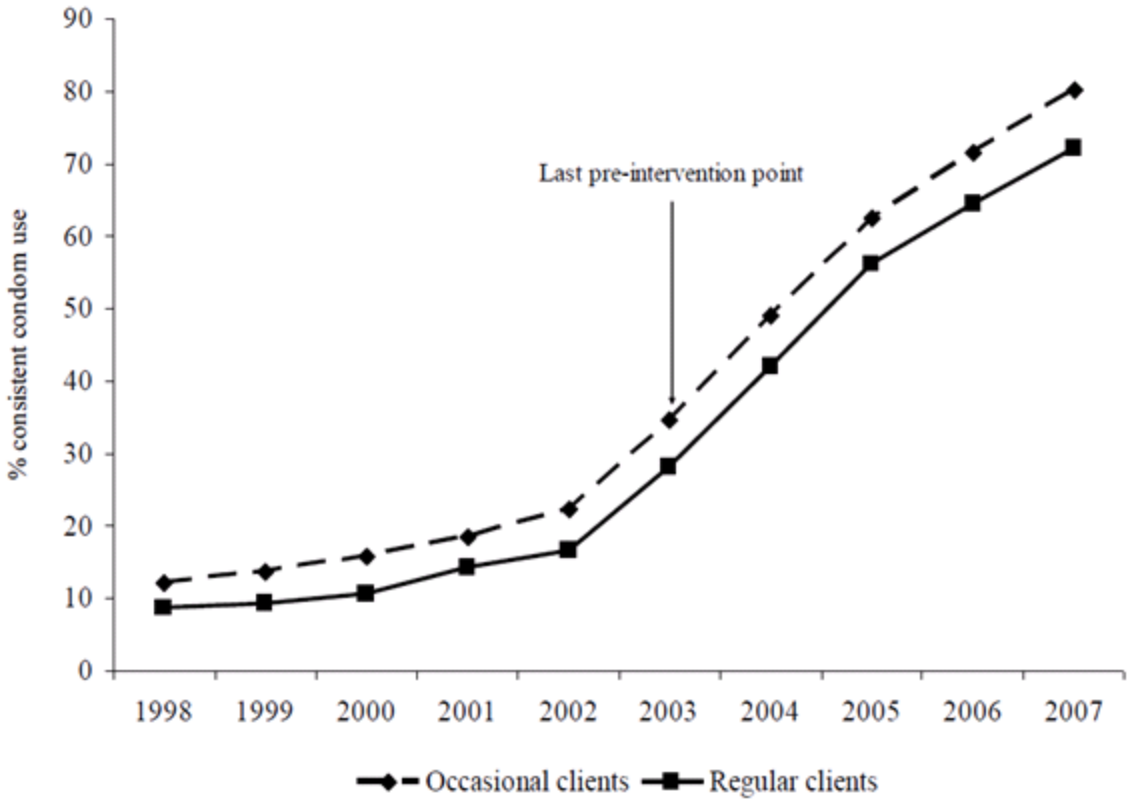
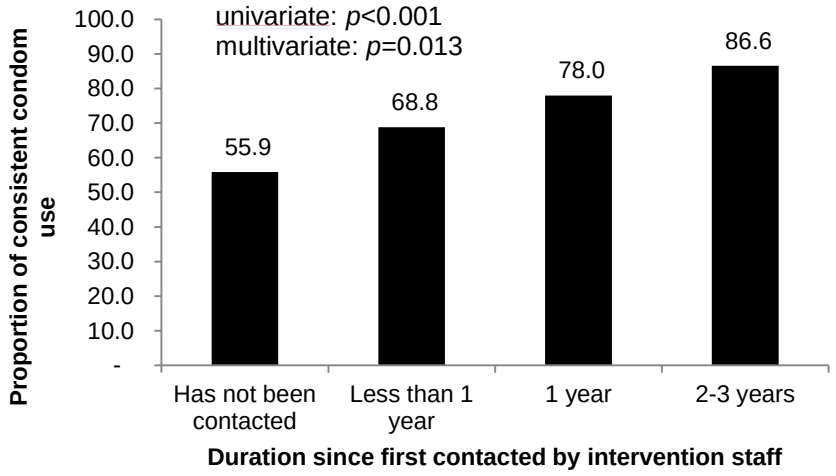
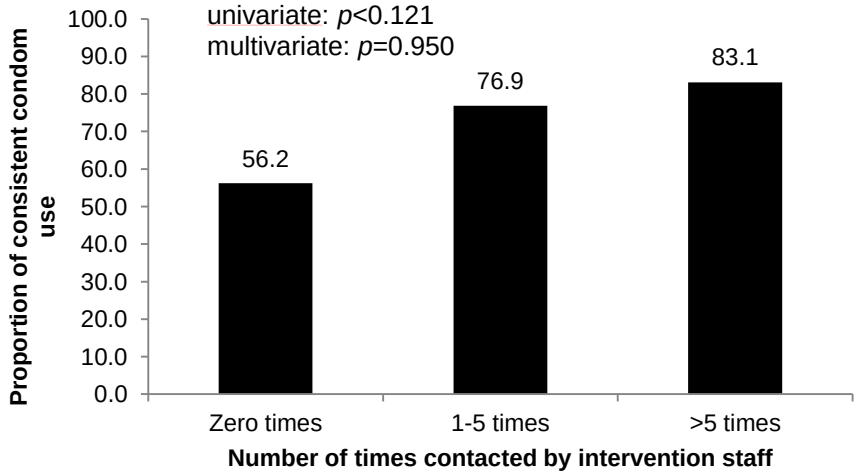


Figure S4: Dose-response relationship between indicators of programme exposure and consistent condom use with occasional clients by female sex workers (FSWs), based on the results of Special Behavioural Surveys (SBS) in Karnataka state. A) Condom use vs. time since first contacted by programme staff (test for trend: p<0.001 in univariate analysis and p=0.012 in multivariate analysis). B) Condom use vs. number of times contacted by staff in the past month (test for trend: p=0.121 in univariate analysis and p=0.950 in multivariate analysis). C) Condom use vs. number of condom demonstrations by staff observed by FSWs in the past month (test for trend: p<0.001 in univariate analysis and p=0.012 in multivariate analysis). The multivariate analyses were adjusted for district, age, literacy, marital status age at first sex work and main place of solicitation.

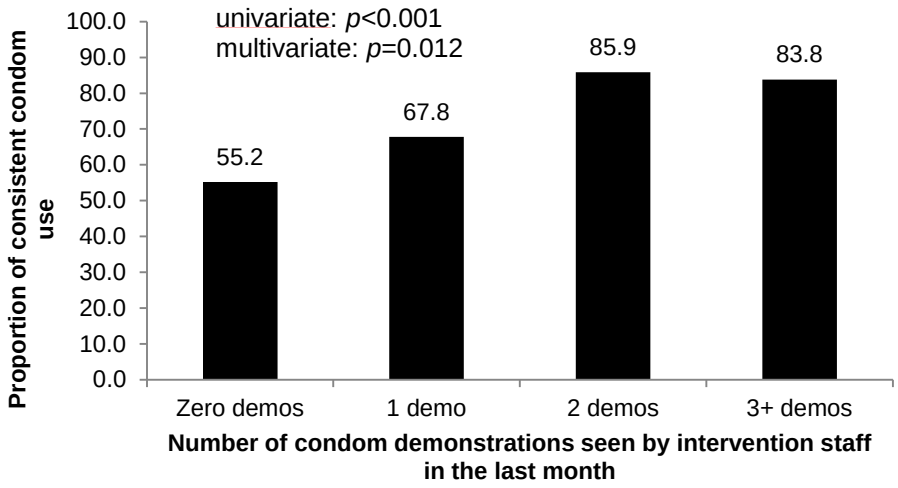
A)



B)



C)



Box 2: Brief description of Habicht and Victora conceptual framework for public health programme evaluations [1].

Adequacy*:* Evidence at the level of *adequacy* indicates simply that the programme was implemented as planned, and that the desired changes in outcome(s) occurred in the desired direction following the intervention. No strong causal link between programme activities and observed changes is demonstrated.

Plausibility**:** Evidence at the level of *plausibility* suggests that the desired changes in outcomes, which occurred following the intervention may have occurred *as a result of* the intervention, with a certain degree of uncertainty. Plausibility assessments attempt to rule out external (confounding) factors, which might have caused the observed effects, using non-randomised historical or concurrent control groups not exposed to the intervention.

Probability: Evidence at the level of *probability* demonstrates that the intervention is highly likely to be the causal determinant of the observed changes. Although statistical methods of causal inference can be used to make such assessments, strong conclusion typically require an experimental design with randomisation of intervention and control groups / communities (thus minimising confounding and other biases) to provide evidence that the probability is very low that the difference between programme and control areas was due to chance.

Additional details can be found in reference [1] and [8].

References (Background section):

1. Habicht JP, Victora CG, Vaughan JP. Evaluation designs for adequacy, plausibility and robability of public health programme performance and impact. Int J Epidemiol 1999;28:10-8.

2. Lowndes C, Alary M, Verma S, et al . Assessment of intervention outcome in the absence of baseline data: "Reconstruction" of condom use time trends using retrospective analysis of survey data. Sex Transm Inf 2010; 86 (Suppl 1): i49-55

3. Verma RK, Shekar A, Khobragade S, et al . Assessment of scale-up and coverage of Avahan: A large scale HIV prevention program among female sex workers and men who have sex with men in four Indian states. Sex Transm Inf 2010; 86 (Suppl 1): i176-82.

4. Saidel T, Adhikary R, Mainkar M, et al. Baseline integrated behavioural and biological assessment among most at-risk populations in six high-prevalence states of India: design and implementation challenges. AIDS 2008;22 (Suppl 5): S17-34.

5. Ramesh BM, Beattie T, Isac S, et al. (2010) Changes in risk behaviours and STI prevalence following HIV preventive interventions among female sex workers in five districts in Karnataka State, South India. Sex Transm Inf 86 Suppl 1: i17-24.

6. Bradley J, Moses S, Blanchard JF, et al. Assessing reported condom use among female sex workers in southern India through examination of condom availability. Sex Transm Inf 2010; 86 (Suppl 1):i44-48.

7. Deering KN, Boily M-C; Lowndes CM; et al. (2011) A dose-response relationship between exposure to a large-scale core group HIV preventive intervention and consistent condom use with different sexual partners of female sex workers in south India. BMC Public Health;11 Suppl 6:S8

8. Boily MC, Lowndes CM, Vickerman P, et al. Evaluating large-scale HIV prevention interventions: study design for an integrated mathematical modeling approach. Sex Transm Infect 2007; 83:582-9.

2. METHDOS

Complementary information on data analysis, model structure, fitting and validation of analytic procedures.

Methods A: *Data collection*

The integrated biological and behavioural assessment (IBBA) consists of anonymised cross-sectional random samples of female sex workers (FSWs) in five Karnataka districts (Mysore, Belgaum, Bellary, Shimoga and Bangalore urban) using traditional cluster (for stable FSWs: home- or brothel-based, etc) and time location clusters (for mobile FSWs: street-based, etc.) sampling[1]. It was determined that a sample of 400 FSWs should provide 90% power (alpha error of 5%) to detects a 10-15% difference across rounds for a binary outcome (e.g. consistency in condom use) with a value of 50% in round one. The five IBBA districts were chosen for monitoring based on Karnataka socio-demographic regions and size of high-risk population[1]. Programmes were initiated in each district between January 2004 and June 2005. The first IBBA survey was conducted between 7-19 months later whereas follow-up surveys were conducted 28-37 months after the first one for round 2 (R2) and more than 63 months after R1 for R3. Behavioural data was obtained by face-to-face interviews using a culturally sensitive and context-specific questionnaire. Blood samples were used to test for HIV and syphilis whereas urine samples were used for chlamydia and gonorrhoea prevalence (PCR urine)(details in [1]). Chlamydia and gonorrhoea tests conducted on samples from Bellary, Belgaum and Bangalore Urban used the Gen-Probe Aptima assay (Gen-Probe Inc, San Diego, California, USA), where as tests on samples from Mysore and Shimoga used the Roche Amplicor system (Roche Molecular Diagnostics, Pleasanton, California,USA) as described in [2]. Due to budget constraints and low prevalences, chlamydia and gonorrhoea testing was not performed at round 3.

Serum for HIV testing was stored at -20°C, and urine aliquots and dried blood spots for HIV testing were stored at 4°C. Urine aliquots for chlamydia, and gonorrhoea testing were stored at -20°C. HIV serological testing used a synthetic peptide enzyme immunoassay (Detect HIV 1/2 system; BioChem

ImmunoSystems, Montreal, Canada), and positive tests were confirmed using a recombinant antigen enzyme immunoassay (Genedia HIV 1/2 ELISA 3.0; Green Cross Life Science Corporation, South Korea). When serum samples were not provided, the same serological tests were used on dried blood spots from fingerprick blood. When neither serum nor fingerprick samples were provided, urine samples were tested for HIV by enzyme immunoassay (Calypte Biomedical Corporation, Berkeley, California, USA) and confirmed by Western blot (Calypte Biomedical Corporation). Serological testing for HSV-2 used an IgG enzyme immunoassay (Kalon Biological Ltd., Aldershot, UK). Serological testing for syphilis used the rapid plasma reagin (RPR) method (Span Diagnostics, Sachin, India), and if positive, confirmation was by the Treponema pallidum haemagluttination assay (TPHA) test (Omega Diagnostics Ltd., Alloa, Scotland). Syphilis infection was defined as being RPR positive (any titre) and TPHA positive. High-titre syphilis was defined as having an RPR titre of 1: 8 or greater and being TPHA positive (data not shown). All positive specimens and 10% of negative specimens were sent to the National AIDS Research Institute (NARI) in Pune, India, for quality assurance. Following the surveys, all participants were referred for a free health check-up and treatment. Following the unexpectedly high syphilis results found in the baseline IBBA, intensive community mobilization was undertaken to promote regular syphilis screening, and services were established at the project clinic.

Statistical analysis

Statistical analysis were performed using the survey methods in STATA, version 10.0 to take into account the weights (due to the differential recruitment of FSW by typology within district and non-response) and the correlated nature of the data due to the cluster sampling[1-2]. Note that women who participated in both rounds were included in all analyses, because as a result of the unlinked, anonymous nature of the surveys it was not possible to know which individuals in round 1 also participated at follow-up rounds. In line with similar analyses of the IBBA data, adjusted (for variables that differed significantly between rounds in each district) logistic regression was used to

examine trends over study rounds while controlling for many different potential confounding variables. The reported [1] response rate (percentage of FSWs who gave an interview and a biological sample of the total who were invited to participate in the survey) varied between 84-89% in all districts evaluated except Mysore (67%) in the first IBBA rounds.

Ethical considerations

The study was approved by the institutional ethical review board of St John's Medical College in Bangalore, India, and the health research ethics board of the University of Manitoba in Winnipeg, Canada. The study was also approved by the health ministry screening committee, Government of India. Due to the unlinked and anonymous testing of samples, it was not possible to trace and treat participants who had an STI. Those willing to know their HIV status were referred to government testing centres for free HIV testing, and STI case management was provided to all participants. Community mobilization for syphilis testing and treatment was also carried out. At the follow-up IBBA, women also received a card through which they could follow up on their syphilis serology result and treatment.

Methods B: *Mathematical modelling*

HIV/STI model equations

The model consists of a set of deterministic ordinary differential equations, which are solved numerically using the C programming language and Runge-Kutta methods. The equations are summarised as follows:

HIV and HSV-2 equations:

$$\frac{dH_{ik}^{00}}{dt} = \varepsilon_{ik} - \xi_{ik}H_{ik}^{00} - \left(\lambda_{Hk}^{00} + \phi_{Hk}^{00}\right)H_{ik}^{00} + \Omega_{ik}^{00} + \Delta_{ik}^{00} - \mu_k H_{ik}^{00}$$

$$\frac{dH_{ik}^{0s}}{dt} = -\xi_{ik}H_{ik}^{0s} + \phi_k^{0s}H_{ik}^{00} - \lambda_k^{0s}H_{ik}^{0s} + \Lambda_{ik}^{0s} + \square_{ik}^{0s} + \Delta_{ik}^{0s} - \mu_k H_{ik}^{0s}$$

$$\frac{dH_{ik}^{h0}}{dt} = -\xi_{ik}H_{ik}^{h0} + \lambda_k^{h0}H_{ik}^{00} - \phi_k^{h0}H_{ik}^{h0} + \Gamma_{ik}^{h0} + \Omega_{ik}^{h0} + \Delta_{ik}^{h0} - \mu_k H_{ik}^{h0}$$

$$\frac{dH_{ik}^{hs}}{dt} = -\xi_{ik}H_{ik}^{hs} + \lambda_k^{hs}H_{ik}^{0s} + \phi_k^{hs}H_{ik}^{h0} + \Gamma_{ik}^{hs} + \Lambda_{ik}^{hs} + \Omega_{ik}^{hs} + \Delta_{ik}^{hs} - \mu_k H_{ik}^{hs}$$

Equation 1

Syphilis equations (decoupled from HIV/HSV-2):

$$\frac{d\widehat{H}_{ik}^{0}}{dt} = \varepsilon_{ik} - \xi_{ik}\widehat{H}_{ik}^{0} - \psi_k^0\widehat{H}_{ik}^{0} + \Omega_{ik}^{0} + \Delta_{ik}^{0} - \mu_k\widehat{H}_{ik}^{0} - \tilde{\Gamma}_{ik}\widehat{H}_{ik}^{0}$$

$$\frac{d\widehat{H}_{ik}^{v}}{dt} = -\xi_{ik}\widehat{H}_{ik}^{v} + \psi_k^v\widehat{H}_{ik}^{0} + \Xi_{ik}^{v} + \Omega_{ik}^{v} + \Delta_{\mathrm{ik}}^{\mathrm{v}} - \mu_k\widehat{H}_{ik}^{v} - \tilde{\Gamma}_{ik}\widehat{H}_{ik}^{v}$$

Equation 2

where the symbols are defined as follows.

Indices:

- The index *h* corresponds to HIV status. *h*=0 uninfected; *h*=1 primary infection; *h*=2 asymptomatic; *h*=3 late stage infection.
- *s* represents HSV-2 status. *s*=0 uninfected; *s*=1 primary infection; *s*=2 asymptomatic infection; *s=3* symptomatic recurrence.
- *v* represents syphilis status. *v*=0 uninfected; *v*=1 primary infection; *v*=2 secondary infection; *v*=3 latent infection; *v*=4 temporary immunity.
- *k* corresponds to gender. *k*=1 is male (clients), and *k*=2 is female (FSWs).
- For FSWs, the behavioural strata i=1-2 represent FSWs stratified by duration (0-1, 2-4, 5-9, 10+ years selling sex), activity level (<median number of clients, > median number of clients)) and level of condom use (“every time”, “sometimes”, “never”).
- For clients the behavioural strata i=1-8 represent clients by duration (0-1, 2-4, 5-9, 10+ years buying sex) and activity level (above below median number of FSWs visited per month or not).
- p represents the type of partnership: short-term (occasional) commercial, regular commercial or long-term non-commercial

Variables:

- H_{ik}^{hs}– high-risk population of gender *k* and gender-specific behavioural stratum *i*, HIV status

h and HSV-2 status *s*. Thus *k*=1 represent clients with behavioural strata *i*=1-8; *k*=2 represent FSWs with behavioural strata *i*=1-2.

- $\widehat{H}_{ik}^{v}$ – high-risk population of gender *k* and gender-specific behavioural stratum *i*, with syphilis stage *v* (where *v*=0 represents uninfected individuals).

Parameters:

- μ_k is the gender-specific rate of ceasing sexually activity for non-HIV-related reasons.
- $\tilde{\Gamma}_{ik}$ is the per-capita rates of progression to AIDS, used in the syphilis system of equations to ensure that the numbers of individuals in each behavioural compartment is the same for the decoupled syphilis and HIV/HSV-2 systems.
- ε_{ik} is the rate of becoming involved with commercial sex (becoming a FSW/client).
- $\tilde{\xi}_{ik}$ is the rate of ceasing involvement with commercial sex.
- λ_{ik}^{hs} is the force of HIV infection term. This term is zero unless *h*=0. It is modified by co-infection with HSV-2 by the presence of cofactors for increasing susceptibility:
- ϕ_{ik}^{hs} is the force of HSV-2 infection term, and is zero unless *s*=0.
- ψ_{Hik}^{v} is the force of syphilis infection term, and is zero unless *v*=1.
- Γ_{ik}^{hs} is the term describing the number of individuals progressing from one stage of HIV to the next for each behavioural compartment *i* and HSV-2 infection state *s*:

$$\Gamma_{ik}^{hs} = \begin{cases} 0 & (\mathrm{h} = 0) \\ -\delta_{h}^{HIV} H_{ik}^{hs} & (\mathrm{h} = 1) \\ \delta_{h-1}^{HIV} H_{ik}^{h-1\,s} - \delta_{h}^{HIV} H_{ik}^{hs} & (\mathrm{h} > 1) \end{cases}$$

Equation 3

where δ_{h}^{HIV} is the average rate of progression of HIV from stage *h* to stage *h*+1.

- Λ_{ik}^{hs} describes the progression of HSV-2 of all individuals of a given type from one stage to the next:

$$\Lambda_{ik}^{hs} = \begin{cases} 0 & (\mathrm{s}=0) \\ -\delta_s^{HSV} H_{ik}^{hs} & (\mathrm{s}=1) \\ \delta_{s-1}^{HSV} H_{ik}^{hs-1} + \delta_{s+1}^{HSV} \eta^h H_{ik}^{hs+1} - \delta_s^{HSV} H_{ik}^{hs} & (\mathrm{s}=2) \\ \delta_{s-1}^{HSV} H_{ik}^{hs-1} - \delta_s^{HSV} \eta^h H_{ik}^{hs} & (\mathrm{s}=3) \end{cases}$$

Equation 4

where η^h is a factor to account for the fact that HSV-2 recurrences are more frequent in HIV positive individuals, and δ_s^{HSV} represents the average rate of progression from stage *s* (*s*=3 represents recurrence of symptoms).

- Ξ_{ik}^v describe the progression of syphilis from one stage to the next, for *v*=0-4, including recovery from syphilis:

$$\Xi_{ik}^v = \begin{cases} \gamma_{Hk2}^{Syp} H_{ik}^2 + \gamma_{k3}^{Syp} H_{ik}^3 + \delta_5^{Syp} H_{ik}^5 & (v=0) \\ -\delta_2^{Syp} H_{ik}^2 - \gamma_{k2}^{Syp} H_{ik}^2 & (v=1) \\ \delta_2^{Syp} H_{ik}^2 - \delta_3^{Syp} H_{ik}^3 - \gamma_{k3}^{Syp} H_{ik}^3 + \delta_{recurr}^{Syp} H_{ik}^4 & (v=2) \\ \delta_3^{Syp} H_{ik}^3 - \delta_4^{Syp} H_{ik}^4 - \delta_{recurr}^{Syp} H_{ik}^4 & (v=3) \\ \delta_4^{Syp} L_k^4 - \delta_5^{Syp} L_k^5 & (v=4) \end{cases}$$

Equation 5

γ_{kv}^{Syp} represents the rate of recovery from primary (*v*=1) and secondary (*v*=2) syphilis in individuals of gender *k*. δ_v^{Syp} represents the rate of progression from stage *v* to *v*+1 (*v*=1-3) or rate of loss of immunity (*v*=4). δ_{recurr}^{Syp} represents the rate of recurrence of symptoms from latent (*v*=3) syphilis.

- Ω_{ik}^{hs} is the number of FSWs (*k*=2) of behavioural class i, HIV state *h* and HSV-2 state *s*, move from one condom consistency class to the next per unit time. There is no corresponding term for clients (*k*=1), in other words Ω_{i1}^{hs}=0.
- Both FSWs and clients are divided by duration of involvement with commercial sex. Δ_{ik}^{hs} represents the number of individuals changing duration class per unit time. The transition from duration class *n*-1 to class *n* (corresponding to moving from behavioural class *i'* to *i=i'+1*) is given by the formula $\Delta_{ik}^{hs} = (1/d_{n-1}) \times H_{i'k}^{hs} - (1/d_n) \times H_k^{hs}$ where d_n is the length of the duration class *n.*

The force of infection can be generically written as:

$$\lambda_{ik}^{0} = \sum_{\substack{x', i', \\ p}} \beta_{k,p}^{xx'} c_{ik}^{p} \rho_{ikxi'k'x'}^{p}$$

Equation 6

where *k'* is the gender of the partner (*k'*=1 if *k*=2; *k'*=2 if *k*=1) and *i'* is the behavioural type of partner being considered. *x* is the co-infection status of the infectee for HIV/HSV-2 if relevant, *x'* is the stage of infection of the partner (including co-infection status for HIV/HSV-2 if necessary). Thus for the HIV or HSV-2 force of infection term, *x* and *x'* represent the pair of indices (*h,s*) and (*h',s'*), while for syphilis they represent *v* and *v'* respectively), c_{ik}^{p} is the number of partners per unit time of individuals of type (*i,k*) for a partnership of type *p*, and $\rho_{ikxi'k'x'}^{p}$ is a random mixing factor of the form (where n_{ikx} is the number of individuals of type (i,k) with stage of infection *x*):

$$\rho_{ikxi'k'x'}^{p} = \frac{c_{i'k'}^{p} n_{i'k'x'}}{\sum_{\bar{i}\bar{k}\bar{x}} c_{\bar{i}\bar{k}}^{p} n_{\bar{i}\bar{k}\bar{x}}}$$

Equation 7

The per-partnership transmission probabilities can be written as:

$$\beta_{k,p}^{xx'} = 1 - \left(1 - \chi_{xx'} p_{k}^{x'}\right)^{N_p(1-\pi_p)} (1 - \kappa\chi_{xx'} p_{k}^{x'})^{N_p \pi_p}$$

Equation 8

where $p_{k}^{x'}$ is the probability of transmission per act depending on the gender of the person *k* and the stage of infection of the partner (which is included in the index *x'*); $\chi_{xx'}$ is a cofactor for infection depending on the co-infection status (included in indices *x* and *x'*) of both partners for other STIs (thus for HIV it is the sum of cofactors due to HSV-2 and one for syphilis averaged by the proportion infected; for HSV-2 it is the cofactor due to HIV; for syphilis this term is 1); N_{part} is the number of acts

in the partnership per unit time, which depends on whether the partnership is short-term commercial, regular commercial or long-term non-commercial, κ is the effectiveness of condoms per act at preventing infection against the STI in question; π is the proportion of acts for which a condom is used, depending on the type of partnership and the level of condom use of the sex worker if the partnership is commercial.

Detailed model structure

The following 24 and 8 behavioural stratifications were used in the model for FSW and clients respectively. FSWs were stratified by their sexual activity level (whether they had above the median number of clients per week or not), by duration of time since beginning to sell sex (0-1, 2-4, 5-9, 10+ years), and by their reported consistency of condom use with occasional clients ('consistently', 'sometimes/often', 'never'). Clients were stratified by duration of time since beginning to buy sex (0-1, 2-4, 5-9, 10+ years) and by high and low level of sexual activity (similarly defined by whether or not their number of visits to FSWs per month was higher than the median). Upon ceasing to sell/buy sex FSWs/clients leave the high-risk group at rates dependent on their activity level and are replaced by uninfected new FSWs/clients at a rate so as to maintain the proportion of the general population who are at high-risk to be constant. This level of heterogeneity was found to be able to reproduce the rapid initial rise in HIV prevalence among FSWs, which was not possible with the simpler models tested during the development stage, and produced comparable results to the more complex model described in [19].

The disease progression in the HIV model assumes high viraemia phases during initial infection and shortly before developing AIDS, and infectees progress from primary to asymptomatic to pre-AIDS stages at rates estimated from the literature[3-4]. Co-circulating HSV-2 infection is modelled dynamically with a short initial infection, a long asymptomatic phase (incorporating low-level

infectious shedding) and infectious symptomatic recurrences[5]. There are cofactors facilitating HIV and HSV-2 acquisition and transmission, reflecting the synergy between them[6-8].

The natural history of syphilis is modelled dynamically with primary and secondary infection stages followed by a latent phase with infrequent recurrences of secondary syphilis[9-10], using the same behavioural structure and taking into account HIV deaths so as to give an average cofactor for increasing HIV susceptibility for each behavioural compartment. Within the model, transmission probabilities for all STIs were modified using risk ratios estimated from the literature to account for the more infectious disease stages.

It is assumed that all individuals with syphilis receive treatment/recover before or during the latent stage, and so do not develop tertiary syphilis. Upon treatment in the latent stage they gain temporary immunity. Individuals may also be treated during the primary and secondary stages, although in this case they will not gain transient immunity, but will instead become susceptible again. The rate of recovery from primary and secondary syphilis increases after the beginning of the intervention due to STI treatment as part of the services offered by NGOs. Syphilis treatment incorporates both syndromic management (whereby FSWs visiting *Avahan* clinics were examined and treated based on the presence of symptoms) and periodic presumptive treatment (PPT: treatment given at fixed intervals to FSWs). These were modelled through an increased rate of recovery from both primary and secondary infection. For PPT, FSWs were given treatment at set intervals (every 3 months prior to 2007; every 6 months after 2007), reflecting programmatic changes. Data on the number of FSWs receiving PPT, recorded in a programme monitoring database, was used to parameterise the proportion of FSWs on PPT, who were then assumed to recover on average 1.5 months after infection prior to 2007, and 3 months after 2007. In all FSW IBBAs, high proportions (>2/3) of FSWs reported visiting the *Avahan* STI clinic in the 6 months prior to the survey; it was thus assumed that all those who have symptoms (10-30% of FSWs) will seek

treatment. The time before seeking treatment after first developing symptoms was derived from IBBA survey data, based on self-reported delays from FSWs.

Due to the presence of these intensive STI treatment programmes in *Avahan* districts, model prevalence of primary and secondary syphilis was fitted to high-titre epidemiological prevalence data (defined as RPR positive and TPHA positive, with RPR titre 1:8 or higher) instead of RPR positive and TPHA positive, to prevent recently treated infections being counted in the modelled prevalence estimates. This is consistent with recent work by Samoff[11], where the majority of primary and secondary infections had RPR titre 1:8 or higher.

The efficacy of condoms in preventing infection is introduced at the per-act level when calculating the transmission hazard, and is specific to each STI[12-15]. The proportion of protected sex acts in commercial partnerships between FSWs and clients varies by FSW condom use (using condoms "every time", "sometimes", or "never" with occasional clients). The percentage of acts for which a condom is used in each category was determined from IBBA survey data, based on reported use at last sex stratified by these categories as reported in Table 1 in main text. For example, those reporting using condoms "every time" do so less than 100% of the time. In addition, as FSWs are likely to over-report condom use due to social desirability bias, we derived an adjustment factor was derived by comparing data from FSWs and clients. As a result, in each stratum of condom use, the proportion of acts in each stratum for which a condom was used is reduced by 0-25%[19]. Data from general population surveys as well as client and FSW IBBAs suggested that few sex acts between long-term partners are protected overall by condoms.

Under the estimated intervention time trends, the proportion of FSWs who used condoms consistently at the beginning of the intervention and the rate of increase in the proportion of FSWs who were consistent condom users prior to the start of the intervention, were derived from the

estimated CCU time trends analysis based on the historical FSW cohort data as explained in Lowndes et al[16](Box 1ii). Condom use was then assumed to increase linearly from the beginning of the intervention to the value measured in the FSW IBBA rounds 1, and subsequently to that in round 2 (and then to round 3 for Mysore, Belgaum, Bellary).

After the last available FSW IBBA in each district (R3 in Mysore, Belgaum, Bellary and R2 in Shimoga and Bangalore Urban), condom use was taken to be constant due to the absence of any further data, and the potential for saturation of coverage. The fraction of FSWs "sometimes" using condoms with occasional clients was found to be low in the IBBA; it was taken to increase linearly to the IBBA round2 value (and thence changes linearly to the R3 value in Mysore, Belgaum and Bellary). (See supplement figures S1). Constraints were introduced when sampling to ensure that proportions of FSWs "every time", "sometimes", and "never" using condoms summed to one. Condom use reported in the IBBA for regular and occasional clients was similar, and thus condom use with regular clients was assumed to be the same for simplicity.

Condom use trends for the control 1 and 2 represent possible scenarios in absence of the *Avahan* intervention, and are also based on the estimate of CCU trends from the reconstructed trends analysis (i.e. "*estimated CCU trends*")[16]. Both controls have the same behaviour as the estimated CCU time trends prior to the start of the intervention. After the start date of *Avahan*, in control 1, the proportion of FSWs in each of the "every time", "sometimes", and "never" strata remain constant, representing a situation where condom use does not change. In contrast, in control 2, the proportion of FSWs in the "every time" and "sometimes" groups continue increasing at the pre-intervention rate suggested by the conduct the "*estimated CCU trends"*, until the time of the last IBBA in that district, corresponding to a scenario in which condom use increases but more slowly than it would in the presence of *Avahan*. Thus, control 2 is more conservative than control 1.

Relationships between FSWs and clients are either occasional (assumed to last 1-3 sex acts), regular or long-term. There is little data on the identity of long-term non-commercial partners of FSWs, but as their risk of infection is high they are included with clients. From IBBA data, clients reported repeated visits to some FSWs (regular FSW-client commercial partnerships), as well as occasional clients. Regular partnerships could last several years, and survey data suggested that regular clients would typically visit once a week.

Proportionate mixing for each type of partnerships is used, whereby individuals choose different types of partner in proportion to their availability. The number of FSWs/clients visited per month by clients varies by activity level of the client/FSW. In both cases these choices of dependence were made to maximise behavioural heterogeneity between groups. FSW sexual activity and population size determine the number of partnerships available, which is in turn used to determine the client size population.

New individuals enter the susceptible population at a recruitment rate equivalent to the sum of those leaving the model through ceasing sex, mortality or migration plus the growth rate of the population (based on the district-level growth rate of the 2001 India census).

Methods C: *Detailed fitting procedure and likelihood method*

For each districts, the following steps are followed in order to identify multiple parameters sets that agree with the HIV prevalence data.

1. *Sampling of parameters*

For each district, N parameters were sampled using Latin hypercube sampling. For Mysore and Shimoga 200,000 parameter sets were sampled; for Belgaum 1 million parameter sets were used; for Bellary 100,000 parameter sets were used; for Shimoga 500,000 were used. Since the number of

clients is a derived quantity, runs with exceptionally high proportions (>30%) of clients in the general population were discarded.

2. *Preliminary screening of parameter sets without HIV*

Once sampled, each parameter set was first pre-screened to reduce the computational time by discarding parameter sets that produce highly unrealistic prevalences. This was achieved by running the model in the absence of HIV with a constant high condom use set at IBBA round 2 levels for HSV-2 and syphilis until these prevalences reached equilibrium. Parameter sets that produced high-titre syphilis or HSV-2 prevalences too far away from the observed were discarded, as they would still not fit the prevalence data even in the presence of co-circulating HIV. The syphilis upper bound reflects the highest prevalence of TPHA positive FSWs in the IBBA, which would measure lifetime infection: 44%. The HSV-2 screening condition was that prevalence was >1% in FSWs. This produced a subset of N_2 parameter sets out of the N initially sampled.

3. *Screening of HIV in 1987*

If the parameter set passed this initial pre-screening, the system was then re-set with condom use as determined by the condom hypothesise scenario under investigation, seeding an initial HIV prevalence of 0.5% across all FSW behavioural classes as initial conditions. As the start time of the epidemic is also a sampled parameter, we used an additional criteria to exclude runs that produce very unrealistic HIV prevalence in 1987, when systematic HIV measurement began in India[18] using the following exclusion criterion based on the available information around this date for FSWs. FSW HIV prevalence in all districts had to be less than 15.6% in 1987, based on the highest observed prevalence at this time [20]. These criteria ensure that we exclude parameter sets, which would be unable to fit the HIV prevalence measured in the round 1 IBBA. This produced a subset of N_3 parameter sets.

4. *Fitting stages: fitting to IBBA data*

The N_3 parameter sets which passed the screening step 3 above were then tested to see if they fitted within the 95% confidence interval (CI) of the FSW round 1 and client IBBA HIV prevalence data, as well as within 3CI of the FSW round 1 HSV-2 and high-titre syphilis prevalence data. They were also required to fit the adjusted R2 and R3 (adjusted to the changes in FSW typology, marital status, literacy, ever having been asked for anal intercourse and localite status when relevant for a given district). The "n" different sets of parameters that provide adequate fits under the "*estimated CCU trends"* constitutes the posterior parameter distribution in what can be seen as the intervention group (used to make prediction and estimate impact).

5. *Model outcomes*

The number of fits ("n" out of the "N" initial parameter sets sampled) for each of the condom use trends hypothesis (*estimated CCU trends*, Control 1 and Control 2) is shown in Table 3 in the main text, and was used to assess the relative ability of each CCU trends hypothesis to fit the IBBA data. For each fitting parameter set, the model was run to 2015. FSW and client HIV/STI prevalences were recorded, as well as the number of HIV infections per unit time.

6. *Intervention impact*

For each district, intervention impact was measured in terms of number of HIV infections averted by re-running each parameter set from the posterior distribution identified with the *estimated CCU trends* (intervention group) and in a simulated control group using the same posterior parameter distribution but with condom use changing in the manner specified for control 1 or 2 (and no increase in Tp treatment). Again, the prevalence and incidence of FSW and client HIV/STI as well as the number of HIV infections per unit time were recorded. The number of infections averted by the modelled intervention between time T1-T2 (i.e. from the start of Avahan at time T1 to time T2) compared to the given control group were calculated from the difference in total number of

infections between the original run (under the *estimated CCU trends i.e.* the intervention group) and the matched control groups run over different time periods. The proportion of infections due to syphilis treatment only was calculated by comparing the number of infections averted with one of the control group (as previously defined) and a slightly modified control group where syphilis treatment is assumed to change as in the intervention group. Impact estimates and 95% credibility intervals (95%CrI) were generated by using the HIV projections from each posterior parameter set, weighted by the likelihood of the model projection given the FSWs and clients HIV/STI prevalence data described below. The 95%CrI reflects the uncertainty in parameter assumptions remaining after the fitting stage, since more than one set of parameters can produce equally good fits and therefore using only one fit could over or underestimate impact.

7. *Likelihood method*

For each fitted run, a corresponding weight was derived based on the likelihood of the IBBA data given the model and associated parameter set, as follows:

1. For every epidemiological prevalence data *X* from the IBBA surveys (for FSWs HIV/HSV-2/Tp for R1/R2 (and R3 in Mysore, Belgaum and Bellary) and for clients HIV/HSV-2/Tp R1), k_X out of n_X people test positive. We assume that for each fit the predicted model prevalence π_X^f is the probability of infection of any given individual, and use a binomial likelihood. Using Stirling's approximation, the corresponding binomial log likelihood $LL_X^f(\pi_X^f)$ of the observed data X can be calculated for each fit *f* and epidemiological data set *X*:

$$LL_X^f = \mathrm{n}_X ln(\mathrm{n}_X) - (\mathrm{n}_\mathrm{X} - \mathrm{k}_\mathrm{X}) ln(\mathrm{n}_X - \mathrm{k}_X) - \mathrm{k}_X ln(\mathrm{k}_X) + 0.5 ln\left(\frac{2\pi \mathrm{n}_X}{\mathrm{k}_X(\mathrm{n} - \mathrm{k}_X)}\right) + \mathrm{k}_X\, ln\left(\pi_X^f\right) + (\mathrm{n}_X - \mathrm{k}_X) ln(1 - \pi_X^f)$$

   We use log likelihoods to avoid numerical errors from multiplying small numbers.

2. For each prevalence, we normalise the range of the corresponding likelihoods over all fits *f* as follows:

$$\widehat{LL_X^f} = \frac{LL_X^f}{(\max_f LL_X^f - \min_f LL_X^f)}$$

The difference between the largest and smallest log likelihood between all fits *f* is then 1 for every epidemiological prevalence *X*, and this ensures that none of the STIs contribute disproportionately to the overall likelihood.

3. The modified log likelihoods for each epidemiological prevalence data *X* are then added together and exponentiated to give the modified likelihood L_f for each fit *f*:

$$L_f = \exp\left[\sum_X \widehat{LL_X^f}(\pi_X^f)\right]$$

4. These are normalised across all fits to give the likelihood weights w_f for each fitted parameter set *f*.

$$w_f = \frac{\mathrm{L_f}}{\sum_{\mathrm{f'}} \mathrm{L_{f'}}}$$

Using these weights, weighted impact and prevalence percentiles were calculated.

Methods D: *Validation of the hypothesis testing procedure*

To test the validity of our results from the hypothesis testing analysis, we tested and validated our hypothesis modelling procedure on simulated data for Mysore district, for which we know if H1 or H0 is true, as follows.

1) Generate "mock observed" prevalence data*:* Using the model and three randomly selected parameter sets from the posterior range of plausible parameters for Mysore under hypothesis H1 ("*estimated CCU trends*"), we simulated one HIV epidemic prevalence curve and used the simulated HIV prevalence at three time point (2004, 2006, 2009) which correspond to the times of the IBBA surveys in that district. These data serve as our simulated "mock observed" prevalence data to fit the model to. We associated a confidence interval of the same width as the empirical ones to each simulated prevalence time point.
2) Fit the model to the mock data: Using the same framework defined and used with the real data, we then randomly selected 200,000 different parameter sets from the prior parameter range for Mysore using Latin hypercube sampling, alternatively using condom prior hypothesis under H1 ("*estimated CCU trends*"), H0 (control 1), and h0b (control2)
3) Success rate: For each CCU hypothesis, in stage 2) we identified the "n" number of parameters sets that fell within the confidence interval of each of the three "mock observed" data sets.
4) As described in the main text, we used the number of fits ("n") to each hypothesis to determine which one is more likely (Table S5A).
5) The same process was repeated using mock data simulated assuming that H0b is true (Supplementary table S5B).
6) Results in supplementary Table S5

References (Methods section)

1) Ramesh BM, Moses S, Washington R, et al. Determinants of HIV prevalence among female sex workers in four south Indian states: analysis of cross-sectional surveys in twenty-three districts. AIDS 2008; 22 (Suppl 5):S35-44.
2) Reza-Paul S, Beattie T, Syed HU, et al. Declines in risk behaviour and sexually transmitted infection prevalence following a community-led HIV preventive intervention among female sex workers in Mysore, India. AIDS 2008; 22 (Suppl 5):S91-100.
3) Wawer MJ, et al., Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai Uganda. J Infect Dis 2005. 191(9): 1403-9.
4) Boily MC, et al., Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis 2009; 9(2):118-29.
5) Foss AM, et al., Dynamic modeling of herpes simplex virus type-2 (HSV-2) transmission: issues in structural uncertainty. Bull Math Biol 2009; 71(3): 720-49.
6) Foss AM, et al. Exploring the interactions between HSV-2 and HIV: model predictions for a southern Indian setting. XVII International AIDS Conference. 2008; Mexico City.
7) Schacker T, et al., Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. J Infect Dis 1998; 178(6): 1616-22.
8) Conant MA, et al., Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002; 13(1): 12-21.
9) Garnett GP, et al., The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis, 1997; 24(4): 185-200.
10) Vickerman P , et al. To what extent is the Indian HIV epidemic in southern India driven by commercial sex? A modeling analysis. AIDS 2010; 24(16): 2563-72.
11) Samoff E, et al., Pre-treatment syphilis titers: distribution and evaluation of their use to distinguish early from late latent syphilis and to prioritize contact investigations. Sex Transm Dis 2009; 36(12): 789-93.
12) Pinkerton SD and Abramson PR. Effectiveness of condoms in preventing HIV transmission. Soc Sci Med, 1997; 44(9): 1303-12.
13) Pinkerton SD, Abramson PR, Turk ME. Updated estimates of condom effectiveness. J Assoc Nurses AIDS Care, 1998; 9(6): 88-9.
14) Wald A, et al., Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001; 285(24): 3100-6.

15) Wald A, et al., The relationship between condom use and herpes simplex virus acquisition. Ann Intern Med 2005; 143(10): 707-13.
16) Lowndes CM, et al., Assessment of intervention outcome in the absence of baseline data: 'reconstruction' of condom use time trends using retrospective analysis of survey data. Sex Transm Infect 2010; 86 Suppl 1: i49-55.
17) Bradley J, et al., Assessing reported condom use among female sex workers in southern India through examination of condom availability. Sex Transm Infect 2010; 86 Suppl 1: i44-8.
18) Bollinger RC, Tripathy SP and Quinn TC. The human immunodeficiency virus epidemic in India. Current magnitude and future projections. Medicine (Baltimore), 1995; 74(2): 97-106.
19) Pickles M, et al. Interim modeling analysis to validate reported increases in condom use and assess HIV infections averted among female sex workers and clients in Southern India following a targeted HIV prevention program. Sex Transm Inf 2010; 86 (Suppl 1):i33-43.
20) Simoes, E.A., et al., Evidence for HTLV-III infection in prostitutes in Tamil Nadu (India). Indian J Med Res, 1987. **85**: p. 335-8.

SUPPLEMENTARY TABLES

Supplementary table S1: Ranges of district specific behavioural and demographic model parameters (prior distribution) sampled from at the fitting stage[a].

Model parameters	Mysore	Belgaum	Bellary	Shimoga	Bangalore
Demography					
Number of FSWs in 2010	1822-2734	1600-2400	3429-5143	1506-2258	9950-14926
Per-capita rate of leaving due to non-HIV death or migration (years^{-1})	0.014	0.016	0.020	0.012	0.030
Annual growth rate of general population	1.4%	1.6%	2.0%	1.2%	3.0%
Sexual behaviour					
Long-term partnerships of FSWs and clients:					
Fraction (%) of FSW currently married or cohabiting	51-61	22-31	25-38	43-54	42-54
Fraction (%) of clients currently married or cohabiting	55-74	50-68	37-59	25-45	37.8-55.4
- Duration 1-4 years	86-93	81-91	82-93	81-90	76.0-86.1
- Duration 5+ years					
- Average frequency of sex acts per month with married/cohabiting partner	5.9-8.2	5.6-9.5	11.9-18.2	6.8-8.6	7.8-9.8
Duration of long-term partnerships (cohabiting or married): (years)	8.6-13.0	16.6-21.7	15.0-19.2	14.1-18.2	16.0-19.2
FSW sexual behaviour:					
Average weekly frequency of clients:					
- Low-activity*	4.5-7.0	7.1-10.8	5.8-8.4	2.3-2.6	3.7-4.2
- High-activity**	6.6-21.9	13.5-20.9	23.5-53.9	7.7-10.3	12.0-13.8
Average number of regular clients per week:					
- Low-activity*	0.72-1.04	1.91-2.60	1.88-2.81	0.93-1.19	1.50-1.92
- High-activity**	0.96-1.92	4.10-5.09	4.04-5.95	1.87-3.12	3.23-4.15
Number of sex acts with each occasional client	1-3	1-3	1-3	1-3	1-3
Number of sex acts per year with each regular client	42.0-55.2	42.0-55.2	42.0-55.2	42.0-55.2	42.0-55.2
Duration of regular FSW-client partnership (months)	38-86	38-86	38-86	38-86	38-86
Average duration of sex work[&] in months for:					
- Low-activity*	38-47	149-201	105-136	51-63	37-45
- High-activity**	52-67	99-131	86-111	62-81	38-46

Client sexual behaviour:					
Number of clients	Determined by number of FSW partnerships				
Proportion of male clients who are:					
- Low activity*	0.51-0.60	0.58-0.69	0.40-0.54	0.72-0.82	0.52-0.65
- High activity**	0.40-0.49	0.31-0.42	0.46-0.60	0.18-0.28	0.35-0.48
Number of FSW visited/month by clients:					
- Low activity*	0.8-1.2	1.71-1.96	0.8-1.2	1.0	1.0
- High activity**	2.9-3.8	4.25-4.93	2.42-2.72	2.16-2.54	2.43-3.26
- Average duration of being client in months					
-Low activity*	139-185	95-120	91-119	131-165	102-123
-High activity**	158-218	106-147	112-147	102-150	125-159
Epidemic dates					
Start of HIV epidemic in India	1976-1985	1976-1985	1976-1985	1976-1985	1976-1985

Low (*High) activity: below (above) the median frequency of visits to FSWs; [&] Overall mean duration in sex work (months) at R1: 62 in Mysore, 154 in Belgaum, 120 in Bellary, 74 in Shimoga, 53 in Bangalore; at R2: 85 in Mysore, 170 in Belgaum, 123 in Bellary, 78 in Shimoga, 56 in Bangalore. [a]Ranges are usually based on the 95% confidence interval estimated from IBBA surveys

Supplementary table S2: Ranges of biological model parameters (prior distribution) sampled from at the fitting stage for all districts

Definition of model input	Model inputs	Reference
Stages of infections		
Average duration of syphilis stages (months):		
• Primary (no treatment)	1.5	Available data was reviewed by[1].
• Secondary (no treatment)	3.0-4.5	
• Primary and secondary stage (with treatment)	1-5	
• Latent phase (including treatment)	2-24	
• Time between recurrences in latent period	6	
• Immune/resistant phase	12-60	
Average duration of HSV-2 stages:		
• Primary stage	0.36-0.66	From[2-9].
• Symptomatic recurrence	0.10-0.16	Using [4, 6, 9-12]
Rate of HSV-2 symptom recurrences per month while:		Using[2, 4,6-7], [13-16].
• HIV negative	0.09-0.41	
• HIV positive	1-2*HIV negative rate	From[14,17]
Average duration of HIV stages (months):		
• Initial HIV high viraemia phase	4-6	Based on [18-19]
• Between initial high viraemia and pre-AIDS	70-91	
• Pre-AIDS high viraemia phase	6-18	
Infectiousness		
Probability of HIV transmission per sex act:		
• Male-to-female	0.06-0.11%	From [21]
• Female-to-male	0.01-0.14%	
Sexual transmission multiplicative co-factor per sex act (RR):		
• Initial high viraemia phase	4.5-18.8	
• Pre-AIDS high viraemia phase	4.5-11.9	
Prob. of syphilis transmission per sex act (male to female):	0.05-0.2	Based on [1,20]
Ratio of syphilis transmission probabilities female to male: male to female	0.33-1.0	

Probability of HSV-2 transmission: • Latent/asymptomatic shedding stage (male to female) • Ratio male-to-female: female-to-male transmission • Primary stage • Symptomatic recurrence stage	 0.05-0.20 % 2-5 2-6*6.7-25 times asymptomatic/latent transmission prob. 1-3*6.7-25 times latent/asymptomatic transmission prob.	 Using [22-23] From [16, 22-23] From [10, 16, 24]
Average syphilis cofactor per sex act for increasing susceptibility to HIV HSV-2 cofactor per sex act for increasing HIV infectivity: • Primary and symptomatic recurrence phases Asymptomatic/latent phase HSV-2 cofactor per sex act for increasing HIV susceptibility: • Asymptomatic/latent phase • Primary phase and symptomatic recurrence phase	2.1-3.3 1.27-2.57*1-2 0.27-1.57* 0.04-0.15*2-3 1-4.75 1.5-4.0 times asympt. cofactor	Using [25] Using [14, 26-38] and [39] to convert from differences in HIV viral load.
HIV cofactor per partnership for increasing HSV-2 infectivity: • Primary phase • Asymptomatic/latent phase • Symptomatic recurrence phase	 1-2.5 2-4 Same as primary	Using [29, 40-42] and converting to probability using [39]

Supplementary table S3: HIV/STI prevalence data from IBBA surveys in each district modelled used to fit the model and in likelihood estimation[&] (Methods C, stages 4 and 7).

Survey	District (date carried out)	% Mean (N) [ranges][&]		
		HIV[a]	HSV-2[b]	High-titre syphilis[b]
FSW				
Round 1	Mysore (Aug 2004)	26.1 (429) [21.9-30.3]	64.4 (393) [50.1-78.6]	14.8 (393) [4.2-25.3]
	Belgaum (Nov 2005)	33.9 (363) [27.6-40.2]	83.9 (359) [68.2-99.6]	3.3 (357) [0.0-11.0]
	Bellary (Nov 2005)	15.6 (426) [11.1 -20.0]	70.2 (420) [50.6-89.8]	2.0 (420) [0.0-6.8]
	Shimoga (Aug 2005)	9.7 (389) [6.3-13.1]	59.5 (386) [40.6-78.4]	2.7 (386) [0.0-8.8]
	Bangalore Urban (July 2006)	12.7 (673) [8.6-16.7]	68.6 (648) [52.4-84.9]	8.4 (649) [0.0-20.4]
Round 2	Mysore (Dec 2006)	24.3 (425)	78.6 (425)	3.1 (425)
	Belgaum (July 2008)	27.3 (399)	na	2.9 (387)
	Bellary (Aug 2008)	14.1 (410)	na	4.8 (401)
	Shimoga (Sept 2008)	9.0 (406)	na	1.9 (403)
	Bangalore Urban (Jan 2009)	8.0 (750)	na	4.3 (680)
Round 3[c]	Mysore (Apr 2009)	10.9 (425)	67.3 (424)	5.2 (425)
	Belgaum (Sept 2010)	22.2 (417)	72.2 (411)	1.1 (412)
	Bellary (Nov 2010)	6.3 (397)	57.2 (390)	3.2 (396)
	Shimoga (Sept 2012)	na	na	na
	Bangalore Urban (Aug 2011)	na	na	na
Client				
Round 1	Mysore (Oct 2008)	5.4 (425) [3.3-7.6]	31.4 (411)	2.2 (411)
	Belgaum (Oct 2007)	6.2 (408) [3.6-8.8]	27.6 (388)	1.9 (386)
	Bellary (Oct 2007)	6.0 (424) [2.6-9.5]	25.8 (406)	2.3 (407)
	Shimoga (Dec 2007)	3.0 (426) [0.9-5.1]	25.7 (421)	0.5 (421)
	Bangalore Urban (Oct 2007)	2.4 (680) [0.9-3.9]	24.1 (634)	1.7 (630)

Data were available for FSW R1&R2&R3 only for Belgaum, Bellary, and Mysore and one round for clients. R3 data Shimoga and Belgaum became available recently and could only be used in logistic regression; na: not available; [a]Ranges for HIV were based on the 95%CI and those for Syphilis and HSV-2 prevalence were based on 3*95%CI; [b]HIV model outcome was fitted to the adjusted R2 and R3 prevalence; N= sample size; na: not available in time for the modelling analysis. [&] The ranges are used for fitting and N are used for binomial likelihood (i.e. chance of getting x positives in your survey out of N people if the true prevalence is p). [c]At the time of the modelling analysis.

Supplementary table S4: Predicted (by the model) annual HIV incidence rate per susceptible FSWs (person-year)

District	IBBA	Median	2.5 percentile	97.5 percentile
Mysore	R1	0.117	0.101	0.146
	R2	0.061	0.045	0.079
	R3	0.033	0.022	0.043
Belgaum	R1	0.071	0.056	0.099
	R2	0.044	0.031	0.058
	R3	0.027	0.018	0.034
Bellary	R1	0.030	0.019	0.042
	R2	0.018	0.009	0.035
	R3	0.007	0.003	0.014
Shimoga	R1	0.026	0.017	0.040
	R2	0.011	0.006	0.021
Bangalore	R1	0.034	0.025	0.048
	R2	0.013	0.009	0.019

Supplementary table S5A: Validation of the hypothesis testing on simulated mock prevalence data for Mysore – when H1 ("E*stimated CCU trends*") is true

Condom use trends	**Number of parameter sets sampled/tested**	**Fit Criteria**					
		(a)= Fits to R1/R2 FSW HIV data and R1 client HIV data (3 data points)			**Fits to (a) & R3 FSW HIV data (4 data points)**		
		Run 1	**Run 2**	**Run 3**	**Run 1**	**Run 2**	**Run 3**
Control 1 (H0)	200,000	209	5	27	0	0	0
Control 2 (H0b)	200,000	508	12	138	28	2	6
"Estimated CCU trends" (H1)	200,000	3262	559	3068	3039	531	2965

Supplementary table S5B: Validation of the hypothesis testing on simulated mock prevalence data for Mysore – when H0b ("*Control 2 trends"*) is true

Condom use trends	**Number of parameter sets sampled/tested**	**Fit Criteria**					
		(a) = Fits to R1/R2 FSW HIV data and R1 client HIV data (3 data points)			**Fits to (a) & R3 FSW HIV data (4 data points)**		
		Run 1	**Run 2**	**Run 3**	**Run 1**	**Run 2**	**Run 3**
Control 1 (H0)	200,000	408	149	756	237	85	437
Control 2 (H0b)	200,000	615	281	1120	567	262	995
"Estimated CCU trends" (H1)	200,000	723	1063	1383	7	12	5

Our validation suggests that the modelling hypothesis testing procedure is very likely to detect (Table S5A) or reject (Table S5B) a hypothesis of substantial CCU increases, especially when we have four HIV prevalence data points. Not surprisingly, it is more difficult to distinguish between Control 1 (no CCU increase) and control 2 (slow CCU increase) even with four data points (3 for FSWs and 1 for clients) given the small difference between these two hypotheses (S5B). When we have only three data points (2 FSWs, 1 client), the results of the hypothesis testing is less precise and may sometimes point to a increase in CCU even in its absence (S5B). However, when our method falsely supports the "*estimated CCU trends*" (H1) when "Control 2" (H0b) is true, the

ratio H1 to H0b fits is typically low (723/616 = 1.17, 1063/281=3.8, 1383 /1120= 1.23) compared to (3262/508=6.4, 559/12 = 47, 3068/138=22.2) when H1 is true. Thus, the ratio of fits is a good indicator of the strength of evidence supporting H1.

References

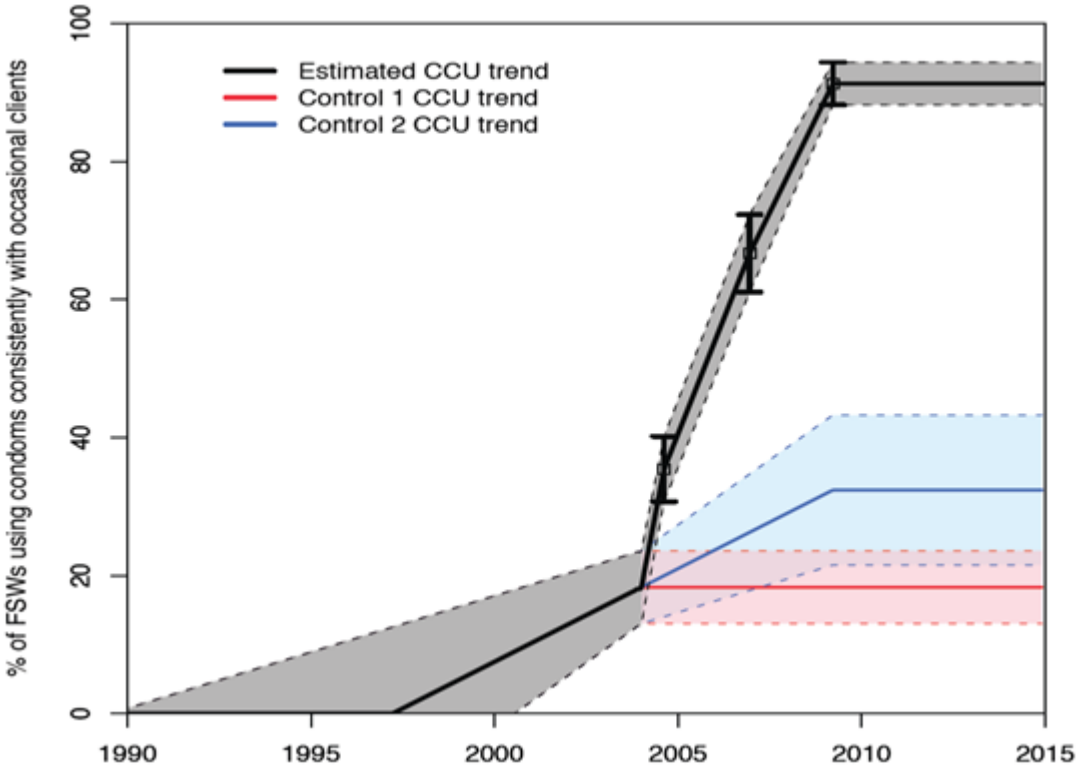
1. Garnett GP, et al. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sex Transm Dis 1997; 24(4): 185-200.
2. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. Ann Intern Med 1999; 131(1):14-20.
3. Cheong WK, et al., Clinical and laboratory study of first episode genital herpes in Singapore. Int J STD AIDS 1990; 1(3):195-8.
4. Corey L, et al. Genital herpes simplex virus infections: clinical manifestations, course, and complications. Ann Intern Med 1983; 98(6):958-72.
5. Corey L, et al. Intravenous acyclovir for the treatment of primary genital herpes. Ann Intern Med 1983; 98(6):914-21.
6. Corey L, et al. Genital Herpes, in Sexually Transmitted Diseases, M.P. Holmes K.K., Sparling PF, et al., Editor. 1999, McGraw-Hill. p. 285-312.
7. Diamond C, et al. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. Sex Transm Dis 1999; 26(4):221-5.
8. Koelle DM, et al. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. Ann Intern Med 1992; 116(6):433-7.
9. Guinan ME, et al. The course of untreated recurrent genital herpes simplex infection in 27 women. N Engl J Med 1981; 304(13):759-63.
10. Wald A, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. J Clin Invest 1997; 99(5):1092-7.
11. Wald A, et al. Genital shedding of herpes simplex virus among men. J Infect Dis 2002; 186(Suppl 1):S34-9.
12. Wald A, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med 2000; 342(12):844-50.
13. Lafferty WE, et al. Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. N Engl J Med 1987; 316(23):1444-9.
14. Schacker T, et al. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. J Infect Dis 1998; 178(6):1616-22.
15. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med 1994; 121(11):847-54.
16. Kim HN, et al. Does frequency of genital herpes recurrences predict risk of transmission? Further analysis of the valacyclovir transmission study. Sex Transm Dis 2008; 35(2):124-8.
17. Conant MA, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002; 13(1):12-21.
18. Grover G., Shivraj SO. Survival pattern of reported HIV infected individuals in the city of Delhi (India). J Commun Dis 2004; 36(2):83-92.
19. Kumarasamy N, et al. Natural history of human immunodeficiency virus disease in southern India. Clin Infect Dis 2003; 36(1):79-85.
20. Korenromp EL. Treatment of sexually transmitted diseases as an HIV prevention strategy? Cofactor magnitudes, syndromic management and a reappraisal of the Mwanza and Rakai trials. 2001, Erasmus University Rotterdam.
21. Boily MC, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis 2009; 9(2):118-29.

22. Wald A, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. JAMA 2001; 285(24):3100-6.
23. Corey L, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med 2004; 350(1):11-20.
24. Wald A, et al. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. J Infect Dis 2003; 188(9):1345-51.
25. Rottingen JA,Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001; 28(10):579-97.
26. Nagot N, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. N Engl J Med 2007; 356(8):790-9.
27. Zuckerman RA, et al. Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. J Infect Dis 2007; 196(10):1500-8.
28. Baeten JM, et al. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. J Infect Dis 2008; 198(12):1804-8.
29. Celum C, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet 2008; 371(9630):2109-19.
30. Dunne EF, et al. Suppressive acyclovir therapy reduces HIV cervicovaginal shedding in HIV- and HSV-2-infected women, Chiang Rai, Thailand. J Acquir Immune Defic Syndr 2008; 49(1):77-83.
31. Delany S, et al. Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. AIDS 2009; 23(4):461-9.
32. Schacker T, et al. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. Ann Intern Med 1998; 128(1):21-8.
33. Mbopi-Keou FX, et al. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. J Infect Dis 2000; 182(4):1090-6.
34. Augenbraun M, et al. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. Ann Intern Med 1995; 123(11):845-7.
35. Nagot N, et al. Longitudinal assessment of HIV-1 and HSV-2 shedding in the genital tract of West African women. J Acquir Immune Defic Syndr, 2005. 39(5):632-4.
36. LeGoff J, et al. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. AIDS 2007; 21(12):1569-78.
37. Serwadda D, et al. Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. J Infect Dis 2003; 188(10):1492-7.
38. Nagot N, et al. Roles of clinical and subclinical reactivated herpes simplex virus type 2 infection and human immunodeficiency virus type 1 (HIV-1)-induced immunosuppression on genital and plasma HIV-1 levels. J Infect Dis 2008; 198(2):241-9.
39. Quinn TC, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 2000; 342(13):921-9.

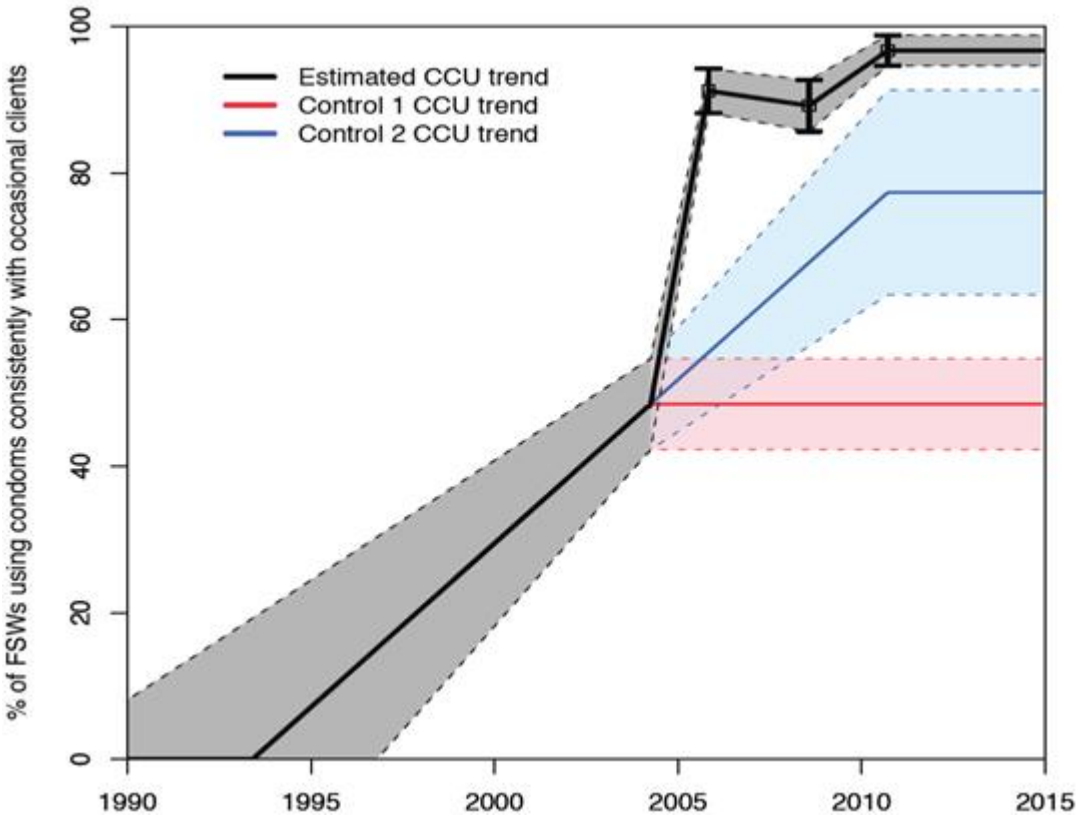
40. Corey L, et al. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. J Acquir Immune Defic Syndr 2004; 35(5):435-45.
41. Freeman EE, et al. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS 2006; 20(1):73-83.
42. Watson-Jones D, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N Engl J Med 2008; 358(15):1560-71.

Supplementary Figure S5

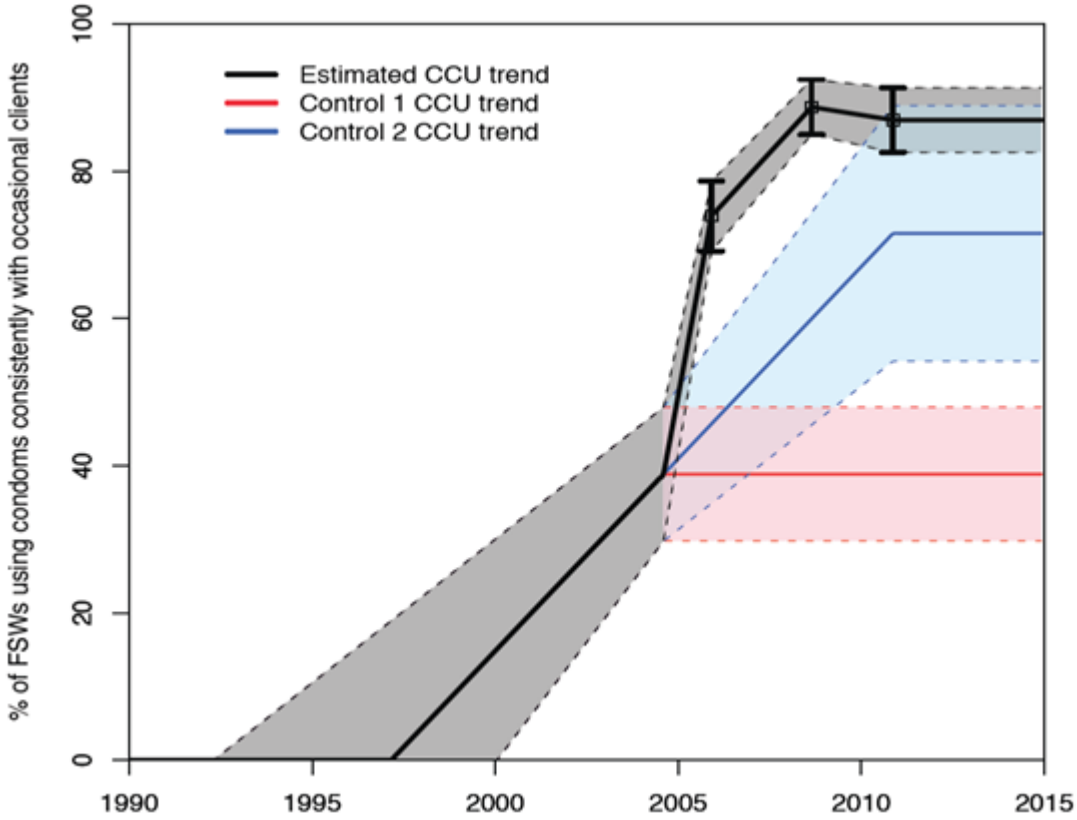
A) Mysore



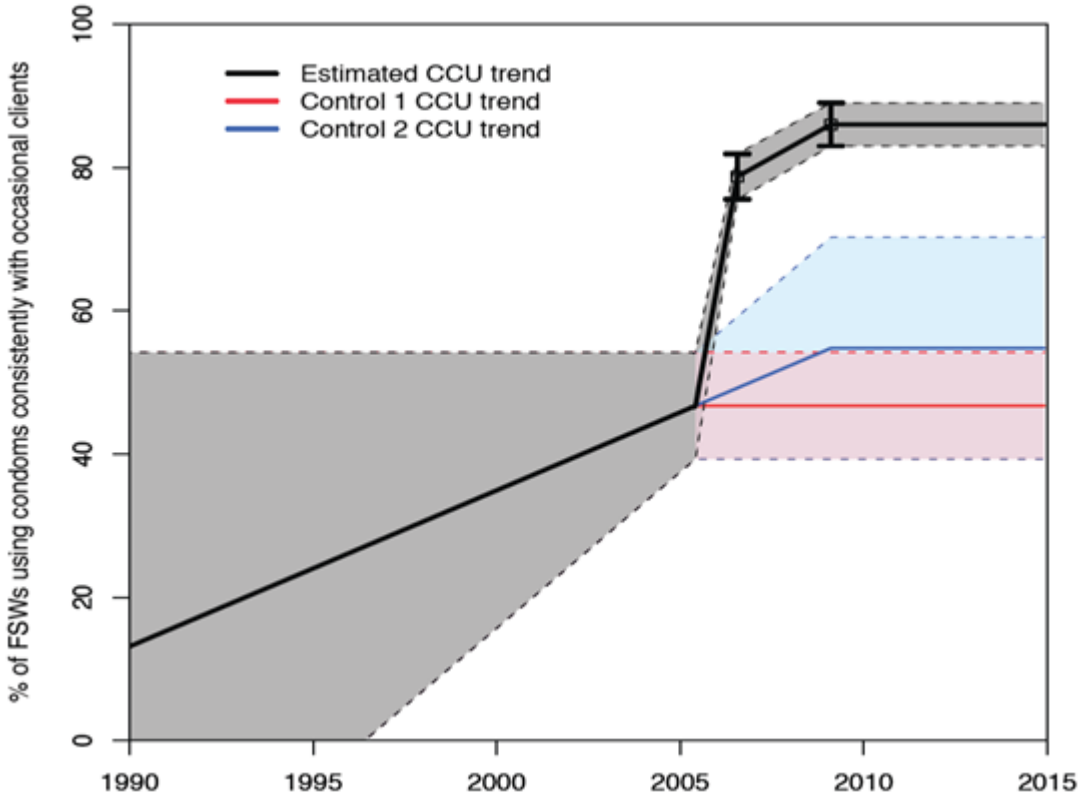
B) Belgaum



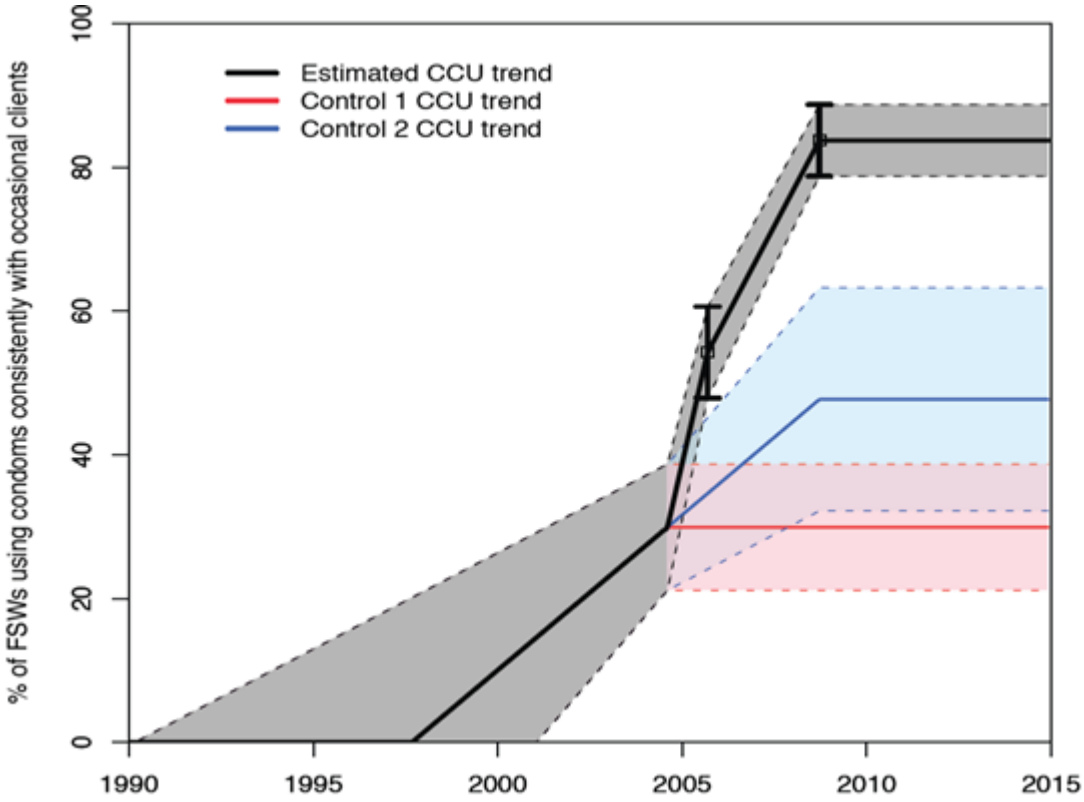
C) Bellary



D) Bangalore Urban



E) Shimoga

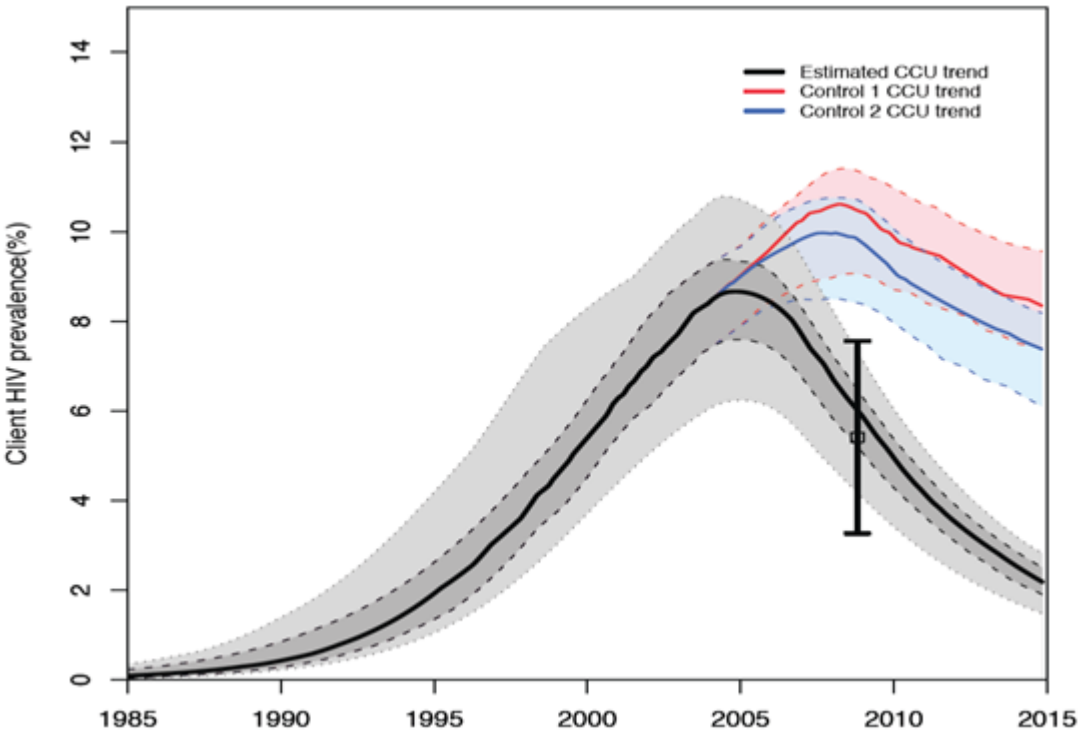


Legend - Supplementary Figure S5:

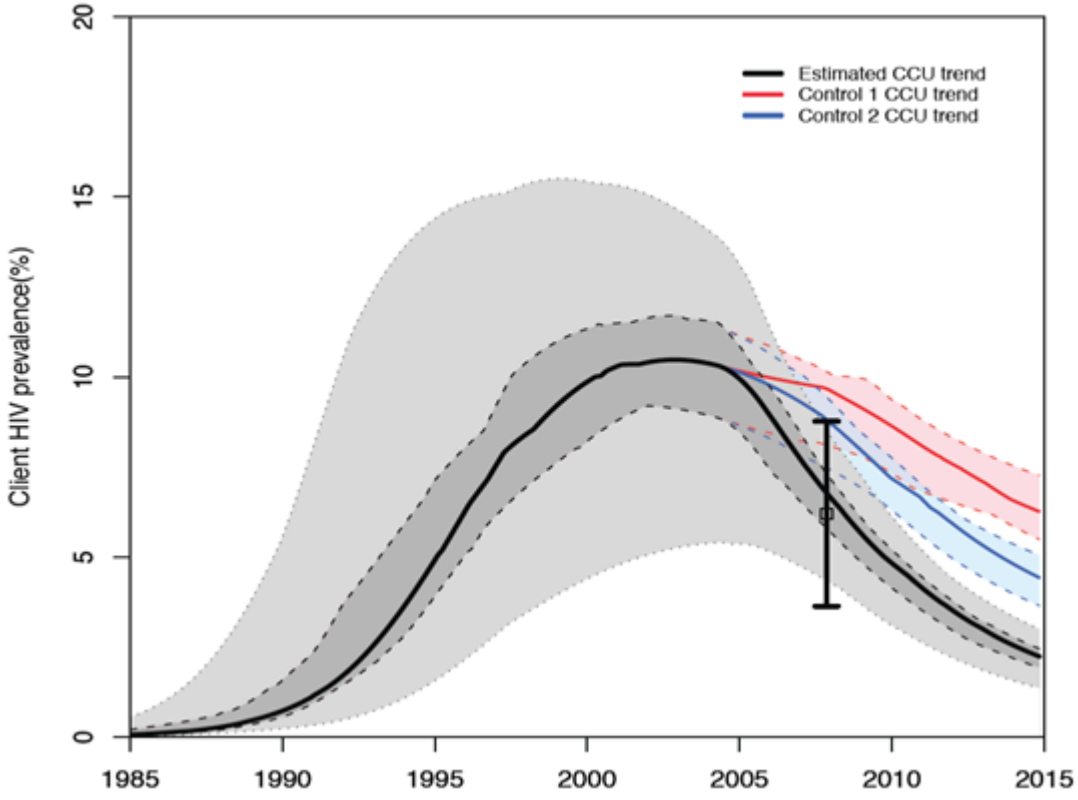
Prior distribution for the increase in the proportion of FSW consistently using condoms (CCU) in commercial sex acts with occasional clients under the *"estimated CCU trends"* in presence of the intervention and for the control group 1 and 2 (most conservative counterfactual) in absence of the intervention in (A) Mysore, (B) Belgaum, (C) Bellary, (D) Bangalore Urban, and (E) Shimoga. The paler grey area represents the 95%CI of the CCU trend estimates. Control 1 and 2 are used to simulate a HIV control group in absence of intervention and assume the same pre-Avahan CCU increase as the "*estimated CCU trends"*. Control 1 assumed no CCU increases *post-Avahan* in absence of intervention. Control 2 assumes that the pre-intervention increases in CCU would have continued even in absence of intervention. Also shown is the CCU estimates from the different rounds of available IBBA surveys (mean and 95%CI).

Supplementary Figure S6

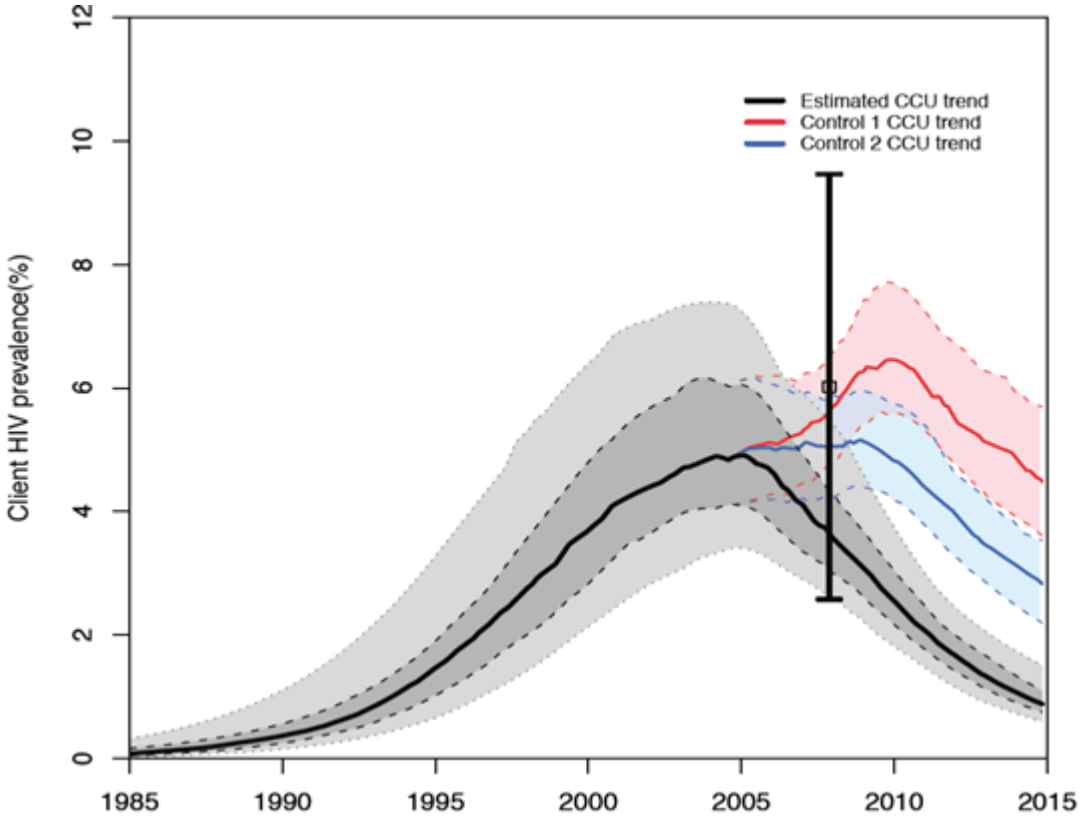
A) Mysore



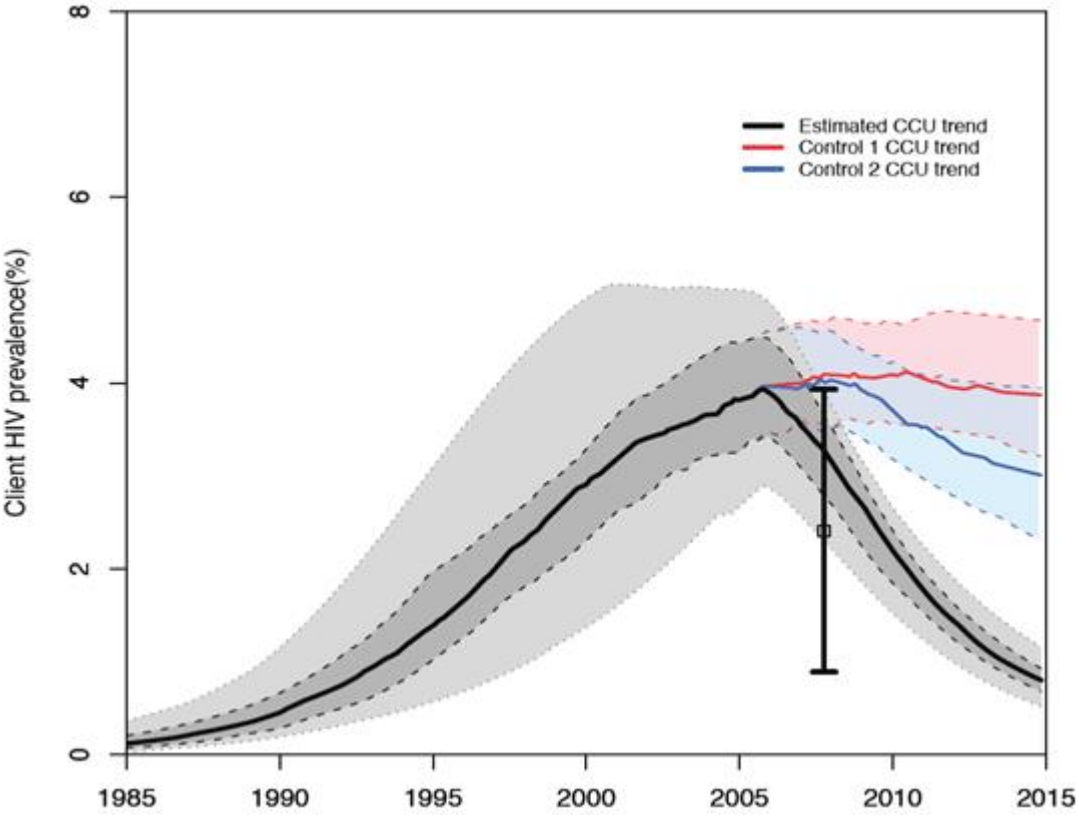
B) Belgaum



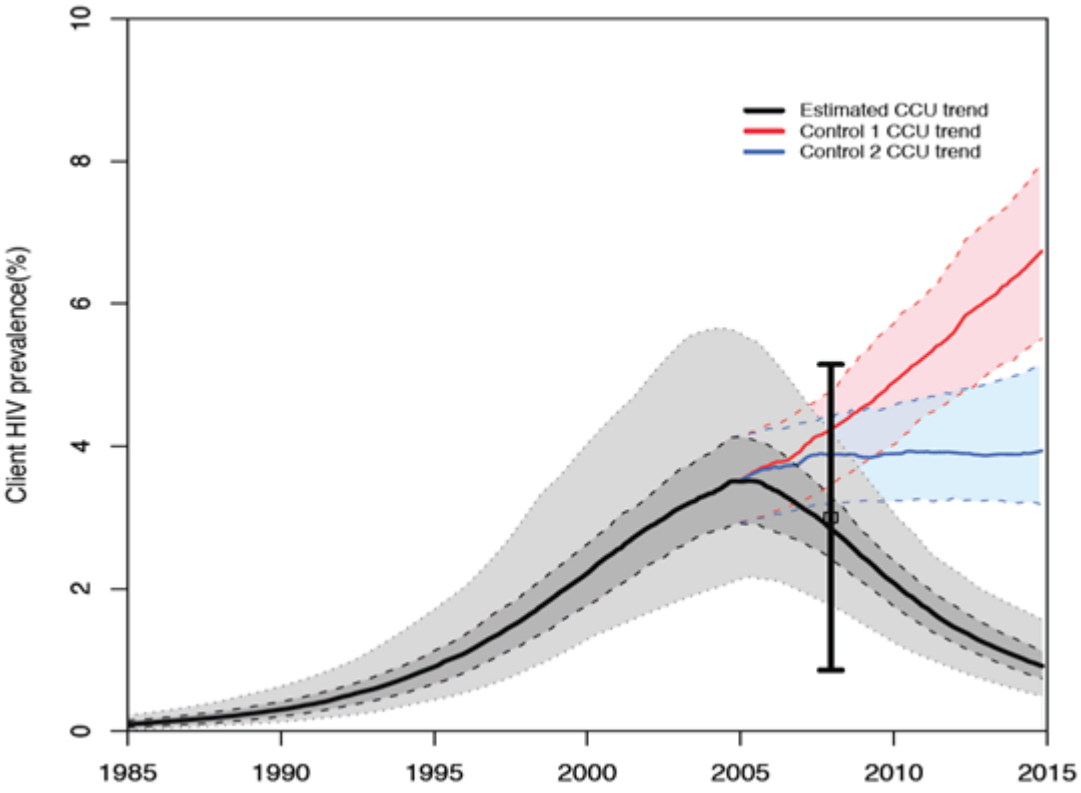
C) Bellary



D) Bangalore Urban



E) Shimoga



Legend - Supplementary Figure S6:

Predicted client HIV prevalence over time under the "es*timated CCU trends"* in presence of the intervention and the two alternative CCU trends (*Control 1* and *Control 2 CCU trends*) to simulate HIV prevalence in absence of the intervention in A) Mysore, B) Belgaum, and C) Bellary D) Bangalore Urban and E) Shimoga districts. Shown on the graphs are the mean (dark lines black, blue and red) and the 75%CrI (shaded area) for each hypothesis. The paler grey area represents the 95%CrI. Also shown is the available IBBA survey prevalence data (mean and 95% CI). As the model was fitted to the adjusted HIV prevalence at round R2 or R3, the HIV prediction may not fall exactly within the 95%CI of the HIV prevalence data. Note, the scale on the y-axis changes.